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Review

Exercise Effects on Depressive Symptoms in Cancer Survivors: A Systematic Review and Meta-analysis

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Abstract

Background: Depression is a distressing side effect of cancer and its treatment. In the general population, exercise is an effective antidepressant.

Objective: We conducted a systematic review and meta-analysis to determine the antidepressant effect of exercise in cancer survivors.

Data Sources: In May 2011, we searched MEDLINE, PsycInfo, EMBASE, CINAHL, CDSR, CENTRAL, AMED, Biosis Previews, and Sport Discus and citations from relevant articles and reviews.

Study Eligibility Criteria: We included randomized controlled trials (RCT) comparing exercise interventions with usual care in cancer survivors, using a self-report inventory or clinician rating to assess depressive symptoms, and reporting symptoms pre- and postintervention.

Study Appraisal: Around 7,042 study titles were identified and screened, with 15 RCTs included.

Synthesis Methods: Effect sizes (ES) were reported as mean change scores. The Q test was conducted to evaluate heterogeneity of ES. Potential moderator variables were evaluated with examination of scatter plots and Wilcoxon rank-sum or Kruskal–Wallis tests.

Results: The overall ES, under a random-effects model, was −0.22 (confidence interval, −0.43 to −0.09; $P = 0.04$). Significant moderating variables ($ps < 0.05$) were exercise location, exercise supervision, and exercise duration.

Limitations: Only one study identified depression as the primary endpoint.

Conclusions: Exercise has modest positive effects on depressive symptoms with larger effects for programs that were supervised or partially supervised, not conducted at home, and at least 30 minutes in duration.

Impact: Our results complement other studies showing that exercise is associated with reduced pain and fatigue and with improvements in quality of life among cancer survivors. *Cancer Epidemiol Biomarkers Prev; 21(1); 3–19. ©2011 AACR.*

Introduction

Depression is a distressing side effect of cancer and cancer treatment and its prevalence varies by cancer site. Rates of depression in head and neck cancer tend to be the highest (25%–52%), whereas pancreatic, liver, colon, lung, brain, bladder/kidney, prostate, and Hodgkin lymphoma are all associated with lower rates ranging from 7% to 9.7% (1–3). The prevalence of depression among breast cancer survivors ranges from 1.5% to 46% (1, 4, 5).

Depression is characterized by feelings of sadness, hopelessness, changes in sleep and appetite, psychomotor retardation, and withdrawal from social contact. These cause reduced quality of life, impaired social and occupational functioning, and intermittent bouts of suffering. Depression is also associated with obesity, diabetes, and the development of cardiovascular disease (6–8). For some, clinical depression is also associated with noncompliance with cancer treatment and reduced survival (9). Thus, depression negatively affects the physical and psychologic health of many survivors.

Several factors contribute to the development of depression in cancer survivors. Some have poor psychologic adjustment to specific symptoms (e.g., sexual, bowel, fatigue), to the severity of symptoms (e.g., pain, fatigue), to the treatment itself (e.g., surgery and disfigurement in head, neck, and breast cancer), or to a poor cancer prognosis (10–13). Likewise, chemotherapy causes hair loss, nausea, weight gain, and effects on fertility and sexuality that may be perceived as distressing (14–16). For others, treatments cause hypothyroidism, electrolyte imbalances, or anemia that can increase the risk of a depressive

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episode (11). Agents such as steroids and IFN are associated with the development of depression and estrogen-depleting interventions may alter serotonin, thus increasing depression risk (14). Finally, lifestyle factors such as tobacco and alcohol use can also contribute to depression risk, whereas a lack of emotional and social support can leave others feeling isolated and alone (11).

Current treatments for depression in cancer survivors include pharmacologic interventions and psychotherapy. For many, these treatments are safe, effective, and provide significant benefit. For others, they may have limited usefulness because of personal, behavioral, or biologic factors. For example, those with head and neck cancer may have impairment in their ability to communicate, making psychotherapy more difficult (11). Similarly, pharmacologic agents such as selective serotonin reuptake inhibitors (SSRI) may be contraindicated for some survivors undergoing certain anti-hormonal therapies (17). Therefore, while existing treatments for depression benefit many cancer survivors, they do not benefit all and may have negative side effects.

Exercise has been identified as a treatment that may provide symptom relief for depression, as well as improve physical health outcomes in cancer survivors (18). In the general population, exercise is an effective antidepressant. Meta-analytic studies indicate that the effect size (ES) of exercise on depression is large, ranging from −0.72 to −1.4 (19–21). Individuals with moderate and more severe depression benefit similarly and exercise is equally effective for men and women across a wide range of ages. Exercise effects are comparable with psychotherapy and medication, particularly for those with mild to moderate depression (19, 20).

No previous meta-analysis has focused on the effects of exercise on depression, as a primary endpoint, in cancer survivors. Some meta-analyses have included depression but they have been limited by a broad definition of depression measures (e.g., emotional well being, psychologic distress, mood), were restricted to a single cancer site, included nonrandomized trials, or have not included more recent studies (22–26). The aim of this meta-analysis was to evaluate the current literature on the antidepressant effects of exercise in cancer survivors. Our review is more comprehensive in terms of the types of cancer included, as well as a more direct examination of the antidepressant effects of exercise. We hypothesized that exercise interventions would reduce depressive symptoms in cancer survivors relative to usual care. As a secondary exploratory aim, we examined potential moderating variables related to participant, cancer, and exercise characteristics.

Method

Search strategy

We searched the following electronic databases to May 2011: MEDLINE, MEDLINE—In Process, PsycInfo, EMBASE, CINAHL, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Allied and Complementary Medicine (AMED), Biosis Previews, and Sport Discus. We used terms related to cancer (e.g., neoplasm, tumor, cancer), exercise (e.g., exercise, physical activity, yoga, strength training), and depression (e.g., cancer-related depression, quality of life, dysthymia). For example, we searched OVID MEDLINE with the following keywords: (cancer OR neoplasm) AND (exercise OR physical activity) AND (depression OR depressive disorder). We also hand searched the reference lists of potentially relevant studies and of relevant review articles of exercise, cancer, and quality of life.

Selection criteria

Studies were considered eligible for inclusion if (i) they were randomized controlled trials (RCT) of adults diagnosed with cancer, (ii) compared an exercise program with usual care, (iii) the exercise program was chronic in nature (i.e., at least 4 weeks in duration), rather than studies examining acute bouts of exercise, (iv) reported depressive symptoms pre- and postintervention, (v) used a depression inventory or a clinician interview to quantify depressive symptoms, and (vi) they were published in English. Because "distress" is less well defined and is often used to represent many conceptualizations of emotion and because an overall sense of "well-being" is often independent of depressed mood, we excluded studies using quality of life inventories or mood scales to assess depressive symptoms as these types of inventories measure constructs that are theoretically different (13, 27). Likewise, while we acknowledge that depressive symptoms often correlate highly with other constructs such as anxiety, negative affect, and stress, depression is thought to be distinct from these other constructs and, as a result, we limited inclusion to those studies that assessed depressive symptoms.

Data extraction

Two reviewers (L.L. Craft and M.H. VanIterson) screened the titles and abstracts of articles that seemed potentially eligible and then reviewed those appearing relevant. There were no disagreements between reviewers about which articles were eligible for inclusion. Data extraction was conducted independently by both reviewers and disagreements were resolved by consensus.

Participant, cancer, intervention, and outcome assessment characteristics were extracted and coded. Participant data included (i) age, (ii) % female, (iii) % Caucasian, (iv) level of education (mean years of school or % high school or less), and (v) recruitment source. Cancer-related information included: (i) cancer site (breast, other), (ii) cancer stage (nonmetastatic, other), and (iii) treatment status at baseline (in primary treatment, other). Exercise intervention information included: (i) exercise format (group or individual), (ii) type of delivery (in person, phone, web-based, other), (iii) type of exercise program (aerobic, other), (iv) mode of exercise (walking, other), (v)

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supervision of exercise (supervised, unsupervised, mixed supervision), (vi) location of exercise (home, other), (vii) exercise intervention length ($\leq$12, >12 weeks), (viii) exercise session duration ($\leq$30, >30 minutes), and (ix) exercise intensity. Finally, outcome assessment characteristics included: (i) primary outcome of interest reported in study, (ii) depression inventory used, and (iii) time point of follow-up assessment. No assumptions were made about these characteristics. Study quality was also coded using the PEDro Scale (28), which is widely used to rate the quality of RCTs. PEDro scores are summarized and high-quality studies are those with scores from 6 to 11, fair quality from 4 to 5, and poor quality less than 4 (29). Items 2 to 9 on the PEDro scale assess internal validity (30). For studies not providing enough information to calculate an effect size, study authors were contacted for additional information.

Statistical considerations

Effect sizes were obtained from the RCTs and were reported in terms of mean change scores (Cohen's *d*). Some studies had available change scores (and SDs). For those that did not, we calculated change scores by subtracting the mean baseline score from the mean follow-up score and calculated the change score SD by using the following formula:

$$\mathrm{Var}(Y_{\mathrm{BL}}) + \mathrm{Var}(Y_{\mathrm{FU}}) - 2\mathrm{COV}(Y_{\mathrm{BL}}, Y_{\mathrm{FU}})$$

Here, Y_{BL} and Y_{FU} are the mean baseline and follow-up scores. From this equation, we could first obtain $\mathrm{COV}(Y_{\mathrm{BL}}, Y_{\mathrm{FU}})$ from studies with an already calculated SD or variance for the change scores and then apply this value to compute the SD for those studies that did not report change scores. Furthermore, separate $\mathrm{COV}(Y_{\mathrm{BL}}, Y_{\mathrm{FU}})$ values were obtained for exercise and control groups. Negative ES values indicated that intervention participants had improved depressive symptoms relative to the control group.

Meta-analysis was then conducted to examine the effect of exercise on depression. The *Q* test for heterogeneity was used to evaluate the assumption that ES were from the same population (31). Differences in ES among studies were analyzed both under a fixed-effects and a random-effects model, as recommended by Dersimonian and Laird (32). However, to acknowledge that there are likely person-level and intervention-level characteristics that may contribute to variation in the magnitude of the effect, the random-effects model ES is reported as our primary analysis (33). Publication bias was assessed via Egger test and graphical examination of a funnel plot of ES (34). All meta-analyses were conducted using Comprehensive Meta Analysis, Version 2.2.044.

To determine if any study variables moderated the effect of exercise on depression, differences in ES were evaluated with graphical examination of scatter plots and using the Wilcoxon rank-sum test for moderator variables with 2 levels and the Kruskal–Wallis test for moderator variables with 3 levels. Assessments involving these moderator variables were conducted in R 2.11.1.

Results

Preliminary abstract screening yielded 60 articles that appeared potentially appropriate (Fig. 1). After review, 21 articles remained potentially relevant, with most being excluded because they used a mood inventory or quality-of-life scale, were not RCTs, or reported secondary outcome data (e.g., adherence) rather than depression data. Of those 21, 3 studies of yoga were excluded because they used relaxing, meditative forms of yoga rather than more physically active forms of yoga (35–37). Two studies were excluded because insufficient depression data were presented in the article and the authors no longer had access to the data (38, 39). One study was excluded because it did not use a usual care or no treatment control group but used a group psychotherapy control group instead (40). No studies were excluded because of using an exercise intervention of less than 4 weeks.

There were 4 studies in which multiple-effect sizes were generated but only one comparison was included in our analyses. One study included a placebo exercise comparison group and a usual care group (41) and another study included a telephone counseling comparison group and a usual care group (42). Only the ES comparing exercise to usual care were included. One study compared an aerobic exercise program and a strength training program to usual care (43) and, thus, two ES were generated. Because there were no other studies that included strength training as a separate intervention arm, only the ES generated from the comparison of aerobic exercise to control was used. Furthermore, one study (44) had 3 arms eligible for inclusion. This study used a control arm, an exercise intervention arm in which participants received the exercise intervention during their cancer treatment, and an exercise intervention arm in which participants received the exercise intervention following the completion of their treatment. Because of the dependency of the two ES (i.e., exercise during treatment compared with control and exercise following treatment compared with the same controls at a later time point), we deemed it inappropriate to include both ES in the analyses or to average the ES. Consequently, we elected to include only the ES reflecting exercise posttreatment as there are multiple other factors during treatment that might influence depression. Therefore, 14 articles describing 15 RCTs (involving 1,371 participants) met the inclusion criteria and were included in this review (41–54).

Characteristics of studies

Nine studies (60%) used breast cancer survivors (41, 42, 45–47, 49, 53, 54). The average age of participants was 51.6 years. Seven studies reported racial/ethnic information, with 76.9% of participants in those studies being Caucasian (41, 42, 44, 45, 47, 50, 54). Of the 12 studies reporting information on cancer stage, 9 (75%) used

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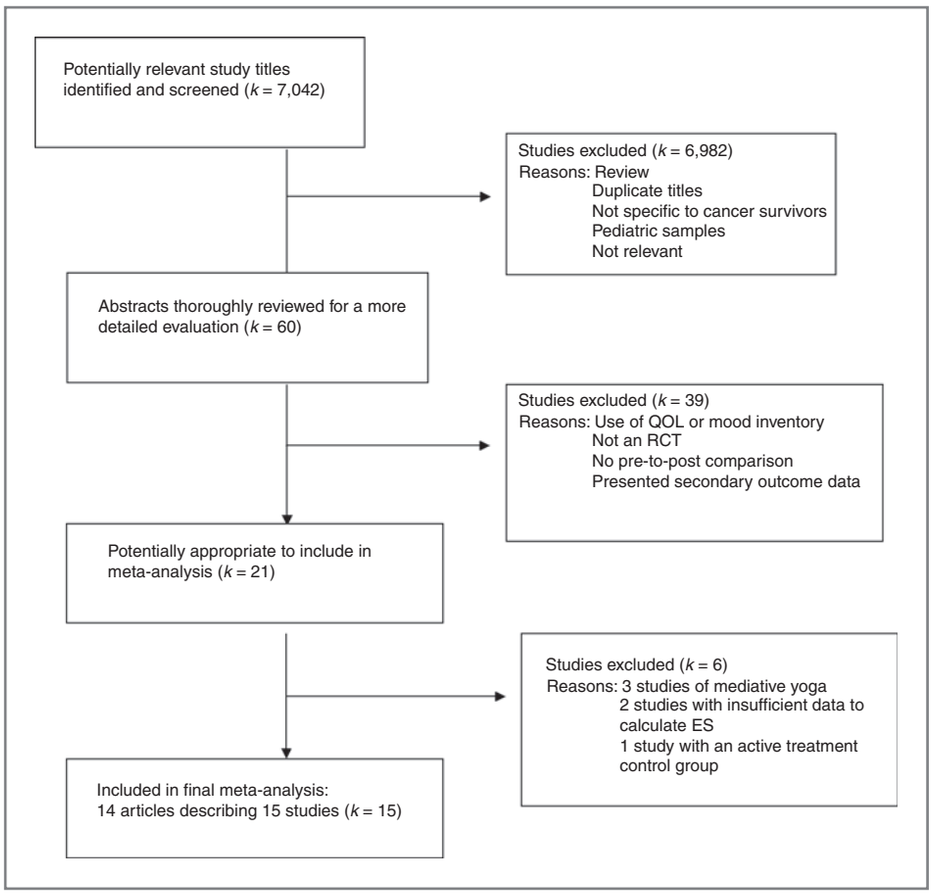

Figure 1. Flow diagram of study selection.

participants with nonmetastatic cancer (refs. 41, 42, 44–46, 49, 50, 54; Table 1).

All studies included an aerobic exercise component (Table 2), with several also including a strength training component (46, 51–54). Exercise programs were initiated either prior to or during adjuvant therapy in 47% of the studies (42, 44–46, 49, 50). Exercise programs ranged from supervised, facility-based programs (41, 49, 50) to unsupervised home-based programs (42, 44, 45, 47, 48, 51), with a few studies having some of the exercise program supervised (45, 46, 52, 54). The majority of the interventions ranged from 4 to 14 weeks with the longest being 52 weeks (44). Table 3 presents depression assessment data.

Most studies used a "life as usual" approach to usual care (41, 43, 45, 47–49, 51–53). Three studies added educational print material (46, 50, 54). In one study (44), the usual care group received periodic phone calls to answer questions about cancer treatment and, in one study (42), usual care participants received both educational print material and periodic phone calls to answer cancer-related questions.

Study quality was very good overall. There was insufficient variability in the PEDro quality scores to examine this as a potential moderator, with all but three studies (44, 49, 54) earning a rating of "high" quality (see Table 4).

Statistical results

We found a small and significant overall mean ES of −0.22 [$P = 0.04$; confidence interval (CI), −0.43 to −0.009] under a random-effects model, when comparing exercise interventions with control groups (Fig. 2). The mean ES was slightly smaller, but still significant, under a fixed-effects model (ES = −0.20; $P = 0.001$; CI, −0.32 to −0.08). Neither the funnel plot nor the Egger test, with a corresponding P value of 0.62, showed evidence of publication bias. The test for heterogeneity was significant ($P < 0.001$), indicating that ES were not from the same population.

Of the potential moderators examined (Fig. 3), exercise location was significant ($P = 0.04$), with home-based exercise associated with increased depressive symptoms (ES = 0.16; CI, −0.15 to 0.47) compared with an improvement in depressive symptoms from exercise interventions in other locations such as community facilities, laboratories, and gyms (ES = −0.45; CI, −0.77 to −0.14). Supervised and partially supervised exercise produced reductions in depressive symptoms, whereas nonsupervised activity was associated with a small increase in depressive symptoms (supervised: ES = −0.67; CI, −1.11 to −0.23; mixed supervision: ES = −0.32; CI, −0.50 to −0.14; and unsupervised: ES = 0.25; CI, −0.01 to 0.50), $P = 0.01$. Furthermore, exercise bout durations of >30 minutes had

Table 1. Sample and cancer characteristics of 15 RCTs examining the effects of exercise on depression in cancer survivors.

Trial	Exercise group (*N*)	Control group (*N*)	Mean age, y	% Female	% Caucasian	Recruitment source	Education	Cancer site	Cancer stage	Treatment status at baseline
Badger and colleagues (2007)	Baseline: $N = 23$ Follow-up: $N = 21$	Baseline: $N = 36$ Follow-up: $N = 33$	54	100	85	Volunteers from cancer center, oncologists' offices, support groups, etc.	21% high school or less	Breast	I–III	In primary treatment
Cadmus and colleagues (2009)	Baseline: $N = 25$ Follow-up: $N = 22$	Baseline: $N = 25$ Follow-up: $N = 23$	54	100	94	Letters to women identified through tumor registry and self-referral	70% college degree	Breast	0–IIIA	In primary treatment
Cadmus and colleagues (2009)	Baseline: $N = 37$ Follow-up: $N = 34$	Baseline: $N = 38$ Follow-up: $N = 33$	56	100	84	Letters to women identified through tumor registry and self-referral	50% college degree	Breast	0–IIIA	Completed primary treatment
Courneya and colleagues (2003)	Baseline: $N = 69$ Follow-up: $N = 62$	Baseline: $N = 33$ Follow-up: $N = 31$	60	42	Not reported	Participants identified by oncologists at weekly Tumor Group at local cancer center	39% college degree	Colorectal	Any stage	Unknown
Courneya and colleagues (2007)	Baseline: $N = 78$ Follow-up: $N = 74$	Baseline: $N = 82$ Follow-up: $N = 73$	49	100	Not reported	Participants recruited from local cancer center, hospital, and regional cancer agency	64% college degree	Breast	I–IIIA	In primary treatment
Courneya and colleagues (2009)	Baseline: $N = 60$ Follow-up: $N = 57$	Baseline: $N = 62$ Follow-up: $N = 60$	53	41	Not reported	Participants recruited from local cancer center	52% college degree	Lymphoma	Any stage	Mix of in and completed treatment
Culos-Reed and colleagues (2010)	Baseline: $N = 53$ Follow-up: $N = 42$	Baseline: $N = 47$ Follow-up: $N = 24$	68	0	Not reported	Not reported	35% high school or less	Prostate	"Any stage" eligible	Mix of in and completed treatment

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Table 1. Sample and cancer characteristics of 15 RCTs examining the effects of exercise on depression in cancer survivors. (Cont'd)

Trial	Exercise group (*N*)	Control group (*N*)	Mean age, y	% Female	% Caucasian	Recruitment source	Education	Cancer site	Cancer stage	Treatment status at baseline
Daley and colleagues (2007)	Baseline: $N = 34$ Follow-up: $N = 33$	Baseline: $N = 38$ Follow-up: $N = 33$	51	100	98	Letters to women identified through hospital records, as well as media advertisements and presentations to cancer support groups	43.5% high school or less	Breast	"Non-metastatic cancers" eligible	Completed primary treatment
Dodd and colleagues (2010)	Baseline: $N = 36$ Follow-up: $N = 35$	Baseline: $N = 39$ Follow-up: $N = 38$	51	100	75	Participants recruited from 6 outpatient clinics	Mean of 16.2 years of school	Breast, colorectal, and ovarian	I–III	Completed primary treatment
Kaltsatou and colleagues (2011)	Baseline: $N = 14$ Follow-up: $N = 14$	Baseline: $N = 13$ Follow-up: $N = 13$	57	100	Not reported	Participants recruited from three breast cancer survivor centers	Not reported	Breast	Stage not reported	Completed primary treatment
Monga and colleagues (2007)	Baseline: $N = 13$ Follow-up: $N = 11$	Baseline: $N = 13$ Follow-up: $N = 10$	68	0	33	Volunteers were recruited from patients referred to radiotherapy service at the Veterans Affairs Medical Center	Mean of 12 years of school	Prostate	"Localized cancers" eligible	In primary treatment
Mutrie and colleagues (2007)	Baseline: $N = 107$ Follow-up: $N = 82$	Baseline: $N = 102$ Follow-up: $N = 92$	52	100	Not reported	Participants recruited during appointments at outpatient clinics for chemotherapy or radiotherapy at 3 oncology centers	Not reported	Breast	0-III	In primary treatment
Payne and colleagues (2008)	Baseline: $N = 10$ Follow-up: $N = 9$	Baseline: $N = 10$ Follow-up: $N = 9$	65	100	90	Participants recruited from breast cancer clinics at a university cancer center	25% High school or less	Breast	Stage not reported	Completed primary treatment

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Table 1. Sample and cancer characteristics of 15 RCTs examining the effects of exercise on depression in cancer survivors. (Cont'd)

Trial	Exercise group (*N*)	Control group (*N*)	Mean age, y	% Female	% Caucasian	Recruitment source	Education	Cancer site	Cancer stage	Treatment status at baseline
Perna and colleagues (2010)	Baseline: *N* = 27 Follow-up: *N* = 20	Baseline: *N* = 24 Follow-up: *N* = 19	51	100	56	Participants identified by oncologists at weekly Tumor Group at local hospital	Not reported	Breast	I–IIIA	In primary treatment
Thorsen and colleagues (2005)	Baseline: *N* = 69 Follow-up: *N* = 59	Baseline: *N* = 70 Follow-up: *N* = 52	39	68	Not reported	Participants recruited from two university cancer clinics	Not reported	Lymphomas, breast, gynecologic, and testicular	Mix of stages	Completed primary treatment

larger effects on depression than exercise bouts ≤30 minutes (>30-minute bout: ES = −0.57; CI, −0.91 to −0.23; ≤30-minute bout: ES = 0.01; CI, −0.20 to 0.22), $P = 0.02$.

Discussion

In this study, exercise produced modest effects on depression in cancer survivors across cancer types (primarily breast), stages (predominantly early stage), treatment status at baseline, and baseline severity of depressive symptoms (most were not depressed). The major qualifier to this conclusion is that most studies did not target depression by selecting depressed cancer survivors, or subgroups of cancer survivors known to be at greater risk of depression, or by selecting exercise interventions known to have the greatest effects on depression in other populations. Thus, positive effects may be even larger for survivors actually experiencing significant levels of depressive symptoms and targeted with appropriate exercise interventions. Previous meta-analyses have reported inconsistent exercise effects. A meta-analyses of 82 RCTs (18 assessed depressive symptoms), involving 6,838 survivors and a mix of cancer types (most were breast cancer), reported no effect of exercise on depression (ES = 0.06; CI, −0.26 to 0.38; ref. 26). Conversely, Duijts and colleagues (23) included 56 RCTs of breast cancer only (29 assessed depressive symptoms), representing 7,164 patients and found that exercise interventions significantly reduced depressive symptoms (ES = −0.26; $P < 0.016$). A final meta-analysis of breast cancer only, included 9 controlled clinical trials (representing 452 patients) and concluded that too little information exists to determine the effect of exercise on mood disturbances (25).

Most participants in our meta-analysis scored within a "normal" range on depression inventories. Thus, a floor effect may have been observed. In the one study reporting depression outcomes separately for those who were and were not depressed at study entry, the authors found that both the depression rate and number of new episodes of depression were significantly lower in the exercise group than in the controls (54). While our findings importantly suggest antidepressant benefits from exercise for cancer survivors, studies are needed that use depression as an entry criterion or target survivors at risk for depression.

Studies of depressed survivors are important if we are to understand the person, exercise, and cancer-related characteristics associated with the largest effects; consequently, several factors need consideration. For instance, while rates of depression may be similar across stages of cancer (including metastatic disease), the causes of distress may differ (55). Only three studies in this review examined survivors with metastatic cancer. Thus, we were likely insufficiently powered to examine cancer stage as a moderator. It is important that future researchers include those diagnosed with metastatic disease, as the antecedents to depression and their response to exercise may differ.

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Table 2. Intervention characteristics of 15 RCTs examining the effects of exercise on depression in cancer survivors

Trial	Exercise format and delivery mode	Type of exercise program	Mode of aerobic exercise	Supervision of exercise program	Exercise bouts per wk	Length of exercise bout	Number of wks of exercise	Exercise intensity	Delivery setting
Badger and colleagues (2007)	Individual Phone delivery	Aerobic	Walking	Unsupervised	4	Not reported	6	Not reported	Home
Cadmus and colleagues (2009)	Individual Phone and print delivery	Aerobic	Mix of types of aerobic	Unsupervised	5	30 min	24	60%–80% heart rate max	Home
Cadmus and colleagues (2009)	Individual In-person delivery	Not reported	Mix of types of exercises	Mixed supervision	3/wk supervised, 2/wk unsupervised	30 min	24	60%–80% heart rate max	Community facility and home
Courneya and colleagues (2003)	Individual In-person delivery	Aerobic	Mix of types of aerobic	Unsupervised	3–5	20–30 min	16	65%–75% heart rate max	Home
Courneya and colleagues (2007)	Individual In-person delivery	Aerobic	Mix of types of aerobic	Supervised	3	45 min	17	60%–80% VO_2 max	University facility
Courneya and colleagues (2009)	Individual In-person delivery	Aerobic	Cycle ergometer	Supervised	3	40–45 min	12	60%–75% VO_2 peak	University facility
Culos-Reed and colleagues (2010)	Both individual and group In-person delivery	Both aerobic and strength training	Walking	Mixed supervision	3–5	60 min	16	"Moderate"	Mix of community facility and home
Daley and colleagues (2007)	Individual In-person delivery	Aerobic	Not reported	Supervised	3	50 min	8	65%–85% heart rate max	University facility
Dodd and colleagues (2010)	Individual Phone delivery	Aerobic	Mix of types of aerobic	Unsupervised	3–5	20-30 min	52	60%–80% VO_2 peak	Home
			Dancing	Supervised	3	60 min	24		Not reported

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Table 2. Intervention characteristics of 15 RCTs examining the effects of exercise on depression in cancer survivors (Cont'd)

Trial	Exercise format and delivery mode	Type of exercise program	Mode of aerobic exercise	Supervision of exercise program	Exercise bouts per wk	Length of exercise bout	Number of wks of exercise	Exercise intensity	Delivery setting
Kaltsatou and colleagues (2011)	Group In-person delivery	Both aerobic and strength training						65%–80% heart rate max	
Monga and colleagues (2007)	Format not reported In-person delivery	Aerobic	Walking	Supervised	3	30 + 20 min of warm-up/ cool-down	8	65% heart rate reserve	Medical facility
Mutrie and colleagues (2007)	Group In-person delivery	Both aerobic and strength training	Mix of types of aerobic	Mixed supervision	3	45 min	12	50%–75% heart rate max	Mix of community facility and home
Payne and colleagues (2008)	Individual In-person delivery	Aerobic	Walking	Unsupervised	4	20 min	14	"Moderate"	Home
Perna and colleagues (2010)	Individual In-person delivery	Mix of aerobic and strength training	Walking	Mix of supervision	3	30–40 min	12	70%–85% heart rate max	Mix of medical facility and home
Thorsen and colleagues (2005)	Individual In-person and print delivery	Mix of aerobic and strength training	Mix of types of aerobic	Unsupervised	2	30 min	14	60%–70% heart rate max	Home

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Table 3. Depression assessments of 15 RCTs examining the exercise effects on depressive symptoms in cancer survivors

Trial	Primary outcome of interest assessed in study	Depression inventory used	Baseline depression score, mean (SD)	Follow-up depression score, mean (SD)
Badger and colleagues (2007)	Depression	CES-D	Intervention: 13.3 (2.4) Control: 9.9 (1.8)	6 wk Intervention: 11.32 (2.10) 14.6% reduction in symptoms Control: 9.35 (1.57) 5.4% reduction in symptoms Groups did not significantly differ at follow-up
Cadmus and colleagues (2009)	QOL	CES-D	Intervention: 10.7 (7.3) Control: 12.2 (6.5)	6 mo Intervention: 7.9 (7.1) 26.2% reduction in symptoms Control: 10.0 (7.6) 18.0% reduction in symptoms Groups did not significantly differ at follow-up
Cadmus and colleagues (2009)	QOL	CES-D	Intervention: 9.3 (6.0) Control: 9.2 (8.6)	6 mo Intervention: 9.6 (9.3) 3.2% increase in symptoms Control: 10.8 (10.1) 17.4% increase in symptoms Groups did not significantly differ at follow-up
Courneya and colleagues (2003)	QOL	CES-D	Intervention: 9.6 (8.1) Control: 10.1 (12.0)	16 wk Intervention: 8.6 (8.7) 10.4% reduction in symptoms Control: 9.6 (10.9) 5.0% reduction in symptoms Groups did not significantly differ at follow-up
Courneya and colleagues (2007)	QOL	CES-D	Intervention: 12.8 (9.8) Control: 13.9 (9.7)	9–24 (~20) wk Intervention: 9.7 (9.3) 24.2% reduction in symptoms Control: 10.8 (9.4) 22.3% reduction in symptoms Groups did not significantly differ at follow-up
Courneya and colleagues (2009)	QOL	Short Form CES-D	Intervention: 7.7 (5.7) Control: 6.0 (4.5)	12 wk Intervention: 5.4 (4.5) 29.9% reduction in symptoms Control: 6.1 (5.0) 1.7% increase in symptoms Groups differed significantly ($P < 0.05$) at follow-up
Culos-Reed and colleagues (2010)	Physical activity levels and QOL	CES-D	Intervention: 8.6 (7.9) Control: 6.7 (6.4)	16 wk Intervention: 8.2 (6.7) 4.7% reduction in symptoms Control: 7.7 (8.6) 14.9% increase in symptoms Groups did not significantly differ at follow-up
Daley and colleagues (2007)	QOL	BDI-II	Intervention: 13.6 (9.1) Control: 10.8 (7.7)	8 wk Intervention: 6.0 (6.5) 55.9% reduction in depression Control: 10.3 (7.2) 4.6% reduction in depression Groups differed significantly ($P < 0.05$) at follow-up
Dodd and colleagues (2010)	Fatigue	CES-D	Intervention: 13.1 (9.8) Control: 10.6 (6.5)	4–6 mo Intervention: 13.0 (9.6) 0.8% reduction in symptoms

(Continued on the following page)

Table 3. Depression assessments of 15 RCTs examining the exercise effects on depressive symptoms in cancer survivors (Cont'd)

Trial	Primary outcome of interest assessed in study	Depression inventory used	Baseline depression score, mean (SD)	Follow-up depression score, mean (SD)
				Control: 10.2 (8.6) 3.8% reduction in symptoms Groups did not significantly differ at follow-up
Kaltsatou and colleagues (2011)	Physical function	BDI	Intervention: 36.4 (7.2) Control: 33.4 (6.9)	24 wk Intervention: 16.5 (1.7) 54.7% reduction in symptoms Control: 22.3 (7.7) 33.2% reduction in symptoms Groups differed significantly ($P < 0.05$) at follow-up
Monga and colleagues (2007)	QOL/fatigue	BDI	Intervention: 3.5 (5.4) Control: 3.6 (5.0)	8 wk Intervention: 2.8 (1.8) 20% reduction in symptoms Control: 4.2 (3.4) 16.7% increase in symptoms Groups did not significantly differ at follow-up
Mutrie and colleagues (2007)	QOL	BDI	Intervention: 11.8 (6.9) Control: 13.0 (7.4)	12 wk Intervention 8.6 (6.8) 27.1% reduction in symptoms Control: 11.5 (8.6) 11.5% reduction in symptoms Groups did not significantly differ at follow-up
Payne and colleagues (2008)	Fatigue/ biomarkers	CES-D	Intervention: 15.1 (7.9) Control: 11.0 (6.7)	14 wk Intervention: 12.7 (8.7) 15.9% reduction in symptoms Control: 11.4 (7.9) 3.6% increase in symptoms Groups did not significantly differ at follow-up
Perna and colleagues (2010)	Fitness/physical activity levels	CES-D	Intervention: 9.95 (8.0) Control: 8.6 (7.4)	3 mo Intervention: 8.8 (8.4) 12.1% reduction in symptoms Control: 12.4 (11.5) 44.2% increase in symptoms No direct comparison of depression scores between groups was conducted
Thorsen and colleagues (2005)	QOL	HADS	Intervention: 2.9 (2.7) Control: 3.1 (3.6)	14 wk Intervention: 2.2 (2.3) 24.1% reduction in symptoms Control: 1.9 (2.5) 38.7% reduction in symptoms Groups did not significantly differ at follow-up

Abbreviations: BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; HADS, Hospital Anxiety and Depression Scale; QOL, quality of life.

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Table 4. Study quality summary

Trials	Badger and colleagues (2007)	Cadmus and colleagues (2009)	Cadmus and colleagues (2009)	Courneya and colleagues (2003)	Courneya and colleagues (2007)	Courneya and colleagues (2009)	Culos-Reed and colleagues (2010)	Daley and colleagues (2007)	Dodd and colleagues (2010)	Kaltsatou and colleagues (2011)	Monga and colleagues (2007)	Mutrie and colleagues (2007)	Payne and colleagues (2008)	Perna and colleagues (2010)	Thorsen and colleagues (2005)
PEDro criterion															
1. Eligibility criteria were specified.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
2. Subjects were randomly allocated to groups.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
3. Allocation was concealed.	X	X	X	X	X	X	—	X	—	—	X	X	X	X	X
4. The groups were similar at baseline regarding most important prognostic indicators.	X	X	X	X	X	X	X	X	X	X	X	X	—	X	X
5. There was blinding of all subjects.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
6. There was blinding of all therapists who administered the therapy.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
7. There was blinding of all assessors who measured at least one key outcome.	—	X	—	—	—	—	—	—	—	—	—	—	X	—	—
8. Measurements of at least one key outcome were obtained from >85% of the subjects initially allocated to groups.	X	X	X	X	X	X	—	X	X	X	—	X	X	—	—
9. All subjects for whom outcome measurements were available received the treatment or control condition as allocated, or where this was not the case, data for at least one key outcome were analyzed by `intention to treat."	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
10. The results of between-group statistical comparisons are reported for at least one key outcome.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
11. The study provides both point measurements and measurements of variability for at least one key outcome.	X	X	X	X	X	X	X	X	—	X	X	X	—	—	X
Total criteria met (item #1 is not included in summary score)	7	8	7	7	7	7	5	7	5	6	7	7	6	5	7

NOTE: Criterion #5 is typically not applicable to behavioral interventions of exercise.

Abbreviations: X, criterion is evidenced in article; —, criterion is not evidenced, not applicable, not coded, or could not be determined in article.

The specific cancer treatment a survivor receives may also affect depression and/or options for treatment. Women who have undergone chemotherapy, and, in particular taxane-based chemotherapies, may be at increased risk for emotional distress and depression (56, 57). Likewise, individuals receiving steroids, IFN, and estrogen-depleting interventions may be at increased risk (14). Many of the studies reviewed herein lacked information about the specific types of medications survivors were receiving. In addition, traditional treatments for depression, such as SSRIs, may be contraindicated for those receiving certain types of cancer therapy. One study has shown that the SSRI, paroxetine, is associated with an increased risk of death from breast cancer in women undergoing treatment with tamoxifen (17). Therefore, researchers should carefully consider how medical treatments may play a role in the complex relationship between exercise and depression and enroll patients accordingly.

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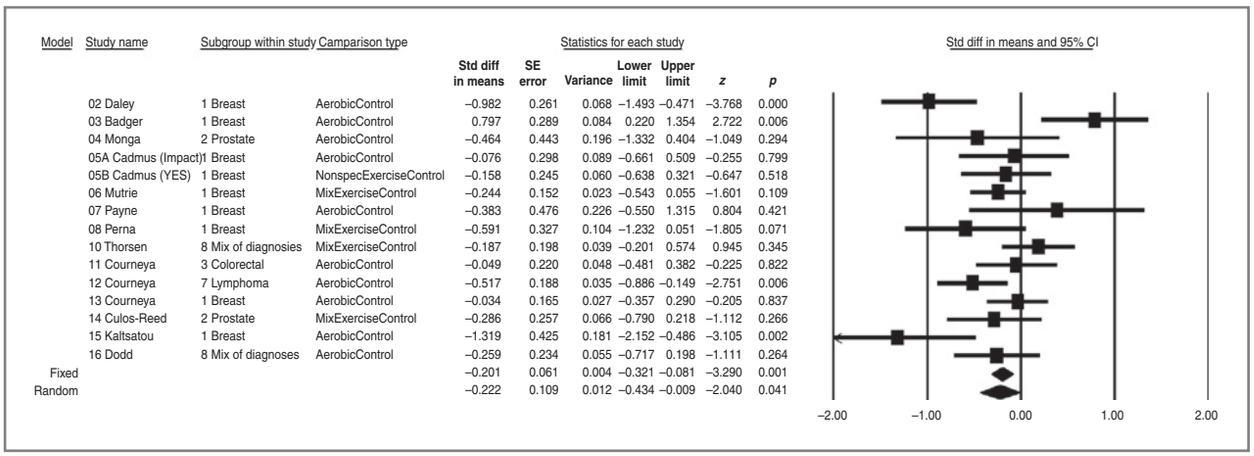

Model	Study name	Subgroup within study	Comparison type	Std diff in means	SE error	Variance	Lower limit	Upper limit	z	p
	02 Daley	1 Breast	AerobicControl	−0.982	0.261	0.068	−1.493	−0.471	−3.768	0.000
	03 Badger	1 Breast	AerobicControl	0.797	0.289	0.084	0.220	1.354	2.722	0.006
	04 Monga	2 Prostate	AerobicControl	−0.464	0.443	0.196	−1.332	0.404	−1.049	0.294
	05A Cadmus (Impact)	1 Breast	AerobicControl	−0.076	0.298	0.089	−0.661	0.509	−0.255	0.799
	05B Cadmus (YES)	1 Breast	NonspecExerciseControl	−0.158	0.245	0.060	−0.638	0.321	−0.647	0.518
	06 Mutrie	1 Breast	MixExerciseControl	−0.244	0.152	0.023	−0.543	0.055	−1.601	0.109
	07 Payne	1 Breast	AerobicControl	−0.383	0.476	0.226	−0.550	1.315	0.804	0.421
	08 Perna	1 Breast	MixExerciseControl	−0.591	0.327	0.104	−1.232	0.051	−1.805	0.071
	10 Thorsen	8 Mix of diagnosies	MixExerciseControl	−0.187	0.198	0.039	−0.201	0.574	0.945	0.345
	11 Courneya	3 Colorectal	AerobicControl	−0.049	0.220	0.048	−0.481	0.382	−0.225	0.822
	12 Courneya	7 Lymphoma	AerobicControl	−0.517	0.188	0.035	−0.886	−0.149	−2.751	0.006
	13 Courneya	1 Breast	AerobicControl	−0.034	0.165	0.027	−0.357	0.290	−0.205	0.837
	14 Culos-Reed	2 Prostate	MixExerciseControl	−0.286	0.257	0.066	−0.790	0.218	−1.112	0.266
	15 Kaltsatou	1 Breast	AerobicControl	−1.319	0.425	0.181	−2.152	−0.486	−3.105	0.002
	16 Dodd	8 Mix of diagnoses	AerobicControl	−0.259	0.234	0.055	−0.717	0.198	−1.111	0.264
Fixed				−0.201	0.061	0.004	−0.321	−0.081	−3.290	0.001
Random				−0.222	0.109	0.012	−0.434	−0.009	−2.040	0.041

Figure 2. Forest plot of effect size.

Third, exercise interventions in these studies were likely not designed to target depressive symptoms. Among depressed patients in the general population, several aspects of the exercise prescription have been identified as important. Although Craft and Landers (19) found that exercise bout duration was not a significant moderator of the effect of exercise on depression, Rethorst and colleagues (20) found that durations of 45 to 59 minutes produced larger antidepressant benefits than shorter bouts of activity. In the current review, programs using exercise bouts of >30 minutes produced the largest effects on depression; however, only 6

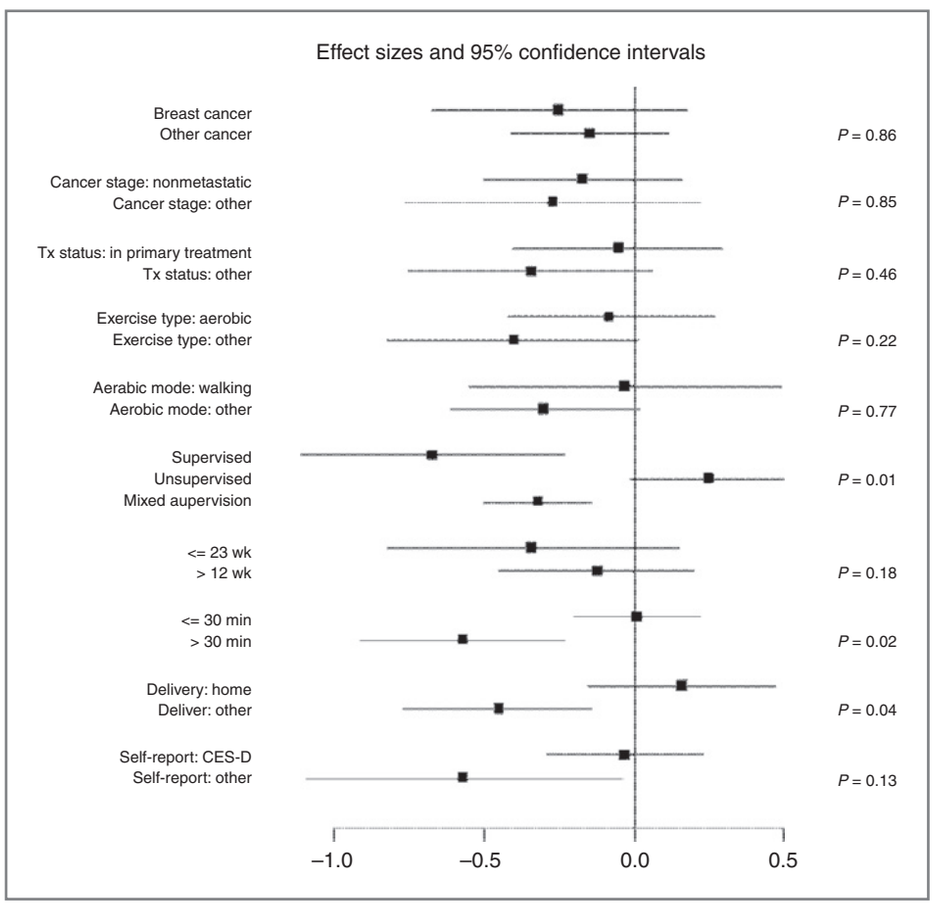

Figure 3. Forest plot of ES from moderator variable analyses.

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studies used exercise bouts of ≥45 minutes. Therefore, exercise bout duration may have been insufficient in some studies to effect depression. Similarly, an exercise frequency of 5 times per week was reported as being significantly more effective than 2 to 4 days of activity (20). In the current review, only 3 studies incorporated programs with an exercise frequency of ≥5 d/wk. As a result, the exercise frequencies may have been inadequate to provide maximal affect on depressive symptoms. Finally, in the general population, exercise programs of 10 to 16 weeks produced larger effects than programs of <9 weeks (19, 20). Conversely, although a nonsignificant difference, we found that effects sizes were larger for those studies using programs of ≤12 weeks. It remains unclear whether these exercise programs characteristics, independently or in combination, contributed to the relatively small observed effect of exercise on depressive symptoms.

As research moves forward, studies can be improved in multiple ways. First, because depression was not the primary outcome of most trials included, no information was collected about the participant's history of depression, ongoing medication or psychotherapeutic treatment for depression, length of current depressive symptoms, or additional psychologic comorbidities. Thus, the current literature is insufficient for understanding that who might benefit most from exercise programs. Participant characteristics related to both depression and exercise (e.g., race, marital status, medical comorbidities, SES) were lacking in most studies, making it impossible to examine these as potential moderators. Future studies should collect information pertaining to the onset, persistence, and treatment of depressive symptoms among participants, as well as pertinent demographic information that might be associated with both depression and exercise. As the risk for recurrence of a major depressive episode can be quite high (50%–90%), those with a history of depression or psychologic illness may be especially vulnerable to developing depression following a cancer diagnosis.

Race and socioeconomic status (SES) are also important considerations. Research shows that low SES women with breast cancer have an increased risk of developing depression and that the symptom burden may differ by race and SES (58–60). Furthermore, older African American cancer survivors who lost their job were 3 times more likely to develop depression than those who were employed (61). Similarly, among colorectal cancer survivors, race, but not employment status, was a determinant of depressive symptoms across time (62). The samples used herein were predominantly Caucasian and middle class. Many studies did not provide information about race and even fewer alluded to the participant's SES. Thus, we were not able to examine these as potential moderator variables. Future studies should include larger numbers of ethnic minority and low SES survivors as their risk for depression, cancer prognosis, and acceptance of exercise as a treatment option for depression may differ from Caucasian survivors of high SES.

Risk for the development of depression may also vary by cancer type (1). Most studies in this meta-analysis were of breast cancer survivors. However, other cancers (e.g., head and neck, prostate, lung) are associated with higher rates of depression. We did not find significant differences in ES when comparing studies of breast cancer ($N = 9$; ES $= -0.25$; CI, -0.68 to 0.18) to "other cancers" ($N = 6$; ES $= -0.15$; CI, 0.41 to 0.12), which were 2 studies of "mixed diagnoses" (predominantly breast cancer), 2 studies of prostate cancer, and 1 study each of lymphoma and colorectal cancer. Thus, we were limited in our ability to compare exercise effects on various types of cancer.

Limited information can be gleaned from our review about exercise program characteristics that are most relevant for cancer survivors. Most of the studies reviewed used walking programs. Other types of aerobic activities and strength training programs should be examined. Clarification about mode of exercise may be important because exercise preference may predict exercise adherence and allowing survivors to choose enjoyable activities may be especially important when targeting depressive symptoms (63).

Among the studies we reviewed, all used moderate-intensity activity. In the general population, even light-intensity exercise has been shown to be an effective antidepressant. Light-intensity activity may be preferred by some and may be easier to incorporate into one's lifestyle, resulting in greater exercise frequency. Conversely, some survivors may enjoy and self-select more vigorous-intensity activities. Thus, it is essential that future researchers use and compare a variety of exercise intensities and varying lengths of exercise bouts so that evidence-based recommendations can be made about the appropriate exercise prescription.

The timing of exercise interventions postdiagnosis must also be carefully considered. Half of the studies in this review examined exercise effects in participants undergoing active treatment. We found that treatment status at baseline was not a significant ($P = 0.61$) moderator. This suggests that exercise can lessen depressive symptoms among those who are and who are not actively undergoing treatment during the exercise intervention. While this is very encouraging, only 2 studies examined exercise effects in survivors who were diagnosed at least 12 months posttreatment (41, 45). For many, depression will resolve after diagnosis and treatment, but for some, it persists or develops during posttreatment and lingers into long-term survivorship (1, 4, 64). Consequently, as the number of cancer survivors and the average length of survivorship continues to increase (65), it will be important to examine exercise effects across the various stages of survivorship.

Finally, the location and supervision of the exercise are also important to consider. Craft and Landers (19) reported the largest antidepressant effects for those exercising in supervised laboratory settings. In the current review, we also found larger effects for those who

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participated in programs in which all or some part of the exercise was supervised and for those exercising in facilities as compared with those exercising in home. Unfortunately, we actually found that home-based and unsupervised exercise were associated with increased depressive symptoms, suggesting caution in how exercise programs are implemented for survivors with distress. Conn (66) conducted a meta-analysis in healthy adults and also found that unsupervised exercise produced larger effects on depressive symptoms when the exercise was completed at a fitness center rather than at home. There may be therapeutic aspects to supervised exercise, such as working with an exercise instructor to learn new skills, collaboratively setting and achieving exercise goals, and receiving positive feedback and social interaction. Thus, more research is needed to determine the type of program, and program components, that lead to the largest antidepressant effect.

Conclusion

Elucidating effective treatments for depression in cancer survivors remains a primary challenge. Depression is associated with poor quality of life, treatment nonadherence, and increased risk of relapse and mortality, independent of cancer stage or site (9, 67–69). In this meta-analysis, exercise produced small improvements in depressive symptoms. Nevertheless, there was only one study that targeted depression as the primary endpoint. Most studies used samples that contained some depressed survivors but the majority was not experiencing depressive symptoms. We cannot be certain whether the modest improvements in depression caused by exercise participation in this study are sufficient to affect quality of life, adherence to treatment, or mortality. However, our results complement the findings of RCTs and other meta-analyses showing that exercise is associated with reduced pain (70) and fatigue (29) and with improvements in quality of life (24) among cancer survivors. As there are few negative side effects of exercise participation, exercise should be recommended to cancer survivors who are experiencing depressive symptoms. Importantly, exercise represents a noninvasive, cost-effective, accessible treatment option, that if found effective, could be implemented into patient care for millions of survivors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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