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REVIEW

Evaluation of resistance training to improve muscular strength and body composition in cancer patients undergoing neoadjuvant and adjuvant therapy: a meta-analysis

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Abstract
Purpose Muscle atrophy and strength decline are two of the most prominent characteristics in cancer patients undergoing cancer therapy, leading to decreased functional ability and reduced quality of life. Therefore, the aim is to systematically review research evidence of the effects of resistance exercise (RE) on lower-limb muscular strength, lean body mass (LBM), and body fat (BF) in cancer patients undertaking neoadjuvant or adjuvant therapy.
Methods This research was conducted using the following online database: Clinical Trial Register, Cochrane Trial Register, PubMed, SPORT Discus, and SciELO, from September 2014 until May 2015. We used the following keywords in various combinations with a systematic search: "Cancer therapy," "Wasting muscle," "Muscle loss," "Muscle function," "Neoadjuvant therapy," "Adjuvant therapy," "Resistance Training," "Weight training," and "Exercise." After selection of 272 full-text articles, 14 publications were included in this meta-analysis.
Results Resistance exercise (RE) during neoadjuvant or adjuvant therapy increased lower-limb muscular strength (mean: 26.22 kg, 95% CI [16.01, 36.43], heterogeneity: P = <0.01, I^2 = 76%, P = 0.00001) when compared to controls over time. Similarly, lean body mass (LBM) increased (mean 0.8 kg, 95% CI [0.7, 0.9], heterogeneity: P = 0.99, I^2 = 0%, P < 0.00001), and decreased body fat (BF) (mean: −1.3 kg, 95% CI [−1.5, 1.1], heterogeneity: P = 0.93, I^2 = 0%, P < 0.00001) compared to controls over time.
Conclusion RE is effective to increase lower-limb muscular strength, increase LBM, and decrease BF in cancer patients undergoing neoadjuvant and adjuvant therapy regardless of the kind of treatment.
Implications for cancer survivors RE increases muscle strength, maintains LBM, and reduces BF in cancer patients undergoing adjuvant and neoadjuvant therapies. Cancer patients and survivors should consider undertaking RE as an effective countermeasure for treatment-related adverse effects to the musculoskeletal system.

Keywords Cancer treatment · Body fat · Skeletal muscle · Resistance exercise

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Introduction

Cancer is an abnormal proliferation of cells caused by external factors, such as alcohol, tobacco, infectious agents, physical inactivity, excessive consumption of unhealthy food, and by internal factors, such as inherent genetic mutations, hormonal disorders, and abnormal immune conditions [1]. According to the American Cancer Society, from 2009 to present day over 1,685,210 new cases of cancer were diagnosed, and about 595,690 are expected to die of cancer in 2016, reflecting more than one person every minute [2]. Breast cancer is the most

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common type of cancer diagnosed in women worldwide, and it is estimated that around 249,260 new cases were diagnosed since 2009, accounting for 40,890 cancer-related deaths. In males, prostate cancer is most prevalent, with 180,890 new cases diagnosed in the same time period, accounting for 26,120 deaths [1, 3].

Cancer cachexia is a metabolic syndrome, characterized by involuntary progressive muscle wasting, which may or not result in the loss of adipose tissue in a short period of time (around 6 months), that cannot be reverted by conventional nutrition therapy [4, 5]. This clinical scenario leads to diminished quality of life in the patient and thus a poor prognosis [6]. About 50% of cancer patients are affected with the cachexia syndrome, and about 80% of patients with pancreatic cancer present severe cachexia [6, 7]. Cancer treatments differ according to stages of the disease with neoadjuvant therapy used to reduce tumor size and improve surgical interventions. On the other hand, adjuvant therapy is commonly used to prevent the recurrence of cancer following primary surgery or radiotherapy [8]. Among different treatments available (e.g. radiotherapy, chemotherapy, immunotherapy, and hormone therapy), the same intervention per se can be used in the adjuvant or neoadjuvant setting according to the treatment purpose [9–12]. These types of treatment worsen the catabolic state already present in cancer patients, leading to negative protein balance and thus abnormal metabolism [4]. Furthermore, muscle wasting and reduced muscle strength are two of the most prominent characteristics in cancer patients undergoing early-stage chemotherapy, leading to decreased functional capacity that may impact quality of life and survival [13].

For a range of well-established theoretical and empirically proven reasons, resistance exercise (RE) is strongly recommended to prevent muscle wasting and improve strength in chronic diseases, including cancer [14]. RE is known to induce positive health effects directly in skeletal muscle and nervous tissue, thus improving the physical autonomy of patients [2, 15, 16]. A roundtable consensus by the American College of Sports Medicine (ACSM) assessed RE to be safe and effective during different oncological therapies [2]. This report, also endorsed by the American Cancer Society has been guiding exercise prescription for cancer patients internationally [17]. In the last few years, the number of published studies about the effectiveness of RE in cancer patients has grown exponentially, which may indicate that physiological and psychological challenges faced by cancer patients might be attenuated, leading to better treatment programs and rehabilitation of patients when engaged in a RE program [2].

In a cohort study conducted by Ruiz et al. (2009) assessing 8762 cancer patients, an inverse association between muscle strength and mortality was observed [18]. Strasser et al. (2013) in meta-analysis, indicated that RE plays a promising role in improving fatigue signals, as well as increasing lean body mass content and decreasing body fat in cancer survivors [19]. However, this study did not consider treatment stage of patients, so in this sense the manifestation and evolution of muscle strength and other health-related outcomes differ due to the initial conditions of patients. Such conditions include more severe acute side effects, such as fatigue signals, diarrhea, toxicity, and cardiotoxicity [13]. In this context, a recent study conducted by Morielli et al. (2016) investigated the feasibility and safety of an aerobic exercise intervention in patients with rectal cancer during and after neoadjuvant chemoradiotherapy. The authors found an increased fatigue in patients with post neoadjuvant treatment. On the other hand, there was an improvement in fatigue during post neoadjuvant to pre-surgery conditions [20].

RE provided long-term mitigated fatigue, and additional benefits in upper and lower body muscle strength, triglycerides, body fat percentage, and improved quality of life in prostate cancer patients undergoing radiotherapy, in comparison to patients completing aerobic exercise [21]. Given the increasing number of studies reporting RE benefits, muscle wasting and muscle strength can be viewed as clinically relevant, and participation of cancer patients in RE has been associated with improved survival. For this reason, the purpose of the present study was to determine and quantify the effects of RE on lower-limb muscular strength, lean body mass (LBM), and body fat (BF) during neoadjuvant and adjuvant therapies.

Methods

Search approach and study selection

This meta-analysis was performed in accordance with Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) [22]. We searched for references on Clinical Trial Register, Cochrane Trial Register, PubMed, SPORT Discus, SciELO, and Cumulative Index to Nursing and Allied Health (CINAHL) of the last 25 years , from September 2014 until May 2015, and we used the following keywords in various combinations with a systematic search:“Cancer therapy,” “Wasting muscle,” “Muscle loss,” “Muscle function,” “Neoadjuvant therapy,” “Adjuvant therapy,” “Resistance Training,” “Weight training,” and “Exercise.” Reference lists from original and review articles were reviewed to identify additional relevant studies. Clinical trials comparing RE and/or combined exercise training (aerobic exercise plus RE) with sedentary participants in cancer patients undergoing chemo or radiotherapy and including lower-limb muscular strength measurement were examined. Two researchers (C.S.P and F.H.B) independently performed the search and the third researcher (P.C.M) checked the search in the case of disagreement on study inclusion. The references of all review articles and original papers were examined and

crosschecked. After exclusion of duplicate publications, the identified articles were included in the review if they matched the following criteria: Patients are receiving neoadjuvant or adjuvant therapy and participating in RE or combined exercise (e.g., resistance and aerobic training). The records were excluded if they presented the following characteristics: (1)studies involving children, (2) unspecified type of patient therapy, (3) studies not presenting measurements of lower-limb muscular strength, (4) studies of combined exercise training with more than 40% of training volume using aerobic exercise, and (5) non-original studies. The selection criteria were not limited by study duration, exercise intensity, baseline levels of physical activity, or cancer types. The search strategy considered two main outcomes: (1) effects of RE in patients undergoing neoadjuvant therapy—Outcome 1 and (2) effects of RE in patients undergoing adjuvant therapy—Outcome 2. The study selection process is described in Fig. 1.

Data collection and analysis

We extracted the following information for each study: gender of the participants, tumor location, purpose of study, resistance training protocol (intensity, frequency, and duration), and main results (lower-limb muscular strength, LBM, and BF) (Table 1). All meta-analysis procedures were conducted as described by Stroup et al. (2000) [23]. Pre and post RE data from one-maximal repetition test (1RM) in lower-limb muscular strength as a dynamic muscle strength parameter, LBM and BF were extracted from all studies selected.

Meta-analysis was conducted using Review Manager Software (RevMan software package version 5.0). RevMan was used to calculate the effect size of patients submitted to RE under neoadjuvant (outcome 1), or adjuvant therapy (outcome 2). We also calculated the effect size of patients submitted to RE undertaking some other classes of therapy shown as secondary outcomes, such as androgen-deprivation therapy (ADT) plus radiotherapy, chemotherapy, radiotherapy, and chemotherapy plus radiotherapy, using the change in muscle strength, LBM, and BM from baseline to post RE intervention vs. control groups over time. In circumstances when standard deviations were not available, these values were calculated using standard statistical methods assuming a correlation of 0.50 between the baseline and post-intervention scores within each subject [24]. Similarly, when studies reported standard error, the values were converted to standard deviation (SD).

For studies with non-parametric data reporting median and range, the equations of Hozo [25] were used to estimate mean and SD. Data from all included studies were used to calculate the weighted mean difference and 95% confidence interval (CI) using a continuous random effects model for both outcomes 1 and 2. Weighted percentages were based on the sample sizes of respective studies. Statistical significance was assumed as $P < 0.05$ in a Z test analysis, to examine whether effect size was significantly different from zero. Study heterogeneity was evaluated using the I^2 statistic and Cochrane's Q. Values of I^2 higher than 50 and 75% were considered moderate and high heterogeneity. For Cochrane's Q, significant heterogeneity is considered to exist when the Q value exceeds the degrees of freedom (df) of the estimate. When meta-analysis

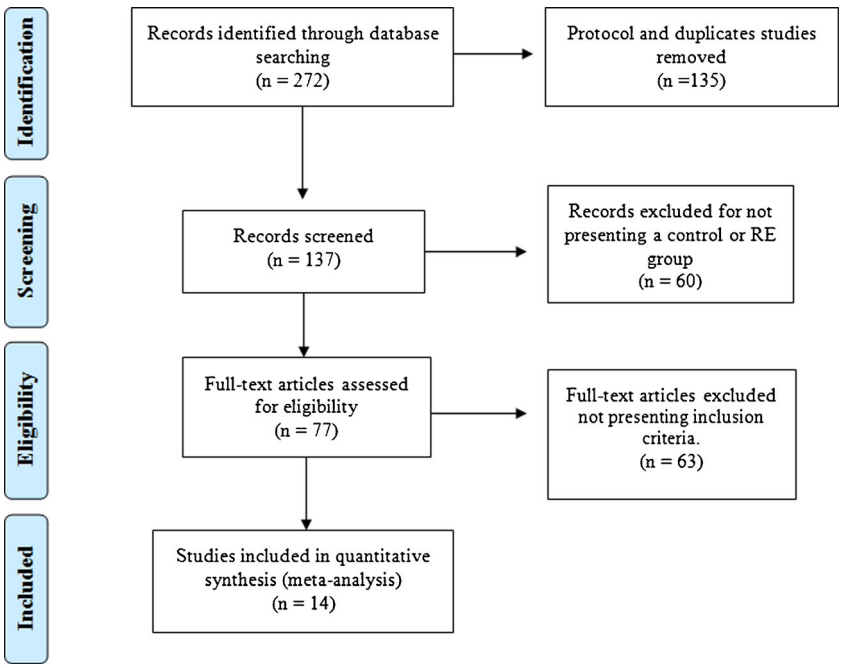

Fig. 1 PRISMA flow diagram of the study selection process

Table 1 Study characteristics included in systematic review and meta-analysis

Author/year	Tumor sites	Aim	Sample	Intervention	Main results
Alberga 2012	Prostate cancer	To examine the effects of 24-week exercise program in prostate cancer patients on changes in body composition and fitness.	*n* = 121(RE training *n* = 40, AE training *n* = 40, control *n* = 41)	3 times per week, performing one set of 8–12 repetitions for weeks 1–2 and increasing to two sets for the remainder of the training program at 60–70% of their estimated 1-RM	Lean mass was preserved in those patients engaged in RE after 24 weeks associated with ADT therapy, besides, lower- limb muscular strength also showed a significant increase in the RE group compared to the control group. Percent body fat remained unchanged in RE and control.
Ahmed 2006	Breast cancer	To examine effects of supervised upper- and lower-body weight training on the incidence and symptoms of lymphedema in 45 breast cancer survivors.	*n* = 56 (RE training *n* = 23, control *n* = 23)	Twice a week for 24 weeks, 9 RE exercises, 3 sets of 8–10 reps weight increased gradually	Self-reported incidence of a clinical diagnosis of lymphedema or symptom changes over 6 months did not vary by intervention status and resistance training group were able to increase their strength
Battaglini 2007	Breast cancer	To determine RE program on changes in body composition and strength of patients being treated for breast cancer.	*n* = 20 (RE training *n* = 10, control *n* = 10)	Low and moderate intensity for 60 min. twice a week for 21 weeks (treadmill and cycle ergometer or elliptical (6–12 min), followed by stretching sessions (5–10 min) and RE training (15–30 min), and stretching activities of approximately 8 min.	RE training promotes changes in body composition and increases strength in patients being treated for breast cancer
Cormie 2013	Prostate cancer	To determine the safety and efficacy of RE training by prostate cancer survivors with bone metastatic disease	*n* = 20 (RE training *n* = 10, control group *n* = 10)	Twice a week for 12 weeks, 8–12 RM, 2–4 sets.	Muscle strength (~11%; submaximal aerobic exercise capacity ~5% and ambulation ~12%), physical activity level (~24%) and lean mass (~3%) with favorable changes in the exercise group compared with the usual care group
Cormie 2014	Prostate cancer	To determine supervised exercise minimizes treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy.	*n* = 61 (RE training *n* = 32, usual care *n* = 31)	Twice a week, 3 months, 60–85% 1RM, 1–4 sets, 6–12 reps.	Changes in cardiovascular fitness, maximal strength, and lower body function (repeated chair rise) differed significantly between groups, with improvements in physical function seen for the exercise group compared with the usual-care group
Courneya 2007	Breast cancer	To examine the relative merits of aerobic and resistance exercise in blunting these effects.	*n* = 242 (RE training *n* = 82, AE training *n* = 78, Control *n* = 82)	3 times per week for duration of CHT, 2 sets, 8–12 reps, 60–70% of 1RM.	RE was superior to usual care for improving muscular strength, LBM, and CHT completion rate. RE did not significantly improve cancer-specific QOL and fatigue.
Galvão 2010	Prostate cancer	To examine the impact of a combined resistance and aerobic exercise program as a countermeasure to these AST-related toxicities.	*n* = 57 (RE training and AE training *n* = 29 or usual care *n* = 28)	RE (twice a week for 12 weeks, 6 to 12 RM, 2–4 sets). AE (15 to 20 min, 65 to 85% maximum heart rate and perceived exertion at 11 to 13(6 to 20 point, Borg scale)	After 12 weeks of program, there was an increase of 0.8 kg for total body lean mass, reflecting differences between groups for upper limb, lower limb, and appendicular skeletal muscle. Differences in strength between groups ranged from 31 kg for the leg press presenting a significant increase.
Nilsen 2015	Prostate cancer	To investigate the effects of strength training on body composition,	*n* = 58 (RE training *n* = 28, usual care *n* = 30)		Did not observe any statistically significant between group effect from 16 weeks of

Table 1 (continued)

Author/year	Tumor sites	Aim	Sample	Intervention	Main results
		physical functioning, and quality of life in prostate cancer patients during androgen deprivation therapy		3 times per week during 16 weeks, 1–3 sets, 6–10 reps, 80–90% of 1RM	high-load strength training on total LBM, but the intervention led to significant beneficial effects on LBM in the extremities, muscle strength, and physical function. No intervention effects were observed for a BMD, fat mass, or HRQOL
Schmitz 2005	Breast cancer	To evaluate body weight, height, body fat, lean mass, body fat %, and waist circumference, as well as fasting glucose, insulin, insulin resistance, insulin-like growth factor-I IGF-I, IGF-II, and IGF-binding protein-1, IGFBP-2, and IGFBP-3.	n = 133 (RE training n = 65, usual care n = 68)	Twice a week for 52 weeks, 10 RE exercises, 3 sets of 10 reps; weight gradually increased	RE did not result in increased incidence of BCRL compared with controls at 52 week Significant improvements in muscle strength and body fat compared with controls at 52 week
Schmitz 2009	Breast cancer	To evaluate the effects of RE on limb swelling, muscle strength, and body composition	n = 129 (RE training n = 58, usual care n = 63)	Twice a week for 52 weeks. 10 exercises, 3 sets of 10 reps; weight increased gradually	RE had no significant effect on limb swelling and resulted in a decreased incidence of exacerbations of lymphedema at 52 week. Further, significant improvements in muscle strength compared with control
Schmitz 2010	Breast cancer	To evaluate the effects of RE on lymphedema onset, muscle strength, and body composition	n = 133 (RE training n = 60, usual care n = 63)	Twice a week for 52 weeks. 10 exercises, 3 sets of 10 reps; weight gradually increased	RE did not result in increased incidence of BCRL compared with controls at 52 week. Significant improvements in muscle strength and body fat compared with controls at 52 week
Segal 2009	Prostate cancer	To evaluate the effects of RE or AET on fatigue, QOL, physical fitness, body composition, PSA, testosterone, lipids, and hemoglobin	n = 121 (RE training n = 40, AE training n = 40, usual care n = 41)	3 times per week for 24 weeks. 10 exercises, 2 sets of 8–12 reps at 60%–70% 1RM	RE significantly improved muscle strength, aerobic fitness, QOL, fatigue, and prevented body fat increases compared with usual care at 24 week
Winters-Stone 2012	Breast cancer	To evaluate the effects of RE on muscle strength and physical function	n = 67 (RE training n = 36, control n = 31)	3 times per week for 52 weeks. 10 RE exercises, 1–3 sets of 8–12 reps at 80% 1RM + impact exercise program	Significant improvements in maximal muscle strength in the RE group compared with controls at 52 week. RE did not improve fatigue
Winters-Stone 2014	Prostate cancer	To evaluate the effects of RE on BMD, body composition	n = 67 (RE training n = 36, control n = 31)	3 times per week for 52 weeks. 10 RE exercises, 1–3 sets of 8–12 reps at 80% 1RM + impact exercise program	RE training improved muscle strength in androgen deprived PCS. Strengthening muscles using functional movement patterns may be an important feature of exercise programs designed to improve perceptions of physical function and disability.

N number of participants, *RE* resistance exercise, *AE* aerobic exercise, *1-RM* one repetition maximal, *ADT* androgen deprivation therapy, *CHT* chemotherapy, *LBM* lean body mass, *QOL* quality of life, *AST* androgen suppression therapy, *BMD* bone mineral density, *HRQOL* health-related quality of life, *IGF-1* insulin-like growth factor-1, *IGF-2* insulin-like growth factor-2, *IGFBP-1* insulin–like growth binding protein-1, *IGFBP-2* insulin –like growth binding protein-2, *IGFBP-3* insulin–like growth binding protein-3, *BCRL* breast cancer–related lymphedema, *PSA* prostate-specific antigen

was considered to be moderate to high heterogeneity, and the random-effects model was used [26], publication bias was tested visually using a funnel plot. The risk of bias was assessed according to the Cochrane collaboration [27].

Forest plots were generated to illustrate the study-specific effect sizes along with a 95% CI.

Results

Studies' characteristics

The selection process generated 272 full-text articles and is documented in the PRISMA flow diagram (Fig. 1). Repeated studies, reviews, and meta-analysis were excluded (n = 135). As a result, 137 studies were then assessed for eligibility by applying the inclusion and exclusion criteria, 60 studies were excluded for not presenting a control or RE group. Sixty-three were excluded for not presenting inclusion criteria. Finally, a total of 14 studies met the specific outcomes proposed in the present meta-analysis, and they presented low risk of bias (Fig. 2). Study characteristics and detailed description of exercise protocol and outcomes are presented in Table 1.

Seven studies included women with breast cancer [28–34] and seven studies in men with prostate cancer [21, 35–40]. The total number of patients in the RE group were 522 and 525 in the control. The duration of RE intervention ranged from 12 to 16 weeks [34, 36–39], 24 weeks [21, 28, 29, 35], and 52 weeks [30–33, 40]. Frequency of RE intervention per week ranged from twice a week [28–32, 36–38] to three times a week [21, 34, 35, 39]. Training intensity was between 40 and 85% of 1RM and 6–12 maximum repetition. Training load was adjusted accordingly to keep maximum possible repetitions per set between 6 and 12 RM. RE machines were most commonly used and incorporated exercises for all major muscle groups.

Lower-limb muscle strength, LBM, and BF were used as main outcomes in our systematic review. Overall, muscular strength increased significantly when compared to controls over time (mean: 26.22 kg, 95% CI [16.01, 36.43], heterogeneity: P = <0.01, I^2 = 76%, P = 0.00001 Fig. 2). When RE response was analyzed separately by neoadjuvant or adjuvant treatments, we observed similar increases in muscle strength in patients undergoing neoadjuvant (mean 23.43 kg, 95% CI [14.51, 32.36], heterogeneity: P = 0.36, I^2 = 10%, P < 0.00001 Fig. 2) and adjuvant therapy compared to controls over time (mean 28.61 kg, 95% CI [10.72, 46.49], heterogeneity: P < 0.001, I^2 = 86%, P = 0.0008 Fig. 2). We observed significant heterogeneity between randomized controlled trials (RCT) in adjuvant analysis (86%), which represents a strong indicator of different manipulation of training variables or patient's condition towards treatment.

Patients receiving ADT plus radiotherapy did not appear to compromise ability to increase lower-limb muscle strength (mean 23.1 kg, 95% CI [12.4, 33.7], heterogeneity: P = 0.27, I^2 = 22%, P = 0.00001) (Table 2). Similarly, patients receiving chemotherapy plus radiotherapy also significantly increased lower-limb muscle strength compared to controls over time (mean 36.2 kg, 95% CI [15.8, 56.6], heterogeneity: P = 0.005, I^2 = 74%, P = 0.001) (Table 2).

We included ten studies specifically reporting body composition in response to RE. We found a significant increase over time for LBM in the RE group compared to controls (mean 0.86 kg, 95% CI [0.76, 0.96], heterogeneity: P = 0.99, I^2 = 0%, P < 0.00001; Fig. 3). When examining groups separately by neoadjuvant and adjuvant therapies, we found a significant increase in LBM in patients on adjuvant therapy (mean 0.86, 95% CI [0.76, 0.96], heterogeneity: P = 0.44, I^2 = 0%, P = 0.0000; Fig. 3) but not for those on neoadjuvant compared to controls over time (mean 0.86 kg, 95% CI [−1.01, 2.61], heterogeneity: P = 1.00, I^2 = 0%, P = 0.39; Fig. 3).

Although the results indicated homogeneity between RCTs, the discrepancy of weight and CI observed in Schmitz et al. (2005) [29] can be explain through the similarity of increased LBM (mean 0.86 kg) across all analyses conducted. Furthermore, it may be also due to the extended training period of 52 weeks and low SD. Interestingly, we also found that patients undertaking chemotherapy plus radiotherapy had a significant increase in LBM (mean: 0.86, 95% CI [0.76, 0.96], heterogeneity: P = 0.55, I^2 = 0%, P = 0.0001; Table 2) but not for

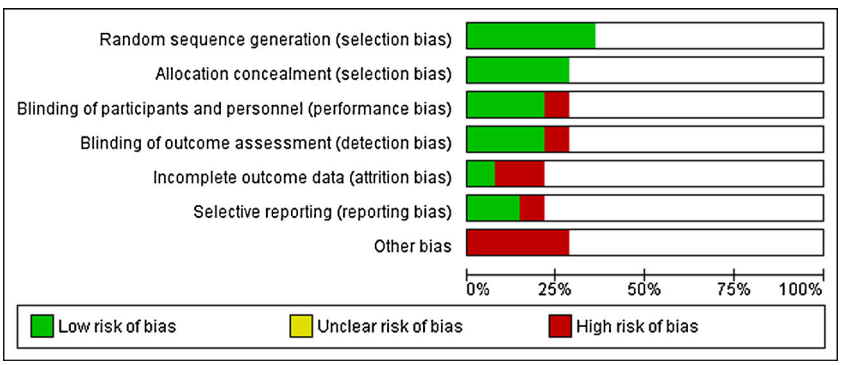

Fig. 2 Risk of bias summary

Table 2 .Meta-analysis performed on the effects of RE on muscular strength (lower-limb RM), LBM, and BF on different types of therapies. Calculation based on random effects model. Results are expressed as weighted mean difference (WMD) and 95% confidence intervals (95% CI)

Outcomes	*N* studies	95% CI	*P*	I^2
Lower-limb muscular strength (Kg)				
ADT plus radiation	6	23.11 [12.44, 33.78]	0.00001	22%
Chemotherapy	2	13.16 [−6.01, 32.32]	0.18	58%
Radiotherapy	1	27.50 [6.74, 48.26]	0.009	NA
Chemotherapy + radiotherapy	4	36.25 [15.88, 56.62]	0.005	74%
Test for overall effect Z		26.46 [16.30, 36.62]	0.0001	76%
LBM (Kg)				
ADT plus radiation	5	0.80 [−1.01, 2.61]	0.39	0%
Chemotherapy	1	0.40 [−1.08, 1.88]	0.60	NA
Chemotherapy + radiotherapy	3	0.86 [0.76, 0.96]	0.0001	0%
Test for overall effect Z		0.85 [0.76, 0.95]	0.0001	0%
BF (%)				
ADT plus radiation	5	−0.72 [−3.70, 2.26]	0.64	0%
Chemotherapy	2	−3.58 [−9.13, 1.97]	0.21	0%
Radiotherapy	1	−2.00 [−12.35, 8.35]	0.70	NA
Chemotherapy + radiotherapy	3	−1.38 [−1.57, −1.19]	0.0001	0%
Test for overall effect Z		−1.38 [−1.57, −1.19]	0.0001	0%

ADT androgen deprivation therapy, *NA* not applicable

those undertaking ADT plus radiotherapy (mean: 0.80, 95% CI [−1.01, 2.61], heterogeneity: $P = 1.00$, $I^2 = 0\%$, $P = 0.39$; Table 2).

We also found that BF significantly decrease following RE (mean: −1.3 kg, 95% CI [−1.5, 1.1], heterogeneity: $P = 0.93$, $I^2 = 0\%$, $P < 0.00001$; Fig.4) with a significant decrease for those undergoing adjuvant therapy (mean: −1.3 kg, 95% CI [−1.5, 1.1], heterogeneity: $P = 0.93$, $I^2 = 0\%$, $P = 0.00001$; Fig. 4). However, there was no change for those undergoing neoadjuvant therapy (mean − 1.1 kg, 95% CI [−5.4, 3.0], heterogeneity: $P = 1.00$, $I^2 = 0\%$, $P = 0.58$; Figs. 4 and 5). Although the results indicated homogeneity between RCTs in neo and adjuvant therapy analyses, the weight and CI discrepancy observed by Schmitz et al. (2005) [29] included in adjuvant therapy analysis may be due to low SD. There was also a decrease in BF in patients undergoing chemotherapy plus radiotherapy (mean: −1.38, 95% CI [−1.57, −1.19], heterogeneity: $P = 1.00$, $I^2 = 0\%$, $P = 0.0001$; Table.2).

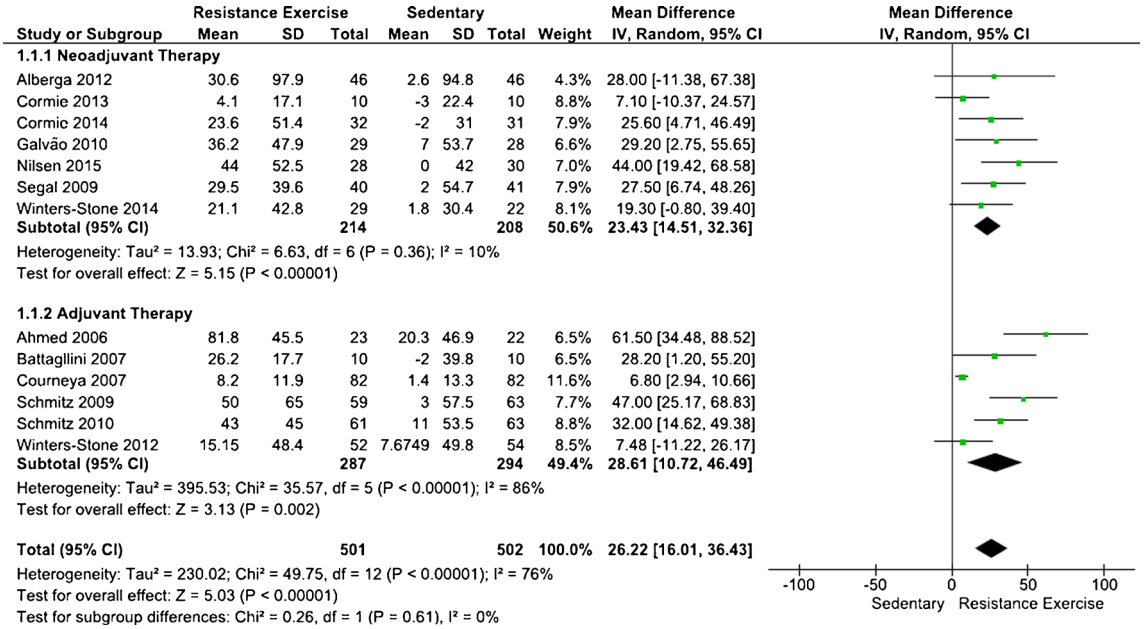

Fig. 3 Meta-analysis performed on the effects of RE on muscular strength (lower-limb RM) on neoadjuvant and adjuvant therapy. Calculation based on random effects model. Results are expressed as weighted mean difference (WMD) and 95% confidence intervals (95% CI)

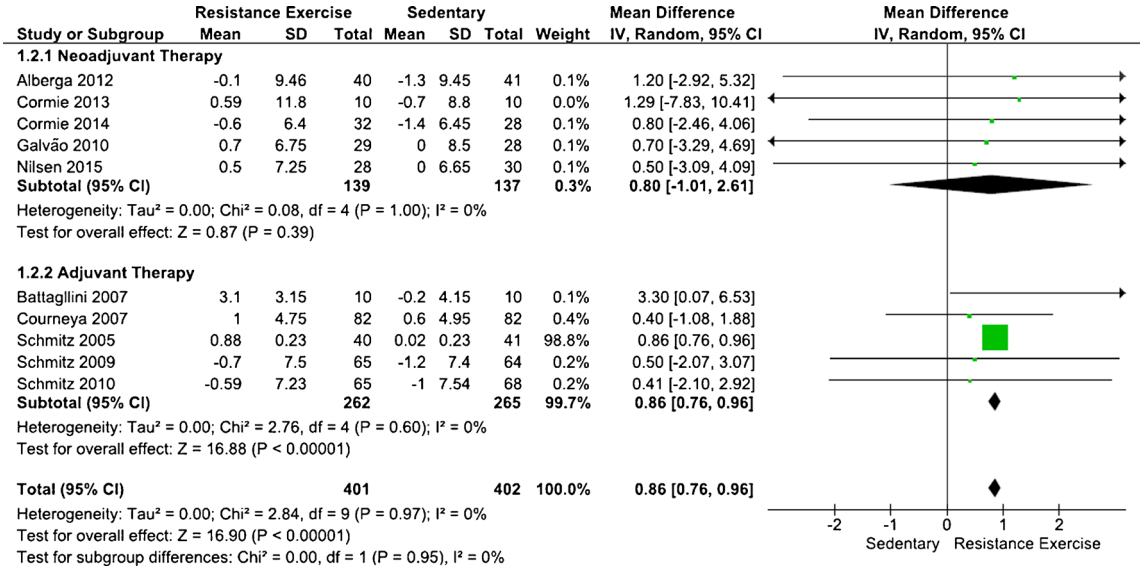

Fig. 4 Meta-analysis performed on the effects of RE on lean body mass (kg) on neoadjuvant and adjuvant therapy. Calculation based on random effects model. Results are expressed as weighted mean difference (WMD) and 95% confidence intervals (95% CI)

Discussion

The exponential increase in the number of quality RCT of RE and/or combined (RE plus aerobic) training for cancer patients has encouraged the publication of reviews and meta-analyses to resolve divergent discussions in the literature. One of the most comprehensive discussions in the literature is the importance of maintaining and/or increasing muscle strength and muscle mass as a strong indicator for tolerance to treatment and increased survival time [41].

This systematic review with meta-analysis investigated whether RE is effective in improving lower-limb muscular strength, preventing loss of LBM, and reducing BF during different stages of cancer therapy (neoadjuvant and adjuvant) (Table 3). Moreover, our systematic review and meta-analysis is novel in that we explored the effects of RE during specific time points in cancer treatment and disease trajectory including when patients initiate treatment, after primary treatment such as surgical procedures, and associated adjuvant therapies. Although potentially curative, neoadjuvant therapies may increase toxicities and this may be associated with increased risks of surgical morbidity. In this case, improvements in musculoskeletal and cardiorespiratory fitness by exercise during neoadjuvant

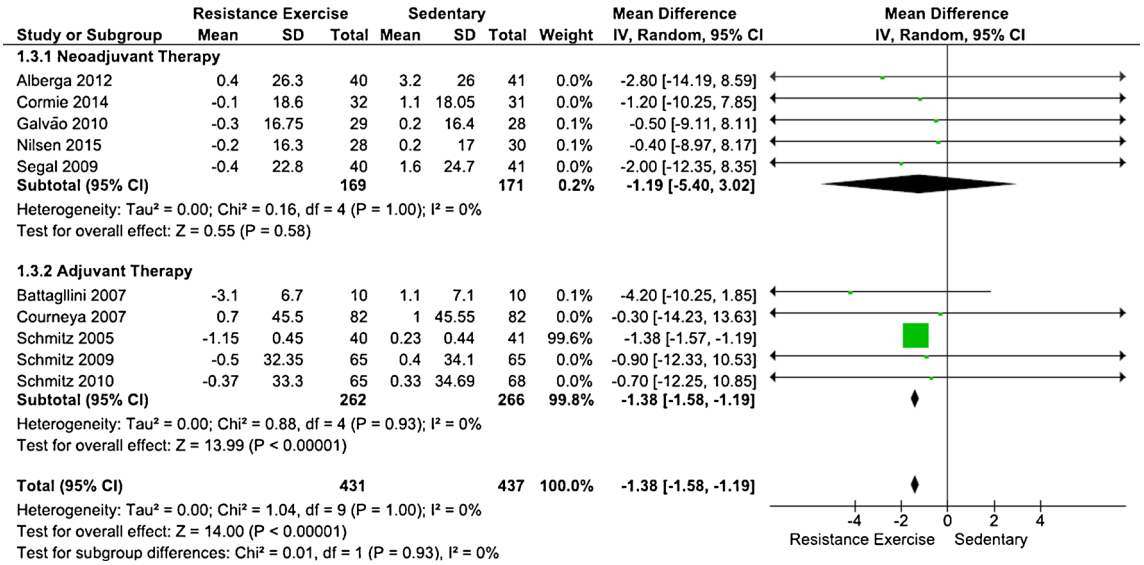

Fig. 5 Meta-analysis performed on the effects of RE on body fat (%) on neoadjuvant and adjuvant therapy. Calculation based on random effects model. Results are expressed as weighted mean difference (WMD) and 95% confidence intervals (95% CI)

Table 3 Summary of outcomes changed in patients undergoing neoadjuvant and adjuvant therapy

Variables	Neoadjuvant	Adjuvant	Overall
Muscle Strength	↑	↑	↑
LBM	→	↑	↑
BF	→	↓	↓

BM lean body mass, *BF* body fat

↑ increase, → maintenance, ↓ decrease

treatment may improve patient outcomes and recovery following surgery [42, 43].

Moreover, the European surgical outcome study has recently highlighted that comorbidity has a great impact on the recovery process post-operative and is associated with reduced survival [44]. As a result, the implementation of exercise–oncology interventions has attracted great interest of researchers and clinicians over recent years with the proposal to reduce post-operative morbidity and side effects during adjuvant therapy [45].

Indeed, there were several important findings; for instance, RE increased lower-limb muscular strength in patients undertaking neoadjuvant and adjuvant therapy compared to controls. However, the high and significant heterogeneity of the RCTs included in the adjuvant studies for LBM analysis (I^2 = 86%) must be considered. Different training periods, as presented in the RCTs included in our review (12–52 weeks), intensities of training (40–80% 1RM), and differences in progression of training load may have contributed to the heterogeneity of analysis. In this scenario, the increase of lower-limb muscular strength in neoadjuvant and adjuvant analysis can be explained initially by neural adaptation, resulting predominantly from increased motor unit recruitment and likely firing rate [46, 47] resulting in increased force development [48]. Other reviews and meta-analyses showed similar increases of lower-limb and upper-limb strength after RE program to those found in our meta-analysis [19, 49, 50]. Additionally, improvements in muscle strength were independent of the treatment type (e.g., chemotherapy, radiotherapy or ADT).

Increased lower-limb muscular strength was concomitant with increase in LBM for those cancer patients only undergoing adjuvant therapy. Due to the discrepancy of weight (98%) in Schmitz et al. (2005) study [30], we suggest that increased LBM reported here was due predominantly to this one study (Fig.3). However, it is important to highlight that patients undergoing neoadjuvant therapy may also preserve LBM after RE intervention. Our data also demonstrated that RE increases LBM in breast cancer patients undergoing chemotherapy and chemoradiotherapy. In studies including men with prostate cancer, patients were treated with ADT which substantially impacts body composition and other skeletal-related muscle adverse effects. For example, substantial decline (~1.4 kg) of LBM following the first year of ADT has been previously reported [51]. In this particular setting, RE can be an effective exercise modality to restore skeletal muscle function [51]. It is noteworthy that the ability to increase or maintain LBM during intensive neo and adjuvant treatment combined with RE program is an important clinical outcome, since accentuated decline of this variable occurs rapidly [52]. Rutten et al. (2016) investigated whether loss of skeletal muscle during neoadjuvant chemotherapy was related to decreased survival in ovarian cancer patients. Their findings were that patients who were able to maintain or gain LBM during neoadjuvant chemotherapy had an increased overall survival relative to patients who decreased LBM. This difference reflected in survival was the most prominent from 2 years after the start of therapy onwards [53]. Furthermore, repeated exposure to RE induces cumulative periods of positive protein balance, which is required for increased muscle cross-sectional area due to the activation of signaling cascades in favor of the anabolic process that occurs after muscle mechanical overload and in the subsequent recovery period [54]. The alterations in muscle metabolism of proteins induced by RE can be very important to cancer patients to counteract the negative protein and energy balance present in cachexia. Hypertrophic adaptation depends on other metabolic events, among them, the necessity of an anabolic environment (e.g., the regenerative/recovery rate), of which mechanisms have been poorly investigated in cancer survivors [55].

Our data demonstrate that RE was able to decrease BF in patients undergoing adjuvant therapy, and maintain in neoadjuvant phases. We highlight that BF results should be interpreted with the same caution as the LBM results, due to the weight discrepancy (99.6%) of the Schmitz et al. (2005) study [30]. In meta-analysis conducted by Strasser et al. (2013), similar reductions of BF were reported to that of our analysis, and they also observed high and significant heterogeneity in their pooled analysis of BF change [19].

There is a wide degree of variability of adipose tissue in women with breast cancer [56]. The increase of BF is a common side effect of cancer treatment, mainly adjuvant therapy, as well as hormonal therapies [57]. Furthermore, excess of fat mass is directly related to increased risk of recurrence and progression of cancer [58] and has been drastically aggravated, and is responsible for 20% of all cancer deaths in women being attributable to overweight and obesity [3]. Increased adiposity is associated with increased mortality by prostate and stomach cancer in men, as well as breast cancer in postmenopausal women, endometrial, uterine, and ovarian cancer [59]. Our data also demonstrated that RE decreased BF in breast cancer patients undergoing chemotherapy and chemoradiotherapy. These results are in agreement with our initial hypothesis that RE could promote significant changes in muscular strength and body composition even during different types of therapy.

Our meta-analysis has some limitations that must be considered. Significant heterogeneity was found in the adjuvant therapy subgroup for lower-limb muscular strength due to the variance in exercise protocols (variable intensities and different durations of the exercise programs) and the variation between diagnostic assessment at beginning of RE (immediate or delayed after diagnosis). As a result, caution is warranted when interpreting our results. This review was carried out only with breast and prostate cancer survivors. The effects of RE in cancer survivors with other tumor sites and hematological malignancies are lacking. Further well controlled RCTs are required to reinforce the importance of incorporating RE following cancer diagnosis and or at the onset of cancer therapies. A further limitation is the limited number of studies (n = 14) included in our meta-analysis.

Conclusion

RE is effective for increasing lower-limb muscular strength, prevent the loss of LBM, and reduce BF in cancer patients undergoing neoadjuvant and adjuvant therapy regardless of the type of treatment. These observations indicate that patients undergoing RE may have greater protection against treatment induced loss of muscle mass and strength hence reducing side-effects of pharmaceutical interventions and improving patient outcomes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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