Review

Controlled Physical Activity Trials in Cancer Survivors: A Systematic Review and Meta-analysis

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Abstract

Background: **Approximately 9.8 million cancer survivors are alive in the United States today. Enthusiasm for prescribing physical activity for cancer survivors depends on evidence regarding whether physical activity during or after completion of treatment results in improved outcomes such as cardiorespiratory fitness, fatigue, symptoms, quality of life, mental health, or change in body size.**

Methods: **A systematic qualitative and quantitative review of the English language scientific literature identified controlled trials of physical activity interventions in cancer survivors during and after treatment. Data from 32 studies were abstracted, weighted mean effect sizes (WMES) were calculated from the 22 high-quality studies, and a systematic level of evidence criteria was applied to evaluate 25 outcomes.**

Results: **There was qualitative and quantitative evidence of a small to moderate effect of physical activity interventions on cardiorespiratory fitness (WMES = 0.51 and 0.65 during and after treatment respectively, $P < 0.01$), physiologic outcomes and symptoms during treatment (WMES = 0.28, $P < 0.01$ and 0.39, $P < 0.01$, respectively), and vigor posttreatment (WMES = 0.83, $P = 0.04$). Physical activity was well tolerated in cancer survivors during and after treatment, but the available literature does not allow conclusions to be drawn regarding adverse events from participation.**

Conclusions: **Physical activity improves cardiorespiratory fitness during and after cancer treatment, symptoms and physiologic effects during treatment, and vigor posttreatment. Additional physical activity intervention studies are needed to more firmly establish the range and magnitude of positive effects of physical activity among cancer survivors.** (Cancer Epidemiol Biomarkers Prev 2005;14(7):1588–95)

Introduction

Approximately 9.8 million cancer survivors are alive in the United States today (1), and the population of long-term cancer survivors continues to grow. Current cancer treatments, although increasingly efficacious for improving survival, are toxic in numerous ways and produce negative short and long-term physiologic and or psychologic effects, including pain, decreased cardiorespiratory capacity, cancer related fatigue, reduced quality of life, and suppressed immune function (2). Physical activity has been proposed as a nonpharmacologic intervention to combat the physiologic and psychologic effects of treatment in cancer patients (3). Moreover, cancer and its treatment may increase the risk of other common chronic diseases, such as diabetes or cardiovascular disease. Among survivors who have completed treatment and are otherwise healthy, the American Cancer Society prescribes physical activity levels similar to those prescribed for the general population, for the purpose of general health promotion (4). These same recently published American Cancer Society guidelines suggest that there may not be sufficient evidence of the safety of regular activity among survivors currently undergoing treatment to warrant the potential risk of participating (4).

Clinicians who wish to prescribe physical activity for patients currently undergoing cancer therapies need to know whether a physical activity program will reduce the physiologic and psychologic negative effects of treatment. The potential benefits and harms from a physical activity program during active cancer therapy must be balanced against the potential harm from remaining inactive, which also has short-term and long-term health risks. A period of inactivity during (and after) cancer treatment may lead to decreased cardiorespiratory fitness (which could affect the ability to do activities of daily living), bone loss and muscle atrophy, as well as worsening of glucose metabolism, insulin sensitivity, digestive function, immune function, and cardiovascular risk factors (5). Given the growing population of survivors, there is a need to establish the extent to which physical activity is appropriate for cancer survivors during and after treatment, as well as whether physical activity is effective for improving the health and well-being of survivors across the cancer control continuum.

The outcomes of interest from a physical activity program for cancer survivors vary according to timing with regard to treatment as well as whether treatment was successful in eradicating the cancer. In addition, clinical advice needs to be based on studies conducted on patients who are at a similar point of the cancer experience (pretreatment, during treatment, and posttreatment). For example, a study that reports that physical activity is useful to combat fatigue among survivors who have *completed* treatment will not assist a clinician in deciding whether to prescribe physical activity for

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cancer fatigue *during* treatment. The Physical Exercise Across the Cancer Experience (PEACE) framework developed by Courneya and Friedenreich (2) suggests that researchers and clinicians consider six possible cancer control time periods when prescribing physical activity. After the point of cancer diagnosis, the PEACE framework identifies the following time periods: buffering before treatment, coping during treatment, rehabilitation immediately posttreatment, long-term health promotion and survival for those with positive treatment outcomes, and palliation for those approaching the end of life.

Prior reviews of physical activity interventions among cancer survivors have focused on specific outcomes and populations, such as weight loss in breast cancer survivors, (6) immune function, (7) fatigue (8-11), and quality of life (12). There are multiple prior narrative reviews that have focused on physical activity interventions and reviewed effects on a variety of physiologic and psychosocial outcomes (4, 8, 12-18). Prior reviews have been qualitative (4, 10, 18). There are no prior quantitative reviews. One limitation of qualitative reviews is the potential to conclude that physical activity has a consistent, positive effect, when the magnitude of the effect is too small to be of value to cancer survivors. None of the previous qualitative reviews addresses magnitude of effects. This systematic, qualitative, and quantitative review examines the evidence that physical activity interventions, alone or combined with diet modification, are effective in helping cancer survivors improve their psychosocial outcomes or physiologic outcomes. A secondary purpose of this review was to examine potential for injuries and other adverse effects from these interventions. For the purpose of this review, *cancer survivors* are 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 (19). The review is restricted to physical activity intervention studies with a concurrent comparison group with results presented separately for treatment and comparison groups (i.e., controlled clinical trials). Furthermore, results are reported separately for interventions conducted during versus after cancer treatment.

Materials and Methods

Literature Search. Sources of candidate studies included online databases, reference lists of all relevant articles and reviews, and files of project staff as well as having a technical expert panel review all search criteria and reference lists obtained at all stages of review. We conducted MEDLINE searches (last search in February 2005) with two search strategies to identify possible articles for inclusion in the review. 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)]. An additional set of search terms was also used, including [(exercise or motor activity or physical activity) and (randomized controlled trial(s), controlled trials, intervention studies, or clinical trials) and cancer]. While reviewing the references of a recent review on the topic of physical activity in cancer survivors (12), we identified 39 additional articles. These lists were combined using the bibliographic software EndNote and duplicates were deleted, yielding a total of 126 unique titles. These titles were reviewed by a representative at National Cancer Institute and the technical expert panel, including several investigators with expertise in physical activity and cancer to determine whether any articles were missing. Several additional titles were suggested, several were deleted as well, resulting in a total of 136 titles to be reviewed for inclusion. Review of titles and abstracts of these 136 titles revealed 77 articles that were not physical activity interventions. The remaining 59 articles were obtained for full review. During the data abstraction of these 59 articles, two additional references were identified and obtained for full review.

To be included in this review, a study had to be published in the English language, focus on adults who have been diagnosed with cancer, include an intervention designed to increase physical activity, 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. The most common exclusion criterion was lack of a concurrent comparison group. After exclusions, 37 articles, representing 32 unique studies, were reviewed (20-56).

Abstraction. The abstraction form for the Guide to Community Preventive Services (57) was used as a template to develop the abstraction form. The form included questions about study design and execution, study quality, the number and characteristics of participants, participant recruitment information, and details on the intervention (such as dose of physical activity and nonphysical activity components). For each trial, 11 study quality questions from the Guide to Community Preventive Services (57) were answered in four categories related to description of the study and participants, study measurement quality, analytic approach, and interpretation of results. Study quality was also assessed through a check list of 10 internal validity characteristics (58). A study with at least 5 of these 10 internal validity characteristics was considered high quality. Only high-quality studies were included in the qualitative and quantitative pooled analysis.

Abstraction was checked by a second project staff member. The outcome data were initially abstracted by a member of the project staff in Excel just to list outcomes. This listing was checked by a second member of the project staff. Then tables of study descriptions and outcomes were developed. These tables were reviewed and checked by a second project staff member as well.

Data Synthesis. Effect sizes were calculated using the software program ES (59) for studies that were found to be high quality ($n = 22$; refs. 20-44). Effect sizes [e.g., standardized mean differences between the treatment and control group(s)] were calculated from all outcomes where raw score means, SDs, and sample sizes were available at postintervention or where between-groups t test on raw post-test scores were available (59). Post minus preintervention change score effect sizes were not computed because preintervention and postintervention correlations were not available for cancer survivors for all 25 outcomes assessed. For studies in which there were no between group differences at baseline, this post-test effect size is an acceptable measure of the effect of the intervention on the outcome. Weighted mean effect sizes and the 95% confidence intervals for these weighted means were calculated using the fixed effects method of Peto et al. (60). Weighted mean effects sizes from random effects models (61) differed for few outcomes and by <10%. An important caveat to interpreting the reported effect size data is that negative studies may be more likely to not allow a calculation of effect size, as they are less likely to present variance estimates or exact P values for nonstatistically significant outcomes. Magnitude of effect sizes are interpreted in this review 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 >0.8 as ''large'' (62). Significance was not corrected for multiple tests. No subgroup analyses were reported; only comparisons between treatment group(s) and control group were considered.

Because effect sizes could not be computed for all of the studies, a qualitative approach was also used to synthesize the data (58). These criteria designated that there was strong evidence of a positive effect if there were at least three high-quality studies with consistent statistically significant results (e.g., 75% of studies with statistically significant results, $P < 0.05$) and weak evidence if there were at least three high-quality studies but with inconsistent results. Evidence that physical

activity was not effective was defined as having at least three high-quality studies and proportion of statistically significant results of ≤25%. Insufficient evidence was denoted when there were less than three studies. Note that the qualitative definitions of strong and weak evidence do not refer to the magnitude of the effect, only to the strength of the evidence that there is any effect.

Results

Study Quality. Twenty-two of the 32 studies described were rated as being of high methodologic quality using the Van der Windt (58) internal validity characteristics. One of these studies (22) met the internal validity characteristics for a high-quality study for all outcomes except for physical strength and physical training. However, of the 32 studies reviewed, only three described the sample adequately with regard to cancer diagnoses and treatment course, race/ethnicity, gender, and sociodemographic variables. The rest either neglected to provide these variables at baseline and/or provided some of these variables. Often, diagnostic, treatment, and demographic data were only provided for those who completed the study only making it difficult to compare who was recruited versus who completed the study. Approximately 41% of all studies did not report any physician's clearance or prescreening of participants to assure there were no cardiac or other contraindications to physical activity before study entry.

Fourteen studies described the physical activity intervention with inclusion of physical activity modality, intensity, frequency, duration per session, and progression of these variables throughout the intervention in a manner that would allow others to repeat what they had done. The majority of studies (81%) did not exclude participants based on physical activity level before study entry. Furthermore, only 28% (35% during and 16% after treatment) reported baseline or prestudy entry physical activity levels of participants.

Of the 32 studies reviewed, one (a small feasibility study) did no statistical testing (47). All but one of the studies (43) included measures repeated at least at two time points (preintervention and postintervention), although many reported only postintervention values or change scores. Approximately half of the studies conducted analyses that were appropriate for repeated measures, such as independent *t* tests for change scores or repeated measures ANOVA when there were no meaningful baseline differences between groups, and ANCOVA when there were meaningful between group differences at baseline. The rest of the studies conducted tests that did not account for within person correlations between repeated measures. Eight studies failed to include information about the reliability and or validity of the measured outcomes of interest. Three of the included studies examined or controlled for differential exposure to the intervention in assessing treatment effects (20, 42, 43).

Populations Studied. Table 1 includes a description of populations studied and the interventions employed. Of the 32 studies included in the review, 63% conducted interventions during active cancer treatment. The sample sizes were often small and the most common diagnosis included in the studies was breast cancer (72%). The percentage of studies that fall within each of the post-diagnosis PEACE framework (2) categories is also provided in Table 1. Note that these categories do not add up to 100 because some studies fell into more than one PEACE framework category. The majority of the studies focused on the time period during or immediately following active cancer therapy. Only one study focused on buffering, five studies addressed health promotion, two studies on survival, and none focused on palliation. Splitting the pooled results by individual PEACE framework categories was not possible due to the small number of studies within each of these categories.

Intervention Characteristics. The majority of the interventions were between 5 weeks and 3 months long, with no follow-up after the end of the intervention. The physical activity prescription was typically for aerobic activity of moderate to vigorous intensity, three to five times per week, for 20 to 30 minutes per session, although 28% of interventions did not specify session duration. Of the 32 studies reviewed, 75% involved preplanned physical activity sessions, usually supervised, in a physical activity or physical therapy facility, with the equipment and supervision provided at no cost to participants. By contrast, 25% of the studies designed to change physical activity behavior did not tell the control group not to increase their physical activity and assessed whether the intervention resulted in behavior change (or some surrogate for behavior change). Based on these characteristics, these studies could be considered behavior change interventions. Furthermore, in four interventions, a physical activity prescription was given, but the program was done entirely independently, in the home, with no supervision (20, 38, 43, 45). The majority (22 studies) had an intervention group and a control group, in which no physical activity or other treatment was prescribed. Four studies provided an intervention for the comparison group (25, 30, 35, 42).

The loss to follow-up from these studies was generally modest, with an average of 11.9% overall and ranging from 0% to 42%. Dropout rates did not differ between studies conducted posttreatment (12.7% average dropout rate) versus during treatment (11.5% average dropout rate). These dropout rates should be viewed in context of the percentage of cancer survivors approached regarding study participation who agree to participate or even to be screened for eligibility. Of the 14 studies that provided data regarding recruitment rates, nine provided the percentage of eligible survivors who agreed to participate and were randomized, with a mean of 65% and a range of 31% to 94%. Furthermore, eight studies provided the percentage of survivors contacted about the study (before establishing eligibility) who were then found eligible, agreed to participate, and were randomized, with a mean of 47% and a range of 16% to 77%.

During Treatment versus Posttreatment Effects. Table 2 displays the qualitative evidence, using the criteria described above, for a significant effect of physical activity on each outcome listed, by timing, with four possible results: evidence that physical activity is *not effective, insufficient evidence, weak evidence*, and *strong evidence*. Table 2 also includes the number of studies with positive and statistically significant effects for each of the 25 outcome categories, the weighted mean effect size, and the 95% confidence interval and *P* value for the weighted mean effect size. Note that only the 22 studies with high internal validity were included in the results reported in Table 2, to reduce the risk of obtaining a biased estimate of the effect of physical activity. Significant weighted mean effect sizes from studies conducted during treatment were observed for physical activity behavior (0.25, $P = 0.01$), cardiorespiratory fitness (0.51, $P < 0.001$), physiologic outcomes (0.28, $P = 0.001$), symptoms/side effects (0.39, $P < 0.001$), and immune variables (0.54, $P = 0.002$). Significant weighted mean effect sizes from studies conducted posttreatment were observed for cardiorespiratory fitness (0.65, $P = 0.003$), vigor/vitality (0.82, $P = 0.04$), body image (1.21, $P = 0.03$), confusion (0.83, $P = 0.04$), body size with a goal of avoiding arm volume gain (1.64, $P = 0.008$), and multiple constructs of mental health (0.34, $P = 0.02$). Note that the weighted mean effect sizes for the effect of physical activity on body image and avoiding arm volume gain posttreatment were based on single studies. There was no baseline between-group differences for any outcomes with statistically significant weighted mean effect sizes. The

Table 1. Description of the interventions

Characteristic of study or intervention	% Studies with this characteristic or mean value		
Timing			
During treatment	63		
Posttreatment	37		
Framework			
PEACE category			
Buffering	3		
Coping	53		
Rehabilitation	41		
Health promotion	16		
Survival	6		
Palliation	0		
Multiple categories in one study	19		
Characteristic of study or intervention	**All**	**During treatment**	**Posttreatment**
Sample size, mean (range)			
Average sample size per control group	26 (4-101)	29 (4-97)	21 (6-101)
Average sample size per intervention group	28 (6-98)	32 (6-119)	21 (6-98)
Cancer diagnoses included			
Breast	72	60	92
Colon	9	5	17
Lung	13	15	8
Ovarian	6	0	17
Leukemia	6	10	0
Lymphoma	9	10	8
Testicular	3	0	8
Sarcoma	13	15	8
Stomach	3	5	0
Prostate	6	10	0
Other	25	25	25
Physician's clearance and/or systematic screening of potential participants for contraindications to activity prior to study entry	59	60	58
Excluded participants based on level of physical activity prior to study entry	19	20	17
Behavioral intervention			
Yes	25	30	17
No	75	70	83
Study design			
Randomized Controlled Trial	85	85	83
Nonrandomized	15	15	17
Physical activity only (versus physical activity plus other intervention components)	84	100	58
Intervention length			
≤1 mo	16	20	8
5 wks to 3 mos	63	50	83
>3 mos	16	20	8
Not clear/reported	6	10	0
Activity mode			
Aerobic (alone or combined with other modes)	91	90	92
Only nonaerobic	6	10	0
Not specified	3	0	8
Activity intensity			
Light (reported as ''low intensity'')	3	0	8
Moderate to vigorous*	78	80	75
Not specified	19	20	17
Activity frequency			
<3 times/wk	3	0	8
3-5 times/wk	72	65	84
>5 times/wk	22	30	8
Not specified	3	5	0
Activity duration			
20-30 min/session	53	60	42
30-45 min/session	9	0	25
>45 min/session	9	5	17
Not specified	28	35	17
Percent lost at follow-up	11.9	11.5	12.7

*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.

two outcomes that met the qualitative criteria for strongly consistent evidence for a positive effect during treatment were physiologic outcomes and symptoms/side effects. Posttreatment outcomes with strong consistent qualitative evidence for a positive effect of physical activity included cardiorespiratory fitness and quality of life. The physiologic outcomes examined in four studies conducted during treatment included 3-methlyhistidine, creatinine, nitrogen balance, body temperature (37); blood transfusions, hematocrit, hemoglobin, in-hospital days, loss of physical function during hospital stay, platelets transfusions (36); prostate specific antigen level, and testosterone level (44); and hemoglobin, hematocrit, and albumin (38). There was weak qualitative evidence for a consistent positive effect of physical activity during treatment for physical activity behavior, cardiorespiratory fitness, fatigue, quality of life, body size (goal to reduce), depression, anxiety, and multiple constructs of mental health. There was weak qualitative evidence for a consistent positive effect of physical activity posttreatment for fatigue, vigor/vitality, psychosocial outcomes, body size (goal to reduce), depression, and anxiety. The physiologic outcomes examined in the three studies conducted posttreatment included interleukin-1 receptor agonist levels, interleukin-1 β, tumor necrosis factor-α, interleukin-6, and s-tumor necrosis factor receptors I and II (30); insulin, glucose, insulin resistance index, insulin like growth factor (IGF)-I, IGF-II, IGFBP-1, IGFBP-2, IGFBP-3, and IGF-I/IGFBP-3 molar ratio (23, 28); and cardiac function and dimensions, ECG function, and hemoglobin (36).

Adverse Event Issues. Of the 32 reviewed studies, 14 commented on the presence or absence of adverse events during the period of the intervention. In the 14 studies that commented on adverse events, 12 indicated that no harm was observed as a result of physical activity during or after cancer treatment. McNeely et al. (35) reported that one participant who was nearing the completion of radiation therapy complained of nausea during one activity session, with no further difficulties in participation. Courneya et al. (23) reported similar overall rates of adverse events between groups of breast cancer survivors, but the rate of lymphedema in the physical activity group was borderline significantly higher. The authors noted that two of the three participants who developed lymphedema had undergone axillary irradiation, a strong risk factor for lymphedema. The authors commented that it was not clear whether the onset of lymphedema was due to the physical activity. Furthermore, another of the reviewed studies was a pilot study specifically to examine the safety of upper body physical activity in breast cancer survivors with lymphedema and reported no increases in arm volume in the treatment compared with the control group (27).

Several studies commented on issues related to the potential for harm from physical activity in cancer survivors. For example, Nieman et al. (29) note evidence from animal studies that high-intensity (>80% of maximum heart rate), high-volume physical activity in cancer patients may increase the spread of the disease (63, 64). The results of the reviewed studies do not allow for evaluation of this possibility in human subjects, but this animal data cannot be ignored in considering the appropriate physical activity prescription for human cancer survivors, particularly in light of a nonsignificant but negative weighted mean effect size in the posttreatment time frame (Table 2).

Mock et al. (46) 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 intention to treat analyses, which were conducted in 19 of the 27 included randomized controlled trials. MacVicar and Winningham (47) and others (4) have noted several conditions during cancer treatment and recovery can preclude any physical activity, including chest pain, irregular pulse, acute vomiting, blurred vision, sudden onset dyspnea, bleeding, and extreme immunocompromised states.

Discussion

This review finds that physical activity was generally well tolerated during and after cancer treatment. A combined qualitative and quantitative evaluation finds a moderately

Table 2. Evidence of positive effects by timing (during versus after treatment) for the 22 studies with high internal validity

Outcome type	During treatment					Posttreatment				
	Qualitative review*	Positive (%)	Significant (%)	Weighted mean ES (95% confidence interval)	*P*	Qualitative review*	Positive (%)	Significant (%)	Weighted mean ES (95% confidence interval)	*P*
Physical activity behavior	Weak	2 (50)	2 (50)	0.25 (0.06, 0.45)	0.01	Insufficient	1 (100)	1 (100)	None calculable	—
Physical fitness										
Cardiorespiratory fitness	Weak	4 (80)	3 (60)	0.51 (0.24, 0.78)	<0.001	Strong	4 (100)	3 (75)	0.65 (0.22, 1.09)	0.003
Strength	Insufficient	1 (100)	1 (100)	None calculable	—	Insufficient	1 (100)	0 (0)	None calculable	—
Flexibility	Insufficient	2 (100)	1 (50)	−0.02 (−0.42, 0.38)	0.93	Insufficient	2 (100)	2 (100)	0.24 (−0.44, 0.92)	0.48
Fatigue/tiredness	Weak	6 (100)	4 (67)	0.13 (−0.06, 0.33)	0.18	Weak	5 (100)	3 (60)	0.16 (−0.23, 0.54)	0.43
Vigor/vitality	Insufficient	1 (50)	1 (50)	0.43 (−0.07, 0.94)	0.09	Weak	3 (100)	2 (67)	0.82 (0.05, 1.60)	0.04
Body image/ dissatisfaction	Insufficient	1 (100)	1 (100)	None calculable	—	Insufficient	2 (100)	1 (50)	1.21 (0.15, 2.26)	0.03
Quality of life	Weak	4 (100)	2 (50)	0.07 (−0.18, 0.32)	0.58	Strong	5 (100)	4 (80)	0.30 (−0.13, 0.73)	0.17
Confusion	Insufficient	—	—	None calculable	—	Insufficient	2 (100)	0 (0)	0.83 (0.05, 1.60)	0.04
Difficulty sleeping	Insufficient	1 (100)	1 (100)	None calculable	—	Insufficient	—	—	—	—
Self-esteem	Insufficient	—	—	None calculable	—	Insufficient	2 (100)	1 (50)	0.04 (−0.50, 0.58)	0.87
Psychosocial outcomes†	Not effective	1 (25)	1 (25)	0.06 (−0.11, 0.22)	0.52	Weak	3 (100)	2 (67)	0.13 (−0.17, 0.43)	0.39
Physiological outcomes	Strong	3 (75)	3 (75)	0.28 (0.12, 0.44)	0.001	Insufficient	2 (100)	2 (100)	0.01 (−0.18, 0.20)	0.90
Hemoglobin	Insufficient	2 (100)	0 (0)	0.16 (−0.18,0.50)	0.35	Insufficient	—	—	None calculable	—
Hematocrit	Insufficient	0 (0)	0 (0)	0.21 (−0.13,0.55)	0.23	Insufficient	—	—	—	—
Body size										
(goal to reduce)	Weak	3 (75)	2 (50)	0.12 (−0.21,0.44)	0.49	Weak	3 (100)	2 (67)	0.07 (−0.35, 0.49)	0.76
(goal to gain or avoid muscle loss)	Insufficient	0 (0)	0 (0)	None calculable	—	Insufficient	—	—	None calculable	—
(goal to avoid arm volume gain)	Insufficient	—	—	None calculable	—	Insufficient	1 (100)	1 (100)	1.64 (0.43, 2.85)	0.008
Pain	Insufficient	2 (100)	1 (50)	−0.08 (−1.03, 0.87)	0.87	Insufficient	1 (100)	1 (100)	None calculable	—
Symptoms/side effects‡	Strong	3 (100)	3 (100)	0.39 (0.17, 0.60)	<0.001	Insufficient	0 (0)	0 (0)	None calculable	—
Immune variables§	Insufficient	2 (100)	2 (100)	0.54 (0.20, 0.88)	0.002	Insufficient	1 (100)	0 (0)	−0.24 (−0.62, 0.15)	0.23
Mental/emotional/psychologic well-being										
Depression	Weak	3 (100)	1 (33)	0.09 (−0.23, 0.42)	0.57	Weak	5 (100)	2 (40)	0.44 (−0.13, 1.01)	0.13
Anxiety	Weak	3 (100)	2 (67)	0.22 (−0.11, 0.54)	0.20	Weak	4 (100)	2 (50)	0.20 (−0.20, 0.61)	0.32
Anger/hostility	Insufficient	1 (100)	1 (100)	0.06 (−0.44, 0.56)	0.81	Insufficient	2 (100)	0 (0)	0.17 (−0.58, 0.91)	0.66
Multiple constructs‖	Weak	3 (100)	1 (33)	0.07 (−0.24, 0.38)	0.66	Not effective	4 (100)	1 (25)	0.34 (0.06, 0.63)	0.02

*Levels of evidence criteria applied with four levels of evidence of a positive effect of physical activity listed in table: Insufficient, fewer than three high-quality studies; Weak, three or more high-quality studies with inconsistent results; Strong, three or more high-quality studies, 75% show a statistically significant positive effect; Not effective, ≤25% of three or more high-quality studies show a significant positive effect.

†Including hope, power, role limitations (emotional and physical), social functioning, satisfaction with life, and social/family well-being (during treatment) as well as cognitive function, communication with staff, information problems, problems with activities at home and in community, sick leave, work status, happiness, social/family well-being, satisfaction with life, and spiritual well being (posttreatment).

‡Including somatization, severity of diarrhea, severity of infection, severity of mucositis, severity of pain, and disability score (during treatment), as well as aversions, mixed symptoms, mucous membrane disturbances, sexual problems, and surgery effects (posttreatment).

§Including duration of neutropenia and thrombopenia (during treatment) as well as T cells, lymphocytes, white blood cells, natural killer cells, mononuclear cells, neutrophils, and leukocytes.

‖Including mental health, trial outcome index, emotional well-being, global psychologic distress, obsessive compulsive traits, and interpersonal sensitivity (during treatment), as well as emotional well being, trial outcome index, positive and negative affect, avoidance, fatalistic, fighting spirit, and hopelessness (posttreatment).

positive effect of physical activity interventions on cardiorespiratory fitness both during and after cancer treatment (weighted mean effect sizes of 0.51 and 0.65 during and after treatment, respectively, $P < 0.003$). Additional consensus across qualitative and quantitative findings was apparent for a small to moderate positive effect of physical activity during treatment on physiologic outcomes (weighted mean effect size of 0.28, $P = 0.001$) and symptoms/side effects (weighted mean effect size of 0.39, $P < 0.001$), based on data from four and five studies, respectively. The lack of between group differences at baseline underscores the validity of the statistically significant weighted mean effect sizes, which were calculated using postintervention values only, due to inconsistent availability of correlations for changes in all 25 outcomes reviewed.

The quantitative null findings for the effect of physical activity on fatigue (during and after treatment) and vigor/vitality (during treatment) reported herein are somewhat at odds with prior reviews, which have all been qualitative (8-11) and which have uniformly supported the use of physical activity for reduction of cancer related fatigue. When we combined the high- and low-quality trials conducted during and after treatment, similar to the approach of prior reviews, our review of the literature also indicates that there is strong qualitative evidence for a consistent positive effect of physical activity. However, recall that the qualitative review approach used in this and prior reviews does not indicate the magnitude of the effect, rather the quality, quantity, and consistency of studies showing *any* positive effect. The weighted mean effect size for fatigue after combining all nine studies conducted both during and after treatment, regardless of study quality, was 0.14 ($P = 0.12$). This indicates that although there may be consistent evidence of a positive effect, the magnitude of the effect may be too small to be of clinical relevance. If we further combine fatigue and vitality into one category, under the assumption that fatigue and vitality are the same attribute, and combine all studies across treatment timing and regardless of study quality ($n = 11$ studies), the weighted mean effect size is 0.19 ($P = 0.03$). However, note that this is still a small effect size and that the increase in the effect size is mostly driven by the increase in vigor/vitality observed in two highly effective interventions conducted posttreatment (21, 26). The weighted mean effect sizes for fatigue and vigor presented by treatment timing in Table 2 support a separation of these variables into two categories as well as the preliminary conclusion that physical activity has a large positive effect (weighted mean effect size of 0.83, $P = 0.04$) on vigor, but not fatigue, during the posttreatment time frame. There is only one high-quality study included in the effect size reported for the effect of physical activity on vigor during treatment, which limits the ability to draw conclusions. Furthermore, because the weighted mean effect size on vigor from posttreatment physical activity interventions among cancer survivors is based on two studies, it should also be interpreted with caution.

There are a variety of outcomes for which there is not consensus across qualitative and quantitative review regarding a positive effect of physical activity. Outcomes with strong or weak qualitative evidence of any positive effect for which the weighted mean effect size was not significant generally represent variables that have been included in three or more high-quality studies but which have not resulted in effects of any magnitude, such as fatigue (during and after treatment) or quality of life (posttreatment). Outcomes with significant, positive weighted mean effect sizes but found to have insufficient evidence for a positive effect from the qualitative review reflect variables for which the weighted mean effect sizes are based on few studies, such as immune variables (during treatment) or body image, confusion, avoiding arm volume gain, and multiple constructs of mental health (post treatment). The magnitude of these effect sizes must be interpreted with caution until additional physical activity interventions further evaluate these outcomes and confirm/refute these preliminary findings.

Although the publications reviewed indicate that physical activity was generally well tolerated by cancer survivors during and after treatment, the current literature does not allow us to establish with certainty whether physical activity has any negative effects on cancer survivors. The reviewed studies generally recruited volunteers and dropped from the analysis those participants who had any worsening of disease or complications of treatment. There were no comments on the extent to which participants differed from nonparticipants or whether physical activity contributed to issues that resulted in dropping out of the study. It is hypothesized that physical activity has positive effects on a variety of outcomes in cancer patients during treatment, including cardiorespiratory fitness and symptoms/side effects. However, intention to treat analyses are needed to adequately test these hypotheses.

Study Limitations and Future Directions. This review uncovered a number of areas that can be addressed in future studies to improve the quality of these studies as well as to facilitate future qualitative and quantitative syntheses. A distinct choice was made to describe all eligible controlled trials in this review, regardless of ratings of study quality. This choice was predicated on the notion that it is of value to describe all completed studies. The results of lower quality studies were not included in the pooled qualitative or quantitative summary, however, to avoid biased estimates of the effect of physical activity on the outcomes examined.

Cancer Control Continuum. Differences in timing, diagnoses, and treatment could alter the effectiveness of physical activity interventions among cancer survivors. The majority of the studies reviewed focused on whether physical activity could positively alter the early and late effects of cancer therapies, within the Framework PEACE cancer control outcome categories of coping during active cancer therapy or rehabilitation immediately following cancer treatment. Few studies have focused on the other Framework PEACE categories, including buffering effects before treatment, palliation of symptoms at the end of life, long-term health promotion, and survival after successful eradication of cancer. As more physical activity studies in cancer survivors are completed, it will become important to conduct syntheses by cancer diagnosis, treatment type, and by time points of the PEACE framework. This review was somewhat limited in its ability to do so given the small number of studies. Therefore, the strong consistent evidence for a positive effect of physical activity on specific outcomes must be interpreted with the caution that cancer is a multifaceted disease with multimodal treatments and that evidence reported herein is from a heterogeneous set of survivors, with a preponderance of data on breast cancer survivors.

Methodologic Issues. The variability of outcomes and interventions in the reviewed studies made the usual techniques for detecting publication bias both impractical and unreliable. It would be difficult to conclude that variations in outcome seen with varying trial size were related to publication bias and not confounded by any of the many other ways that the trials differed from each other.

There is a need for the research community to agree on the measures to be used for each outcome and interventions of greatest interest. Because of the paucity of data, this review did not examine outcomes by intervention dose. We also mixed supervised with unsupervised interventions without regard to the potential differences on outcomes of interest from behavior modification interventions compared with supervised, lab-based exercise interventions. Clarification of dose-response issues by outcome and within cancer diagnoses and treatments

will be important as more studies are completed. Future reviews of a larger number of trials will be able to test potential moderators of the effectiveness of physical activity interventions in cancer survivors.

Documenting study procedures and reporting results is also important for evaluating study quality, computing effect sizes, pooling study results, and reporting negative effects. In this review, evaluation criteria were used to assess study quality; however, these evaluations are somewhat confounded by the lack of documentation and reporting of the study quality variables in the reviewed studies. This situation is not unique to this literature, but guidelines as to standardization of methods for physical activity interventions, as well as measuring and reporting cancer control outcomes of greatest interest would also assist the field in reaching consensus more efficiently. A set of steps for successful assessment of physical activity in cancer survivors has been reported in a recent review (13).

Summary. The potential to make important contributions to the health and well-being of the growing population of cancer survivors should inspire physical activity researchers to develop knowledge of the effects of physical activity across the cancer continuum. The current literature allows for compelling conclusions with regard to small to moderate positive effects of physical activity interventions on physical activity behavior, cardiorespiratory fitness, physiologic outcomes, and symptoms/side effects during cancer treatment. After treatment is complete, physical activity shows a moderate to large positive effect on cardiorespiratory fitness and vigor/vitality. There are other outcomes for which significant weighted mean effect sizes from physical activity interventions were noted. However, these are based on too few studies to draw conclusions as of yet. Despite prior qualitative reviews that have concluded that physical activity reduces cancer related fatigue, the pooled quantitative analysis reported herein indicates that the magnitude of this effect may be too small to be clinically meaningful. Additional studies will be needed to more firmly establish physical activity benefits to cancer survivors and to provide greater assurance of the safety of participation during treatment.

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Controlled Physical Activity Trials in Cancer Survivors: A Systematic Review and Meta-analysis

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