



Contemporary Issues in Cancer Rehabilitation

A Systematic Review of Exercise Systematic Reviews in the Cancer Literature (2005-2017)

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Abstract

Background: Evidence supports the benefits of exercise for patients with cancer; however, specific guidance for clinical decision making regarding exercise timing, frequency, duration, and intensity is lacking. Efforts are needed to optimize clinical recommendations for exercise in the cancer population.

Objectives: To aggregate information regarding the benefit of exercise through a systematic review of existing systematic reviews in the cancer exercise literature.

Data Sources: PubMed, CINAHL Plus, Scopus, Web of Science, and EMBASE.

Study Eligibility Criteria: Systematic reviews and meta-analyses of the impact of movement-based exercise on the adult cancer population.

Methods: Two author teams reviewed 302 abstracts for inclusion with 93 selected for full-text review. A total of 53 studies were analyzed. A Measurement Tool to Assess Systematic Reviews (AMSTAR) was used as a quality measure of the reviews. Information was extracted using the PICO format (ie, participants, intervention, comparison, outcomes). Descriptive findings are reported.

Results: Mean AMSTAR score = 7.66/11 (± 2.04) suggests moderate quality of the systematic reviews. Exercise is beneficial before, during, and after cancer treatment, across all cancer types, and for a variety of cancer-related impairments. Moderate-to-vigorous exercise is the best level of exercise intensity to improve physical function and mitigate cancer-related impairments. Therapeutic exercises are beneficial to manage treatment side effects, may enhance tolerance to cancer treatments, and improve functional outcomes. Supervised exercise yielded superior benefits versus unsupervised. Serious adverse events were not common.

Limitations: Movement-based exercise intervention outcomes are reported. No analysis of pooled effects was calculated across reviews due to significant heterogeneity within the systematic reviews. Findings do not consider exercise in advanced cancers or pediatric populations.

Conclusions: Exercise promotes significant improvements in clinical, functional, and in some populations, survival outcomes and can be recommended regardless of the type of cancer. Although generally safe, patients should be screened and appropriate precautions taken. Efforts to strengthen uniformity in clinical trial reporting, develop clinical practice guidelines, and integrate exercise and rehabilitation services into the cancer delivery system are needed.

Introduction

Exercise interventions are well-established as safe and beneficial for individuals receiving cancer treatment [1]. Exercise contributes to improved health and functional outcomes in the cancer population [2,3]. Although most national guidelines recommend that cancer survivors meet the public health guidelines for physical activity, exercise prescription is nuanced and

requires consideration of many factors to positively and safely impact individuals with a cancer diagnosis [4,5]. Different types of exercise interventions have been studied in the cancer population and have resulted in general recommendations for increasing overall physical activity and including specific resistive or aerobic exercise regimens to the cancer care plan [1,6,7]. Therapeutic exercise also is recommended as a rehabilitative approach for individuals

experiencing more specific functional impairments and disability [8].

Oncology care providers are challenged to identify and synthesize the significant volume of relevant literature on exercise prescription. The complexities of the health status, clinical history, and functional abilities of the individual being treated for cancer introduce a spectrum of considerations that further challenge exercise recommendations [4]. Models of care that provide access to exercise and rehabilitation professionals have been developed but are not used broadly and the workforce supporting them is still developing [9]. As a result, exercise prescription frequently is overlooked in cancer care planning [10,11]. Although recommendations have urged greater integration of exercise into the cancer care continuum, active integration will require more precise guidelines to support provider decision making [12].

The cancer exercise research generally demonstrates significant and positive impact on variables of interest; however, most studies have focused on exercise within specific types of cancer (breast, colorectal, etc) or on a single cancer-related impairment (cancer-related fatigue [CRF], muscle weakness, etc) using widely variable modes of exercise. Further complicating the ability to harmonize information around exercise prescription is the variability across studies regarding optimal timing, frequency, duration, and intensity for exercise prescription. Systematic reviews, although prevalent in the cancer exercise literature, tend to follow a disease-specific or impairment-specific focus (eg, systematic review of strength training in androgen-deprived patients with prostate cancer) whereas in the clinical setting, providers see a wide range of oncologic patients with varying disease stages often experiencing multiple comorbidities and functional impairments. A review of the existing literature is needed to compile and synthesize evidence from the numerous and varied systematic reviews to aggregate the most meaningful literature with a broad perspective on exercise and rehabilitation interventions for individuals with cancer [13].

The purpose of this report is to present the results of a systematic review of published systematic reviews on exercise interventions for the cancer population to identify key common features of exercise programs in the cancer population. The aggregate findings provide a comprehensive resource of current evidence that support health care providers in selecting exercise-based interventions for the individual being treated for or with a history of cancer.

Methods

The methodology for conducting a systematic review of systematic reviews is supported by the Cochrane group and articulated by Smith et al [13]. This approach is recommended when attempting to appraise,

summarize, and aggregate research findings from separate systematic reviews to compare and contrast results to provide clinical decision makers with relevant evidence [13].

Search

The search strategy was designed to identify existing, published systematic reviews and meta-analyses. Search terms were formulated using the PICO structure, ie, participants (P) included adults (18-80 years old) with any type of cancer who were not considered to have advanced cancer or were not receiving palliative care. Intervention (I) included exercise and its various forms, including therapeutic exercise, physical activity, strength training, aerobic conditioning, rehabilitative exercise, and stretching, etc. Comparisons (C) broadly addressed exercise intervention versus none, supervised versus unsupervised, varied frequency and duration of exercise interventions, as well as comparison of different types of exercise. Outcomes (O) included functional gains such as neuromusculoskeletal and cardiometabolic function, improvement in physical impairment, functional measures, overall quality of life, blood count and biomarker improvements, and psychological and psychosocial gains.

The search terms and strategy were developed by an informationist at the National Institutes of Health, National Institutes of Health Library in consultation with the author team. The comprehensive search strategy is provided in Table 1. Five databases were searched: PubMed, CINAHL Plus, Web of Science, EMBASE, and Scopus with date range from 2000 to 2017.

Study Identification and Selection

Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. The initial search yielded 9337 results. Additional filters were then added for systematic reviews and meta-analyses only, yielding 5453 records. After we removed duplicate records and abstracts not available in English, as well as those not relevant to the topic of interest, 302 abstracts were agreed on by the author team for screening. Authors worked in paired teams for the initial abstract screening reviews (J.B./K.W.S. and A.S./N.S.), and each team reviewed one half of the abstracts. In instances of disagreement by the team, the co-lead authors (N.S. and J.B.) made a final determination of inclusion.

A priori, the authors agreed that reviews focusing on movement-based exercise, such as yoga, qigong, etc, would be included, as well as studies that used various traditional forms of exercise, including aerobic and resistive conditioning, flexibility, and muscle retraining activities. Studies that reviewed behavioral interventions to promote exercise or to encourage lifestyle

Table 1
Search terms and yield

| Search Criteria | | | | |
|--|---------------------|-----------------|----------------|-------------------------|
| (neoplasms[majr] OR cancer[tiab] OR cancers[tiab] OR carcinoma[tiab] OR carcinomas[tiab] OR leukemia[tiab] OR lymphoma[tiab] OR neoplasm[tiab] OR neoplasms[tiab]) AND (exercise[majr] OR exercise movement techniques[majr] OR exercise therapy[majr] OR rehabilitation[majr] OR activity[tiab] OR activities[tiab] OR aerobic[tiab] OR aerobics[tiab] OR exercise[tiab] OR exercises[tiab] OR exercising[tiab] OR exertion[tiab] OR "occupational therapy"[tiab] OR "physical therapy"[tiab] OR physiotherapy[tiab] OR recreation[tiab] OR recreational[tiab] OR reflexology[tiab] OR rehabilitate[tiab] OR rehabilitated[tiab] OR rehabilitation[tiab] OR rehabilitative[tiab] OR stretch[tiab] OR stretching[tiab] OR strengthen[tiab] OR strengthened[tiab] OR strengthening[tiab] OR "tai chi"[tiab] OR train[ti] OR trained[ti] OR training[ti] OR walk[tiab] OR walks[tiab] OR walked[tiab] OR walking[tiab] OR yoga[tiab]) AND (activities of daily living[majr] OR emotions[majr] OR pain management[majr] OR physical fitness[majr] OR exercise test[majr] OR recovery of function[majr] OR mobility limitation[majr] OR "activities of daily living"[tiab] OR "aerobic capacity"[tiab] OR "aerobic endurance"[tiab] OR anemia[tiab] OR anorexia[tiab] OR anxiety[tiab] OR anxious[tiab] OR balance[tiab] OR balancing[tiab] OR "body image"[tiab] OR biomarker[tiab] OR biomarkers[tiab] OR "blood count"[tiab] OR "blood counts"[tiab] OR "body mass index"[tiab] OR "body strength"[tiab] OR "bone density"[tiab] OR breathless[tiab] OR "breathlessness"[tiab] OR "cardiopulmonary strength"[tiab] OR depressed[tiab] OR depression[tiab] OR discomfort[tiab] OR distress[tiab] OR distressed[tiab] OR drowsy[tiab] OR drowsiness[tiab] OR dyspnea[tiab] OR edema[tiab] OR edematous[tiab] OR endurance[tiab] OR energy[tiab] OR "exercise capacity"[tiab] OR fall[tiab] OR falls[tiab] OR falling[tiab] OR fatigue[tiab] OR fatigued[tiab] OR fitness[tiab] OR flexible[tiab] OR flexibility[tiab] OR fracture[tiab] OR fractures[tiab] OR fractured[tiab] OR frailty[tiab] OR function[tiab] OR functions[tiab] OR functioning[tiab] OR functional[tiab] OR happiness[tiab] OR "heart failure"[tiab] OR immobile[tiab] OR immobility[tiab] OR impairment[tiab] OR impairments[tiab] OR insomnia[tiab] OR "lean mass"[tiab] OR lymphedema[tiab] OR lymphoedema[tiab] OR mental[tiab] OR mobile[tiab] OR mobility[tiab] OR mood[tiab] OR moods[tiab] OR morbidity[tiab] OR "muscle strength"[tiab] OR nausea[tiab] OR neuropathy[tiab] OR neuropathies[tiab] OR "quality of life"[tiab] OR pain[tiab] OR "physical performance"[tiab] OR "physical strength"[tiab] OR "psychological stress"[tiab] OR "range of motion"[tiab] OR relax[tiab] OR relaxed[tiab] OR relaxing[tiab] OR relaxation[tiab] OR "self-care"[tiab] OR "self-concept"[tiab] OR "self-esteem"[tiab] OR "shortness of breath"[tiab] OR "sit to stand"[tiab] OR sleep[tiab] OR swelling[tiab] OR symptom[tiab] OR symptoms[tiab] OR vigor[tiab] OR vigorous[tiab] OR vomiting[tiab] OR "walk test"[tiab] OR "walk tests"[tiab] OR weakness[tiab] OR weight[tiab] OR "well-being"[tiab] OR wellbeing[tiab]) AND (randomized controlled trial[ptyp] OR systematic[sb] OR "randomized controlled trial"[tiab] OR "randomised controlled trial"[tiab] OR "systematic review"[tiab]) | | | | |
| Search Yield = 9337 | | | | |
| PubMed: 2526 | CINAHL Plus: 544 | EMBASE: 4313 | Scopus: 827 | Web of Science: 1127 |

behaviors to increase exercise engagement were excluded. Reviews of exercise in the pediatric population were excluded. The pediatric population was defined as study participants who were younger than the age of 18 years when the exercise intervention took place. Studies of exercise in individuals receiving palliative care or those with advanced cancer also were excluded.

Eighty abstracts were approved for full-text review, and an additional 13 abstracts were self-identified by the author team for inclusion, resulting in 93 abstracts retrieved for full-text review. After final full-text review, 51 articles were included in this analysis. Data were extracted from the full-text articles by one author and reviewed and confirmed by their paired

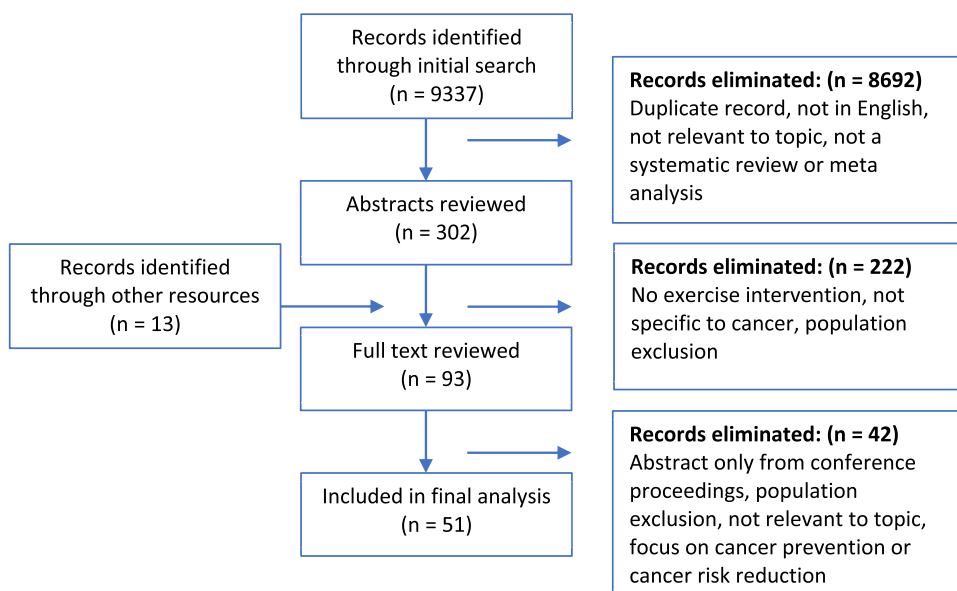


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

counterpart. All authors reviewed and approved the final inclusion list and extracted content.

Summary Measures and Study Quality Assessment

Because of significant heterogeneity within the various systematic reviews, pooled effects were not assessed and rather descriptive findings are provided. Each author scored her respective articles using A Measurement Tool to Assess Systematic Reviews (AMSTAR). AMSTAR is a validated qualitative tool that evaluates the quality of systematic reviews [13,14]. The AMSTAR online calculator queries 11 items of relevance that provide insight on the quality of the systematic review methodology. The authors scored each of the included articles using the online AMSTAR calculator (https://amstar.ca/Amstar_Checklist.php).

Results

Information was extracted and synthesized from 51 articles. Table 2 provides a summary of the included studies [15-65]. Quality analysis, revealed a mean score of 7.7 (± 2.0), and median of 8 with a range of 3-11. Descriptive findings are provided because pooled effects were not calculated.

In general, findings demonstrate an overall positive benefit of exercise interventions among a variety of cancer types using various forms of movement-based exercise. There was significant variability regarding frequency, duration, and intensity of commonly prescribed exercise regimens. Some reviews cited that many of the studies examined failed to meet the definition of physical activity [25], whereas others reported well-defined, if disparate, exercise parameters [15,57,58,63]. The mode of exercise varied widely in reports, spanning both aerobic and resistive training protocols [15,26,27,30,32,35,36,39,45,57,59,60,63,66], as well as described mixed (aerobic plus resistance training) interventions [16,17,19,20,22,24,28,31,32,37,41,43,47,48,53,58,60], yoga [38,47,50,54,64,65,67], tai chi [42,64,65], dance [18], progressive resistive exercise (PRE) [21,30,53], and therapeutic exercises (focused on targeted body region impairments) [21,23,44,53,62]. Exercise programs were structured in various settings (home-based, outpatient ambulatory clinic, hospital-based) and provided various levels of provider supervision. A general trend toward improved outcomes was noted when exercise was conducted in a supervised setting [19,44,45,52,61].

The reviews included in this analysis identified exercise intervention across the cancer care continuum, including exercise interventions before the initiation of oncologic treatment [51,53,55,62], during active oncology-directed treatment [16,22,41,44], and after the completion of oncologic treatment [26,30,32,36,58,63]. The results

suggest that timing and type of exercise may impact various biological and physiological markers, psychosocial factors, and functional impairments differently [24,35,47,51,57,60] and suggest overall improvements in tolerance to cancer treatment and functional outcomes when exercise is initiated before or during cancer treatment [22,53,55,62]. Reviews included a wide sampling of various types of cancers, with breast, prostate, and colorectal cancers most commonly studied.

Some reviews focused on exercise interventions targeting one specific cancer treatment-related impairment, such as CRF [27,41,45,48,58,61] or lymphedema [34,66], and many reported on the impact of exercise on common treatment-related side effects, such as body weight and body mass index (BMI) [19,28,30,32,36,43,58], depression [16,24,38,67], anxiety [16,32,38,47,50,67], bone density [63], other physical and functional impairments [18,21,22,30,31,35,50,40,60,62,66], and various biomarkers associated with cancer progression [22,32,36,42,46,57,58,59,64].

Several large observational cohort study reviews examined patient self-reported levels of physical activity at various points in the cancer care continuum and offered longitudinal perspective on the association with meaningful endpoints such as disease-free survival and mortality risks [29,33,49,51]. Although these reviews do not reflect comparisons of exercise intervention trials, they do provide substantive support for the impact of physical activity on meaningful endpoints such as disease progression and overall mortality. Overall, across all reviews, there was poor reporting of trial and intervention adherence, adverse events, and a lack of specific characterization of exercise interventions.

Exercise Intensity

A general theme emerged regarding the intensity of aerobic exercise, favoring moderate-to-vigorous exercise, as compared with controls who did not exercise or who exercised at a lower level of intensity [17,35,36,39,47]. This effect was noted in trials both during and after cancer treatment and was supported by observational study reviews that identified high versus low self-reported levels of physical activity [29,33,51]. Results differ regarding the superiority of vigorous versus moderate intensity exercise, with no clear evidence to demonstrate more significant or longer-term carry-over of positive outcomes based on the level of intensity. In general, exercise interventions at moderate and vigorous intensity are safe in supervised settings, with small numbers of adverse events noted [16,57]. Moderate and vigorous exercise resulted in improvements in measures of fitness, including peak oxygen consumption [30,32,43], maximum rate of oxygen consumption [28], muscle strength and endurance [30,39], and in measures of function, including 6- and 12-minute walk distance outcomes [35,56], as well as improved

measures of immune function [32,36,46,57]. Although moderate-to-vigorous exercise interventions significantly improved various physical and functional indicators, the impact on cognitive recovery, depression, and anxiety was mixed in several reports, with some noting no significant impact from exercise [24,35,38,47,61]. Low-intensity exercise interventions demonstrated improvements for more deconditioned populations over time and positively impacted CRF, depression, anxiety, and overall physical functioning [16,17,26,50].

Reviews that looked specifically at therapeutic exercises, targeting one body region or specific impairment, frequently did not characterize intensity of the intervention. These interventions focused on a set of rehabilitative exercises based on a practice protocol and frequently included progressive forms of exercise. Although PREs frequently were identified as a therapeutic exercise intervention, rarely was the specific intensity, number of repetitions, or activity duration defined. Many of the PRE interventions were targeted therapeutic exercises designed for impairment rehabilitation [21,23]. In general, these interventions were supervised by a health care provider in a structured care setting and resulted in significant improvements in various domains of physical and functional status as compared to controls [21-23,44,62].

Reviews of yoga, tai chi, and qigong exercise interventions frequently identified the type of yoga or specific tai chi exercises, program duration, and frequency [38,42,50,54,64,65]. Although the intensity of these programs was not defined frequently, most are characteristically lower intensity exercises, as defined by the level of energy demand produced by the activity [67,68]. The benefits from yoga were stronger with a greater duration of yoga practice (>3 months), and yoga tended to have greater impact on affective and psychosocial domains, with mixed positive benefits on physical domains and inflammatory biomarkers [46,50,54,65].

Exercise Program Structure

Most reviews examined exercise interventions in ambulatory settings, with some including a home-based component. One review, exclusive to hematologic cancers, examined exercise interventions in hospital-based settings and demonstrated positive impact on various physical, functional, and psychological outcomes [16]. Of importance, this review identified no significant adverse events reported with exercise in this controlled study population [16].

Several reviews reported that supervised exercise interventions yielded superior benefits compared with unsupervised exercise programs in a variety of outcome measures, including health-related quality of life (HRQOL) and adherence to exercise, as well as other

physical and psychosocial outcomes [19,24,52,61]. Unsupervised programs were found to be useful in promoting adherence to exercise recommendations over time [52,57]. Structured group exercise programs such as yoga, qigong, and other group movement-based classes demonstrated outcomes superior to controls [38,42,46,47,60,54]. The question was raised in one report as to whether the impact of supervision by a health care provider creates an environment in which more attention is given to the participant and therefore positive outcomes are attributable to the individualized experience rather than to the physiological impact of the exercise intervention [19]. In the context of therapeutic exercise interventions, supervision was regarded as necessary because of the targeted nature of the prescribed exercise and the need to correct a physical or functional deficit. Supervision of therapeutic exercise interventions yielded significant improvements in overall functional outcomes [21,44,53,61,62].

No evidence was found in these reviews to suggest superior impact of one setting over another on outcomes; however, considering that supervised exercise programs exceeded unsupervised in effect, supervision should be considered regardless of the setting. There were several reviews that included aspects of computer-aided technology and telehealth as supportive adjuncts to the exercise intervention and suggest positive outcomes were enhanced when technology complemented the exercise intervention [15].

Aside from setting and supervision, an additional factor considered in the structure of the exercise program was highlighted in a Cochrane review regarding multidimensional rehabilitation programs (MDRPs) [52]. MDRPs were defined as addressing both a physical and a psychosocial component through the same intervention. Interestingly, although MDRPs contributed to greater improvements in physical health, the greatest successes were notable when the program focused on a single physical domain (eg, exercise or dietary change) rather than when trying to impact multiple domains at once.

Time Course

The timing of exercise interventions spanned pretreatment, active cancer treatment, and posttreatment through survivorship. Exercise and physical activity interventions demonstrated beneficial effects regardless of the specific timing of exercise; however, introducing exercise at different time points in the cancer care continuum demonstrated different magnitude of effects on cancer treatment tolerance [22], overall function [57], mitigation of side effects [27,43], and improvements in quality of life (QOL) [19,54,55,60]. Effect sizes suggest that the impact of exercise on QOL, upper body and lower body strength, and physical function may be somewhat greater when exercise is introduced after the

Table 2
Synopsis of findings

| Reference | Review Characteristics | Participants | Intervention | Comparison | Outcomes |
|----------------------------|---|--|---|--|--|
| Babatunde et al* 2016 [15] | Two intervention trials Five observational studies Evaluating physical activity levels. AMSTAR score 6/11 | Endometrial cancer survivors with cross-sectional, self-report. | Self-report of PA Intensity: Moderate Duration: 150 min/wk at least 30 min/d Session frequency: 5 d/wk Complemented with computer technology/ accelerometer and intervention with computer-based or mobile app. | Cross-sectional and single-arm intervention (one with baseline data from prospective lifestyle intervention trials). | Increased physical activity contributes to improved QOL. Higher BMI correlated with lower QOL. |
| Bergenthal et al 2014 [16] | 9 RCTs Evaluating the efficacy, safety, or feasibility of aerobic physical exercise. Moderate selection bias. High bias in patient-reported outcomes. AMSTAR score 9/11 | n = 818 adults with hematologic cancers, including ALL, AML, malignant lymphoma, and multiple myeloma. | AT programs mostly walking programs. Duration and intensity: variable. | No exercise intervention or "usual care." | QOL outcomes: Significant improvements but small effect size (SMD = 0.26; 95% CI 0.03-0.49; $P = .03$). Physical functioning: Significant improvements but small effect size (SMD = 0.33; 95% CI 0.13-0.52; $P = .0009$). Depression: Significant improvements but small effect size (SMD = 0.25; 95% CI -0.00 to 0.50; $P = .05$). Anxiety: No significant changes. Fatigue: Significant improvement but small effect size (SMD = 0.24; 95% CI 0.08-0.40; $P = .003$). Physical performance: Individual trials demonstrated significant improvements favoring exercise intervention vs none; however, results could not be pooled. Serious adverse events: No significant difference in events between exercise intervention vs none. (RR 1.44; 95% CI 0.96-2.18; $P = .06$). |

| | | | | | |
|-------------------------|---|--|--|---|---|
| Bourke et al 2013 [17] | 14 RCTs Cochrane review AMSTAR score 10/11 Low selection and reporting bias. Moderate attrition bias. | n = 648 Various cancer types, including breast, colorectal, prostate, and others. | AT with or without RT RT alone Only "6 trials would meet current recommendations for aerobic exercise." Questionnaires or exercise log reported 2-5 times/wk. | Control group with the same type of cancer. (Standard care did include physiotherapy in at least one trial.) | Aerobic exercise tolerance improved at 8-12 wk postintervention with large effect size. (SMD = 0.73, 95% CI 0.51-0.95). and at 6 months with large effect size. (SMD = 0.84, 95% CI 0.45-0.94). |
| Bradt et al* 2014 [18] | One quasi-experimental RCT One RCT *Cochrane review AMSTAR score 9/11 | N = 68 Women with breast cancer within 5 y of treatment. | Dance/movement therapy. | Wait-list control group. | Body image: No significant effect. Individual studies reviewed trend towards significance in QOL and fatigue, but no pooled effects analyzed. No effect on shoulder ROM and arm circumference, but large variability was reported in these measures. |
| Buffart et al 2017 [19] | 34 RCTs AMSTAR score 9/11 | n = 4519 Various types of cancers, including breast, male GU, hematologic, GI, GYN, respiratory, and other. Postcompletion of active cancer treatment. | AT and RT exercise programs. Supervised and unsupervised exercise programs. Session frequency: 2-5 times/wk. | Control groups varied; usual care, wait-list, attention. | QOL: Significantly improved with small effect size. (0.5, 95% CI 0.10-0.20) Physical function: Significantly improved with exercise but with small effect size (0.18, 95% CI 0.13-0.23). Effects of supervised exercise twice as large as unsupervised exercise. Suggested that impact of attention from physiotherapist, better equipment, more challenging prescriptions, or better adherence from supervised programs needed further investigation. No significant effect on BMI. Studies may not adequately measure and reflect adiposity. |

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Table 2 (continued)

| Reference | Review Characteristics | Participants | Intervention | Comparison | Outcomes |
|---------------------------|---|---|--|---|--|
| Capozzi et al* 2016 [20] | Sixteen observational studies Eight experimental trials Moderate selection bias. Low-to-moderate outcomes reporting bias. AMSTAR score 8/11 | Various cancers of the head and neck, including hypopharynx, larynx, oropharynx, lip, oral cavity, tonsil, salivary glands, nasopharynx, nasal cavity, paranasal sinus, and middle ear. During and after cancer treatment. | RT, hydrotherapy, walking, walking + exercise. Exercise frequency was highly variable. Intensity: Moderate to vigorous. Duration was highly variable. Supervised and unsupervised trials. | Four trials with control groups of usual care. Remaining trials with no control comparison group. | Significant improvement in lean body mass, strength, physical function, QOL, fatigue management. (75% of patients reported “possibly” or “definitely” interested in physical activity counseling). |
| Carvalho et al 2012 [21] | Three controlled trials Low selection, attrition and reporting bias. (Cochrane review) AMSTAR score 9/11 | n = 104 Head and neck cancer survivors (primarily oropharynx) with shoulder dysfunction. Range 2-180 months postsurgery. | PRE with ROM and stretching. Frequency Average 3 times/wk. Program duration: 12 wk. Intensity: Variable. | Control groups with “standard care,” some of which included shoulder ROM exercises (but not progressive). | Progressive resistive training was more effective than standard physiotherapy for restoring shoulder function however effect is small. (−6.26, 95% CI −12.2 to −0.31). |
| Cheema et al 2008 [22] | Five RCT Four uncontrolled trials 1 nonrandomized intervention trial AMSTAR score 5/11 | Women only, during or after chemotherapy and radiation, Variable disease stage. Variable extent of surgery. No males. | Various AT and RT programs with PRE. Duration: 8-24 wk. Supervision: 6 trials with complete supervision. 3 with partial supervision. 1 with no supervision. Progressive resistive exercise was referred to but parameters were not defined. | “Non-exercise” control group. | PRE significantly improved: endurance, strength, flexibility, lean mass, cardiorespiratory fitness, immune system, mood, self-esteem. Large effect size seen with change in grip strength. Moderate effect size with peak power and VO ₂ improvements. Chemotherapy dose tolerance significantly improved. Immune function: Increased % T-helper lymphocytes. Increased total activated CD-4 cells. Increased lymphocyte proliferation. Improved IFN gamma to IL-6 ratio. Increased circulating IGF-II. |
| Cheifetz et al* 2010 [23] | Ten trials focusing on the role of exercise in lymphedema High selection and outcomes measurement bias. AMSTAR score: 4/11. | Breast cancer | Early physiotherapy. RT. Primarily supervised exercise programs. Frequency or duration not defined. | “Non-intervention” group. | Exercise is beneficial and safe for secondary lymphedema. Postoperative rehabilitation improves shoulder ROM. Supervised PRE does not worsen lymphedema. |

| | | | | | |
|----------------------------------|---|---|--|---|---|
| Chipperfield et al* 2014 [24] | Four interventional trials Two pilot studies One cross-sectional survey High selection and outcomes reporting bias. AMSTAR score 6/11 | Prostate cancer patients during ADT administration. | Variable RT and AT programs. One cross-sectional of PA. Program duration: 12 wk to 6 mo. Intensity: Most trials moderate intensity. Most trials supervised intervention. | Two pilot studies and one cross-sectional without a control group. "considerable variability in sample sizes." | Significant improvement in QOL. Inconclusive findings regarding impact on cognitive changes, depression, and anxiety. (Only 45% of reported PA met guideline standards.) |
| Cramer et al 2017 [25] | 24 RCTs of yoga interventions (Cochrane review) Moderate attrition and reporting bias. AMSTAR score 9/11 | n = 2166 Breast cancer patients. During or after cancer treatment. | Program duration: Range of 6 sessions to 6 mo. Session frequency: 1-3 times/wk. Session duration: 20-120 min. | Wait-list controls. One trial with exercise intervention control. | Significant improvements in: QOL with small effect size (SMD = 0.22, 95% CI 0.04-0.40). Fatigue with medium effect size (SMD = -0.48, 95% CI -0.75 to -0.40). Sleep disturbance with small effect size (SMD = -0.25, 95% CI -0.40 to -0.09). Depression with very small effect size (SMD = -0.13, 95% CI -0.31 to 0.05). Anxiety with medium effect size (SMD = -0.53, 95% CI -1.10 to 0.04). |
| Cramer et al 2014 [26] | Five RCTs AMSTAR score 7/11 | n = 238 Colorectal cancer patients from 3 to 60 postcancer treatment. | AT Intensity: Low vs moderate. Duration: 2-16 wk. Three trials with supervision. Two trials home-based. | Usual care or different exercise program. One trial with attention control with phone calls at same interval as program interventions. | Significant short-term improvement of overall physical fitness. (SMD = 0.59, 95% CI 0.25-0.93, P < .01). No evidence for significant effects on QOL or fatigue biomarkers. Inflammatory profile: Significantly improved with moderate exercise. Greater DNA damage noted with moderate exercise. |
| Cramp and Byron-Daniel 2012 [27] | A total of 56 controlled trials on cancer-related fatigue. High detection bias. (Cochrane review) AMSTAR score 9/11 | n = 4068 Various types of cancer with the majority including breast cancer. During and after completion of cancer treatment. | AT Frequency and duration: Variable. Mode: Walking or cycling. | Usual care or wait-list. At least 2 trials controlled with psychotherapy interventions. | Significant improvement in cancer-related fatigue with AT but with small effect size. (SMD = -0.27, 95% CI -0.37 to -0.17). |
| D'Souza et al* 2016 [28] | Eight studies reviewing survivorship care plans. Two studies reviewed use of PA. | Various types of cancers. | Physical activity, various modes, duration, intensity, and controls. | Variable. | Body composition: Significant reduction in BMI and body weight. |

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Table 2 (continued)

| Reference | Review Characteristics | Participants | Intervention | Comparison | Outcomes |
|----------------------------|--|--|---|---|---|
| | Five trials included but were not limited to RCTs. AMSTAR score 7/11 | | | | Endurance: Significant increase in peak O ₂ consumption and peak power. Fatigue: Significantly less with greater levels of reported PA. QOL: Improved with greater levels of PA. |
| Davies et al* 2011 [29] | Review of studies with varied methodology, including: Four RCTs with biomarker of recurrence as outcome. Four prospective cohort studies. Two cross-sectional studies. Three systematic reviews/meta-analysis. Significant heterogeneity in included studies. High risk of selection bias. AMSTAR: 3/11 | Breast, prostate, and colorectal cancer patients both during and after completion of cancer treatment. | Observational studies: Self-reported physical activity. RCTs: One moderate-intensity AT. Two AT + RT. Program duration: 12-36 wk. | For observational studies and systematic reviews: Active PA group compared to inactive/lowest PA group; For RCTs: Exercise vs usual care. | Physical activity participation: Improved survival and reduced risk of recurrence, mostly based on observational studies. Threshold of moderate intensity may be necessary to achieve positive impact on survival. Dose response improved with longer or more intense exercise. |
| De Backer et al* 2009 [30] | A total of 24 trials postchemotherapy: Ten RCTs Four controlled intervention trials Ten uncontrolled trials High risk of attrition and outcomes reporting bias. AMSTAR score: 7/11 | All trials postchemotherapy. Thirteen breast. Three prostate. Six various types of cancer. One poststem cell transplant. | RT with or without additional AT. RT was mostly machine based; total body program. Frequency: 2-3 d/wk. Program duration: 3-24 wk (median = 12 wk). Intensity: Moderate to vigorous. Detailed reporting of exercise parameters of included studies. | Not reported. | Body composition: No effect of resistance exercise on adiposity. Trend towards significance in improved lean body mass. Cardiopulmonary function: Increased. Muscle function: Improved muscle strength and muscle endurance. Lymphedema: Exercise at any level had no impact on swelling. Immune function: No significant impact from exercise. Endocrine function: Decrease in insulin family proteins. Hematologic function: No influence on hemoglobin levels. |
| Egan et al* 2013 [31] | Exercise interventions postcancer treatment only. Thirteen systematic reviews. | Various types of cancers. | Mixed AT and RT. PA. Supervised settings. | Low levels of PA or no PA or Usual care. | Physical function: Moderate improvements in overall function. |

Six RCTs
AMSTAR Score: 6/11

Fong et al 2012 [32]

A total of 34 RCTs evaluating the effects of PA after cancer treatment.
AMSTAR score: 9/11

Twenty-two breast cancer trials.
Three colorectal cancer trials.
One endometrial cancer trial.
Eight trials including various cancer types.
Average age 55 y (range = 39–74 years)

A total of 27 trials AT.
Six trials AT + RT.
Duration:
Average 13 wk (range = 3-60 wk).
Intensity:
11 trials: moderate
2 trials: vigorous.

Sedentary comparisons or assigned no exercise.

Fatigue:
Significant improvements.
Depression:
Small effect trending towards positive impact.
Physiological markers:
Significant reduction in IGF-I (95% CI –23.3 to –0.5; $P = .04$).
No effect on insulin, glucose, and homeostatic model assessment.
Body composition:
Slightly reduced BMI (–0.4, 95% CI, –0.6 to –0.2; $P < .01$) and body weight (–1.1 kg, 95% CI, –1.6 to –0.6 kg; $P < .001$).
No effect on waist/hip ratio.
Physical functions:
Significant increase in peak oxygen consumption (2.2 mL/kg/min, 1.0-3.4; $P < .01$).
Peak power output (21 W, 13.0-29.1; $P < 0.01$).
Distance walked in 6 min (29 m, 4-55; $P = .03$).
Bench press weight (6 kg, 4-8; $P < .01$).
Leg press weight (19 kg, 9-28; $P < .01$).
Right hand grip strength (3.5 kg, 0.3-6.7; $P = .03$).
Psychological outcomes:
Reduced depression using Beck Depression Inventory (–4.1, –6.5 to –1.8; $P < .01$).
Reduced fatigue using Piper Fatigue scale (–1.0, –1.8 to –1.0: $P = .03$).
Quality of Life outcomes:
Significant improvement on SF-36 physical function, social function, and mental health functions.
Cancer specific survival and all-cause mortality:
36%-67% decrease in rate of

Fontein et al* 2013 [33]

Fourteen prospective observational studies.
Two RCTs.

Breast cancer only.

Self-report levels of PA.

Inactive or low self-reported PA.

Cancer specific survival and all-cause mortality:
36%-67% decrease in rate of

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Table 2 (continued)

| Reference | Review Characteristics | Participants | Intervention | Comparison | Outcomes |
|----------------------------------|---|--|---|---|--|
| | Two retrospective case control studies. AMSTAR score 7/11 | | | | disease-specific mortality of highest PA levels vs lowest PA levels. Significant benefit on all-cause mortality in the highest PA group ranging from 14%-56% decrease compared with low PA. |
| Fu et al* 2014 [34] | Nine RCTs Two uncontrolled trials Three systematic reviews AMSTAR score: 5/11 | Various types of cancers. | "Full body exercise" not characterized. Some reported use of resistance training. | Not described. | Full body exercise: Does not worsen lymphedema and may improve shoulder mobility. Resistive training: Safe if progressive, starting with low intensity. |
| Granger et al* 2011 [35] | Nine case series. Two RCTs. Three cohort studies. AMSTAR: 11/11 | Non-small cell lung cancer at any phase of treatment. | All studies included aerobic. 54% added RT. 31% added stretching. Intensity: Moderate to vigorous Program duration: 4-12 wk Session frequency: 2-7 d/wk | Not described. | Preoperative exercise: Improvements in 6-min walk distance posttreatment. No change in HRQOL. Postoperative exercise: Improvement in 6MWD but only small significance as compared with usual care. Conflicting evidence for HRQOL between trials. |
| Guinan et al* 2013 [36] | Seven RCTs. Two nonrandomized trials. Moderate attrition bias. AMSTAR score: 8/11 | Early-stage, postadjuvant treatment breast cancer survivors. | Seven trials AT with or without RT. One trail RT only. Intensity: Moderate to vigorous. Program duration: 8-36 wk. | Nonexercise control group. | Body composition: Mixed findings for impact on % body fat, BMI, and waist and hip circumferences. Insulin resistance markers: No effect on insulin or FBG. Decreased levels of IGF-I. Mixed results for IGF-II or IGFBP3 levels. |
| Hackshaw-McGeagh et al 2015 [37] | Four RCTs with exercise only. Six RCTs with exercise + diet. AMSTAR: 10/11 | Prostate cancer survivors at various stages of disease and phases of treatment. | AT + RT. One trial RT only Three aerobic only. Program duration: 13-104 wk. | Nonexercise control group in most studies. | No impact from exercise on disease progression markers, eg, PSA, testosterone. |
| Harder et al* 2012 [38] | Eighteen RCTs Moderate bias in randomization, attrition, and blinding. AMSTAR score: 8/11 | Breast cancer survivors at various phases of treatment and with stages of disease. | Yoga. Program duration: 4-36 weeks (most were between 4 and 12 weeks). Program frequency: 1-2 sessions per week + home practice. | Education only Rehabilitation intervention Wait-list control. | Psychological/symptom distress: Significantly reduced depression (ES: 0.24-0.33) anxiety (ES: 0.31) and negative affect (ES: 0.59-0.84). HRQOL: Significantly improved |

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|------------------------|---|--|---|------------------------------|---|
| Keogh et al* 2011 [39] | Twelve intervention trials. AMSTAR score: 7/11 | Prostate cancer survivors. | RT, AT or RT + AT. Intensity: Moderate to vigorous. Frequency: 2-5 d/wk. Program duration: 8-25 wk. | Not described. | function scales: Social well-being (ES: 0.22) physical functioning (ES: 0.44) and emotional function (ES: 0.71). Significantly improved symptom or single-item symptom measures were 0.47 or below (insomnia and appetite loss). Fatigue (ES: 0.33-1.5). Resistance training: Grade A evidence for improves fatigue, QOL and muscle endurance. Grade C for body composition impact, muscle strength and general function. Aerobic training: Grade B evidence for aerobic endurance, sit to stand time, fatigue, QOL. Grade C evidence for body composition and strength. RT + AT Grade B evidence for muscle mass, muscle strength and endurance, walk speed, QOL. Grade C evidence for aerobic endurance, and fatigue. |
| Kwan et al 2011 [40] | Thirteen RCTs. Two case series. Four cohort studies. AMSTAR scores: 7/11 | Breast cancer survivors. | RT or RT + AT. Intensity: Low to moderate. Frequency: 2-3 d/wk. Program duration: Up to 39 wk. Also included physiotherapy directed programs. | Usual care. | RT is safe and does not increase risk of lymphedema in breast cancer. AT + RT trends towards positive but results are inconclusive due to limited studies. |
| Larkin et al 2014 [41] | Five interventional trials. AMSTAR score: 9/11 | Prostate cancer survivors on androgen deprivation therapy (ADT) and/or radiation therapy | Mix of RT, AT, and RT + AT. Program duration: 8-16 wk. | Not described. | Significant effect of exercise on reducing fatigue. |
| Löf et al* 2012 [42] | Nine RCTs. AMSTAR score: 3/11 | Breast cancer survivors mostly early stage. | Tai chi, AT, AT + RT. Intensity: Moderate. Session duration: 30-60 min. | Usual care or support group. | No conclusive evidence for positive effect on insulin axis proteins or interleukins. |

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Table 2 (continued)

| Reference | Review Characteristics | Participants | Intervention | Comparison | Outcomes |
|-------------------------|--|---|---|---|---|
| McNeely et al 2006 [43] | Fourteen RCTs. High risk of blinding bias in methodology and reporting. AMSTAR score: 9/11 | n = 717 Women with a history of breast cancer stage 0-III. Surgery ± adjuvant treatment. | Frequency: 3-5 d/wk. Program duration: 8-36 wk. Mixed AT + RT and AT alone. | Placebo, controlled comparison, or standard care. | QOL: Significant improvement using FACT-B (6.62, 95% CI 1.21-33.64). Endurance: Significant improvement in peak oxygen consumption. Body composition: Nonsignificant reduction in body weight and BMI. Fatigue: Significant improvement with exercise after active treatment with moderate effect size (SMD = 0.46, 95% CI 0.23-0.70). but not significant during active treatment (SMD = 0.28, 95% CI -0.02 to 0.57). |
| McNeely et al 2010 [44] | Total of 24 RCTs evaluating interventions for breast cancer-related upper limb dysfunction. *Cochrane Review AMSTAR score: 10/11 | n = 2132 Women with breast cancer receiving therapeutic exercise for upper limb recover after breast cancer treatment. | Targeted upper limb exercises, AT, RT, and mixed AT + RT. Supervised vs unsupervised exercise. Timing: Early postsurgical exercise and delayed exercise during cancer treatment. | Usual care control group. | Early vs delayed postoperative upper limb exercise: Significant increase in return to ROM postoperatively with early exercise (WMD = 10.6; 95% CI 4.51-16.6). Significant increase in wound drainage volume (SMD = 0.31, 95% CI 0.13-0.49) and in duration of drain placement (WMD 1.15, 95% CI, 0.65-1.65) with early exercise. Supervised vs unsupervised exercise: Significant improvement with physical therapy supervised exercise in shoulder ROM postoperatively (WMD = 12.92, 95% CI, 0.69-25.16) in shoulder function following intervention |

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|---------------------------------|--|--|---|---|---|
| Meneses-Echavez et al 2015 [45] | Nine RTCs examining impact of exercise on CRF. AMSTAR score: 9/11 | n = 772 Various types of cancer during adjuvant cancer treatment. Average time since diagnosis 8.2 mo (SD ± 10.7). Adults mean age 55.5 years (SD ± 7.2). | Supervised, multi-modal exercise interventions including AT, RT, and stretching for CRF. | Controls with no intervention. | (SMD = 0.77; 95% CI 0.33-1.21). and at 6-mo follow-up (SMD = 0.75; 95% CI 0.32-1.19). 61.3% adherence rate. Significant improvement in CRF (SMD = -0.23; 95% CI -0.37 to -0.09, P = .001). Gains maintained at average 12 wk, 24 wk, and 6 mo. Subsets - AT + RT + stretching experienced significant reduction in CRF (P = .001). - RT alone no significant improvement in CRF levels (P = .30). |
| Meneses-Echavez et al 2016 [46] | Nine trials evaluating inflammatory mediators in breast cancer patients. AMSTAR score: 9/11 | n = 478 (253 exercise/225 control). Age mean 54 ± 4 (range 49-56) Breast cancer stage 0-IIIb. Majority of patients were postmenopausal. | AT ± RT, yoga, tai chi. Program duration: Mean 19 weeks (± 13 wk). Frequency mean 3 (±1) sessions/wk. Session duration 69 (±34) min. | No exercise or "usual care." | Inflammatory markers: IL-6 Significant reduction in concentration (WMD = -0.55 pg/mL, 95% CI -1.02 to -0.09). Tumor necrosis factor α Significant reduction in concentration (WMD = -0.64 pg/mL, 95% CI -1.21 to -0.06). IL-8 Significant reduction in concentration (WMD = -0.49 pg/mL, 95% CI -0.89 to -0.09). IL-2 Significant reduction in concentration (WMD = 1.03 pg/mL, 95% CI 0.04-1.67). CRP No significant effect. IL-10 No significant effect. HRQOL: Overall improvement with exercise from baseline to 12-wk follow-up (SMD = 0.33, 95% CI 0.12-0.55). Improvement at 12 wk in Physical functioning (SMD = 0.69, 95% CI 0.16-1.22). |
| Mishra et al 2012 [47] | A total of 56 RCTs or quasi-randomized trials evaluating the effectiveness of exercise on HRQOL and HRQOL domains. *Cochrane Review AMSTAR score: 9/11 | n = 4826 Various types of cancers both during and after active cancer treatment. | Mode: Walking, cycling, RT, strength training, mixed AT + RT, yoga, and Qigong. | Controls with no exercise intervention, or education only as an intervention. | Overall improvement with exercise from baseline to 12-wk follow-up (SMD = 0.33, 95% CI 0.12-0.55). Improvement at 12 wk in Physical functioning (SMD = 0.69, 95% CI 0.16-1.22). |

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Table 2 (continued)

| Reference | Review Characteristics | Participants | Intervention | Comparison | Outcomes |
|-------------------------|---|--|--|--|---|
| | | | | | <p>Role function (SMD = 0.48, 95% CI 0.07-0.9).</p> <p>Social function.</p> <p>Improvement at 6 mo in physical functioning.</p> <p>Fatigue:</p> <p>Significant difference in fatigue levels favoring the exercise group at 12 wk.</p> <p>Subset disease state:</p> <p>Breast cancer:</p> <p>Significant reduction in anxiety as compared with other cancer types.</p> <p>Cancers other than breast:</p> <p>Greater reduction in depression, fatigue, sleep disturbance as compared with breast cancer.</p> <p>Greater improvement in HRQOL, emotional wellbeing, physical functioning, and role function as compared with breast cancer.</p> <p>Subset exercise intensity:</p> <p>Greater improvements in HRQOL and physical functioning, and significant reductions in fatigue, anxiety, and sleep disturbance with moderate or vigorous exercise versus mild or none.</p> |
| Mustian et al 2017 [48] | <p>Total of 113 trials comparing exercise, psychological, and pharmaceutical interventions to treat CRF.</p> <p>AMSTAR score: 11/11</p> | <p>n = 11,525</p> <p>Various types of cancer.</p> <p>78% female</p> <p>22% male</p> <p>Mean age 54 y (range, 35-72 y).</p> | <p>AT, RT, and mixed AT + RT.</p> <p>Program duration:</p> <p>Average 43 sessions (range = 1-364) over 14 wk (range = 1-60 wk).</p> <p>Session duration:</p> <p>Average 60 min (range = 16-150).</p> | <p>68% used standard care, no intervention or wait-list control.</p> <p>31% used placebo, time attention or education control.</p> | <p>Significant moderate improvement in CRF from pre- to posttreatment with exercise intervention (WES = 0.30; 95% CI 0.25-0.36, $P < .001$).</p> <p>and with psychological intervention (WES = 0.27; 95% CI 0.21-0.33; $P < .001$).</p> <p>and with exercise + psychological intervention (WES = 0.26; 95% CI 0.13-0.38; $P < .001$).</p> |

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|----------------------|--|---|---|----------------------------|--|
| Otto et al 2015 [49] | Seven observational studies examining self-reported levels of PA and impact on QOL and survival. AMSTAR score: 10/11 | n = 4487 colorectal cancer patients (2089 examining QOL end points and 2398 examining survival end points). Self-reported change in physical activity during cancer treatment. | Patient self-reported recall regarding levels of physical activity prediagnosis, during treatment, and posttreatment. Variety of patient-reported outcomes measures used to quantify level of PA. Assessment time points varied among trials. | None | Exercise, psychological, exercise + psychological interventions were superior to pharmaceutical interventions in improving CRF. QOL: Increasing levels of PA during or post treatment associated with improved QOL (SMD = 0.74, CI 0.66-0.82). Survival: Increasing physical activity levels postdiagnosis improved survival. (HR = 0.70, 95% CI 0.55-0.85). (Weight gain did not affect disease-related mortality.) Depression: Significant improvement for yoga cohort. (SMD = -0.17, 95% CI -0.32 to -0.01; P = .00). Anxiety: Significant reduction for yoga cohort. (SMD = -0.98, 95% CI: -1.38 to -0.57; P < .00). Physical well-being No significant improvement for yoga cohort. (SMD = 0.23, 95% CI -0.04, 0.52; P = .10). Overall HRQOL: Significant improvement for yoga cohort. (SMD = 0.85, 95% CI 0.37-1.34; P = .001). Fatigue: No significant reduction in yoga cohort. (SMD = -0.22, 95% CI -0.53 to -0.09; P = .17). Sleep quality: No significant improvement in yoga cohort (SMD = -0.19, 95% CI -0.39-0.00; P = .05). |
| Pan et al 2015 [50] | Sixteen RCTs AMSTAR score: 6/11 | n = 538 yoga/493 control Breast cancer patients stage 0-III. ± hormonal therapy | Supervised, guided yoga interventions. Program duration: Average 3 wk to 6 mo. Session frequency: Average 1-3 session(s)/wk. Session duration: Average 60-90 min. Yoga interventions included: - Integrated yoga program - Iyengar - Modified yoga - Restorative - Mindfulness - Viniyoga - Hatha - Yoga Sutras | Wait-listed control group. | |

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Table 2 (continued)

| Reference | Review Characteristics | Participants | Intervention | Comparison | Outcomes |
|------------------------|---|--|---|------------|---|
| Schmid et al 2014 [51] | <p>A total of 23 prospective longitudinal studies.</p> <p>Sixteen studies breast cancer. Seven studies colorectal cancer.</p> <p>AMSTAR score: 9/11</p> | <p>n = 49,095</p> <p>Breast and colorectal cancer patients self-reported levels of physical activity prediagnosis, during cancer treatment, and postdiagnosis.</p> | <p>Patient self-reported level of physical activity converted to METS.</p> <p>Used pooled RRs to compare high vs low categories of PA at each time point.</p> <p>Duration/intensity: Estimated at 150 min of moderate physical activity per week.</p> | | <p>Gastrointestinal symptoms</p> <p>Significant improvement in yoga cohort (SMD = -0.09, 95% CI -0.64, 0.46; $P = .74$).</p> <p>Duration of Intervention</p> <p>Significantly improved effects with yoga program duration of > 3 mo. (SMD = 0.40, 95% CI 0.00-0.79; $P = .04$).</p> <p>Breast cancer survivors:</p> <p>High vs low PA prediagnosis: Associated with decreased risk of total mortality (RR = 0.77; 95% CI 0.69-0.88). and decreased risk of disease mortality (RR = 0.77); 95% CI 0.66-0.90).</p> <p>Each 5, 10, or 15 MET-h/wk increase from prediagnosis PA level was associated with 7%, 13%, or 19% reduced mortality.</p> <p>High vs low PA postdiagnosis: Associated with decreased risk of total mortality (RR = 0.52; 95% CI 0.42-0.64). and decreased risk of disease mortality (RR = 0.72; 95% CI 0.60-0.85).</p> <p>Each 5, 10, or 15 MET-h/wk increase in postdiagnosis PA levels was associated with 13%, 24%, or 34% reduced mortality.</p> <p>Colorectal cancer survivors:</p> <p>High vs low PA prediagnosis Associated with decreased risk of total mortality (RR = 0.74; 95% CI 0.63-0.86). and decreased risk of disease mortality (RR = 0.75; 95% CI 0.62-0.91).</p> <p>Each 5, 10, or 15 MET-h/wk increase in prediagnosis PA levels was associated with 7%, 14%, or 20% reduction in total mortality.</p> |

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|------------------------------|---|--|---|--|---|
| Scott et al 2013 [52] | 12 RCTs. AMSTAR score: 4/11 | n = 1669 Various types of cancers. All participants had completed primary cancer treatments. | MDRP: Inclusive of a physical (exercise, dietary regime) and psychosocial (counseling, cognitive behavior therapy) component carried out on 2 or more occasions. Individual supervised. Group supervised. Unsupervised. | No intervention or lower-level intensity program, or different mode of administration. | High vs low PA postdiagnosis Associated with strong risk reduction for total mortality (RR = 0.58; 95% CI 0.48-0.70). and colorectal cancer mortality (RR = 0.61; 95% CI 0.40-0.92). Each 5, 10, or 15 MET-h /wk increase in postdiagnosis PA levels was associated with a 15%, 28%, or 38% lower risk of mortality. Significant improvement in the SF-36 physical health component score (mean difference = 2.22; 95% CI 0.12-4.31, P = .04). MDRP most successful when focusing on one behavior area (exercise or stress management) rather than focusing on several different behaviors at the same time. Significant improvements noted in supervised vs unsupervised settings, but the type of provider delivering services had no impact on improvements. Maximum benefit to MDRP was noted by 6 mo. Pulmonary function: Significant increase postoperatively in FEV ₁ (SMD = 0.27, 95% CI 0.11-0.42). and in FVC (SMD = 0.38, 95% CI 0.14-0.63). Trend towards significance in VO ₂ peak. Improvement noted but pooled effects were not possible. Functional recovery: Significant reduction in postoperative hospital length of stay (mean difference = -4.83, 95% CI -5.90 to -3.67). |
| Sebio Garcia et al 2016 [53] | Twenty-one controlled trials evaluating the impact of pre-operative exercise interventions. AMSTAR score: 8/11 | n = 1189 (595 intervention/ 594 controls). Lung cancer stage I-IIIa during adjuvant or neoadjuvant treatment. 62% male Average age 64.8 y (±5.28)/ 64.3 y (±6.3) | Outpatient-based exercise programs. AT, RT, or mixed AT + RT with or without breathing or incentive spirometry intervention. Duration: Average 4 wk (range = 1-10 wk) Intensity: Moderate to vigorous | No exercise | |

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Table 2 (continued)

| Reference | Review Characteristics | Participants | Intervention | Comparison | Outcomes |
|---------------------------|---|--|--|--|---|
| Shneerson et al 2013 [54] | Five RCTs evaluating the effect of yoga. Four of five studies had high risk for selection and outcome reporting bias. AMSTAR score 7/11 | n = 66 Breast cancer, after completion of active treatment. Age range 50-63 y | Yoga programs: 3 trials of hatha 1 trial restorative 1 trial Iyengar) Program duration: 7 wk to 6 mo. Frequency: At least twice a week. Session duration: 1-1.5 h. | All RCTs, with wait-list controls. | Significant reduction in postoperative complications (RR = 0.45, 95% CI 0.28-0.73). HRQOL: No significant improvements. Breathing exercises: No evidence to support that adding breathing exercises or incentive spirometry provides additional benefit. Very small effect sizes overall. QOL: Improved in only 1 study vs controls. Emotional subscale of FACT-B improved in only 1 study (ES 0.51, 95% CI 0.18-0.84) for overall QOL at 3 mo, no difference at 6 mo. Physical QOL no difference at 3 mo. Mental QOL better than controls at 3 months (ES 0.46, 95% CI 0.14-0.77). |
| Singh et al* 2013 [55] | 18 controlled trials evaluating prehabilitation or pre-operative exercise programs. (10 RCTs) AMSTAR score: 7/11 | n = 966 Lung, prostate, abdominal and GI cancers receiving exercise training or intervention before surgery. Age range 54.1 y (±8.53) to 71.1 y (±6.3) | AT, RT, and mixed forms AT + RT ± muscle re-education exercises. Supervised and unsupervised programs. Timing of intervention before surgery: Median 21 days (range = 7-52 d). Frequency: 5-7 times/wk. Intensity: Aerobic: range 40%-80% max capacity. Resistance: 60%- 80% 1RM or repetitions as a proxy for intensity. Session duration: 15 min to up to 3 h/session. | Education-only or No intervention or Different training program. | Functional walking capacity: Trend towards significance, only 2 studies showed significance. Pooled effects not calculated. Cardiorespiratory fitness: Significant increases (8%-32%). Pooled effects not calculated. QOL: Mixed results. Significant variability in measurement tools prevented pooled calculations. Three of five studies measuring QOL showed no improvement. Rate of return to continence: Trend towards significance, study heterogeneity prevented pooled calculations. |

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|------------------------|--|--|--|---|--|
| Smits et al* 2015 [56] | Eight controlled trials (3 RCTs). AMSTAR score 7/11 | n = 413 Endometrial and ovarian cancers. After completion of active cancer treatment. | Predominately walking, and unspecified physical activity home-based program. Program duration: 4 wk to 6 mo. Frequency: 5 times/wk. Session duration: 30 min. 80% had combined exercise AT+RT programs. Mode was primarily AT. Intensity: Not specified. Assessed frequency during vs after treatment. Program duration: Most interventions > 5 wk. Session frequency: Average 3-5 times/wk. | Mixed controlled and single-arm trials. Comparisons not specified. | Length of hospital stay: Significant improvements noted, pooled calculations not possible. Endurance: 12-min walk and aerobic capacity improved at 3 and 6 mo postintervention. Strength: Improved at 6 mo. QOL: No improvement noted at 3 or 6 mo. |
| Speck et al 2010 [57] | Total of 82 studies. A total of 66 of 82 "high-quality" controlled studies included in meta-analysis. AMSTAR score 7/11 | n = 6838 Breast (83%), colon, lung, ovarian, leukemia, lymphoma, prostate, sarcoma, stomach, testicular, and other cancer types. 40% during active cancer treatment. 60% posttreatment. | 80% had combined exercise AT+RT programs. Mode was primarily AT. Intensity: Not specified. Assessed frequency during vs after treatment. Program duration: Most interventions > 5 wk. Session frequency: Average 3-5 times/wk. | All studies included comparison groups but were unspecified. | Exercise during active cancer treatment: Significant WMES improvement in Overall physical activity level (0.38, $P = .001$). Aerobic fitness (0.33, $P = .009$). Upper body strength (0.39, $P = .005$). Lower body strength (0.24, $P = .006$). Body weight (-0.25, $P = .05$). Body fat percentage (-0.25, $P = .04$). Functional QOL (0.28, $P = .04$). Positive mood (0.39, $P = .002$). Anxiety (-0.21, $P = .02$). Self-esteem (0.25, $P = .02$). No significant adverse effects were reported (eg, blood counts). Exercise after completion of cancer treatment: Significant WMES improvement in Physical activity level (0.38, $P < .0001$). Aerobic fitness (0.32, $P = .03$). Upper body strength (0.99, $P < .0001$). Lower body strength, (0.90, $P = .024$). Body weight (-0.18, $P = .004$). Body fat percentage (-0.18, $P = .006$). BMI (-0.14, $P = .002$). Overall quality of life (0.29, $P = .03$). |

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Table 2 (continued)

| Reference | Review Characteristics | Participants | Intervention | Comparison | Outcomes |
|----------------------------|--|---|--|--|--|
| Spence et al* 2010 [58] | Ten studies (4 RCTs, 3 controlled nonrandomized, 2 intervention, noncontrolled, 1 single group design) AMSTAR score 8/11 | n = 483 Four trials included breast cancer only. Three trials included mostly breast cancer. Two trials included only colorectal cancer. Age range 16-71 y. | AT and RT Program duration: 2-26 wk. Intensity: Moderate. Frequency: 3 times/wk during "rehab period" up to 12 mo after adjuvant treatment. | Current activity Stretching 3 trials with no comparison group. | Breast cancer-specific concerns (0.62, $P = .003$). Perception of physical condition (0.57, $P = .04$). Mood disturbance (-0.39, $P = .04$). Confusion (-0.57, $P = .05$). Body image (-0.26, $P = .03$). Fatigue (-0.54, $P = .003$). General symptoms and side effects (-0.30, $P = .03$) IGF-1 (-0.31, $P = .03$). Physical function and endurance: Significantly improved VO ₂ peak and strength. Fatigue: Reduced. Physiological biomarkers: Trend towards improvement but somewhat mixed. Improvements immune cell function, lower reported neutropenia, lower inflammatory markers. Modest improvements in body composition. Immune function: Significant improvement in NK cell activity. Lower antagonist/cytokine ratio at end of program vs controls. (Initially exercise induced a decrease in NK cell activity.) During cancer treatment: QOL was modestly improved or no change was identified. Fatigue modestly improved. Physical function improved. After cancer treatment: Consistent improvement in QOL. No significant difference for fatigue levels. Mixed results on endurance measures (6MWD, VO ₂ peak). |
| Steel et al* 2014 [59] | Two studies. Both trials in hospital-based settings immediately after surgery. AMSTAR score 8/11 | n = 58 GI cancers primarily stomach and colorectal. | Arm and leg cycling exercises. Intensity: Moderate. Frequency: 5 times/wk. Program duration: 2 wk. Session duration: 40 min. | Lower intensity exercise or no exercise controls. | |
| Van Dijck et al* 2016 [60] | Thirteen RCTs. AMSTAR score 4/11 | n = 2180 Breast cancer patients during and after cancer treatment. | AT Program duration: 1-12 mo. Unspecified duration, intensity, and frequency. Primarily unsupervised (as part of "physical self-management" program). | Usual physical activity, usual care or written materials | |

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|--------------------------------|---|---|--|--|---|
| van Vulpen et al 2016 [61] | 5 RCTs (784 patients). High risk of performance and attention bias. AMSTAR score 8/11 | n = 784 Breast cancer patients during adjuvant cancer treatment. (defined as either chemotherapy or radiation therapy). Mean age 50-56 y. | RT and AT. Session frequency: 2-5 times/wk. Session duration: 30-60 min. Intensity: AT: Moderate. RT: >60% of 1RM. Supervised. | Usual care or sham. | Fatigue: Small-to-medium effect sizes (ES 0.20-0.50) for general fatigue and physical fatigue improvements vs controls during chemotherapy. No significant effect on cognitive fatigue. Supervised programs had larger effect sizes than unsupervised. |
| Visser et al* 2014 [62] | Five studies (2 prospective cohort, 2 retrospective cohort, 1 case control). AMSTAR score 7/11 | n = 321 Rectal cancer Mean age 55-67 y | Pelvic floor and core muscle training. Program duration: 7-15 sessions. Supervised. 50% AT. 50% RT. Program duration: 12-52 wk. Session frequency: 2-7 times/wk. Intensity: Predominately moderate. 50% supervised. 50% unsupervised. | Two trials pre-post comparison. Three trials compared with no rehabilitation. | QOL: Significantly improved. Improved incontinence and pelvic floor muscle function. |
| Winters Stone et al* 2010 [63] | Eight studies investigating impact of exercise on bone density (5 RCT, 5 uncontrolled intervention). AMSTAR score 9/11 | n = 567 Seven trials breast. One trial prostate. During survivorship period. Mean age range 48 - 55 y. | 50% AT. 50% RT. Program duration: 12-52 wk. Session frequency: 2-7 times/wk. Intensity: Predominately moderate. 50% supervised. 50% unsupervised. | Usual care or drug therapy without exercise. | Most exercise groups maintained BMD while controls experienced decline in levels of BMD. Modest increase in BMD in some exercise groups. Trend towards positive improvement in BMD with exercise. |
| Zhu et al 2016 [64] | Total of 33 RCTs. Moderate allocation and reporting bias. AMSTAR 7/11 | n = 2659 Breast cancer survivors. | AT with or without RT, tai chi, yoga. Frequency and duration not reported. | Usual care, wait-list, brief supportive therapy. | Significant improvement in QOL ($I^2 = 0\%$, $P = .006$, 95% CI 0.11-0.62). General health ($I^2 = 95\%$, $P = .02$, 95% CI 0.70-8.48). Emotional well-being ($I^2 = 2\%$, $P = .0006$, 95% CI 0.12-0.43). Social well-being ($I^2 = 0\%$, $P = .01$, 95% CI 0.19-1.69). No significant improvement in fatigue. Muscle strength significantly improved. ($I^2 = 48\%$, $P = .0009$, 95% CI 1.76-6.78). BMI significantly improved ($I^2 = 0\%$, $P = 0.00001$, 95% CI -1.09, -0.47). Significant reduction in Insulin ($I^2 = 95\%$, $P = -0.05$, 95% CI -13.64 to 0.06) and IGFBP-1 ($I^2 = 46\%$, $P = .00001$, 95% CI -4.40, to 1.91). |

(continued on next page)

Table 2 (continued)

| Reference | Review Characteristics | Participants | Intervention | Comparison | Outcomes |
|-------------------------|--|---|--|--|--|
| Zimmer et al* 2016 [65] | Fourteen studies (6 RCTs, 1 non-randomized, 2 prospective non-controlled, 1 case series, 1 observational study, 3 cross-sectional studies). AMSTAR score 7/11 | Mostly breast and some prostate cancer survivors. | 11 trials yoga of various forms. 1 trial AT. 1 trial RT. 1 trial tai chi. Program duration: 4 wk to 6 mo. Session frequency 1-3 times/wk. Session duration: 60-90 min. | Most with no comparison group. 2 trials with usual care comparison. | Cognitive function: Significant improvement with yoga. Significant improvement with other exercise types (AT, RT, and tai chi). Inflammatory markers: Profile improved in both yoga and other exercise groups. |

AMSTAR = A Measurement Tool to Assess Systematic Reviews; PA = physical activity; BMI = body mass index; QOL = quality of life; RCT = randomized controlled trial; ALL = acute leukocytic leukemia; AML = acute myeloid leukemia; AT = aerobic training; SMD = standard mean difference; CI = confidence interval; RR = risk ratio; RT = resistance training; ROM = range of motion; GU = genitourinary; GI = gastrointestinal; GYN = gynecologic; PRE = progressive resistive training; VO2max = maximal oxygen consumption; IFN = interferon; IL = interleukin; IGF = insulin-like growth factor; ADT = androgen deprivation therapy; SF-36 = Short Form-36; HRQOL = health-related quality of life; 6MWD = 6-minute walk distance; FBG = fasting blood glucose; IGFBP = insulin-like growth factor binding protein; PSA = prostate-specific antigen; ES = effect size; WMD = weighted mean difference; WES = weighted effect size; CRF = cancer-related fatigue; SD = standard deviation; HR = hazard ratio; MET = metabolic equivalent of task; MDRP = multidimensional rehabilitation program; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; RM = rep max; WMES = weight mean effect size; NK = natural killer; BMD = bone mineral density.
* ES calculations not provided in the review.

completion of cancer treatment, but the effect of exercise has greater impact on CRF during treatment [35,54,60]. This suggests that the timing of the intervention is important in the context of individual factors, including cancer type [47,51] and adjuvant treatment phase [22,43,49,60].

A small number of systematic reviews explored pre-treatment or prehabilitation exercise interventions [35,53,55,62]. The prehabilitation and presurgical exercise reviews demonstrated improvements in adherence to exercise, tolerance to active cancer treatment specifically to chemotherapy, and mitigation of functional decline after the initiation of active cancer treatment [53,55]. The concept of prehabilitation is relatively new in oncology rehabilitation practice, and although the body of evidence is maturing, a robust systematic review has not yet been conducted to inform broad intervention recommendations. The existing qualitative reviews identified improvements in meaningful endpoints related to posttreatment functional recovery [55,62] and demonstrated reductions in postoperative hospital length of stay [53,55], postoperative complications [53], and return to preoperative functional status [55].

Numerous reviews highlighted the benefits of exercise programs during active cancer treatment with notable positive impact on a variety of side effects of cancer treatment, including CRF [16,20,25,27,28,38,41,45,47,48,60,61], depression [16,25,38,47], anxiety [25,38,47], sleep [47], HRQOL [16,20,24,25,35,47,52,57,60], and physical function [16,20,22,35,47,52,60]. In addition, support for early targeted therapeutic exercises to alleviate impairments of specific body structures and function was identified for upper limb and shoulder in both the breast and head and neck cancer populations [20,21] as well as for the pelvic floor in the gynecological and prostate cancer populations [62]. These reviews support early therapeutic exercise to restore upper limb range of motion [21,23,44] and to prevent or reverse incontinence [62].

Importantly, 2 reviews noted no adverse events associated with blood counts when the exercise intervention was undertaken during active cancer treatment [16,57]. In addition, several reviews cited improved immune function [22,46] and tolerance to chemotherapy [22] with exercise during cancer treatment. Reviews suggest that timing of exercise interventions should consider the phase of treatment to maintain blood counts [16,32,47]. This may be beneficial to improving tolerance to treatment and may mitigate the risk for adverse events related to blood counts such as neutropenia and thrombocytopenia.

Several reviews identified no adverse events associated with either the onset or progression of lymphedema as a result of exercise interventions both during and after breast cancer treatment [18,23,30,34,40,44,57].

Cancer Type

The majority of reviews examined exercise across various types of cancer and demonstrated overall positive results from exercise regardless of the primary cancer diagnosis [17,19,26,27,28,30-32,45,47,48,52,51,55,57,65]. Some reviews provided breakout comparisons that demonstrated slightly different nuanced outcomes from exercise interventions based on the type of cancer [47,51]. For example, one report identified that patients with breast cancer experienced greater reduction in anxiety with exercise compared with other cancer types but made notably fewer gains in physical functioning and role function compared with other cancer types [47]. Table 3 outlines the clinical implications of exercise across different types of cancer.

Cancer Treatment–Related Side Effects and Functional Impairments

Systemic and local antineoplastic treatments often include similar treatment modalities, chemotherapeutic drugs, and polypharmacy administered in different doses and combinations based on the disease and disease severity introducing anticipated side effects that contribute to greater risk for cardiovascular and neuromuscular impairments. Several reviews focused on the effect of exercise on a single physical impairment [34,40,45,48,63], whereas the majority aggregated findings and provided subanalyses data on specific impairments.

Cancer-Related Fatigue

CRF was the most commonly identified physical impairment in systematic reviews examining the impact of exercise in the cancer population. The evidence presented in these reviews overwhelmingly supports a significant benefit from exercise in reducing CRF [16,18,20,25,27,28,31,32,35,38,41,45,47,48,57,58,61]. Two reviews reported greater magnitude of effect from exercise during active cancer treatment than after [43,60]. Yoga interventions demonstrated mixed results regarding impact on CRF [25,50,65].

Most notably a recent, large, high-quality systematic review by Mustian et al [48] identified exercise as the most impactful intervention to reduce CRF compared with pharmaceutical intervention or psychological intervention alone. The elements of effective exercise programs identified by Mustian et al averaged 14 weeks in duration with 60-minute average session length and included aerobic, resistive, and mixed aerobic and resistive forms of exercise.

Physical Fitness

Exercise interventions demonstrated a strong positive impact on physical fitness measures, including peak oxygen consumption [28,32,43,58,60], aerobic exercise

tolerance [17,53,56], peak power [28,32], strength [20,22,30,32,39,56,57], flexibility [22], and various measures of cardiorespiratory fitness [22,26,28,30,55,57]. These trials included aerobic, resistance, and mixed forms of exercise interventions, with the majority of positive outcomes and larger effects associated with moderate-to-vigorous exercise intensity.

Psychological Function

Reviews demonstrated variable impact of exercise on psychological functioning and ranged from positive benefits [22,25,32,38,50,57] to inconclusive [16,24,31] results regarding mood, depression, and anxiety. Rationale for the disparity in findings among was attributed to the use of varied and disparate measurement tools in the trials of interest [24,25]. Cognitive improvements with exercise also were reported to be absent or only moderate in effect, although the volume of studies that included cognitive outcomes were more limited in our sample [61,65].

Physical Function

Measures of physical function were positively impacted by exercise interventions [16,20,31,47,52,55,58,60]. The outcome measures varied widely among studies and included positive gains in measures of endurance and general physical function [16,30,32,35,53,56,60]. Therapeutic exercises that targeted restoration of function in specific body regions, including flexibility and PREs for the upper extremity [21,23,44] and pelvic floor strengthening, were beneficial [62].

Body Composition

Reviews regarding the impact of exercise on various measures of body composition varied in the type of measures used as well as the body tissue compartment measured (eg, fat, lean mass, bone mass, etc). BMI and body weight ranged from positive impact from exercise [28,57] to mixed results from exercise [32,35,36] to null findings [19,30,43,58]. Weight gain was not found to impact mortality in one cohort study [49]; however, subset analysis by one review suggested that individuals with greater BMI experienced less benefit from exercise interventions in both physical and psychosocial measures [57]. Disparity was reported in the use of measures of adiposity as well as in measurement methodology which may account for the variation in findings. Exercise positively impacted lean mass [20,22] and weak evidence supported benefits of exercise on bone mineral density [63].

QOL and HRQOL

QOL and HRQOL were defined and delineated by the specific research report reviewed and based on the measurement tools used in the trial. Generally, the impact of exercise on both QOL and HRQOL measures

Table 3
Findings by cancer type

| Review Synopsis | Intervention | Average Duration | Clinical Pearls |
|---|--|--|--|
| Breast cancer | | | |
| Total of 33 trials, 25 trials postcompletion of cancer treatment and 8 during cancer treatment | 11 trials with aerobic exercise only 8 trials with aerobic and resistance components 1 trial resistance exercise only | 16 wk | Exercise across all groups improved QOL and reduced insulin, IGF-II, and IGF-I. |
| Total of 24 trials | Therapeutic exercise for upper limb: aerobic, resistive, and mixed 4 trials were supervised by a physiotherapist | Early vs delayed exercise Early = postoperative day 1 to day 3 Late = postoperative day 4 or later | Early exercise is beneficial but may increase time to wound healing. Concerns raised that studies may overestimate wound protection from delayed exercise. Significant improvement with supervised vs unsupervised. |
| Total of 24 trials during or after treatment | Yoga | Total = 1205 min | Improvements in QOL, depression, anxiety and fatigue, and GI symptoms. |
| Total of 18 trials during or after treatment | Yoga | (frequency × duration of session × duration of treatment) | Improvements in mood and QOL. |
| Total of 16 trials | Yoga | Median = 8 wk Mean = 9 wk Mean = 9.8 wk | *Significant improvement when duration of yoga >3 mo. |
| Total of 14 trials | 6 aerobic and resistance 1 resistance alone 1 tai chi 9 trials conducted in supervised settings | 13 wk | Improvements in peak oxygen consumption and QOL. Improvement in cancer-related fatigue with exercise after cancer treatment was completed. |
| Total of 13 trials; 8 trials during cancer treatment 5 after completion of cancer treatment | Predominately aerobic exercise, some with walking program as recommended exercise intervention Intensity: moderate to vigorous in 3 studies | 1-12 mo | Improvements in fatigue, endurance, physical function, and QOL. *Threshold identified for seated exercise: >3-mo exercise duration may have more significant effect on outcomes. |
| Total of 13 trials all conducted exercise after completion of cancer treatment | 7 resistance exercises only 2 weight lifting 1 moderate-intensity progressive resistive exercise, supervised 2 ROM and strength supervised by physiotherapist 1 supervised by exercise trainer | 30 wk (including supervised and unsupervised portions) | Resistance training is safe in breast cancer survivors and does not increase the risk of lymphedema. Education for unsupervised exercise supported adherence after supervised portion of program. |
| Total of 10 trials during or after cancer treatment | 9 aerobic and resistance 1 trial resistance only | 14 wk | Progressive resistance exercise may improve endurance, strength, flexibility, lean mass, cardiorespiratory fitness, immune system, mood, self-esteem, and chemotherapy dose tolerance. |
| Total of 9 trials conducted after cancer completion of cancer treatment | 8 of 9 trials had at least one supervised exercise component. 4 aerobic and resistance 4 aerobic (1 with weight belt) 1 progressive resistive exercises | 16 wk | 24 wk of aerobic or resistance training may decrease body fat. Aerobic training may decrease IGF-I and resistance training may decrease IGF-II. |

| | | | |
|--|--|-----------------------------------|---|
| Total of 9 trials | 4 aerobic and resistance combined 3 aerobic alone 1 weight training alone 1 tai chi | 19 wk | Exercise may favorably affect insulin levels in obese or sedentary women. *Tamoxifen was found to lower IGF levels; it was inconclusive as to whether exercise impacts this effect. |
| Total of 2 trials conducted within 5 years of treatment | Dance and movement therapy | Total program duration = 1035 min | May benefit QOL in survivors. |
| Gastrointestinal cancers Total of 5 studies | 4 pelvic floor muscle retraining and activation with biofeedback and/or rectal balloon 1 pelvic floor muscle and movement exercise. | 8 wk | Improvements in QOL and reduced incontinence rates in exercise group. |
| Total of 5 studies all after completion of cancer treatment | 2 home-based aerobic exercise programs 1 supervised high-intensity aerobic 1 supervised moderate intensity aerobic 1 partial supervised aerobic and resistance | 9 wk | Improvements in short-term physical fitness. Supervised participants demonstrated greater adherence. |
| Total of 2 studies after completion of cancer treatment | 1 arm and cycle ergometers twice daily, 5 d/wk 1 individualized moderate intensity exercise (40 min) daily | 2 wk | Improvement in immune function overall. Initially exercise induced a decrease in natural killer cell activity in the first week and improvement was noted after the second week. *Only 2 wk of exercise may favorably affect immune function. |
| Head and neck cancers | | | |
| Total of 8 of 24 trials during or after completion of cancer treatment | 4 resistance exercise 1 walking program 1 brisk walking and active exercises 1 hydrotherapy 1 aerobic and resistance | 9 wk | Improvements in lean body mass, strength, physical function, QOL, and fatigue. 75% of patients reported “possibly” or “definitely” interested in physical activity counseling after completion of the trial. |
| Total of 3 trials acutely after cancer surgery | Progressive resistive exercise with ROM and stretching Supervised initially and educated for unsupervised following initial therapy | 3 times/wk for 12 wk | Progressive resistive training was more effective than standard physiotherapy stretching for shoulder dysfunction in head and neck cancer. |
| Endometrial and ovarian cancers | | | |
| Total of 8 trials during and after completion of cancer treatment | 3 multimodal, including exercise intervention and nutrition counseling, education for health behaviors, and cognitive therapies 2 multimodal, including only physical activity and nutrition counseling 1 walking program 1 physical activity program 1 dietary intervention and education alone | 17 wk | Improvements in fatigue, cardiovascular fitness, strength, and physical function Improvements in weight (in multimodal studies when nutrition intervention was provided). |

(continued on next page)

Table 3 (continued)

| Review Synopsis | Intervention | Average Duration | Clinical Pearls |
|--|--|--|--|
| Total of 7 trials after completion of cancer treatment | 5 studies reported only cross-sectional self-report of physical activity levels | Self-reported "moderate intensity" exercise defined as: at least 150 min/wk at least 30 min/d, 5 d/wk Intervention with computer/accelerometer and intervention with computer/mobile app to support supervised contact 3 studies: "60 minutes strenuous or 150 minutes moderate exercise weekly" 3 studies: "moderate intensity exercise for at least 30 minutes per day, 5 days per week" 1 study: moderate-intensity cardiorespiratory exercise training ≥ 150 min/wk or vigorous exercise for ≥ 40 min/wk, and resistance exercises for major muscle groups | Increased physical activity can contribute to improved QOL. Greater benefit seen in the obese/overweight population. |
| Prostate cancer Total of 12 trials after completion of cancer treatment | Primarily aerobic exercise training 7 group-based programs and 5 home-based programs 5 study groups included resistive exercise 4 home-based programs also included some group intervention | 17 wk | Resistance training may improve fatigue, QOL, and muscle endurance. Aerobic training may improve endurance, sit to stand, fatigue, and QOL. Combined forms of exercise may improve muscle mass, muscle strength and endurance, walk speed, and QOL. *Group-based training programs were overall more effective than home-based programs. Exercise may improve QOL. |
| Total of 7 trials during androgen deprivation therapy administration | 6 trials included exercise interventions: 4 aerobic and resistance exercise interventions 2 resistive training only 4 supervised programs 2 unsupervised programs | 13 wk | |
| Total of 5 trials during and after cancer treatment | 2 combined resistance and aerobic exercise training 1 resistance only 1 aerobic only 1 aerobic compared with resistance | 14 wk | Both aerobic and resistance exercise significantly mitigate cancer-related fatigue. Resistance exercise demonstrates longer-term improvement in positive outcomes and improved QOL to a greater degree. |
| Lung cancer Total of 21 trials before the initiation of cancer treatments. | 20 supervised exercise programs 1 home-based exercise programs 16 preoperative exercise programs 5 pre- and postoperative exercise programs | 4.2 wk | Improvements in postoperative pulmonary function. Reduced length of hospital stay. Reduced postoperative complications. |

| | | | |
|---|---|--|---|
| Total of 14 trials, 5 preoperative, 7 postoperative, 2 advanced disease | All trials included some form of aerobic exercise 54% included component of resistance exercise 6 conducted in an inpatient setting 6 conducted in an outpatient setting 2 home-based exercise programs | 7 wk | Exercise may improve preoperative and postoperative aerobic exercise tolerance. Exercise improves overall mortality rates in the lung cancer population. |
| Hematological cancers Total of 9 trials during cancer treatment | 3 aerobic and resistance training programs 2 walking programs 1 aerobic exercise and resistance exercise and stretching 1 aerobic exercise and resistance exercise and sensorimotor training 1 cycle ergometer and activity of daily living training program 1 cycle ergometer program alone All programs in a supervised inpatient setting | 10 wk | Improvements in physical performance and function, QOL, fatigue, and depression. No serious adverse events reported, no adverse events related to blood counts. |
| Various cancers Total of 113 trials with 53 of the trials specific to breast cancer treatment. Trials were both during and after cancer treatment | 69 studies included exercise interventions 10 studies included combined exercise and psychological interventions | Average 14 wk Average 43 sessions Average 60 min | Exercise with or without a psychological intervention improves fatigue and is superior to pharmaceuticals or psychologic intervention alone. Internet delivery was the most effective form of treatment delivery as compared with telephone, print, or in-person. Combination of 2 modalities yielded inconsistent results. |
| Total of 82 trials in breast, colon, lung, ovarian, leukemia, lymphoma, prostate, sarcoma, stomach, testicular, and other cancers | 80% of trials included aerobic exercise 60% of aerobic programs were at moderate-to-vigorous intensity 59% of programs were conducted 3-5 times/wk 40% of trials were of 30-45 min per session duration 60% of trials were conducted postcancer treatment and 40% during cancer treatment | 48% of programs were 5-12 wk in duration | Improvements in strength, fatigue, fitness, cancer-related treatment symptoms, QOL, reduced confusion, and reduction in IGF-I. Recommended duration of 8-12 wk. |
| Total of 56 trials with 28 specific to breast cancer | 37 exercise programs were supervised and institution-based 43 trials included various types of aerobic exercise: 23 general aerobic 14 walking program 6 cycling exercises 6 yoga exercises 4 trials included resistance training only 2 trials used qigong exercises 1 seated exercise program | Various | Walking and cycling significantly reduced fatigue during and after cancer treatment, especially in breast and prostate cancers. |

Table 3 (continued)

| Review Synopsis | Intervention | Average Duration | Clinical Pearls |
|---|--|---|--|
| Total of 34 trials including breast, male genitourinary, hematologic, gastrointestinal, gynecological, respiratory, and other types of cancer both during and after completion of cancer treatments | 15 programs included both resistance and aerobic components 12 programs were aerobic exercise alone 7 programs included resistance alone with or without weight bearing components | 21 wk | Improvements in HRQOL. No effect was noted on BMI. *Concern was raised that measures of adiposity were not either not used or were incorrectly used. |
| Total of 56 trials across various cancer populations | 32 trials included aerobic exercise: 22 included walking alone or in combination with another form of exercise training. 8 included cycling alone or in combination with another form of exercise training 9 yoga trials 2 qigong trails 18 programs were facility-based 18 programs included facility-based exercise and a home component 16 programs were home-based only | Modal exercise intervention of 12 wk | Improvements in HRQOL, fatigue, sleep disturbance, mood disorder, and physical function. Greater benefit with moderate or vigorous exercise. |
| Total of 34 trials: 22 breast only 3 colorectal only 1 endometrial only 8 various cancers | 27 aerobic exercise only 6 aerobic and resistive training Intensity: moderate-to-vigorous in most studies | 13 wk | Exercise significantly reduced IGF-I, BMI, and weight. Significant gains in physical function, depression, fatigue, and overall physical performance. |
| Total of 14 trials including breast, colorectal, prostate cancer populations | 6 trials aerobic exercise only 6 trials aerobic and resistance exercise 1 trial with aerobic and water and land resistance 1 with aerobic with Greek traditional dances and upper body training and cool down | Variable duration of exercise programs 4-24 wk | Improvements in overall measures of aerobic exercise tolerance and endurance. |
| Total of 14 trials primarily in the breast cancer population but inclusive of other cancer types | Yoga or yoga-type exercises, aerobic programs, resistance training, and tai chi exercises 3 physical activity alone Otherwise, 7 different interventions (physical activity behavior change) | 4 wk to 6 mo 1-3 times/wk 60-90 min | Improvements in cognitive function. Decreased levels of inflammatory markers. |
| Total of 10 trials including 4 breast cancer, 3 predominantly breast, 2 colorectal cancer populations | 7 trials included aerobic exercise alone 3 trials included aerobic and resistance exercises | Average 1334 minutes total exercise program | Exercise interventions improve VO2max, strength, QOL, fatigue, immune function, and body composition. |
| Total of 9 trials including various cancer populations investigating impact of exercise on cancer-related fatigue Interventions were supervised and multimodal | 5 trials included aerobic and resistance exercise 3 trials include aerobic, resistance, and stretching exercise 1 trial resistance exercises only | Average program duration: 16 wk Average session duration: 50 min Average frequency: 2.7 times/wk | Significant improvements in fatigue. Stronger effect from exercise when the intervention included aerobic, resistance, and stretching. |

Total of 8 trials, including 7 breast and 1 prostate cancer populations

3 trials resistance exercise only
 3 trials aerobic exercise only
 1 trial walking with weight belt
 1 trial resistance and aerobic exercise
 50% supervised
 50% unsupervised

Program duration: 12-52 wk
 Session frequency: 2-7 times/wk
 Intensity of exercise was predominately "moderate"

Weak support for exercise improving bone density.
 Questionable whether sufficient load was utilized to impact bone density. Noted as potential mitigating factor for exercise impact.
 Questionable benefit over and above bisphosphonates if the patient is doing both for bone health.

QOL = quality of life; IGF = insulin-like growth factor; GI = gastrointestinal; ROM = range of motion; HRQOL = health-related quality of life; BMI = body mass index; VO2max = maximal oxygen consumption.

* Noteworthy finding.

was positive [15,16,20,24,25,28,32,39,43,47,50,52,57,62,64] or showed an overall positive trend toward significance, although effect size was relatively small in many of the QOL outcomes [18,38,55,59]. A small number of reviews failed to demonstrate significant impact on QOL [26,35,53,54,56]. One report identified that greater BMI was associated with lower reported QOL [15]. One review reported the effect of supervised exercise on HRQOL to be twice as high compared with unsupervised exercise [19].

Biomarkers Associated With Cancer Progression

Exercise positively impacted biomarkers, specifically immune and inflammatory markers, both during and after cancer treatment. Significant improvements in biomarker profiles were noted with exercise interventions, including improved insulin-like growth factor (IGF)-I [32,57,58,64] and IGF-II [22,32,36], increased CD-4 cells [22], improved immune function [58,59], and decreased inflammatory markers [26,46,65]. No effect was noted on prostate specific antigen nor on testosterone in prostate cancer survivors [37]. Reviews on the effects of exercise on circulating insulin levels were mixed, with some reporting an exercise-lowering effect [30,64] and others reporting mixed results or no response on insulin and insulin-like markers [36,42,58]. Exercise interventions that supported positive outcomes favored moderate or vigorous exercise versus low-intensity or nonexercising controls [30,32].

Observational Studies

Several systematic reviews aggregated information from longitudinal, observational studies [29,49,51]. These studies relied on patient self-reported levels of physical activity during and after treatment. Although no specific exercise interventions are articulated through these reports, the results provide consistent epidemiologic evidence of the positive association between reported levels of physical activity and meaningful endpoints such as overall mortality [29,49,51], disease-specific mortality [51], and QOL [49] in individuals with breast, prostate, or colorectal cancers. In addition, one study demonstrated incremental improvements in mortality with increasing intensity of self-reported physical activity [51].

Limitations

A significant limitation of this report is the inability to pool results and calculate effects across systematic reviews regarding specific exercise interventions and exercise parameters. Within individual systematic reviews, heterogeneity often was reported as significant, which challenged valid calculation of effects. Based on the AMSTAR scores of the selected studies, there also was significant concern about the lack of data

Table 4
A framework for cancer exercise guidelines[†]

| At Cancer Diagnosis Pretreatment/Prehabilitation | During Cancer Treatment | After Cancer Treatment |
|---|--|---|
| <p>All patients</p> <ul style="list-style-type: none"> • Assess physical activity level • Clinical measures of endurance and function • Screen to establish appropriate safety parameters for exercise intervention[†] <p>Prehabilitation exercise*</p> <ul style="list-style-type: none"> • Moderate intensity aerobic, 3-5 times/wk, +/- resistive exercise • Supervised individual or group setting or unsupervised <p>Therapeutic exercise</p> <ul style="list-style-type: none"> • Indicated based on presenting functional impairment or disability • Supervised • Preconditioning in select populations for proactive impairment management including pelvic floor muscle biofeedback for gynecologic, prostate, and other genitourinary cancers, pulmonary conditioning for lung and colorectal cancer populations | <p>All patients</p> <ul style="list-style-type: none"> • Assess endurance and functional measures • Screen for functional impairment related to side effects of cancer treatment <p>Exercise to maintain or improve endurance*</p> <ul style="list-style-type: none"> • Moderate-to-vigorous aerobic exercise, +/- resistive exercise, 3-5 times/wk (150 min/wk) • Supervised or unsupervised depending on functional status and side effects of cancer treatment <p>Exercise for reconditioning</p> <ul style="list-style-type: none"> • Movement-based exercises/progressive resistive exercises • Moderate-to-vigorous aerobic if safe • Supervised <p>Therapeutic exercise</p> <ul style="list-style-type: none"> • Indicated based on presenting functional impairment or disability • Supervised • Proactive for select populations at risk for impairment, including early mobilization of the upper limb for breast cancer, progressive resistive exercises for the upper limb and shoulder in head and neck and breast cancer populations | <p>All patients</p> <ul style="list-style-type: none"> • Assess endurance and functional measures • Screen for late effects and emerging functional impairment related to previous or ongoing cancer treatment <p>Exercise to maintain or improve endurance*</p> <ul style="list-style-type: none"> • Moderate to vigorous aerobic exercise, +/- resistive exercise, 3-5 times/wk (150 min/wk) • Supervised or unsupervised <p>Exercise for reconditioning</p> <ul style="list-style-type: none"> • Movement-based exercise • Supervised • Intensity specific to level of deconditioning <p>Therapeutic exercise</p> <ul style="list-style-type: none"> • Indicated based on presenting functional impairment or disability • Supervised • Screening for specific functional impairments related to cancer therapy late effects |

* As recommended by the American College of Sports Medicine's Exercise Guidelines for Cancer Survivors.

[†] All exercise intervention should be preceded by clinical assessment to identify safety concerns, precautions and contraindications.

extraction and disparity in reported outcomes. To maintain the integrity of the findings, the authors decided against pooled effects and instead provide descriptive findings. In addition, there is significant variability in the type of studies analyzed in the included systematic reviews. Many reviews included uncontrolled, observational, or case series design studies. Those that identified as controlled studies often poorly identified the control group intervention. These methodologic shortcomings have the potential to introduce significant bias into these findings.

This review is limited in that it focused only on movement-based forms of exercise. As a result, some therapeutic exercise interventions that restore and support vital aspects of function, such as swallowing and daily task retraining, were not included. In addition, behavioral interventions designed to increase exercise participation and attitudes towards physical activity were not included. Although behavioral interventions are an important supportive element of exercise prescription, the inclusion of these strategies was beyond the scope of the stated goals of this manuscript.

In addition, these systematic reviews largely assess findings from controlled trials that are likely to have exclusion criteria that aim to optimize safety. In the relatively controlled setting of a study protocol, fewer safety issues and adverse events would be anticipated compared with an uncontrolled clinical setting. Therefore, safety considerations should not be overlooked in exercise the prescription and ongoing vigilance for safety during training is necessary.

Discussion and Clinical Considerations

This systematic review of existing cancer-related, exercise-specific systematic reviews is the first of its kind to aggregate outcomes associated with movement-based exercise across cancer types, cancer treatment time course, and cancer-related impairments. The overall quality of the included systematic reviews was moderate, limiting our ability to draw decisive conclusions about specific elements of exercise prescription. The evidence presented in this review strongly supports a multitude of physical and functional benefits from exercise at any time point before, during, or after cancer treatment with consideration for the cancer type, presenting or anticipated side effects of treatment, and the presence of physical impairments. Moderate-to-vigorous intensity exercise is safe and appears to provide greater benefit than lower intensity exercise. However, low-intensity exercise benefits deconditioned individuals and promotes a dose response that positively impacts physical function and fitness.

The impact of exercise interventions was better when the program was supervised versus unsupervised. This may be attributed to greater individualized attention from the health care provider. The actual dose of

exercise may be greater in supervised settings where effort and volume are better controlled, thereby enabling greater impact of exercise effects.

These findings are a useful beginning to guide health care providers in exercise prescription and planning. Any health care provider interfacing with individuals before, during, and after cancer treatment should encourage exercise as a part of the cancer care plan and should work to incorporate specific recommendations for exercise. It is important to recognize, however, that these findings were elucidated through controlled trials that possibly excluded participants deemed unsafe based on exclusion criteria and therefore these results should be interpreted with appropriate caution in a clinical setting where exercise capacity among patients could vary widely. The individual with cancer does require different attention to their exercise recommendations and a plan should be developed in the context of their known and anticipated risk for disease treatment-related side effects. This is ideally guided by a health care provider who is an exercise specialist such as a physiatrist, physical therapist, occupational therapist, exercise physiologist, or other medical rehabilitation professional with robust knowledge of cancer and its treatment. It is of critical importance that providers understand the limitations of exercise training to alleviate more complex, underlying neuromusculoskeletal conditions as well as recognize that exercise prescription, when incorrectly applied, may magnify such conditions. Rehabilitative, ie, therapeutic, interventions may be more appropriate to manage these underlying conditions and discipline-specific triage is warranted. Exercise and rehabilitation disciplines should work collaboratively to ensure that safe and effective exercise training is implemented. The exercise prescription should ultimately seek to optimize an individuals' ability to independently perform their exercise program while affording them a supportive care interface if complications or physical impairments limit their ability to complete the exercise program or disrupt their ability to function. For example, a physical therapist could prescribe therapeutic exercises to address balance impairments associated with chemotherapy-induced neuropathy to better prepare the individual to safely work with an exercise physiologist to engage in a moderate-to-vigorous intensity exercise conditioning program to restore aerobic fitness.

This review supports exercise prescription for the cancer population should follow the principles of exercise training as they are applied to other impaired or chronic disease populations. Consideration for specificity of exercise based on the individual's initial fitness and functional levels, treatment-related side effects and personal health goals should guide recommended exercise interventions [5]. Initial values and baseline measures should be obtained and repeated over time to gauge meaningful change and assure the effectiveness

of the program. Exercise precautions/contraindications and safety monitoring should be readily observed specific to cancer treatment-related side effects [4].

Our findings demonstrate that the elements of exercise prescription should be relatively controlled and guided by a health care provider to optimize benefit and overall safety. This review, however, demonstrates that positive outcomes can be achieved using widely variable exercise frequency, intensity, duration, and mode, suggesting that recommendations can be flexible while still enabling overall benefits. The significant heterogeneity in exercise interventions exposed by these systematic reviews is both a shortcoming and an opportunity for providers seeking optimal exercise prescription guidance and enables providers to use broad license in recommending exercise. This is also beneficial for individuals as it enables them to engage in activities that may be meaningful and enjoyable to them, rather than constraining them to highly specified parameters.

This review demonstrates a significant challenge regarding clinical measurement. One primary barrier identified by many systematic reviews was the significant variability in the clinical measurement tools, both objective and patient-reported, across trials and studies. The differences between trials prevent strong statistical analysis to support definitive recommendations. Specifically, robust analysis is impeded by disparity in domain-specific outcomes measurement tools, disparate methods of quantifying exercise dose, lack of reporting of specific elements of the exercise prescription including frequency, duration, and intensity, and dissimilarity in terminology used to quantify and qualify exercise interventions. Outcome reporting could be markedly improved if the exercise and medical rehabilitation communities collaborated towards a common lexicon to define the various modalities and interventions that comprise this body of knowledge. Exercise, physical activity, therapeutic exercise, aerobic conditioning, physical fitness, physical functioning, and other terminology often are used interchangeably and without clear delineation among them. Standardized reporting of intervention parameters in exercise trials would also be helpful to researchers and would enable aggregation of findings across trials. Peer-review journals and entities such as the Cochrane Rehabilitation group (<http://rehabilitation.cochrane.org/>) could encourage standardized exercise reporting to include the specific intervention protocol as well as basic parameters such as frequency, intensity, and duration. This would enable significant contribution to the evidence base to guide intervention recommendations in the future.

Few studies, outside of population-based cohort studies, reported long-term follow-up regarding survival and disease-specific endpoints. Controlled intervention trials rarely reported the long-term impact of exercise and often failed to investigate any carry over of the

positive outcomes achieved through the intervention. Although it is accepted widely that exercise is positive under controlled circumstances, uncertainty persists regarding adherence to exercise and long-term impact. Future research should seek to better understand the long-term impact of exercise on endpoints such as time to disease recurrence, duration of overall survival, and overall mortality rates.

Although not illustrated in the included systematic reviews, there is a body of evidence that speaks to the importance of exercise preferences and individual personality and attitudinal preferences of significant factors impacting the effectiveness of exercise interventions [69]. These preferences should be considered along with other factors that are known to underlie adherence and intention. Although behavioral modification studies were excluded from our review, strong support for the theory of planned behavior is evident in the cancer literature as a driver of motivation towards exercise [70]. Behavioral models such as this should be considered by health care providers who are prescribing exercise and encouraging exercise behavior carry over in the cancer population. One review did identify a significant increase in participants willingness to seek physical activity counseling as a result of their participation in the exercise intervention study [20]. This suggests that exercise interventions present an opportunity to initiate behavior change. Critical questions for future research should include long-term adherence to exercise and carry over of physiological and psychological changes after a trial of supervised exercise as well as the impact an exercise trial has on patient attitudes and self-activation towards health behavior changes. This will require the use of research paradigms that follow a more protracted timeline and will encourage longitudinal studies to closely examine and document exercise interventions, in addition to patient self-report, to track survival endpoints.

The findings reported in this review suggest that timing of an exercise intervention may impact the overall benefit for some populations. The prehabilitation model of care shows promise in promoting a proactive approach to introducing exercise and rehabilitation into the cancer care plan from the point of diagnosis. Important findings regarding improved recovery and tolerance to treatment are reported and suggest not only functional improvements but economic benefits. Accelerated functional recovery as well as potential cost mitigation from prehabilitation should be further explored.

Very little description was provided in any review regarding screening to identify indications for conditioning exercise or therapeutic exercise during or after cancer treatment. Screening for deconditioning and early identification of emerging impairments such as CRF, neuropathy, lymphedema, or depression may expedite triage for early therapeutic exercise

intervention to mitigate functional decline [71,72]. Although the body of evidence continues to grow in support of therapeutic exercise and rehabilitative exercise programs for individuals with cancer treatment-related impairments, trials are generally small and poorly controlled, making it difficult to provide guidance regarding optimal timing for functional impairment screening and management. The prehabilitation and prospective surveillance models of care should be studied in future research to identify optimal indications and timing for screening as well as triage models that enable application of exercise interventions at the right time and of appropriate intensity.

This review also highlights the importance of timing of exercise and its impact on physiological markers like IGF-I and IGF-II, and other immune protective biomarkers. The current evidence base regarding exercise, in general, supports improvements in critical biomarkers and inflammatory profiles. Reduction of inflammatory markers has significant metabolic and immune protective implications for an individual recovering from cancer treatments. IGF overexpression is linked to breast, prostate, and lung cancers. A recent meta-analysis found that exercise reduced serum levels of IGF-I and IGF-II in the breast cancer population [73]. Furthermore, although exercise has been found to increase local levels of IGF-I after aerobic exercise, which may be helpful to rebuild skeletal muscle, exercise does not impact circulating IGF serum levels nor receptor overexpression [74]. This is an important consideration unique to the cancer population, which requires further research to investigate optimal timing and dose of exercise to maximize the positive effect on biomarkers of relevance.

Overall, the impact of exercise is positive and significantly improves a wide range of functional, psychological, and physiological markers in individuals before, during, and after cancer treatment. The synthesis of these findings enables high level recommendations in the areas of functional and fitness assessment, exercise prescription, and therapeutic exercise throughout the time course of the cancer treatment continuum. Currently, no interdisciplinary guidelines exist to provide insight to optimal timing, intensity, duration, and frequency of exercise and therapeutic exercise screening and intervention. Although the American Cancer Society provides general guidelines for physical activity and nutrition for the cancer survivor [75] and the American College of Sports Medicine has published general guidelines for exercise in the cancer population [1], these efforts fall short of providing specific context for timing of exercise interventions and the necessary screening for side effects, toxicities, and functional impairments that define the specialized needs of the cancer population. Greater attention is needed to promote exercise prescription and future work should focus on developing exercise guidelines that support recommendations at various

time points in the cancer care continuum with consideration for the presenting and anticipated treatment side effects, and with regard for the individual's health status. A suggested framework for exercise prescription is outlined in Table 4 and could serve as the basic construct for future work in guideline development.

An interdisciplinary effort to create a set of exercise guidelines would be an important step forward in integrating exercise into the continuum of oncology care and acknowledging the nuances of prescribing exercise for individuals versus sample study populations. Wide stakeholder input would be required for the success of such an effort and should be sought from a variety of disciplines including: oncologic, psychological, psychosocial, exercise, rehabilitation, nutrition, and other supportive services.

Conclusion

The growing population of cancer survivors warrants an urgent need to define clinical interventions that optimize function and survival. Symptom management over the course of cancer treatment and through the lifespan of survivorship is noted to be one of the most significant challenges faced by both patients and health care providers. Based on this review, exercise interventions have a strong evidence base to support their inclusion in most cancer care plans. The exercise plan of care is ideally designed in the context of known disease treatments and anticipated side effects of treatment and is overseen by a health care provider with specialized knowledge and skills in cancer-specific exercise and cancer rehabilitation. Despite a robust and growing body of evidence to support myriad exercise interventions across various cancer disease states and cancer treatment-related impairments, the supporting infrastructure for exercise planning and implementation for the cancer population is essentially absent. Efforts to strengthen uniformity in clinical trial reporting, develop clinical practice guidelines, and integrate exercise and rehabilitation services into the cancer delivery system are needed.

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Supplementary Data

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