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Review

The role of resistance training in mitigating cancer-induced cachexia: A systematic review

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ABSTRACT

Background: Cancer induced cachexia, the involuntary loss of lean body mass and adipose tissue, is a debilitating syndrome experienced in up to 80% of all cancer patients. Cachexia is associated with poor treatment outcomes including decreased quality of life, increased risk of infection, disease progression, and mortality. Recent research suggests that exercise interventions may improve cachexia; however, there is a need for comprehensive and systematic review of the literature to evaluate the role of specific interventions on cancer-induced cachexia.
Methods: We conducted a systematic review examining the efficacy of physical activity interventions, particularly resistance training, on cancer-induced cachexia outcomes. We searched seven electronic databases (PubMed, Embase, EBSCO, SCOPUS, Web of Science, PsychINFO, Cochrane) for articles published up to September 2023, yielding 7 eligible studies.
Results: Sample sizes ranged from 20 to 190 participants per study. Studies included pancreatic ($n = 3$), head & neck ($n = 3$), and Gastrointestinal ($n = 1$) cancers. Mean age ranged from 51.90 to 67.1 years old and females comprised 51% of the participants. Most studies implemented resistance training interventions (73%), ranging from 3 months to 6 months in duration. Although the patterns of outcomes indicate promising results, the effect sizes for all models were small and not statistically significant.
Conclusions: The science of exercise interventions to improve outcomes in those with cancer-related cachexia is still emerging although progressive resistance training appears to be the most promising countermeasure. Authors encourage the development of high-quality, fully powered randomized controlled trials (RCTs) examining physical exercise interventions aimed at mitigating cancer-induced cachexia.

1. Introduction

Cachexia, a metabolic syndrome linked to underlying illness and defined by the depletion of muscle mass, which may or may not be accompanied by loss of adipose tissue, is observed in chronic conditions (e.g., chronic renal failure, chronic obstructive pulmonary disease, multiple sclerosis) including cancer.[1] Cancer-induced cachexia (CIC), a cachexia subtype, is marked by the loss of skeletal and/or adipose tissue mass.[1] Additionally, patients may have additional features including decreased muscle strength, increased fatigue, anorexia, low fat free mass index, abnormal biochemistry, increased inflammatory markers, anemia and low serum albumin.[2] CIC is estimated to occur in up to 80% of cancer patients and has been associated with mortality up to 30%.[3,4] The prevalence of CIC is higher in certain cancer types, including 87% of patients with pancreatic and gastric cancer.[5,6] CIC is a complex, multifactorial, metabolic syndrome with multiple co-existing processes ultimately leading to a progressively debilitating state. Furthermore, patients with CIC suffer from a host of catabolic disfunctions including increased protein catabolism and decreased anabolism ultimately resulting in a net negative protein balance.[1] CIC leads to reduced therapeutic effects of chemotherapy, radiation, and targeted therapy resulting in dose reductions, delays, and discontinuations of treatment thus lower survival rates.[7,8] Understanding and addressing the complexities of

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List of abbreviations

CIC	Cancer induced cachexia
BMI	Body Mass Index
QoL	Quality of Life
NIS	Nutrition impact symptoms
GI	Gastrointestinal
EPA	Eicosapentaenoic acid
PA	Physical Activity
RCT	Randomized Controlled Trial
RT	Resistance Training
HRQoL	Health Related Quality of Life
DEXA	Dual Energy Xray Absorptiometry
ACS	American Cancer Society
PROs	Patient Reported Outcomes
ADL	Activities of Daily Living
NCCN	National Comprehensive Cancer Network
ASCO	American Society of Clinical Oncology
BW	Body Weight
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-30
FACT-An	Functional Assessment of Cancer Therapy-Anemia
FHNSI-22	Functional Assessment of Cancer Therapy Head and Neck Symptom Index
VFR	Visceral to Subcutaneous Fat Ratio
MA	Muscle Area
SMI	Skeletal Muscle Index
$\dot{V}O_{2max}$	Maximal Oxygen Consumption

cachexia are crucial for improving outcomes in cancer patients.

Despite its clinical significance, there is no uniform standard for the measurement of cachexia. CIC is traditionally defined as loss of muscle mass with or without the loss of adipose tissue in pre-clinical models, its assessment in cancer patients relies on broader indicators such as body mass index (BMI) and/or weight loss.[9] Various clinical tools have been used to assess CIC but there remains a lack of consensus (i.e., body composition, physical functioning, strength, or a combination of these).[5,6,9] For example, Kamel et al.[5] characterizes CIC by physical performance metrics such as a 400-meter (m) walk and muscle strength tests, while Grote et al.[6] characterize CIC utilizing body composition (e.g., BMI, lean muscle mass), strength (e.g., leg press, chest press), functional performance (e.g., 6-minute [min] walk test), and symptom burden (e.g., fatigue, quality of life [QoL]). To address inconsistencies throughout the literature, Fearon et al.[9] proposed a continuum based on energy depletion, body reserves, including clinical factors such as dietary intake, muscle mass, strength, and functional impairment. The Cachexia Endpoints Working Group[10–13] has also reviewed various endpoints recommending a combination of body weight and body composition assessment (e.g., CT imaging).[11] Additionally, hand grip strength is most used measurement although other measures of physical function may be more sensitive to changes.[13] Although these guidelines offer some direction they highlight the ongoing challenges in fully defining and measuring CIC within clinical practice.

Conventional interventions, including dietary guidance and pharmacotherapy, aim to address symptoms associated with cachexia. Pharmacological treatments like Megace and Eicosapentaenoic acid (EPA) can improve appetite and weight, they do not effectively increase muscle mass,[1,14–21] and nutritional strategies have shown limited evidence regarding optimal timing and comprehensive effectiveness.[15,16,22–24] Furthermore cancer treatments such as chemotherapy and radiation cause a cascade of nutrition impact symptoms (NIS)[24] such as chemosensory alterations and gastrointestinal (GI) disturbances (e.g., nausea, vomiting, diarrhea), which exacerbate the negative protein and energy balance in patients with CIC.

1.1. The therapeutic potential of exercise

Given the limitations of conventional interventions in addressing CIC, exploring alternative or complementary approaches such as physical activity (PA) may offer new avenues for treatment and/or prevention. Exercise is a subset of PA that is planned, structured, repetitive, and purposive, with the objective of improving or maintaining physical fitness. Systematic reviews by Mavropalais et al.[25] and Grande et al.[26] focused on multimodal interventions including PA, have highlighted potential benefits of PA for cachexic patients. The American College of Sports Medicine (ACSM) has issued exercise guidelines for cancer patients[27] advocating for moderate intensity aerobic exercise combined with resistance training (RT) to improve physical and psychosocial outcomes.[28–32]

Meta analyses have shown that moderate intensity exercise can significantly reduce depression among cancer patients during and after treatment,[33,34] and participating in moderate aerobic activity during and after treatment has been shown to improve cancer related fatigue.[35–38] Combined moderate intensity aerobic activity plus RT improves health related quality of life (HRQoL) during and after treatment.[28,39,40] Exercise, tailored to individual needs and guided by evidence-based principles, such as the FITT (frequency, intensity, time, type) principle offer a highly personalized approach that can enhance treatment outcomes and improve physical fitness and demonstrates considerable benefits for enhancing various aspects of psychosocial outcomes, symptom burden, and overall QoL.

1.2. Biological mechanisms underpinning the benefits of exercise

Biological evidence derived from animal models presents compelling insights into the potential of exercise to counteract the effects of CIC.[41] Multiple studies suggest that exercise improves outcomes in pre-clinical models by reducing metabolic characteristics of CIC such as inflammation and oxidative stress.[42–44] On a cellular level, exercise, and particularly RT, can upregulate PCG-1α, a transcriptional coactivator responsible for mitochondrial biogenesis and oxidative adaptations. Although PCG-1α overexpression has not been shown to mitigate CIC in animal models[45]; PCG-1α4, an isoform of PCG-1α, has been associated with increasing muscle mass by inducing IGF-1 and repression myostatin,[41] this is one aspect of the broader mechanisms at play. Muscle mass preservation during CIC can also be explained by restoration of protein synthesis and breakdown as well as the activation of myogenic regulatory factors. Exercise, particularly RT, exhibits the capacity to modulate key metabolic pathways associated with cachexia, offering insights into its potential to combat muscle wasting. These key pathways have been thoroughly reviewed and discussed by Matei et al.[42] and Gould et al.[46]; notably, systemic inflammation secondary to pro-inflammatory cytokines (IL-6, Tumor Necrosis Factor α [TNF-α]) and altered protein metabolism. Exercise helps prevent muscle wasting by increasing protein synthesis through the activation of phosphoinositide-3 kinase and mTOR. mTOR is the main signaling pathway that promotes protein synthesis and reduces muscle atrophy by inhibiting pathways such as ubiquitin proteasome system.[42] An important pro-inflammatory cytokine, TNF-α, promoted protein degradation while exercise upregulates anti-inflammatory cytokines that block TNF-α.[46] Given these promising findings regarding exercise improving physiological outcomes in animal models and healthy participants it is imperative to analyze its efficacy in patients with CIC. This review aims to review the academic

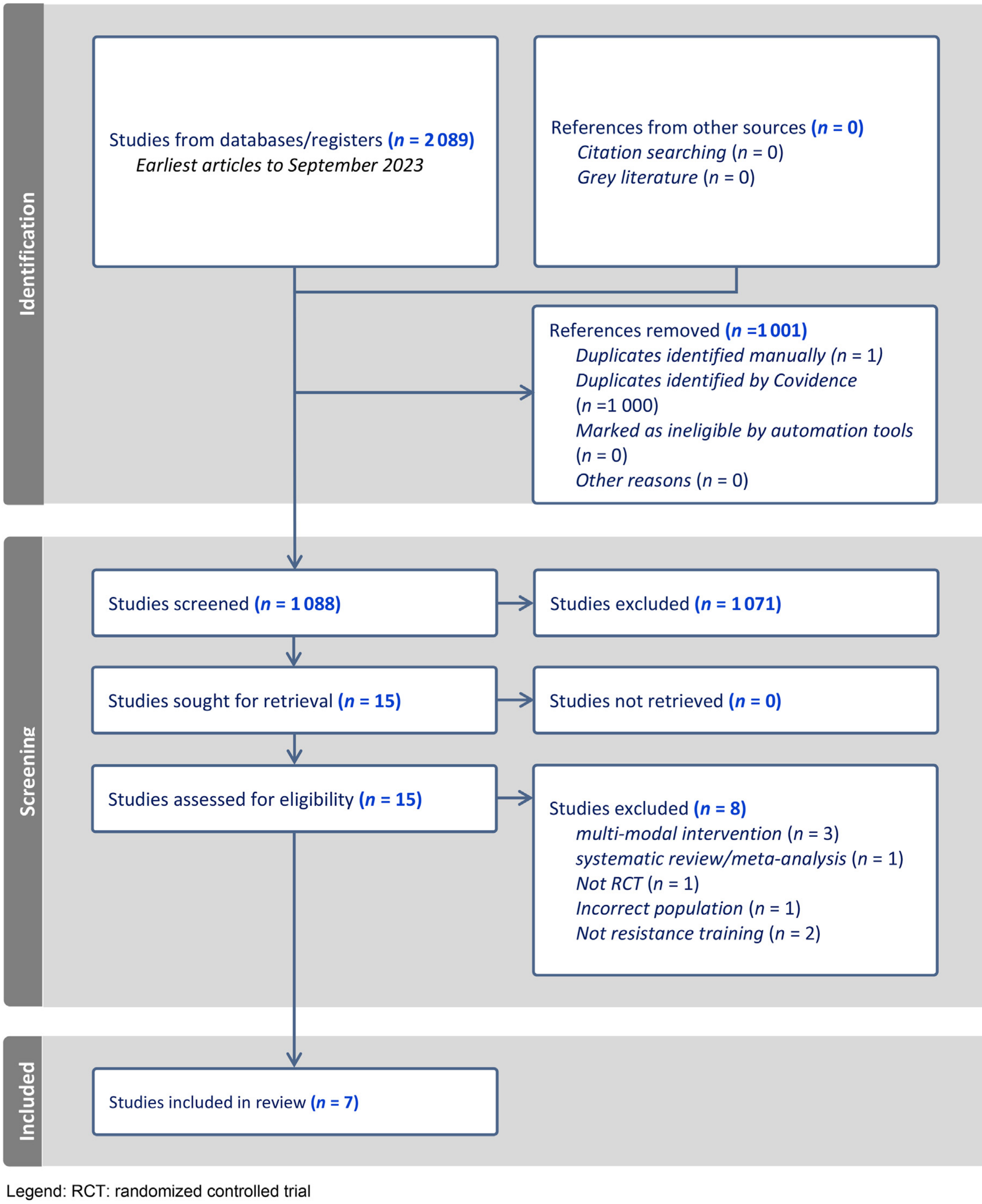

Fig. 1. PRISMA Diagram
Legend: RCT: randomized controlled trial.

understanding and discuss clinical applications and feasibility of RT as a therapeutic intervention.

1.3. The current study

The current study's primary aims were to conduct a systematic review on the impact of exercise interventions on functional and body composition measures in adults diagnosed with CIC. This review provides a comprehensive analysis of RT interventions across various cancer types (e.g., breast, head and neck, GI), cancer stages, and intervention durations. We focus exclusively on RT-based interventions and expand the scope to include the most recent literature, incorporating the latest research findings and advancements in intervention techniques. Our emphasis is on clinical trials, while we reference previous reviews that cover preclinical research on exercise in cachexia. Additionally, we highlight ongoing clinical trials currently recruiting patients.

While many earlier reviews, such as those by Mavropalias et al.[25] and Grande et al.,[26] have explored the broader spectrum of exercise and multimodal interventions, this review specifically targets RT as a focused strategy to combat muscle wasting and functional decline in cachexia. Moreover, we include studies published between 2021 and 2024, providing updated insights that were not addressed in prior reviews. By

Table 1
Risk of bias summary.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Lonbro et al.[51]	?	?	+	–	+	?	+
Capozzi et al.[52]	+	?	?	+	?	–	–
Grote et al.[6]	?	?	–	–	+	–	+
Wiskemann et al.[53]	+	–	–	?	+	+	+
Wochner et al.[54]	+	?	–	+	+	+	+
Kamel et al.[5]	+	+	–	–	+	+	+
Hong et al.[55]	?	?	–	–	+	+	+

Key.
Low risk +.
High risk -
Undefined risk ?

comparing outcomes from supervised, home-based, and combined RT interventions, we explore the feasibility, efficacy, and safety of RT across different cancer types and stages, offering a novel perspective to the ongoing discussion of exercise in cancer care.

We hypothesize that exercise interventions will significantly improve or mitigate CIC as measured by body composition (i.e., BMI, lean muscle mass) and physical functioning (i.e., $\dot{V}O_{2max}$, hand grip strength, and 6-m walk) in cancer survivors.

2. Methods

2.1. Manuscript registration

The protocol was pre-registered in PROSPERO (CRD42023457237) following PRISMA guidelines.[47] We searched seven electronic databases (PubMed, Embase, EBSCO, SCOPUS, Web of Science, PsychINFO, Cochrane) for English-language articles published up to September 2023. The search terms included: ((cancer) AND (cachexia) AND ((physical activity) OR (exercise) OR (resistance training)) AND ((RCT) OR (Randomized Controlled Trial) OR (trial) OR (program) OR (intervention))). We conducted manual reviews of reference lists of relevant reviews and contacted authors in the field to supply unpublished data.

2.2. Inclusion/exclusion criteria

Published research, abstracts, dissertations, and unpublished manuscripts were eligible for inclusion. Studies were included if they: (1) employed a randomized controlled trial or a quasi-experimental study design of an exercise and/or PA intervention; (2) included a sample of cancer survivors[48] defined by the National Cancer Institute as a person from the time of their cancer diagnosis until the end of life; (3) participants met any staging of criteria of the current international definition of CIC by Fearon et al.[9] (pre-cachexia, weight loss of 5% with anorexia and metabolic changes; cachexia, weight loss > 5% in the past six months or BMI < 20 $kg{\cdot}m^{-2}$ and ongoing weight loss > 2% or sarcopenia, anorexia or systemic inflammation; and refractory cachexia, active catabolism, ongoing weight loss, unresponsive to treatment and life expectancy of < 3 months); and (4) had an outcome measure of body composition and/or functional or strength outcomes. Studies were excluded if: (1) study authors were unreachable or unable to provide this information; (2) the study reported only qualitative data, quality improvement design, or protocol only; or (3) the article was in a language other than English.

2.3. Extraction, coding, and reliability

After removal of duplicate studies, the initial search yielded 1 088 articles. Of these, 1 071 were excluded after title and abstract screening. The remaining articles ($n = 15$) met the inclusion criteria for full-text screening. After full-text screening, 7 studies met inclusion criteria, see Fig. 1.

The first author (J.L.H.) and co-authors (S.F.P, M.G.W., M.L.P, E.K) independently screened article titles, abstracts, and full text against the inclusion/exclusion criteria to identify eligible studies. A Cohen's kappa was calculated at each stage of screening to determine inter-rater reliability. Inter-rater reliability was moderate agreement ($\kappa = 0.55$) at title screening and substantial agreement ($\kappa = 0.66$) at abstract and full-text screening. Conflicting opinions were adjudicated by senior author (T.M.B.).

Covidence,[49] a screening and data extraction tool for systematic reviews and meta-analyses, was utilized for article screening and extraction of study characteristics and effect size data. Data extracted included authors, publication year, study design, intervention design and strategy, intervention target, sample size, study period, location/setting, intervention duration, age, sample proportions of race/ethnicity and gender, outcome measures, outcome measure scales, and effect size data. J.L.H and M.G.W independently coded each study.

2.4. Assessment of risk of bias

The risk of bias of the studies was evaluated using the Cochrane Collaboration risk of bias tool[50] to independently assess the risk of bias in included RCTs. Assessment items included: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; (7) other bias. All of the above biases were assessed and classified into low risk, high risk, and undefined risk. If disagreements arose during the evaluation, a third investigator, T.M.B, was consulted. A trial was considered low risk if all of its assessed items were low risk, or if there were fewer than three items of undefined risk. A trial was rated as high risk if two or more items in the trial were assessed as high risk. Other trials were classified as having uncertain risks. (See Table 1 for Risk of Bias Summary).

3. Results

3.1. Study characteristics

The systematic review of RT effects on CIC yielded 7 studies. Table 2 presents study characteristics. There was a total of 420 participants across the 7 studies. Mean age ranged from 51.90 to 67.1 years old, females comprised 51% of the participants. No studies reported any adverse outcomes associated with the intervention. Interventions ranged from 8 weeks to 6 months. Studies were conducted in Germany ($n = 3$),[6,53,54] Canada ($n = 1$),[52] China ($n = 1$),[55] Egypt ($n = 1$),[5] and Denmark ($n = 1$).[51] Sample sizes ranged from 20 to 190 participants per study. Cancer types included pancreatic ($n = 3$),[5,53,54] head & neck ($n = 3$) [6,51,52] and GI ($n = 1$).[55] Cancer staging included I-IV ($n = 5$),[5,6,52–54,51] II-IV ($n = 1$).[55] Interventions were completed while actively undergoing radiotherapy ($n = 2$),[6,52] actively undergoing

Table 2
Study characteristics.

Author	Year	Country	# Participants	Age (mean)	Cancer Type	Cancer Stage & Treatment	Cachexia Definition	Intervention Duration & Frequency	Delivery Modality	Adherence rate	Adverse Outcomes	Study Quality	Variables Measured
Lonbro et al.[56]	2013	Denmark	34	56	Head and Neck	I-IV Radiotherapy or Chemoradiation, completed	< or > 8.5% BW Mean BMI: 23 $kg \cdot m^{-2}$	12 weeks; 30 sessions	In person with exercise therapist for 2 weeks then home based, self-guided	N/A	None	Acceptable	QoL (EORTC QLQ-C30), whole body lean body mass (DEXA), Functional performance (10 m max gait speed, 30 s max chair rise, max stair climb, 30 s max arm curl)
Capozzi et al.[55]	2016	Canada	60	56.1	Head and Neck	I-IV Radiotherapy, actively receiving or after completion	N/A	12 weeks; 2 × /week	2 × /week in person with exercise therapist 2 × /week at home self-guided	N/A	None	Acceptable	Body composition (BMI, lean body mass, % body fat), QoL (FACT-An, FHNSI-22), physical fitness (6 min walk, total grip, sit to stand)
Grote et al.[9]	2018	Germany	20	60.9	Head and Neck	I-IV Radiotherapy, actively receiving	> 5% weight loss/6 months Average −7.1% BW	13 training sessions	In person with physiotherapist	100%	None	Acceptable	Fatigue, activity, motivation, fat mass, lean mass
Wiskemann et al.[53]	2019	Germany	48	60.4	Pancreatic	I-IV (Neo)adjuvant Chemotherapy±surgery, actively receiving	N/A	6 months; 2 × /week	In person with exercise therapist or home-based self-guided;	82% of participants completed > 50% of sessions	None	Acceptable	Muscle strength for knee, elbow, and hip extensors and flexors and cardiorespiratory fitness and body weight
Wochner et al.[54]	2020	Germany	28	62.1	Pancreatic	I-IV (Neo)adjuvant Chemotherapy±surgery, actively receiving	N/A	6 months; 60 min 2 × /week	In person with exercise therapist or home-based self-guided	N/A	None	Acceptable	Quantification of total-fat-area, visceral-fat-area, subcutaneous-fat-area, intramuscular-fat-area, VFR, MA, muscle-density and SMI
Kamel et al.[8]	2020	Egypt	40	51.9	Pancreatic	I-IV Surgery±chemotherapy, actively receiving	> 5% weight loss/6 months Mean BMI: 21.15 $kg \cdot m^{-2}$	3 months; 2 × /week	In person with physiotherapist	N/A	None	Acceptable	400 m walk (seconds), chair rise, lean mass upper and lower, appendicular skeletal muscle, body fat %
Hong et al.[57]	2020	China	190	53.8	GI	II-IV Chemotherapy±radiotherapy, actively receiving	N/A	12 weeks; 2 × /week	In person with exercise therapist	N/A	None	Acceptable	QoL (EORTC QLQ-C30), muscular strength (chest press, seated row, leg press, leg extension), muscular endurance (chest press, leg press), physical performance (6 min walk, 400 m walk, chair rise)

Legend: BW: body weight; QoL: quality of life; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-30; DEXA: dual energy xray absorptiometry; BMI: body mass index; FACT-An: Functional Assessment of Cancer Therapy-Anemia; FHNSI-22: Functional Assessment of Cancer Therapy Head and Neck Symptom Index; VFR: visceral to subcutaneous fat ratio; MA: muscle area; SMI: skeletal muscle index.

Table 3
Physical activity intervention descriptions.

Study	Physical Activity Intervention
Lonbro et al.[56]	In person with exercise therapist for 2 weeks then home based, self-guided; 30 sessions; 2–3 sets, 8–15 repetitions; leg press, knee extension, hamstring curls, chest press, sit ups, back extension, lateral pull down
Capozzi et al.[55]	2 × /week in person with exercise therapist 2 ×/week at home self-guided; warm up 5–7 min, 2 sets of 8 repetitions exercised major muscle groups
Grote et al.[9]	In person with physiotherapist; Warm up 5 min on bicycle; leg press, latissimus pull down and chest press for 3 sets, 8–12 repetitions
Wiskemann et al.[53]	In person with exercise therapist or home-based self-guided; 2 × /week; resistance exercises for major upper and lower muscle groups. Leg press, leg extension, leg curl, seated row, latissimus pull down, back extension, butterfly reverse and crunch. They completed 2 familiarization sessions then did the first 5 exercises for 1–2 sets, 20 repetitions for 4 weeks. At week 5, they increased to 8 exercises, 3 sets, 12 repetitions
Wochner et al.[54]	In person with exercise therapist or home-based self-guided; 60 min 2 × /week; resistance exercises for upper and lower extremities. 4-week adaptation phase 8 exercises per session for 2–3 sets of 8–12 repetitions
Kamel et al.[8]	In person with physiotherapist; 2 × /week; general flexibility and one set of upper and lower exercise was performed for warm up. Machine based exercises were leg press, leg extension, leg curl, seated row, latissimus pull down, back extension, butterfly reverse and crunch. 2 familiarization sessions. For 4 weeks, 1–2 sets of 20 repetitions of the first 5 exercises. At 5 weeks, they performed 8 exercises for 3 sets of 8–12 repetitions
Hong et al.[57]	In person with exercise therapist; 2 × /week; 60 min, leg extension, leg curl, leg press, shoulder internal and external rotation, seated row, latissimus pull down, shoulder flexion and extension, butterfly and butterfly reverse. 3 sets, 8–12 repetitions. If 3 sets of 12 repetitions were completed 5% weight increase next session

chemotherapy±radiotherapy ($n = 1$),[55] completion of chemotherapy or radiotherapy ($n = 1$),[51] actively receiving (neo)adjuvant chemotherapy ($n = 3$).[5,53,54] In the seven included studies, six studies examined functional outcomes (e.g., hand grip strength, shuttle walk test, sit to stand),[5,53,51,52,55] five examined BMI and body composition (e.g., lean muscle mass, percent body fat),[5,6,52–54] and HRQoL,[6,51,52,55] and six analyzed various measures of strength (e.g., chest press, leg press, isokinetic and isometric muscular strength).[53,51,52,55] Article primary aims included: (1) optimal timing of RT intervention,[52] (2) feasibility and efficacy of RT in patients with CIC,[6,53] (3) impact on patients' symptoms, QoL, and physical function,[55] and muscle strength and body composition.[6,54,51]

Table 3 presents the intervention descriptions. Interventions were completed in person ($n = 5$) [5,6,53–55] or a combination of in person and at home ($n = 2$).[52,51] Primary outcomes included: (1) functional performance ($n = 2$),[55,51] (2) muscular strength ($n = 3$),[5,53,51] (3) quantification of body compartments ($n = 1$),[54] (4) QoL ($n = 2$),[6,51] (5) feasibility of intervention ($n = 2$),[6,53] and (6) body composition (e.g., lean body mass, BMI; $n = 4$).[5,6,52,51] Secondary outcomes included QoL ($n = 1$) [52] and cardiorespiratory fitness ($n = 2$).[52,55] Studies evaluated outcomes after 8 weeks ($n = 1$),[6] 12 weeks ($n = 4$),[5,51,52,55] 24 weeks ($n = 1$), [51] and 6 months ($n = 2$).[53,54]

3.2. Narrative synthesis

The systematic review of RT interventions in CIC revealed mixed results across studies. Capozzi et al.[52] reported no significant improvements in lean body mass ($p = 0.756$), BMI ($p = 0.698$), percent body fat ($p = 0.741$), 6-min walk ($p = 0.687$), grip strength ($p = 0.086$), or sit-to-stand ($p = 0.079$). However, they did note increased activity minutes in the delayed intervention group compared to the immediate intervention group.

Kamel et al.[5] found significant increases in walking efficiency (400 m walk: $p = 0.005$; 6-min walk: $p = 0.001$) and chair rise ($p = 0.001$). They also reported gains in lean mass in the upper limb, lower limb, and appendicular skeletal muscles in the RT group ($p < 0.001$), though there were no differences in body fat percentage. Additionally, the RT group saw significant improvements in maximum voluntary isometric contraction of knee and elbow flexors ($p < 0.01$).

Grote et al.[6] reported a 30% loss of fat mass in the intervention group, compared to 20% in the control group, and noted that training loads were increased within the first five sessions. Wiskemann et al.[53] showed greater improvement in elbow flexion and extension with supervised RT compared to home-based RT ($p < 0.05$). Although there were no significant differences between home exercise and control groups, the supervised RT group saw a slight increase in body weight (3.2%), while the home-based RT group remained relatively unchanged (−0.4%), and the control group had a minimal increase (0.8%). Hong et al.[55] demonstrated statistically significant improvements in leg press ($p = 0.021$), leg extension ($p = 0.041$), 6-m fast walk ($p = 0.008$), and chair rise ($p = 0.031$). Conversely, Wochner et al.[54] found no significant differences in RT outcomes between the intervention and control groups.

Lastly, Lonbro et al.[51] reported a 4.3% increase in lean body mass in the early exercise group during the first 12 weeks ($p < 0.001$) compared to a 1.5% increase in the delayed exercise group. After the subsequent 12 weeks, the delayed group saw a 4.2% increase in lean body mass ($p < 0.001$), whereas the early group showed only a 0.5% change ($p < 0.001$). The early exercise group also increased knee extension isometric strength by 20% in the first 12 weeks, while the delayed group achieved a 21% increase in the last 12 weeks ($p < 0.001$). Although there were no differences in functional performance between the groups after the first 12 weeks, the delayed intervention group later improved in chair rise and arm curl performance.

Significant improvements in lean body mass, strength, and functional outcomes were observed in several studies however, other studies reported no significant changes in these outcomes, highlighting the variability in response to RT interventions among CIC patients. This suggests that, while RT can have beneficial effects, the degree of impact may vary depending on the type of intervention, timing, and patient characteristics.

Additionally, Hong et al.[55] investigated RTs effects on QoL showing improvement in physical function ($p = 0.035$), role function ($p = 0.041$), social function ($p = 0.047$), appetite loss ($p = 0.012$) and fatigue ($p = 0.024$). In contrast, Capozzi et al.[52] showed improvement of QoL scores by 12 weeks ($p < 0.001$) but return to baseline by 24 weeks.

3.3. Comparison with control groups

Exercise interventions were generally compared to usual care or no structured exercise regimen. Several studies incorporated early and late exercise interventions. In these comparisons, exercise interventions generally led to significant improvements in muscle strength, lean body mass, and functional performance, indicating a clinical benefit over standard care. However, not all studies showed improvements in body composition or functional outcomes, underscoring the need for personalized approaches in CIC management.

3.4. Consistency across studies

The findings across the included studies were somewhat inconsistent. While some studies demonstrated clear benefits of exercise on muscle mass and strength, others found no significant changes. This variability could be attributed to differences in intervention protocols, patient populations, and study designs, suggesting that further research with standardized methodologies is needed to draw more definitive conclusions.

3.5. Adverse events and safety

None of the studies reported significant adverse events associated with the exercise interventions, indicating that these programs are generally safe for CIC patients. This supports the feasibility of incorporating structured exercise into the care plans of CIC patients, provided that the interventions are tailored to individual capabilities and closely monitored.

4. Discussion

In this systematic review, we synthesized data from 7 studies investigating the relationship between RT and its impact on functional and body composition measures in patients with CIC. Although our findings did not support our primary hypothesis that RT interventions will significantly improve or mitigate CIC as measured by body composition and physical functioning, there were important trends suggesting it as a potential countermeasure for CIC. Notably, progressive RT, appears to stabilize functional and body composition measures. Maintaining function and body composition are equally important, especially in the context of CIC where deterioration is common.

Underlying biologic mechanisms have been explored within bench medicine highlighting the importance RT has on upregulating PCG-1α4 and its ability to counteract the muscle loss associated with CIC.[41] However, in cachectic populations, particularly those undergoing surgery, radiation or several rounds of chemotherapy the goal is not to achieve large muscular or strength gains. Instead, it may be to prevent or slow the progressive of muscle wasting, which could allow patients to maintain physical function, tolerate more treatment cycles and enhance overall QoL. Neo et al.[57] discussed that one third of adults with cancer have difficulty performing activities of daily living (ADL's) (i.e. walking, transferring, housework) and one half require assistance performing instrumental ADL's. Although effect sizes were not significant, the included studies consistently show that RT is beneficial for cancer patients, leading to improvements in muscle strength, lean body mass, and physical performance. These benefits, although subtle, can be clinically meaningful mitigating the impact of severe muscle wasting rather than reversing it completely.

Adverse events were not associated with exercise, indicating that RT is a safe intervention for cancer patients. It is important to note that there are contraindications to exercise in CIC. The National Comprehensive Cancer Network (NCCN) guidelines state that exercise is contraindicated in those with severe anemia, worsening condition or active infection.[58] The American Society of Clinical Oncology (ASCO) emphasize that patients with advanced cancer undergo a medical evaluation to assess for cardiac or pulmonary disease, sarcopenia, thrombocytopenia, anemia, neutropenia, fracture risk, neurotoxicity, lymphedema and metastases prior to initiating an exercise regimen.[59] The high adherence rates observed in several studies also highlight the feasibility of incorporating RT into cancer care. Our review indicates trends suggesting exercise helps patients maintain strength, enabling them to continue their ADL's.

The present study had several limitations that warrant consideration. The overall number of studies available for inclusion was limited, thus hindering the ability to make definitive conclusions regarding the impact of exercise on CIC outcomes. We noted that most studies were conducted in Europe while none were in the US, perhaps limiting generalizability. Secondly, another notable limitation stemmed from the variability in the measurements across the studies included. Future prospective studies, including longitudinal RCTs, are needed to validate our findings and elucidate the causal mechanisms underlying the observed associations.

Our study highlights several areas where additional research is warranted. First, the limited sample size and the heterogeneity in the measurement of variables across studies necessitates more robust and standardized research. Future research should focus on elucidating the biological mechanisms through which exercise exerts its effects on CIC. Particularly, progressive RT appeared to be a potential countermeasure for CIC. Investigating molecular and cellular pathways could provide deeper insights into the interaction between exercise and cancer metabolism. Research should also explore the optimal types and intensities of exercise that yield the most significant benefits for different cancer types and stages. Longitudinal RCTs comparing different exercise regimens could provide valuable guidance for clinical practice. Investigating personalized exercise interventions tailored to individual patient characteristics, such as genetic profiles, treatment regimens, and comorbidities, may enhance the efficacy of these interventions and improve patient outcomes. There is a need for standardized protocols and measures to facilitate comparisons and meta-analyses. Collaborative efforts among research institutions may aid in developing these standards and conducting multicenter trials. Future research should also incorporate patient-reported outcomes to capture factors such as QoL, psychosocial (e.g., anxiety, depression), symptom burden (e.g., fatigue, nausea), and overall well-being. Additionally, an interdisciplinary approach is likely needed, including oncologists, exercise physiologists, nutritionists, and behavioral scientists to develop comprehensive and holistic interventions to address the complexity of CIC.

In addition to the studies reviewed, several active clinical trials are currently investigating the effects of exercise on CIC. At the time of writing this manuscript, on clinicaltrials.gov, there were 6 active trials looking at exercise and nutrition,[56,60–63] one of which was looking at RT and protein supplementation.[64] These trials are looking at GI (n = 3),[56,63,64] lung (n = 1),[62] ovarian (n = 1) [60] and all cancers (n = 1).[61]

Our study, in combination with recommendations from organizations such as ACSM,[27] American Cancer Society (ACS)[65] and ASCO[59] for promotion of exercise during cancer treatment and survivorship, suggest further exercise intervention studies are warranted to evaluate the ability to continue further treatment and therapy. Exercise, particularly RT, appears to be a valuable component of supportive care for cancer patients, maintaining physical function and muscle mass with better outcomes during supervised interventions. The authors emphasize that generalizing these findings across all cancers is challenging due to the varying biological factors and treatment regimens involved. While the effects on QoL are less clear, the overall benefits suggest that RT should be considered in the management of cancer-related physical decline. Further research with larger sample sizes and standardized protocols is needed to better understand the full impact of exercise on diverse cancer populations.

CRediT authorship contribution statement

Jennifer L. Horawski: Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Conceptualization. **Sara E. Fleszar-Pavlovic:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Melissa Lopez-Pentecost:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Tracy E. Crane:** Writing – review & editing, Methodology. **Madalyn G. Wheeler:** Writing – original draft, Investigation, Data curation. **Eric Kholodovsky:** Investigation. **Thomas M. Best:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Availability of data and materials

The data that support the findings of this study are available upon reasonable request from the corresponding author, Jennifer L. Horawski.

Manuscript registration statement

This study followed the PRISMA guidelines for systematic reviews and was pre-registered with PROSPERO (CRD42023457237).

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Declaration of conflict of interest

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We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from jlh371@miami.edu.

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