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An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis

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Abstract
Introduction Approximately 11.1 million cancer survivors are alive in the United States. Activity prescriptions for cancer survivors rely on evidence as to whether exercise during or after treatment results in improved health outcomes. This systematic review and meta-analysis evaluates the extent to which physical activity during and post treatment is appropriate and effective across the cancer control continuum.
Methods A systematic quantitative review of the English language scientific literature searched controlled trials of physical activity interventions in cancer survivors during and post treatment. Data from 82 studies were abstracted, weighted mean effect sizes (WMES) were calculated from 66 high quality studies, and a systematic level of evidence criteria was applied to evaluate 60 outcomes. Reports of adverse events were abstracted from all studies.
Results Quantitative evidence shows a large effect of physical activity interventions post treatment on upper and lower body strength (WMES=0.99 & 0.90, $p<0.0001$ & 0.024, respectively) and moderate effects on fatigue and breast cancer-specific concerns (WMES=−0.54 & 0.62, $p=0.003$ & 0.003, respectively). A small to moderate positive effect of physical activity during treatment was seen for physical activity level, aerobic fitness, muscular strength, functional quality of life, anxiety, and self-esteem. With few exceptions, exercise was well tolerated during and post treatment without adverse events.
Conclusions Current evidence suggests many health benefits from physical activity during and post cancer treatments. Additional studies are needed in cancer diagnoses other than breast and with a focus on survivors in greatest need of improvements for the health outcomes of interest.

Keywords Exercise · Cancer · Survivorship · Adults · Outcomes

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Introduction

Approximately 11.1 million cancer survivors are alive in the United States today [1] and the population of long-term cancer survivors continues to grow. Physical activity has been increasingly researched as a non-pharmacological intervention to combat the physiologic and psychological effects of treatment in cancer patients [2]. However, in order for clinicians to prescribe physical activity for patients during and post cancer treatment, there needs to be clarity in the evidence supporting whether a physical activity program will reduce the negative physiologic and

psychological effects of treatment. Given the growing population of survivors and increased volume of literature on physical activity interventions for cancer survivors, there is a need to evaluate and determine the extent to which physical activity during and post treatment is appropriate and effective for health outcomes across the cancer control continuum.

Multiple systematic reviews of physical activity interventions among cancer survivors have been conducted since the publication of our systematic review and meta-analysis in July 2005 [3]. These reviews have focused on specific outcomes, primarily fatigue and quality of life, and populations, including elderly survivors, patients during treatment, or certain cancer types [4–12]. Galvão et al. [13] provided a qualitative review of exercise intervention studies during and post treatment for all cancers, and a quantitative meta-analyses on physical activity interventions in all adult cancers was published in 2006 [14]. However, study inclusion was not limited to randomized controlled trials, and single group pre-post studies were included. As such, there is a need to update our previous findings and examine the evidence published since 2005 on the effect of physical activity interventions on cancer survivors' physiologic or psychosocial outcomes.

For the purpose of this review, a *cancer survivor* is defined as "any individual that has been diagnosed with cancer, from the time of discovery and for the balance of life", as suggested by the National Coalition for Cancer Survivorship [15]. The review is restricted to physical activity intervention studies delivered outside of the physical therapy setting with a concurrent comparison group and results presented separately for the intervention and comparison groups (i.e, controlled clinical trials). Results of this review are reported for interventions conducted during and post cancer treatment independently. Except where noted, methods from our 2005 publication [3] are repeated, in part to allow for a comparison of the state of the field over the intervening 4+ years.

Methods

Literature search

Sources of candidate studies included online databases, reference lists of relevant articles and reviews, files of project staff, and a peer review of search criteria and reference lists obtained. MEDLINE® searches of literature published since our original systematic qualitative and quantitative review (February 2005–November 2009) were conducted using the same search strategy [3]. One set of search terms included the following: [(exercise or physical activity) and cancer and (randomized controlled trial(s), controlled clinical trial, intervention studies, or clinical trial)]. The second set of search terms included: [(exercise or motor activity or physical activity) and (randomized controlled trial(s), controlled trials, intervention studies, or clinical trials) and cancer]. To be included in this review, a study had to be published in the English language, focused on adults diagnosed with cancer, include an intervention designed to increase physical activity outside of the physical therapy setting (could not be delivered by a physical therapist), and include a concurrent (i.e., parallel) comparison group. Two project staff members, both trained in the critical analysis of scientific literature, independently reviewed each of the identified articles to determine eligibility.

Abstraction

The methods of abstraction followed those of the 2005 review [3]. Briefly, the abstraction form for the Guide to Community Preventive Services [16] was used as a template for article abstraction, which included questions about study design and execution, study quality, number and characteristics of participants, participant recruitment information, and details of the intervention (such as dose of physical activity and non-physical activity components). Each trial was evaluated using eleven study quality questions related to description of the study and participants, study measurement, analytic approach, and interpretation of results. Studies were also assessed through a checklist of 10 internal validity characteristics [17]. A study with 5 or more of the 10 internal validity characteristics was considered to be high quality. Only high quality studies were included in the quantitative pooled analysis. Outcomes reported in at least two high quality studies were abstracted, which differs from the prior review in which outcomes with even one study were abstracted and reported. Outcome data were initially abstracted in Excel to list and categorize outcomes. Tables of study descriptions and outcomes were developed and reviewed by a second study investigator for completeness and accuracy.

Data synthesis

Effect sizes were calculated for studies of high quality (n=66) [18–92]. Effect sizes (e.g. standardized mean differences between the treatment and control group(s)) were calculated from outcomes where raw score means, standard deviations, and sample sizes were available at post intervention or where between-groups t-test on raw post-test scores were available [93]. Post minus pre-intervention change score effect sizes were not computed because pre- and post-intervention correlations were not reported consistently throughout the literature. Weighted mean effect sizes (WMES) and 95%

confidence intervals of the weighted means were calculated using the fixed effects [94] and random effects [95] methods. Weighted mean effects sizes from fixed effects models did not differ from random effects models for the majority of outcomes. However, WMES generated by random effects models are reported, as well as the I-squared value in order to best quantify the consistency of study effect [96]. The previous review reported results from fixed effects models [94]. Higgins et al. [96] suggests that I-squared values of 25%, 50% and 75% coincide with adjectives of low, moderate, and high for describing heterogeneity. Calculations were completed using Stata 10.0 Data Analysis and Statistical Software [97]. Magnitude of effect sizes are interpreted using the original criteria proposed by Cohen, with effects of 0.2 to 0.5 described as 'small to moderate', 0.51 to 0.8 as 'moderate to large', and greater than 0.8 as 'large' [98]. No subgroup analyses are reported; only comparisons between treatment group(s) and control group. A key methodologic difference from our prior publication is the elimination of the qualitative approach to data synthesis, due to the volume of data reviewed and complexities of comparisons between the two approaches.

The Physical Exercise Across the Cancer Experience (PEACE) framework developed by Courneya & Friedenreich [99, 100] was utilized to assess the timing of intervention delivery with regard to treatment. The PEACE framework identifies the following six outcomes in the post diagnosis time period: buffering prior to treatment, coping during treatment, rehabilitation immediately post treatment, long term health promotion, survival, and palliation for those approaching the end of life. All studies, including those not meeting criteria for high quality [101–121] were critiqued using the PEACE framework.

Results

The MEDLINE search and referral from topic experts resulted in a total of 380 titles reviewed for inclusion. The most common exclusion criteria were lack of a concurrent comparison group, and delivery of the intervention by a physical therapist in a medical setting. After exclusions, 67 new articles, representing 52 new studies were added to 35 articles (30 studies) included in the 2005 publication [3]. The total number of articles meeting inclusion criteria for this updated review is 102, representing 82 unique studies. Sixty-six of the 82 studies described were rated as being of high methodologic quality using the Van der Windt [17] internal validity characteristics. Descriptions of the populations studied, intervention characteristics, and study quality are summarized in Tables 1 and 2.

Populations studied

Table 1 includes a description of populations studied and interventions employed. Of the 82 studies, 40% conducted interventions during active cancer treatment. The most common diagnosis included in all studies was breast cancer (83%). The percentage of studies within each of the post diagnosis PEACE framework [99, 100] categories is also provided in Table 1. These categories do not add up to 100 because some studies fall into more than one PEACE framework category. Only two studies included in this review focus on buffering [35, 56], none on palliation.

Intervention characteristics

The majority of the interventions were longer than 5 weeks, 40% being more than 3 months in length. Aerobic or combined activity interventions were the most common (80%) and typically of moderate to vigorous intensity, three to five times per week, for 30–45 min per session. These characteristics were consistent for both physical activity interventions during and post treatment. Of the 82 studies, 30% of during treatment interventions and 51% of post treatment interventions were behavioral change interventions in which the primary aim was to increase physical activity behavior. The loss to follow-up from the studies was generally modest, with an average of 11.2% overall, ranging from zero to 43.8%. Mean loss to follow-up rates did not differ significantly between studies conducted post treatment (10.2%) versus during treatment (12.7%).

Study quality

Of the 82 studies reviewed, 20 (24%) described the sample adequately with regard to cancer diagnoses and treatment course, race/ethnicity, gender, and sociodemographic variables. In the 62 (76%) studies failing to adequately describe the population, they either neglected to collect the variables at baseline, and/or only reported on some of the variables, race being the variable most consistently overlooked. Often diagnostic, treatment, and demographic data were only provided for those who completed the study, making it difficult to draw any conclusions regarding differential loss to follow-up. Physician's clearance or pre-screening was reported in 69 (84%) studies, assuring no cardiac or other contraindications to physical activity were present prior to study entry.

Forty-seven studies (57%) described the physical activity intervention, including details of the intervention length, physical activity modality, intensity, frequency, duration per session, and progression throughout the intervention in a

Table 1 Description of the interventions

Characteristic of Study or Intervention		Percent of Studies with this Characteristic or Mean Value		
Timing	During treatment	40%		
	Post treatment	60%		
Framework PEACE category	Buffering	2%		
	Coping	41%		
	Rehabilitation	43%		
	Health promotion	27%		
	Survival	11%		
	Palliation	0%		
	Multiple categories in one study	23%		
		All	**During Tx**	**Post Tx**
Sample size	Average sample size per control group	41 (mean)	32 (mean)	47 (mean)
		4–322 (range)	4–150 (range)	6–322 (range)
	Average sample size per intervention group	42 (mean)	33 (mean)	49 (mean)
		6–319 (range)	6–150 (range)	6–319 (range)
Cancer diagnoses included	Breast	83%	79%	86%
	Colon	9%	3%	12%
	Lung	11%	9%	6%
	Ovarian	6%	3%	8%
	Leukemia	6%	9%	4%
	Lymphoma	6%	3%	8%
	Prostate	10%	15%	6%
	Sarcoma	4%	6%	2%
	Stomach	2%	0%	4%
	Testicular	2%	0%	4%
	Other	15%	16%	12%
Physician's clearance and/or systematic screening of potential participants for contraindications to activity prior to study entry		84%	88%	82%
Excluded participants based on level of physical activity prior to study entry		43%	33%	49%
Behavioral intervention[a]	Yes	43%	30%	51%
	No	57%	70%	49%
Study design	Randomized Controlled Trial (RCT)	90%	90%	90%
	Non-randomized	10%	10%	10%
Physical activity only (versus physical activity plus other intervention components)		74%	82%	69%
Intervention length	1 month or less	9%	6%	10%
	5 weeks to 3 months	48%	52%	45%
	More than 3 months	40%	33%	45%
	Not clear/reported	4%	9%	0%
Activity mode	Aerobic (alone or combined with other modes)	80%	88%	76%
	Only non aerobic	11%	6%	14%
	Not specified	9%	6%	10%
Activity intensity	Light (reported as 'low intensity')	11%	18%	6%
	Moderate to Vigorous[b]	60%	61%	59%
	Not specified	29%	21%	35%
Activity frequency	<3 times per week	13%	6%	18%
	3–5 times per week	59%	64%	55%
	>5 times per week	20%	21%	18%
	Not specified	8%	9%	8%

Table 1 (continued)

Characteristic of Study or Intervention		Percent of Studies with this Characteristic or Mean Value		
Activity duration	20–30 min per session	18%	24%	14%
	30–45 min per session	40%	33%	45%
	>45 min per session	23%	12%	31%
	Not specified	18%	30%	10%
Percent lost at follow-up		11.2%	12.7%	10.2%

[a] Primary outcome was physical activity behavior change

[b] Moderate to vigorous intensity was defined as aerobic exercise of at least 40% heart rate reserve or resistance training of at least 60% of one repetition maximum

manner allowing others to repeat what they had done. Forty-seven studies (57%) did not exclude participants on the basis of physical activity level prior to study entry.

All but one of the 82 studies [40] included measures repeated at a minimum of two time points (pre and post intervention), though the majority reported only post intervention values or change scores. Half (54%) of the studies conducted analyses that were appropriate for repeated measures, such as independent *t*-tests for change scores or repeated measures analysis of variance when there were no meaningful baseline differences between groups, and ANCOVA when there were meaningful between group differences at baseline. Four (5%) of the included studies failed to limit bias appropriately through randomization, restriction, matching, stratification, or statistical adjustment [37, 103, 106, 116].

During versus post treatment effects

Table 3 includes results for the 66 studies with high internal validity. Significant WMES from studies conducted during treatment were observed for physical activity level (0.38, $p=0.001$), aerobic fitness (0.33, $p=0.009$), upper body strength (0.39, $p=0.005$), lower body strength (0.24, $p=0.006$), body weight (–0.25, $p=0.05$), body fat percentage (–0.25, $p=0.04$), functional quality of life (0.28, $p=0.04$),

Table 2 Study quality description per the guide to community preventive services criteria [16]

Criteria of Study Quality	Percent of Studies meeting criteria		
	All	During Tx	Post Tx
Description			
1. Was the study sample well described as to race/ethnicity, sociodemographics, cancer diagnosis and treatment, as well as age?	24%	18%	29%
2. Was the intervention well described (what, how, who, where)?	82%	76%	86%
Measurement			
3. Were the outcome and other independent (or predictor) variables valid?	85%	91%	82%
4. Were the outcome and other independent (or predictor) variables reliable (consistent and reproducible)?	85%	88%	84%
Analysis			
Did the authors conduct appropriate statistical testing by:			
5. conducting statistical testing (when appropriate)?	98%	94%	100%
6. reporting which statistical tests were used?	98%	94%	100%
7. controlling for repeated measures in samples that were followed over time?	54%	45%	59%
8. controlling for differential exposure to the intervention?	0%	0%	0%
Results			
9. Did at least 80% of enrolled participants complete the study?	83%	76%	88%
10. Did the authors assess if the units of analysis were comparable prior to exposure to the intervention?	88%	76%	96%
11. Did the authors institute study procedures to limit bias appropriately (e.g., randomization, restriction, matching, stratification or statistical adjustment)?	95%	94%	96%

Table 3 Evidence of positive effects by timing (during versus post treatment) for the 66 studies with high internal validity

Outcome Type	During Treatment						Post Treatment					
	Quantity of Evidence[a] *N*	Positive *N* (%)	Significant *N* (%)	WMES (95% CI)	*P*-value	I-squared	Quantity of Evidence[a] *N*	Positive	Significant	WMES (95% CI)	*P*-value	I-squared
Physical activity level	12	10 (83%)	4 (25%)	0.38 (0.15–0.61)	0.001	46.6%	16	12 (75%)	6 (38%)	0.38 (0.22–0.54)	0.0001	58.6%
Objectively measured physical function	Insufficient	1 (100%)	1 (100%)	None calculable			Insufficient	1 (50%)	1 (50%)	-0.39 (-0.86–0.08)	0.11	0%
Physical fitness:												
Aerobic fitness	17	15 (88%)	5 (29%)	0.33 (0.08–0.57)	0.009	73.0%	14	13 (93%)	8 (57%)	0.32 (0.036–0.59)	0.03	65.6%
Upper body strength	8	8 (100%)	4 (50%)	0.39 (0.12–0.65)	0.005	57.7%	6	6 (100%)	3 (50%)	0.99 (0.67–1.32)	0.0001	14.6%
Lower body strength	7	7 (100%)	4 (57%)	0.24 (0.07–0.41)	0.006	0%	7	7 (100%)	4 (57%)	0.90 (0.12–1.68)	0.024	80.9%
Shoulder flexibility	Insufficient	1 (100%)	1 (100%)	None calculable	–	–	5	3 (60%)	1 (20%)	0.04 (−0.31–0.39)	0.81	21.1%
Lower body flexibility	Insufficient	–	–	None calculable	–	–	4	4 (100%)	2 (50%)	0.16 (−0.16–0.47)	0.34	17.5%
Body size:												
Body weight	8	2 (25%)	0 (0%)	−0.25 (−0.49—0.00)	0.05	51.4%	14	7 (50%)	2 (14%)	−0.18 (−0.31–0.06)	0.004	9.5%
Fat mass	Insufficient	0 (0%)	0 (0%)	−0.19 (−0.40-0.02)	0.07	0%	5	4 (80%)	1 (20%)	−0.25 (−0.57–0.07)	0.12	44.4%
Lean mass	5	3 (60%)	2 (40%)	0.12 (–0.24–0.47)	0.52	61.0%	5	4 (80%)	3 (60%)	0.13 (−0.08–0.34)	0.22	0%
Body fat %	7	2 (29%)	1 (14%)	−0.25 (−0.48—0.02)	0.04	39.0%	15	10 (66%)	6 (40%)	−0.18 (−0.31—0.05)	0.006	1.3%
BMI	4	1 (25%)	0 (0%)	−0.07 (−0.30–0.16)	0.54	0%	16	8 (50%)	3 (19%)	−0.14 (−0.22—0.05)	0.002	0%
Waist circumference	Insufficient	0 (0%)	0 (0%)	−0.06 (−0.41–0.30)	0.76	0%	5	3 (60%)	1 (20%)	−0.19 (−0.48–0.11)	0.22	37.9%
Arm volume[b]	Insufficient	NA	0 (0%)	−0.06 (−0.29–0.17)	0.59	0%	Insufficient	NA	0 (0%)	0.38 (−0.32–1.07)	0.29	58.7%
Quality of life:												
Overall	10	10 (100%)	4 (40%)	0.13 (–0.005–0.26)	0.06	0%	16	12 (75%)	9 (56%)	0.29 (0.03–0.54)	0.03	84.8%
Mental	Insufficient	0 (0%)	0 (0%)	None calculable	–	–	7	5 (71%)	0 (0%)	0.05 (–0.28–0.37)	0.78	79.2%
Physical	Insufficient	2 (100%)	0 (0%)	None calculable	–	–	7	5 (71%)	2 (29%)	0.17 (–0.09–0.42)	0.20	83.6%
Functional	4	3 (75%)	1 (25%)	0.28 (0.02–0.54)	0.04	0%	16	11 (69%)	5 (31%)	0.17 (−0.12–0.45)	0.25	84.7%
Social	3	1 (33%)	0 (0%)	0.11 (−0.15–0.36)	0.41	0%	11	7 (64%)	4 (36%)	0.07 (−0.13–0.27)	0.49	56.4%
Emotional	3	1 (33%)	0 (0%)	0.24 (−0.02–0.50)	0.07	0%	10	4 (40%)	1 (10%)	0.11 (−0.10–0.31)	0.32	50.9%
Trial outcome index	Insufficient	–	–	None calculable	–	–	3	2 (67%)	2 (67%)	0.78 (−0.59–2.15)	0.27	95.2%
Satisfaction with life	Insufficient	1 (100%)	0 (0%)	None calculable	–	–	3	2 (67%)	0 (0%)	−0.09 (−0.38–0.21)	0.58	31.8%
Role physical	Insufficient	0 (0%)	0 (0%)	None calculable	–	–	3	0 (0%)	0 (0%)	006 (−0.09–0.21)	0.45	0%
General	Insufficient	0 (0%)	0 (0%)	None calculable	–	–	Insufficient	1 (100%)	0 (0%)	None calculable	–	–
Breast cancer-specific concerns	Insufficient	–	–	None calculable	–	–	3	3 (100%)	3 (100%)	0.62 (0.22–1.03)	0.003	43.1%
Psychosocial:												
Sexual attractiveness	Insufficient	–	–	None calculable	–	–	Insufficient	2 (100%)	0 (0%)	0.29 (−0.11–0.69)	0.15	0%
Weight concerns	Insufficient	–	–	None calculable	–	–	Insufficient	2 (100%)	1 (50%)	0.56 (−0.28–1.40)	0.19	59.0%
Physical condition	Insufficient	–	–	None calculable	–	–	Insufficient	2 (100%)	1 (50%)	0.57 (0.03–1.11)	0.04	23.3%
Positive mood	Insufficient	2 (100%)	1 (50%)	0.39 (0.14–0.63)	0.002	0%	Insufficient	2 (100%)	1 (50%)	0.37 (−0.12–0.86)	0.14	0%
Mood disturbance	Insufficient	–	–	None calculable	–	–	Insufficient	2 (100%)	0 (0%)	−0.39 (−0.77—0.02)	0.04	0%

Anger	Insufficient	0 (0%)	0 (0%)	None calculable	–	–	Insufficient	1 (50%)	0 (0%)	−0.14 (−0.83–0.54)	0.68	0%
Confusion	Insufficient	–	–	None calculable	–	–	3	2 (66%)	0 (0%)	−0.57 (−1.14–0.005)	0.05	34.3%
Body image	Insufficient	1 (100%)	0 (0%)	None calculable	–	–	3	3 (100%)	1 (33%)	–0.26 (–0.49– –0.02)	0.03	0%
Vigor/Vitality	Insufficient	0 (0%)	0 (0%)	0.22 (−0.18–0.61)	0.28	0%	6	5 (83%)	3 (50%)	0.17 (−0.30–0.64)	0.47	80.4%
Fatigue	15	12 (80%)	6 (40%)	–0.01 (–0.35–0.33)	0.95	86.8%	14	13 (93%)	7 (50%)	−0.54 (−0.90– -0.19)	0.003	84.9%
Depression	8	7 (88%)	1 (13%)	0.06 (−0.26–0.38)	0.70	76.1%	10	7 (70%)	3 (30%)	−0.30 (−0.65–0.05)	0.10	55.0%
Anxiety	6	5 (83%)	2 (33%)	−0.21 (−0.39–−0.03)	0.02	0%	7	6 (86%)	2 (29%)	−0.43 (−0.88–0.03)	0.07	69.5%
Self-esteem	3	2 (67%)	2 (67%)	0.25 (0.04–0.46)	0.02	0%	Insufficient	2 (100%)	1 (50%)	None calculable	–	–
Physiological outcomes												
Bone mineral density	3	2 (67%)	1 (33%)	0.06 (−0.28–0.39)	0.74	0%	Insufficient	–	–	None calculable	–	–
Hemoglobin	5	3 (60%)	0 (0%)	0.50 (−0.55–1.55)	0.35	95.6%	Insufficient	0 (0%)	0 (0%)	None calculable	–	–
Hematocrit	Insufficient	0 (0%)	0 (0%)	1.25 (−1.20–3.70)	0.32	97.6%	Insufficient	0 (0%)	0 (0%)	None calculable	–	–
Total cholesterol	3	2 (67%)	0 (0%)	None calculable	–	–	3	3 (100%)	0 (0%)	−0.25 (−0.67–0.16)	0.23	27.6%
LDL	3	2 (67%)	0 (0%)	None calculable	–	–	Insufficient	2 (100%)	0 (0%)	−0.19 (−0.60–0.23)	0.38	27.5%
HDL	3	1 (33%)	0 (0%)	None calculable	–	–	Insufficient	2 (100%)	0 (0%)	0.05 (−0.49–0.60)	0.85	56.8%
Triglycerides	Insufficient	1 (50%)	1 (50%)	None calculable	–	–	Insufficient	2 (100%)	2 (100%)	−0.10 (−0.96–0.75)	0.81	82.6%
Glucose	Insufficient	–	–	None calculable	–	–	3	1 (33%)	0 (0%)	−0.03 (−0.37–0.30)	0.86	32.4%
Insulin	Insufficient	1 (100%)	0 (0%)	None calculable	–	–	4	4 (100%)	1 (25%)	−0.05 (−0.31–0.20)	0.68	13.6%
HOMA	Insufficient	–	–	None calculable	–	–	3	2 (67%)	0 (0%)	0.03 (−0.25–0.30)	0.84	0%
IGF-I	Insufficient	1 (100%)	0 (0%)	None calculable	–	–	3	3 (100%)	2 (66%)	−0.31 (−0.59–0.03)	0.03	0%
IGF-II	Insufficient	–	–	None calculable	–	–	Insufficient	2 (100%)	0 (0%)	0.11 (−0.57–0.79)	0.75	71.8%
IGF-BP-I	Insufficient	–	–	None calculable	–	–	Insufficient	2 (100%)	0 (0%)	−0.09 (−0.44–0.27)	0.63	0%
IGF-BP-III	Insufficient	–	–	None calculable	–	–	3	2 (66%)	2 (66%)	−0.21 (−0.80–0.38)	0.49	77.0%
Testosterone	3	3 (100%)	0 (0%)	0.14 (−0.17–0.45)	0.38	0%	Insufficient	–	–	None calculable	–	–
PSA	3	3 (100%)	0 (0%)	0.07 (−0.24–0.38)	0.67	0%	Insufficient	–	–	None calculable	–	–
Immune parameters	Insufficient	1 (50%)	0 (0%)	−0.18 (−1.10–0.75)	0.71	83.5%	4	3 (75%)	2 (50%)	−0.73 (−1.93–0.47)	0.24	77.1%
Resting heart rate	Insufficient	1 (50%)	0 (0%)	−0.69 (−2.07–0.68)	0.32	92.3%	Insufficient	2 (100%)	0 (0%)	−0.23 (−0.57–0.11)	0.18	0%
Pain	3	1 (33%)	1 (33%)	−0.33 (−1.32–0.66)	0.52	86.8%	6	3 (50%)	2 (33%)	−0.12 (−0.71–0.47)	0.69	94.8%
Symptoms/side effects	4	1 (25%)	0 (0%)	–0.07 (–0.57–0.43)	0.79	79.9%	4	3 (75%)	3 (75%)	−0.30 (−0.57–−0.04)	0.03	0%
Relative dose intensity	Insufficient	2 (100%)	1 (50%)	None calculable	–	–	Insufficient	–	–	None calculable	–	–
Number of nights in hospital	Insufficient	2 (100%)	1 (50%)	None calculable	–	–	Insufficient	–	–	None calculable	–	–

Cohen defined magnitude of effects of 0.2 to 0.5 as 'small to moderate', 0.51 to 0.8 as 'moderate to large', and greater than 0.8 as 'large'. I-squared values of 25%, 50% and 75% coincide with adjectives of low, moderate, and high for describing heterogeneity

WMES weighted mean effect size

[a] Quantity of Evidence = number of studies assessing the outcome. "Insufficient" means two or less studies were contributing

[b] Positive difference in treatment vs. control for arm volume is not applicable. The intervention goal is to achieve no change. Lack of significant difference in arm volume indicates the intervention was effective

positive mood (0.39, p=0.002), anxiety (–0.21, p=0.02), and self esteem (0.25, p=0.02). Significant WMES from studies conducted post treatment were observed for physical activity level (0.38, p<0.0001), aerobic fitness (0.32, p=0.03), upper body strength (0.99, p<0.0001), lower body strength, (0.90, p=0.024), body weight (–0.18, p=0.004), body fat percentage (–0.18, p=0.006), BMI (–0.14, p=0.002), overall quality of life (0.29, p=0.03), breast cancer-specific concerns (0.62, p=0.003), perception of physical condition (0.57, p=0.04), mood disturbance (–0.39, p=0.04), confusion (-0.57, p=0.05), body image (-0.26, p=0.03), fatigue (-0.54, p=0.003), general symptoms and side effects (-0.30, p=0.03), and IGF-1 (-0.31, p=0.03). The majority of studies found a positive and significant impact of physical activity interventions during treatment for upper and lower body strength, and self esteem. The majority of studies found a positive and significant impact of physical activity interventions post treatment for aerobic fitness, upper and lower body strength, lower body flexibility, lean body mass, overall quality of life, trial outcome index, breast cancer subscale, vigor/vitality, fatigue, IGF-I, IFG-BP-III, immune parameters, pain, and symptoms and side effects. Immune parameters included neutrophil count, NK cell activity, C-reactive protein and cytokines. Symptoms and side effects included lymphedema symptoms, nausea, neck symptoms, and a mixed symptom instrument.

Adverse events issues

All studies were reviewed for comments on adverse events. In the 36 studies that commented on the presence or absence of adverse events during the intervention, 29 indicated no harm was observed as a result of physical activity during or after cancer treatment. Morey et al. [86] reported a total of 201 events, only 5 directly attributable to exercise (increased blood pressure, hip pain, pulled hamstring, fall, and calf pain). Analysis of events concluded there was no difference in the intervention and control group in total number of events or event type reported. A number of studies (N=25) commented on issues related to the potential for harm from physical activity in cancer survivors. A theme across comments was fear of harm from exercise during or close to the end of treatment, specifically in regards to anemia, lymphedema, and weight loss (cachexia). Some authors suggest anemia is a contraindication to exercise during active treatment. However, Dimeo et al. [106] did not exclude for anemia and observed no adverse effects of a 6 week vigorous aerobic exercise intervention immediately upon hospital discharge after high dose chemotherapy and autologous peripheral stem cell transplantation. Dimeo proposed thresholds of 20,000/microliter for platelet counts and 1,500/microliter for leukocyte counts for values above which it is safe to perform vigorous activity, having used that threshold and observed no adverse events. Courneya [82] also noted no adverse effects of exercise training among anemic cancer patients receiving darbepoetin alfa, a drug intended to increase hemoglobin during cancer treatment. In fact, there appeared to be a synergistic effect of exercise with darbepoetin alfa, such that cancer patients receiving this drug who choose to exercise might need extra monitoring to ensure that the drug dose does not 'overshoot' the intended increase in hemoglobin.

In regards to lymphedema, with the exception of a small number of patients in two studies [21, 81], aerobic, lifestyle, and upper body resistive exercise was tolerated by breast cancer survivors with no adverse effect on the development or exacerbation of lymphedema. Herrero et al. [58] excluded breast cancer survivors with lymphedema for fear of negative effects of one repetition maximum testing. Schmitz et al., Ahmed et al., and Schwartz et al. [42, 43, 66] included breast cancer survivors with and without lymphedema in one repetition maximum testing with no reported adverse events. The primary outcome of Schmitz et al. 2009 [87], was to test the safety of strength training in breast cancer survivors with lymphedema. There were no adverse events as a result of strength training and the intervention group experienced a reduced risk of lymphedema exacerbations (RR=0.47, p=0.04).

Finally, Hayes et al. [114], noted that most individuals are told to 'take it easy' and 'get plenty of rest' during and immediately following peripheral stem cell transplantation, for fear that increasing energy expenditure will exacerbate weight loss at a time when it is assumed that patients are in negative energy balance. However, a 3 month thrice weekly aerobic and resistance exercise program resulted in more recovery of fat free mass after stem cell transplantation, compared to a stretching control group, with no difference in body weight changes over the same time period [114].

As noted in our prior review, Mock et al. [102] commented that self-reported data collection of worsening of side effects leaves open the possibility that survivors with more extreme side effects brought on by exercising may not have felt well enough to complete data collection at the end of the study. This highlights the importance of minimal loss to follow-up; 72 of the 82 studies reviewed for adverse events had 20% loss to follow-up or less.

Discussion

This review is an update to a systematic review and meta-analysis published in 2005 [3], in which authors concluded that physical activity was generally well tolerated during

and post cancer treatment. A similar conclusion can be drawn from this updated review, which includes a more than doubling in the volume of literature on physical activity interventions for cancer survivors. The previous review included 32 studies, 22 of high quality, and reported effects for 25 outcomes. This review includes 82 studies involving 6,838 cancer survivors, 66 studies of which are high quality, and has expanded the results to include 60 outcomes.

One notable result of the surge in eligible studies published since 2005 is the generation of new outcome categories, allowing for greater specificity in evaluating interventions. In the prior review, quality of life was one outcome. In the current review, quality of life encompasses eleven outcomes. Other new outcome categories were a result of new outcomes having been introduced in the literature (i.e. bone mineral density and relative dose intensity). One outcome category was eliminated for this review that had been included in the previous publication (difficulty sleeping), because in this review an outcome had to be assessed in two or more high quality studies (as opposed to only one for the 2005 review). This was done to avoid having nearly 100 outcomes in Table 3.

Highlights and new conclusions from this updated review include large effects of physical activity interventions on upper and lower body strength and breast cancer-specific concerns, as well as strong evidence as to the lack of effects of physical activity on arm volume among breast cancer survivors. For many of the 60 outcomes, there remains insufficient evidence to draw conclusions regarding the efficacy of physical activity interventions during or post treatment.

The previous review reported quantitative null findings for the effect of physical activity on fatigue, both during and post treatment. By contrast, this updated review finds evidence that physical activity interventions significantly reduced fatigue post treatment. Since 2005 the number of studies with fatigue as an outcome increased from 5 to 14 for post treatment interventions, 93% of which saw positive results, 50% of them statistically significant. Though statistically significant, the WMES for fatigue should be interpreted with an elevated I-squared value of 84.9% in mind. This elevated I-squared suggests that the strength of effect size was not consistent and highly heterogeneous across studies [96]. By study, the raw data for fatigue include effect sizes ranging from (0.06 to 2.26). One possible explanation for the lack of consistent evidence is that physical activity interventions for cancer have not targeted participants on a needs-based approach. In other words, participants are not recruited for physical activity intervention studies based on their need for improvement in the targeted outcome (i.e. low fatigue level, poor quality of life, low physical function, etc.). Instead, a 'take all comers' approach is often used, suggesting intervention effects may be underestimated for a specific outcome. In a review of fatigue interventions for cancer survivors, Jacobsen et al. [5] stated that none of the reviewed studies had eligibility criteria related to the outcome, making it possible that many of the participants experienced little or no fatigue at the time of recruitment, therefore limiting the ability to detect any intervention effects. With the exception of excluding individuals who were already adequately active, this phenomenon extends beyond the outcome of cancer-related fatigue and is a potential flaw in study design of physical activity interventions for cancer survivors.

There are multiple study design and quality differences between the studies included in this systematic review and meta-analysis and those of the 2005 publication. In the previous review 63% of the interventions occurred during treatment, while 40% are reported here. As a result, in describing interventions using the PEACE framework categories, there are now larger percentages of studies measuring outcomes that meet the descriptions of "health promotion" as compared to the previous publication. Additionally, more recent studies have excluded participants based on their current physical activity level (19% vs. 43% in the prior and current review, respectively). Finally, there has been an increase in the percentage of studies requiring physician's clearance or pre-screening for participation, 84% vs. 59% as previously reported.

There remains some justification for caution in prescribing exercise to survivors. The inverted J shaped association of exercise training with immune outcomes is well described [122], and was commented on by multiple authors as a reason to avoid high intensity exercise in cancer survivors, particularly close to the end of active treatment, when immune function may be compromised. The results from Dimeo provide the only published thresholds for blood counts above which it is safe to exercise that have empirical support. Further, the myths connecting lymphedema risk with exercise continue to be a barrier. There is tremendous fear of overusing the arm among cancer survivors, particularly noted in the qualitative comments reported in Hayes et al [81]. The women in this study were so concerned about whether the exercise they were performing was harmful to them that interim measures were needed to allay their fears. These participants also reported that they felt that doing the exercise in a supervised setting was vital to reducing their fear of overuse, injury, and lymphedema onset or worsening [81]. These fears are likely to be overcome as more data on the safety of exercise and lymphedema emerges [87]. Finally, it is notable that there are no published studies on the topic of exercise among survivors with lower limb lymphedema.

Study limitations and future directions

This review highlights clear improvement in study quality of more recent studies compared to those included in the original review. This was an important area uncovered in the original systematic qualitative and quantitative review as needing attention in future studies [3]. As in the previously published review, the choice was made to describe all eligible controlled trials, however, the results of lower quality studies were not included in the pooled quantitative summary in effort to avoid biased estimates of the effect of physical activity on examined outcomes.

Cancer control continuum

Variation in physical activity intervention timing, cancer diagnosis and treatment could impact the effectiveness of physical activity interventions for cancer survivors. The proportion of studies focusing on the Framework PEACE cancer control outcome categories of *coping* during active cancer treatment or *rehabilitation* alone or in combination with *health promotion*, reflect the proportion of studies reporting on physical activity interventions during or post treatment. Few studies have focused on the other Framework PEACE categories, including *palliation* of symptoms at the end of life and *survival* after successful eradication of cancer. Two studies, one included in the previous review [123], the other published in 2005 [124] have focused on buffering effects prior to treatment, the other Framework PEACE category. Neither study was included in this review because the intervention design and outcomes assessed are unique to the pre treatment population, limiting the generalizability of their findings to cancer survivors during and post treatment.

Consistent with the previous review, breast cancer is the most widely studied cancer for physical activity interventions both during and post treatment. There is a need to increase the evidence for physical activity interventions for other cancers. Until the volume of literature expands in other cancers, it is not possible to summarize qualitative or quantitative findings by cancer diagnosis, treatment type and by time points of the PEACE framework. As such, the evidence for a positive effect of physical activity on specific outcomes must be interpreted with caution in that cancer is a generalized term for many biologically different diseases requiring various treatments. The evidence reported herein has been compiled from physical activity interventions completed in over a twenty year span in heterogeneous survivors, the data from which are predominately breast cancer survivors.

Methodologic issues

As with our prior review, a choice was made not to assess publication bias, due to the large number of outcomes and the variability in interventions tested in the reviewed studies. However, inclusion of I-squared values for WMES results provides valuable information in assessing consistency and heterogeneity. A benefit to using I-squared values is that they can be directly compared across meta-analyses with variability in the number of studies and type of outcome data.

As suggested by others [125], there is a need for the research community to agree on outcome measures and intervention assessment. Currently there is variability in the outcome measures across studies. The development and use of standardized measures will aid in drawing conclusions about the effect of exercise. Examining the role of dose response by outcome, cancer diagnoses, and treatment will be more realistic and meaningful as more studies are completed. In addition, rather than categorizing and examining effect by intervention modality, we combined supervised with unsupervised interventions, not accounting for the potential differences on outcomes of interest from home-based or behavior modification interventions compared to supervised exercise interventions. Two systematic reviews and meta-analyses specific to the outcome of cancer related fatigue have accounted for intervention type and modality, neither reporting a significant interaction [5, 6]. Given the growing body of literature, future reviews should assess potential moderators of the effectiveness of physical activity interventions on outcomes in addition to cancer related fatigue.

The assessment of study quality for the purposes of this review was dependent on the presence of documentation or reporting of study quality elements of interest. That evaluation is limited by the documenting and reporting procedures adopted by the study investigator. Establishing a model or standardizing not just the methods and measures of physical activity interventions, but also documenting and reporting practices would be extremely helpful to the literature and in moving science in this area forward.

Summary

There is a growing body of evidence as to the effects of physical activity interventions for cancer survivors on health outcomes. Physical activity interventions that aim to provide further development of the knowledge throughout the cancer continuum and in cancer diagnoses other than breast are needed. The current literature allows for conclusions as to a large effect on upper and lower body strength and breast cancer-specific concerns in post treatment interventions, and small to moderate effects on physical activity level, aerobic fitness, overall quality of life, fatigue, IGF-I, and symptoms and side effects. A small to moderate effect of physical activity during treatment was seen for aerobic fitness, upper and lower

body strength, body weight, functional quality of life, anxiety, and self esteem. There are many outcomes for which there have been too few studies to draw conclusions. Future studies would be aided by agreement of researchers working in this field with regards to outcome measures and documenting and reporting standards. Adoption of such practices and procedures would help synthesize study results and allow for the effects of physical activity interventions to be more firmly concluded. Perhaps most importantly, future studies that seek to demonstrate effectiveness of exercise interventions in cancer survivors should focus on those survivors at greatest need for improvement for the targeted outcomes.

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