Effect of physical exercise on muscle mass and strength in cancer patients during treatment - A systematic review

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Abstract (max 150 words)

Cancer treatment and its side effects may cause muscle wasting. Physical exercise has the potential to increase muscle mass and strength and to improve physical function in cancer patients undergoing treatment. A systematic review was conducted to study the effect of physical exercise (aerobic, resistance or a combination of both) on muscle mass and strength in cancer patients with different type and stage of cancer disease. Electronic searches were performed up to January 11th 2012, identifying 16 randomised controlled trials for final data synthesis. The studies demonstrated that aerobic and resistance exercise improves upper and lower body muscle strength more than usual care. Few studies have assessed the effect of exercise on muscle mass. Most studies were performed in patients with early stage breast or prostate cancer. Evidence on the effect of physical exercise on muscle strength and mass in cancer patients with advanced disease is lacking. More exercise studies in patients with advanced cancer and at risk of cancer cachexia are warranted.

Key words: physical exercise, cancer, muscle mass, muscle strength, cachexia

Table of content

1. Introduction

Cancer patients are faced with a range of disease- and treatment-related effects that might alter metabolism, food intake and body composition and cause significant physical and psychosocial impairment. Physical exercise has in general a positive impact on many biological processes such as energy expenditure, insulin resistance, inflammation and most body organs and tissues. In cancer patients, there is evidence that physical exercise contributes to reduce fatigue[1], improves quality of life[2, 3] and relieves many of the adverse side-effects experienced both during and after treatment[4, 5].

Physical exercise is defined as an activity that is planned, structured, repetitive and purposeful, with the aim to improve or maintain one or more components of physical fitness i.e. endurance, muscular strength and body composition [6]. According to national and international physical activity recommendations, 150 minutes of weekly moderate intensity aerobic exercise, or alternatively 75 minutes of high-intensity exercise, are required to promote and maintain health in adults. Additionally, muscle-strengthening exercise is recommended to be performed twice weekly [7].

In principle, the same activity recommendations apply to patients with cancer[8]. However, a range of factors beyond those usually encountered when providing exercise advice in healthy populations must be considered, especially in patients who are undergoing cancer treatment or experience adverse side-effects of treatment [9, 10]. Physical exercise is considered to be well-tolerated, feasible and safe during and following cancer treatment [5, 11] and even cancer patients with advanced stages of disease are willing to engage in physical exercise[12]. Thus, based on current knowledge, it is considered clinically sound to advise most cancer patient to perform physical exercise.

Cancer cachexia is “a multifactorial condition characterised by an on-going loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment” [13]. As much as 60 - 80 % of patients with advanced cancer, depending on diagnosis, develop this condition and at present there are few efficient therapeutic options [14]. Physical exercise may be of particular importance for cancer patients with advanced disease in a pre-cachectic or cachectic stage because of its potential effects on muscle mass and strength[15]. Experimental trials have demonstrated possible anti-inflammatory

effects of exercise in cachectic mice [16] as well as partial rescue of muscle mass and strength in tumour –bearing mice when exercise was combined with eicosapentiaenoic acid[17]. Furthermore, a small number of clinical studies have demonstrated the contribution of exercise to reduce or delay cachexia in patients with chronic diseases other than cancer [18, 19]. Previous reviews on effects of physical exercise in patients with cachexia have been narrative and not specific to cancer patients[20, 21], or have mainly discussed biological and pathophysiological effects of exercise on cachexia-related muscle wasting[22, 23].

Primarily, our idea for a systematic review was to examine the scientific evidence of effects of physical exercise on muscle mass and strength in cancer patients in a pre-cachectic or cachectic stage. Our first systematic search, per January 2012, did not identity controlled studies to answer this question, and therefore we re-defined our aims to include a wider group of cancer patients. We consider it appropriate to guide further clinical studies in patients with advanced cancer by extrapolating data from general cancer.

The overall aim of this systematic review was to evaluate the scientific evidence of effect of physical exercise on muscle mass and strength in patients with cancer. The following research questions were formulated:

1. What type of physical exercise intervention i.e. aerobic, resistance or combined aerobic and resistance exercise, is most effective on muscle mass and strength?
2. Is the effect on muscle mass and strength consistent between different cancer patient cohorts with different diagnoses and stage of disease?

2. Methods

2.1. Search strategy and selection criteria

Electronic searches were performed on January 11th 2012 in PubMed (National Library of Medicine), Pedro (Centre for Evidence-Based Physiotherapy), Embase (Elsevier through OvidSP, edition 1980 – 2012, week 1) and Cochrane Central Registry of Controlled Trials (CENTRAL) through the Cochrane Library (John Wiley and sons Ltd), edition 2011 October, issue 4 of 4. Additionally, the bibliographies of included studies and relevant systematic reviews were reviewed.

The searches consisted of combinations of controlled terminology and free-text terms expressing the concepts; (1) physical exercise, (2) cancer and (3) muscle mass and strength (including terms such as cachexia, anorexia, malnutrition, wasting, and asthenia), and were adapted to each database (PubMed search details in Table 1).

To be eligible for inclusion, studies should 1) include patients aged 18 years or more with a confirmed cancer diagnosis and who were about to start or undergoing active cancer treatment at trial entry, 2) physical exercise had to be repetitive (more than once), consist of aerobic[1] or strength exercise[2] or a combination of both, and be delivered either as a single intervention or as part of a multimodal approach and finally 3) published in a peer reviewed journals and written in English language.

2.2. Trial selection and data extraction

All identified records were screened for duplicates and irrelevant titles by the first author (GBS) and one of the co-authors (IIR). Remaining abstracts were screened by two reviewers (GBS, LMO) and subsequently full-text papers were reviewed independently in pairs of two and two reviewers (GBS, LMO, TRB, JLH). In both instances, cases of disagreement about eligibility between two reviewers warranted a third reviewer's opinion.

Eligible studies were then submitted to data extraction using a custom made pre-piloted electronic form using a Microsoft Office Excel 2010 software spread sheet. Data on study design, participants, interventions, outcome measures, results and conclusions were extracted independently by two reviewers. Disagreements on final inclusion and exclusion were resolved by consensus by two of the authors (GBS, LMO).

2.3. Assessment of study limitations

All included studies were subject to an assessment of study quality performed independently by two reviewers. The assessment was based on the criteria for "risk of bias" within the GRADE system for rating quality of evidence [24]. These criteria are: randomisation procedures, allocation concealment, blinding, power-estimation, loss to follow-up, intention-to-treat analysis and selective end-point reporting. Study limitations for each trial were summarized in a table and described in the text.

2.4. Data synthesis

In the included trials treatment effects for each of the two or more groups are presented as differences in change between the groups. In order to compare effects across studies and outcomes (muscle strength and muscle mass) effect sizes were calculated according to Cohen's method[25]. Standardised mean difference (SMD) was calculated based on descriptive data (mean, standard deviation) at post-intervention and sample sizes for each trial. The formula for SMD is: mean values for experimental

[1] The use of oxygen is adequate to meet energy demands during exercise via aerobic metabolism e.g. low or moderate intensity running, cycling etc.

[2] The use of resistance against gravity or elastic tension to muscular contraction in order to build the strength, anaerobic endurance and size of muscles.

group minus mean values for control group divided by the pooled [3] standard deviation[26]. The SMD and the 95 % confidence intervals are presented in the text. According to Cohen's "rule of thumb" a SMD of 0.2- 0.5 is considered small to moderate, 0.51 - 0.8 moderate to large and greater than 0.8 large[25].

3. Results

3.1. Search results and selection of studies

The database searches retrieved 1321 records which were reduced to 405 after removal of duplicates and exclusion of irrelevant records by title. After screening of abstracts, 76 records were found to meet the inclusion criteria. Furthermore, nine records were identified by manual searches, giving 85 full text publications to be screened for eligibility. Out of these, 67 papers did not meet the selection criteria and were excluded. Thus, data extraction was performed on 18 papers. Two of the papers were publications based on the same study and were excluded [27, 28], leaving 16 trials for final synthesis. Figure 1 shows the outcome of the search process and selection of studies.

Ten trials compared one physical exercise regime against usual care (UC). Of these, three trials used aerobic exercise (AE) alone {[29];Mello, 2003 #17;Monga, 2007 #7}, while seven trials used AE and resistance exercise (RE) in a combined intervention (CAE) [30-36]. Four trials compared AE or RE against UC[37-40].One trial compared two different RE interventions (three or five days per week) against usual care[41]. One trial compared RE alone or together with a low fat vegetable diet against a control group. All groups in this trial received calcium-rich diet [42]. Details of the content of the physical exercise programs are provided in Table 2.

3.2. Effects on muscle mass

Detailed results on muscle mass are presented in Table 3. Two trials reported better effect on muscle mass for patients randomised to CAE compared with UC. In Battaglini and colleagues [31], the CAE group (exercise three days per week for six weeks) increased their lean body mass (LBM) compared to patients in the UC group (3.1 % ↑ versus 0.2 % ↓; p=0.004). In Coleman and colleagues [32], the CAE group (exercise two days per week for eight weeks) increased LBM while the UC group lost LBM (0.4 % ↑versus 0.4 % ↓; $p<0.01$).

In a study by Courneya and colleagues [37], both AE and RE groups exercised three days per week for 17 weeks. Patients in the RE group demonstrated significantly better effect on LBM than

[3] Pooled standard deviation is calculated using the formula: square root of SD for experimental group^2 + SD of control group^2 divided by 2.

patients in the AE group (1.0 kg ↑ versus 0.5 kg ↑; p=0.004) and UC (1.0 kg ↑ versus 0.2 kg ↓; p=0.015). No statistically significant differences in change in LBM between AE and UC were found.

No effects were reported in the trials by Cunningham and colleagues [41], comparing two RE groups exercising three or five days per week with UC, the study by Mustian and colleagues [34] comparing a CAE group exercising seven days a week for four weeks with UC, or in the trial by Demark-Wahnefried and colleagues [42] comparing three groups: calcium-rich diet only, calcium-rich diet + RE and calcium rich + RE + low fat vegetable diet. In the latter study, patients in the RE groups exercised five days a week for 26 weeks.

Effect sizes could be calculated for two studies using Dual Energy X-ray Analysis (DEXA) as outcome. In the study by Courneya and colleagues [37] the post-treatment effect was better for RE than UC however the effect was small (SMD = 0.22; CI - 0.1 to 0.6). There was no additional effect of AE compared with UC. In the study by Demark-Wahnefried et al[42], a small to moderate effect size was found in favour of the UC (receiving calcium rich diet only) compared with the two experimental groups I) calcium rich diet + RE (SMD = 0. 27; CI -2.9 to 2.2) and II) calcium rich diet + RE + low-fat vegetable diet (SMD= 0.36; CI -2.8 to 2.3).

3.3. Effect on muscle strength

Details on results on muscle strength are provided in Table 4. Four trials reported statistically significant differences in change between groups on muscle strength for CAE compared with usual care (UC): These studies included Jarden and colleagues [33] (five days per week for 4-6 weeks) for 1 RM chest press (2.6 kg ↑ versus 8.7 kg ↓; p<0.001) and 1 RM leg extension (3 kg ↑ versus 17.2 kg ↓; p=0.0003); Adamsen and colleagues (3 days per week for six weeks) for chest press (7.3 kg ↑ versus 0.5 kg ↓; p<0.0001), pull down (7.6 kg ↑versus 0.8 kg ↑; p<0.0001) and leg press (31.6 kg ↑versus 2.8 kg ↑); Battaglini and colleagues for total upper and body muscle strength (2.4 kg ↑ versus 12.6 kg ↓; p<0.05), and Oldervoll and colleagues for grip strength (1.1 kg ↑ versus 1.3 kg ↓; p<0.05). No statistically significant group differences in change in muscle strength were reported by Mustian and colleagues [34]; Coleman and colleagues [32] and Wiskemann and colleagues [36].

Three trials reported that RE was better than UC in improving muscle strength. In Courneya and colleagues [37], patients in the RE group exercised three days per week for 17 weeks (chest press: 3.3 kg ↑ versus 1.5 kg ↑; p<0.001 and leg press: 8.2 kg ↑ versus 1.4 kg ↑; p=0.001). In a trial by Segal and colleagues [40], patients in the RE group exercised three days a week for 24 weeks (chest press: 10.9 kg ↑ versus 2.5. kg ↓; p<0.001 and leg press 25.6 kg ↑ versus 0.4 kg ↑; p<0.001). In the two trials by Schwartz et al[38, 39], better effects for RE than UC was only reported in the most recent study[38] for 1RM overhead press (1.3 kg ↑ versus 0.9 kg ↓; p<0.05), seated row (31.7 kg ↑ versus 1.4 kg ↓; p<0.05) and for leg extension (21.1 kg ↑ versus 1.8 kg ↑; p<0.05).

Better effects of AE than UC on muscle strength was reported in five studies; Baumann and colleagues [29] for isometric quadriceps muscle strength (10 % ↓ versus 24 % ↓; p=0.002); Monga and colleagues [43] for time to complete a five repetition sit to stand test (1.3 sec ↓ versus 0.4 sec ↑; p<0.001); Segal and colleagues [40] for 8RM chest press (1.3 kg ↑ versus 2.5 kg ↓; p=0.006); Schwartz and colleagues 2007[39] for 1RM seated row (1.5 kg ↑ versus 0.1 kg ↓; p=0.02) and 1RM leg extension (14.6 kg ↑ versus 4.6 kg ↑; p=0.001). A more recent trial by Schwartz and colleagues from 2009[38] confirmed previous findings for 1 RM overhead press (4.2 kg ↑ versus 0.9 kg ↓; p<0.05); 1RM seated row (7.7 kg ↑ versus 1.4 kg ↓; p<0.05) and 1 RM leg extension (33.6 kg ↑ versus 1.8 kg ↑; p<0.05).). No statistically significant differences between AE and UC in change in muscle strength were reported by Mello and colleagues [44].

The effect sizes calculated for seven trials with comparable outcomes for upper and lower body muscle strength are illustrated in Figure 2.

For AE, moderate to large effect sizes were found in the two trials by Schwartz and colleagues [38, 39] for overhead press (SMD 0.7; CI -0.8 to 12.2 and SMD 0.5; CI 0.0 to 1.0); seated row (SMD 0.8; CI 0.3 to 1.5 and SMD 0.8; CI 0.3 to 1.3) and leg extension (SMD 0.3; CI -0.3 to 8.8 and SMD 1.0; CI 0.6 -1.6). Equally, in the same two trials, effect sizes in favour of RE compared to UC were large for seated row (SMD 0.8; CI 0.3 to 1.8 and 0.9; CI 04 to 1.4) and leg extension (SMD 0.8; CI 0.3 to 1.2 in Schwartz 2009 only) but small for overhead press (SMD 0.2; CI -0.4 to 0.8 and 0.2; CI -0.3 to 0.7) leg extension in Schwartz and colleagues (2007) (SMD 0.2; CI -0.4 to 0.8).

Effect sizes in favour of AE compared to UC were small in two trials by Courneya and colleagues [37] and Segal and colleagues [40] for the outcomes chest press (SMD 0.0; CI -0.3 to 0.3 and SMD 0.2; CI -0.3 to 0.6) and leg extension (SMD 0.1; CI -0.3 to 0.4 and 0.2; CI -0.3 to 0.6). In comparison, effect sizes were moderate to large in the trials by Courneya and Segal when comparing RE with UC for chest press (SMD 0.8; CI 0.5 to 1.1 and SMD 0.6; CI 0.1 to 1.0) and for leg extension (SMD 0.4; CI 0.1 to 0.7 and SMD 0.3; CI 0.1 to 0.8).

Effect sizes were moderate to small both for upper and lower body strength in favour of CAE compared with UC in three trials[30, 33, 36]. Effect sizes were largest in the study by Jarden and colleagues [33] for both leg extension (SMD 1.7; CI -3.5 to 6.9) and chest press (0.8; CI -5.5 to 7.1). More moderate effects were found by Adamsen and colleagues [30] for leg extension (0.5; CI 0.3 to 0.8) and chest press (0.3; CI 0.1 to 0.6) and by Wiskemann and colleagues [36] for isometric strength in upper body (SMD 0.2; CI -0.3 to 0.6) and lower body (SMD 0.3; CI -0.1 to 0.8).

For grip strength (not illustrated in Figure 2) effect sizes were small in favour of CAE versus UC (SMD = 0.23; CI -0.5 to 0.1) [35].

3.4. Comparing effects across patient cohorts

The majority of trials were performed on stage I-III breast cancer patients undergoing adjuvant chemotherapy and prostate cancer patients receiving radiation therapy. A few trials included some other cancer diagnoses, such as bowel or colon cancer [30, 31, 34, 37-40, 42, 43]. Six trials included patients with various haematological malignancies, mainly acute or chronic leukaemia or lymphomas, undergoing hematopoietic stem cell transplants (HSCT)[29, 33, 36, 41]. Only one trial included patients with advanced stage IV cancer undergoing palliative cancer treatment. These patients were diagnosed with tumours in the gastro-intestinal tract, breast, lung or bladder [35].

Muscle mass was reported in only six trials, and except for two trials involving HSCT patients[32, 41], these were conducted on patients with breast cancer or prostate cancer[31, 34, 37, 42]. Overall, the tendency in these six trials was that the experimental groups (either AE, RE or CAE) maintained or modestly improved muscle mass from pre to post-test while the CG reduced muscle mass.

For muscle strength outcomes, moderate to large effects were demonstrated in the trials on breast and prostate cancer patients[30, 31, 37-40] and in trials on HSCT patients[29, 32, 33, 36] but not in patients with advanced stage IV cancer[35], where effects on grip strength were small.

3.5. Study limitations (risk of bias)

The quality assessment of the included trials is provided in Table 5.

Nine trials described methods used for random allocation. Six trials used concealed allocation [31-34, 37, 40, 41]. The majority of trials had small sample sizes; eight trials had less than 50 participants [29, 31-34, 41, 43, 44]. Four trials were feasibility trials [29, 32, 34, 42].

Overall, the most frequent study limitation was lack of blinding of assessors. In only two trials blinding was applied [34, 40]. Six trials had drop-out rates above > 20% [29, 32, 35, 36, 41, 44]. In case of three of these trials, it was not reported how missing data were dealt with [32, 41, 44]. Nine of the trials reported data analysis by using intention-to-treat principles [29, 30, 32-36, 38, 40].

The majority of trials described one primary outcome, which was muscle mass or muscle strength in only two trials [31, 44].

3.6. Outcome measurements

Six trials used muscle mass as an outcome. Two trials measured muscle mass as Lean body Mass (LBM) using a Skinfold Calliper, in which one expressed LBM in percentage [31] and the other as arm muscle area (mm^2)[41]. Two trials measured LBM, expressed as kilograms, using Dual X-ray Absorptiometry [37, 42]. One trial measured LBM in kilograms by using Air Displacement Plethysmography [32]. Finally, one trial measured skeletal muscle mass (kg) using Bioelectrical Impedance Analysis [34].

Fourteen trials had muscle strength as an outcome. Estimations of one repetition maximum (1RM) for upper and lower body strength were most frequently used [30-33, 37-40]. Chest press (involving major muscles of the chest, shoulders and triceps), seated row (involving the Lattisimus Dorsi and the Rhomboid muscles, predominantly) and leg extension (involving all major leg muscle groups such as Quadriceps, Hamstrings and Gluteus maximum), were most commonly used. Maximum isometric strength was measured in four trials [29, 33, 36, 44], grip strength by dynamometry in two trials[34, 35], and a functional test to assess leg strength in one trial [43]. Except for the functional strength test (sit-to-stand measured in seconds), all trials reported muscle strength in kilograms or Newton (1 kg equals 9.81 N).

4. Discussion

4.1. Summary of results

In this systematic review of 16 trials with cancer patients during active treatment, both aerobic and resistance exercise, and a combination of these, improves upper and lower body muscle strength more than usual care. Muscle mass was reported in only six trials and shows a tendency towards an effect of physical exercise on maintaining muscle mass during treatment. There are some indications that resistance exercise (RE) is more effective than aerobic exercise (AE) both on muscle mass and strength, though the evidence is not very strong. Large effects on muscle strength were demonstrated across different patient cohorts. However, most trials involved patients with early stage cancer while only one trial was on patients with advanced cancer.

4.2. Effects of physical exercise

This review shows a possible effect of physical exercise on muscle mass during cancer treatment, as three trials reported significantly better effects of physical exercise compared to usual care[31, 32, 37]. The findings are in line with a systematic review and a meta-analysis by Speck et al[5] based on five trials reporting muscle mass as outcome. This review concluded with small effects sizes in favour of different physical activity interventions compared with usual care in cancer survivors. One of the trials by Demark-Wahnefried et al [42] included in the present review reported negative findings for resistance training and low fat diet on LBM compared to usual care. The negative result can likely be explained by a higher non-adherence rate in the experimental groups. In summary, because of few exercise trials using muscle mass as outcome, most of them having methodological shortcomings, there is still too little evidence to draw a firm conclusion on the effect of physical exercise on muscle mass for patients undergoing cancer treatment.

The present review of 14 trials using muscle strength as outcome, demonstrated a positive effect of physical exercise compared to usual care. These findings are also in line with Speck and

colleagues [5] who, based on eight trials, concluded with small to moderate effect of physical exercise on muscle strength.

From the review, as compared to UC, we found positive effects of exercise on muscle strength in favour of AE in five trials [29, 38-40, 43]; RE in three trials [37, 38, 40] and CAE in four trials [30, 31, 33, 35]. Only two trials compared effects of AE and RE, and both reported significantly better effect of RE on change in muscle strength [37, 40]. Furthermore, the study by Courneya and colleagues from 2007[37] also found a significant effect in favour of RE compared to AE on muscle mass. Although the evidence is not very strong, the result could support the use of RE in future clinical trials.

4.3. Populations

The majority of trials in the present review included breast or prostate cancer patients. Only three trials included patient groups with other types of solid tumors, such as gastro-intestinal, bowel or lung cancer [30, 35, 39]. Possible explanations for this are that recruitment into exercise trials in very sick patients is challenging due to a high disease and symptom burden, side-effect of treatment, and gate-keeping from health personnel. [45]

This review found six trials conducted in patients with hematological malignances undergoing hematopoietic stem cell transplant (HSCT) and high dose chemotherapy, and only one trial[35] conducted in cancer patients with advanced disease. Muscle wasting is a common symptom, reported in more than 60 % of patients with advanced cancer[14] and patients with hematological malignancies undergoing stem cell transplants [46]. For both groups there is a need for treatment strategies that contribute to reduce side-effect of treatment, maintain muscle mass and strength in order to maintain quality of life, and prolong survival. Future exercise trials are therefore needed in cancer populations at high risk for developing cachexia.

Even if the search criteria were set to detect papers with patients prone to cachexia, the present review only identified one trial with advanced cancer patients. In this study, patients with advanced incurable cancer were randomized to eight weeks of CAE performed twice weekly in a supervised hospital setting, or to usual care. The increased grip strength in the CAE relative to UC supports previous uncontrolled trials in advanced cancer [47, 48] on efficacy of exercise on muscle strength also in this population. In conclusion, the findings from our review support the effect of exercise on muscle strength in cancer patient undergoing curative treatment. The evidence is however sparse with regards to the effects in patients with advanced cancer.

4.4. Methodological quality of the included trials

Conclusions that can be drawn from any literature review are based on the quality of the trials included. Thus, identifying possible biases in the conducted trials are essential [24]. The included

trials in the present review had some shortcomings: First, the trials varied considerably in terms of sample size. Eight trials had less than 50 participants[31-34, 39, 41, 43, 44], and only one of performed a sample size estimation[33]. Second, nine trials lacked or did not report use of concealed allocation [29, 30, 35, 36, 38, 39, 42-44]. Third, in most trials, the assessment and interventions was performed by the same persons.

4.5. Outcomes

Previous reviews on effects of physical exercise in patients with cachexia have been narrative and not been specific to cancer patients[20, 21] or have mainly discussed biological and pathophysiological aspects of exercise on cachexia-related muscle wasting [22, 23]. Existing systematic reviews and meta-analyses on the effects of physical exercise in cancer patients have evaluated multiple end-points both during and after anti-cancer treatment[5, 49], and many have primarily focused on specific outcomes such as fatigue[1] and quality of life[3]. At present, no systematic review has primarily been designed to examine the effect of physical exercise on muscle mass and strength in cancer patients during active treatment. Considering that depletion of muscle mass is associated with more toxic side-effects, poor response of cancer treatment and short survival in advanced cancer populations, muscle mass as outcome should be of clinical interest. Furthermore, preventing loss of muscle mass and function during active cancer treatment may contribute to maintaining activities of daily living. In advanced cancer patients, reduction in daily physical activity is linked to impaired quality of life [50]. Further trials are needed to assess the effect of exercise on muscle mass and secondary on quality of life in these patients.

Several factors are to be considered when using muscle mass as endpoint. Precise measurements of skeletal muscle mass require expensive equipment and experienced personnel that might not always be a feasible option in a clinical research setting. In addition, the type and dose of exercise required to gain muscle mass remains unclear, making it difficult to interpret what are clinically relevant changes in muscle mass following exercise interventions. Further trials should also assess whether muscle strength can be used as a surrogate outcome for muscle mass in clinical trials in advanced cancer patients.

4.6. Study limitations

The search strategy in this systematic review was pre-defined and designed by a trained research librarian and performed in multiple biomedical and therapeutic databases in order to reduce publication bias. A large group of different search terms were used to represent muscle outcomes as well as cachexia however it was acknowledged that search terms for outcomes are not always represented in abstracts of indexing terms (i.e. Mesh). To account for this, additional manual searches were performed by the first author (GBS) in bibliographies of the 85 full-text articles.

Although we searched for trials of relevance for patients with cachexia, only one RCT conducted in patients with advanced stage cancer was detected. As only RCT's were included, two uncontrolled trials performed in patients with advanced lung cancer [47, 48] were not described in our results. These trials showed improvement in muscle strength after eight weeks of CAE but none of these studies used muscle mass as outcome. Furthermore, an observational study of a multimodal rehabilitation intervention (nutrition, exercise and symptom management) involving cancer patients with advanced disease and significant anorexia/weight loss, was identified but not included[51]. After two months of intervention, patients who were still in the study increased their body weight and physical function, and reduced their symptom burden. This is the only study identified through the literature search that provides data concerning physical exercise in cancer cachexia. However, a few study protocols of ongoing trials were identified [52, 53]; suggesting that the research focus in this field will increase in the time to come.

4.7. Conclusion and future directions

This systematic review provides evidence that both aerobic and resistance exercise or a combination of these, can contribute to improve muscle strength more than usual care in cancer patients during treatment. Whether these different types of exercise have specific effects remains unclear. Improvements in muscle mass were demonstrated in favor of resistance exercise; however the evidence was not strong. Few trials measured muscle mass and besides one large trial; the studies included a small number of patients. Although effects were similar across different patients cohorts included in this review, there was a predominance of trials conducted in patients with early stage cancer, and conclusions cannot be drawn with regard to advanced cancer populations. Future research in this field should include studies of effects of physical exercise on muscle mass in patients with advanced cancer and at risk of cancer cachexia.

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8. Conflict of interest

The author (s) has no conflicts of interest associated with this manuscript.

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Table 1. Search strategy in PubMed.docx

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#8	#7 AND English [la]
#7	(#1 OR #2) AND #3 AND #4 NOT (#5 OR #6)
#6	Child[ti] OR children[ti] OR pediatric[ti] OR paediatric[ti] OR ((child[mesh] OR infant[mesh] OR adolescent[mesh]) NOT adult[mesh])
#5	case reports[pt] OR case study[ti] OR case report[ti] OR comment[pt] OR letter[pt] OR news[pt]
#4	"Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR "Exercise Movement Techniques"[Mesh:noexp] OR exercise[tiab] OR exercises[tiab] OR Gymnastics[mesh] OR gymnastics[tiab] OR "Hydrotherapy"[Mesh:noexp] OR hydrotherapy[tiab] OR "physical activity"[tiab] OR pilates[tiab] OR "Swimming"[Mesh] OR swimming[tiab] OR training[tiab] OR Walking[mesh] OR walking[tiab]
#3	Neoplasms [MeSH] OR cancer[tiab] OR "Palliative Care"[Mesh] OR palliative[tiab] OR palliation[tiab]
#2	("Muscle Strength"[Mesh:noexp] OR "muscle strength"[tiab] OR "muscular strength"[tiab] OR "muscular endurance"[tiab] OR "muscle mass" [tiab] OR "muscle function"[tiab] OR "muscle functions"[tiab] OR "Physical endurance" [tw] OR "muscle capacity"[tiab] OR "muscle force"[tiab] OR ((muscle[tw] OR muscles[tw] OR muscular[tw]) AND ("body composition"[tw] OR anabolic[tiab] OR strengthening[tiab]))) AND ("Quality of Life" [Mesh] OR "quality of life" [tiab] OR Fatigue[Mesh] OR fatigue[tiab] OR catabolism[tiab] OR deterioration[tiab] OR deteriorated[tiab] OR depletion[tiab] OR decline[tiab] OR reduced[tiab] OR reduction[tiab] OR reductions[tiab] OR loss[tiab] OR decrease[tiab] OR decreasing[tiab])
#1	Anorexia[mesh] OR anorexia[tiab] OR anorectic[tiab] OR Asthenia[mesh] OR asthenia[tiab] OR asthenic[tiab] OR cachexia[tiab] OR cachectic[tiab] OR Emaciation[MeSH] OR emaciation[tiab] OR emaciated[tiab] OR Malnutrition [Mesh] OR malnutrition[tiab] OR "muscle wasting"[tiab] OR "muscular wasting"[tiab] OR "Muscle Weakness"[Mesh] OR "muscle weakness"[tiab] OR "muscular weakness"[tiab] OR "Muscular atrophy" [MeSH] OR "muscle atrophy" [tiab] OR "muscular atrophy" [tiab] OR "Muscle, Skeletal/physiopathology"[Mesh:noexp] OR "Muscle, Skeletal/pathology"[Mesh:noexp] OR "Muscle, Skeletal/physiology"[Mesh:noexp] OR Muscles/pathology[Mesh:noexp] OR Muscles/physiopathology[Mesh:noexp] OR Muscles/physiology[Mesh:noexp] OR sarcopenia[tiab] OR "Wasting syndrome" [MeSH:noexp] OR "wasting syndrome" [tiab]

Table 2. Description of type and content of physical exercise in the included studies..doc

Table 2. Description of type and content of physical exercise in the included studies.

Study	**Delivery**	**Duration and frequency**	**Resistance exercise**			**Aerobic exercise**			**Additional exercise**
			Mode of exercise	Dose *Number of reps x sets*	Intensity *% of 1RM*	Mode of exercise	Dose *Minutes per session*	Intensity *% o HR_{max}*	Type
Adamsen, 2009	Combined AE and RE exercise, supervised, group in hospital	6 weeks -3 days per week	Exercise performed on stationary machines incl. leg press, chest press, pull down	5-8 x 3	85-95	Interval training on stationary bikes	15	60-100	Relaxation Body awareness Massage
Battaglini, 2007	Combined AE and RE exercise, supervised, group in hospital	15 weeks- 2 days per week	8-12 exercises for large muscle groups performed on stationary machines or using dumb bells, elastic bands, therapeutic balls	6-12 x 2-3	40 - 60	Treadmill/ergometer cycle	6-12	40-60	Flexibility exercises
Baumann, 2010	Aerobic exercise, individually supervised in hospital	8 weeks-7 days per week	None			Cycle ergometer	10-20	80	Activities of Daily Living training
Coleman, 2003	Combined AE and RE, self-directed, in the patients home	26 weeks- (frequency not reported)	Exercise stretch bands with variable resistance for LL (chair stand, knee flexion/ extension) and UL (biceps/triceps extension, upright row)	8 x 1-2	15-17 (*RPE)*	Fast speed walking (if relevant running or cycling)	18	12-15 *(RPE)*	Stretching
Courneya, 2007	Two exercise groups, either RE or AE, supervised, group in hospital	17 weeks-3 days per week	9 exercises for major muscle groups I whole body	8-12 x 2	60-70	Ergometer cycle, treadmill or elliptical trainer	15-20	60-80	None
Cunningham, 1986	Resistance exercise, individual supervised in hospital	4 weeks, two groups either 5 days or 3 days per week,	Exercises for whole body	15 reps (sets not reported)	Not reported	None			None
Demark-wahnefried, 2008	Resistance exercise, self-directed in the patients home	26 weeks-3 days per week	7 exercises using body weight resistance, elastic bands, ankle weights	Not reported	Not reported	None			Calcium rich diet with or without Low Fat Vegetable Diet

Jarden, 2009	Combined AE and RE exercise, supervised, group in hospital	4 – 6 weeks-5 days per week	Exercise for major muscle groups using free hand and ankle weights	10-12 x1-2	Not reported	Stationary cycling	15-30	50-75	Relaxation + psycho-education
Mello, 2003	Aerobic exercise, individually supervised in hospital	6 weeks, 7 days per week	None			Treadmill walking	15-20	70	Flexibility exercises
Monga, 2007	Aerobic exercise, individual supervised in hospital	8 weeks- 3 days per week	None			Treadmill walking	30	Not reported	None
Mustian, 2009	Combined AE and RE, self-directed in the patient home	4 weeks, 7 days per week	11 exercises for upper body using elastic bands	8-15 to 4-15 x 1	Not reported	Individually tailored walking	Not reported	60-70	None
Oldervoll, 2011	Combined exercise, supervised, group in hospital	8 weeks, 2 days per week	Circuit training (strength exercises for whole body)	Not reported	Not reported	Circuit training (stepping, stationary cycling)	30	Not reported	Stretching Relaxation
Schwartz, 2007	Two exercise groups, either RE or AE, self-directed in the patient home	26 weeks, 4 days per week	8 exercises for upper and lower body using resistance bands	8-10 x 2	Not reported	Activity of own choice (walking, jogging etc.)	15-30	Moderate	None
Schwartz, 2009	Two exercise groups, either RE or AE, self-directed in the patient home	52 weeks, 4 days per week	3-4 exercises for upper and lower body using resistance bands and free weights	12 x 3 or 18-20 x 2	Not reported	Activity of own choice (walking, jogging, dancing etc.)	20-30	Moderate	None
Segal, 2009	Two exercise groups, either RE or AE, supervised, group in hospital	24 weeks, 3 days per week	10 exercises for major muscle groups in whole body	8-12 x 2	60-70	Cycle ergometer, treadmill or elliptical trainer	15-45	70-75	None
Wiskemann, 2011	Combined AE and RE, individually supervised (in hospital) and self-directed home (after discharge from hospital)	16 weeks,5 days per week	3 exercise regimes; extremities only, whole body or bed bound with or without use of resistance bands	8-20 x 2-3	14-16(RPE)	Brisk walking, bicycling, treadmill walking, Nordic walking, jogging	20-40	12-14 (RPE)	None

Abbreviations: AE = aerobic exercise, RE=resistance exercise, UL= Upper Limb, LL= Lower Limb, RPE=rate of perceived exertion, max HR= maximal heart rate, 1RM = one repetition maximum,

Table 3. Results from studies on the outcome muscle mass..docx

Table 3. Results from studies on the outcome muscle mass.					
Studies	**Study population characteristics**	**Design/Intervention**	**Data collection points**	**Outcomes**	**Results**
Battaglini 2007 USA	20 patients, mean age 56.6 years, with breast cancer post-surgery and starting chemotherapy	Experimental group: - combined aerobic and resistance exercise Control group: - Usual care (no exercise)	1. Post- surgery (week 4) 2. End of intervention (week 21)	Relative lean body mass (%) measured by Lange Skinfold Caliper	Experimental group increased muscle mass by 3.1 % (Δ 7.1±3.4 to 74.1 ±2.9) compared to control who reduced by 0.2 % (Δ 69.1 ±4.2 to 68.9 ±4.1). The change within groups (time effect) was not statistically significant for either group (p=0.82). Interaction effect between groups were statistically significant at end of intervention (p=0.004).
Coleman, 2003 USA	24 patients, mean age 55 years, with multiple myeloma undergoing a tandem HSCT and conditioning chemotherapy/total body irradiation Half of the patients (in both groups) were given Thalidomide (anti-nausea and sedative drug).	Experimental group: - combined aerobic and resistance exercise Control group: - Usual care (encouragement to remain active and walk 20 min at least 3 times per week)	1. Before transplant (week 1) 2. After transplant (week 12)	Lean body mass (kg), measured by Air Displacement Plethysmography [a]	Experimental group increased muscle mass by 0.4 kg per month compared to control who reduced by 0.44 kg per month. Average difference of 0.84 kg per month between groups (rate of change in muscle mass) was statistically different (p<0.01).
Courneya 2007 Canada	242 patients, mean age 49.2 years, breast cancer stage I-IIIA, beginning adjuvant chemotherapy	Experimental group: a. Aerobic exercise b. Resistance exercise Control group: - Usual care (no exercise)	1. Before chemotherapy (week 0) 2. After chemotherapy (week 17 ± 4 weeks)	Total LBM (kg) measured by Dual X-Ray Absorptiometry (DEXA)	Exp. group (resistance) had a larger increase in muscle mass - 1.0 kg (Δ 40.3±4.6 to 41.3±4.9) compared to exp. group (aerobic) who increased by 0.5 kg (Δ 40.3±4.8 to 40.9±5.1). The control group reduced muscle mass by 0.2 kg (Δ 40.8±5.3 to 40.9±5.6). Muscle mass was superior in the exp. group (resistance) compared to control group (p=0.015).
Cunningham, 1985 USA	30 patients, mean age 26 years, with acute leukemia undergoing allogeneic HSCT and high dose chemotherapy/total body irradiation	Experimental group: a. Resistance exercise 3 days per week b. Resistance exercise 5 days per week Control group: - Usual care (no exercise)	1. Day of transplant (baseline) 2. 35th day after transplant (post-test)	Arm muscle area (mm^2) measured by Lange Skinfold Caliper [b]	Exp. group (resistance ex. 5 days per week) increased muscle mass more (Δ 4.0 % than the exp. groups (resistance ex. 3 days per week) – 1.5 % increase. Control group reduced muscle mass by 5.7 %. No statistically significant change within groups over time. There were no statistically significant differences in change in muscle mass between groups.
Demark-Wahnefried, 2008 USA	90 patients, mean age 42 years, with breast cancer stage I-IIIA undergoing adjuvant chemotherapy/radiotherapy + hormone therapy	Experimental group: a. Resistance + calcium rich diet: b. Resistance + Low Fat Diet + Calcium rich diet	1. Baseline 2. 6 months	Total lean body mass (kg) measured by Dual X-Ray Absorptiometry (DEXA)	Control group (CA only) increased muscle mass by 0.7 kg (Δ 42.5±6.6 to 43.2±7.4) compared to both experimental groups who reduced muscle mass: R+CA reduced by 0.4 kg (Δ 41.1±7.1 to 40.6±7.1) and R+ LFVD + CA reduced by 0.3 kg (Δ 41.6±5.6 to 41.3±7.0) No statistically significant differences over time within groups.

		Control group: - Calcium rich diet			There was no statistically significant difference in post-treatment scores detected for muscle mass between groups.
Mustian, 2008 USA	38 patients, mean age 60 years, with breast cancer (71%) and prostate cancer (29 %) undergoing radiotherapy	Experimental group: - combined aerobic and resistance exercise	1. Baseline 2. Post – intervention (week 4)	Skeletal muscle mass (kg) measured by Bioelectrical Impedance Analysis	Experimental group (combined AE and RE) Increased muscle mass by 0.06 kg (Δ 24.5±8.8 to 25.5±9.0, while control group reduced by 0.2 kg (Δ 23.6±5.6 to 23.4±5.4). No statistically significant differences in muscle mass between groups at post-treatment.

a Reported as change baseline- post – transplant/ number of months participated in study

b Change reported as percent of admission values (median (range))

Table 4. Result from studies on the outcome muscle strength.

Studies	Study population characteristics	Study design/ intervention	Data collection points	Outcomes	Results
Adamsen, 2009	269 patients, mean age 47 years, with 21 different diagnosis (solid tumors), mainly breast cancer (44%), bowel cancer (13 %) + hematological malignancies (10 %) Including both early and advanced stage cancer patients (no formal staging system used to report stage)	Experimental group: - combined aerobic and resistance exercise Control group: - usual care (no exercise)	1, Baseline 2, End of study (week 6)	1RM(kg) leg press, chest press, pull-down	Exp. group: - Leg press increase 31,6kg (Δ 100,8±30,6 to 132,4±42,3) - Chest press increase 7,3 kg (Δ (37,9±15,6 to 45,2±17,9) - Pull down increase 7,6 kg (Δ 39,6±14 to 47,2±14,4) Control group: - Leg press increase 2,8 kg (Δ 107,6±33,3 to 110,4±36) - Chest press decrease 0,5 kg (Δ 40,2±39,7±17,2 to 39,7±17,2) - Pull down increase by 0,8kg (Δ 42±16,3 to 42,8±16,1) At post-treatment, statistically significant improvements in muscle strength was found in favor of the exp. group versus control group for: - Leg press: mean difference 29,7 (95 % CI 23,4 to 34,9); p<0,0001 - Chest press 7,5 (95 % CI 5,6 to 9,4); p<0,0001 - Pull-down 6,4 (95 % CI 4,5 to 8,3); p<0,0001
Battaglini, 2007	20 patients, mean age 56,6 years, with breast cancer post-surgery and starting chemotherapy	Experimental group: - combined aerobic and resistance exercise Control group: - Usual care (no exercise)	1, Post- surgery (week 4) 2, End of intervention (week 21)	Predicted RM (kg)[1] by submaximal muscle endurance protocol	Exp. group increase muscle strength by 25,9 kg (Δ 269,8±12,8 to 295,6±22,7) Control group reduced by 1,6 kg (Δ 262,5 ±40,9 to 260,9±38,8) At post-treatment, statistically significant improvements in muscle strength was found in favor of the exp. group versus control group (p=0,025)
Baumann 2010	64 patients, mean age 45 years, with mixed hematological malignancies (mainly acute and chronic leukemia) undergoing autologous/allogeneic HSCT + high dose chemotherapy/ TB)	Experimental group: - aerobic exercise Control group - low intensity exercise (passive and active mobilization, coordination, stretching)	1, Hospital admission (day 0) 2, After discharge (mean duration of hospitalization 41 days)	Maximal isometric strength quadriceps (Newton) measured by Digimax-2000 load cell	Both groups decreased muscle strength; exp. group 10 % (Δ 439 to 395) and control by 24 % (Δ 448 to 342) At post-treatment, there was a statistical significant difference between groups in favor of exp. group (p=0,002)
Coleman, 2003	24 patients, mean age 55 years, with multiple myeloma undergoing a tandem HSCT and conditioning chemotherapy/total body	Experimental group: - combined aerobic and resistance exercise Control group: - Usual care (encouragement to remain active and walk 20 min at	1, Before transplant (week 1) 2, After transplant (week 12)	1RM (Newton) * specification of muscle group not reported	Exp. group Increased muscle strength by 2,4 kg, while control group reduced by 12,6 kg No statistically significant differences between groups at post-test

[1] - Based on sum score for all tests: leg extension, seated leg curl, lateral pull down, seated chest press.

	irradiation Half of the patients (in both groups) were given Thalidomide (anti-nausea and sedative drug),	least 3 times per week)			
Courneya 2009	242 patients, mean age 49,2 years, breast cancer stage I-IIIA, beginning adjuvant chemotherapy	Experimental group: a. Aerobic exercise b. Resistance exercise Control group: - Usual care (no exercise)	1, Before chemotherapy (week 0) 2, After chemotherapy (week 17 ± 4 weeks)	Estimated 1RM by sub-maximal testing: 8RM chest press and leg extension (kg)	All groups increased muscle strength for: Chest press: - Aerobic 2,6kg (Δ 22,1±7,5 to 24,4±7,5) - Resistance 3,3 kg (Δ 23,2±7,2 to 31,9±10,8) -Control 1,5 kg (Δ 22,8±8,9 to 24,6±7,8) Leg extension: - Aerobic 8,8 kg (Δ 24,8±12,5 to 28,2±14,2) - Resistance 8,2 kg (Δ 24,4±11,2 to 32,8±12±6) - control 1,4 kg (25,6±12,6 to 27,1±14,1) At post- test, there was a statistically significant difference between groups in favor of resistance exercise versus control for chest press (mean difference 7,7 kg; p=0,001) and leg extension (mean difference 6,8 kg; p=0,001) There were no statistically significant difference between the groups aerobic and control.
Jarden, 2009	34 patients, mean age 39 years, with mixed hematological malignancies (mainly acute and chronic leukemia) undergoing allogeneic HSCT + high dose chemotherapy/TBI	Experimental group - combined aerobic and resistance exercise Control group: - Usual care (offered standard care in terms of physiotherapy)	1, Baseline 2, Post – intervention (week 12)	1RM chest press; leg press (kg) Isometric right elbow and right knee flexion (Newton)	Chest press - Exp. group 2,4 % increase (Δ 50,6±21,8 to 53,2±22,1) - Control 20,5 % decrease (Δ 47,1±16,7 to 38,4±14,6); p<0,0001 Leg extension - Exp. group 2,4% increase (Δ 63,6±18 to 66,6±17,8) - Control 25,1 % decrease (Δ 56,6±19,7 to 39,4±12,6); p=0,0003 Elbow flexion: - Exp. group 4,8 % increase (Δ 2,34±0,9 to 2,49±0,9) - Control 20 % decease (Δ 2,5±0,9 to 1,9±0,5); p =0,0009 Knee extension - Exp. group 2,2 % increase (Δ 4,0±1,5 to 4,1± 1,6) - control 20,1 % decrease (Δ 3,9±1,5 to 3,1±1,2); p<0,0001 Statistical significant differences between groups in change in muscle strength was found in favor of exp. group versus control group for chest press (p < 0,001), leg extension (p=0,0003), elbow flexion (p=0,0009) and knee extension (p<0,0001)

Mello, 2003	32 patients, mean age 30,2 years with mixed hematological malignancies undergoing allogeneic HSCT + high dose chemotherapy/TBI,	Experimental group: - aerobic exercise Control group: - no exercise	1, Pre –transplant (week 0) 2, Discharge from hospital (week 6)	Max isometric strength (Newton) measured by strain-gauge dynamometer for dominant and non-dominant muscles in the upper body (shoulder, elbow) and lower body (hip, knee and ankle)	In exp. group, there were no statistically significant changes in upper body muscle strength but for control group, muscle strength was significantly reduced in all muscle groups, except dominant elbow extensors For lower body muscle strength, significant reductions were found for the exp. group in dominant (p=0,033) and non-dominant (p=0,0001) knee flexors, The control group significantly reduced lower body muscle strength in knee flexors (p<0,01), ankle flexors (p<0,01) There were statically significant differences between groups at post –test in favor of exp. group versus control group for non-dominant hip-flexors (p<0,01)
Monga, 2007	30 patients, mean age 68 years with first time diagnosis of localized prostate cancer (stage not reported) undergoing radiotherapy	Experimental group: - aerobic exercise Control group: - standard care (no exercise)	1, Pre-radiotherapy (week 0) 2, Post –radiotherapy (week 8)	Time to complete 5 times sit to stand, measured in seconds	Exp. group improved by reducing time to complete test with 1,3 sec (Δ 12,6 ±2,3 to 11,3±1,9) while the control used 0,4 sec longer time to complete test (Δ 10,8±1,6 to 11,3±1,6) At post – test there was a statistically significant difference between groups in change in time to complete test in favor of exp. group versus control of 1,7 sec (p=0,000)
Mustian, 2008	38 patients, mean age 60 years, with breast cancer (71%) and prostate cancer (29 %) undergoing radiotherapy	Experimental group: - combined aerobic and resistance exercise Control group - no exercise	1, Baseline 2, Post – intervention (week 4)	Grip strength (kg) measured by dynamometry	Both groups reduced muscle strength, in exp. group by 0,5 kg (Δ 26,0±2,1 to 25,5±7,3) and control by 0,8 kg (Δ 24,9±7,9 to 24,1±8,7) There were no statistically significant differences in muscle strength between groups at post intervention,
Oldervoll 2011	231patients, mean age 62 years, with advanced incurable stage Iv cancer (stage IV), mainly gastrointestinal tract, breast, lung, urological undergoing palliative chemotherapy/radiotherapy hormone therapy/targeted therapy	Exp, group: - combined aerobic and resistance exercise Control group: - Usual care (no exercise)	1, Baseline (week 0) 2, End of intervention (week 8)	Grip strength (kg) measured by dynamometry	Exp. group increased grip strength from 26,4 ±0,9 to 27,5±1,0 while control group reduced from 29,6±0,9 to 28,3 ±1,0 At post –test, statistically significant between group effects were found in favor of exp. group versus control group (estimated mean difference 2,0; CI 95 % 0,4 to 3,5; p=0,01)
Schwartz 2007	66 patients, mean age 50 years, with stage stage I-III breast cancer undergoing adjuvant chemo/radiotherapy	Experimental group: c. Aerobic exercise d. Resistance exercise Control group: - Usual care (no exercise)	1, Baseline (week 0) 2, End of study (week 26)	1 RM (kg) overhead press, seated row, leg extension	Overhead press: - Aerobic increase (Δ 12,2±5,9 to 13,7±6,4) - Resistance increase (Δ 9,5±6,9 2, 10,8±5,1) - Control reduce (Δ 9,6±4,5 2, 9,5±4,1) Seated row: - Aerobic increase (Δ 32,3±12,1 to 40,1±13,6) - Resistance increase (Δ 32,7±12,5 to 38,1±8,6) - Control increase (Δ 30,5±10,8 to 30,7±9,1)

					Leg extension: - Aerobic increase (Δ 64±26 to 78,6±30,5) - Resistance increase (Δ 60,4±31,8 to 75,3±34,5) - Control increase (Δ 65,9±27,7 to 70,5±28,1) There was a statistically significant difference between groups in favour exp. group (aerobic) versus control for overhead press (p=0,02) and leg extension (p= 0,01) No statistically significant differences between exp. groups (resistance) versus control group were found
Schwartz 2009	101patients, mean age 48 years, mainly stage I-III breast cancer (76 %) and colon (13 %), lymphoma (11 %) undergoing chemotherapy + steroids	Experimental group: e. Aerobic exercise f. Resistance exercise Control group: - Usual care (no exercise)	1, Baseline 2, End of intervention (week 52)	1 RM (kg) overhead press, seated row, leg extension	Overhead press: - Aerobic increase (Δ 24,9±13,6 to 29,1±13,7) - Resistance increase (Δ 24,1±13,6 to 25,4±13,6) - Control reduce (Δ 22,7±9,9 to 23,6±10,4) Seated row: - Aerobic increase (Δ 35,8±14,9 to 43,5±12,7) - Resistance increase (Δ 36,7±15,8 to 44,9±13,2) - Control reduce (Δ 33,6±17,1 to 32,2±15,8) Leg extension:: - Aerobic increase (Δ 74,4±32,2 to 108,0±29,5) - Resistance increase (Δ 74,8±34,8 to 98,9±30,8) - Control reduce (Δ 73,9±35,8 to 76,2±29,5) Statistical significant between group differences in favor of both exp. groups (aerobic and resistance) versus control were found for all muscle strength outcomes (p<0,05)
Segal 2009	121 patients, mean age 66 years, with stage I-III prostate cancer undergoing radiotherapy with or without androgen suppression therapy	Experimental group: g. Aerobic exercise h. Resistance exercise Control group: - Usual care (no exercise)	1, Baseline (week 0) 2, Post –test (week 24)	Estimated 1RM by sub-maximal testing: 8RM chest press and leg extension (kg)	Chest press: - Aerobic 1,3 kg increase (Δ 53,4±12,1 to 54,9±13) - Resistance 10,9 kg increase (Δ 49,5±11,1 to 60,8±14) - Control 2,5 kg decrease (Δ 55,2±13,3 to 52,9±14,6) Leg extension - Aerobic 4,4 kg increase (Δ 126,6±55,8 to 128±60,9) - Resistance 25,6 kg increase (Δ 104,6±37,7 to 134,1±41,6) - Control 0,4 kg increase (Δ 117,3±53,5 to 119,2±55,9) Statistically significant differences in muscle strength between groups were found in favor of: - exp. group (resistance) versus control group for chest press (mean difference 13,7 kg; p<0,001) and leg extension (mean difference 25,1 kg; p<0,001) - exp. group (aerobic) versus control for chest press (mean difference 4 kg; p<0,006)

Wiskemann 2011	105 patients, mean age 49 years, with mixed haematological malignancies (mainly acute and chronic leukaemia) undergoing allogeneic HSCT + high dose chemotherapy/TBI	Experimental group: - combined aerobic and resistance exercise Control group - no exercise, but not discourage to be physically active	1, Pre-transplant 3, End of intervention (6-8 weeks after discharge)	Isometric upper and lower body strength (kg)	Muscle strength was reduced in both exp. group (upper body Δ 155,5±50,6 to 132,3±36,8 and lower body Δ 192,2±65,9 to 167,8±49,5) and in the control group (upper body Δ 154,5±51 to124,9±46,2 and lower body Δ 188,7±61,9 to 149,3±58,7), but no statistically different changes in muscle strength over time was found for either group, Between-group comparison was not reported

Table 5. Assessment of study limitations ("risk of bias") according to GRADE.docx

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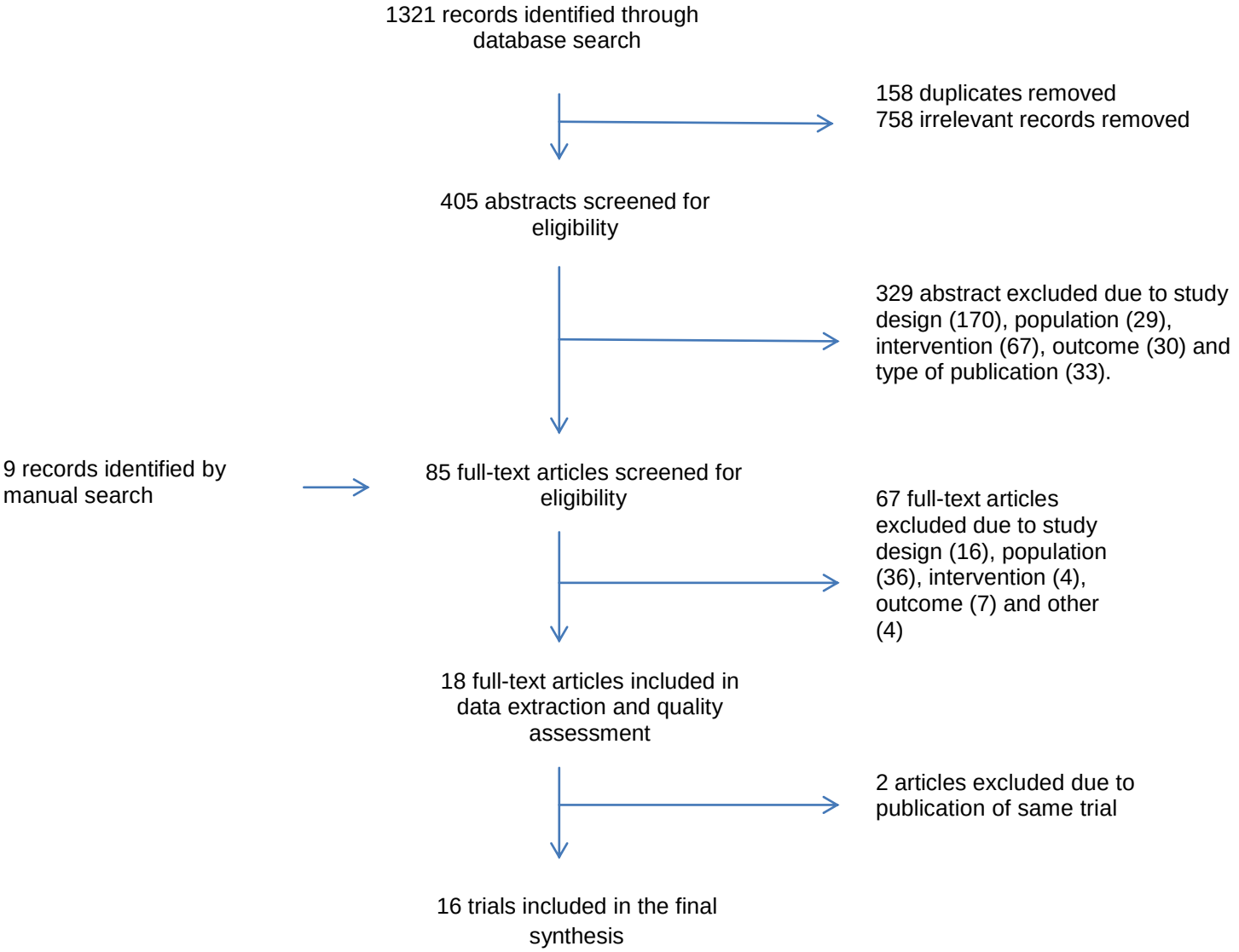
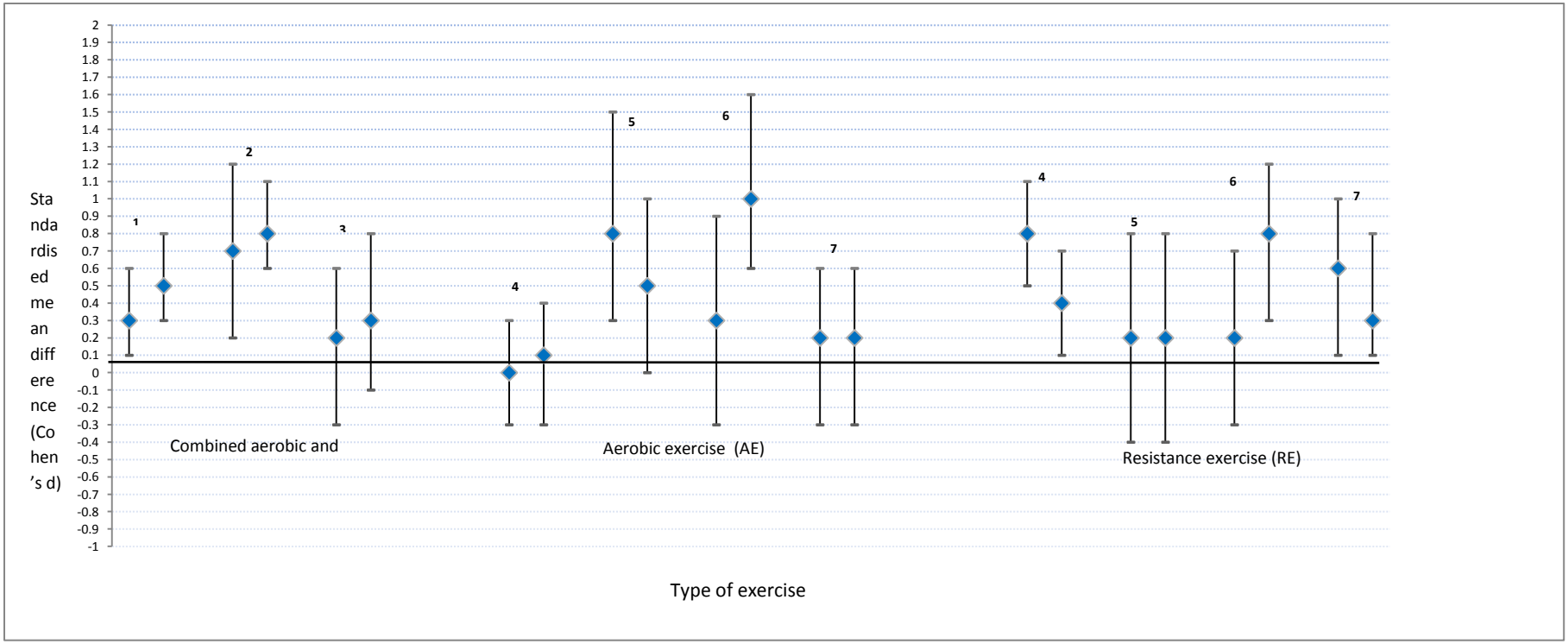
Study	**Randomization**	**Allocation concealment**	**Blinding of outcome assessor**	**Adherence to intention-to-treat principle**	**Other limitations**
Adamsen, 2009	Yes - computer generated numbers	No	No	Yes – participants with missing data included as MR	Heterogeneous sample in terms of diagnosis and stage
Battaglini, 2007	Yes -drawing of random numbers by the patient	Yes - sealed envelopes	Not stated	Not stated (no drop-out)	Inclusion criteria not described Small sample size
Baumann, 2010	Yes – no detail	Not stated	Not stated	Yes – no details	Pilot study – small sample size Loss to follow up 23.5 %
Courneya, 2007	Yes - computer generated numbers	Yes – external site	Not stated	Yes - participants with missing data included as MR	
Coleman, 2003[a]	Yes, drawing of random numbers by the patient	Yes - sealed envelopes	Not stated	Not stated	Pilot study - small sample size Loss to follow up 42 %
Cunningham, 1986	Yes - computer generated	Yes – no details	Not stated	Not stated	Loss to follow up 20 %
Demark-Wahnefried, 2008	Yes - stratified block randomization	Not stated	Not stated	Not stated	Pilot study
Jarden 2009	Yes -computer generated – stratified by age and gender	Yes -	Not stated	Yes - participants with missing data included as MR	Small sample size
Mello, 2003	Yes – no detail	Not stated	Not stated	Not stated	Small sample size Loss to follow up 44 %
Monga, 2007	Yes – no detail	Not stated	Not stated	Not stated	Small sample size
Mustian, 2009	Yes – no detail	Yes – no details	Blinded	Yes – patients analyzed according to allocated group	Pilot study – small sample size
Oldervoll, 2011	Yes - block randomization	Not stated	Not stated	Yes - participants with missing data included as MR	Loss to follow up 29 %
Schwartz, 2007	Yes – no detail	Not stated	Not stated	Not stated	
Schwartz, 2009	Yes – no detail	Not stated	Not stated	Yes – no details	Multiple end-points.
Segal, 2009	Yes - computer generated	Yes	Blinded	Yes – no details	
Wiskemann, 2011	Yes – no detail	Not stated	Not stated	Yes – no details	Between group comparison not reported Loss to follow up 23 %

For details on criteria, see Guyatt et all 2010. GRADE guidelines: 4. Rating the quality of evidence – study limitations (risk of bias). Journal of Clinical Epidemiology.

Figure 1. Flow chart.docx



Figur 2.docx



1. Adamsen et al (n=269), 2. Jarden et al (n=2), 3. Wiskemann et al (n=105), 4. Courneya et al (n=242), 5. Schwartz et al (n=66), 6. Schwartz et al (n=101), 7. Segal et al (n=121)

Figure legends

Figure 1. Flow chart over literature selection and reason for exclusion.

Figure 2. Effect sizes for muscle strength, measured in kilograms, for physical exercise including a) combined aerobic and strength exercise, b) aerobic exercise alone and c) strength exercise alone. The bars illustrate the standardised mean difference (dots) and the upper and lower 95 % confidence intervals for each outcome (upper body and lower body strength measured as kilograms) in the presented studies (n=7)*. Effect sizes above zero represent the magnitude of the effect in favour of physical exercise compared to treatment as usual. Effect sizes < 0.2 are interpreted as small; 0.2 – 0.5 small to moderate; 0.51 -0.8 moderate to large; >0.8 large.

* Out of 12 studies measuring muscle strength, 7 studies using repetition maximum or isometric testing is reported in figure. 4 studies measuring muscle strength as a sum score for whole body, grip strength and functional sit to stand test, is not presented in the figure. One study did not provide calculable data for muscle strength.

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