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Effects of preoperative combined aerobic and resistance exercise training in cancer patients undergoing tumour resection surgery: a systematic review of randomised trials

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Conflict of interest
All authors declare no conflict of interest\textsuperscript{1}

Abbreviations: 6MWT, 6-minute walk test; CT, Combined endurance and resistance training; EORTC-QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cancer 30; EORTC BLS24= European Organization for Research and Treatment of Cancer Quality of Life Superficial Bladder Cancer questionnaire; EORTC BLM30= European Organization for Research and Treatment of Cancer Quality of Life Muscle Invasive Bladder Cancer Questionnaire; QoL, Quality of life; LOS, Length of stay; RCTs, randomised controlled trials.

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Abstract

Background: Surgical management remains the cornerstone of treatment for many cancers, but is associated with a high rate of postoperative complications, which are linked to poor preoperative functional capacity. Prehabilitation may have beneficial effects on functional capacity and postoperative outcomes. We evaluated the effects of prehabilitation combining endurance and resistance training (CT) on physical fitness, quality of life (QoL) and postoperative outcomes in cancer patients undergoing tumour resection surgery.

Methods: We performed a literature search in PubMed, PEDro, EMBASE (via Scopus) and the Cochrane library for clinical trials until September 2017. Randomised controlled trials investigating the effects of CT in adult cancer patients undergoing surgery were included when at least one of the following outcomes was reported: physical capacity, muscle strength, QoL, length of stay (LOS), postoperative complications and mortality.

Results: Ten studies (360 patients) were retrieved and included patients with lung, colorectal, bladder and oesophageal cancer. No adverse effects of CT were reported. Compared with the control group, CT improved physical capacity (3 of 5 studies), muscle strength (2 of 3 studies) and some domains of QoL (2 of 4 studies), shortened LOS (1 of 6 studies) and reduced postoperative pulmonary complications (2 of 6 studies).

Conclusions: The benefits of CT in cancer population are demonstrated. CT may improve physical fitness and QoL and decrease LOS and postoperative pulmonary complications. However, our conclusions are limited by the heterogeneity of the preoperative CT programs, patient characteristics and measurement tools. Future research is required to determine the optimal composition of CT.

Keywords: exercise therapy; surgery; neoplasms; preoperative care
1. Introduction

Surgical management remains the cornerstone of treatment for many cancers [1]. Nevertheless, major surgery is associated with substantial postoperative complication rates, which lead to increased functional recovery time and length of stay (LOS) and decreased quality of life (QoL) [2-4]. Preoperative physical status is often reduced in patients with cancer [5] and is predictive of postoperative complications and poor prognosis. Preoperative status is therefore an important factor to consider when trying to improve postoperative outcomes in these patients [5].

Over the last few years, several studies have evaluated the possibility of improving preoperative physical function by using prehabilitation to overcome surgical stress and thus improve postoperative recovery times [5, 6]. Prehabilitation consists mainly of endurance and resistance exercises. Endurance training is the most effective approach for improving cardiorespiratory fitness [7]. Resistance training increases muscle mass, which leads to a better aerobic response [8]. Previous systematic reviews on prehabilitation in cancer populations have been published with diverse results [9-13]. Some reported that preoperative exercises may improve physical fitness but noted non-significant effects on postoperative outcomes [9, 10, 12]. Others concluded that prehabilitation is effective in reducing functional recovery time, LOS and postoperative complications [11, 13]. Consequently, the beneficial effects of prehabilitation in these patients remain unclear. The authors of one previous systematic review [10] concluded that further randomised controlled trials (RCTs) incorporating combined preoperative endurance and resistance training (CT) were needed. Since that publication, the results of several RCTs that included preoperative CT have been published.
In this review, we therefore systematically evaluated the effects on physical fitness, QoL and postoperative outcomes of prehabilitation combining endurance and resistance training in cancer patients undergoing tumour resection surgery.

2. Methods

2.1. Literature search and selection

This review was recorded on the PROSPERO database (https://www.crd.york.ac.uk/PROSPERO/; registration number CRD42017076316). A systematic literature search, based upon the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14], was performed using four databases: PubMed, PEDro, EMBASE (via Scopus) and the Cochrane library for clinical trials. The data search was updated in September 2017.

The search strategy used in PubMed was divided into three distinct categories: (a) Participant: (cancer or tumour or neoplasms or malignancy); (b) Intervention: (prehabilitation, pre-operative, presurgical, surgery, pre-conditioning) AND (Training or physical exercise or fitness or strength training or aerobic or concurrent strength and endurance training or concurrent training or exercise therapy or physical training or strength exercise or resistance training or resistance exercise or rehabilitation or progressive resistive and resistance aerobic); and (c) Study design: (randomised controlled trial or RCT). For other electronic databases, we adapted the search using key terms combined with Boolean operators. The lead author also performed manual tracking of citations in the selected articles.

2.2. Inclusion and exclusion criteria

We included studies that recruited adult subjects diagnosed with cancer and scheduled to undergo tumour resection. RCTs comparing the effects of CT with no exercise or with another exercise modality were included. CT was defined as the combination of an aerobic and a
resistance training component performed at least twice a week before surgery. Studies that included, in addition to CT, breathing exercises, pelvic muscle training, nutritional supplements, health education and psychological intervention were included. Studies needed to report at least one of the following parameters as an outcome: functional capacity, muscle strength, fatigue, QoL, anxiety, depression, LOS, postoperative complications and mortality. We included studies published in any language and without date restriction. Abstracts, reviews, prospective and retrospective observational cohort studies, editorials, letters and case reports were excluded. Studies including patients with benign diseases and duplicated data reported in earlier publications were also excluded.

2.3. Study Selection

Eligible studies were identified independently by two reviewers (EP and GR) and reviewed against selection criteria. After removing duplicates, studies were screened based on title and then on the abstracts. Full-text articles were screened when the title and abstracts were unclear. Discrepancies in selecting studies were resolved by a third independent reviewer (GC).

2.4. Data extraction and analysis

Data were extracted by two reviewers (EP and GR). Characteristics of studies (authors, year, country), patient data (sex, age, height, weight, cancer type and cancer stage), characteristics of the preoperative intervention (setting, length, duration per session, frequency, type, volume, progression) and outcome data (change in physical, psychological and postoperative outcomes) were extracted.

2.5. Risk of bias
The methodological quality of the selected studies was assessed using the Downs and Black checklist. This tool contains 27 questions classified in five categories: reporting, external validity, bias, confounding factors and power, with a maximum score of 28. A score of < 14 was considered poor quality, between 14 and 18 fair quality, between 19 and 23 good quality and a score of ≥ 24 excellent quality. The studies were scored by the lead author (EP). Any uncertainty was discussed with a second assessor (GR) until consensus was reached.

3. Results

3.1. Selection of studies

The PRISMA flow chart displaying the study selection process is shown in Figure 1 [14]. A total of 1981 citations were retrieved using the search strategy and five additional studies from hand-searching the references. Ten articles were retained for the review [15-23], of which three were from the same population but the outcomes were different and they met the inclusion criteria [18-20]. Benzo and colleagues included the results of two distinct RCTs in one publication [16]; these were analysed as separate studies.

3.2. Quality of studies

Scores for the five categories of the Downs and Black checklist are shown in Table 1. Four of the 10 included studies were considered to be of fair quality [16, 21, 22]. The six other studies were of good quality with total scores between 19 and 23 [15, 17-20, 23]. The following items were reported in all studies: objectives, main results, patients lost to follow-up, clear “data dredging”, appropriate statistical tests, participants recruited from the same population and randomisation. Because of study design, it was impossible to blind subjects to the intervention.
3.3. Settings

Studies were conducted in the USA [16], the Netherlands [17], Canada [15], Denmark [18-20], Brazil [21], Spain [22] and Japan [23]. All studies were single centre, except the two studies by Benzo and colleagues that were each conducted in two centres [16].

3.4. Participants

The characteristics of the studies included in the systematic review are shown in Table 2. Four studies (40%) included patients with lung cancer, two (20%) included patients with colorectal cancer, three (30%) patients with bladder cancer and one (10%) patients with oesophageal cancer; there was a total of 360 participants, 177 in the prehabilitation group and 183 in the control group. The mean ages of the prehabilitation and control groups were 68.6 ± 2.5 years and 68.8 ± 2.3 years, respectively. Among the included patients, there were more men than women (69% vs 31%). Body mass index was reported in seven studies (70%) and ranged from 21.8 ± 2.7 to 29.4 ± 4.3 kg/m² for the prehabilitation group and from 20.9 ± 2.5 to 28.5 ± 4.3 kg/m² for the control group. Surgery was the first cancer treatment for all the included patients, except in one study in which 60% had received neoadjuvant therapy [23]. Eight studies (80%) compared a prehabilitation intervention with usual care (no exercise training) [15, 16, 18-20, 22, 23]. In the other two studies (20%), the prehabilitation group was compared to a group that received home-based exercise advice [17] and to a group that received breathing exercises for lung expansion [21].

3.5. Intervention

Prehabilitation in all included studies combined an aerobic and resistance program (Table 3). The prehabilitation also included inspiratory muscle training in three studies (30%) [16, 17, 21]; breathing exercises in one study (10%) [17]; respiratory muscle and thoracic cage
stretching, deep inspiration training and deep diaphragmatic breathing in one study (10%) [23]; flexibility, stretching and balance exercises in one study (10%) [21]; and nutritional and psychological interventions in one study (10%) [15]. The prehabilitation program was supervised in hospital in five studies (50%) [16, 21-23], unsupervised and home-based in four studies (40%) [15, 18-20] and a combination of both in one study (10%) [17]. No adverse events occurred in the five studies (50%) that reported this parameter [16, 17, 22, 23]. The length of the prehabilitation program ranged from 7 days to 54 days. Training frequency varied from twice a day to three per week.

Nine of the studies (90%) reported the type of endurance training. Patients could walk, cycle, run, swim and do step exercises on fitness machines inside or outside. The duration was between 10 and 30 minutes for each session. The intensity of the endurance training was specified in only four studies (40%) and was measured using different methods and reported differently [15, 17, 21, 22]. Sebio and co-workers were the only investigators to include intermittent endurance training [22].

Muscle strengthening in the resistance training session was different between studies. Five studies (50%) targeted the major muscle groups [15, 18-20, 22], one (10%) the lower limbs [17], one (10%) the upper limbs with a proprioceptive neuromuscular facilitation method [21], one (10%) the lower limbs and abdominal muscles with a weight [23] and one (10%) the lower and upper limbs with elastic resistance bands [16]. The exercise volume ranged from one to three sets and 8 to 15 repetitions. The desired optimal intensity was reported in four studies (40%), calculated based on the one-repetition maximum in one study [17] or the perceived rate of exhaustion according to the Borg Scale (one study) [15], modified Borg Scale (one study) [16] and the OMNI-Resistance Scale (one study) [22]. Adherence to the program, reported in five studies (50%), varied between 66% and 97% (Table 4) [15, 17-20].
3.6. Effects of intervention on physical fitness

Physical capacity was assessed in 5 of the 10 studies included in the systematic review and all used a submaximal test (Table 4) [15-17, 21, 22]. The most widely used method was the 6-minute walk test (6MWT) (3 of 5 studies). Among the five studies, three showed significant improvement in physical capacity from baseline to post-intervention in the prehabilitation group [15, 21, 22]. Compared to the control group, two of five studies showed a significant difference after prehabilitation and this difference was maintained in follow-up [15, 22]. Muscle strength was evaluated in three studies (30%). In two of these studies, muscle strength was significantly improved in the prehabilitation group after intervention compared to the control group [19, 22].

3.7. Effects of intervention on quality of life

Effects of CT on QoL were investigated in four (40%) of the studies (Table 4) [15, 17, 18, 22]; two used the EORTC QLQ-C30 questionnaire and the other two the SF-36 questionnaire. In two of the four studies, significant improvements in some domains of QoL were reported in the prehabilitation group compared to the control group [18, 22].

3.8. Effects of prehabilitation intervention on postoperative outcomes

Among the 10 studies, eight evaluated postoperative clinical outcomes (Table 4) [15-17, 20-23]. LOS was evaluated in 7 of the 8 studies [15-17, 20-22]. Of these, one study showed a significant decrease in LOS in the prehabilitation group compared to the control group and another study reported a trend towards a significant result [16, 21]. Postoperative pulmonary complications were evaluated in 6 of 8 studies and 2 of them reported a significantly lower incidence in the intervention group compared to the control arm [21, 23]. Compared to
patients in the control group, those in the prehabilitation group in the study by Morano and colleagues needed a chest tube for fewer days and there were fewer cases of bronchopleural fistula, atelectasis and bronchospasm [21]. Patients in the intervention group in the study by Benzo and others (Part 2) required a chest tube for fewer days and the incidence of prolonged chest tubes was lower than for patients in the control group [16]. Global postoperative complications (including pulmonary complications) were measured in two studies and there were no significant differences between groups [15, 20]. Mortality data were recorded in only one study: there was no significant difference between groups at 90 days postoperatively [20].

4. Discussion and conclusion

This systematic review investigated the effects of a combined preoperative prehabilitation program on physical fitness, QoL, postoperative complications, LOS and mortality in patients diagnosed with cancer who were undergoing surgical resection of the tumour. Ten RCTs with fair to good methodological quality were included. A combined prehabilitation intervention significantly improved physical capacity [15, 21, 22], muscular strength [19, 22] and QoL [18, 22], reduced postoperative pulmonary complications [21, 23] and shortened LOS [21]. However, given the varied results of the included studies, it seems premature to draw robust conclusions regarding the optimal composition of CT. These variable results may be explained by differences in the types and stages of cancers and patient comorbidities, and by heterogeneity among the interventions and measurement tools.

4.1. Effects of prehabilitation

Physical capacity is an important preoperative factor to assess before major tumour resection because it has been strongly associated with postoperative complications, prolonged LOS and mortality [24, 25]. Peak oxygen uptake and the anaerobic threshold are considered
as the most widely accepted measures of cardiorespiratory fitness [26]. Among the five included studies that evaluated this parameter, all used reliable and valid submaximal measures [27-29] and three of the five reported significant clinical improvement in cardiorespiratory fitness after the intervention and in follow-up [15, 21, 22]. Our findings are in line with previous systematic reviews in patients with cancer [10, 30]. Discrepancies in physical fitness results may be explained by the small number of patients in some studies that were thus underpowered to detect significant effects [16, 17]. Another possible explanation for the different results is that the measurement tools used to assess physical capacity were heterogeneous among studies. The 6MWT was the most frequently used measurement method in our review and in previous ones [10, 30]. The distance walked is correlated with peak oxygen consumption and can predict complications [31]. Therefore, the 6MWT should be used when measurement of peak oxygen uptake cannot be performed.

In addition to the benefits of improving cardiorespiratory capacity, it is known that increased muscle mass leads to a better response to aerobic conditioning [8]. Moreover, this improvement decreases the risk of falls [32], enhances the capacity to perform activities of daily living and promotes functional independence [33]. Despite this important role, this outcome was evaluated in only three studies included in our systematic review [17, 19, 22]. Of these three studies, two reported that muscle power improved significantly in the lower limbs in the prehabilitation group compared to the control group [19, 22]. The non-significant results in the study by Dronkers and colleagues may be explained by the fact that the control group received home-based exercise advice and had a higher activity level at baseline than the prehabilitation group, as measured by the LASA Physical Activity Questionnaire scores and the daily number of steps [17]. It is likely that the advice to perform exercise helped maintain or improve preoperative exercise capacity and may explain the non-significant results.
Interestingly two studies reported physical capacity and muscle strength in their outcomes [17, 22]. Although one of the studies reported no difference between the prehabilitation group and the control group in these parameters, the other noted a significant improvement in exercise capacity and muscle strength compared with the control group three months after surgery. This result can be explained in part by better oxidative capacity of the muscle as a result of the increase in the strength of the major muscles [8].

After diagnosis and during treatment (e.g., surgery, chemotherapy), cancer patients may experience several adverse effects that have a negative effect on QoL [34]. It has been shown that exercise interventions during and after cancer treatment positively influence QoL [35, 36] but evidence in the preoperative period is not clear. Half of the studies that assessed QoL in this systematic review showed an improvement in some domains of the EORTC QLQ-C30, the bladder cancer disease-specific items (EORTC QLQ-BLS24 and QLQ-BLM30) and in the SF-36 physical component, but not in mental health [18, 22]. These results are in agreement with a previous meta-analysis [13]. This benefit on some domains of QoL may in part be explained by an improvement in muscle strength in the prehabilitation group. It is known that this improvement is associated with better functional independence and this has a positive effect on QoL [37, 38].

Concerning postoperative outcomes, one study showed a significant decrease in LOS and another study reported a trend towards a significant result [16, 21]. Both studies were conducted in patients with lung cancer. On the other hand, Sebio and colleagues, also in patients with lung cancer, showed a decrease in LOS and postoperative complications but the difference was not significant between groups. The authors reported that these results could be explained by the experience of the thoracic surgery team and the low-risk profile of the included patients [22]. Other studies, in patients with colorectal and bladder cancer, reported no differences in LOS or complication rates between groups [15, 20]. One explanation for
these contradictory results is that resection in these studies was performed using the enhanced recovery after surgery pathway in elective colorectal resection [15] and radical cystectomy [20]. This pathway has significantly reduced LOS and complication rates, which may have led to the non-significant results for these two parameters [39, 40]. Our results are consistent with a previous systematic review, which focused inclusion criteria on lung malignancy and showed that a preoperative exercise program could significantly shorten LOS (ranging from 5.4 to 21.0 days and from 9.66 to 29.0 days for the intervention and the control groups, respectively) [11]. Another systematic review that included colorectal cancer patients reported no significant effects on LOS (from 4 to 16.2 days for the intervention group and from 5 to 21.6 days for the control group) or postoperative complications [9].

4.2. Prehabilitation intervention

We tried to compare studies with homogeneous exercise programs by including only studies that combined aerobic and resistance training. However, studies remained heterogeneous in the precise composition of the programs (modality, intensity, frequency and duration). Implementing a preoperative exercise program in patients with cancer is challenging in clinical practice because of the limited period between diagnosis and surgery. Stage of disease, motivation and willingness should also be considered to define the optimal duration of prehabilitation [5]. Debes et al. reported that a length of six to eight weeks seemed to be a good compromise between feasibility and effectiveness [41]. Unfortunately, for patients with cancer, the time available for prehabilitation is often less than six weeks if surgery is the first treatment step. For example, the median time from colorectal cancer diagnosis to surgery is 30 days in the UK (interquartile range: 18 to 42) [42]. Recently, a study examined whether time between diagnosis and surgery was related to overall survival in patients with colorectal adenocarcinoma. The authors observed no differences in long-term
survival in patients operated on within 4, 8 and 12-weeks [43]. These results should reassure patients that prehabilitation can be performed safely and encourage healthcare providers to promote this program. The length of the prehabilitation intervention in the included studies ranged from 7 days [16, 23] to 54 days [22]. Yamana and co-workers showed that one week of CT seemed to be effective at reducing postoperative pulmonary complications [23], unlike the study by Benzo et al. (Part 2) [16]. This difference can be explained by the fact that Yamana and colleagues had a sufficient sample size to detect effects of the intervention and used valid tools to evaluate postoperative pulmonary complications. Nevertheless, despite the good methodological quality of the study, it is difficult to interpret the results due to the poor description of the CT. The study by Benzo and colleagues (Part 1) was stopped prematurely because patients or healthcare practitioners were not willing to allow weeks to pass before lung cancer resection [16]. However, Morano and others managed to perform 4 weeks of prehabilitation before lung resection surgery [21] and another study confirmed that result [44].

For endurance training, various types of intervention were used, including walking, biking, swimming, running or step exercises. All modalities were shown to be feasible and accessible to all. The type of modality selected should consider various parameters including age, preference, musculoskeletal disease and equipment available for the patient. For example, a bike may be preferred in patients with musculoskeletal disease whereas walking remains accessible to all, even the elderly [45]. The intensity at which endurance training is performed is a key parameter to be considered. Some programs were performed at moderate intensity whereas others were completed at high intensity [15, 17, 22]. In the literature, high intensity training seems to be more effective and time-efficient than moderate-intensity training in cancer survivors [46, 47]. As poor preoperative cardiovascular fitness is a strong predictor of increased postoperative complications, prolonged hospital stay and mortality [24, 25], this modality of exercise, which has been associated with greater improvement in
cardiovascular fitness would seem to be more useful for clinical practice implementation. It may be interesting to compare the effectiveness of high intensity training to moderate intensity in prehabilitation.

Muscle strengthening, using resistance training, sustains the beneficial effects of aerobic training. Indeed, improvement in muscle strength, neuromuscular activity and muscle mass optimise the oxidative capacity of the muscle and resistance training may therefore be a complementary component for enhancing physical capacity [48]. Although resistance training was included in all studies, the composition was different between studies, contributing to the variation in the training response. Most of the studies strengthened major muscle groups in the range of one to three sets and from 8 to 15 repetitions with varied duration and intensity. It has been previously reported that exercises that stress the largest amount of muscle mass achieve the greatest rate of oxygen uptake and increase metabolic demand [49]. This approach is in accordance with the guidelines of the American College of Sports Medicine and the American Cancer Society that recommend at least one set of 8-12 repetitions for all major muscle groups [50, 51]. Therefore, there is a need to standardise preoperative endurance and resistance programs with the best effective combination (type, duration, intensity and frequency) and adherence.

Exercise adherence was reported in five studies. In these, adherence was better when the exercise program used a combination of hospital- and home-based settings (97%) than either setting alone [17]. A recent systematic review observed the greatest adherence for hospital-based programs (97-100%) [30], whereas another review reported a similar level of adherence for hospital-based and home-based programs, ranging from 72% to 97% and 74% to 97%, respectively [26]. In our systematic review, no adverse events were reported for either setting. The setting in which the exercise program is performed should, therefore, be personally adapted to the patient. Some patients with cancer have associated comorbidities that require
supervised exercise sessions [52]. Others have barriers to performing outpatient hospital-based sessions, such as travel distance, time constraints or financial considerations. For these patients, home-based training would seem to be a better option. To meet the needs of today's society, use of technologies to deliver exercise program must be developed [53]. Evidence is growing that exercise programs delivered by telerehabilitation systems may facilitate access to therapy [54]. Moreover, telerehabilitation enables patients to interact with healthcare practitioners by videoconference, phone call or mail. This feedback has been shown to be positive for the patient and to improve adherence. The effectiveness of prehabilitation is dependent on the effectiveness of the exercise training but also on the adherence of the patient to this program. Therefore, studies investigating the effectiveness and adherence of telerehabilitation during preoperative training are needed.

4.3. Limitations and future directions

This review has some limitations that need to be highlighted. Firstly, the review included studies with patients with different cancer diagnoses. We decided to extend the review to all cancer types that required major resection surgery because there were not many high quality studies combining endurance and resistance preoperative training. The studies included had patients with lung [16, 21, 22], colorectal [15, 17], bladder [18-20] and oesophageal [23] cancer, which represent 29% of total cancers [55]. It would be interesting in the future to perform studies in patients with other cancer types (e.g., brain tumour) awaiting major surgery, to evaluate the role of a combined prehabilitation intervention on physical fitness, QoL and postoperative outcomes in these patients. Secondly, the sample size was not estimated in 40% of included studies and, therefore, these may have been underpowered to detect significant effects. Thirdly, while we attempted to include studies with homogeneous interventions, the endurance and resistance training were different in modality, intensity,
frequency and duration among studies. Moreover, studies did not correctly report information regarding the exercise interventions. Hence, the external validity of our results is limited. To improve this situation, researchers should provide complete details of the exercise intervention using the modified Consensus on Exercise Reporting Template [56]. It seems important to determine the training variables that can achieve the greatest benefit in this context. Future studies are needed to determine the most effective combination of exercises and to compare different training programs (e.g., aerobic training vs combined training) and different settings (e.g., hospital-based vs home-based vs telerehabilitation) in order to identify differences in training response. In addition, it may be interesting to compare the effectiveness of high intensity training to moderate intensity training in the context of prehabilitation. Finally, measurement tools used to evaluate outcomes were heterogeneous between studies. There is a need to standardise the measurement parameters used to evaluate the effects of prehabilitation on order to homogenise the results and to facilitate comparison among studies.

In conclusion, the results of this systematic review demonstrate the benefits of a preoperative combined prehabilitation program in patients with cancer undergoing tumour resection surgery. CT may improve cardiorespiratory fitness, muscular strength and QoL and decrease hospital LOS and postoperative pulmonary complications. However, our conclusions are limited because of the large heterogeneity of the preoperative program composition, patient characteristics and measurement tools. Because of the paucity of studies that have included combined prehabilitation, further and larger RCTs are needed to determine the most effective combined prehabilitation in all types of cancer. It would also be interesting to compare CT to different training programs, in different settings and with different program combinations. These results may motivate patients to perform prehabilitation and healthcare providers to include such programs in clinical practice in order to improve care pathways.
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Authors’ contributions

Conception, design, literature search, data extraction, bias analysis, interpretation of data and drafting of article: E.P.

Conception, design, literature search, data extraction, interpretation of data and revision of manuscript: G.R.

Conception, design and revision of manuscript: G.R.
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## Table 2. Characteristics of the studies included in the systematic review

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<td>Benzo, 2011 (Part 2)</td>
<td>n=19</td>
<td>IG: 5 ♂; 5 ♀</td>
<td>CG: 4 ♂; 5 ♀</td>
<td>IG: 70.2±8.6</td>
<td>CG: 72.0±6.7</td>
<td>Lung</td>
<td>NR</td>
</tr>
<tr>
<td>Dronkers, 2010</td>
<td>n=42</td>
<td>IG: 15 ♂; 17 ♀</td>
<td>CG: 16 ♂; 4 ♀</td>
<td>IG: 71.1±6.3</td>
<td>CG: 68.8±6.4</td>
<td>Colon</td>
<td>NR</td>
</tr>
<tr>
<td>Gillis, 2014</td>
<td>n=77</td>
<td>IG: 21 ♂; 17 ♀</td>
<td>CG: 27 ♂; 12 ♀</td>
<td>IG: 65.7±13.6</td>
<td>CG: 66.0±9.1</td>
<td>Colorectal</td>
<td>I-III</td>
</tr>
<tr>
<td>Jensen, 2014</td>
<td>n=107</td>
<td>IG: 39 ♂; 11 ♀</td>
<td>CG: 40 ♂; 17 ♀</td>
<td>IG: 69 (66-72)</td>
<td>CG: 71 (68-73)</td>
<td>Bladder</td>
<td>I-IV</td>
</tr>
<tr>
<td>Jensen, 2015</td>
<td>n=107</td>
<td>IG: 39 ♂; 11 ♀</td>
<td>CG: 40 ♂; 17 ♀</td>
<td>IG: 69 (66-72)</td>
<td>CG: 71 (68-73)</td>
<td>Bladder</td>
<td>I-IV</td>
</tr>
<tr>
<td>Jensen, 2016</td>
<td>n=107</td>
<td>IG: 39 ♂; 11 ♀</td>
<td>CG: 40 ♂; 17 ♀</td>
<td>IG: 69 (66-72)</td>
<td>CG: 71 (68-73)</td>
<td>Bladder</td>
<td>I-IV</td>
</tr>
<tr>
<td>Morano, 2013</td>
<td>n=24</td>
<td>IG: 4 ♂; 8 ♀</td>
<td>CG: 5 ♂; 7 ♀</td>
<td>IG: 64.8±8.8</td>
<td>CG: 68.8±7.3</td>
<td>Lung</td>
<td>I-IIIA</td>
</tr>
<tr>
<td>Sebio, 2016</td>
<td>n=22</td>
<td>IG: 9 ♂; 1 ♀</td>
<td>CG: 11 ♂; 1 ♀</td>
<td>IG: 70.9±6.1</td>
<td>CG: 69.4±9.4</td>
<td>Lung</td>
<td>NR</td>
</tr>
<tr>
<td>Yamana, 2015</td>
<td>n=60</td>
<td>IG: 24 ♂; 6 ♀</td>
<td>CG: 23 ♂; 7 ♀</td>
<td>IG: 68.3±7.6</td>
<td>CG: 65.9±9.5</td>
<td>Oesophageal</td>
<td>0-IVb</td>
</tr>
</tbody>
</table>

Values are mean±SD or mean (95% CI)
6MWT= 6-Min Walk Test; BMI= Body Mass Index; CCET= Constant-load Cycle Endurance Test; EORTC-QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cancer 30; EORTC BLS24= European Organization for Research and Treatment of Cancer Quality of Life Superficial Bladder Cancer questionnaire; EORTC BLM30= European Organization for Research and Treatment of Cancer Quality of Life Muscle Invasive Bladder Cancer Questionnaire; IG= Intervention Group; LL= Lower Limb; LOS= Length Of Stay; NR= Not Reported; PC= Postoperative Complications; PPC= Postoperative Pulmonary Complications; PWC= Physical Work Capacity; QoL= Quality of life; SF-36= the 36-Item Short Form Health Survey; TUG= Timed-Up-and-Go-Test; UPSS= Utrecht Pneumonia Scoring System; wk= week
<table>
<thead>
<tr>
<th>First author, year</th>
<th>Setting</th>
<th>Length of intervention</th>
<th>Duration (min per session)</th>
<th>Frequency</th>
<th>Endurance training (T: Type; I: Intensity; D: duration)</th>
<th>Resistance training (T: Type; V: Volume; I: Intensity; P: Progression)</th>
<th>Supplementary intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzo, 2011 (Part 1)</td>
<td>Hospital-based Supervised</td>
<td>4 wks</td>
<td>NR</td>
<td>2x/day</td>
<td>T: NR “used current guidelines for exercise prescription” I: NR D: NR</td>
<td>T: NR “used current guidelines for exercise prescription” V: NR I: NR</td>
<td>Nil</td>
</tr>
<tr>
<td>Benzo, 2011 (Part 2)</td>
<td>Hospital-based Supervised</td>
<td>1 wk</td>
<td>NR</td>
<td>2x/day</td>
<td>T: Lower limbs (Treadmill or Nu-Step) and upper limbs (Arm ergometer or Nu-Step) I: NR D: 20min</td>
<td>T: Lower and upper limbs with Thera-Bands V: 2 sets of 10-12 reps with lowest Thera-band resistance. I: Borg modified ≥ 2 P: Resistance ↑ if it is “too easy” or “requires no effort”</td>
<td>IMT and respiratory physiotherapy (15-20min, 1x/day)</td>
</tr>
<tr>
<td>Dronkers, 2010</td>
<td>Hospital-and-home-based Supervised</td>
<td>2-4 wks</td>
<td>60</td>
<td>7x/wk (2x in hospital and 5x at home)</td>
<td>T: Walking/Cycling (Hospital &amp; home) I: 55-75% MHR or Borg 11-13 (Hospital) D: 20-30min (Hospital), 30min (Home)</td>
<td>T: Lower limbs (Hospital) V: 1 set of 8-15 reps (Hospital) I: 60-80% 1RM (Hospital) P: NR (Hospital)</td>
<td>IMT (15min), Training functional activities, Breathing exercises</td>
</tr>
<tr>
<td>Gillis, 2014</td>
<td>Home-based Unsupervised</td>
<td>4 wks</td>
<td>50</td>
<td>3x/wk</td>
<td>T: Walking/Running/Swimming/Cycling I: 40% of heart rate reserve D: 20min</td>
<td>T: Major muscle groups with Thera-Bands (8 exercises) V: 1 set of 8-12 reps I: Borg ≥ 12 P: Resistance ↑ if Borg ≤ 12 or the participant could complete 15 reps</td>
<td>Nutrition intervention (Whey protein), reduction anxiety</td>
</tr>
<tr>
<td>Jensen, 2014</td>
<td>Home-based Unsupervised</td>
<td>2 wks</td>
<td>NR</td>
<td>2x/day</td>
<td>T: Lower limbs on step trainer I: NR D: 15 min</td>
<td>T: Muscle groups involved in activities such as mobilisation, in and out of bed, chair raise performance, stair climbing, and gait speed (6 exercises) V: 1 set of 10-15 reps to start I: NR P: ↑ number of exercise repetitions through the training program</td>
<td>Nil</td>
</tr>
<tr>
<td>Jensen, 2015</td>
<td>Home-based Unsupervised</td>
<td>2 wks</td>
<td>NR</td>
<td>2x/day</td>
<td>T: Lower limbs on step trainer I: NR D: 15 min</td>
<td>T: Muscle groups involved in activities such as mobilisation, in and out of bed, chair raise performance, stair climbing, and gait speed (6 exercises) V: 1 set of 10-15 reps to start I: NR P: ↑ number of exercise reps through the training program</td>
<td>Nil</td>
</tr>
<tr>
<td>Jensen, 2016</td>
<td>Home-based Unsupervised</td>
<td>2 wks</td>
<td>NR</td>
<td>2x/day</td>
<td>T: Lower limbs on step trainer I: NR D: 15 min</td>
<td>T: Muscle groups involved in activities such as mobilisation, in and out of bed, chair raise performance, stair climbing, and gait speed (6 exercises) V: 1 set of 10-15 reps to start I: NR P: ↑ number of exercise repetitions through the training program</td>
<td>Nil</td>
</tr>
<tr>
<td>Morano, 2013</td>
<td>Hospital-based Supervised</td>
<td>4 wks</td>
<td>NR</td>
<td>5x/wk</td>
<td>T: Walking on a treadmill I: 80% of the max workload D: 10min increasing to 30min</td>
<td>T: Upper limbs with proprioceptive neuromuscular facilitation method V: 15 rep/min. I: NR P: The initial load is 500g, with an increase of 500g each</td>
<td>IMT (10-30min), Flexibility, Stretching and Balance exercises</td>
</tr>
<tr>
<td>Study</td>
<td>Type of Intervention</td>
<td>Duration</td>
<td>Frequency</td>
<td>Type of Exercise</td>
<td>Mode of Exercise</td>
<td>Additional Details</td>
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<td></td>
</tr>
<tr>
<td>Sebio, 2016</td>
<td>Hospital-based Supervised</td>
<td>54 days</td>
<td>60</td>
<td>3-5x/wk</td>
<td>T: Cycling on a cycle-ergometer I: HIIT (1 min at 80% of Wpeak plus 4 min at 50% of Wpeak) D: 30 min (with 5 min warm-up and 4 min cool down)</td>
<td>T: Major muscle groups with Thera-Bands and body-weight exercises (6 exercises) V: 3 sets of 15 reps I: Moderate perceived rate of exhaustion according to the OMNI-Resistance Scale P: From the tenth onwards, the number of repetitions was maintained and the number of sets was increased to four</td>
<td></td>
</tr>
<tr>
<td>Yamana, 2016</td>
<td>Hospital-based Supervised</td>
<td>7 days</td>
<td>60</td>
<td>7x/wk</td>
<td>T: Cycling on a cycle-ergometer I: NR D: 20 min</td>
<td>T: Lower limbs and abdominal muscles with a weight V: NR I: NR P: NR</td>
<td></td>
</tr>
</tbody>
</table>

1RM= One Repetition Maximum; IMT= Inspiratory Muscle Training; HIIT= High Intensity Interval Training; LL= Lower Limb; MHR= Maximal Heart Rate; NR= Not Reported; Reps= repetitions; UL= Upper Limb; wk= week
<table>
<thead>
<tr>
<th>First author, year</th>
<th>Adherence</th>
<th>Physical fitness</th>
<th>Quality of life</th>
<th>Postoperative outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzo, 2011 (Part 1)</td>
<td>NR</td>
<td>NA</td>
<td>NA</td>
<td>All results NS</td>
</tr>
<tr>
<td>Benzo, 2011 (Part 2)</td>
<td>NR</td>
<td>Shuttle test</td>
<td>IG: p&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>Dronkers, 2010</td>
<td>IG: 97% (hospital-based)</td>
<td>PWC, 0.mL/kg/min ± SD (Baseline, day 21)</td>
<td>IG: -1.7 ± 8.4 (p=0.47)</td>
<td></td>
</tr>
<tr>
<td>Gillis, 2014</td>
<td>IG: 78%</td>
<td>6MWD, m ± SD</td>
<td>IG= +25.2 ± 50.2 vs CG= -16.4 ± 46.0 (p&lt;0.001) (Baseline, wk 4)</td>
<td></td>
</tr>
<tr>
<td>Jensen, 2014</td>
<td>IG: 66%</td>
<td>NA</td>
<td>EORTC QLQ-C30, score ± SD (Baseline, day 21)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4. Results of the included studies**
### Constipation

**IG:** +1.6 (5.7;8.8) vs **CG:** +14.4 (6.4;22.4) (p=0.02)

Disease-specific scale (BLM30 and BLS24), score (95% CI)

(Baseline, postop month 4) (Only significant results)

Abdominal flatulence

**IG:** +4.3 (-3.6;12.1) vs **CG:** +10.7 (3.0;18.3) (p=0.05)

### Jensen, 2015

**IG:** 66%  
**NA**  
**LOS** days [range]

**IG:** 8 [3–30] vs **CG:** 8 [4–55] (p=0.68)

PC, Clavien-Dindo (grade≥1), n (%)

**IG:** 30 (60) vs **CG:** 34 (60) (p=0.64)

30-day readmission, n (%)

**IG:** 13 (30) vs **CG:** 12 (23) (p=0.49)

90-day mortality, n (%)

**IG:** 3 (6) vs **CG:** 4 (7) (p=0.84)

### Jensen, 2016

**IG:** 66%  
**NA**  
**Muscle leg power test, W/kg (95% CI) (Baseline, wk 2)**

**IG:** +0.35 (0.12;0.54) (p < 0.002)

**CG:** + 0.03 (1.78; 2.22) (p = 0.48)

**IG vs CG** (p<0.006)

### Morano, 2013

**NR**  
**6MWD, m ± SD (Baseline, wk 4)**

**IG:** +49.5 (p<0.001)

**CG:** -4.6 (p=0.75)

### Sebio, 2016

**NR**  
**CCET, seconds ± SD**

**IG:** +396.6 ± 197.9 (p<0.001) (Baseline, after intervention)

**IG:** +226.0 ± 269.4 vs **CG:** -137.8 ± 221.7 (p=0.005) (Baseline, postop month 3)

6MWWT (m)

**IG:** +1.88 ± 34.7 vs **CG:** -31.5 ± 64.6 (p=0.186) (Baseline, postop month 3)

Arm curl (no. repet)

**IG:** +2.9 ± 2.1 (p=0.002) (Baseline, after intervention)

**IG:** +1.8 ± 3.5 vs **CG:** -1.8 ± 3.5 (p=0.045) (Baseline, postop month 3)

30s Chair-to-Stand Test (no. repet)

**IG:** +0.9 ± 1.2 (p=0.041) (Baseline, after intervention)

**IG:** +2 ± 2.2 vs **CG:** -1.3 ± 1.8 (p=0.002) (Baseline, postop month 3)

**SF-36, PCS, score ± SD**

**IG:** +4.5 ± 4.2 (p=0.08) (Baseline, after intervention)

**IG:** +4.3 ± 4.0 vs **CG:** -4.8 ± 5.8 (p=0.001) (Baseline, postop month 3)

**SF-36, MCS**

**IG:** +1.65 ± 7.7 (p=0.511) (Baseline, after intervention)

**LOS, days ± SD**

**IG:** 7.8 ± 4.8 vs **CG:** 12.2 ± 3.6 (p=0.04)

**PPC, n (%)**

**IG:** 2 (16.7) vs **CG:** 7 (77) (p=0.01)

Days with chest tubes, days ± SD

**IG:** 4.5 ± 2.9 vs **CG:** 7.4 ± 2.6 (p=0.03)

Pneumonia, n (%)

**IG:** 0 (0) vs **CG:** 2 (22.2) (p=0.17)

Ventilation >48h, n (%)

**IG:** 1 (8.3) vs **CG:** 3 (33.3) (p=0.20)

Bronchopleural fistula, n (%)

**IG:** 2 (16.7) vs **CG:** 7 (77.8) (p=0.009)

Atelectasis, n (%)

**IG:** 0 (0) vs **CG:** 3 (33.3) (p=0.06)

Bronchoaspiration, n (%)

**IG:** 0 (0) vs **CG:** 6 (66) (p=0.002)

### Yamana, 2016

**NR**  
**PPC, Clavien-Dindo (grade≥1), n (%)**

**IG:** 2 (3.5) vs **CG:** 5 (50) (p=0.353)

PPC, Melbourne Group Scale (Score≥1), n (%)

**IG:** 5 (50) vs **CG:** 8 (66) (p=0.361)
IG: 8 (27) vs CG: 18 (60) (p=0.014)

PPC, UPSS (Score≥1), n (%)

POD1: IG=10 (33); CG=17 (63); p=0.031
POD2: IG=22 (73); CG=19 (63); p=0.87
POD3: IG=22 (73); CG=15 (50); p=0.13
POD4: IG=6 (20); CG=8 (27); p=0.51

6MWT= 6-Min Walk Test; CG= Control Group; CCET= Constant-load Cycle Endurance Test; EORTC-QLQ-C30/SS= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cancer/Symptom Scale; EORTC BLS24= European Organization for Research and Treatment of Cancer Quality of Life Superficial Bladder Cancer questionnaire; EORTC BLM30= European Organization for Research and Treatment of Cancer Quality of Life Muscle Invasive Bladder Cancer Questionnaire; IG= Intervention Group; LOS= Length Of Stay; NA= Not Assessed; NS= No Significant; PC= Postoperative Complications; POD= Postoperative Days; PPC= Postoperative Pulmonary Complications; PWC= Physical Work Capacity; QoL= Quality of Life; SF-36= the 36-Item Short Form Health Survey; TUG= Timed-Up-and-Go Test; UPSS= Utrecht Pneumonia Scoring System
Caption of figure 1

Fig 1. PRISMA Flow diagram
Records identified through database searching (n = 3442) (PubMed: n = 1700, Scopus: n = 1590, Cochrane Library: n = 44, PEDro: n = 108)

Records after duplicates removed (n = 1981)

Records screened (n = 1981)

Full-text articles assessed for eligibility (n = 18)

Studies included in qualitative synthesis (n = 10)

Records excluded (n = 1963)

Full-text articles excluded, with reasons (n = 8)

Additional records identified through other sources (n = 5)
Highlights

- Prehabilitation combining endurance and resistance training is beneficial
- It improves physical fitness, quality of life and postoperative outcomes
- Conclusions are limited by heterogeneity of the interventions and measurement tools