Prehabilitation Programs for Cancer Patients: a Systematic Review of Randomized-controlled Trials

Jose F Meneses-Echavez (✉ jose.meneses@fhi.no)

Folkehelseinstituttet <https://orcid.org/0000-0003-4312-6909>

Andrés F. Loaiza-Betancur

Universidad de Antioquía: Universidad de Antioquia

Víctor Díaz-López

Universidad de Antioquía: Universidad de Antioquia

Andrés M. Echavarría-Rodríguez

University of Antioquia: Universidad de Antioquia

Hector R Triana-R

Universidad Santo Tomas

Research

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Abstract

Background: Prehabilitation programs focusing on exercise training as the main component are known as a promising alternative for improving patients' outcomes before surgical treatment of different cancers. This systematic review aimed to determine the effects of prehabilitation programs compared with usual care for cancer patients.

Methods/design: We searched CENTRAL, MEDLINE, and EMBASE from inception to 2020, and hand-searched clinical trial registries. We included randomized controlled trials (RCTs) in adults, survivors of any type of cancer, that compared prehabilitation programs focusing on exercise training as the major component with usual care or other active interventions. Outcome measures were health-related quality of life (HRQL), muscular strength, postoperative complications, average length of stay (ALOS), handgrip strength, and physical activity levels. Two reviewers independently selected the studies, extracted data, assessed the risk of bias and the quality of evidence using the GRADE approach.

Results: 14 RCTs published between 2010-2020 met our inclusion criteria (n=1044 participants). Colorectal and lung cancers were the most common diagnoses with 5 studies (36%) each. The studies showed concerns regarding outcome measurement, selective reporting, and attrition. Four comparisons were identified: combined training vs rehabilitation/usual care; high-intensity interval training vs usual care; respiratory muscle training plus aerobic training vs usual care, and pelvic floor training vs usual care. The studies provided no clear evidence of an effect between groups. We assessed the certainty of the body of evidence as very low, downgraded due to serious study limitations and imprecision.

Conclusion: It is uncertain whether prehabilitation programs compared with usual care have an effect in cancer patients. We have very little confidence in the results and the true effect is likely to be substantially different from these. Further research is needed before we could draw a more certain conclusion.

Systematic review registration: CRD42019125658

Background

The National Cancer Institute in the USA defines cancer as a chronic disease in which abnormal cells divide without control, can invade nearby tissues, and can spread to other parts of the body through the blood and lymph systems (1). GLOBOCAN reported 18.1 million new cases of cancer and 9.6 million deaths in 2018 (2). Cancer treatment might comprise surgery, chemotherapy, radiation therapy, immunotherapy, hematopoietic stem cell transplant, and hormone therapy; it all depends on the type of cancer and its stage (1).

In most cases, cancer treatments require surgery and postoperative care that lead to long periods of physical inactivity and deconditioning with loss of muscle function and a higher rate of medical complications (3). Further, inactivity-induced loss of muscle mass predominantly affects the lower body musculature, being larger during the first days of inactivity (4–6). Exercise training interventions during

and after medical treatment are associated with improvements in the quality of life (7) and decreases in fatigue and depression (7), and this is accompanied by lower tumor activity (8, 9) in cancer patients.

Cancer prehabilitation represents “a process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment. It includes physical and psychological assessments that establish a baseline functional level, identifies impairments, and provides targeted interventions that improve a patient’s health to reduce the incidence and the severity of current and future impairments” (10). This systematic review focuses on cancer prehabilitation programs that include exercise training as the main component before surgical treatment. Recent data from a Swedish cohort study showed that higher values of walking distance, leg strength, grip strength, gait speed, and inspiratory muscle strength are associated with fewer postoperative complications and shorter length of stay after abdominal cancer resection (11). Prehabilitation programs might also improve lean mass and muscular strength, and delay the incidence of sarcopenia (12).

However, most research in cancer patients has focused on the impact of exercise training interventions during the postoperative period (rehabilitation) (4, 13). The period known as rehabilitation might be too late for people over 60 years with cancer, who are considered as a high-risk population because the physical capacity in this population is often diminished due to inactivity especially before surgery. High values of muscular strength and cardiorespiratory fitness in cancer patients may make them better prepared for recovery after surgery (13). A recent systematic review conducted by Hamaker and colleagues (14) found relatively small benefits of prehabilitation programs and therefore questioned the investments that prehabilitation interventions require from both health care providers and patients.

Findings from previous systematic reviews (14, 15) have discussed the need for an appraisal of the reporting completeness of the prehabilitation programs in order to facilitate transferability of research findings, as well as the relevance of grading the quality of the evidence. This systematic review aimed to determine the effects of prehabilitation programs compared with usual care for cancer patients.

Methods

This systematic review was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions (16) and reported in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) declaration (17). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42019125658).

Search methods

We conducted a systematic search according to Chapter 4 of the Cochrane Handbook (16). A research librarian searched Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE in November 2019 (latest update in August 2020). The search strategy used in MEDLINE is available in the protocol (18). No restrictions were applied for publication date or language. In terms of additional

sources, one reviewer (JM) searched the following registers for ongoing studies: WHO International Clinical Trials Registry Platform (www.who.int/ictcp/) and ClinicalTrials (<https://clinicaltrials.gov/>). Two reviewers (JM and ALB) independently reviewed the reference lists from key journals, identified articles, meta-analyses, and reviews; scrutinized all promising or potential references; and added appropriate titles to the search output.

Inclusion criteria and study eligibility

We included randomized-controlled trials (RCTs) in participants older than 13 years old, survivors of any type of cancer, defined according to the Centers for Disease Control and Prevention (CDC), as anyone who has been diagnosed with cancer, from the time of diagnosis through the rest of life (19). We applied no restrictions regarding nationality, ethnicity, gender, duration of illness, or treatment setting. We included prehabilitation programs, in which exercise training was the major component. Definitions are provided in the protocol (18). We accepted for inclusion different training modes, such as aerobic, resistance, and flexibility training, as well as yoga, Qi-gong, and Tai-Chi, and carried out in any environment or setting (20). RCTs with usual care or also named sham intervention, usual care, or wait-list controls were included.

In order to provide a more comprehensive and clinically relevant set of outcome measures, three reviewers (ALB, VD, and AE) conducted a scoping search of recent systematic reviews and mapped out the outcome measures explored among them. All team members reviewed and discussed the final set of outcomes that were included in this systematic review. Further details are presented in the protocol (18). We included the following outcomes:

Primary outcomes: Health-related quality of life (HRQoL), muscular strength, and postoperative complications

Secondary outcomes: average length of stay (ALOS), handgrip strength, physical activity levels (both light and moderate).

Pairs of reviewers independently evaluated all references for eligibility. The retrieved references were exported to Rayyan (21). In case of discrepancy, we discussed this with the other reviewers and if the resolution had been difficult, we contacted the study authors for clarification.

Data Extraction and Risk of Bias Assessment

Pairs of reviewers independently used a structured and piloted electronic form to extract information from each study, and assessed the risk of bias by using the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions (16,21). Further details are provided in the protocol (18).

Completeness of Reporting of exercise training interventions in the prehabilitation programs

We used the CERT tool (Consensus on Exercise Reporting Template) to evaluate the completeness of reporting of exercise training interventions in the prehabilitation programs (23,24). Two independent reviewers (AE and VD) applied the tool to the included studies.

Data synthesis

One reviewer (ALB) entered the extracted data in Review Manager (RevMan), and data were checked by a second reviewer (JM). We calculated risk ratio (RR) and its 95% confidence interval (CI) for binary outcomes, whereas continuous data were expressed as group post-test means and standard deviations (SDs) to calculate effect sizes. We presented effect sizes preferentially in the form of mean difference (MD) and 95% CIs, but when different scales were used to measure the same outcome, we calculated standardized mean difference (SMD) instead. If needed, we used the quantile estimation (QE) method to estimate the sample mean and standard deviation from median, minimum and maximum values, and sample size (25,26)

Given heterogeneity across trials, DerSimonian-Laird random-effects models were constructed, as it incorporates an assumption that the different studies are estimating different, yet related, intervention effects (16). We used the I^2 statistic to quantify the proportion of variability attributable to between-study heterogeneity (16); I^2 values were interpreted qualitatively as low (25%-50%), moderate (50%-75%), and high (75%-100%). All studies included in the meta-analysis had comparable baseline characteristics between intervention and control groups.

Considering the high variability in the time points used to report outcome data across studies, we registered all relevant data reported in the studies, and organized them as clinically relevant follow-up periods of before surgery, after surgery or post-intervention, 4 weeks, 8-9 weeks, 12 weeks, and 24-26 weeks post-intervention.

Certainty of the evidence: GRADE approach

We followed the GRADE approach to assess the certainty (or quality) of evidence in six major outcomes (27). The GRADE approach considers the risk of bias and the body of evidence to rate the certainty of the evidence into one of four levels:

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate—the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited—the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect.

Results

Search results

The search resulted in a total of 2917 records. We did not identify any relevant trial registry records. After 315 duplicates were removed, 2602 records remained to be screened. We excluded 2542 records on title and abstract screening. We assessed 61 full-text articles for eligibility and excluded 47 full-text articles. Fourteen studies met the inclusion criteria for this systematic review (see Fig. 1). Additional file 1 presents the list of excluded studies.

Characteristics of the included studies

All RCTs used a parallel two-arm design except for Laurienzo et al (28). The studies included 1044 participants (mean age 71 years, ranging from 46 to 84 years). Publication year varied between 2010 to 2020. Colorectal and lung cancers were the most common diagnoses with 5 studies (36%) each, followed by prostate carcinomas (4 studies, 29%). Most of the studies compared prehabilitation programs against usual care (8 studies, 57%) (28–35), whereas three studies (21%) (36–38) evaluated the comparison with rehabilitation (i.e., a combination of aerobic and resistance training after surgery). Table 1 presents further details on the included studies.

Table 1
Characteristics of the included studies (n = 14)

Study ID, year Country (Trial registry record)	Participants Type of cancer (N, age)	Intervention and control groups	Outcomes and measurement tools
Bousquet-Dion, 2018 (36) Canada (NCT02586701)	Colorectal N: 63 Int: 37, age (yr): median 74 (IQR 67 to 78) Con: 26, age (yr): median 71 (IQR 54 to 74)	Int: combined training (aerobic plus resistance) Con: rehabilitation	Postoperative complications Handgrip strength Physical activity levels
Carli, 2010 (39) Canada (NCT00227526)	Colorectal N: 112 Int: 58, age (yr) mean 61 (SD 16) Con: 54, age (yr) mean 60 (SD 15)	Int: combined training (aerobic plus resistance) Con: physiotherapy (walk/breathing group)	Postoperative complications ALOS Physical activity levels
Carli 2020 (37) Canada (NCT02502760)	Colorectal N: 110 Int: 55, age (yr): median 78 (IQR 72 to 82) Con: 55, age (yr): median 82 (IQR 75 to 84)	Int: combined training (aerobic plus resistance) Con: rehabilitation	HRQoL Postoperative complications ALOS Physical activity levels
Centemero, 2010 (40) Italy (NR)	Prostate N: 118 Int: 59, age (yr): 60 (range: 48–68) Con: 59, age (yr): 57 (range: 46–67)	Int: pelvic floor training Con: postoperative pelvic floor training	HRQoL

Average length of stay, ALOS; Control, Con; Interquartile range, IQR; Intervention, Int; Not reported, NR; Number of participants analyzed in the study, N; Standard deviation, SD; Health-related quality of life, HRQoL

Study ID, year Country (Trial registry record)	Participants Type of cancer (N, age)	Intervention and control groups	Outcomes and measurement tools
Dunne 2016 (29) United Kingdom (NCT01523353)	Colorectal N: 34 Int:19, age (yr): median 61 (IQR 56 to 66) Con:15, age (yr): median 62 (IQR 53 to 72)	Int: high-intensity interval training (HIIT) Con: usual care	HRQoL Postoperative complications
Gillis, 2014 (38) Canada (NCT01356264)	Colorectal N: 77 Int: 38, age (yr): mean 66 (SD 14) Con: 39, age (yr): mean 66 (SD 9)	Int: combined training (aerobic plus resistance) Con: rehabilitation	HRQoL Postoperative complications ALOS Physical activity levels
Lai, 2017 (30) China (ChiCTR-IOR-16008109)	Lung N: 101 (23% female) Int: 51, age (yr): 64 Con: 50, age (yr): 65	Int: respiratory muscles training and aerobic training Con: usual care	HRQoL Postoperative complications
Laurienzo, 2013 (28) Brasil (NR)	Prostate N: 49 Int: 17, age (yr): mean 62 (SD 8) Con 1: 17, age (yr): mean 64 (SD 7) Con 2: 15, age (yr): mean 60 (SD 8)	Int: preoperative pelvic floor training Con 1: pelvic floor training plus electrical stimulation Con 2: usual care	HRQoL
Average length of stay, ALOS; Control, Con; Interquartile range, IQR; Intervention, Int; Not reported, NR; Number of participants analyzed in the study, N; Standard deviation, SD; Health-related quality of life, HRQoL			

Study ID, year Country (Trial registry record)	Participants Type of cancer (N, age)	Intervention and control groups	Outcomes and measurement tools
Licker, 2016 (31) Switzerland (NCT01258478)	Lung N: 151 Int: 74, age (yr): 64 Con: 77, age (yr): 64	Int: combined training (aerobic plus resistance) Con: usual care	Postoperative complications ALOS
Liu, 2019 (35) China (NCT03068507)	Lung N:73 Int: 37, age (yr): mean 56 (SD 10) Con: 36, age (yr): mean 56 (SD 9)	Int: combined training (aerobic plus resistance) Con: usual care	Postoperative complications ALOS
Ocampo-Trujillo, 2014 (32) Colombia (NR)	Prostate N: 16 Int: 8, age (yr): 57 Con: 8, age (yr): 66	Int: pelvic floor training Con: usual care	HRQoL
Pehlivan, 2011 (33) Turkey (NR)	Lung N: 60 Int: 30, age (yr): 54 Con: 30, age (yr): 55	Int: respiratory muscles training and aerobic training Con: usual care	Postoperative complications ALOS
Santa Mina, 2018 (41) Canada (NCT02036684)	Prostate N:61 Int: 33, age (yr): mean 61 (SD 8) Con: 28, age (yr): mean 62 (SD 7)	Int: combined training (aerobic plus resistance) Con: pelvic floor training	HRQoL Muscular strength Postoperative complications ALOS Handgrip strength Physical activity levels

Average length of stay, ALOS; Control, Con; Interquartile range, IQR; Intervention, Int; Not reported, NR; Number of participants analyzed in the study, N; Standard deviation, SD; Health-related quality of life, HRQoL

Study ID, year Country (Trial registry record)	Participants Type of cancer (N, age)	Intervention and control groups	Outcomes and measurement tools
Sebio-García, 2017 (34) Spain (NCT01963923)	Lung N:19 Int: 9, age (yr): mean 71 (SD 6) Con: 10, age (yr): mean 69 (SD 9)	Int: combined training (aerobic plus resistance) Con: usual care	HRQoL Muscular strength Postoperative complications ALOS
Average length of stay, ALOS; Control, Con; Interquartile range, IQR; Intervention, Int; Not reported, NR; Number of participants analyzed in the study, N; Standard deviation, SD; Health-related quality of life, HRQoL			

Description of the interventions

Eight studies (57%) evaluated combined training (31, 34–39, 41); three studies (21%) evaluated pelvic floor training programs (28, 32, 40), and two studies (14%) included a combination of aerobic training and respiratory exercises (30, 33). Dunne et al (29) evaluated the effects of high-intensity interval training (HIIT). The most common description of the prehabilitation programs comprised an initial warm-up period of 5 to 10 minutes, followed by 30 minutes of combined training (i.e., aerobic and resistance training), and a cool-down period of 5–10 minutes.

On average, the prehabilitation programs were implemented for 3 weeks (SD 2 weeks, ranging from 1 to 8 weeks), each session had a mean duration of 38 minutes (SD 24 minutes). The mean frequency was 3 sessions per week (SD 1 session).

The majority of the prehabilitation programs were provided by a multidisciplinary team that comprised physiotherapists, physicians, and nutritionists (9, 64%) (28, 30, 31, 34–38, 40). Around half of the studies were conducted at either clinics or hospitals (6, 43%) (29–33, 40). The prehabilitation programs were fully supervised in six studies (43%) (29–34), partially supervised in four studies (29%) (36, 37, 39, 40), while the remaining four studies included unsupervised programs (28, 35, 38, 41).

The intensity of the exercise training varied considerably among the included studies. Based on data from seven studies (29, 34, 36–39, 41), the mean intensity was 60% of the maximum heart rate (HR) (SD 12%), ranging between 40–70% HR.

On average, 68% of the cancer patients completed the prehabilitation programs (SD 25%, ranging from 16–98%). Bousquet-Dion et al (36) reported the highest rates of adherence (98%). Five studies did not provide data on adherence (28, 32, 33, 35, 40). The mean number of prehabilitation sessions before

surgery was 9 (SD 5 sessions); eight studies (57%) reported more than 10 sessions before surgery (28, 29, 32, 34, 36–39). Additional file 2 provides further details on the prehabilitation programs.

Completeness of reporting of the exercise training interventions in the prehabilitation programs

The 14 included studies reported 20 exercise training interventions. Completeness of reporting ranged from 5–90% among the CERT items (Fig. 2). 15 out of the 19 CERT items were reported in at least 10 or more interventions. The most reported items were: the *setting* in which exercise is performed (item 12) with 90%, whether exercises are *supervised* or *unsupervised* (item 4) with 85%, the type of exercise *equipment* (item 1) together with the *description of the exercise intervention* (item 13) with 80% each, and whether the exercises are *generics* or *tailored* (item 14a) with 75%. Apart from the least reported items (item 8, item 11, and item 15) with 5%, 20%, and 10% respectively, the reporting of the remaining items varied between 45% and 70%. Exercise interventions in participants with colorectal cancer had the highest level of reporting relative to those in lung cancers. Combined training was the exercise mode that exhibited the highest level of reporting. See Additional file 3 for a full description of the subgroup analysis undertaken for the completeness of reporting.

Outcome measures

Primary outcomes

Health-related quality of life (HRQoL): Nine studies (64%) measured this outcome; five of them used the Short Form Health Survey (SF-36) (28, 29, 37, 38), and one study used the second version (SF-36 v2) (34). Ocampo-Trujillo et al (32) used the SF-12 questionnaire, whereas Centemero et al (40), Santa Mina et al (41) and Lai (30) applied the International Continence Society (ICS) ICS male questionnaire, the Functional Assessment of Cancer Therapy-Prostate (FACT-P) scale, and the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30), respectively.

Muscular strength: Two studies (14%) evaluated muscular strength. Santa Mina et al (41) used elbow flexion and extension, whereas Sebío-García et al (34) applied the "Senior Fitness Test".

Postoperative complications: Being the most common outcome reported in this systematic review, eleven studies (79%) provided outcome data for postoperative complications. Six studies used The Clavien-Dindo Classification of surgical complications (29,35,36,38,39,41). Sebío-García et al (34) classified postoperative pulmonary complications according to the Melbourne Group Scale; Carli et al (37) used the Comprehensive Complication Index (ICC), and Licker et al (31) reported postoperative complications according to the Thoracic Mortality and Morbidity (TMM) classification system. Both Lai et al (30) and Pehlivan et al (33) did not provide any data about the tool used to report postoperative complications.

Secondary outcomes

Average length of stay (ALOS): Eight studies (57%) reported length of Stay (LOS),

Handgrip strength: Santa Mina et al (41) measured this outcome by using handgrip dynamometry (Sammons Preston, Bolingbrook, IL, USA).

Physical activity levels: Five studies (36%) measured changes in physical activity levels by applying the Community Health Activities Model Program for Seniors (CHAMPS) physical activity questionnaire (36–39,41). Table 2 describes the follow-up periods reported for each outcome in the included studies.

Table 2
Outcome measures in the included studies: measurement tools and follow-up periods.

Outcome	Measurement tools, studies	Follow-up periods: number of studies
Health-related quality of life	SF-36 (28,29,37,38) SF-36 v2 (34) ICS male SF (40) FACT-P (41) EORTC QLQ-C30 (30)	Before surgery: four studies (34,37,38,41) Post-surgery: one study (34) 4 weeks post-intervention: seven (28–30,37,38,40,41) 8 weeks post-intervention: two studies (32,38) 12 weeks post-intervention: four studies (28,34,40,41) 24 weeks post-intervention: one study (28) 26 weeks post-intervention: one study (41)
Muscular strength	Elbow flexion and extension (41) Senior Fitness Test (34)	Before surgery: both studies (34,41) Post-surgery: one study (34) 4 weeks post-intervention: one study (41) 9 weeks post-intervention: one study (41) 12 weeks post-intervention: one study (34) 26 weeks post-intervention: one study (41)

CHAMPS: The Community Healthy Activities Model Program for Seniors, EORTC QLQ-C30: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, FACT-P: The Functional Assessment of Cancer Therapy-Prostate, ICC: The Comprehensive Complication Index, ICS SF: the International Continence Society male Short Form, SF-36: The Short Form-36 Health Survey, SF-36 v2: The Short Form-36 Health Survey version 2, The Clavien-Dindo: classification for surgical complications, TMM: thoracic morbidity and mortality.

Outcome	Measurement tools, studies	Follow-up periods: number of studies
Postoperative complications	The Clavien-Dindo Classification (29,35,36,38,39,41) Melbourne Group Scale (34) ICC (37) TMM (31)	1-week post-intervention: one study (33) 4 weeks post-intervention: five studies (30,31,35–37) 8 weeks post-intervention: one study (38) 9 weeks post-intervention: one study (29) 12 weeks post-intervention: two studies (29,34) 26 weeks post-intervention: one study (41)
Average length of stay	Administrative data	Before surgery: one study (35) 4 weeks post-intervention: three studies (31,35,37) 9 weeks post-intervention: one study (39) 12 weeks post-intervention: one study (34) 26 weeks post-intervention: one study (41)
Handgrip strength	Handgrip dynamometry (41)	Before surgery 4 weeks post-intervention 12 weeks post-intervention 26 weeks post-intervention

CHAMPS: The Community Healthy Activities Model Program for Seniors, EORTC QLQ-C30: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, FACT-P: The Functional Assessment of Cancer Therapy-Prostate, ICC: The Comprehensive Complication Index, ICS SF: the International Continence Society male Short Form, SF-36: The Short Form-36 Health Survey, SF-36 v2: The Short Form-36 Health Survey version 2, The Clavien-Dindo: classification for surgical complications, TMM: thoracic morbidity and mortality.

Outcome	Measurement tools, studies	Follow-up periods: number of studies
Physical activity levels	CHAMPS (36–39,41)	<p>Before surgery: five studies (36–39,41)</p> <p>4 weeks post-intervention: five studies (36–39,41)</p> <p>8 weeks post-intervention: two studies (36,38)</p> <p>9 weeks post-intervention: one study (39)</p> <p>26 weeks post-intervention: one study (41)</p>
CHAMPS: The Community Healthy Activities Model Program for Seniors, EORTC QLQ-C30: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, FACT-P: The Functional Assessment of Cancer Therapy-Prostate, ICC: The Comprehensive Complication Index, ICS SF: the International Continence Society male Short Form, SF-36: The Short Form-36 Health Survey, SF-36 v2: The Short Form-36 Health Survey version 2, The Clavien-Dindo: classification for surgical complications, TMM: thoracic morbidity and mortality.		

In order to provide a comprehensive overview of the body of evidence in the field of prehabilitation programs, we mapped out other outcome measures reported in the included studies that were not considered in the current systematic review (Additional file 4).

Risk of bias in included studies

Most of the studies (13, 93%) adequately described the method used to generate the random sequence; therefore, we judged these studies to be at low risk of bias for this domain (28–40). Ten studies (71%) followed adequate methods for allocation concealment (29–31, 34–38, 40), whereas three studies (21%) did not offer details on this domain (unclear risk of bias) (28, 32, 33). In terms of blinding of participants and personnel, we judged six studies to be at high risk of bias (30, 32, 36, 38, 40, 41). On the other hand, half of the studies (7, 50%) adequately reported the blinding of the outcome assessors (low risk of bias) (29, 30, 34–38). Nine of the fourteen studies (65%) reported attrition rates in intervention and control groups that were approximately identical (low risk of bias for incomplete outcome data) (28, 30–33, 36–38, 40), whereas three studies (21%) reported important differences in attrition rates (high risk of bias) (34, 39, 41). We observed few inconsistencies between outcomes listed in study registrations and those reported in publications for ten studies (71%) (29, 31–34, 37–40). We refer the reader to Fig. 3 and Additional file 5 for an overview of the risk of bias assessment.

Effects of prehabilitation programs

We present the effects of interventions per comparison (combined training vs rehabilitation/usual care, HIIT vs usual care, respiratory muscle training plus aerobic training vs usual care, pelvic floor training vs usual care), followed by primary and secondary outcomes. In cases where data could not be pooled, we

report the results narratively. Additional file 6 presents the effect estimates reported in the primary studies sorted by comparison and outcome measure. In most cases, a meta-analysis was deemed as inappropriate due to the different follow-up periods, the use of measurement tools that impeded any standardization of the effect estimates, and clinical heterogeneity. These reasons restrict the potential of any overall estimate to be informative. At this point, we underline that readers must interpret effect estimates with caution owing to the very low level of certainty of the evidence (Tables 3–6).

Comparison 1: combined training vs rehabilitation/usual care

Eight RCTs provided data for this comparison: four RCTs compared combined training with rehabilitation (36–39); three compared with usual care (31, 34, 35), and one compared with rehabilitation through pelvic floor training (41). Results are summarized below and in Table 3.

Health-related quality of life (HRQoL)

Four studies reported data before surgery, which corresponds to our post-intervention estimate (34, 37, 38, 41). Two studies ($n = 152$ participants with colorectal cancer) (37, 38) provided data for the meta-analysis, which showed evidence of no difference in effect between groups in the physical component (MD -0.52, 95% CI -8.67 to 7.63) or the mental health component of HRQoL (MD -2.75, 95% CI -11.35 to 5.84) (Fig. 4). Similar results were found in Santa Mina et al. (41) (effect estimate 2.1, 95% CI -4.25 to 8.47). Sebio-García et al. (34) observed higher HRQoL scores in the combined training group (mean change 4.5 points higher), but outcome data for the control group were not reported. It is uncertain whether combined training improves HRQoL before surgery because the quality of this evidence is very low (Table 3).

Sebio-García et al. (34) provided data at post-surgery in 19 participants with lung cancer; those in combined training reported less decline in their HRQoL than those who received usual care (MD prehabilitation -2.8, standard error 5.8 vs. MD usual care -7.4, standard error 5.3; p -value for the interaction effect 0.06). Further, pooled analysis from the two studies that reported outcome data at 4 weeks post-intervention (145 participants with colorectal cancer) (37, 38) revealed a lack of evidence of an effect between groups in the physical component of HRQoL (SMD 0.42, 95% CI -7.07 to 7.91) or the mental component (SMD -3.97, 95% CI -12.09 to 4.16).

Three studies reported long-term data (34, 38, 41). Gillis et al. (38) found evidence of no difference between combined training (mean score 74.3, SD 26.1) and usual care (mean score 72.3, SD 24.2) at 8 weeks post-intervention. Similar findings were reported by Sebio-García et al. (34) in participants with lung cancer, and by Santa Mina (41) in participants with prostate cancer at 12 weeks, and at 26 weeks. These studies indicated a lack of evidence of an effect between groups in HRQoL in the long term. Therefore, it is uncertain whether combined training improves HRQoL in the long term because the quality of this evidence is very low (Table 3).

Muscular strength

Two studies found lack of evidence of an effect between groups in elbow strength in participants with lung and prostate cancer before and immediately after the surgery (34, 41). Similar findings were reported at 12- and 26-weeks post-intervention in participants with prostate cancer (41). It is uncertain whether combined training improves muscular strength because the quality of this evidence is very low (Table 3).

Postoperative complications

Pooled data from two studies (136 participants with colorectal and lung cancer) (35, 36) found evidence of no difference between groups in the incidence of grade 1 complications (RR 1.05, 95%CI 0.88 to 1.24), grade 2 complications (RR 0.95, 95%CI 0.26 to 3.38), or grade 3 complications (RR 3.55, 95%CI 0.18 to 71.07) at 4 weeks after surgery (Fig. 5). Similar effects were reported by Licker et al. (31) using the Thoracic Morbidity and Mortality (TMM) system, and by Carli et al. (39) with the 30-day Comprehensive Complications Index (adjusted mean difference - 3.2, 95% CI - 11.8 to 5.3; $p = 0.45$).

This evidence of no difference in the effect of combined training was confirmed by two studies at 8- and 9-weeks after surgery in participants with colorectal cancer (38, 39), by Sebio Garcia et al. (34) at 12 weeks, and finally by Santa Mina et al. (41) at 26 weeks after surgery. Overall, it is uncertain whether combined training reduces the incidence of postoperative complications because the quality of this evidence is very low (Table 3).

Average length of stay (ALOS)

Imputed data through the quantile estimation method from three studies (31, 35, 37) provided evidence of no difference in effects between groups in ALOS at 4 weeks after surgery (MD -0.01 days, 95%CI -0.61 to 0.59) (Figure x). Similar findings were reported for the remaining follow-up periods of 8 weeks (38), 9 weeks (39), 12 weeks (34), and 26 weeks (41) after surgery. It is uncertain whether combined training reduces ALOS because the quality of this evidence is very low (Table 3).

Handgrip strength

Santa Mina et al. (41) found lack of evidence of an effect between groups in handgrip strength in 61 participants with prostate cancer up to 26 weeks post-intervention (difference at 26 weeks: 4.44, 95%CI 0.65 to 8.23). It is uncertain whether combined training improves handgrip strength because the quality of this evidence is very low (Table 3).

Physical activity levels

Light physical activity

Five studies reported data at before surgery (36–39, 41). Pooled data from two of them (36, 37), with 150 participants with colorectal cancer, showed evidence of no difference in effect between groups in light physical activity levels (MD 2.56 kcal/kg/wk, 95%CI -7.69 to 12.81). These findings were confirmed for the remaining three studies at before surgery (37, 38, 41), as well as for the pooled data at 4 weeks post-

intervention (MD -0.59, 95%CI -8.10 to 6.92). Based on this evidence, it is uncertain whether combined training improves light physical activity levels because the quality of this evidence is very low (Table 3).

Moderate physical activity

Pooled data from two studies (36, 37) yielded lack of evidence of an effect between groups in moderate physical activity levels at before surgery (MD 13.9 kcal/kg/wk, 95%CI 11.3 to 16.5), and at 4 weeks after surgery (MD 0.28 kcal/kg/wk, 95%CI -3.03 to 3.58). Similar findings were reported in the remaining three studies at that follow-up period (38, 39, 41), and later confirmed by those studies that reported outcome data at 8 weeks (36, 38), 9 weeks (39), 12 weeks (41), and 26 weeks (41) post-intervention, respectively. Therefore, it is uncertain whether combined training improves moderate physical activity levels because the quality of this evidence is very low (Table 3).

Table 3

Summary of findings for the comparison: combined training vs rehabilitation/usual care

Prehabilitation programs for cancer patients					
Population: adults with lung, prostate, and colorectal cancer					
Intervention: combined training					
Comparison: rehabilitation, usual care					
Setting: Mixed (home and clinic/hospital),					
Outcomes	Relative effect (95% CI)	Anticipated absolute effect* (95% CI)		N° of participants (studies)	Certainty of the evidence (GRADE)
		Assumed risk with control	Assumed risk with intervention		
HRQoL (physical component) ** at before surgery	MD -0.52 (-8.67 to 7.63)	57 to 59 points	Mean HRQoL in intervention was 0.52 lower (8.6 lower to 7.6 higher)	152 (2 RCTs)	⊕●●●● VERY LOW ^{1,2}
HRQoL (mental component) ** at before	MD -2.75 (-11.35 to 5.84)	66 to 70 points	Mean HRQoL in intervention was 2.75 lower (11.3 lower to 5.8 higher)	152 (2 RCTs)	⊕●●●● VERY LOW ^{1,2}
HRQoL (overall score) ** at before surgery	-	-	-	61 (1 RCT)	⊕●●●● VERY LOW ^{3,4}
HRQoL (overall score) ** long term (up to 26 weeks)	Not estimable	-	-	157 (3 RCTs)	⊕●●●● VERY LOW ^{3,5}
Muscular strength: elbow (before surgery up to 26 weeks) ***	Not estimable	-	-	80 (2 RCTs)	⊕●●●● VERY LOW ^{1,2}

Prehabilitation programs for cancer patients					
Postoperative complications: Grade 1 (4 weeks) ****	RR 1.05 (0.88 to 1.24)	6 per 10	6 per 10 (5 fewer to 8 more)	136 (2 RCTs)	⊕●●●● VERY LOW ^{3,4}
Postoperative complications: Grade 2 (4 weeks)****	RR 0.95 (0.26 to 3.38)	1 per 10	1 per 10 (2 fewer to 3 more)	136 (2 RCTs)	⊕●●●● VERY LOW ^{3,4}
Postoperative complications: Grade 3 (4 weeks)****	RR 3.55 (0.18 to 71.07)	No cases	3 per 10 (8 fewer to 67 more)	136 (2 RCTs)	⊕●●●● VERY LOW ^{3,4}
Average length of stay (4 weeks) *****	MD -0.01 (-0.61 to 0.59)	Mean stay ranged in control groups from 5 to 9 days	Mean stay in the intervention group was 0.01 shorter (0.61 shorter to 0.59 longer)	334 (3 RCTs)	⊕●●●● VERY LOW ^{3,5}
Handgrip strength long term (up to 26 weeks) *****	MD 4.44 (0.65 to 8.23)	Not reported	Mean strength intervention group was 4.4 higher (0.65 to 8.23 higher)	61 (1 RCT)	⊕●●●● VERY LOW ^{3,4}
Physical activity levels: light (before surgery) *****	MD 2.5 (-7.6 to 12.8)	Mean levels ranged in control groups from 13 to 17	Mean levels in the intervention groups were 2.5 higher (7.6 lower to 12.8 higher)	150 (2 RCTs)	⊕●●●● VERY LOW ^{3,4}
Physical activity levels: light (4 weeks) *****	MD -0.59 (-8.10 to 6.92)	Mean levels ranged in control groups from 10 to 17	Mean levels in the intervention groups were 0.59 lower (8.1 lower to 6.9 higher)	131 (2 RCTs)	⊕●●●● VERY LOW ^{3,4}
Physical activity levels: moderate (before surgery) *****	MD 13.9 (11.3 to 16.5)	Mean levels ranged in control groups from 3 to 13	Mean levels in the intervention groups were 13.9 higher (11 higher to 16 higher)	150 (2 RCTs)	⊕●●●● VERY LOW ^{3,4}

Prehabilitation programs for cancer patients					
Physical activity levels: moderate (4 weeks) *****	MD 0.28 (-3.03 to 3.58)	Mean levels ranged in control groups from 11 to 14	Mean levels in the intervention groups were 0.28 higher (3.03 lower to 16 3.5 higher)	131 (2 RCTs)	⊕●●●● VERY LOW ^{2,3}
<p>*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; HRQoL: Health-related quality of life; MD: Mean Difference; RR: Risk ratio</p> <p>** Short Form Health Survey (SF-36 and -12); International Continence Society (ICS) ICS male questionnaire; The Functional Assessment of Cancer Therapy-Prostate (FACT-P): high scores indicate worse physical function; The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30): higher scores indicate better functioning (scaled from 0 to 100)</p> <p>*** Elbow flexion and extension strength: high mobilized weight indicates higher levels of strength</p> <p>**** The Clavien-Dindo Classification; The Comprehensive Complication Index (CCI): high grades indicate worse outcome</p> <p>***** Administrative data: High number of days indicate worse response to intervention</p> <p>***** Handgrip dynamometry: Higher levels indicate better outcome</p> <p>***** The Community Healthy Activities Model Program for Seniors (CHAMPS): High scores indicate higher levels of physical activity (light, moderate, and vigorous)</p> <p>1. Downgraded by two levels due to no blinding of personnel and outcome measurement (detection bias), and attrition bias.</p> <p>2. Downgraded by one level due to small sample size and wide confidence intervals (imprecision)</p> <p>3. Downgraded by two levels due to no blinding of personnel (performance bias), and selective outcome reporting (reporting bias).</p> <p>4. Downgraded by one level due to small sample size (imprecision).</p> <p>5. Downgraded by one level due to wide confidence intervals (imprecision).</p>					

Comparison 2: high-intensity interval training (HIIT) vs usual care

Dunne et al. 2016 (29) reported outcome data for this comparison (34 participants with colorectal cancer). We found lack of evidence of an effect between groups in HRQoL and postoperative complications. It is uncertain whether HIIT improves HRQoL or reduces the incidence of postoperative complications because the quality of this evidence is very low (Table 4).

Table 4

Summary of findings for the comparison: high-intensity interval training (HIIT) vs usual care

Prehabilitation programs for cancer patients					
Population: adults with colorectal cancer Intervention: HIIT Comparison: usual care Setting: Clinic/Hospital					
Outcomes	Relative effect (95% CI)	Anticipated absolute effect* (95% CI)		N° of participants (studies)	Certainty of the evidence (GRADE)
		Assumed risk with control	Assumed risk with intervention		
HRQoL (physical component) ** (4 weeks)	MD 13 (-5 to 30)	59 points	Mean HRQoL in intervention was 13 higher (5 lower to 30 higher)	34 (1 RCT)	⊕●●●● VERY LOW ^{1,2}
Postoperative complications: All grades*** (12 weeks)	RR 0.9 (0.4 to 1.9)	5 per 10	4 fewer (2 fewer to 9 more)	34 (1 RCT)	⊕●●●● VERY LOW ^{1,2}
Postoperative complications: Grades III and IV*** (12 weeks)	RR 2.3 (0.2 to 20.5)	1 per 10	2 more (1 fewer to 20 more)	34 (1 RCT)	⊕●●●● VERY LOW ^{1,2}
<p>*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; HRQoL: Health-related quality of life; MD: Mean Difference; RR: Risk ratio</p> <p>** Short Form Health Survey (SF-36): high scores indicate worse physical function</p> <p>*** The Clavien-Dindo Classification: high grades indicate worse outcome</p> <p>¹. Downgraded by one level due to incomplete outcome data (attrition bias).</p> <p>². Downgraded by two levels due to small sample size and wide confidence intervals (imprecision).</p>					

Comparison 3: Respiratory muscle training plus aerobic training vs usual care

Two studies reported data for this comparison in 161 participants with lung cancer (30, 33). Results are summarized below and in Table 5.

Health-related quality of life (HRQoL)

Lai et al. (30) found evidence of no difference in effect between groups in HRQoL at 4 weeks post-intervention (MD 1.1, 95% CI -1.9 to 4.2). It is uncertain whether respiratory muscle training plus aerobic training improves HRQoL because the quality of this evidence is very low (Table 5).

Postoperative complications

Lai et al. (30) found evidence of no difference in effect between groups in the incidence of postoperative complications within 30 days after surgery (RR 0.35, 95% CI 0.14 to 0.90). Pehlivan et al. (33) reported similar findings (RR 0.2, 95% CI 0.02 to 1.6). The studies did not report the tool used to measure outcome data. It is uncertain whether respiratory muscle training plus aerobic training reduces the incidence of postoperative complications because the quality of this evidence is very low (Table 5).

Average length of stay (ALOS)

Pehlivan et al. (33) reported evidence of no difference in effect between groups in ALOS at one week after surgery (MD -4.2 days, 95%CI -5.7 to -2.7). It is uncertain whether respiratory muscle training plus aerobic training reduces ALOS because the quality of this evidence is very low (Table 5).

Table 5

Summary of findings for the comparison: respiratory muscle training + aerobic training vs usual care

Prehabilitation programs for cancer patients					
Population: adults with lung cancer					
Intervention: respiratory muscle training plus aerobic training					
Comparison: Usual care					
Setting: Clinic / Hospital					
Outcomes	Relative effect (95% CI)	Anticipated absolute effect* (95% CI)		N° of participants (studies)	Certainty of the evidence (GRADE)
		Assumed risk with control	Assumed risk with intervention		
HRQoL (overall)** (4 weeks)	MD 1.1 (-1.9 to 4.2)	69 points	Mean HRQoL in intervention was 1 higher (1.9 lower to 4.2 higher)	101 (1 RCT)	⊕●●● VERY LOW ^{1,2}
Postoperative complications (4 weeks)	Not estimable	-	-	161 (2 RCTs)	⊕●●● VERY LOW ^{1,2}
Average length of stay (1 week)***	MD -4.2 (-5.7 to -2.7)	9.6	ALOS was 4.2 days shorter (5.7 to 2.7 days shorter)	60 (1 RCT)	⊕●●● VERY LOW ^{2,3}
<p>*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; HRQoL: Health-related quality of life; MD: Mean Difference; RR: Risk ratio</p> <p>** EORTC QLQ-C30: higher scores indicate better functioning (scaled from 0 to 100)</p> <p>*** Administrative data: higher number of days indicate worse outcome</p> <p>¹. Downgraded by one level due to no blinding of personnel (performance bias)</p> <p>². Downgraded by two levels due to small sample size and wide confidence intervals (imprecision).</p> <p>³. Downgraded by one level due to allocation concealment, no blinding of personnel (performance bias)</p>					

Comparison 4: Pelvic floor training vs usual care

Three studies provided outcome data for HRQoL in participants with prostate cancer (28, 32, 40). None of the studies reported evidence of an effect in this outcome between groups across the follow-up periods. Centemero et al. (40) and Laurienzo et al. (28) found evidence of no effect in HRQoL at 4 weeks post-intervention. Ocampo-Trujillo et al. (32) observed similar findings at 8 weeks post-intervention. Finally, Centemero et al. (40) and Laurienzo et al. (28) confirmed these findings up to 24 weeks post-intervention. It is uncertain whether pelvic floor training improves HRQoL because the quality of this evidence is very low (Table 6).

Table 6
Summary of findings for the comparison: pelvic floor training vs usual care

Prehabilitation programs for cancer patients					
Population: adults with prostate cancer					
Intervention: pelvic floor training					
Comparison: usual care					
Setting: Clinic / Hospital					
Outcomes	Relative effect (95% CI)	Anticipated absolute effect* (95% CI)		N° of participants (studies)	Certainty of the evidence (GRADE)
		Assumed risk with control	Assumed risk with intervention		
HRQoL (overall) ** (up to 24 weeks)	Not estimable	-	-	183 (3 RCTs)	⊕●●● VERY LOW ^{1,2}
<p>*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; HRQoL: Health-related quality of life; MD: Mean Difference; RR: Risk ratio</p> <p>** Short Form Health Survey (SF-36 and - 12); International Continence Society (ICS) ICS male questionnaire: high scores indicate worse physical function</p> <p>¹. Downgraded by one level due to random sequence generation, no blinding of personnel (performance bias), and selective outcome reporting</p> <p>². Downgraded by two levels due to small sample size and wide confidence intervals (imprecision)</p>					

Discussion

Summary of main results

This systematic review aimed to determine the benefits and harms of prehabilitation programs compared with usual care for cancer patients. The body of evidence is formed by 14 RCTs published recently. The

risk of bias across the studies showed no major concerns regarding randomization procedures, but some concerns were identified for outcome measurement, selective outcome reporting, and attrition. The studies provided outcome data for four comparisons (i.e., combined training vs rehabilitation/usual care, HIIT vs usual care, respiratory muscle training plus aerobic training vs usual care, pelvic floor training vs usual care).

Data from 8 studies suggested that prehabilitation programs of combined training compared to rehabilitation or usual care confer little to no effect on HRQoL, muscular strength, postoperative complications, ALOS, handgrip strength, or physical activity levels. One small study (29) evaluated the effects of HIIT into a prehabilitation program but found no evidence of an effect in HRQoL or postoperative complications. This lack of evidence of an effect in those outcomes was also observed for prehabilitation programs of respiratory muscle training plus aerobic training. Finally, three studies provided evidence of no difference between prehabilitation programs of pelvic floor training and usual care in HRQoL.

Overall completeness and applicability

The knowledge base of this systematic review applies mostly to participants aged 60 to 70, with colorectal, prostate, and lung cancer. Data about sex and ethnic characteristics were scarce across studies. Besides, the studies failed to provide information about key aspects of the prehabilitation programs implementation, such as rules for starting level and program progression. This represents a barrier to the applicability of our findings to a particular context.

To date, the 14 studies included in this systematic review are not sufficient to fully address our main objective. However, we believe that the 8 studies that compared combined training to rehabilitation or usual care offer a consistent evidence base of the lack of effect for this comparison. Conversely, few unpowered studies provide no clear evidence for the remaining comparisons. Hence, it is likely that new well-conducted studies would substantially change our findings.

Certainty of the evidence

The included studies evaluated different modes of prehabilitation programs, where combined training (i.e., aerobic and resistance training) was the main comparison. We found incomplete information for characteristics of the participants, implementation of the prehabilitation programs, and weak reporting of outcome data in some studies.

Very low-quality evidence formed all the comparisons in this systematic review. Our certainty in the evidence was downgraded due to limitations in the risk of bias assessment, including lack of both allocation concealment and blinding of participants and providers, and uncertainty regarding selective reporting. The lack of blinding of both participants and providers can lead to an overestimation of the effect estimate (42, 43) Blinding participants in exercise training trials is not easy (44), and it is likely that participants who are aware of their intervention may differ from blinded participants in how they report

outcomes or on their performance in the study (45). These aspects gain relevance in the context of this systematic review due to the large number of self-reported outcomes across studies.

Furthermore, most of the studies had low numbers of participants, wide confidence intervals, and high heterogeneity in the effects across them. Undertaking a sensitivity analysis to explore these limitations was not appropriate due to the low number of studies, which could bias any effect estimate.

Potential biases in the review process

The strengths of this systematic review were the prioritization process undertaken to define clinically relevant outcome measures, the use of systematic methods to assess both the completeness of reporting of the exercise training interventions within the prehabilitation programs, and the certainty or quality of the evidence. The integration of these processes enhances the use of this study in evidence-informed decision-making scenarios. Regarding the limitations in the review process, we believe that the comparisons in this review may be biased due to the incomplete reporting of intervention-related domains across the studies. We contacted the authors for further details, but the response rate was low. In order to tackle this limitation, we searched clinical trial registries to detect unpublished trials.

Agreements and disagreements with other reviews

Several systematic reviews have addressed the effects of prehabilitation programs for cancer patients in different outcome measures (46–58). The methods used in those reviews varied considerably, and so did their findings. Our findings of very low- quality evidence about the effects of prehabilitation programs for HRQoL align with those reported by seven systematic reviews published recently (47, 49, 54–56, 59, 60). Contradictory findings in different HRQoL domains have been reported by other systematic reviews (46, 48, 50, 53, 58, 61). Similarly, our findings of very low certainty in the effects of prehabilitation programs to reduce postoperative complications coincide with those of low certainty reported by Xiang Li and colleagues in 2016 (57). Other systematic reviews have reported significant reductions in this outcome (47–49, 51–54, 58, 61, 62). A similar trend is observed in the literature about other outcome measures in this review.

The discrepancies between our findings and those of other systematic reviews are explained by several factors, such as differences in both baseline characteristics of the participants and program implementation. Besides, the lack of an assessment of the quality of the evidence has an impact on the review findings, and the use of different approaches to conducting this assessment influences authors' judgments about the body of evidence (63). Of note, the restriction of exercise training as the main component of the prehabilitation programs in our review did not explain the discrepancies with other systematic reviews, since our findings are similar to those reported by reviews that included prehabilitation programs of both exercise training plus dietary counseling (61, 62, 64).

Implications for practice and further research

Findings from this systematic review highlight the need for further well-conducted RCTs to better inform recommendations pertaining to prehabilitation programs for cancer patients. The scope of our findings to provide insight in a decision-making context is constrained because the quality of the evidence about the benefits and harms of prehabilitation programs is very low. There is a lack of safety data, and the use of heterogeneous tools for outcome measurement poses additional limitations to this body of evidence. In order to strengthen the quality of the evidence, further studies may benefit from addressing the gaps identified in our assessment of the reporting level of the prehabilitation programs, and should adhere to reporting checklists, such as CONSORT and CERT.

Conclusion

We are uncertain of the benefits and harms of prehabilitation programs compared with usual care for cancer patients. Further well-conducted randomized controlled trials are still required to test the role of exercise training as the main component of prehabilitation programs to improve patients' outcomes. We assessed the certainty of the body of evidence as very low, downgraded due to serious study limitations, imprecision and indirectness. We have very little confidence in the results and the true effect is likely to be substantially different from these. Further research is needed before we could draw a more certain conclusion.

Abbreviations

ALOS: Average length of stay; CI: Confidence interval; CERT: Consensus on Exercise Reporting Template; CHAMPS: The Community Healthy Activities Model Program for Seniors; Con: Control; EORTC QLQ-C30: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-P: The Functional Assessment of Cancer Therapy-Prostate; GRADE: Grading of Recommendations, Assessments, Development and Evaluation; HRQoL: Health-related quality of life; HIIT: High-intensity interval training; HRR: Heart rate reserve; ICC: The Comprehensive Complication Index, ICS SF: the International Continence Society male Short Form; Int: Intervention; IQR: Interquartile range; MHR: Maximum heart rate; MD: Mean difference; MCS: mental component summary; N: Number of participants analyzed in the study; NR: Not reported; PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analyses Protocol; PROSPERO: Prospective Register of Systematic Reviews; PCS: physical component summary; RM: Repetition maximum; RR: Risk ratio; SF-36: The Short Form-36 Health Survey, SF-36 v2: The Short Form-36 Health Survey version 2; SD: Standard deviation; SE, Standard error; SMD: Standardized mean difference; The Clavien-Dindo: classification for surgical complications, TMM: thoracic morbidity and mortality; WR: Work rate; W: Workload.

Declarations

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Authors' contributions

JM conceptualized the idea for this review. ALB, VD, and AE mapped out systematic reviews to identify outcomes of interest. All reviewers contributed to the development of the selection criteria, the risk of bias assessment, and the data extraction criteria, the completeness of reporting of the exercise training interventions, and the GRADE approach (JM, ALB, VD, AE, RT). JM and ALB entered and checked the extracted data in Review Manager. JM is the guarantor and drafted the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Study flow diagram for the screening process (as recommended by the PRISMA statement)

Figure 2

Completeness of reporting of the exercise training interventions: total sample (n 14 RCTs; 20 exercise training interventions) Final version of the CERT checklist used in this study (16 items): 1. What (materials), 2. Who (provider), 3. Individually or in a group, 4. Supervised or unsupervised, 5. Adherence report, 6. Motivation strategies, 7. a. Exercise progression, 7. b. Program progression, 8. Exercise replication, 9. Home components, 10. Non-exercise components, 11. Adverse events report, 12. Setting, 13. Description of the exercise, 14. a. Exercises generic or tailored? , 14. b. Description of the adaptation made in the exercises, 15. Rules for starting level, 16. a. How adherence to exercise was measured, 16. b. Is the intervention carried out according to how it was planned?

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bousquet-Dion et al., 2018	+	+	●	+	+	?	+
Carli et al., 2010	+	●	?	?	●	+	+
Carli et al., 2020	+	+	+	+	+	+	+
Centemero et al., 2010	+	+	●	●	+	+	+
Dunne et al., 2016	+	+	+	+	?	+	+
Gillis et al., 2014	+	+	●	+	+	+	+
Lai et al., 2017	+	+	●	+	+	●	+
Laurienzo et al., 2013	+	?	?	?	+	●	+
Licker et al., 2016	+	+	?	?	+	+	+
Liu et al., 2019	+	+	+	+	?	?	+
Ocampo-Trujillo et al., 2014	+	?	●	●	+	+	+
Pehlivan et al., 2011	+	?	?	?	+	+	+
Santa Mina et al., 2018	?	+	●	●	●	+	+
Serbio-Garcia et al., 2017	+	+	?	+	●	+	+

Figure 3

Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Figure 4

Effects of combined training vs rehabilitation/usual care in HRQoL (physical and mental component) before surgery

Figure 5

Effects of prehabilitation programs vs rehabilitation/usual care in Postoperative complications (The Clavien-Dindo Classification: high grades indicate worse outcome)

Figure 6

Effects of prehabilitation programs vs. rehabilitation/usual care in hospital stay at 4 weeks post-surgery

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