Critical Reviews in Oncology / Hematology 136 (2019) 79–85

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Impact of exercise on chemotherapy completion rate: A systematic review of the evidence and recommendations for future exercise oncology research

Kelcey A. Bland[a], Kendra Zadravec[b], Taryne Landry[c], Sarah Weller[b], Logan Meyers[b], Kristin L. Campbell[b,c,d,*]

[a] Mary MacKillop Institute for Health Research, Australian Catholic University, Melbourne, VIC, Australia
[b] Rehabilitation Sciences Graduate Program, University of British Columbia, Vancouver, BC, Canada
[c] Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada
[d] Department of Physical Therapy, University of British Columbia, Vancouver, BC, Canada

ARTICLE INFO

Keywords:
Exercise
Neoplasm
Antineoplastic agents
Adjuvant chemotherapy

ABSTRACT

Receipt of full chemotherapy dose is associated with improved treatment efficacy and survival following a diagnosis of cancer. Exercise has emerged as a supportive care intervention that may improve chemotherapy completion rate by managing dose-limiting toxicities. We conducted a systematic review to evaluate the impact of exercise interventions on outcomes of chemotherapy completion rate in adult cancer patients. Relevant literature was retrieved from CINAHL, Medline (Ovid) and EMBASE based on subject headings and keywords pertaining to cancer, exercise and antineoplastic agents. Eligible articles were randomized control trials (RCTs) that prescribed aerobic or resistance exercise and included end-points relating to chemotherapy completion rate. Overall, eight RCTs were included in the final analysis. Only two RCTs (25%) that enrolled women with early-stage breast cancer reported a significant beneficial effect of exercise on chemotherapy completion rate, including higher mean relative dose intensity and fewer chemotherapy dose adjustments, relative to usual care. The remaining six studies reported no difference with exercise. Altogether, despite the growing number of exercise oncology trials to-date, information pertaining to the effect of exercise on chemotherapy completion rate is limited. Current data suggest exercise does not worsen chemotherapy tolerability. However, full interpretation of these findings is limited by the small number of trials. Future research involving rigorous study design is needed to confirm whether exercise can influence chemotherapy treatments.

1. Introduction

Observational evidence from meta-analyses indicates an inverse dose-response relationship between physical activity and cancer-specific mortality among the general population and cancer survivors (Li et al., 2016). The most consistent evidence suggests a survival benefit with exercise following a diagnosis of breast cancer, and possibly colorectal and prostate cancer (Li et al., 2016; Schmid and Leitzmann, 2014; Cormie et al., 2017). While mechanisms underpinning this relationship are unclear, a possible explanation includes the beneficial role of exercise or physical activity during cancer therapies, including chemotherapy. Preclinical evidence demonstrates the potential ability of exercise to modulate the standard response to treatment via direct effects on the tumour (Ashcraft et al., 2019). Alternatively, exercise may also improve patient tolerability of the planned chemotherapy dose through the mediation of common treatment toxicities. As a result, understanding whether exercise positively impacts chemotherapy completion rate is a growing area of clinical and scientific interest.

Receipt of the full chemotherapy dose according to the planned treatment schedule predicts improved patient outcomes, including treatment efficacy, disease recurrence and survival (Lyman, 2009). Adverse chemotherapy drug reactions or treatment toxicities, such as haematological toxicities (e.g. neutropenia) or peripheral neuropathy, still frequently occur among patients and can result in chemotherapy dose reductions (i.e. amount of dose administered), dose delays (i.e. timing of administration) or a combination of both (Speck et al., 2013; Lyman et al., 2010, 2003; Bosly et al., 2008). Delivery of full chemotherapy dose intensity is thus considered a quality of care indicator in clinical oncology (Lyman, 2009). Relative dose intensity (RDI) is the *ratio* of delivered dose intensity versus the planned dose intensity (Weycker et al., 2012) and a RDI < 85% is a commonly accepted clinical threshold whereby adjuvant chemotherapy effectiveness and

* Corresponding author at: 2177 Wesbrook Mall, Vancouver, BC, V6T 1Z3, Canada.
E-mail address: kristin.campbell@ubc.ca (K.L. Campbell).

https://doi.org/10.1016/j.critrevonc.2019.02.005
Received 16 October 2018; Received in revised form 13 February 2019; Accepted 13 February 2019

patient prognosis significantly worsen (Lyman et al., 2003, 2004; Kwak et al., 1990; Bonadonna et al., 1995; Wildiers and Reiser, 2011). Accordingly, identifying strategies to improve chemotherapy dosing and tolerability is a priority.

Oncologists often consider indicators of physical health, such as body mass index (Hanna et al., 2013; Denduluri et al., 2015; Griggs et al., 2003), performance status (Lyman et al., 2004), and the presence of comorbidities (Lyman et al., 2003, 2004; Shayne et al., 2006), in treatment-related decisions and subsequent chemotherapy dose modifications. Engaging in an exercise intervention during chemotherapy has the potential to directly address these physical health factors. Combined with the knowledge that exercise may ameliorate negative chemotherapy side effects, such as fatigue (Speck et al., 2010; Fong et al., 2012), a rationale to explore the effect of exercise on patient chemotherapy tolerability exists. To better understand the clinical relevance of prescribing exercise during chemotherapy, this systematic review evaluated the impact of exercise during chemotherapy on outcomes of chemotherapy completion rate in adults with cancer.

2. Methods

2.1. Literature search

This systemic review was performed in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) statement (Moher et al., 2009). A literature search was conducted using CINAHL, Medline (Ovid) and EMBASE from all available years up to December 2017. Search strategies were pre-defined and created in collaboration with a trained research librarian at the University of British Columbia. Subject headings and keywords included those relating to cancer (e.g. neoplasm, cancer, tumour or malignancy), exercise (e.g. exercise, physical activity, aerobic, strength or endurance training) and chemotherapy (e.g. adjuvant chemotherapy or antineoplastic) were combined with an "AND" term. Search terms were modified according to suggestions from the different search engines and are reported in full in Appendix A. No language restrictions were placed on the search. Reference lists of eligible articles were also hand searched for additional potentially eligible trials.

2.2. Inclusion and exclusion criteria

Eligible trials had to enroll participants ≥18 years of age with a cancer diagnosis and deliver an exercise intervention concurrent to chemotherapy treatments. Trials were limited to randomized control trials (RCTs) that included at least one exercise arm. Exercise interventions had to include continuous aerobic exercise (e.g. walking or cycling), aerobic interval training (e.g. high-intensity interval training) and/or strength or resistance exercise (e.g. weight lifting machines, free weights, body weight or band exercises). Physical activity counseling trials with a specific focus on behavior change, alternative exercise interventions (e.g. yoga, Pilates or Tai Chi) or specific therapeutic interventions (e.g. physical therapy or rehabilitation exercise for limb mobility) were excluded. Trials had to incorporate a defined post-intervention end-point relating to chemotherapy completion rate (e.g. dose intensity or RDI). Cross-sectional studies, quasi-experimental, case reports, published abstracts, dissertations, reviews and conference presentations were excluded.

2.3. Data extraction and analysis

Four reviewers inspected the titles and abstracts of the identified articles in the search to generate two complete independent lists to determine eligibility (KB, TL, SW and LM). Identified articles were then obtained in full and further reviewed by two independent reviewers to make a final decision regarding study inclusion (KB and KZ). Any papers in question were resolved by consensus and input from the senior study team member (KC). All title, abstract and full text screening was performed using online software (Covidence systematic review software, 2019). Risk of bias was evaluated using the Cochrane Collaboration's tool at the outcome level to describe eligible trials (Higgins et al., 2011). Each parameter of bias was graded as high, low or unknown risk. Among exercise trials, blinding of participants is challenging and can result in a high risk of performance bias (Day and Altman, 2000). This foreseeable bias is acknowledged by the reviewers and should not infer poor methodological quality of the trial. Attrition bias was rated as 'high' if > 20% of outcome data was missing. Adherence to the exercise intervention (i.e. exercise session attendance) below 75% or contamination of the control group (i.e. control group participants engaged in exercise) was criteria for high risk of 'other sources' of bias (Furmaniak et al., 2016). Given the limited number of eligible trials and considerable heterogeneity in participant characteristics, outcome definitions and exercise interventions, a narrative synthesis was conducted.

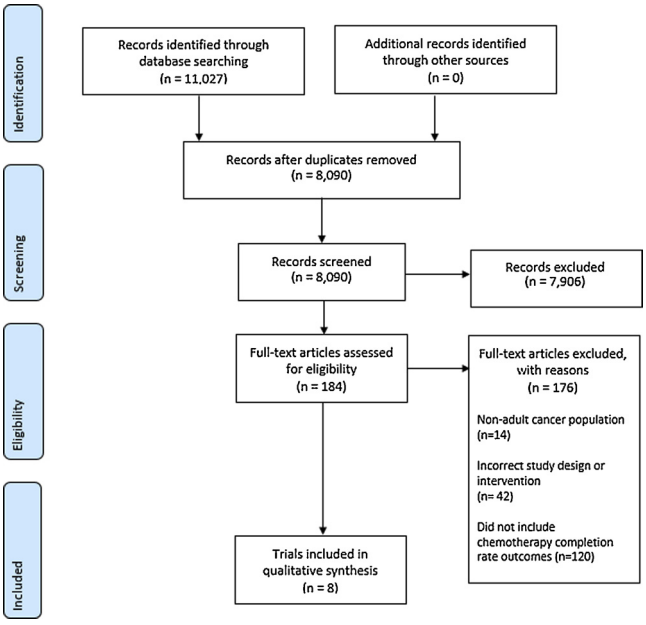

Fig. 1. PRISMA Flow Diagram.

3. Results

The PRISMA flow diagram is depicted in Fig. 1. The initial search generated a total of 11,027 articles. Following removal of duplicates, 8090 remained and 7906 articles were excluded upon reviewing title and abstracts. A total of 184 articles were reviewed as full-texts for a more detailed evaluation, resulting in 176 being excluded and eight trials left for inclusion in the final analysis.

Characteristics of all included trials, including sample, exercise intervention and outcomes of chemotherapy completion rate are reported in Table 1. All trials delivered a supervised aerobic-only, resistance-only, or combined aerobic and resistance exercise intervention during chemotherapy treatments to at least one study group (Courneya et al., 2007, 2009, 2013; Alibhai et al., 2015; van Waart et al., 2015, 2018; Xu et al., 2015; Van Vulpen et al., 2016). In total, seven RCTs compared exercise interventions to usual care (Courneya et al., 2007, 2009; Alibhai et al., 2015; van Waart et al., 2015, 2018; Xu et al., 2015; Van Vulpen et al., 2016), while one three-arm trial compared different exercise types and doses, namely 25–30 min versus 50–60 min of moderate intensity aerobic-only exercise versus combined moderate intensity aerobic (25–30 min) and resistance exercise (Courneya et al., 2013). Exercise intervention duration ranged from 4 to 18 weeks (Courneya et al., 2007, 2009, 2013; Alibhai et al., 2015; Xu et al., 2015;

Table 1
Impact of exercise on chemotherapy completion rate.

First Author, Year	Population	Study Arms	Intervention	Exercise Attendance	Exercise Prescription	Results
(Courneya et al., 2007)	Breast (stage I-IIIa)	AET n = 78 RET n = 82 UC n = 82	Supervised, 3x/wk 17 wks total (median)	AET: 72.0% RET: 68.2%	AET: aerobic exercise (15-45 min, 60-80 VO_2max) RET: resistance exercise (60-70% estimated 1RM, 2 × 8-12 reps)	↑ mean RDI in RET vs UC RET: 89.8%* AET: 87.4% UC: 84.1% ↔ RDI ≥ 85% RET: 78.0% AET: 74.4% UC: 65.9%
(Courneya et al., 2009)	Lymphoma (stage I-IV)	AET n = 62 (n = 28)[a] UC n = 60 (n = 26)[a]	Supervised, 3x/wk 12 wks total	AET: 77.8%	Aerobic exercise (15-45 min, 60-75% VO_2peak; 1 interval session/wk at VT by wk 7 and at VO_2peak by wk 9)	↔ planned minimum cycles AET: 103% UC: 99% ↔ planned maximum cycles AET: 94% UC: 89% ↔ complete chemotherapy response AET: 46.4% UC: 30.8%
(Courneya et al., 2013)	Breast (stage I-IIIc)	STAN n = 96 HIGH n = 101 COMB n = 104	Supervised, 3x/wk 16.4 wks total (mean)	STAN: 87.8% HIGH: 81.6% COMB: 78.0%	STAN: aerobic exercise (25-30 min, 55-75% VO_2peak) HIGH: aerobic exercise (50-60 min, 55-75% VO_2peak) COMB: aerobic exercise (25-30 min, 55-75% VO_2peak) & resistance exercise (2 × 10-12 reps at 60-75% estimated 1RM)	↔ mean RDI STAN: 93.9% HIGH: 91.6% COMB: 92.7% ↔ RDI ≥ 85% STAN: 87.5% HIGH: 82.2% COMB: 85.6%
(Alibhai et al., 2015)	Acute myeloid leukemia	EX n = 59 (n = 56)[a] UC n = 24	Supervised, 4-5x/wk, 5.2 wks total (mean)	EX: 54%	Aerobic exercise (10-40 min, RPE 3-6 out of 10) & resistance exercise (10-25 min, body weight, elastic bands & free weights)	↔ time from start of induction chemotherapy to cycle 2 EX: 47.6 days UC: 49.4 days
(van Waart et al., 2015)	Breast (stage I-III)	OnTrack n = 76 OncoMove n = 77 UC n = 77	OnTrack: Supervised, 2x/wk; home-based, 5x/wk for duration of chemotherapy OncoMove: Home-based, 5x/wk for duration of chemotherapy	OnTrack Supervised: 71% Home-based: 48% achieved target 75% of the time OncoMove: 55% achieved target 75% of the time	OnTrack: aerobic exercise (30 min, 50-80% max workload) & resistance exercise (2 × 8 reps at 80% 1RM); home-based aerobic exercise (same as OncoMove) OncoMove: aerobic exercise (30 min, RPE 12-14 out of 20)	↓ participants requiring dose adjustments in OnTrack relative to UC & OncoMove OnTrack: 12%* OncoMove: 34% UC: 34% ↓ mean dose adjustment in OnTrack & OncoMove relative to UC OnTrack: 9.8%* OncoMove: 9.7%* UC: 25.2%
(Xu et al., 2015)	Oesophagus (stage IIb or higher)	EX n = 28 UC n = 28	Supervised, 3x/wk 4-5 wks total	EX: number of walking sessions: 8.5 (mean)	Aerobic exercise (20 min, 60% APMHR)	↔ rates of chemotherapy interruption EX: 28.6% UC: 63.6%
(Van Vulpen et al., 2016)	Colorectal (stage M0)	EX n = 17 UC n = 16	Supervised, 2x/wk; home-based, 3x/wk 18 wks total	EX: Supervised: 89% Home-based: 88% achieved 210 min MVPA/wk	Supervised: aerobic exercise (intervals at VT, 18-21 min) & resistance exercise (2 × 10 reps at 65% to 1 × 20 reps at 45% 1RM) Home-based: aerobic exercise (30 min)	↔ median RDI EX: 82% UC: 76% ↔ RDI ≥ 85% EX: 35% UC: 33%
(van Waart et al., 2018)	Colon (stage I-IV)	OnTrack n = 7 OncoMove n = 8 UC n = 8	OnTrack: Supervised, 2x/wk; home-based, 5x/wk for duration of chemotherapy OncoMove: Home-based, 5x/wk for duration of chemotherapy	OnTrack Supervised: 61% Home-based: 71% achieved target 75% of the time OncoMove: 100% achieved target 75% of the time	OnTrack: aerobic exercise, (30 min, 50-80% max workload) & resistance exercise (2 × 8 reps at 80% 1RM); home-based aerobic exercise (same as OncoMove) OncoMove: aerobic exercise (30 min, RPE 12-14 out of 20)	↔ receipt of planned dose[b] OnTrack: 87% OncoMove: 92% UC: 78%

AET: Aerobic exercise; APMHR: age-predicted maximum heart rate; COMB: Combined aerobic and resistance exercise; EX: exercise (intervention) group; HIGH: Higher dose aerobic exercise (duration), MVPA: moderate to vigorous physical activity; RDI: relative dose intensity; RET: Resistance exercise; RM: repetition maximum; RPE: rating of perceived exertion; STAN: Standard dose aerobic exercise; UC: usual care; VT: ventilatory threshold; ↑: significant increase; ↓: significant decrease; ↔: nonsignificant difference.

* Significantly different from usual care.

[a] n received chemotherapy and chemotherapy completion rate evaluated out of the total larger sample.

[b] statistical test not performed.

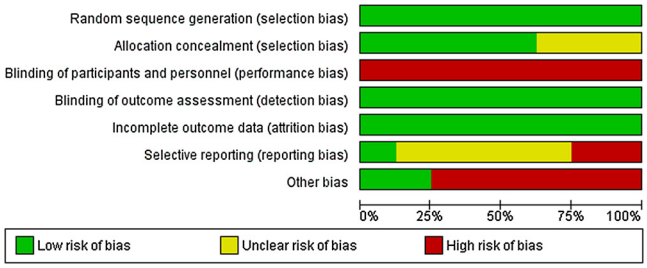

Fig. 2. Review authors' judgements about each risk of bias item presented as percentages across all included studies.

Van Vulpen et al., 2016) or was reported as spanning the duration of chemotherapy treatments (van Waart et al., 2015, 2018). Average exercise adherence (i.e. session attendance) ranged from 54 to 89%. No study measured chemotherapy completion rate as the primary outcome. Chemotherapy completion rate definitions included: mean/median RDI or RDI ≥ 85% (n = 3) (Courneya et al., 2007, 2013; Van Vulpen et al., 2016); planned minimum/maximum cycles and chemotherapy response (n = 1) (Courneya et al., 2009); rate of chemotherapy interruption (n = 1) (Xu et al., 2015); percentage of participants requiring a dose adjustment/mean dose adjustment (n = 1) (van Waart et al., 2015); receipt of planned dose (n = 1) (van Waart et al., 2018); and time (mean number of days) to start chemotherapy cycle 2 (n = 1) (Alibhai et al., 2015).

3.1. Risk of bias

Risk of bias for all included trials is reported in Fig. 2. Risk of selection bias for adequate random sequence generation was reported and judged as low in all eight trials (100%). Selection bias based on allocation concealment was reported using the appropriate methods and therefore judged as low in five trials (63%) (Courneya et al., 2007, 2009, 2013; Alibhai et al., 2015; Van Vulpen et al., 2016). Performance bias was judged as high for all trials (100%), given participants were un-blinded to group assignment. Blinding of the individual extracting outcomes of chemotherapy completion rate was typically not reported. However, detection bias was judged as low risk, as the assessment of chemotherapy completion rate data is normally abstracted from patient medical records. Attrition bias was judged as low in all eight trials (100%), as participant withdrawal rates and missing outcome data were consistently < 20%. Reporting bias was judged in seven trials (88%) as either unclear or low. Four trials (50%) had unclear selective reporting bias due to vague chemotherapy completion rate outcome descriptions reported within the clinical trial registration (Alibhai et al., 2015; Courneya et al., 2007, 2009, 2013). The remaining three trials (38%) were graded as high risk of bias for selective reporting due to disagreement between the published protocol and the reported chemotherapy completion rate outcomes (van Waart et al., 2015, 2018; Van Vulpen et al., 2016). For bias from other sources, all trials were graded as high risk of bias except for two (25%) (Courneya et al., 2009, 2013) primarily due to exercise intervention attendance below 75% (Courneya et al., 2007; Alibhai et al., 2015; van Waart et al., 2015, 2018; Xu et al., 2015) or contamination of the control group (Van Vulpen et al., 2016).

3.2. Impact of exercise on chemotherapy completion rate

In all trials, exercise did not interfere with measured indices of chemotherapy completion rate. A significant beneficial effect of exercise on outcomes of chemotherapy completion rate relative to usual care was reported in two trials and both were conducted in women with early-stage breast cancer (Courneya et al., 2007; van Waart et al., 2015). In a three-arm trial by Courneya et al., 242 women were randomized to moderate-intensity aerobic-only exercise, resistance-only exercise or usual care (Courneya et al., 2007). Significantly higher mean RDI was reported with supervised, resistance-only exercise (89.8%) relative to usual care (84.1%; mean difference = 5.7%, p = 0.033) (Courneya et al., 2007). Resistance exercise was performed using machines and free-weights three times/week (9 exercises, 2 sets of 8–12 repetitions at 60–70% estimated 1-repetition maximum (1RM)). No significant difference was reported for mean RDI between aerobic-only exercise (87.4%) and usual care (mean difference = 3.3%, p = 0.266). There was no difference in the percentage of participants who received ≥85% of their planned RDI between the usual care group (65.9%, 54 of 82 patients) versus the resistance-only exercise group (78.0%, 64 of 82 patients, p = 0.082) or the aerobic-only exercise group (74.4%, 58 of 78 patients, p = 0.241) (Courneya et al., 2007). Exercise adherence in both exercise groups was also positively associated with a higher mean RDI (r = 0.17, p = 0.035) (Courneya et al., 2007). In a three-arm trial by van Waart et al., 230 women were randomized to a twice weekly, supervised, combined aerobic and resistance exercise program (OnTrack), a home-based exercise program (OncoMove) or usual care (van Waart et al., 2015). A significantly smaller proportion of women in OnTrack required chemotherapy dose adjustments (12%, 9 of 76 patients) relative to usual care (34%, 26 of 77 patients) or OncoMove (34%; 26 of 77 patients, odds ratio: 0.26, p = 0.002) (van Waart et al., 2015). The authors also reported that the average dose reduction among participants randomized to OnTrack and OncoMove was approximately 10% relative to 25% in the usual care group (mean difference = 15%, p = 0.014) (van Waart et al., 2015).

The remaining six trials did not report a significant effect of exercise on outcomes of chemotherapy completion rate. In a trial of lymphoma patients by Courneya et al., the effect of exercise on chemotherapy completion rate was analysed in a subgroup of participants who underwent chemotherapy (n = 54, 44%) (Courneya et al., 2009). Relative to usual care, supervised aerobic exercise had no effect on the number of cycles completed out of the minimal (p = 0.45) and maximal number of cycles planned (p = 0.20). The number of lymphoma patients who had a complete chemotherapy response relative to a progressive, stable or partial chemotherapy response also did not differ between exercise (46.4%, 13 of 28 patients) or usual care groups (30.8%, 8 of 26 patients, p = 0.24) (Courneya et al., 2009). In the trial by Xu et al., a non-significant difference was reported in rates of chemotherapy interruption, defined as any chemotherapy dose reduction or discontinuation, among participants with oesophagus cancer (n = 56) randomized to a supervised walking intervention (28.6%) relative to usual care (63.6%, p = 0.10) (Xu et al., 2015). Van Vulpen et al. also reported no effect of supervised combined aerobic and resistance exercise on median RDI (82%) versus usual care (76%, p = 0.8) or the percentage of exercise participants who received ≥85% RDI (35%) versus usual care (33%, p = 0.9) among colon cancer patients (n = 33) (Van Vulpen et al., 2016). In another trial of colon cancer patients (n = 23) by van Waart et al., the percentage of the planned chemotherapy dose received among exercisers (OnTrack: 87% or OncoMove: 92%) was higher than usual care (78%) but a statistical test for group comparisons was not performed due to the small sample size (van Waart et al., 2018). Alibhai et al. reported no difference in the mean number of days from the start of induction chemotherapy to the second chemotherapy cycle in 80 patients with acute myeloid leukemia randomized to a supervised combined aerobic, resistance and flexibility exercise intervention (47.6 days) relative to usual care (49.4 days, p = 0.63) (Alibhai et al., 2015). Lastly, Courneya et al. conducted a three-arm trial comparing 25–30 minutes of aerobic-only exercise (STAN), 50–60 minutes of aerobic-only exercise (HIGH) and combined aerobic (25–30 min) and resistance exercise (9 exercises, 2 × 10–12 reps at 60–75% estimated 1RM) in 301 women with early-stage breast cancer (Courneya et al., 2013). There were no between group differences in mean RDI (STAN: 93.9%, HIGH: 91.6%, COMB: 92.7%, p = 0.34) or the percentage of participants who achieved ≥85% RDI (STAN: 87.5%, HIGH: 82.2%,

COMB: 85.6%, p = 0.57) (Courneya et al., 2013).

4. Discussion

To our knowledge, this is the first systematic review to report on the impact of exercise on chemotherapy completion rate as its primary aim in adults with cancer. Eight RCTs were identified that evaluated the effect of exercise on chemotherapy completion rate. However, all trials included outcomes of chemotherapy completion rate within secondary analyses. Findings from this review are limited, but suggest exercise does not impede the delivery of chemotherapy treatment. Whether there is a beneficial effect of exercise on chemotherapy treatments remains an important topic for future investigations.

Preliminary evidence from RCTs identified in this review suggests investigation into the relationship between exercise and higher chemotherapy tolerance is worthwhile. Two RCTs in women with early stage breast cancer reported a significant positive effect of exercise on outcomes of chemotherapy completion rate relative to usual care. Courneya et al. reported supervised resistance exercise significantly influenced RDI relative to usual care, while no effect was observed with supervised aerobic exercise (Courneya et al., 2007). Importantly, the 5.7-percentage point increase in RDI observed in the resistance exercise group is of unclear clinical relevance. van Waart et al. also reported a significant difference in the proportion of participants who received any dose adjustment and mean dose adjustment with a supervised, combined aerobic and resistance exercise relative to a home-based exercise intervention or usual care (van Waart et al., 2015). The presence of any dose reduction or discontinuation of chemotherapy (coded as 'yes' or 'no') was also used as an outcome in the trial by Xu et al. in patients with oesophagus cancer, which showed a positive trend favouring the exercise group (Xu et al., 2015). Yet, in the trials by Xu et al. and van Waart et al., the occurrence of *any* dose reduction is not a well-established clinically-relevant outcome and participants may have, for example, still received > 85% RDI. Specific to van Waart et al. a significant difference in the dose reduction percentage between groups was also reported (10% for exercise groups vs. 25% for usual care). This finding holds greater clinical relevance, as dose reductions exceeding 15% significantly predict worse overall survival (Denduluri et al., 2018). Beyond the lack of clinically meaningful findings, the exploratory nature of these analyses and differences in delivered exercise interventions, indicate more research is needed to confirm whether exercise improves chemotherapy completion rate.

Results from other trials included in this review showed no significant effect of exercise on chemotherapy completion rate; however, these trials had several limitations. In the randomized trial of 301 women with early stage breast cancer by Courneya et al. (2013), different types and doses (duration) of exercise were prescribed and RDI was evaluated, yet there was no usual care group included for comparison. The trial by Van Vulpen et al. that reported no difference in RDI between colon cancer patients randomized to exercise versus usual care was limited by contamination of the usual care group (56% of usual care group participants reported more than 210 minutes of moderate to vigorous physical activity per week) (Van Vulpen et al., 2016). Exercise adherence challenges were also common among trials, with exercise session attendance frequently less than 75%. Moreover, most trials had small sample sizes or only had chemotherapy completion rate data for a small proportion of their sample. Specifically, the trial by Courneya et al. enrolled 122 patients with lymphoma, while only 54 patients received chemotherapy during the exercise intervention (Courneya et al., 2009). Despite these limitations, results from all trials consistently suggest exercise does not interfere with patient chemotherapy tolerability and adherence. Namely, patients engaging in exercise did not have worse outcomes for chemotherapy completion rate relative to usual care.

The findings presented in this systematic review, combined with a biological rationale supporting the role of exercise in improving chemotherapy completion rate, serve as a foundation for future investigations. Loss of skeletal muscle mass and associated reductions in physical function are emerging determinants of treatment toxicity and chemotherapy tolerance (Prado et al., 2007, 2009; Collins et al., 2018; Cespedes Feliciano et al., 2017). Exercise may serve as a safe and effective intervention to preserve these outcomes. The odds of completing three or more cycles of chemotherapy has been shown to be 11 times greater in patients with faster sit-to-stand times and gait speeds ≥ 0.8 m/s in patients with lung cancer (Collins et al., 2018). Indeed, patients with higher physical function may be more resilient to aggressive chemotherapy treatment. The quantity of skeletal muscle mass may also influence chemotherapy pharmokinetics and metabolism, and ultimately, the occurrence and severity of dose-limiting treatment toxicities. Patients with lower total lean body mass have a higher dose of chemotherapy per kilogram of lean body mass, which is related to increased treatment toxicity and early chemotherapy discontinuation, dose delays and dose reductions (Cespedes Feliciano et al., 2017). Exercise, especially resistance exercise, can preserve and potentially increase skeletal muscle mass during adjuvant cancer therapies, including chemotherapy (Padilha et al., 2017; Stene et al., 2013). Among the exercise trials in this review that identified a possible benefit of exercise on chemotherapy completion rate, supervised, progressive resistance exercise was a commonality.

For future studies to effectively explore the impact of exercise interventions on outcomes of chemotherapy completion rate, several considerations and recommendations are provided. First, it is imperative that validated outcomes of chemotherapy completion rate, such as dose intensity or RDI, are used and appropriately calculated within exercise trials. Chemotherapy RDI should be estimated based on the ratio of delivered dose intensity to the reference standard dose intensity Weycker et al. (2012) (Table 2). Beyond statistically significant differences, demonstrating clinically meaningful changes in treatment tolerance, such as achievement of RDI ≥ 85% in the adjuvant treatment setting, is vital for the development of persuasive evidence. Secondly, more information on predictors of chemotherapy dose intensity is needed. Several trials to-date have identified non-modifiable predictors of chemotherapy dose intensity, such as demographic variables (e.g. age and race), cancer stage or chemotherapy regimen (Lyman et al., 2003; Bosly et al., 2008; Lyman et al., 2004; Hanna et al., 2013; Denduluri et al., 2015; Griggs et al., 2003; Shayne et al., 2006). Less is known regarding modifiable physical health factors that may predict chemotherapy tolerance, such a cardiorespiratory fitness, muscular strength, skeletal muscle mass and quality, or physical function. Finally, a greater understanding of mechanisms by which exercise may impact chemotherapy completion rate is needed. Such information will also help identify the optimal exercise type and dose to improve chemotherapy tolerance and subsequent treatment completion rate outcomes. Of note, a handful of ongoing clinical trials have set out to

Table 2
Calculation of chemotherapy relative dose intensity.

RDI = (DDI/SDI) x 100%, where:
DDI = (delivered total dose, in mg/m^2)/(actual time to complete chemotherapy with imputation for missed cycles, in weeks)
SDI = (standard total dose, in mg/m^2)/(standard time to complete chemotherapy, in weeks)
Delivered total dose = total amount of drug administered over chemotherapy course
Actual time to complete chemotherapy with imputation for missed cycles = observed number of weeks between initiation and final receipt of chemotherapy plus expected number of weeks for missing cycles
Standard total dose = total standard amount of drug for administration over chemotherapy course
Standard time to complete chemotherapy = standard number of weeks between initiation and final receipt of chemotherapy

From Weycker, D., et al., Incidence of reduced chemotherapy relative dose intensity among women with early stage breast cancer in US clinical practice. Breast Cancer Res Treat, 2012.

evaluate the effect of exercise or physical activity interventions on outcomes of chemotherapy completion rate, including RDI, for early-stage or advanced breast cancer (ClinicalTrials.gov identifiers: NCT02159157, NCT03314688, NCT02802826) and advanced gastrointestinal cancer (ClinicalTrials.gov identifier: NCT02597075).

4.1. Limitations

This review has several limitations. Despite the large number of records identified through database searching, only a small number of eligible trials (n = 8) were found. Trials included in this review also had varying exercise interventions and patient populations, as well as heterogeneous outcomes used to measure chemotherapy completion rate. Trials were frequently limited by their small sample sizes and lack of statistical power to explore the effect of exercise on outcomes of chemotherapy completion rate. Exploration of this question in types of cancer where optimal chemotherapy dose intensity delivery is more of a challenge than early-stage breast cancer is also warranted.

5. Conclusion

The current evidence suggests exercise does not negatively impact cancer patients' ability to complete chemotherapy treatments. It is unclear if exercise has a beneficial impact on outcomes of chemotherapy completion rate, especially in adults with cancer other than breast cancer. Ultimately, demonstrating an influence of exercise on chemotherapy treatments could provide oncology clinicians with a supportive care intervention that directly impacts the ability to deliver the intended chemotherapy treatment dose and alter patient disease-recurrence and survival outcomes.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Authors' conflict of interest

None to declare.

Appendix A

Search Strategy

Database		Concept 1: Cancer	Concept 2: Exercise	Concept 3: Chemotherapy
CINAHL	Keywords	(neoplasm* or cancer* or tumo#r or malignan*).mp	(exercis* or physical activit* or aerobic training or strength training or endurance training).mp	(chemotherapy* or antineoplastic*).mp
	Subject Headings (CINAHL Headings)	(MH "Neoplasms + ")	(MH "Exercise + ")	(MH "Antineoplastic agents + ") (MH "Chemotherapy, adjuvant + ")
EMBASE	Keywords	(neoplasm* or cancer or malignan* or tumo#r).mp	(exercis* or physical activit* or aerobic training or strength training or endurance training).mp	(antineoplastic* or chemotherapy*).mp
	Subject Headings (EMBASE Terms)	exp Neoplasm/	exp Exercise/	exp Antineoplastic agent/ exp Chemotherapy, adjuvant/
Medline (Platform: Ovid)	Keywords	(neoplasm* or cancer or malignan* or tumo#r).mp	(exercis* or physical activit* or aerobic training or strength training or endurance training).mp	(antineoplastic* or chemotherapy*).mp
	Subject Headings (MeSH)	exp Neoplasms/	exp Exercise/	exp Antineoplastic agents/ exp Chemotherapy, adjuvant

References

Alibhai, S.M., et al., 2015. A phase II exercise randomized controlled trial for patients with acute myeloid leukemia undergoing induction chemotherapy. Leuk. Res. 39 (August (11)), 1178–1186.
Ashcraft, K.A., Warner, A.B., Jones, L.W., Dewhirst, M.W., 2019. Exercise as adjunct therapy in cancer. Semin. Radiat. Oncol. 29 (January (1)), 16–24.
Bonadonna, G., Valagussa, P., Moliterni, A., Zambetti, M., Brambilla, C., 1995. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. N. Engl. J. Med. 332 (April (14)), 901–906.
Bosly, A., et al., 2008. Achievement of optimal average relative dose intensity and correlation with survival in diffuse large B-cell lymphoma patients treated with CHOP. Ann. Hematol. 87 (April (4)), 277–283.
Cespedes Feliciano, E.M., et al., 2017. Muscle mass at the time of diagnosis of non-metastatic colon cancer and early discontinuation of chemotherapy, delays, and dose reductions on adjuvant FOLFOX: the C-SCANS study. Cancer 123 (December (24)), 4868–4877.
Collins, J.T., et al., 2018. The value of physical performance measurements alongside assessment of sarcopenia in predicting receipt and completion of planned treatment in non-small cell lung cancer: an observational exploratory study. Support. Care Cancer 26 (January (1)), 119–127.
Cormie, P., Zopf, E.M., Zhang, X., Schmitz, K.H., 2017. The impact of exercise on Cancer mortality, recurrence, and treatment-related adverse effects. Epidemiol. Rev. 39 (January (1)), 71–92.
Courneya, K.S., et al., 2007. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. J. Clin. Oncol. 25 (October (28)), 4396–4404.
Courneya, K.S., et al., 2009. Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. J. Clin. Oncol. 27 (September (20)), 4605–4612.
Courneya, K.S., et al., 2013. Effects of exercise dose and type during breast cancer chemotherapy: multicenter randomized trial. J. Natl. Cancer Inst. 105 (December (23)), 1821–1832.
Covidence systematic review software, ed. Melbourne, Australia: Veritas Health Innovation.
Day, S.J., Altman, D.G., 2000. Blinding in clinical trials and other studies. BMJ 321 (504).
Denduluri, N., et al., 2015. Dose delays, dose reductions, and relative dose intensity in patients with Cancer Who received adjuvant or neoadjuvant chemotherapy in community oncology practices. J. Compr. Canc. Netw. 13 (November (11)), 1383–1393.
Denduluri, N., et al., 2018. Chemotherapy dose intensity and overall survival among patients with advanced breast or ovarian Cancer. Clin. Breast Cancer 18 (Febraury (5)), 380–386.
Fong, D.Y., et al., 2012. Physical activity for cancer survivors: meta-analysis of randomised controlled trials. BMJ 344 (January (30)) p. e70.
Furmaniak, A.C., Menig, M., Markes, M.H., 2016. Exercise for women receiving adjuvant therapy for breast cancer. Cochrane Database Syst. Rev. 9 (September (21)) p. CD005001.
Griggs, J.J., Sorbero, M.E., Stark, A.T., Heininger, S.E., Dick, A.W., 2003. Racial disparity in the dose and dose intensity of breast cancer adjuvant chemotherapy. Breast Cancer Res. Treat. 81 (September (1)), 21–31.
Hanna, R.K., et al., 2013. Predictors of reduced relative dose intensity and its relationship to mortality in women receiving multi-agent chemotherapy for epithelial ovarian cancer. Gynecol. Oncol. 129 (April (1)), 74–80.
Higgins, J.P., et al., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343 (Octoberr (18)) p. d5928.
Kwak, L.W., Halpern, J., Olshen, R.A., Horning, S.J., 1990. Prognostic significance of actual dose intensity in diffuse large-cell lymphoma: results of a tree-structured

survival analysis. J. Clin. Oncol. 8 (June (6)), 963–977.
Li, T., et al., 2016. The dose-response effect of physical activity on cancer mortality: findings from 71 prospective cohort studies. Br. J. Sports Med. 50 (March (6)), 339–345.
Lyman, G.H., 2009. Impact of chemotherapy dose intensity on cancer patient outcomes. J. Compr. Canc. Netw. 7 (January (1)), 99–108.
Lyman, G.H., Dale, D.C., Crawford, J., 2003. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. J. Clin. Oncol. 21 (Decemebr (24)), 4524–4531.
Lyman, G.H., Dale, D.C., Friedberg, J., Crawford, J., Fisher, R.I., 2004. Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: a nationwide study. J. Clin. Oncol. 22 (November (21)), 4302–4311.
Lyman, G.H., Michels, S.L., Reynolds, M.W., Barron, R., Tomic, K.S., Yu, J., 2010. Risk of mortality in patients with cancer who experience febrile neutropenia. Cancer 116 (December (23)), 5555–5563.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339 (July (21)) p. b2535.
Padilha, C.S., et al., 2017. Evaluation of resistance training to improve muscular strength and body composition in cancer patients undergoing neoadjuvant and adjuvant therapy: a meta-analysis. J. Cancer Surviv. 11 (June (3)), 339–349.
Prado, C.M., et al., 2007. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. Clin. Cancer Res. 13 (June (11)), 3264–3268.
Prado, C.M., et al., 2009. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin. Cancer Res. 15 (April (8)), 2920–2926.
Schmid, D., Leitzmann, M.F., 2014. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. Ann. Oncol. 25 (July (7)), 1293–1311.
Shayne, M., Crawford, J., Dale, D.C., Culakova, E., Lyman, G.H., Group, A.N.C.S., 2006. Predictors of reduced dose intensity in patients with early-stage breast cancer receiving adjuvant chemotherapy. Breast Cancer Res. Treat. 100 (December (3)), 255–262.
Speck, R.M., Courneya, K.S., Masse, L.C., Duval, S., Schmitz, K.H., 2010. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. J. Cancer Surviv. 4 (June (2)), 87–100.
Speck, R.M., et al., 2013. Impact of chemotherapy-induced peripheral neuropathy on treatment delivery in nonmetastatic breast cancer. J. Oncol. Pract. 9 (September (5)) e234-40.
Stene, G.B., Helbostad, J.L., Balstad, T.R., Riphagen, I.I., Kaasa, S., Oldervoll, L.M., 2013. Effect of physical exercise on muscle mass and strength in cancer patients during treatment-A systematic review. Crit. Rev. Oncol. Hematol. 88, 573–593.
Van Vulpen, J.K., et al., 2016. Effects of an exercise program in Colon Cancer patients undergoing chemotherapy. Med. Sci. Sports Exerc. 48 (May (5)), 767–775.
van Waart, H., et al., 2015. Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: results of the PACES randomized clinical trial. J. Clin. Oncol. 33 (June (17)), 1918–1927.
van Waart, H., et al., 2018. Recruitment to and pilot results of the PACES randomized trial of physical exercise during adjuvant chemotherapy for colon cancer. Int. J. Colorectal Dis. 33 (January (1)), 29–40.
Weycker, D., Barron, R., Edelsberg, J., Kartashov, A., Lyman, G.H., 2012. Incidence of reduced chemotherapy relative dose intensity among women with early stage breast cancer in US clinical practice. Breast Cancer Res. Treat. 133 (May (1)), 301–310.
Wildiers, H., Reiser, M., 2011. Relative dose intensity of chemotherapy and its impact on outcomes in patients with early breast cancer or aggressive lymphoma. Crit. Rev. Oncol. Hematol. 77 (March (3)), 221–240.
Xu, Y.J., Cheng, J.C., Lee, J.M., Huang, P.M., Huang, G.H., Chen, C.C., 2015. A walk-and-Eat intervention improves outcomes for patients with esophageal cancer undergoing neoadjuvant chemoradiotherapy. Oncologist 20 (October (10)), 1216–1222.