KCE REPORT 185C

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SUPPORTIVE TREATMENT FOR CANCER

PART 1: EXERCISE TREATMENT

Belgian Health Care Knowledge Centre

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KCE REPORT 185C
GOOD CLINICAL PRACTICE

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SUPPORTIVE TREATMENT FOR CANCER

PART 1: EXERCISE TREATMENT

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FOREWORD

The KCE already published many reports with clinical recommendations about cancer. However, these recommendations are often limited to diagnostic procedures and therapeutic interventions, such as chemotherapy, radiotherapy and surgery. Of course, these are the interventions that are used to stop or eradicate the tumour for most cancer types.

Yet, other, more supportive interventions are also frequently used in daily practice, and appear to be of huge importance for the well-being of the patient during the very burdensome treatment for their cancer. Therefore, there is no reason at all, even on the contrary, to show no interest in these interventions. The question is which of these interventions are proven to be effective, when, and for which cancer type.

The present report about exercise treatment introduces a series of four reports that evaluate different types of supportive treatment for patients undergoing curative treatment for their cancer.

These four reports do not concern just one specific cancer type. They evaluate the use of these supportive treatments in a transversal way for all cancer types. We hope that they will be a useful aid for all professionals that fight against cancer in the most human and tolerable way for their patient.

Jean-Pierre CLOSON
Assistant Chief Executive Officer

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EXECUTIVE SUMMARY

INTRODUCTION

There is a wide body of evidence and a large consensus in society that physical activity is beneficial for health. Likewise, everybody will agree that cancer patients deserve to get ample support, including for their non medical needs, especially during the difficult period when they undergo chemotherapy or radiotherapy. But, can we be more precise and include specific recommendations in our cancer guidelines? The question is not trivial, since the development of guidelines is one of the main action points of the Belgian National Cancer Plan 2008-2010 and one of the tasks of the College of Oncology. KCE collaborates with the College of Oncology and provides scientific support in the joint development of clinical practice guidelines. Until now guidelines were developed on breast cancer, colorectal cancer, testicular cancer, pancreatic cancer, upper gastrointestinal cancer and cervical cancer (www.kce.fgov.be).

Since many guidelines already now cover different aspects of supportive care, which are often not cancer type specific, it was decided to go deeper into the question and to develop a separate series of four reports on the supportive care of cancer patients under treatment. The following aspects will be covered:

- Exercise treatment during chemotherapy and/or radiotherapy;
- Treatment of adverse events related to chemotherapy and/or radiotherapy;
- Psychosocial support;
- Treatment of cancer-related pain.

The present report aims to formulate, on the basis of scientific evidence, recommendations relative to exercise treatment for adult patients receiving chemo- and/or radiotherapy for cancer. Exercise treatment or physiotherapy targeted to specific symptoms related to a certain cancer type, e.g. lymphoedema in breast cancer patients or urinary incontinence in prostate cancer patients, are out of the scope of the present report.

METHODS

The following research question was addressed in this review:

What is the effect of exercise treatment for adult cancer patients during active curative treatment?

The following outcomes are considered:

1. Quality of life (as measured by validated scales or instruments, such as FACT scales, WHOQOL-BREF, QOL EQ-5D, SF-36, EORTC-C30. *See text box*);
2. Cardiopulmonary function (as measured by absolute or relative VO_2max, heart rate, Metabolic Equivalence of Task or 6 or 12 minute walk tests);
3. Fatigue (as measured by validated scales or instruments, such as Piper Fatigue Scale, Brief Fatigue Inventory, FACT-F or FACT fatigue subscales, FACIT-F, Multidimensional Fatigue Inventory);
4. Safety of exercise treatment (i.e. frequency and type of adverse events).

Text box 1: Scales to mesure Quality of Life

FACT	Functional Assessment of Cancer Therapy
WHOQOL-BREF	WHO quality of life assessment instrument
EQ-5D	EuroQol-5D instrument
SF-36	Short Form Health Survey
EORTC-C30	European Organisation for Research and Treatment of Cancer- Quality of Life-C30
FACIT	Functional Assessment of Chronic Illness Therapy

Active treatment encompassed radiotherapy and chemotherapy. Hormone therapy (for breast or prostate cancer) was excluded. The "active treatment" period was defined as the period from diagnosis until either 3 weeks post-surgery, or one week after the last radiotherapy or from diagnosis until 3 weeks after the last chemotherapy, cycle. The exercise intervention had to begin within the period defined above, but could continue after this period.

The literature search initially focused on systematic reviews and meta-analyses. However, after an evaluation of the reviews, it was obvious that no recent systematic review had used exactly the same definitions as those developed for the present report. Consequently, it was decided:

- to analyse the individual RCTs from the reference lists of the systematic reviews, and
- to perform a full literature search for RCTs in order to ensure the inclusion of all relevant studies.

Systematic reviews and meta-analyses were searched in the following databases: OVID Medline and PreMedline, EMBASE, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database. RCTs were searched in: OVID Medline, PreMedline, EMBASE and CENTRAL. Searches were run between December 2011 and February 2012.

The AMSTAR instrument was applied for the critical appraisal of the systematic reviews. Risk of bias for the included RCTs was determined using the Cochrane Collaboration's tool for assessing risk of bias. The GRADE system was used to assign the levels of evidence and grades of recommendations.

RESULTS

Effectiveness

A total of 33 RCTs were identified with studies on breast cancer patients being most common (12 studies). For breast cancer it was therefore possible to compare institution-based with home-based interventions and aerobic exercise (e.g. walking, cycling) with resistance exercise (e.g. muscle strengthening). This comparison was not possible for the remaining cancer types due to a limited number of trials. The conclusions on the effectiveness of exercise treatment are presented by cancer type in the table below.

Safety

In about half of the included studies, data on the safety of exercise treatment was available. From these studies, we conclude that exercise treatment seems to be safe in patients undergoing treatment for cancer.

Cancer type	N studies	Conclusions
Breast cancer	12	• Conflicting evidence *(i.e. a mix of studies reporting a positive effect and studies with no effect)* on the effect of exercise treatment on quality of life, regardless of it being institution- or home-based, aerobic and/or resistance exercise (very low level of evidence) • Conflicting evidence on the effect of exercise treatment on cardiopulmonary function (very low level of evidence) • Evidence suggests that aerobic exercise is superior to resistance exercise in improving cardiopulmonary function (low level of evidence) • Conflicting evidence on the effect of exercise treatment on fatigue (very low level of evidence)
Prostate cancer	4	• Conflicting evidence on the effect of exercise treatment on quality of life, cardiopulmonary function and fatigue (very low level of evidence)
Lung cancer	1	• A combination of preoperative hospital-based and postoperative home-based exercise does not seem to have an effect on quality of life and cardiopulmonary function (low level of evidence)
Colorectal cancer	2	• The evidence suggests that exercise treatment has no effect on quality of life or cardiopulmonary function (very low level of evidence) • There are indications that exercise treatment has no effect on fatigue (low level of evidence)
Haematological cancers		
Haematopoietic stem cell transplantation	4	• Exercise treatment does not seem to have a significant effect on quality of life (very low level of evidence) • Conflicting evidence on the effect of exercise treatment on cardiopulmonary function and fatigue (very low level of evidence)
Lymphoma	1	• It is plausible that exercise treatment has a significant effect on quality of life, although the effect disappears after 6 months after the end of exercise treatment (moderate level of evidence) • It is plausible that exercise treatment has a significant effect on cardiopulmonary function and fatigue (moderate level of evidence)
Acute myelogenous leukemia	1	• Exercise treatment seems to have a temporary effect on fatigue (very low level of evidence)
Mixed cancer populations	8	• Conflicting evidence on the effect of exercise treatment on quality of life, cardiopulmonary function and fatigue (very low level of evidence)

CONCLUSIONS

In this study, we analysed the published RCTs on the benefits and harms of exercise treatment for adult cancer patients undergoing chemotherapy and/or radiotherapy.

For most cancer types, only a small number of RCTs could be included, except for breast cancer. Most of these studies suffered from methodological limitations. Moreover, the included studies were very heterogeneous, both in terms of study populations (different cancer stages, different treatment regimens), and in terms of outcome scales. Across these scales, they report conflicting results:

- For most cancer types, we found no consistent evidence on the benefits of exercise treatment, including quality of life, cardiopulmonary function and fatigue; i.e. there was a mix of studies reporting a positive effect and of studies reporting no effect. The only exception was one single study (of moderate quality) in lymphoma patients, which reported statistically significant positive results on all included outcomes.
- Neither did we find consistent evidence that exercise would harm quality of life or cardiopulmonary function, or would increase fatigue symptoms. Furthermore, there was some evidence that exercise is safe during adjuvant therapy for cancer patients, although not all trials reported on exercise-related adverse events.

A generalization of the results and conclusions might not be appropriate due to the above-mentioned population differences across the included studies. Moreover, the available evidence did not allow us to express a recommendation in favour of a particular exercise intervention. The good news is that there is no reason to fear that physical exercise would be harmful during cancer treatment.

RECOMMENDATIONS[a]

Clinical recommendations for the healthcare providers

- **In the absence of consistent evidence on the short-term beneficial effects of exercise treatment on quality of life, cardiopulmonary function and fatigue for cancer patients undergoing active treatment, we cannot formulate more precise recommendation in favour of a specific type of exercise treatment, over and above the generally accepted counseling that physical activity is beneficial for health (weak recommendation; very low level of evidence). Hence, it is advisable to take the local context and the preferences of the patient into account.**
- **As there is no consistent evidence either that exercise treatment would be harmful for cancer patients under treatment, they should not be discouraged to do physical activities. (weak recommendation; very low level of evidence).**

Agenda for the research community

- **Since there is a lack of consistent and high-quality evidence on the effectiveness (in terms of quality of life, cardiopulmonary function and fatigue) and on safety of exercise treatment for cancer patients undergoing active treatment, large high-quality RCTs are needed.**
- **For outcomes such as quality of life and fatigue, researchers should use standardized, validated scales and the research community should agree on a generic and on a disease-specific instrument to render the results comparable.**
- **For future studies it is crucial to pre-define main outcomes and the magnitude of effect for outcome measures based on clinical significance.**

[a] These recommendations are under the sole responsibility of the KCE

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
95%CI	95% confidence interval
ADL	Activities of daily living
ADT	Androgen depression therapy
AMSTAR	Quality appraisal tool to assess systematic reviews
BFI	Brief Fatigue Inventory
bpm	Beats per minute
CG	Control group
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer- Quality of Life-C30
EQ-5D	EuroQol-5D instrument
FACIT	Functional Assessment of Chronic Illness Therapy
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FACT	Functional Assessment of Cancer Therapy
FACT-AN	Functional Assessment of Cancer Therapy - Anemia scale
FACT-B	Functional Assessment of Cancer Therapy - Breast Cancer
FACT-C	Functional Assessment of Cancer Therapy - Colorectal Cancer
FACT-F	Functional Assessment of Cancer Therapy - Fatigue
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-GP	Functional Assessment of Cancer Therapy - General Population
FACT-P	Functional Assessment of Cancer Therapy - Prostate Cancer
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Heart rate
HSCT	Haematopoietic stem cell transplantation
HTA	Health technology assessment
IG	Intervention group
ITT	Intention to treat
KCE	Belgian Healthcare Knowledge Centre
LASA	Linear Analogue Scales of Assessment

MD	Mean difference
MET	Metabolic Equivalent of Task
min	Minutes
MOS	Medical Outcome Study
NSCLC	Non-small cell lung cancer
POMS	Profile of Mood States
QOL	Quality of life
RCT	Randomized controlled trial
SD	Standard deviation
SDS	Symptom distress scale
SF-36	Short Form Health Survey
SR	Systematic review
STAI	Spielberger's state-trait anxiety inventory
TOI-AN	Trial Outcome Index-Anemia
VAS	Visual analogue scale
VO_2max	Maximal Oxygen Consumption
WHOQOL-BREF	WHO quality of life assessment instrument

SCIENTIFIC REPORT

1 INTRODUCTION

The development of care pathways is one of the main items within the Belgian National Cancer Plan 2008-2010 and one of the tasks of the College of Oncology. KCE collaborates with the College of Oncology and provides scientific support in the development of clinical practice guidelines. Up to this date guidelines were jointly developed on breast cancer, colorectal cancer, testicular cancer, pancreatic cancer, upper gastrointestinal cancer and cervical cancer (www.kce.fgov.be).

Since many cancer-specific guidelines also cover aspects of supportive care, which are often not specific to a certain cancer type, it was decided to develop a separate series of four reports on the supportive care of adult cancer patients receiving active treatment for their cancer. The following aspects will be covered by this series: treatment of adverse events related to chemotherapy and/or radiotherapy, exercise treatment, psychosocial support, and treatment of cancer-related pain.

The present report aims to formulate, on the basis of scientific evidence, recommendations relative to exercise treatment for adult cancer patients receiving active curative treatment (chemo- and/or radiotherapy) for their cancer. Exercise treatment or physiotherapy for specific cancer-related symptoms, e.g. lymphoedema in breast cancer patients or urinary incontinence in prostate cancer patients, are out of the scope of the present report.

This report is intended to be used by health care professionals involved in the supportive care of cancer patients during active treatment.

2 METHODS

2.1 Scoping

2.1.1 Methodology

On 8 November 2011, a stakeholder meeting took place at the KCE. On the basis of a web-survey conducted prior to the meeting, a list of potential research questions and outcomes related to exercise treatment was presented to an expert group in order to discuss themes of interest to clinical practice. A final selection and prioritization of outcomes was made by the KCE in collaboration with a content expert (Sophie Hanssens) and validated by the experts via email.

2.1.2 Research questions and outcomes

For exercise treatment the following research question was defined as being of primary interest:

- Which evidence exists on exercise programs for adult cancer patients during active curative treatment?

The reason for focusing on the active treatment period is that most cancer guidelines developed by the KCE focus on this period.

Additionally, the experts expressed an interest in the effect of exercise during the period immediately following treatment – a period sometimes referred to as the "rehabilitation" period. One systematic review covering this period was found[1]. This review included four RCTs. However, only two of these RCTs measured outcomes within the scope of our project. In collaboration with the content expert, it was consequently decided to solely focus on cancer patients during active treatment.

Exercise treatment as part of a multidisciplinary program also involving psychosocial support was considered to be out-of-scope. These multidisciplinary programs will be discussed in a separate report on psychosocial support.

The list of outcomes to be studied was similarly defined in collaboration with the content expert and ranked according to importance:

- Quality of Life (measured by FACT scales, WHOQOL-BREF, QOL EQ-5D, SF-36, EORTC-C30, FACIT scale or similar instrument);
- Cardiopulmonary function (measured by absolute or relative VO_2max, heart rate, MET or 6 or 12 minute walk tests);
- Fatigue (Piper Fatigue Scale, Brief Fatigue Inventory, FACT-F or FACT fatigue subscales, FACIT-F, Multidimensional Fatigue Inventory or similar instrument);
- Safety (expressed as adverse events related to the exercise-intervention or relapse).

2.2 Definitions

Definitions for the "active treatment" phase were developed with inspiration from the literature, including a recent Dutch systematic review[2] and in close collaboration with the content expert to ensure our definitions were aligned with the current Belgian context. The "active treatment" period was defined as being from diagnosis until 3 weeks post-surgery, from diagnosis until one week after the last radiation treatment or from diagnosis until 3 weeks after the last chemotherapy treatment. This was regardless of cancer type or treatment form. Patients being on hormone therapy (including breast cancer patients and patients on ADT for prostate cancer) were not considered to be on active treatment unless they also fell within the definitions described above. The exercise intervention had to begin within the period defined and described above, but could continue after this period.

Exercise treatment included all exercise interventions performed in any setting and measured by the defined outcomes.

The results in chapter 4 are described per cancer type. The section on mixed cancer populations contains the RCTs with at least two different cancer types.

2.3 Literature search

For all research topics, the search first focused on systematic reviews and meta-analyses. If guidelines were identified that were clearly based on a systematic review of the literature, they were included and treated as a systematic review. The following sources were used:

- OVID Medline and PreMedline
- EMBASE (Embase.com)
- Cochrane Database of Systematic Reviews (Wiley)
- DARE (Wiley)
- HTA database (Wiley)
- National Guideline Clearinghouse.

Depending on the quality and currency of the identified reviews, an additional search for randomized controlled trials (RCTs) was done. The following sources were used:

- OVID Medline and PreMedline
- EMBASE (Embase.com)
- CENTRAL (Wiley)

Medline and EMBASE searches for systematic reviews and meta-analyses were run on 13 December 2011. The search in the Cochrane Library was run on 27 February 2012. The National Guideline Clearinghouse was searched on 29 February 2012. The search for primary studies (RCTs) was run in Medline on 12 January 2012 and in EMBASE on 16 January 2012. Detailed search strategies can be found in appendix 2.

2.4 Selection criteria

The selection criteria are summarized in Table 1.

Table 1 – In- and exclusion criteria

Selection criteria	Inclusion criteria
Population	Adult cancer patients during active treatment. Active treatment is defined as being from diagnosis until 3 weeks post-surgery (regardless of cancer type and treatment) or from diagnosis until one week of last radiation treatment or from diagnosis until 3 weeks of last chemotherapy treatment
Intervention	Exercise-programs performed in any setting
Outcome	Quality of life, cardiopulmonary function, fatigue and safety
Design	Meta-analysis, systematic review, evidence-based guideline, HTA, RCT
Language	English, Dutch, French

2.5 Selection process

For the selection of systematic reviews, one reviewer (Kirsten Holdt Henningsen) performed a first selection based on title and abstract. Doubtful cases were discussed with a second reviewer (Anja Desomer) and consensus was achieved with a third reviewer (Joan Vlayen). After this first selection, the full-text of the selected abstracts was retrieved.

Before assessing the methodological quality of each review, a quick critical appraisal was performed of each full-text. The criteria of the critical appraisal were:

- Searched in Medline and at least one other database
- Data of search mentioned
- Quality appraisal of included primary studies performed (not yet looking at the quality of appraisal and the used tool)

Reviews not meeting these criteria were excluded from further review.

After a review of the finally selected systematic reviews it was evident that no recent systematic review had defined the study population in a way that was completely comparable to the definition used for this review. Consequently, it was decided to select relevant and potentially relevant primary studies from the reference lists of the systematic review and to perform an additional literature search for RCTs in order to ensure the inclusion of all relevant studies. The selection process of RCTs was similar to that of systematic reviews. The first selection was based on title and abstract (AD), a second selection was based on the full-text of selected abstracts (AD), which was also discussed with the second reviewer (KHH). Doubtful cases were discussed with the third reviewer (JV).

2.6 Quality appraisal

For the quality appraisal of systematic reviews, the AMSTAR instrument was used (see appendix 1). Three items of this checklist were considered key for labelling a review as high quality:

- Item 3: Was a comprehensive literature search performed?
- Item 7: Was the scientific quality of the included studies assessed and documented?
- Item 9: Were the methods used to combine the findings of studies appropriate?

For the quality appraisal of RCTs, the Cochrane Collaboration's tool for assessing risk of bias[3] was used (see appendix 1). Judgement of each item includes three categories: 'low risk of bias', 'high risk of bias', and 'unclear risk of bias'. For each criterion the definitions as described in the Cochrane Handbook[3] were used. If applicable, risk of bias for the items regarding detection bias and attrition bias were assessed per class of outcomes (e.g. subjective and objective outcomes). At the end, each study was labelled as low risk of bias, unclear risk of bias or high risk of bias according to the criteria described in the Cochrane Handbook[3]. For each individual study, the risk of bias is reported in the evidence tables (see appendix 4).

2.7 Grading of evidence

Data extraction was done by one reviewer using the standard KCE template for evidence tables (see appendix 4).

For each clinical question, conclusions were formulated at the level of individual treatment outcomes. A level of evidence was assigned to each conclusion using the GRADE system[4] (Table 2). The quality of evidence was down- or upgraded based on predefined criteria (Table 3).

Table 2 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological quality of supporting evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	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	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Table 3 – Down- or upgrading the evidence according to the GRADE system

Study design	Quality of evidence	Lower if	Higher if
RCT	**High**	Risk of bias: -1 Serious -2 Very serious	Large effect: +1 Large +2 Very large
	Moderate	Inconsistency: -1 Serious -2 Very serious	Dose response: +1 Evidence of a gradient
Observational study	**Low**	Indirectness: -1 Serious -2 Very serious	All plausible confounding: +1 Would reduce a demonstrated effect +1 Would suggest a spurious effect when results show no effect
	Very low	Imprecision: -1 Serious -2 Very serious Publication bias: -1 Likely -2 Very likely	

2.8 Formulation of recommendations

Based on the retrieved evidence, a first draft of updated recommendations was prepared by a small working group (KH, AD, SH, JV). This first draft together with the evidence tables was circulated to the expert group about 2 weeks prior to the face-to-face meeting. The expert group met on one occasion (22 May 2012) to discuss the first draft. Recommendations were changed if important evidence supported this change. Based on the discussion meetings a second draft of recommendations was prepared. A grade of recommendation was assigned to each recommendation using the GRADE system (Table 4 and Table 5). The second draft was once more circulated to the guideline development group for final approval.

Table 4 – Strength of recommendations according to the GRADE system

Grade	Definition
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not
Weak	The desirable effects of an intervention probably outweigh the undesirable effects, or probably do not

Table 5 – Factors that influence the strength of a recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention – that is, the greater the resources consumed – the lower the likelihood that a strong recommendation is warranted

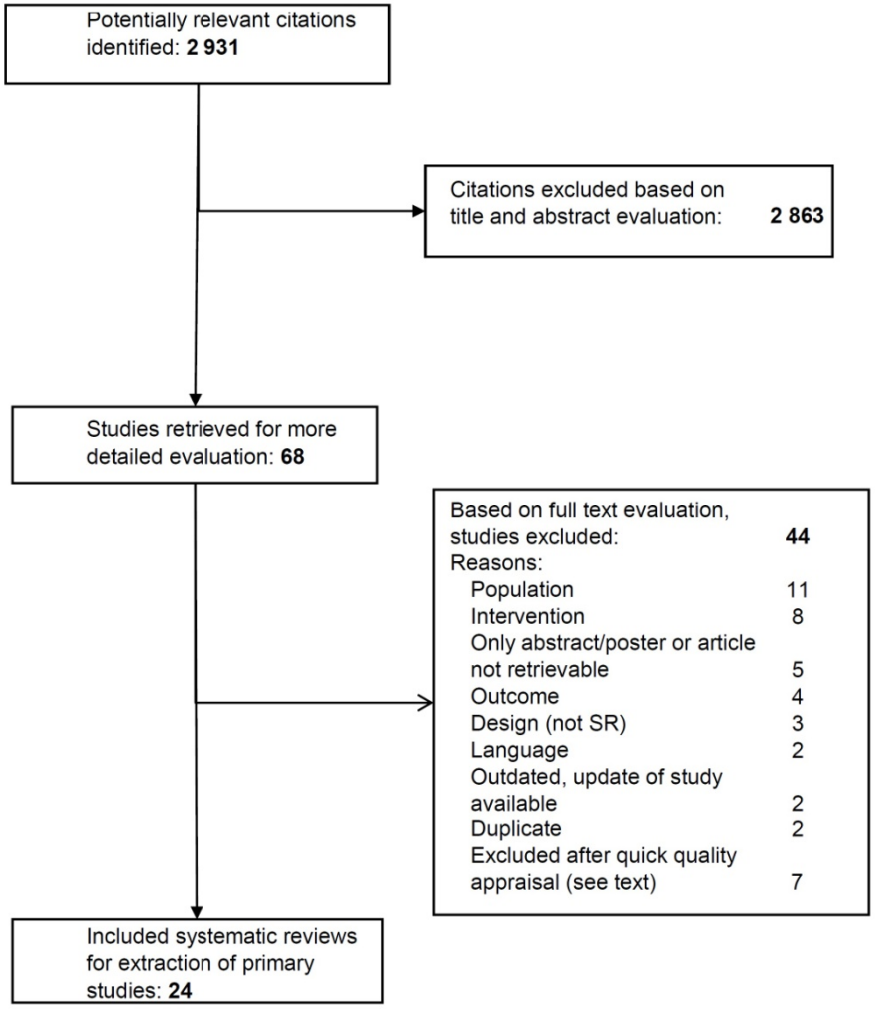
3 SEARCH RESULTS

3.1 Systematic reviews

The searches yielded the following number of hits per database:

Database	Number of hits
Cochrane Database of Systematic Reviews	89
Medline	1 685
PreMedline	23
EMBASE	1 066
DARE	61
HTA database	6
National Guideline Clearinghouse	1

After a review of title and abstract (2 931 hits) 68 papers were selected for full-text review. Based on the full-text (and the quick critical appraisal) 24 papers fulfilled the inclusion criteria[1,2,5-25]. After a review of the selected systematic reviews it became evident that no recent systematic review fully comprised a comparably defined study population for this guideline. Consequently it was decided to select relevant primary studies from the reference lists of the systematic reviews and to perform an additional search on primary studies during the full period in order to ensure the inclusion of all relevant studies.

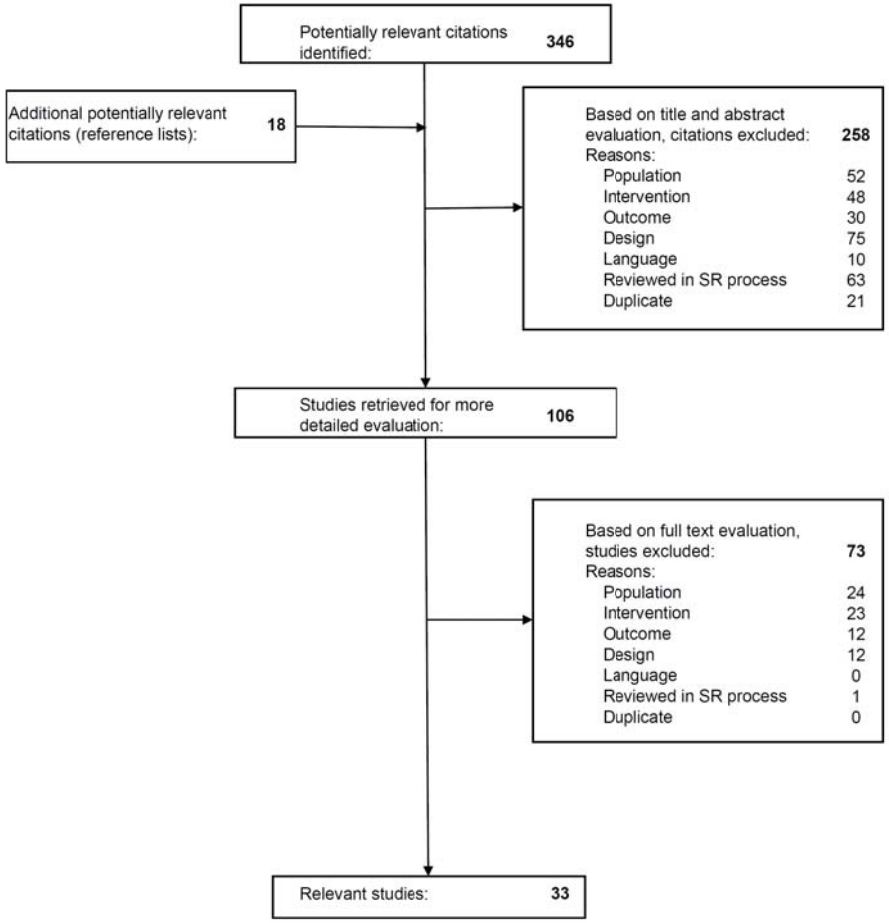


3.2 Randomized controlled trials

The search for primary studies through the reference lists initially revealed 44 primary studies of which 25 fulfilled inclusion criteria.

The additional search for primary studies revealed 67 studies of which 8 fulfilled the inclusion criteria. Thus, in total 33 primary studies were selected for the report[26-59].

Database	Number of hits
CENTRAL	132
Medline	191
PreMedline	2
EMBASE	2 088



4 EVIDENCE REPORT

4.1 Breast cancer

A total of 12 studies on breast cancer patients assessing one or more of our predefined outcomes were included. Sample size ranged from 22 to 242, with a mean of 92 women. Interventions ranged from a moderate intensity seated exercise program[48] to progressive aerobic or resistance exercise programs at targeted heart rate or maximal repetitions[45].

4.1.1 Quality of Life

4.1.1.1 Institution-based interventions

Five RCTs reported quality of life (QOL) measures for institution-based interventions[44,45,49,53,56]. One study had a low risk of bias[53], while the remaining had an either moderate[44,45,49,53,56] or high risk of bias[44,49]. QOL measurement scales varied and included FACT-G, FACT-B, FACT-AN, WHOQOL-BREF and SF-36 with some studies using more than one scale.

Estimates of the effect of institution-based exercise on quality of life and on physical subscales of QOL differed widely across the studies (Table 6).

Two small studies reported a positive effect of supervised exercise on overall QOL. One study found the effect at 5 weeks (WHOQOL-BREF)[49] and the other study at 12 weeks (FACT-G)[44]. The three larger studies found no significant effect on overall QOL at any measure point[45,53,56].

One small study found a positive effect on a physical subscale of QOL ($p<0.001$, WHOQOL-BREF subscale “physical”)[49]. Three studies found no effect on physical subscales[44,53,56]. One study did not report a physical subscale[45].

Conclusions

- **Conflicting evidence is available on the effect of institution-based exercise treatment on overall quality of life in breast cancer patients (very low level of evidence; Campbell 2005, Courneya 2007, Mutrie 2007, Hwang 2008, Segal 2001).**
- **Conflicting evidence is available on the effect of institution-based exercise treatment on physical subscales of quality of life in breast cancer patients (very low level of evidence; Campbell 2005, Hwang 2008, Mutrie 2007, Segal 2001).**

Table 6 – Effect of institution-based exercise on quality of life (QOL) and physical subscales of QOL in patients with breast cancer

Study	N	Overall QOL	Physical subscale	Measure point(s)	Intervention characteristics
Courneya 2007[45]	N=242	No effect on overall QOL (measured by FACT-AN) for any of the two intervention arms at post-test (median 17 weeks) and at 6-months follow-up	No physical subscale reporting	Baseline Post-test (median 17 weeks) 6-months follow-up	RET (resistance arm): 3 x weekly 2 sets of repetitions at 60-70% of one repetition maximum AET (aerobic arm): 3 x weekly on cycle ergometer, treadmill or elliptical at 60% of VO_2max Control group received usual care and were asked not to initiate exercise program
Mutrie 2007[53]	N=203	No effect for FAGT-G at any measure point Effect for FACT-B at 12 weeks (p=0.0007) and 6 months (p=0.039)	No effect for subscale "Physical" (FACT-G) at any measure point	Baseline 12 weeks 6 months (follow-up)	45 min of moderate level group exercise 2 x weekly + an additional exercise session at home Control group received usual care
Segal 2001[56]	N=123*	No effect for FACT-G and FACT-B	No effect for "physical functioning" (SF-36) in institution-based study arm for patients receiving chemotherapy (primary outcome)	Baseline 26 weeks	Supervised arm: exercise 3 x weekly (walking exercise at prescribed pace) + exercise at home 2 other weekdays Two control groups, one group performed self-directed exercise and one group received usual care i.e. general advice
Hwang 2008[49]	N=40	Positive effect for WHOQOL-BREF (p<0.001)	Positive effect, p<0.001 (WHOQOL-BREF subscale "physical")	Baseline 5 weeks	Exercise 3 x weekly for 50 min (stretching and aerobic exercise). Heart rate: 50-70% of age adjusted maximum Control group performed shoulder exercises and could continue their normal activities
Campbell 2005[44]	N=22	Positive effect FACT-G (p=0.46) No effect for FACT-B	No effect for "physical well-being" subscale (FACT-B)	Baseline 12 weeks	Supervised exercise 2 x weekly at 60-75% age adjusted heart rate maximum Control group received usual care

** Data on the 83 women receiving chemotherapy are reported.*

4.1.1.2 Home-based interventions

Six RCTs (including a total of 453 patients) reported QOL measures for home-based interventions[43,47,48,51,56,58]. All studies had methodological limitations. Four studies had a moderate risk of bias[43,47,51,56] and two studies had a high risk of bias[48,58]. QOL measurement scales included EQ-5D, EORTC C30, FACT-G, FACT-B, SF-36 and FACIT-F with some studies using more than one scale.

Estimates of the effect of home-based exercise on QOL and on physical subscales of QOL differed across the studies (Table 7).

One study found a positive effect on overall QOL (FACT-G), measured as linear growth rate difference between groups (t70=3.76, p<0.001) and quadratic growth rate difference between groups (t70=2.64, p=0.011)[58].

One 3-arm study compared a home-based exercise intervention with a supervised intervention or usual care and found no effect on overall QOL (FACT-B, FACT-G), but an effect on SF-36 “physical functioning” in the home-based intervention arm and not in the supervised intervention arm[56]. One study found a positive effect on generic health-related QOL (EQ-5D) at 3 months (p=0.006) and on EORTC C30 “physical functioning” at 3-months (p=0.02). Neither of these effects remained after 6-months[47].

Three studies had an unclear or limited reporting of group comparison measures for QOL[43,48,51]. One of these studies suggested a positive effect measured as less decline in overall QOL (p=0.0254) in the exercise group [48] and one study suggested no effect for exercise on overall QOL[43]. In one study it was not possible to assess whether there was a suggested effect on the SF-36 subscale “Physical Functioning“ or not[51].

Conclusions

- **Conflicting evidence is available on the effect of home-based exercise treatment on overall quality of life of breast cancer patients (very low level of evidence; Cadmus 2009, Haines 2010, Headley 2004, Segal 2001, Wang 2011).**
- **Conflicting evidence is available on the effect of home-based exercise treatment on physical subscales of quality of life of breast cancer patients (very low level of evidence; Cadmus 2009, Haines 2010, Headley 2004, Mock 2005, Segal 2001).**

Table 7 – Effect of home-based exercise on quality of life (QOL) and physical subscales of QOL in patients with breast cancer

Study	N	Overall QOL	Physical subscale	Measure point	Intervention characteristics
Segal 2001[56]	N=123*	No effect for FACT-G and FACT-B	Effect on SF-36 "Physical functioning" (p=0.03) for patient receiving chemotherapy (primary outcome)	Baseline 26 weeks	Self-directed arm: Exercise at home 5 x weekly performing a progressive walking program Two control groups: one group performed supervised exercise and one group received usual care i.e. general advice
Mock 2005[51]	N=119	No reporting of overall QOL	Unclear reporting of group comparison measures (SF-36 "Physical Functioning" subscale)	Baseline After intervention Intervention length was dependent on length of adjuvant therapy (either 6 weeks of radiotherapy or 3-6 months of chemotherapy)	Prescription to exercise 5-6 x weekly at 50-70% of maximum heart rate, starting with 15 minutes walk that increased to 30 min as training progressed Control group was encouraged to maintain usual activity level Possible dilution of treatment effect as 39% of usual care group exercised and 28% of the exercise group did not
Haines 2010[47]	N=89	Positive effect on generic health-related QOL (EQ-5D) at 3 months (p=0.006) No effect on generic QOL (EQ-5D) at 6 months	Positive effect on EORTC C30 physical functioning subscale (p=0.02) at 3-months No effect on EORTC C30 physical functioning subscale at 6-months	Baseline, 3, 6 and 12-months follow-up	Home-based strength, balance, shoulder mobility and cardiovascular endurance program; recommended to make exercises harder every 2-4 weeks Control group participated in relaxation and flexibility activities Participant adherence higher in the first 3 months than in the second 3 months

Wang 2011[58]	N=72	FACT-G change between the 2 groups significantly different at linear growth rate (t70=3.76, p <0.001) and quadratic growth rate (t70 = 2.64, p=0.011)**	No reporting of physical subscales	4 measure points; Pre-surgery baseline (time 1), 24 hours prior to first day of chemotherapy (time 2), day of expected nadir, which is 7-10 days after chemotherapy (time 3) and end of 6-weeks intervention (time 4)	6-weeks, home-based, walking program, 3 to 5 sessions per week Low to moderate intensity measured by a heart rate maximum (HR max) from 40 to 60% Control group received usual care
Cadmus 2009[43]	N=50***	Unclear reporting of QOL (FACT-B and FACT-G) group comparison measures Authors suggest no significance	Unclear reporting of group comparison measures on SF-36 subscale "physical" Authors suggest significance (p<0.05) favouring usual care group****	Baseline 6 months	30 min of activity 5 days weekly. Instructed to maintain activity at 60-80% of predicted maximum heart rate. Each participant received weekly phone calls Control group could exercise if they chose but the study program was not available to these patients 64% of participants met the goal of exercising 150 min per week
Headley 2004[48]	N=32	Statistics between endpoints not provided Overall QOL (FACIT-F) declined for both groups Exercise group declining at slower rate than control group (p=0.0254, only graphical presentation of results)	Insufficient data reporting Statistics between endpoints not provided Physical well-being (FACIT-F subscale): exercise group declining at a slower rate than control, (p=0.0252, only graphical presentation of results)	Baseline At the beginning of each course of chemotherapy for 12 weeks (a total of four measurements)	30 min of seated exercise 3 x weekly using a commercially available video Program consisted of 20 min moderate-intensity repetitive motion exercise Control group received no specific exercises but were permitted to continue any usual physical activity

** Data on the 83 women receiving chemotherapy are reported.*
***Results provided in text and graphs only.*
**** Only data from IMPACT study are retrieved.*
***** The mean decrease of -1.5 points in the exercise group did not reach clinical significance (information retrieved from http://www.sf-36.org/cgi-bin/discuss/msg.cgi?msg=1592).*

4.1.1.3 Aerobic interventions

Nine RCTs reported quality of life (QOL) measures for aerobic interventions[43-45,48,49,51,53,56,58]. One study had a low risk of bias[53], while the remaining had an either moderate[43,45,51,56] or high risk of bias[44,48,49,58].

QOL measurement scales included FACT-G, FACT-B, FACT-AN, WHOQOL-BREF, FACIT-F and SF-36 with some studies using more than one scale.

Estimates of the effect of aerobic exercise on quality of life and on physical subscales of QOL differed widely across the studies (Table 8).

Overall quality of life

Two studies found a positive effect of aerobic exercise on overall QOL. One of these studies (N=72) found a positive effect for FACT-G, measured as linear growth rate difference between groups ($p<0.001$) and quadratic growth rate difference between groups ($p=0.011$)[58]. The other study (N=40) found a positive effect on overall QOL measured by WHOQOL-BREF ($p<0.001$)[49].

One small study (N=22) found a positive effect of aerobic exercise on overall QOL measured by FACT-G ($p=0.46$), but no effect for FACT-B[44]. A larger study (N=203) found a positive effect for FACT-B at 12 weeks ($p=0.0007$) and 6 months ($p=0.039$) and no effect for FACT-G[53].

Two studies found no effect of aerobic exercise on overall QOL measured by FACT-AN and (FACT-G + FACT-B), respectively[45,56].

Two other studies had an unclear or limited reporting of group comparison measures for QOL[43,48]. One of these studies suggested a positive effect measured as less decline in QOL in the exercise group[48] and one study suggested no effect for exercise on overall QOL[43].

Physical subscale of quality of life

One small study (N=40) found a positive effect of aerobic exercise on QOL measured by WHOQOL-BREF subscale physical ($p<0.001$)[49].

One study found an effect of aerobic exercise on “physical functioning” (SF-36) for patients in a self-directed (home-based) study arm ($p=0.03$), but not for patients in a supervised (institution-based) study arm[56].

Two studies did not find an effect for physical QOL subscales, measured by “physical” (FACT-GP)[53] and by “physical well-being” (FACT-B)[44].

Two studies had an unclear or limited reporting of group comparison measures for physical QOL subscales. One of these studies suggested a positive effect on physical well-being (FACIT-F subscale; $p=0.0252$). The other study suggested an effect ($p<0.05$) in favour of the control group on SF-36 subscale “physical”. In another study it was not possible to assess whether there was a suggested effect or not[51].

One study did not include a physical QOL subscale as an outcome measure[45].

Table 8 – Effect of aerobic interventions on quality of life (QOL) and physical subscales of QOL in patients with breast cancer

Study	N	Overall QOL	Physical subscale	Measure point	Intervention characteristics
Courneya 2007[45]	N=242	No effect (FACT-AN) at any measure point	No physical subscale reporting	Baseline Post-test (median 17 weeks) 6-months follow-up	AET (aerobic arm): 3 x weekly on cycle ergometer, treadmill or elliptical beginning at 60% of VO_2max
Mutrie 2007[53]	N=203	No effect for FAGT-G at any measure point Effect for FACT-B at 12 weeks (p=0.0007) and 6 months (p=0.039)	No effect for Physical (FACT-G) at any measure point	Baseline 12 weeks 6 months (follow-up)	See Table 6
Mock 2005[51]	N=119	No reporting of overall QOL	Unclear reporting of MOS SF-36 “Physical Functioning” subscale group comparison measures	Baseline After intervention Intervention length was dependent on length of adjuvant therapy (either 6 weeks of radiotherapy or 3-6 months of chemotherapy)	See Table 7
Segal 2001[56]	N=123*	No effect for FACT-G and FACT-B	No effect for “physical functioning” (SF-36) in institution-based study arm for patients receiving chemotherapy Positive effect on SF-36 “Physical functioning” (p=0.03) for patient in self-directed arm receiving chemotherapy	Baseline and 26 weeks	Supervised arm: exercise 3 x weekly (walking exercise at prescribed pace) + expected to exercise at home 2 other weekdays Self-directed arm: Exercise at home 5 x weekly. Participants performed a progressive walking program at 50-60% of maximal oxygen uptake Control group received usual care i.e. general advice
Wang 2011[58]	N=72	FACT-G change between the 2 groups significantly different at linear growth rate (t70=3.76,	No reporting of physical subscales	4 measure points; Pre-surgery baseline (time 1), 24 hours prior to first	See Table 7

Study	N	Overall QOL	Physical subscale	Measure point	Intervention characteristics
		p<0.001) and quadratic growth rate (t70=2.64, p=0.011)**.		day of chemotherapy (time 2), day of expected nadir, which is 7-10 days after chemotherapy (time 3) and end of 6-weeks intervention (time 4)	
Cadmus 2009[43]	N=50***	Unclear reporting of QOL (FACT-B and FACT-G) group comparison measures. Authors suggest no significance	Unclear reporting of group comparison measures on SF-36 subscale "physical" Authors suggest significance (p<0.05) favoring usual care group****	Baseline 6 months	See Table 7
Hwang 2008[49]	N=40	Positive effect for WHOQOL-BREF (p<0.001)	Positive effect, p<0.001 (WHOQOL-BREF subscale "physical")	Baseline 5 weeks	See Table 6
Headley 2004[48]	N=32	Statistics between endpoints not provided Overall QOL (FACIT-F) decline for both groups Exercise group declining at slower rate than control group (p=0.0254, only graphical presentation of results)	Insufficient data reporting. Statistics between endpoints not provided Physical well-being (FACIT-F subscale): Exercise group declining at a slower rate than control (p=0.0252, only graphical presentation of results)	Baseline At the beginning of each course of chemotherapy for 12 weeks (a total of four measurements)	See Table 7
Campbell 2005[44]	N=22	Positive effect FACT-G (p=0.46) No effect for FACT-B	No effect for "physical well-being" subscale (FACT-B)	Baseline 12 weeks	See Table 6

** Data on the 83 women receiving chemotherapy are reported.*
*** Results provided in text and graphs only.*
**** Only data from IMPACT study are retrieved.*
***** The mean decrease of -1.5 points in the exercise group did not reach clinical significance (information retrieved from http://www.sf-36.org/cgi-bin/discuss/msg.cgi?msg=1592)*

Conclusions

- **Conflicting evidence is available on the effect of aerobic exercise on overall quality of life for breast cancer patients (very low level of evidence; Cadmus 2009, Campbell 2005, Courneya 2007, Headley 2004, Hwang 2008, Mock 2005, Mutrie 2007 Segal 2001,Wang, 2011).**
- **Conflicting evidence is available on the effect of aerobic exercise on physical subscales of quality of life for breast cancer patients (very low level of evidence; Cadmus 2009, Campbell 2005, Courneya 2007, Headley 2004, Hwang 2008, Mock 2005, Segal 2001, Mutrie 2007).**

4.1.1.4 Resistance interventions

One three-armed RCT, with a moderate risk of bias, reported overall QOL (FACT-AN) for a resistance exercise intervention (Table 9). The study observed no effect on overall QOL for resistance exercise at post-intervention or at 6-months follow-up. No physical QOL subscale was reported[45].

Table 9 – Effect of resistance interventions on quality of life (QOL) and physical subscales of QOL in patients with breast cancer

Study	N	Overall QOL	Physical subscale	Measure point	Intervention characteristics
Courneya 2007[45]	N=242	No effect (FACT-AN) at post-test (median 17 weeks) or at 6-months follow-up	No physical subscale reporting	Baseline Post-test (median 17 weeks) 6-months follow-up	RET (resistance arm): 3 x weekly, sets of repetitions at 60-70% of estimated one repetition maximum Control group received usual care and were asked not to initiate exercise program

Conclusion

- **Very little evidence exists on the effect of resistance training on overall quality of life for breast cancer patients (very low level of evidence; Courneya 2007).**

4.1.1.5 Combined aerobic and resistance exercise interventions

One RCT, with a moderate risk of bias, deployed a combined aerobic and resistance exercise intervention (Table 10). The authors observed an overall effect on QOL (EQ-5D) at 3 months (p=0.006) and on the EORTC subscale "physical functioning" at 3 months (p=0.02). The effect did not persist at the 6 months assessment[47].

Table 10 – Effect of combined aerobic and resistance interventions on quality of life (QOL) and physical subscales of QOL in patients with breast cancer

Study	N	Overall QOL	Physical subscale	Measure point	Intervention characteristics
Haines 2010[47]	N=89	Positive effect on generic health-related QOL (EQ-5D) at 3 months (p=0.006) No effect on generic QOL (EQ-5D) at 6 months	Positive effect on EORTC C30 physical functioning subscale (p=0.02) at 3-months No effect on EORTC C30 physical functioning subscale at 6-months	Baseline, 3 and 6 months	See Table 2

Conclusion

- **Very little evidence exists on the effect of a combined aerobic and resistance exercise intervention on quality of life and on subscales of quality of life for breast cancer patients (very low level of evidence; Haines 2010).**

4.1.2 Cardiopulmonary function

Four RCTs reported changes in cardiopulmonary function (changes in VO_2max, heart rate [HR] or aerobic capacity measured by a walk test) after institution-based or home-based exercise interventions for breast cancer patients undergoing adjuvant therapy. Two of these studies had a moderate risk of bias[45,56] and two studies had a high risk of bias[50,55]. VO_2max measures included absolute VO_2max (ml/min or l/min)[45,50] and relative VO_2max (ml/kg/min)[45,56]. Heart rates were measured as resting HR and maximum HR (beats/min)[50]. One RCT measured aerobic capacity by the 12-minute walk test[55].

Estimates of the effect of exercise interventions on cardiopulmonary function differed across the studies (Table 11).

Four RCTs reported changes in VO_2max, heart rate measures or aerobic capacity measured by a walk test after exercise interventions for breast cancer patients undergoing adjuvant therapy. One three-armed RCT reported an effect on both absolute and relative VO_2max for aerobic exercise compared with usual care (VO_2 l/min: MD 0.13 [95%CI 0.04-0.22], p=0.004; VO_2 ml/kg/min: MD 1.8 [95%CI 0.5-3.2], p=0.006) and for aerobic exercise compared with resistance exercise (VO_2 l/min: MD 0.09 [95%CI 0.01-0.18], p=0.035; VO_2 ml/kg/min: MD 1.6 [95%CI 0.3-2.9), p=0.014)[45]. Similarly, one RCT found an effect for an aerobic exercise intervention measured by the 12-minute walk test. After 6 months the exercise group had covered a greater distance in the test than the resistance group and the usual care group (p=0.002 for difference between groups)[55]. One other RCT found no VO_2 effect for a self-directed intervention arm compared with control or for a supervised intervention arm compared with control when only patients undergoing adjuvant therapy were considered[56].

Similarly, one small RCT (N=41) found no significant group difference for VO_2max or heart rate measures after an exercise intervention[50].

Conclusions

- **Conflicting evidence exists on the effect of exercise intervention on cardiopulmonary function (VO_2max, heart rate or walk test) for breast cancer patients (very low level of evidence; Courneya 2007, Segal 2001, Schwartz 2007, Kim 2006).**
- **Evidence suggests that aerobic exercise is superior to resistance exercise in improving aerobic capacity in breast cancer patients (low level of evidence; Courneya 2007, Schwartz 2007).**

Table 11 – Effect of exercise treatment on cardiopulmonary function in patients with breast cancer

Study	N	Absolute VO_2max (ml/min or l/min)	Relative VO_2max (ml/kg/min)	Other cardiopulmonary function measures	Measure point	Intervention characteristics
Courneya 2007[45]	N=242	Effect for aerobic exercise versus usual care measured in l/min; unadjusted MD 0.13 (95%CI 0.04-0.22, p=0.004) Effect for aerobic exercise versus resistance exercise measured in l/min; unadjusted MD 0.09 (95%CI 0.01-0.18, p=0.035) No effect for resistance exercise versus usual care	Effect for aerobic exercise versus usual care; unadjusted MD 1.8 (95%CI 0.5-3.2, p=0.006) Effect for aerobic exercise versus resistance exercise; unadjusted MD 1.6 (95%CI 0.3-2.9, p=0.014)	Not reported	Baseline Post-test (median 17 weeks) 6-months follow-up	See Table 6
Segal 2001[56]	N=123*	Not reported	No effect for self-directed intervention arm compared with control* No effect for supervised intervention arm compared with control*	Not reported	Baseline 26 weeks	See Table 8

Schwartz 2007[55]	N=66	Not reported	Not reported	After 6 months the aerobic exercise group had covered greater distance on the 12 -minute walk test (p=0.02)**	Baseline 6 months (post-intervention)	Aerobic arm: home-based, instructed to choose an aerobic activity they enjoyed (e.g. walking or jogging) and exercise for 15-30 min four days per week Resistance arm: instructed to exercise at home four days per week using Thera-Band resistance band and tubing. Control group were instructed to continue with usual activities
Kim 2006[50]	N=41***	No significant group difference in VO_2max (ml/min)****	Not reported	No significant group difference in resting or maximum heart rate (beats/min)****	Baseline 8 weeks (post-intervention)	Institution based, supervised and individually prescribed aerobic exercise 3 days weekly for 30 min Intensity corresponding to 60-70% of individuals heart rate reserve Control group received usual care including general information on benefits of exercise

** Data on the 83 women receiving chemotherapy are reported.*
*** The p-value reflects the significant difference between the three groups.*
**** 11 of 74 randomized women withdrew from the study for reasons including personal problems (n=2), problems at home (n=2), problems related to chemotherapy (n=3), thrombophlebetis (n=2), non-exercise related injuries (n=1) or death (n=1). Another 22 women did not complete either pre- or post-intervention exercise tests. It is unclear if any of these 33 women participated or partly participated in the exercise intervention. Study reports on 41 women.*
***** Only intervention group showed significant positive changes in VO_2 peak and resting HR over time but measures did not reach significance in group difference.*

4.1.3 Fatigue

Eight RCTs on exercise treatment for breast cancer patients reported outcome measures on fatigue. One study had a low risk of bias[53], while the remaining had an either moderate[45,47,51] or high risk of bias[44,48,49,58]. Fatigue measurement scales varied and included the Piper Fatigue Scale, Multi-dimensional fatigue inventory, FACT-AN subscale "Fatigue", FACIT-F, FACIT-F subscale "Fatigue", Brief Fatigue Inventory and FACT-F.

Six of the studies were on aerobic interventions[44,48,49,51,53,58]. One RCT deployed a combined aerobic and resistance exercise intervention[47]. One other RCT was a three-arm study with an aerobic intervention arm, a resistance training intervention arm and a control group[45]. Four of the trials were institution-based[44,45,49,53] and four were home-based[47,48,51,58].

Estimates of the effect of exercise treatment on fatigue differed across the studies and did not seem to be dependent on whether the intervention was institution- or home-based. Neither did the results seem to depend on the exercise type chosen for the trial (aerobic, resistance or a combination). Studies are summarized in Table 7. Two RCTs, both with insufficient data reporting, suggested an effect of exercise on fatigue for breast cancer patients. One aerobic and institution-based study suggested that the control group had an increase in fatigue, that the exercise group had a decrease in fatigue and that there was a significant difference in the mean fatigue level (measured by Brief Fatigue Inventory) between groups ($p<0.05$)[49]. One small home-based study suggested that the intervention group had less decline in fatigue over time compared with the control group ($p=0.0078$), measured by the FACIT-F subscale "Fatigue"[48]. One aerobic, home-based RCT found an effect on fatigue measured by FACIT-F at two out of three measure points: 24 hours prior to the first day of chemotherapy (measure point 2) no effect was observed for fatigue, 7-10 days after chemotherapy (measure point 3) an effect for fatigue was observed ($p<0.001$) and, similarly, at the end of the intervention (measure point 4) the study suggested an effect on fatigue ($p<0.001$).

Five RCTs found no effect of exercise on fatigue for breast cancer patients[44,45,47,51,53]. These RCTs were a combination of institution-based[44,45,53] and home-based interventions[47,51], and additionally a mix of aerobic interventions[44,51,53], aerobic versus resistance interventions[45] and an intervention with both aerobic and resistance elements combined[47].

Conclusions

- **Conflicting evidence exists on the effect of exercise treatment on fatigue for breast cancer patients (very low level of evidence; Mutrie 2007, Courneya 2007, Mock 2005, Haines 2010, Campbell 2005, Headley 2004, Hwang 2008, Wang 2011).**
- **The evidence did not indicate whether institution-based exercise was superior to home-based exercise in reducing fatigue or vice versa.**
- **The evidence did not indicate whether aerobic exercise was superior to resistance exercise in reducing fatigue or vice versa.**

Table 12 – Effect of exercise treatment on fatigue in patients with breast cancer

Study	N	Fatigue	Measure point	Intervention characteristics
Courneya 2007[45]	N=242	No effect for fatigue (measured by FACT-AN subscale "Fatigue") for any of the two intervention arms at post-test (median 17 weeks) and at 6-months follow-up	Baseline Post-test (median 17 weeks) 6-months follow-up	See Table 6
Mutrie 2007[53]	N=203	No effect for fatigue (measured by FACT-F) at 12 weeks (post-intervention) and at 6-months follow-up	Baseline 12 weeks 6 months (follow-up)	See Table 6
Mock 2005[51]	N=119	No effect for fatigue (measured by Piper Fatigue Scale) at post-intervention*	Baseline After intervention Intervention length was dependent on length of adjuvant therapy (either 6 weeks of radiotherapy or 3-6 months of chemotherapy)	See Table 7
Haines 2010[47]	N=89	No effect for any measures of fatigue at 3 and 6 months Fatigue was measured by "Multidimensional fatigue inventory" that includes scales on "general fatigue", "physical fatigue", "reduced activity", "reduced motivation" and mental fatigue"	Baseline 3 months 6 months	See Table 7
Wang, 2011[58]	N=72	FACIT-F: Significant differences between the 2 groups detected only at the "nadir", (time 3: p<.001) and at the end of the program (time 4: p<.001)**	4 measure points; Pre-surgery baseline (time 1), 24 hours prior to first day of chemotherapy (time 2), day of expected nadir, which is 7-10 days after chemotherapy (time 3) and end of 6-weeks intervention (time 4)	See Table 7
Hwang 2008[49]	N=40	Insufficient data is provided. Figure suggests that the control group had a increase in fatigue, that the exercise group had a decrease in fatigue and that there was a significance in difference in the mean fatigue level (measured by Brief Fatigue Inventory) between groups (p<0.05)	Baseline 5 weeks	See Table 6
Headley 2004[48]	N=32	Insufficient data reporting. Statistics between endpoints not provided	Baseline At the beginning of each course of	See Table 7

		Graph suggests that intervention group had less decline in fatigue over time compared with control group (p=0.0078), measured by FACIT-F subscale "Fatigue"	chemotherapy for 12 weeks (a total of four measurements)	
Campbell 2005[44]	N=22	No effect for fatigue measured by Piper Fatigue Scale	Baseline 12 weeks	See Table 6

** Possible dilution of treatment effect as 39% of usual care group exercised and 28% of the exercise group did not.*
*** Results provided in text and graphs only.*

4.1.4 Safety

Adverse events were reported in five of the 12 RCTs included on breast cancer patients. All five RCTs reported that no adverse events had been observed during the trial[43,45,48,49,53].The remaining six RCTs did not include reporting of adverse events[44, 50,51,55,56,58]. Relapse was not reported in any of the included studies.

Conclusion

- **There is evidence that exercise is safe during breast cancer treatment (low level of evidence; Courneya 2007, Headley 2004, Hwang 2008, Mutrie 2007, Haines 2010).**

4.2 Prostate Cancer

A total of four studies on prostate cancer patients assessing one or more of our predefined outcomes were included. Sample size ranged from 21 to 121 with a mean of 66 men. Interventions ranged from a home-based moderate intensity, continuous walking exercise[59] to an institution-based progressive aerobic or resistance exercise program at targeted heart rate and maximal repetitions[57].

4.2.1 Quality of Life

Three RCTs reported QOL measures for exercise interventions in prostate cancer patients undergoing adjuvant therapy[46,52,57]. Two studies had a moderate risk of bias[46,57] and one study a high bias risk[52]. QOL measurement scales varied and included SF-36, QLQ-C30, FACT-G and FACT-P with some studies using more than one scale.

Estimates of the effect of exercise on QOL and on physical subscales of QOL differed across the studies (Table 13).

One three-armed RCT suggested an effect of resistance exercise but not of aerobic exercise on overall QOL (measured by FACT-G) in prostate cancer patients[57]. This effect was found both at 12 weeks (p=0.017) and 24 weeks (p=0.015). The same study did not find an effect on overall QOL for neither resistance nor aerobic exercise when measured by FACT-P. One other RCT with a combined resistance and aerobic intervention found an effect for exercise on QOL measured by SF-36 "general health" (p=0.022) [46]. Finally, one RCT found an effect for aerobic exercise on overall QOL, measured by FACT-P (p=0.006)[52].

One RCT suggested an effect of combined aerobic and resistance exercise on SF-36 "physical health composite" (p=0.02), but no effect on QLQ-C30 "physical"[46]. One RCT suggested an effect for aerobic exercise on FACT-P "physical well-being" (p<0.001). One RCT did not include QOL physical subscale measures [57].

Conclusions

- **Conflicting evidence exists on the effect of exercise treatment on quality of life in prostate cancer patients (very low level of evidence; Segal 2009, Galvao 2010, Monga 2007).**
- **Conflicting evidence exists on the effect of exercise treatment on physical subscales of quality of life in prostate cancer patients (very low level of evidence; Galvao 2010, Monga 2007).**

Table 13 – Effect of exercise treatment on quality of life in prostate cancer patients

Study	N	QOL	Physical subscale	Measure point(s)	Intervention characteristics
Segal 2009[57]	N=121	Positive effect of resistance intervention vs. usual care at 12-weeks (midpoint) measured by FACT-G; MD 4.76 (95%CI 0.86-8.65), p=0.017 Positive effect of resistance intervention vs. usual care at 24-weeks (post-intervention) measured by FACT-G; MD 4.34 (95%CI 0.88-7.80), p=0.015 No effect for aerobic intervention vs. usual care measured by FACT-G at any measure point No effect for FACT-P in any intervention arm at any measure point	Not reported	Baseline Midpoint (12 weeks) Post-intervention (24 weeks)	Resistance exercise training group (RET) exercising 3 x per week (2 x 8-12 repetitions at 60-70% of 1 maximum repetition) Aerobic training group (AET) exercising 3 x per week on a cyclo-ergometer, treadmill, or elliptical trainer beginning at 50-60% of VO_2 peak Usual care group (UC); UC was asked not to initiate exercise
Galvao 2010[46]	N=57*	Positive effect for exercise vs. usual care measured by SF-36 “general health”; MD 12.9 (95%CI 1.9-23.9), p=0.022	Positive effect for exercise versus usual care measured by SF-36 “physical health composite”; MD 5.0 (95%CI 0.81-9.2), p=0.02 No effect for QLQ-C30 “physical” (p=0.062)**	Baseline Post-intervention (12 weeks)	Institution-based Combined progressive resistance and aerobic exercise 2 x weekly for 12 weeks. The aerobic component included 15-20 min of cardiovascular exercise at 65% to 85% maximum heart rate Control group: usual care
Monga 2007[52]	N=21	Positive effect for exercise vs. usual care measured by FACT-P; MD 13.8 (SD ±10.1), p=0.006	Positive effect for FACT-P “physical well-being”; MD 3.6 (SD ± 2.0), p<0.001	Baseline Post-intervention (8 weeks)	Supervised aerobic exercise program 3 x weekly for 8 weeks consisting of 40 min aerobic exercise (walking on a treadmill) at targeted heart rate Control group: standard care

** 37.9% of exercise group and 39.3% of control group were on radiation before trial. 27.6% of exercise group and 21.4% of control group were on radiation during trial.*
*** Results provided in text only.*

4.2.2 Cardiopulmonary function

Three RCTS reported changes in VO_2max, heart rate or cardiopulmonary function measured by a walk test after exercise interventions for prostate cancer patients. One of these studies had a moderate risk of bias[57], while two had a high bias risk[52,59].

VO_2max measures included relative VO_2max (ml/kg/min)[57] and respective metabolic equivalents (MET 3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$)[52]. One study measured heart rate as resting HR and exercise HR (beats/min) and, additionally, performed a modified shuttle test pre- and post intervention[59].

Estimates of the effect of exercise interventions on cardiopulmonary function differed across the studies (Table 14).

One three-armed RCT observed an effect for resistance exercise on cardiopulmonary function in men with prostate cancer (MD 1.5; 95%CI 0.06-3.0; p=0.041). The same study did not find an effect for aerobic exercise[57]. One other RCT observed an effect after an aerobic intervention on MET (mean 2.8; SD ± 1.8; p=0.006)[52]. Finally, one RCT observed no effect of exercise on neither resting nor exercise heart rate measures. However, the same study did observe a between-group effect on distance covered in a shuttle-test post-intervention (p=0.0025)[59].

Conclusion

- **Conflicting evidence exists on the effect of exercise treatment on cardiopulmonary function in prostate cancer patients (very low level of evidence; Segal 2009, Windsor 2004, Monga 2007).**

Table 14 – Effect of exercise treatment on cardiopulmonary function in prostate cancer patients

Study	N	Cardiopulmonary function	Measure point	Intervention characteristics
Segal 2009[57]	N=121	Positive effect of the resistance intervention versus usual care at 24-weeks (post-intervention) measured by relative VO_2max: MD 1.5 (95%CI 0.06-3.0), p=0.041 No effect of the aerobic intervention versus usual care (p=0.052)	Baseline Post-intervention(24 weeks)	See Table 13
Windsor 2004[59]	N=66	No effect of exercise on resting heart rate No effect of exercise on exercise heart rate Significant difference between groups in shuttle-test distance at the end of intervention (p=0.0025)*	Baseline Post-intervention (4 weeks)	Home-based, moderate-intensity, continuous walking 3 days weekly for 30 min during radiotherapy. Heart rate 60-70% of maximum heart rate Control group were not discouraged to perform activities but were advised to rest if they became fatigue
Monga 2007[52]	N=21	Effect of exercise on cardiopulmonary function measured by MET (MET=3.5 ml O2·kg−1·min−1) ; MD 2.8 (SD ±1.8), p=0.006	Baseline Post-intervention (8 weeks)	See Table 13

**No significant difference between groups were observed at baseline.*

4.2.3 Fatigue

Four RCTs reported fatigue measures for exercise interventions in prostate cancer patients undergoing adjuvant therapy[46,52,57,59]. Two studies had a moderate risk of bias[46,57] and two studies had a high risk of bias[52,59]. Fatigue measurement scales varied and included FACT-F, Brief Fatigue Inventory (BFI), revised Piper Fatigue Scale (PFS-revised) and QLQ-C30 subscale "fatigue".

Estimates of the effect of exercise on fatigue differed across the studies (Table 15).

One three-armed RCT observed a positive effect for both aerobic exercise (MD 4.64, 95%CI 1.47-7.80, p=0.004) and resistance exercise (mean 4.11, 95%CI 0.87-7.35, p=0 .010) on fatigue in men with prostate cancer, measured by FACT-F after 12 weeks (mid-point)[57]. In the same study only resistance exercise maintained a significant effect after the intervention, at 24 weeks (MD 4.78, 95%CI:1.77-7.78, p=0.002). Two RCTs found a positive effect of exercise treatment on fatigue. In one of these studies the positive effect was measured by QLQ-C30 subscale "fatigue" (p=0.21)[46]. In the other study the effect was measured by Piper Fatigue Scale (MD -4.3, SD ± 2.1, p<0.001)[52]. One RCT found no effect of exercise on fatigue at any measure point (Brief Fatigue Inventory)[59].

Conclusion

- **Conflicting evidence exists on the effect of exercise treatment on fatigue in prostate cancer patients (very low level of evidence; Segal 2009, Windsor 2004, Galvao 2010, Monga 2007).**

Table 15 – Effect of exercise treatment on fatigue in prostate cancer patients

Study	N	Fatigue	Measure point	Intervention characteristics
Segal 2009[57]	N=121	Positive effect of the resistance intervention versus usual care at 12-weeks (midpoint) measured by FACT-F; MD 4.11 (95%CI 0.87-7.35), p=0.010 Positive effect of the resistance intervention versus usual care at 24-weeks (post-intervention) measured by FACT-F; MD 4.78 (95%CI 1.77-7.78), p=0.002 Positive effect of the aerobic intervention versus usual care at 12-weeks (midpoint) measured by FACT-F; MD 4.64, (95%CI 1.47-7.80), p=0.004 No effect of the aerobic intervention versus usual care at 24-weeks (post-intervention)	Baseline 12 weeks (midpoint) 24 weeks (post-intervention)	See Table 13
Windsor 2004[59]	N=66	No effect of exercise on Brief Fatigue Inventory at any measure point	Baseline Post-intervention (week 4) 4 weeks after ended radiotherapy (week 8)	See Table 14
Galvao 2010[46]	N=57*	Positive effect on QLQ-C30 subscale “fatigue”, p=0.21**	Baseline Post-intervention (12 weeks)	See Table 13
Monga 2007[52]	N=21	Positive effect of exercise on Piper Fatigue Scale : MD -4.3 (SD ± 2.1), p<0.001	Baseline Post-intervention (8 weeks)	See Table 13

** 37.9% of exercise group and 39.3% of control group were on radiation before trial. 27.6% of exercise group and 21.4% of control group were on radiation during trial.*
*** Results provided in text only.*

4.2.4 Safety

Adverse events were reported in two of the four RCTs included on prostate cancer patients. One of these RCTs (N=121) reported that three participants experienced adverse events related to exercise; one was deemed serious (i.e. resulting in hospitalization or disability)[57]. One RCT reported that no adverse events had occurred during testing or exercise[46]. The remaining two RCTs did not include reporting of adverse events[52,59]. Relapse was not reported in any of the included studies.

Conclusion

- **Limited evidence exists on the safety of exercise in prostate cancer patients (very low level of evidence; Segal 2009, Galvao 2010).**

4.3 Lung cancer

The evidence on the effects of exercise treatment in lung cancer patients is very limited. Two systematic reviews[10, 23] were identified that included the same single RCT[27]. No additional RCTs were found.

4.3.1 Quality of life

Arbane et al.[27] included 53 patients with non-small cell lung cancer (NSCLC) undergoing lung resection. The exercise intervention consisted of preoperative hospital-based exercise (strength and mobility training) and was continued after discharge in a 12-week home-based program. QOL was measured using the EORTC-QLQ-C30 questionnaire, and was only measured preoperatively and after the 12-week home program. The study had a moderate risk of bias.

There were no significant changes in overall QOL over time (between the preoperative assessment and the assessment after the 12-week home-based program) and no significant differences between the control and intervention group (p-values not provided). Also, for the different components of the questionnaire no significant differences could be found between the two groups (functional component: MD 2.0 [95%CI -5.5 to 9.3] in exercise group vs. 2.7 [95%CI -4.7 to 10.0] in control group; symptom component: MD -2.5 [95%CI -7.8 to 2.9] vs. -3.2 [95%CI -8.3 to 2.1]; global health: MD 6.5 [95%CI -7.7 to 20.7] vs. 2.2 [95%CI -5.2 to 9.6]) and over time.

In the absence of an assessment at discharge it is impossible to distinguish the possible effects of the hospital-based versus the home-based program.

Conclusions

- **A combination of preoperative hospital-based and postoperative home-based exercise does not seem to have an effect on quality of life in patients with lung cancer (low level of evidence; Arbane 2011).**

4.3.2 Cardiopulmonary function

In the same study[27] cardiopulmonary function was expressed by aerobic capacity and measured with the six minute walking test. In both the intervention and control group a significant decline was found at the fifth day postoperatively ($p<0.05$). At 12 weeks postoperatively the control group returned to the preoperative level of aerobic capacity. In the intervention group a slightly (non-significant) increased level of aerobic capacity was found (from 466.6m at baseline to 480.2m at 12 weeks postoperatively).

Conclusions

- **A combination of preoperative hospital-based and postoperative home-based exercise does not seem to have an effect on aerobic capacity in patients with lung cancer (low level of evidence; Arbane 2011).**

4.3.3 Fatigue

Fatigue is one of the subdomains of the EORTC-QLQ-C30, but was not reported separately by Arbane et al.[27].

4.3.4 Safety

Two *a priori* defined postoperative complications (defined as X-ray changes reported by radiologist as pneumonia, respiratory complications requiring additional ventilator support and or necessitating a return to high dependency care) were reported in the active group compared to 3 complications in the control group, but these were not related to the exercise intervention. Relapse was not reported in the study.

Conclusions

- **The evidence suggests that exercise treatment is safe for lung cancer patients (low level of evidence; Arbane 2011).**

4.4 Colorectal cancer

4.4.1 Quality of Life

Only one study was found reporting on the effects of exercise treatment on QOL in colorectal cancer patients. Courneya et al.[32] randomized 102 patients with colorectal cancer to an exercise group (n=69) and a control group (n=33). All patients underwent surgery within the past 3 months and a considerable amount was potentially receiving chemotherapy at inclusion (67.7% in the control group vs. 63.9% in the intervention group). However, it is unclear how many patients actually were on active treatment at baseline. The exercise intervention consisted of a 16-week home-based exercise program with individualized cardiovascular and flexibility exercises. QOL was measured using the FACT-C scale. The study had a high risk of bias.

No differences in QOL were found between both groups at baseline, nor were there differences in change in QOL over time. However, an ancillary analysis comparing a group of participants with an increased treadmill time (measured at baseline and post-intervention to indicate the physical performance status) and a group of participants with an unchanged or decreased treadmill time showed no significant differences at baseline, but a significant difference at post-intervention assessment for FACT-C (p=0.038) and Trial outcome index (p=0.044). These significant differences could indicate an association between change in fitness and change in QOL.

Conclusions

- **The evidence suggests that exercise treatment in colorectal cancer patients has no effect on quality of life (very low level of evidence; Courneya 2003).**

4.4.2 Cardiopulmonary function

Courneya et al.[32] also reported on the effects of exercise treatment on cardiopulmonary function (measured with the Modified Balke Treadmill Test) in colorectal cancer patients. The test consists of walking on the treadmill until 70% of the age-predicted maximum heart rate is reached or until voluntarily indicated by the participant, and is scored by the number of seconds to reach this maximum. No significant difference in resting heart rate was found between the control and intervention group at post-intervention assessment (difference in mean change from baseline: -2.7 bpm [95%CI 3.2 to -8.6], p=0.361).

Conclusions

- **The evidence suggests that exercise treatment in colorectal cancer patients has no effect on cardiopulmonary function (very low level of evidence; Courneya 2003).**

4.4.3 Fatigue

Two RCTs evaluated the effect of exercise treatment on fatigue in colorectal cancer patients (Table 16). Houborg et al.[38] randomized 119 patients with colorectal cancer to an intervention group (n=60) or control group (n=59). All patients were aged at least 60 years and underwent elective abdominal colorectal surgery. The exercise intervention consisted of a mix of aerobic and strength training of upper and lower extremities. Fatigue was measured preoperatively and on day 7, 30 and 90 postoperatively on a visual analogue scale. The study had a low risk of bias.

At baseline already a significant difference in fatigue score between both groups was found (intervention group 3.8 cm [95%CI 2.5-5.1] vs. control group 2.7 cm [95%CI 1.5-4.2], p=0.03). Postoperatively at day 7 the fatigue score of the control group increased 2.3 cm more than the intervention

group (p=0.0007). At day 30 and day 90 no significant differences in change in fatigue were found between both groups.

Courneya et al.[32] assessed fatigue using the 13-item Fatigue Scale of the FACT instrument. They found no significant differences between the intervention and control group at baseline (p=0.579) and at the post-intervention assessment (p=0.810).

Conclusions

- **There are indications that exercise treatment in colorectal cancer patients has no effect on fatigue (low level of evidence; Houborg 2006, Courneya 2003).**

Table 16 – Effect of exercise treatment on fatigue in patients with colorectal cancer

Study	N	Fatigue	Measure point	Intervention characteristics
Houborg 2006[38]	N=119	Visual Analogue Scale Postoperative day 7: more increase in control group (p=0.0007) Postoperative day 30 and 90: no significant differences between groups in change in fatigue score	Pre-operative, post-operative day 7, day 30 and day 90	Control group: stretching and tightening and relaxation exercises (45 min/session) Intervention group: Institution-based + continued at home mix of mobilizations, strength and aerobic training, 45 min/session, load of 50-80% of one repetition maximum 6 times a week (+ filling in diary), once a week the physiotherapist home visit
Courneya 2003[32]	N=102	FACT-C Post-intervention (difference in change from baseline to post-intervention): no significant difference between groups (p=0.810)	At baseline, post-intervention (after 16 weeks)	Control group: asked not to initiate any structured exercise during intervention Intervention group: a home-based, personalized cardiovascular and flexibility exercises (3-5 times per week for 20-30 min, 65-75% of predicted heart rate maximum) + weekly telephone call by project director

4.4.4 Safety

Houborg et al.[38] reported on adverse events, but none of the complications were related to the exercise intervention. Courneya et al. did not report safety data[32]. Relapse was not reported in the included studies.

Conclusions

- **The evidence suggests that exercise treatment is safe for colorectal patients (low level of evidence; Houborg 2006).**

4.5 Haematological cancers

4.5.1 Quality of life

4.5.1.1 Patients undergoing haematopoietic stem cell transplantation

Two RCTs evaluated the effect of exercise treatment on QOL in patients undergoing allogeneic haematopoietic stem cell transplantation (HSCT) (Table 17).

Baumann et al.[28] included 47 patients (mainly with haematological cancers) undergoing allogeneic HSCT (n=17 in exercise group, n=16 in control group). The exercise intervention included strength and endurance training during hospitalization. Next to physical and anthropometric assessments, QOL was measured with the EORTC-QLQ-C30 questionnaire at admission and at discharge. The study had a high risk of bias.

Of the 47 initially randomized patients, 33 patients were able to complete their exercise program until the day of hospital discharge. Seven patients in both groups deceased during hospitalization because of transplant-related complications. QOL increased in the intervention group (63.7 vs. 68.6; change: 7.7%) and decreased in the control group (62.5 vs. 56.3; change: -9.9%) without reaching statistical significance. Physical functioning decreased significantly over time in both groups (exercise group p=0.005 and control group p=0.002). No significant time by group effects were found (no p-value mentioned).

Jarden et al.[39] included 42 patients (mainly with haematological cancers) undergoing allogeneic HSCT (n=21 in intervention group, n=21 in control group). The exercise intervention included a structured and supervised adjuvant multimodal program of physical exercise, progressive relaxation and psycho-education. QOL was also measured with the EORTC-QLQ-C30 questionnaire. The study had a high risk of bias.

No significant difference was found in physical functioning and global health status, nor during hospitalisation (difference between admission and discharge: physical functioning p=0.089, global health status p=0.817), nor at follow-up (3- and 6-months after discharge: physical functioning p=0.325, global health status p=0.841 and physical functioning p=0.131, global health status p=0.603 respectively).

Conclusions

- **In patients undergoing allogeneic haematopoietic stem cell transplantation, exercise treatment does not seem to have a significant effect on overall quality of life and on physical functioning (very low level of evidence; Baumann 2011, Jarden 2009).**

Table 17 – Effect of exercise treatment on quality of life in patients undergoing haematopoietic stem cell transplantation

Study	N	Quality of life	Measure point	Intervention characteristics
Baumann 2011[28]	N=47	Quality of life (EORTC-QLQ-C30): no significant difference over time in exercise group (63.7±19.7 vs. 68.6±11.2, +7.7%) nor in the control group (62.5±23.9 vs. 56.3±17.6, -9.9%) (no p-values mentioned) Physical functioning: a significant decrease over time in the exercise group (83.1±16.9 vs. 65.9±16.5, -20.7%, p=0.005) and in the control group (79.6±19.2 vs. 59.6±22.9, -25.1%, p=0.002)	Baseline (during first 2 days after admission) and day before hospital discharge	Control group: clinic's standard physiotherapy program (active and passive mobilizations with low intensities 20 min/session, 5 days/week, conducted by physiotherapist, start one day after transplantation until day before discharge Intervention group: aerobic endurance training (cycle ergometer, training intensity achieved watt load -20%, 10-20 min) and ADL-training (strength, coordination, stretching, walking and stair climbing, 20-30 min/day), twice a day, conducted by professional therapist, start 6 days prior to transplantation until discharge
Jarden 2009[39]	N=42	Physical functioning (EORTC-QLQ-C30): no significant differences between baseline and discharge (p=0.089), between baseline and 3-months follow-up (p=0.325) and between baseline and 6-months follow-up (p=0.131) FACT-G: no significant difference between baseline and discharge (p=0.298), between baseline and 3-months follow-up (p=0.241) and between baseline and 6-months follow-up (p=0.620) FACT-AN: no significant difference between baseline and discharge (p=0.225), between baseline and 3-months follow-up (p=0.167) and between baseline and 6-months follow-up (p=0.395)	Baseline (first day after admission), post-intervention (at discharge), 3- and 6-months follow-up	Control group: usual care (range of motion, resistance and massage) Intervention group: usual care plus multimodal intervention, consisting of 4 min warm-up, stationary cycling (15-30 min,<75% of max heart rate, 5 days/week), dynamic and stretching exercises (15-20 min, 5 days/week), resistance training (15-20 min, 3 days/week), progressive relaxation (20 min, 2 days/week) and psycho-education

4.5.1.2 Lymphoma patients

Only one study was retrieved on the effects of exercise treatment on QOL of lymphoma patients. Courneya et al.[34] randomized 122 lymphoma patients to an exercise group (n=60) or a control group (n=62). Of all patients, 44.3% were on active chemotherapy. The exercise intervention consisted of aerobic exercise training on a cycle ergometer (intensity began at 60% of peak power output, increased by 5% each week to 75%, 15-20 to 40-45min/session). QOL was measured with the FACT-AN scale. The study had a low risk of bias.

At post-intervention assessment, overall QOL was significantly better in the exercise group (unadjusted group difference in mean change: +9.5, p=0.021; adjusted group difference in mean change: +7.2, p=0.039). Physical functioning, a sub-domain of the FACT-AN scale (TOI-An), also was significantly better in the exercise group at post-intervention (unadjusted group difference in mean change: +9.0, p=0.012; adjusted group difference in mean change: +7.2, p=0.017). In the control group, that received usual care, the scores on overall QOL and physical functioning remained stable over time.

At six months follow-up a trend towards improved QOL in the exercise group was found, but the differences did not reach statistical significance (p=0.121 for physical functioning, p=0.054 for overall QOL).

Conclusions

- **In lymphoma patients, exercise seems to have a significant effect on overall quality of life and physical functioning, although the effect disappears after 6 months (moderate level of evidence; Courneya 2009).**

4.5.2 Cardiopulmonary function

4.5.2.1 Patients undergoing haematopoietic stem cell transplantation

Two RCTs reported on the effect of exercise treatment on cardiopulmonary function in patients undergoing allogeneic HSCT. Both studies had a high risk of bias.

Jarden et al.[39] included 42 patients (mainly with haematological cancers) undergoing allogeneic HSCT (n=21 in intervention group, n=21 in control group). The exercise intervention included a structured and supervised adjuvant multimodal program of physical exercise, progressive relaxation and psycho-education. The effect of exercise treatment on aerobic capacity was measured with the VO_2max. At baseline, i.e. the first day after admission, no significant difference was found between the exercise and the control group (p-value not mentioned). At discharge, the VO_2max decreased in the control group, resulting in a significant difference between both groups (p<0.0001).

Dimeo et al.[35] randomized 70 patients undergoing high-dose chemotherapy and autologous peripheral HSCT to an exercise group (n=33) or a control group (n=37). The exercise intervention included a daily program of aerobic exercise on a bed cycle ergometer. No significant difference in maximal heart rate in the stress test was found between both groups at baseline (p=0.58) and at discharge (p=0.84). This study has a high risk of bias.

Conclusions

- **Conflicting evidence is available on the effect of exercise treatment on cardiopulmonary function in patients undergoing allogeneic haematopoietic stem cell transplantation: a significant improvement in VO_2max, without a difference in maximal heart rate (very low level of evidence; Jarden 2009, Dimeo 1997).**

Table 18 – Effect of exercise treatment on cardiopulmonary function in patients undergoing haematopoietic stem cell transplantation

Study	N	Cardiopulmonary function	Measure point	Intervention characteristics
Jarden 2009[39]	N=42	At baseline: no significant difference in VO_2max between both groups At post-intervention (at discharge): significant difference between groups (p<0.001)	Baseline (first day after admission), post-intervention (at discharge) A single stage 6-min submaximal exercise test (Aastrand-Rhyming cycle ergometer test) to define VO_2max (l/min)	Control group: usual care (range of motion, resistance and massage) Intervention group: usual care plus multimodal intervention, consisting of 4 min warm-up, stationary cycling (15-30 min, <75% of max heart rate, 5 days/week), dynamic and stretching exercises (15-20 min, 5 days/week), resistance training (15-20 min, 3 days/week), progressive relaxation (20 min, 2 days/week) and psycho-education
Dimeo 1997[35]	N=70	Maximal heart rate in stress-test: no significant difference between both groups at admission (p=0.58) and no significant difference at discharge (p=0.84) % of estimated maximal heart rate: no significant difference between both groups at admission (p=0.89) and no significant difference at discharge (p=0.69)	Baseline (before transplantation), at discharge Treadmill stress-test starting at 3 km/h and 1.5% elevation, acceleration of 1 km/h every third minute	Control group: not in detail described Intervention group: daily program of aerobic exercise (biking with bed ergometer), 1 min with heart rate equivalent to 50%, 15 repetitions, total of 30 min per day

4.5.2.2 *Lymphoma patients*

One study evaluated the effect of exercise treatment on cardiopulmonary function in lymphoma patients. Courneya et al.[34] randomized 122 lymphoma patients to an exercise group (n=60) or a control group (n=62). Of all patients, 44.3% were on active chemotherapy. The exercise intervention consisted of aerobic exercise training on a cycle ergometer (intensity began at 60% of peak power output, increased by 5% each week to 75%, 15-20 to 40-45min/session). After the 12-week aerobic exercise program a significant difference was found in VO_2max between both groups (VO_2max, l/min: unadjusted and adjusted group difference in mean change: +0.43, p<0.001; VO_2max, ml/kg/min: unadjusted and adjusted group difference in mean change: +5.2, p<0.001).

Conclusions

- **In lymphoma patients, exercise seems to have a significant effect on cardiopulmonary function measured as VO_2max (moderate level of evidence; Courneya 2009).**

4.5.3 *Fatigue*

4.5.3.1 *Acute myelogenous leukemia*

Chang et al.[30] randomized 22 patients with acute myelogenous leukemia undergoing chemotherapy to a walking exercise program (n=11) or a control group (n=11). Fatigue was measured using the Brief Fatigue Inventory (BFI). The study had a high risk of bias.

Patients in the exercise group had significantly lower levels of average and worst fatigue intensity and fatigue interference at day 7 and day 14: at day 7 average fatigue score mean 4.1 ± 2.3 in exercise group versus mean 5.5 ± 2.4 in control group (p=0.02), worst fatigue score mean 5.6±2.7 in exercise group versus mean 7.5 ± 2.4 in control group (p=0.02) and fatigue interference mean 3.6 ± 2.5 in exercise group versus 4.6 ± 2.2 in control group (p=0.04), at day 14 average fatigue score mean 4.4 ± 2.4 in exercise group versus mean 5.8 ± 3.1 in control group (p=0.01), worst fatigue score mean 5.6 ± 3.1 in exercise group versus mean 7.1 ± 2.7 in control group (p=0.01) and fatigue interference mean 4.3 ± 2.8 in exercise group versus 5.6 ± 2.7 in control group (p=0.04). However, the differences became non-significant at day 21 for average and worst fatigue intensity.: average fatigue score mean 4.6 ± 3.0 in exercise group versus mean 4.8 ± 3.5 in control group (p=0.1), worst fatigue intensity mean 5.7 ± 3.8 in exercise group versus 6.3 ± 3.8 in control group (p=0.05).

Conclusions

- **In patients with acute myelogenous leukemia, exercise treatment seems to have a temporary effect on fatigue (very low level of evidence; Chang 2008).**

4.5.3.2 *Patients undergoing haematopoietic stem cell transplantation*

Three RCTs reported on the effect of exercise treatment on fatigue in patients undergoing allogeneic HSCT. All three studies had a high risk of bias.

Baumann et al.[28] included 47 patients (mainly with haematological cancers) undergoing allogeneic HSCT (n=17 in exercise group, n=16 in control group). The exercise intervention included strength and endurance training during hospitalization. QOL was measured with the EORTC-QLQ-C30 questionnaire at admission and at discharge. One of the sub-domains of the EORTC-QLQ-C30 is the patient's perception on his fatigue. In the exercise group no significant differences over time were found (no p-value mentioned) in contrast to the control group, where a significant increase was noticed (p=0.046). No significant time by group effects were found (no p-value mentioned).

Jarden et al.[39] included 42 patients (mainly with haematological cancers) undergoing allogeneic HSCT (n=21 in intervention group, n=21 in control group). The exercise intervention included a structured and supervised adjuvant multimodal program of physical exercise, progressive relaxation and psycho-education. They also found no significant difference in fatigue scores (EORTC-QCQ-C30), FACT-G scores and FACT-AN scores between the control and exercise group.

Coleman et al.[31] randomized 24 patients with multiple myeloma receiving tandem transplantation (chemotherapy, stem cell collection, high-dose melphalan and peripheral blood stem cell transplantation) to exercise treatment (n=14) or usual care (n=10). The exercise intervention consisted of a home-based exercise program with resistance and aerobic exercises.

Fatigue was measured with the Profile of Mood States (POMS) fatigue-inertia adjective rating scale. For the evaluation of the effect of exercise treatment on fatigue, 14 patients receiving thalidomide were excluded from the analysis because of its effect on sleep. The exercise group showed a decrease in fatigue (-1.2), whereas the usual care group did not (+0.3). However, no p-values were provided.

Conclusions

- **Conflicting evidence is available on the effect of exercise treatment on fatigue in patients undergoing allogeneic haematopoietic stem cell transplantation (very low level of evidence; Baumann 2011, Jarden 2009, Coleman 2003).**

Table 19 – Effect of exercise treatment on fatigue in patients undergoing haematopoietic stem cell transplantation

Study	N	Fatigue	Measure point	Intervention characteristics
Baumann 2011[28]	N=47	EORTC-QLQ-C30 Exercise group: no significant difference over time (41.8 ± 25.3 vs. 43.8 ± 22.7, +4.8%, no p-value mentioned) Control group: significant increase over time (36.1 ± 24.5 vs. 52.8 ± 27.1, +46.3%, p=0.046)	Baseline (during first 2 days after admission) and day before hospital discharge	Control group: clinic's standard physiotherapy program, (active and passive mobilizations with low intensities), 20 min/session, 5 days per week, conducted by physiotherapist, start one day after transplantation until day before discharge Intervention group: aerobic endurance training (cycle ergometer, training intensity achieved watt load -20%, 10-20 min without interruption) and ADL-training (strength, coordination, stretching, walking and stair climbing, 20-30 min/day), twice a day, conducted by professional therapist, start 6 days prior to transplantation until discharge
Jarden 2009[39]	N=42	Fatigue (EORTC-QLQ-C30): no significant differences between baseline and discharge (p=0.405), between baseline and 3-months follow-up (p=0.302) and between baseline and 6-months follow-up (p=0.097) FACT-G: no significant	Baseline (first day after admission), post-intervention (at discharge), 3- and 6-months follow-up	Control group: usual care (range of motion, resistance and massage) Intervention group: usual care plus multimodal intervention, consisting of 4 min warm-up, stationary cycling (15-30 min,<75% of max heart rate, 5 days/week), dynamic and stretching exercises (15-20 min, 5 days/week), resistance training (15-20 min, 3 days/week), progressive relaxation (20 min, 2 days/week) and psycho-education

Study	N	Fatigue	Measure point	Intervention characteristics
		difference between baseline and discharge (p=0.298), between baseline and 3-months follow-up (p=0.241) and between baseline and 6-months follow-up (p=0.620) FACT-AN: no significant difference between baseline and discharge (p=0.225), between baseline and 3-months follow-up (p=0.167) and between baseline and 6-months follow-up (p=0.395)		
Coleman 2003[31]	N=24	Decrease in fatigue in exercise group, not in control group (no p-values mentioned)	Baseline (app. 3 months before transplantation), after transplantation, 3 months after transplantation POMS	Individualized home-based exercise program combining strength resistance training and an aerobic component Control group: usual care (remain active and walk 20 min at least 3 times a week) Weekly phone calls for both groups + weekly activity log

4.5.3.3 Lymphoma patients

One study evaluated the effect of exercise treatment on fatigue in lymphoma patients. Courneya et al.[34] randomized 122 lymphoma patients to an exercise group (n=60) or a control group (n=62). Of all patients, 44.3% were on active chemotherapy. The exercise intervention consisted of aerobic exercise training on a cycle ergometer (intensity began at 60% of peak power output, increased by 5% each week to 75%, 15-20 to 40-45min/session). Fatigue was measured using a sub-domain of the FACT-AN scale. At post-intervention assessment, fatigue was significantly better in the exercise group (unadjusted group difference in mean change: +4.6, p=0.013; adjusted group difference in mean change: +4.0, p=0.012).

Conclusions

- **In lymphoma patients, exercise seems to have a significant effect on fatigue (moderate level of evidence; Courneya 2009).**

4.5.4 Safety

In the study of Courneya et al.[34] no serious adverse events were reported, but three adverse events (back, hip and knee pain) related to exercise lead to a modification of the exercise program in two patients, while one patient (with knee pain) withdrew from the study. Dimeo et al.[35] reported the complications related to the toxicity of high-dosis chemotherapy without differentiating the adverse events related to the exercise treatment. The severity of pain was for patients in exercise group lower than in control

group (p=0.01). The other studies including patients with haematological cancers did not report on adverse events.

Conclusions

- **Exercise treatment seems to be save in patients with haematological cancers, although many trials omit to report on adverse events (low level of evidence; Courneya 2009).**

4.6 Mixed cancer populations

Seven additional RCTs were included reporting on the effects of exercise treatment in mixed cancer populations.

4.6.1 Quality of life

Four RCTs reported on the effect of exercise treatment on QOL. Two studies had a low risk of bias[26,40], while one study had a moderate risk of bias[33] and the fourth study had a high risk of bias[41]. QOL measurement scales varied and included Spitzer QOL Uniscale, Linear Analogue Scales of Assessment (LASA), EORTC-QLQ-C30, MOS SF-36, FACIT-F and FACT-AN scale, with some studies using more than one scale.

Estimates of the effect of institution-based exercise on quality of life and on physical subscales of QOL differed widely across the studies (Table 20).

A structured intervention (n=49 in intervention group and n=54 in control group), consisting of conditioning exercises with educational instruction on several domains of QOL (cognitive, physical, emotional, spiritual and social functioning), resulted in an overall lack of difference in overall QOL score between both groups[41]. Only at week 4 a significant difference is found between both groups (p=0.469) but this difference disappeared at week 8 (p=0.4229)and at week 27 (p=0.9922). This study had a high risk of bias.

Adamsen et al.[26] randomized 269 patients with cancer (including 119 women with breast cancer) to exercise treatment (n=135) or conventional care (n=134). All patients had received at least one cycle of chemotherapy for advanced disease or as adjuvant treatment, and were still receiving active treatment. The exercise intervention consisted of a 6-week exercise program, combining high and low intensity exercises. No significant effect on QOL (measured by EORTC-QLQ-C30) was found for exercise compared with the control group (p=0.4). Physical functioning was assessed with two different instruments, i.e. the EORTC-QLQ-C30 and the MOS SF-36. For the EORTC-QLQ-C30 scale, no significant difference over time between groups was found (p=0.09), whereas the MOS SF-36 showed a significant increase in physical functioning with exercise (p=0.01).

Slightly different results were reported by Mustian et al.[40], who randomized 38 cancer patients to exercise treatment (n=19) or a control group (n=19). The exercise intervention consisted of a walking and resistance band program during 4 weeks. Only small improvements in QOL, measured with the FACIT-F, were found in the exercise group at post-intervention (Cohen's d=0.26) and at 3-months follow-up (Cohen's d=0.41) compared with a small decline in the control group at post-intervention (Cohen's d=-0.02) and a small improvement at 3-months follow-up (Cohen's d=0.28). However, the intervention group showed a significantly better QOL at post-intervention and at 3-months follow-up compared with the control group (both p<0.05).

Courneya et al.[33] randomized 55 mild-to-moderately anaemic patients with solid tumours to darbepoetin alfa alone (n=29) or combined with a 12-week aerobic exercise training (n=26). The mean change in QOL scores, measured with the FACT-AN scale, did not differ significantly between both groups (p=0.363 for unadjusted group differences and p=0.637 for adjusted group differences). However, a significant improvement in QOL for each group separately was found (+20.3 for darbepoetin alfa alone vs. +13.4 in the exercise group, no p-values mentioned in the primary study). Stratification for some baseline characteristics, such as baseline value of the outcome, age, sex, marital status, education, primary tumour type, metastatic disease, current chemotherapy and prior blood transfusion, did not alter the findings.

Conclusions

- **Conflicting evidence is available on the effect of exercise treatment on quality of life in mixed cancer populations (very low level of evidence; Adamsen 2009, Mustian 2009, Courneya 2008, Rummans 2006).**

Table 20 – Effect of exercise treatment on quality of life in mixed cancer populations

Study	N	Quality of Life	Measure point	Intervention characteristics
Rummans 2006[41]	N=103	Baseline: no significant difference between both groups (p=0.4829) At week 4: a significant difference between both groups (p=0.469) At week 8: no significant difference between both groups (p=0.4229) At week 27: no significant difference between both groups (p=0.9922)	Baseline, week 4, 8, 27 Spitzer QOL Uniscale Linear Analogue Scales of Assessment (LASA) of QOL Assessment scores were converted to a 0-100 scale	Control group: usual care Intervention group: eight 90 min-sessions on ambulatory basis, completed within 4 weeks after enrollment, led by psychiatrist or psychologist co facilitated by nurse, physical therapist, chaplain or social worker, 20 min conditioning exercises, educational instruction and 20 min relaxation exercises
Adamsen 2009[26]	N=269	Global health status (EORTC-QLQ-C30): no significant differences over time between both groups (estimated mean difference 2.2, 95%CI -2.7 to 7.1, p=0.4) Physical functioning (EORTC-QLQ-C30): no significant differences over time between both groups (estimated mean difference 2.4, 95%CI -0.4 to 5.1, p=0.09) Physical functioning (MOS SF-36): significant differences over time between both groups (estimated mean difference 4.4, 95%CI 1.1 to 7.7, p=0.01)	Baseline and after intervention (6 weeks) EORTC-QLQ-C30, subdomain global health status/quality of life and physical functioning MOS SF-36: subdomain physical functioning	Control group: allowed freely to increase physical activity + exercise program after the six week assessment Intervention group: 6-week (9 h/week) high intensity physical training (30 min dynamic exercises at 4.5 MET hours, 45 min resistance training at 70-100% of one repetition maximum test at 4 MET hours per training session, 15 min cardiovascular training (stationary bicycles, 70-250W, 85-95% maximum heart rate at 3.75 MET hours) for 90 min followed by 30 min relaxation training + 2 times per week massage. Low intensity sessions: relaxation (30 min, 4 times per week, body awareness and restorative training (90 min once a week), massage (30 min twice a week)

Mustian 2009[40]	N=38	Exercise group: small improvements between baseline and post-intervention (Cohen's d=0.26) and continued modest improvements from baseline to 3-months follow-up (Cohen's d=0.41) Control group: small decrease between baseline and post-intervention (Cohen's d=-0.02) but small improvements between baseline and 3-months follow-up (Cohen's d=0.28) Significant higher QOL in exercise group, compared to control group, at post-intervention and at 3-months follow-up (all p<0.05)	Baseline, after intervention (4weeks) and at 3-months follow-up FACIT-F	Control group: conventional medical care (radiation therapy) Intervention group: radiation therapy + individually tailored home-based, progressive walking (60-70% of heart rate, 7 days a week for 4 weeks) and therapeutic resistance band program (moderately intense progressive resistance exercise, 7 days a week for 4 weeks, focused on upper body)
Courneya, 2008[33]	N=55	No significant differences between groups (p=0.363 for unadjusted group differences, p=0.637 for adjusted group differences) Both groups improved QOL over time	Baseline (within 10 days prior to starting darbepoetin alfa) and at post-intervention (1-2 weeks after the 12-week exercise program) FACT-AN scale	Control group: asked not to initiate a structured exercise program during intervention period Intervention group: aerobic exercise training (cycle ergometry sessions) 3 times per week at 60-100% of baseline exercise capacity, for 12 weeks on ambulatory basis

4.6.2 Cardiopulmonary function

Five studies reported on the effect of exercise treatment on cardiopulmonary function in mixed cancer populations. Three studies reported changes in VO_2max[26,33,37], while 2 studies evaluated cardiopulmonary function with a walking test[40,42]. Two studies had a low risk of bias[26,40], while 3 studies had either a moderate[33] or high risk of bias[37,42].

Estimates of the effect of exercise interventions on cardiopulmonary function differed across the studies (Table 21).

Griffith et al. [37] randomized 126 patients undergoing active treatment with chemotherapy and/or radiotherapy for solid tumours to exercise treatment (n=68) or usual care (n=58). The exercise intervention consisted of a home-based walking intervention.

No significant difference in change over time between both groups could be found for the VO_2max. Surprisingly, the authors found a 2.9% decrease in post-pre change in the exercise group vs. a 5.6% increase in the control group. Sub-analysis according to cancer type showed a significant difference between prostate cancer patients and non-prostate cancer patients, with a nearly 8% increase in VO_2max in prostate cancer patients vs. a > 9% decrease in VO_2max in non-prostate cancer patients (p=0.008). This difference was explained by the authors by the more easily tolerated treatment of prostate cancer patients (radiotherapy in combination with androgen deprivation therapy) in contrast to chemotherapy (with or without radiotherapy).

Adamsen et al.[26] randomized 269 patients with cancer (including 119 women with breast cancer) to exercise treatment (n=135) or conventional care (n=134). All patients had received at least one cycle of chemotherapy for advanced disease or as adjuvant treatment, and were still receiving active treatment. The exercise intervention consisted of a 6-week exercise program, combining high and low intensity exercises. A significant mean difference over time in VO_2max was found between the intervention and control group (p<0.0001). The VO_2max remained stable in the control group (at baseline mean VO_2max of 1.90 l/min and after 6weeks mean VO_2max of 1.88l/min), whereas it increased in the intervention group (at baseline mean VO_2max of 1.82l/min and after 6 weeks mean VO_2max of 1.96l/min).

The more clear differences in effect can be explained by the different components of the exercise intervention (combination of high and low intensities trainings).

Courneya et al.[33] randomized 55 mild-to-moderately anaemic patients with solid tumours to darbepoetin alfa alone (n=29) or combined with a 12-week aerobic exercise training (n=26). They found a significant difference in VO_2max (expressed as ml/kg/min and l/min, unadjusted group differences in mean change +3.0 (95%CI 1.2-4.7) and +0.21 (95%CI 0.08-0.34) respectively, both p=0.001) between both groups. After adjusting for covariates, the mean change over time in VO_2max between groups remained significantly different (expressed as ml/kg/min and l/min, adjusted group differences in mean change +3.0 (95%CI 1.1-5.0) (p=0.003) and +0.22 (95%CI 0.08-0.37) (p=0.004) respectively) .

Mustian et al.[40] evaluated the effect of exercise treatment on aerobic capacity, assessed with the 6-minute walking test, in a mixed population of breast and prostate cancer patients during radiation therapy. At post-intervention the exercise group showed small improvements in aerobic capacity (difference between baseline and post-intervention: + 43.58 ±227.84 ft, Cohen's d=0.16), whereas the control group showed a decline of the aerobic capacity (difference between baseline and post-intervention: -28.44 ±303.75 ft, Cohen's d=-0.13). At 3 months follow-up the improvement in the exercise group continued, but was not significantly different from baseline anymore (Cohen's d=0.37). In the control group a non-significant increase in aerobic capacity was found compared with baseline (Cohen's d=0.28).

Schwartz et al.[42] compared the effects of an aerobic versus a strength exercise program and versus usual care in a mixed sample consisting of breast cancer, prostate cancer and lymphoma patients. The aerobic capacity, measured with the 12-minute walking test, significantly improved at 6 and 12 months in both exercise groups compared to the control group (both p<0.05): at 6 months in aerobic exercise group mean 1219.2 m (SD178), in resistance exercise group mean 1174.7 m (SD 191), in control group mean 911.1 m (SD 194), at 12 months in aerobic exercise group mean 1201 m (SD183), in resistance exercise group mean 1144 m (SD 185), in control group mean 983m (SD 193). The aerobic exercise group showed the highest improvement (16%) in aerobic capacity, followed by the resistance exercise group (11%). The control group showed a decline in aerobic capacity of 12% at 6 months, but at 12 months the decline decreased to 5% from baseline value.

Conclusions

- **Conflicting evidence is available on the effect of exercise treatment on cardiopulmonary function in mixed cancer populations (very low level of evidence; Griffith 2009, Adamsen 2009, Courneya 2008, Mustian 2009, Schwartz 2009).**

Table 21 – Effect of exercise treatment on cardiopulmonary function in mixed cancer populations

Study	N	Cardiopulmonary function	Measure point	Intervention characteristics
Griffith 2009[37]	N=126	ITT-analysis: no significant difference in change (-8.4%) between both groups (p=0.26) with a 2.9% decrease in pre-post change in exercise group and 5.6% increase in control group Dose-response analysis: significant difference in% change pre-post between prostate and non prostate patients (p=0.008, 17.45%)	Baseline (before start chemotherapy/radiotherapy), post-test (after completion of cancer treatment) Peak oxygen uptake (VO_2max) directly measured by treadmill testing (modified Balke Protocol, increase by 2.5% grade each 3 min) or estimated from the 12-min walk test	Control group: biweekly phone calls by study nurse + patients were encouraged to maintain their current level of activity Intervention group: home-based walking intervention, 50-70% of maximum heart rate, brisk 20-30 min walk followed by 5 min slower walking (cool down), 5 times per week + biweekly telephone call by study nurse
Adamsen 2009[26]	N=269	Significant mean difference between both groups (0.16l:min, 95%CI 0.1-0.2, p<0.0001): no difference over time in control group, increase over time in intervention group	Baseline and after intervention (6weeks) Peak oxygen uptake (VO_2max) indirectely estimated by use of stepwise work capacity on stationary exercise cycle (started with workload of 67W over 8 min, increased by 20W with each consecutive min)	Control group: allowed freely to increase physical activity + exercise program after the six week assessment Intervention group: 6-week (9 h/week) high intensity physical training (30 min dynamic exercises at 4.5 MET hours, 45 min resistance training at 70-100% of one repetition maximum test at 4 MET hours per training session, 15 min cardiovascular training (stationary bicycles, 70-250W, 85-95% maximum heart rate at 3.75 MET hours) for 90min followed by 30 min relaxation training + 2 times per week massage. Low intensity sessions: relaxation (30 min, 4 times per week, body awareness and restorative training (90 min once a week), massage (30 min twice a week)
Courneya 2008[33]	N=55	Significant difference in mean change in VO_2max (ml/kg/min) over time between groups (unadjusted group differences p=0.001, adjusted group differences p=0.003) Significant difference in mean change in VO_2max (l/min) over time between groups	Baseline (within 10days prior to starting darbepoetin alfa) and at post-intervention (1-2weeks after the 12-week exercise program) VO_2max on electronically braked cycle ergometer with breath-by-breath expired gas analysis on a	Control group: asked not to initiate a structured exercise program during intervention period Intervention group: aerobic exercise training (cycle ergometry sessions) 3 times per week at 60-100% of baseline exercise capacity, for 12 weeks, on ambulatory basis

Study	N	Cardiopulmonary function	Measure point	Intervention characteristics
		(unadjusted group differences p=0.001, adjusted group differences p=0.004)	calibrated metabolic measurement system, workloads increased 5-20 watts/minute until exhaustion	
Mustian, 2009[40]	N=38	Control group: at baseline 1478.21 ± 401.02, post-intervention 1 425.28 ± 438.27, at 3months follow-up 1 600.33 ± 468.86. Mean change of -28.44 ± 303.75 between baseline and post-intervention, mean change of 78.73 ± 484.12 between post-intervention and follow-up Exercise group: 1894.37 ± 296.78, post-intervention 1937.95 ± 261.99, at 3 months follow-up 2020.59 ± 386.36. Mean change of 43.58 ± 227.84 between baseline and post-intervention, mean change of 133.53 ± 396.79 between post-intervention and follow-up	At baseline, post-intervention and at 3-months follow-up Aerobic capacity measured with 6-min walk test	Control group: instructed not to initiated any new physical exercise program Intervention group: home-based aerobic and progressive resistance exercise program consisting of walking prescription at 60-70% of heart rate reserve and therapeutic resistance ban exercise prescription
Schwartz, 2009[42]	N=101	Aerobic exercise group: at baseline 1017.3 ± 210, at 6-months 1219.2 ± 178, at 12 months 1201 ± 183 Resistance exercise group: at baseline 1021.7 ± 186, at 6-months 1174.7 ± 191, at 12 months 1144 ± 185 Aerobic exercise group: at baseline 1035.4 ± 200, at 6-months 911.1 ± 194, at 12 months 983 ± 193	At baseline, 6 months and 12 months Aerobic capacity measured with 12-minute walk test (m)	Control group: usual care Aerobic exercise group: weight-bearing aerobic activities at moderate intensities Resistance exercise group: specific exercises with thera-bands of weight equipment

4.6.3 Fatigue

Five studies reported on the effect of exercise treatment on fatigue in mixed cancer populations[26,29,33,36,40]. Two studies had a low risk of bias[26,40], while 3 studies had either a moderate[33,36] or high risk of bias[29].

Estimates of the effect of exercise interventions on fatigue differed across the studies (Table 22).

Brown et al.[29] compared an 8-session structured multidisciplinary intervention (n=49) with usual care (n=54) in newly diagnosed cancer patients receiving radiotherapy. The multidisciplinary intervention started with 20 minutes of exercise (consisting of seated range of motion exercises of upper and lower extremities progressing to resistive exercises with elastic band, stretching exercises, functional lower extremity exercises to increase endurance, relaxation exercises and a individualized home program), followed by educational information, cognitive-behavioural strategies, discussion and support. Fatigue was measured at baseline, after the intervention (week 4) and at follow-up (week 8 and 27) using POMS Fatigue-Inertia subscale, SDS Fatigue, LASA. No significant difference was found between the exercise and control group. Importantly, in the analysis no difference was made between the effects of the different components of the intervention.

Dodd et al.[36] randomized 119 women with breast, colorectal or ovarian cancer beginning their first chemotherapy treatment to individualized exercise during and after chemotherapy (n=44), after having completed chemotherapy (n=36) or usual care (n=39). The exercise intervention consisted of an individualized home-based exercise program (with weekly phone calls). Fatigue was measured using Piper Fatigue Scale. No significant difference in fatigue scores was found (p=0.084).

Adamsen et al.[26] randomized 269 patients with cancer (including 119 women with breast cancer) to exercise treatment (n=135) or conventional care (n=134). All patients had received at least one cycle of chemotherapy for advanced disease or as adjuvant treatment, and were still receiving active treatment. The exercise intervention consisted of a 6-week exercise program, combining high and low intensity exercises. Fatigue was measured using fatigue subscale of the EORTC QLQ-C30 A significant difference in fatigue over time was found between the intervention and control group (p=0.02) (estimated MD -6.6, 95%CI -12.3 to -0.9) after 6 weeks.

Mustian et al.[40] evaluated the effect of exercise treatment on fatigue in a mixed population of breast and prostate cancer patients during radiation therapy. The exercise intervention consisted of a combined walking and resistance training. Fatigue was measured with two different scales, i.e. BFI and FACIT-G. Both scales showed an improvement in fatigue level in the exercise group.

Courneya et al.[33] randomized 55 mild-to-moderately anaemic patients with solid tumours to darbepoetin alfa alone (n=29) or combined with a 12-week aerobic exercise training (n=26). Fatigue was measured using FACT-AN scale. No significant differences were found between both groups (p=0.694 for unadjusted group differences, p=0.388 for adjusted group differences), but an improvement over time was noticed (mean change from baseline +9.1 for darbepoetin alfa alone vs. +7.8 for the exercise group).

Conclusions

- **Conflicting evidence is available on the effect of exercise treatment on fatigue in mixed cancer populations (very low level of evidence; Brown 2006, Dodd 2010, Adamsen 2009, Mustian 2009, Courneya 2008).**

Table 22 – Effect of exercise treatment on fatigue in mixed cancer populations

Study	N	Fatigue	Measure point	Intervention characteristics
Brown 2006[29]	N=103	At baseline: no significant difference between groups, except for POMS vigor activity (p=0.0445) At week 4: overall higher fatigue QOL-scores (p=0.047) in exercise group, but overall no significant difference between both groups at any week (p-values not mentioned) At week 8: no significant differences, but trend towards better fatigue-score in control group (POMS Fatigue-inertia p=0.065 and SDS Fatigue p=0.098)	Baseline (before radiotherapy), week 4, week 8, week 27 POMS (profile of mood states) fatigue-inertia POMS (profile of mood states) vigor-activity SDS (symptom distress scale) Fatigue LASA (linear analogue self assessment) average level of fatigue STAI (spielberger's state-trait anxiety inventory) I feel rested (only assessed at baseline) Each score was transformed to a 0-100 point scale, a 10 point difference is considered as clinically significant	Control group: standard medical care (not further described) Intervention group: eight 90-min sessions over 4 weeks on ambulatory basis, seated range of motion exercises of upper and lower extremities progressing to resistive exercises with elastic band, stretching exercises, functional lower extremity exercises to increase endurance, relaxation exercises and a individualized home program
Dodd 2010[36]	N=119	No significant group differences in the changing scores over time (p=0.084)	Baseline: week before second chemotherapy, T2: end of cancer treatment (4-6 months after baseline), T3: end of study (approximately 1 year after baseline) Piper Fatigue Scale	Control group: usual care (no exercise prescription) + weekly phone calls by research nurse Intervention group: exercise prescription with weekly phone calls from exercise trainers, consisting of individualized cardiovascular/aerobic exercises, 3-5 times per week, heart rate at 60-80% VO_2max, 20-30 min of continuous exercises

Study	N	Fatigue	Measure point	Intervention characteristics
Adamsen 2009[26]	N=269	Significant difference over time between groups (estimated mean difference -6.6, 95%CI -12.3 to -0.9, p=0.02)	Baseline and after intervention (6 weeks) EORTC-QLQ-C30, subdomain fatigue	Control group: allowed freely to increase physical activity + exercise program after the six week assessment Intervention group: 6-week (9 h/week) high intensity physical training (30 min dynamic exercises at 4.5 MET hours, 45 min resistance training at 70-100% of one repetition maximum test at 4 MET hours per training session, 15 min cardiovascular training (stationary bicycles, 70-250W, 85-95% maximum heart rate at 3.75 MET hours) for 90 min followed by 30 min relaxation training + 2 times per week massage. Low intensity sessions: relaxation (30 min, 4 times per week, body awareness and restorative training (90 min once a week), massage (30 min twice a week)
Mustian 2009[40]	N=38	Exercise group (BFI): small improvements between baseline and post-intervention (Cohen's d=-0.15) and continued modest improvements from baseline to 3-months follow-up (Cohen's d=-0.58) Control group (BFI): smaller improvement between baseline and post-intervention (Cohen's d=-0.08) but worsened between baseline and 3-months follow-up (Cohen's d=0.04) Non-significant lower fatigue in exercise group, compared to control group, at post-intervention (p=0.07) but significant at 3-months follow-up (p<0.05) (BFI) Exercise group (FACIT-F): small improvements between baseline and post-intervention (Cohen's d=0.29) and continued modest improvements from baseline to 3-months follow-up (Cohen's	Baseline, after intervention (4 weeks) and at 3-months follow-up FACIT-F BFI	Control group: conventional medical care (radiation therapy) Intervention group: radiation therapy+ individually tailored home-based, progressive walking (60-70% of heart rate, 7 days a week for 4 weeks) and therapeutic resistance band program (moderately intense progressive resistance exercise, 7 days a week for 4 weeks, focused on upper body)

Study	N	Fatigue	Measure point	Intervention characteristics
		d=0.45) Control group (FACIT-F): a decline between baseline and post-intervention (Cohen's d=-0.09) but improved between baseline and 3-months follow-up (Cohen's d=0.29) Significant lower fatigue in exercise group, compared to control group, at post-intervention and at 3-months follow-up (p<0.05) (FACIT-F)		
Courneya 2008[33]	N=55	No significant differences between groups (p=0.694 in unadjusted group differences, p=0.388 for adjusted group differences) Both groups improved fatigue over time	Baseline (within 10days prior to starting darbepoetin alfa) and at post-intervention (1-2 weeks after the 12-week exercise program) FACT-AN scale	Control group: asked not to initiate a structured exercise program during intervention periodIntervention group: aerobic exercise training (cycle ergometry sessions) 3 times per week at 60-100% of baseline exercise capacity, for 12 weeks

4.6.4 Safety

No adverse events related to the exercise intervention were reported.

Conclusions

- **No evidence is available.**

5 DISCUSSION

This report provides an overview of studies that evaluated a range of physical exercise interventions involving cancer patients during active treatment with chemotherapy and/or radiation. A total of 33 RCTs were identified, with studies on breast cancer patients being most common. For outcomes of effectiveness, including quality of life, cardiopulmonary function and fatigue, there was no clear or consistent evidence on the benefits of exercise, with trials often reporting conflicting results. This was true for most cancer types with the exception of the study performed on lymphoma patients that reported significantly positive results on all included outcomes without the reporting of adverse events. It is not clear why the exercise intervention in this cancer type produced such a positive effect, since the patients in the study did not differ from other study populations in terms of age or treatment type.

On the contrary, we found no consistent evidence that exercise hampered quality of life or cardiopulmonary function, or increased fatigue symptoms. Furthermore, there was some evidence that exercise is safe during adjuvant therapy for cancer patients, although not all trials reported on exercise-related adverse events. Importantly, our conclusions need to be interpreted with caution due to the low number of RCTs included for most cancer types, heterogeneity between studies and methodological limitations.

In systematic reviews and guidelines, evidence-based conclusions depend on the quality of the supporting evidence. Of the 33 studies assessed for this report, only very few trials had a low risk of bias (4 studies), while the remaining had an either moderate (11 studies) or high risk (18 studies). A decision was made from the start of the project to include RCTs only. However, an adequate method of allocation concealment was described in a very limited number of the trials. Inadequate methods of generating and concealing allocation sequences are prone to selection bias and associated with overestimations of the intervention effect[54]. In behavioural interventions, including exercise, it is not possible to perform double-blinding. The option of blinding the assessment of outcome measures was commonly lacking in the study designs. Consequently, there is an increased risk of biased assessment and inflated treatment effect.

A number of studies failed to analyze data on an intention-to treat principle thus failed to take advantage of randomization and risking the possibility that efficacy estimates become too high. Additionally, a large threat to the validity of the studies are the relatively small sample sizes that were often not based on power calculations.

Due to major differences in disease- and treatment-related factors and patient demographics it was decided to only treat studies on patients receiving active cancer treatment and to synthesize studies per cancer type. A generalization of the results (including the reporting of uptake or adherence) and conclusions might still not be appropriate due to population differences in cancer stage and treatment regimes. The populations selected for the trials were often recruited on a voluntary basis and/or carefully screened before participation. Above this, the choice to only include RCTs has led to a selective reporting on the effects of exercise treatment for those cancer types for which RCTs are available. For other cancer types, evidence from observational studies might be available, but this type of evidence was not taken into account in our conclusions.

The large variety of exercise interventions with respect to intensity, mode, frequency and duration made a comparison of study interventions somewhat elusive. An attempt to compare institution-based with home-based interventions and aerobic exercise with resistance exercise was only possible for breast cancer and did not produce consistent results. Therefore, it is impossible to recommend in favour of a particular intervention. To allow for the development of more cancer-specific recommendations new studies should focus on optimal exercise modalities that take cancer type, stage and treatment side-effects into account.

Exercise studies often assess multiple outcome measures. In collaboration with Belgian exercise and cancer specialists a list of four key outcomes was defined for cancer patients in the acute phase, i.e. quality of life, cardiopulmonary function, fatigue and safety. There is some evidence that patients undergoing adjuvant treatment for cancer can perform several types of exercise without the risk of major adverse events. For other outcomes it was not possible to elucidate consistent results on the benefits of exercise, i.e. studies had conflicting results within the various cancer types on all remaining outcomes.

The large variety in outcome measure points across studies further hampered our ability to compare treatment effects.

There were a broad selection of outcome scales used to measure the same outcome. When studies deployed more than one scale for the same outcome conflicting results were often reported. It was consequently difficult to assess whether the effect measure was due to the intervention, or a result of difference in sensitivity among the large variety of measure scales. Within the subjective outcome measures, including quality of life, there seem to be a lack of agreement on whether to use a generic and/or a disease-specific instrument. It can be assumed that health professionals and patients first and foremost are interested in the dimensions of life that are affected by a disease. However, by only assessing quality of life by a disease-specific instrument there is a risk that important domains are overlooked. Preferably, studies should measure quality of life by both a disease-specific and a generic instrument. Our primary objective outcome measure, cardiopulmonary function, was measured in a variety of ways in the included studies. A decision was made to include measures of heart rate, timed walking tests and VO_2max measures, with the awareness that a direct comparison of these measures might not be appropriate.

The literature search did not identify many guidelines on exercise treatment for cancer patients in the acute phase that were based on a systematic review. A consensus guideline of the American College of Sports Medicine appears to be widely accepted[63], but was subjected to important bias and therefore not included in our evidence review. The expert panel, which involved many authors of the RCTs included in the present report, focused on RCTs with positive results and ended up with very positive conclusions and recommendations about exercise treatment for cancer patients. The Comprehensive Cancer Centre The Netherlands (IKNL) recently published evidence-based guidelines on oncological rehabilitation[64]. Part of this guideline was published as a systematic review and was identified through our search[1]. In general, the same evidence was found as for the present report, but more positive conclusions were drawn. A potential explanation is that the conclusions of the present report exclusively are based on a critical appraisal at the level of the primary study, enabling a more in-depth analysis and criticism. The Dutch guideline refers to systematic reviews and meta-analyses that included studies on cancer patients both in the acute and post-acute treatment phase[9,25].

Combination of these trials in a meta-analysis, partly because of the heterogeneity of the used outcome scales, was considered inappropriate for these guidelines. Nevertheless, the Dutch recommendations are much in line with ours (see Chapter 6).

According to the consulted experts, most Belgian oncological rehabilitation programs focus on the (post-acute) rehabilitation period. This was not the scope of the present report, as it was intended to be a supportive document for the cancer guidelines that are developed by the KCE in collaboration with the College of Oncology, guidelines that mainly focus on the acute phase encompassing diagnosis, staging and treatment of specific cancer types. Nevertheless, a separate report focusing on the rehabilitation period after cancer treatment continues to be relevant. In fact, a controlled trial is being set up by Belgian rehabilitation specialists to evaluate the effectiveness of multimodality treatment (including exercise treatment and psychological support) after the treatment for breast cancer.

Finally, it should be stressed that physical activity has beneficial effects on health in general, regardless of the health status of a person. Numerous trials and meta-analysis showed a positive effect of physical activity on mortality and the risk of cardiovascular disease[65, 66].

6 RECOMMENDATIONS

6.1 Clinical recommendations

- In the absence of consistent evidence on the short-term beneficial effects of exercise treatment on quality of life, cardiopulmonary function and fatigue for cancer patients undergoing active treatment, we cannot formulate more precise recommendation in favour of a specific type of exercise treatment, over and above the generally accepted counselling that physical activity is beneficial for health (weak recommendation; very low level of evidence). Hence, it is advisable to take the local context and the preferences of the patient into account.
- As there is no consistent evidence either that exercise treatment would be harmful for cancer patients under treatment, they should not be discouraged to do physical activities. (weak recommendation; very low level of evidence).

6.2 Research agenda

- Since there is a lack of consistent and high-quality evidence on the effectiveness (in terms of quality of life, cardiopulmonary function and fatigue) and on safety of exercise treatment for cancer patients undergoing active treatment, large high-quality RCTs are needed.
- For outcomes such as quality of life and fatigue, researchers should use standardized, validated scales and the research community should agree on a generic and on a disease-specific instrument to render the results comparable.
- For future studies it is crucial to pre-define main outcomes and the magnitude of effect for outcome measures based on clinical significance.

7 APPENDICES

7.1 Appendix 1: Quality appraisal instruments

7.1.1 AMSTAR

Question	Answer
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	□ Yes □ No □ Can't answer □ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	□ Yes □ No □ Can't answer □ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	□ Yes □ No □ Can't answer □ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	□ Yes □ No □ Can't answer □ Not applicable

Question	Answer
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

Question	Answer
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	□ Yes □ No □ Can't answer □ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	□ Yes □ No □ Can't answer □ Not applicable

7.1.2 Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		
Blinding of participants and personnel **Assessments should be made for each main outcome (or class of outcomes)**	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study

Domain	Support for judgement	Review authors' judgement
Detection bias		
Blinding of outcome assessment **Assessments should be made for each main outcome (or class of outcomes)**	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessors
Attrition bias		
Incomplete outcome data **Assessments should be made for each main outcome (or class of outcomes)**	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any reinclusions in analyses performed by the review authors	Attrition bias due to amount, nature or handling of incomplete outcome data
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Reporting bias due to selective outcome reporting
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry	Bias due to problems not covered elsewhere in the table

7.2 Appendix 2: Search syntax by database

7.2.1 Systematic reviews

7.2.1.1 OVID Medline

1 exp Neoplasms/ (2327365)
2 Neoplasm Staging/ (103545)
3 cancer$.ti,ab. (863951)
4 tumor$.ti,ab. (820330)
5 tumour$.ti,ab. (175521)
6 carcinoma$.ti,ab. (407798)
7 neoplasm$.ti,ab. (85745)
8 lymphoma.ti,ab. (97206)
9 melanoma.ti,ab. (64929)
10 staging.ti,ab. (41905)
11 metastas$.ti,ab. (183033)
12 metastatic.ti,ab. (117234)
13 exp Neoplasm Metastasis/ (141345)
14 exp neoplastic processes/ (298816)
15 neoplastic process$.ti,ab. (2088)
16 non small cell.ti,ab. (23591)
17 adenocarcinoma$.ti,ab. (81736)
18 squamous cell.ti,ab. (55422)
19 nsclc.ti,ab. (12889)
20 osteosarcoma$.ti,ab. (13022)
21 phyllodes.ti,ab. (1142)
22 cystosarcoma$.ti,ab. (544)
23 fibroadenoma$.ti,ab. (2715)
24 (non adj small adj cell).ti,ab. (23591)
25 (non adj2 small adj2 cell).ti,ab. (23800)
26 (nonsmall adj2 cell).ti,ab. (1482)
27 plasmacytoma$.ti,ab. (4946)
28 myeloma.ti,ab. (31766)
29 multiple myeloma.ti,ab. (19914)
30 lymphoblastoma$.ti,ab. (259)
31 lymphocytoma$.ti,ab. (252)
32 lymphosarcoma$.ti,ab. (3572)
33 immunocytoma.ti,ab. (400)
34 sarcoma$.ti,ab. (65098)
35 hodgkin$.ti,ab. (47627)
36 (nonhodgkin$ or non hodgkin$).ti,ab. (27245)
37 or/1-36 (2667070)
38 exp Exercise/ (58830)
39 exp Exercise Therapy/ (24668)
40 exp Exercise Therapy/ (24668)
41 exp Musculoskeletal Manipulations/ (10808)
42 Rehabilitation/ (16315)
43 "Physical Therapy (Specialty)"/ (1843)
44 Exercise Movement Techniques/ (271)
45 "physical training".mp. (3957)
46 "physical fitness".mp. (20947)
47 motor activity.mp. or Motor Activity/ (73372)
48 (treatment adj3 exercise) {Including Related Terms} (8200)
49 (treatment adj3 exercise).mp. (1965)
50 (therapy adj3 exercise).mp. (23618)
51 (training adj3 exercise).mp. (9686)
52 (fitness adj3 exercise).mp. (671)
53 (activity adj3 exercise).mp. (2519)
54 (movement adj3 exercise).mp. (421)
55 (treatment adj3 physical).mp. (2736)
56 (therapy adj3 physical).mp. (31743)
57 (training adj3 physical).mp. (14740)
58 (fitness adj3 physical).mp. (21202)
59 (activity adj3 physical).mp. (40715)
60 (movement adj3 physical).mp. (300)
61 (physical and exercise).mp. (80606)
62 rehabilitation.mp. (98440)
63 or/38-62 (351321)
64 37 and 63 (13676)
65 meta-analysis.mp,pt. (50355)
66 review.pt. (1707163)
67 search:.tw. (174318)
68 or/65-67 (1843870)
69 64 and 68 (2608)

70 limit 69 to yr="2002 - 2011" (1685)

7.2.1.2 OVID PreMedline

1 tumor$.ab,ti. (31351)
2 tumour$.ab,ti. (7527)
3 carcinoma$.ab,ti. (15670)
4 neoplasm$.ab,ti. (2990)
5 lymphoma.ab,ti. (3167)
6 melanoma$.ab,ti. (2194)
7 Staging.ab,ti. (1846)
8 metastas$.ab,ti. (7988)
9 metastatic.ab,ti. (5370)
10 neoplastic process$.ab,ti. (59)
11 non small cell.ab,ti. (1707)
12 adenocarcinoma$.ab,ti. (3200)
13 squamous cell.ab,ti. (2377)
14 nsclc.ab,ti. (1139)
15 osteosarcoma$.ab,ti. (469)
16 phyllodes.ab,ti. (40)
17 cystosarcoma$.ab,ti. (10)
18 fibroadenoma$.ab,ti. (98)
19 (non adj small adj cell).ab,ti. (1707)
20 (non adj2 small adj2 cell).ab,ti. (1712)
21 (nonsmall adj2 cell).ab,ti. (92)
22 plasmacytoma$.ab,ti. (88)
23 myeloma.ab,ti. (967)
24 multiple myeloma.ab,ti. (742)
25 lymphoblastoma$.ab,ti. (11)
26 lymphocytoma$.ab,ti. (5)
27 lymphosarcoma$.ab,ti. (78)
28 immonocytoma.ab,ti. (0)
29 sarcoma$.ab,ti. (2641)
30 hodgkin$.ab,ti. (1246)
31 (nonhodgkin$ or non hodgkin$).ab,ti. (772)
32 cancer$.ab,ti. (43124)
33 or/1-32 (79297)
34 "physical training".mp. (112)
35 "physical fitness".mp. (244)
36 motor activity.mp. (259)
37 (treatment adj3 exercise) (2720)
38 (treatment adj3 exercise).mp. (118)
39 (therapy adj3 exercise).mp. (191)
40 (training adj3 exercise).mp. (473)
41 (fitness adj3 exercise).mp. (46)
42 (activity adj3 exercise).mp. (158)
43 (movement adj3 exercise).mp. (15)
44 (treatment adj3 physical).mp. (191)
45 (therapy adj3 physical).mp. (763)
46 (training adj3 physical).mp. (181)
47 (fitness adj3 physical).mp. (299)
48 (activity adj3 physical).mp. (2993)
49 (movement adj3 physical).mp. (24)
50 (physical and exercise).mp. (1536)
51 rehabilitation.mp. (4218)
52 or/34-51 (9491)
53 33 and 52 (465)
54 meta-analysis.mp,pt. (2791)
55 review.pt. (463)
56 search:.tw. (14775)
57 or/54-56 (16781)
58 53 and 57 (25)
59 limit 58 to yr="2002 - 2011" (23)

7.2.1.3 EMBASE

'neoplasm'/exp OR 'cancer staging'/exp OR 'metastasis'/exp OR 'oncogenesis and malignant transformation'/exp AND ('exercise'/exp OR exercise OR 'motor activity'/exp OR 'motor activity' OR 'movement'/exp OR movement OR ('exercise'/exp OR exercise AND ('therapy'/exp OR therapy)) OR 'rehabilitation'/exp OR rehabilitation OR 'physical therapy'/exp OR 'physical therapy' OR ('gait'/exp OR gait OR 'locomotion'/exp OR locomotion OR motor AND activity) OR (physical AND near AND ('therapy'/exp OR therapy)) OR ('exercise'/exp OR exercise AND near AND ('therapy'/exp OR therapy)) OR (physical AND near AND ('exercise'/exp OR exercise)) OR (physical AND near AND activity) OR ('exercise'/exp OR exercise AND near AND ('movement'/exp OR movement)) OR ('exercise'/exp OR exercise AND near AND ('rehabilitation'/exp OR rehabilitation)) OR (physical AND near AND ('rehabilitation'/exp OR rehabilitation)) OR 'physical training'/exp OR 'physical training' OR 'physical fitness'/exp OR 'physical fitness') AND (2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py) AND ([cochrane review]/lim OR [meta analysis]/lim OR [systematic review]/lim)

7.2.1.4 Cochrane Library

#1 MeSH descriptor Neoplasms explode all trees
#2 MeSH descriptor Neoplasm Staging, this term only
#3 cancer*:ti,ab
#4 tumor*:ti,ab
#5 tumour*:ti,ab
#6 carcinoma*:ti,ab
#7 neoplasm*:ti,ab
#8 lymphoma:ti,ab
#9 melanoma:ti,ab
#10 staging:ti,ab
#11 metasta*:ti,ab
#12 MeSH descriptor Neoplasm Metastasis explode tree 1
#13 MeSH descriptor Neoplastic Processes explode tree 1
#14 neoplastic process*:ti,ab
#15 non small cell:ti,ab
#16 adenocarcinoma*:ti,ab
#17 squamous cell:ti,ab
#18 nsclc:ti,ab
#19 osteosarcoma*:ti,ab
#20 phyllodes:ti,ab
#21 cystosarcoma*:ti,ab
#22 fibroadenoma*:ti,ab
#23 (non NEXT small NEXT cell):ti,ab
#24 (nonsmall NEAR/2 cell):ti,ab
#25 plasmacytoma*:ti,ab
#26 myeloma:ti,ab
#27 lymphoblastoma*:ti,ab
#28 lymphocytoma*:ti,ab
#29 lymphosarcoma*:ti,ab
#30 immunocytoma:ti,ab
#31 sarcoma*:ti,ab
#32 hodgkin*:ti,ab
#33 nonhodgkin*:ti,ab
#34 non hodgkin*:ti,ab
#35 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34)
#36 MeSH descriptor Exercise explode tree 1
#37 MeSH descriptor Exercise Therapy explode tree 1
#38 MeSH descriptor Musculoskeletal Manipulations explode tree 1
#39 MeSH descriptor Rehabilitation, this term only

#40 MeSH descriptor Physical Therapy Specialty, this term only
#41 MeSH descriptor Exercise Movement Techniques, this term only
#42 physical training:ti,ab
#43 physical fitness:ti,ab
#44 motor activity:ti,ab
#45 MeSH descriptor Motor Activity, this term only
#46 (treatment NEAR/3 exercise):ti,ab
#47 (therapy NEAR/3 exercise):ti,ab
#48 (training NEAR/3 exercise):ti,ab
#49 (fitness NEAR/3 exercise):ti,ab
#50 (activity NEAR/3 exercise):ti,ab
#51 (movement NEAR/3 exercise):ti,ab
#52 (treatment NEAR/3 physical):ti,ab
#53 (therapy NEAR/3 physical):ti,ab
#54 (training NEAR/3 physical):ti,ab
#55 (fitness NEAR/3 physical):ti,ab
#56 (activity NEAR/3 physical):ti,ab
#57 (movement NEAR/3 physical):ti,ab
#58 (physical NEXT exercise):ti,ab
#59 rehabilitation:ti,ab
#60 (#36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59)
#61 (#35 AND #60)
#62 (#61), from 2001 to 2012

7.2.2 Randomized controlled trials

7.2.2.1 OVID Medline

1 exp Neoplasms/ (2100323)
2 Neoplasm Staging/ (101800)
3 cancer$.ab,ti. (837076)
4 tumor$.ab,ti. (796216)
5 tumour$.ab,ti. (174567)
6 carcinoma$.ab,ti. (398903)
7 neoplasm$.ab,ti. (84170)
8 lymphoma.ab,ti. (94917)
9 melanoma.ab,ti. (63512)
10 staging.ab,ti. (41340)
11 metastas$.ab,ti. (178868)
12 metastatic.ab,ti. (114774)
13 exp Neoplasm Metastasis/ (138329)
14 exp Neoplastic Processes/ (292261)
15 neoplastic process$.ab,ti. (2068)
16 non small cell.ab,ti. (23260)
17 adenocarcinoma$.ab,ti. (79787)
18 squamous cell.ab,ti. (54228)
19 nsclc.ab,ti. (12735)
20 osteosarcoma$.ab,ti. (12755)
21 phyllodes.ab,ti. (1125)
22 cystosarcoma$.ab,ti. (538)
23 fibroadenoma$.ab,ti. (2675)
24 (non adj small adj cell).ab,ti. (23260)
25 (non adj2 small adj2 cell).ab,ti. (23454)
26 (nonsmall adj2 cell).ab,ti. (1462)
27 plasmacytoma$.ab,ti. (4865)

28 myeloma.ab,ti. (31190)
29 multiple myeloma.ab,ti. (19470)
30 lymphoblastoma$.ab,ti. (249)
31 lymphocytoma$.ab,ti. (252)
32 lymphosarcoma$.ab,ti. (3533)
33 immunocytoma.ab,ti. (397)
34 sarcoma$.ab,ti. (63959)
35 hodgkin$.ab,ti. (46774)
36 (nonhodgkin$ or non hodgkin$).ab,ti. (26683)
37 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 (2556911)
38 exp Exercise/ (90515)
39 exp Exercise Therapy/ (24053)
40 exp Musculoskeletal Manipulations/ (10765)
41 Rehabilitation/ (15723)
42 Physical Therapy Specialty/ (1834)
43 Exercise Movement Techniques/ (254)
44 physical training.mp. (3895)
45 physical fitness.mp. (20540)
46 motor activity.mp. or Motor Activity/ (70785)
47 (treatment adj3 exercise).mp. (1913)
48 (therapy adj3 exercise).mp. (22952)
49 (training adj3 exercise).mp. (9422)
50 (fitness adj3 exercise).mp. (654)
51 (activity adj3 exercise).mp. (2445)
52 (movement adj3 exercise).mp. (402)
53 (treatment adj3 physical).mp. (2672)
54 (therapy adj3 physical).mp. (31510)
55 (training adj3 physical).mp. (14583)
56 (fitness adj3 physical).mp. (20788)
57 (activity adj3 physical).mp. (39437)
58 (movement adj3 physical).mp. (290)
59 (physical and exercise).mp. (79111)
60 rehabilitation.mp. (96515)
61 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 (365943)
62 37 and 61 (13200)
63 62 (13200)
64 limit 63 to yr="2010 -Current" (1823)
65 limit 64 to randomized controlled trial (191)

7.2.2.2 OVID PreMedline

3 cancer$.ab,ti. (41236)
4 tumor$.ab,ti. (30141)
5 tumour$.ab,ti. (7065)
6 carcinoma$.ab,ti. (15000)
7 neoplasm$.ab,ti. (2928)
8 lymphoma.ab,ti. (2987)
9 melanoma.ab,ti. (2043)
10 staging.ab,ti. (1772)
11 metastas$.ab,ti. (7702)
12 metastatic.ab,ti. (5133)
15 neoplastic process$.ab,ti. (55)
16 non small cell.ab,ti. (1557)
17 adenocarcinoma$.ab,ti. (3047)
18 squamous cell.ab,ti. (2231)
19 nsclc.ab,ti. (1020)
20 osteosarcoma$.ab,ti. (460)
21 phyllodes.ab,ti. (43)

22 cystosarcoma$.ab,ti. (9)
23 fibroadenoma$.ab,ti. (95)
24 (non adj small adj cell).ab,ti. (1557)
25 (non adj2 small adj2 cell).ab,ti. (1562)
26 (nonsmall adj2 cell).ab,ti. (87)
27 plasmacytoma$.ab,ti. (93)
28 myeloma.ab,ti. (932)
29 multiple myeloma.ab,ti. (711)
30 lymphoblastoma$.ab,ti. (11)
31 lymphocytoma$.ab,ti. (5)
32 lymphosarcoma$.ab,ti. (79)
33 immunocytoma.ab,ti. (1)
34 sarcoma$.ab,ti. (2568)
35 hodgkin$.ab,ti. (1179)
36 (nonhodgkin$ or non hodgkin$).ab,ti. (735)
37 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 (75988)
44 physical training.mp. (118)
45 physical fitness.mp. (239)
46 motor activity.mp. (264)
47 (treatment adj3 exercise).mp. (116)
48 (therapy adj3 exercise).mp. (191)
49 (training adj3 exercise).mp. (459)
50 (fitness adj3 exercise).mp. (46)
51 (activity adj3 exercise).mp. (153)
52 (movement adj3 exercise).mp. (16)
53 (treatment adj3 physical).mp. (178)
54 (therapy adj3 physical).mp. (745)
55 (training adj3 physical).mp. (185)
56 (fitness adj3 physical).mp. (288)
57 (activity adj3 physical).mp. (2772)
58 (movement adj3 physical).mp. (23)
59 (physical and exercise).mp. (1498)
60 rehabilitation.mp. (3986)
61 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 (9005)
62 37 and 61 (445)
63 62 (445)
64 limit 63 to yr="2010 -Current" (313)
65 limit 64 to randomized controlled trial (2)

7.2.2.3 EMBASE

'neoplasm'/exp OR 'cancer staging'/exp OR 'metastasis'/exp OR 'oncogenesis and malignant transformation'/exp OR cancer*:ab,ti OR tumor*:ab,ti OR tumour*:ab,ti OR carcinoma*:ab,ti OR neoplasm*:ab,ti OR lymphoma:ab,ti OR melanoma:ab,ti OR staging:ab,ti OR metastas*:ab,ti OR metastatic:ab,ti OR (neoplastic:ab,ti AND process*:ab,ti) OR (non:ab,ti AND small:ab,ti AND cell:ab,ti) OR adenocarcinoma*:ab,ti OR (squamous:ab,ti AND cell:ab,ti) OR nsclc:ab,ti OR osteosarcoma*:ab,ti OR phyllodes:ab,ti OR cystosarcoma*:ab,ti OR fibroadenoma*:ab,ti OR (non:ab,ti AND small:ab,ti AND next:ab,ti AND cell:ab,ti) OR (small NEAR/2 cell):ab,ti OR (nonsmall NEAR/2 cell):ab,ti OR plasmacytoma*:ab,ti OR myeloma:ab,ti OR (multiple:ab,ti AND myeloma:ab,ti) OR lymphoblastoma*:ab,ti OR lymphocytoma*:ab,ti OR lymphosarcoma*:ab,ti OR immunocytoma:ab,ti OR sarcoma*:ab,ti OR hodgkin*:ab,ti OR nonhodgkin*:ab,ti OR (non:ab,ti AND hodgkin*:ab,ti) AND ('exercise'/exp OR exercise OR 'motor activity'/exp OR 'motor activity' OR 'movement'/exp OR movement OR ('exercise'/exp OR exercise AND ('therapy'/exp OR therapy)) OR 'rehabilitation'/exp OR rehabilitation OR 'physical therapy'/exp OR 'physical therapy' OR ('gait'/exp OR gait OR 'locomotion'/exp OR locomotion OR motor AND activity) OR (physical AND near AND ('therapy'/exp OR therapy)) OR ('exercise'/exp OR exercise AND near AND ('therapy'/exp OR therapy)) OR (physical AND near AND ('exercise'/exp OR exercise)) OR (physical AND near AND activity) OR ('exercise'/exp OR

exercise AND near AND ('movement'/exp OR movement)) OR ('exercise'/exp OR exercise AND near AND ('rehabilitation'/exp OR rehabilitation)) OR (physical AND near AND ('rehabilitation'/exp OR rehabilitation)) OR 'physical training'/exp OR 'physical training' OR 'physical fitness'/exp OR 'physical fitness') AND [randomized controlled trial]/lim AND [embase]/lim AND [2001-2012]/py

7.2.2.4 CENTRAL

#1 MeSH descriptor Neoplasms explode all trees
#2 MeSH descriptor Neoplasm Staging, this term only
#3 cancer*:ti,ab
#4 tumor*:ti,ab
#5 tumour*:ti,ab
#6 carcinoma*:ti,ab
#7 neoplasm*:ti,ab
#8 lymphoma:ti,ab
#9 melanoma:ti,ab
#10 staging:ti,ab
#11 metasta*:ti,ab
#12 MeSH descriptor Neoplasm Metastasis explode tree 1
#13 MeSH descriptor Neoplastic Processes explode tree 1
#14 neoplastic process*:ti,ab
#15 non small cell:ti,ab
#16 adenocarcinoma*:ti,ab
#17 squamous cell:ti,ab
#18 nsclc:ti,ab
#19 osteosarcoma*:ti,ab
#20 phyllodes:ti,ab
#21 cystosarcoma*:ti,ab
#22 fibroadenoma*:ti,ab
#23 (non NEXT small NEXT cell):ti,ab
#24 (nonsmall NEAR/2 cell):ti,ab
#25 plasmacytoma*:ti,ab
#26 myeloma:ti,ab
#27 lymphoblastoma*:ti,ab
#28 lymphocytoma*:ti,ab
#29 lymphosarcoma*:ti,ab
#30 immunocytoma:ti,ab
#31 sarcoma*:ti,ab
#32 hodgkin*:ti,ab
#33 nonhodgkin*:ti,ab
#34 non hodgkin*:ti,ab
#35 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34)
#36 MeSH descriptor Exercise explode tree 1
#37 MeSH descriptor Exercise Therapy explode tree 1
#38 MeSH descriptor Musculoskeletal Manipulations explode tree 1
#39 MeSH descriptor Rehabilitation, this term only
#40 MeSH descriptor Physical Therapy Specialty, this term only
#41 MeSH descriptor Exercise Movement Techniques, this term only
#42 physical training:ti,ab
#43 physical fitness:ti,ab
#44 motor activity:ti,ab
#45 MeSH descriptor Motor Activity, this term only
#46 (treatment NEAR/3 exercise):ti,ab
#47 (therapy NEAR/3 exercise):ti,ab
#48 (training NEAR/3 exercise):ti,ab
#49 (fitness NEAR/3 exercise):ti,ab

#50	(activity NEAR/3 exercise):ti,ab
#51	(movement NEAR/3 exercise):ti,ab
#52	(treatment NEAR/3 physical):ti,ab
#53	(therapy NEAR/3 physical):ti,ab
#54	(training NEAR/3 physical):ti,ab
#55	(fitness NEAR/3 physical):ti,ab
#56	(activity NEAR/3 physical):ti,ab
#57	(movement NEAR/3 physical):ti,ab
#58	(physical NEXT exercise):ti,ab
#59	rehabilitation:ti,ab
#60	(#36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59)
#61	(#35 AND #60)
#62	(#61), from 2001 to 2012

7.3 Appendix 3: GRADE profiles by intervention and outcome

Institution-based exercise treatment for breast cancer patients.

Outcome	N studies	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Level of evidence
QOL	5	-1	-2	0	0	0	Very low
QOL, physical subscale	4	-1	-1	-1	0	0	Very low

Home-based exercise treatment for breast cancer patients.

Outcome	N studies	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Level of evidence
QOL	5	-2	-2	0	0	0	Very low
QOL, physical subscale	5	-2	-2	-1	0	0	Very low

Aerobic exercise treatment for breast cancer patients.

Outcome	N studies	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Level of evidence
QOL	8	-1	-2	0	0	0	Very low
QOL, physical subscale	7	-1	-2	0	0	0	Very low

Resistance exercise treatment for breast cancer patients.

Outcome	N studies	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Level of evidence
QOL	1	-1	0	-2	0	0	Very Low

Combined resistance and aerobic exercise treatment for breast cancer patients

Outcome	N studies	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Level of evidence
QOL	1	-1	0	-2	0	0	Very low
QOL, physical subscale	1	-1	0	-2	0	0	Very low

Exercise treatment for breast cancer patients

Outcome	N studies	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Level of evidence
VO_2 peak, absolute	2	-1	-2	-1	0	0	Very low
VO_2 peak, relative	2	-1	-2	-1	0	0	Very low
Other cardiopulmonary function measures	2	-2	-1	-2	0	0	Very low
Fatigue	8	-1	-2	0	0	0	Very low
Safety	5	-2	0	0	0	0	Low

Exercise treatment for prostate cancer patients

Outcome	N studies	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Level of evidence
QOL	3	-1	-1	-1	0	0	Very low
QOL, physical subscale	2	-2	-1	-1	0	0	Very low
Cardiopulmonary function	3	-2	-1	-1	0	0	Very low
Fatigue	4	-2	-1	-1	0	0	Very low
Safety	2	-1	-2	-1	0	0	Very low

Exercise treatment for lung cancer patients.

Outcome	N studies	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Level of evidence
QOL	1	-1	0	-2	0	0	Very low
Exercise tolerance	1	-1	0	-1	-1	0	Very low

Exercise treatment for colorectal cancer patients.

Outcome	N studies	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Level of evidence
QOL	1	-2	0	-1	0	0	Very low
Heart rate	1	-2	0	-1	0	0	Very low
Fatigue	2	-1	0	-1	0	0	Low

Exercise treatment for patients undergoing allogeneic hematopoietic stem cell transplantation.

Outcome	N studies	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Level of evidence
QOL	2	-2	0	-1	0	0	Very low
VO_2max	1	-2	0	-1	0	0	Very low
Heart rate	1	-2	0	-1	0	0	Very low
Fatigue	2	-2	-1	-1	0	0	Very low

Exercise treatment for lymphoma patients

Outcome	N studies	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Level of evidence
QOL	1	0	0	-1	0	0	Moderate
VO_2peak	1	0	0	-1	0	0	Moderate
Fatigue	1	0	0	-1	0	0	Moderate

Exercise treatment for leukemia patients

Outcome	N studies	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Level of evidence
Fatigue	1	-2	0	-1	0	0	Very low

Exercise treatment for mixed cancer patients

Outcome	N studies	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Level of evidence
QOL	4	-2	-1	0	0	0	Very low
VO_2peak	3	-2	-1	-1	0	0	Very low
fatigue	5	-2	-2	-2	0	0	Very low

7.4 Appendix 4: Evidence tables

7.4.1 Breast cancer

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Cadmus 2009[43]	• Design: Double trial, 2 arms per trial. Only data from IMPACT study is retrieved. • Sources of funding: Lance Armstrong Foundation, American Cancer Society, Susan G. Komen Foundation and supported in part by a General Clinical Research Center grant Setting: home-based intervention of Connecticut women identified through Yale-New Haven Hospital Tumor Registry • Sample size: 50 • Duration: 6 months	• Inclusion criteria: • Pre- or post-menopausal women, ages 35-75 years, AJCC Stages 0-IIIa breast cancer, recently diagnosed, not yet begun or recently begun adjuvant treatment (≤2 weeks radiation or ≤ 2 cycles chemotherapy), physically able to exercise and physician consent to begin an exercise program, any activity level • Exclusion criteria: Diagnosis of other recurrent or primary cancer event, current smoker • Patients characteristics: • Mean age (+-SD): IG=54.5 (8.2), CG=54.0 (10.9) • Treatment: • Radiation: IG=32%, CG=32% • Chemotherapy: IG=8%, CG=20% • Radiation and Chemotherapy: IG=56%, CG=44%	• Intervention: home-based intervention, 30 min activity 5 days/week. At trial start pt received an educational book, a binder containing specialized information and a Polar heart rate monitor (to maintain activity at 60-80 % of predicted max HR). Each participants received weekly phone calls • Comparator: CG were told they could exercise on their own if they chose but that the study physical activity program would not be available to them	Unclear reporting of QOL (FACT-B and FACT-G) group comparison measures Authors suggest no significance Unclear reporting of group comparison measures on SF-36 subscale “physical” Authors suggest significance ($p<0.05$) favouring usual care group	• No adverse events related to the intervention was observed	• Moderate risk of bias • 64% of pt meet the goal of exercising 150 min per week • Small sample size • Difficult to assess the statistics provided

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Campbell 2005[44]	• Design: RCT, 2 arms, pilot study • Sources of Funding: Greater Glasgow NHS trust • Setting: Large West of Scotland Cancer Centre • Sample size: 22 women with breast cancer • Duration: 12 weeks	• Eligibility criteria: • Patients who had received breast cancer surgery and were currently receiving adjuvant radiotherapy/chemotherapy • Patients characteristics: • IG ; (n=12) mean age yrs (SD+-)=48 (+/- 10) • CG; (n=10) mean age=47(+/- 5) • Chemotherapy (n=6) • Radiotherapy (n=6) • Combination (n=10)	• IG: supervised exercise 2 x weekly at 60-75% age adjusted heart rate maximum for 12 weeks. Classes consisted of warm-up, 10-20 min of exercise and a cool down and relaxation period. • CG: usual care. At the end of study period they received help in constructing a personalized exercise plan.	QOL (FACT-G) Significant p-value group comparison favoring exercise group (p=0.046) QOL (FACT-B): NS group comparison p-value (p=0.094)	• No effect for fatigue measured by Piper Fatigue Scale	• High risk of bias • Analysis of some variables not appropriately powered, small sample size a total of 19 women finalized the trial IG=10, CG=9) • No ITT analysis
Courneya 2007[45]	• Design: RCT, 3 arms • Sources of Funding: Supported by a grant from the Canadian Breast Cancer Research Alliance; the Canadian Research Chairs Program, a grant from NCIC with funds from the Canadian Cancer	• Eligibility criteria: • English – or French speaking non-pregnant women ≥18 years old with stage I-IIIA breast cancer beginning first line adjuvant therapy. • Patients characteristics: • Mean age 49.2 (range 25-78)	• UC: usual care and asked not to initiate an exercise program during trial. • RET(resistance): 3 x weekly 2 sets of 8-12 rep of 9 diff exercises at 60-70% of their estimated one rep max. Resistance	NS for QOL (FACT-An) Unadjusted: RET vs. UC: MD 4.7 (CI=-2.7-12.1), p=0.216 AET vs. UC: MD 3.7(CI=-3.8-11.1), p=0.338, RET vs. AET: MD 1.0 (CI=-6.4-8.5) At 6 month	• No effect for fatigue (measured by FACT-AN subscale "Fatigue") for any of the two intervention arms at post-test (median 17 weeks) and at 6-months	• Moderate risk of bias • Allocation concealed • No blinding of outcome assessment

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	society. • Setting: The Cross Cancer Institute (Edmonton, Alberta), the Ottawa Hospital Integrated Cancer Program (Ottawa, Ontario) and The British Columbia Cancer Agency (Vancouver, British Columbia) • Sample size: 242 breast cancer patients, 201 at 6months follow-up • Duration: duration of pt chemotherapy (median duration 17 weeks, CI=9-24 week)		increased by 10% when participants completed more than 12 rep. • AET(aerobic): 3 x weekly on cycle ergometer, treadmill or elliptical beginning at 60% of VO_2 max for week 1-6, progressing to 70% and 80% beyond week 12.	follow-up: Unadjusted: RET vs. UC: MD+2.3 (CI=-6.9-11.5), p=0.620 AET vs. UC: MD 1.9(CI=-7.4-11.3), p=0.686, RET vs. AET: MD 0.4 (CI=-8.6-9.4)	follow-up • Objectively measured outcomes • VO_2 peak AET group superior compared with UC and RET: • Unadjusted: AET vs. UC; MD1.8, (CI=0.5-3.2), p=0.006 • Adjusted: AET vs. UC; MD 2.0, CI=0.6-3.3, P=0.004 • Unadjusted: AET vs. RET; MD 1.6, CI=(0.3-2.9),p=0.014 • Adjusted: AET vs. RET; MD 1.4, (CI=0.1-2.7), p=0.031 • Adverse events: No adverse events reported	
Haines	• Design: 2-group	• Eligibility criteria: women	• Exercise group:	3-month:	• Participant	• Moderate risk

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
2010[47]	randomized controlled trial with blinded outcome assessment and active (sham intervention) control group • Funding: project grant from the Princess Alexandra Hospital Cancer Collaborative Group • Setting: Princess Alexandra Hospital (Australia) • Sample size: 89 at baseline, 73 at 12-month follow-up • Duration: 3, 6 and 12months follow-up	with newly diagnosed breast cancer undergoing adjuvant therapy (radiation, chemo and hormonal) following surgery; exclusion criteria were severe cardiac disease, uncontrolled hypertension, orthopedic injury, participation in exercise program • Patient characteristic: mean age intervention group 55.9y (SD 10.5), control 54.2y (SD 11.5) (p=0.47)	home-based strength, balance, shoulder mobility, cardiovascular endurance program; multimedia instructional package; equipment. • Control group: active sham intervention (flexibility and relaxation activities); video material; no progression of activities	Generic health-related QOL (EQ-5D instrument): VAS exercise group superior 80.6 (11.6) vs. control 74.1 (20.6), (p=0.006). Utility exercise group 0.78 (0.19) vs. control 0.84 (0.17) (p=0.54) EORTC C30: physical functioning exercise group superior; 86.9 (10.7) vs. control 86.7 (14.9) (p=0.02); fatigue exercise group 31.8 (20.1) vs. control 34.5 (27.9) (p=0.12) Multidimensional fatigue inventory: general fatigue exercise group 11.9 (3.7) vs. control 12.6 (4.3) (p=0.52); physical fatigue	adherence higher in first 3 months than in second 3 months • Adverse events: musculoskeletal pain 9 patients, odds ratio 2.39 (95%CI 0.58-89.92) (p=0.23); fall 8patients, odds ratio 0.58 (95%CI 0.14-2.42) (p=0.48)	of bias • Large number of between-group comparisons (increase in chance of type I statistical error • Considerable number of patients took up form of exercise during trial • Possible beneficial effect of SHAM intervention

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
				exercise group 10.7 (4.6) vs. control 10.9 (4.6) (p=0.51); reduced activity exercise group 9.8 (4.6) vs. control 10.4 (5.3) (p=0.07) 6 months No effect on Generic QOL (EQ-5D instrument): VAS exercise group 80.4 (12.7) vs. control 79.3 (14.1) (p=0.09); Utility exercise group 0.80 (0.21) vs. control 0.83 (0.18) (p=0.87) EORTC C30: physical functioning exercise group 83.6 (15.8) vs. control 87.5 (10.8) (p=0.64); fatigue exercise group 27.3 (26.4) vs. control 28.1		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
				(20.5) (p=0.29) Multidimensional fatigue inventory: general fatigue exercise group 11.1 (4.2) vs. control 11.9 (4.5) (p=0.40); physical fatigue exercise group 10.1 (4.5) vs. control 10.0 (4.1) (p=0.95).		
Headley 2004[48]	• Design: RCT 2 arms • Sources of funding: study funded by the 1999 Hoechst Marion Roussels, Inc. Research Grant from the ONS Foundation and the University of Texas Health Science Center in the Houston School of Nursing. • Setting: Outpatient clinic of comprehensive cancer center, southwestern United States	• Eligibility criteria: English speaking, at least 18 years, stage IV breast cancer, scheduled to initiate outpatient chemotherapy, having a performance status of 2 or less on Zubrod scale, being able to sit in a straight back chair for 30 min and having access to a television and a video cassette player; • Patients characteristics: Mean age (SD): IG=50.0 (7.10) CG=52.25 (11.43)Mean education (SD): IG=14.4 (3.12) CG=12.6 (2.5)	• Intervention: 30 min seated exercise 3 x weekly using a commercially available video (Armchair Fitness: Gentle Exercise). Program consisted of 5 min warm-up, 20 min moderate-intensity repetitive motion exercise and 5 min cool down. Comparator: No seated exercise program,	Insufficient data reporting Statistics between endpoints not provided Overall QOL (FACIT-F) declined for both groups Exercise group declining at slower rate than control group (p=0.0254, only graphical presentation of results)	• No adverse events reported	• High risk of bias • Small sample size • No ITT analysis • Overall adherence 75%

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	• Sample size: 32 women • Duration: exercise intervention during 4 cycles of chemotherapy		permitted to continue any usual physical activity	Physical well-being (FACIT-F subscale): exercise group declining at a slower rate than control, (p=0.0252, only graphical presentation of results) Graph suggests that intervention group had less decline in fatigue over time compared with control group (p=0.0078), measured by FACIT-F subscale "Fatigue"		
Hwang 2008[49]	• Design: RCT 2 arms • Sources of funding: none stated • Setting: clinical setting, Seoul, Korea • Sample size: 40 women • Duration: 5 weeks	• Eligibility criteria: women post-surgery on outpatients waiting list for radiotherapy with no concurrent major health problems that could affect participation in exercise program, including uncontrolled hypertension, cardiovascular disease,	• Intervention: supervised exercise 3 x weekly for 50 min (10 min warm up, 30 min stretching and aerobic exercise, 10 min cool down) Heart	• Positive effect for WHOQOL-BREF (p<0.001) • Positive effect, p<0.001 (WHOQOL-BREF subscale	• No significant exercise-related adverse events were reported	• High risk of bias • No allocation concealment • No ITT analysis • Small sample size • QOL Scale not

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
		acute or chronic respiratory disease, and cognitive dysfunction. • Patients characteristics: • Mean age control group=46.3 (+-9.5) • Mean age exercise group=46.3 (+-7.5) • No significant difference on outcome measures at baseline	rate monitored through exercise with encouragement to work at 50-70% of age adjusted max. • Comparator: • Patients in control were shown how to perform shoulder ROM exercise and were encouraged to continue with normal activities	"physical") • Figure suggests that the control group had a increase in fatigue, that the exercise group had a decrease in fatigue and that there was a significance in difference in the mean fatigue level (measured by Brief Fatigue Inventory) between groups ($p<0.05$)		cancer specific
Kim 2006[50]	• Design: RCT 2 arms • Sources of funding: supported by grant from the National Institute of Nursing Research and a postdoctoral fellowship award from the Korea science and Engineering	• Eligibility criteria: women newly diagnosed with breast cancer and no previous history of cancer, all stages of breast cancer, ages ≥40 years and receiving cancer treatment • Patients characteristics: • Mean age IG=51.3 (SD=6.7) • Mean age CG=48.3	• Intervention: Aerobic exercise, 3 x weekly for 30 min (+ 5 min warm up and 5 min cool down) at 60-70% of HR reserve or VO_2 peak at baseline. Weekly assessment for	• No significant group difference in VO_2 peak (ml/min) • No significant group difference in resting or maximum heart rate	• Secondary outcomes not part of project outcomes	• High risk of bias • Allocation concealment not described • High number of drop-outs (33 of 74) • no ITT analysis

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	Foundation • Setting: Exercise facility within the School of Nursing, Maryland, Baltimore • Sample size: 41 women newly diagnosed with breast cancer • Duration: 8 weeks	(SD=8.8) • 40.9% receiving chemotherapy • 31.8% receiving radiotherapy • 27.3% receiving a combination of chemotherapy and radiotherapy	the first 3 weeks to adjust for participants HR responses • Comparator: usual care including general information of benefits of exercise but no specific instructions or further guidance for exercise	(beats/min)		
Mock 2005[51]	• Design: RCT 2 arms • Sources of funding: study funded by a competitive FIRE (Fatigue Initiative in Research and Education) multi-institutional award from the Oncology Nursing Society Foundation to Dr. Mock. • Setting: 4 University teaching hospitals of National Cancer Institute designated Cancer Centers and 4 community cancer	• Eligibility criteria: Women aged 18-70 years, Stage 0-III breast cancer by definite surgery, scheduled to receive outpatient radiation therapy or adjuvant chemotherapy. Excluded if concurrent major health problems that could affect participation. Patients already exercising >45 min pr week were excluded • Patients characteristics: • Mean age IG (SD)=51.3 (8.9) • Mean age CG (SD)=51.6 (9.7) • Therapy type IG: Chemotherapy 41.7%,	• Intervention: home-based with written prescription to walk 5-6 x weekly at a moderate pace at app. 50-70% of max heart rate. Patients kept daily diaries and sent these to coordinators 1 x weekly. Patient was contacted by coordinators biweekly • Comparator: usual care, encouraged to	• No effect for fatigue (measured by Piper Fatigue Scale) at post-intervention	• No reporting of overall quality of life measure • Unclear reporting of group comparison measures (SF-36 “Physical Functioning” subscale)	• Moderate risk of bias • possible dilution of treatment effect; 39% of CG exercised, 28% of IG did not exercise • unclear reporting

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	centers in the Eastern US • Sample size: 119 • Duration: patients stratified for adjuvant therapy form either Radiation therapy (RT) or Chemotherapy (CT). • RT pt duration of intervention=6 weeks • CT pt duration of intervention=3-6 months	Radiation 58.3% • Therapy type CG: Chemotherapy 42.4%, Radiation 57.6%	maintain current level of activity			
Mutrie 2007[53]	• Design: RCT 2 arms • Sources of funding: Cancer Research UK. CE funded by the UK Medical Research Council. Funders independent from conduct and outcome of the study. • Setting: Three National Health Service Oncology clinics in Scotland and community exercise facilities	• Eligibility criteria: women during treatment for early stage breast cancer (stage I-III) • Patients characteristics: Mean age=51.6 years. Chemotherapy= • 15:201, Radiotherapy=57:201, Chemo+Radiotherapy=129: 201	• Intervention: Encouraged to attend 45 minutes of moderate level exercise 2 x weekly and do an additional exercise session at home each week (women monitored to ensure 50-75% age adjusted maximum heart rate) • Comparator: usual care	• Significant effect for FACT-B: • 12 weeks effect estimate: 2.5 (CI=1.0-3.9), p=0.0007 • 6 months effect estimate 1.5 (CI=0.1-2.9), p=0.039 • No effect for FAGT-G at any measure point • Non-Significant	• No adverse events reported • Other secondary outcomes not part of project outcomes	• Low risk of bias • Allocation concealment, blinding of outcome assessment, ITT-analysis • Number of classes attended by the participants not reported

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	• Sample size: 203 women • Duration: 12 weeks			effect for FACT-F subscale (fatigue) at 12 weeks and 6 months		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Schwartz 2007[55]	• Design: RCT 3 arms (aerobic, resistance or usual care) • Sources of funding: Not stated • Setting: Two National Cancer Institute-designated cancer centers in metropolitan area (US) • Sample Size: 66 women • Duration:6 months	• Patient characteristics • Breast cancer patients, stage I-III beginning chemotherapy • Mean age aerobic exercise group=48 years • Mean age resistance exercise group=50 years • Mean age usual care group=46 years	• Usual care: instructed to continue with their usual activities • Aerobic: home-based, instructed to choose an aerobic activity they enjoyed (e.g. walking or jogging) and exercise for 15-30 minutes four days pr. Week during study duration • Resistance: instructed to exercise at home four days per week using Thera-Band resistance band and tubing. Participants were given two different sets of exercises and were asked to complete two sets of 8-10 repetitions and	• Primary outcomes were not part of project defined outcomes	• Aerobic capacity at 6 months : Effect on 12 minute walk-test for aerobic exercise, mean change all groups=94.5 (95%CI=81-2-104.6), p=0.02. Resistance exercise group had slight increase in aerobic capacity. Usual Care group had decline in aerobic capacity.	• High risk of bias • No description of allocation concealment or blinding of outcome assessment • Small sample size • Authors used ITT principles

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
			alternate the exercise sets within each week.			
Segal 2001[56]	• Design: RCT 3 arms (self-directed, supervised or usual care) • Sources of funding: Supported by the National Cancer Institute of Canada with funds from the Canadian Cancer Society • Setting: Ottawa Regional Cancer Center, Canada • Sample size: 123 women • Duration:26 weeks	• Eligibility criteria: • Women with stages I and II breast cancer recruited within 2 weeks of initiation of prescribed adjuvant therapy • Patient characteristics: • Mean age ; CG=50.3 (SD 8.7) • SD exercise G=51.0 (SD 8.7) • Supervised exercise G=51.4 (SD 8.7)	• Intervention: o arm: self-directed exercise at home exercising 5 x weekly o arm: supervised exercise 3 x pr week (mainly walking exercise at prescribed pace) + expected to exercise at home 2 other weekdays • Control arm: usual care (general advice)	• No effect for FACT-G and FACT-B in patients receiving chemotherapy • No effect for "physical functioning" (SF-36) in institution-based study arm for patients receiving chemotherapy • Positive effect on SF-36 "Physical functioning" (p=0.03) for patient in self-directed arm receiving chemotherapy	• Relative VO_2 peak(ml/kg/min): • No effect for self-directed intervention arm compared with control (based data from patients receiving adjuvant therapy) • No effect for supervised intervention arm compared with control (based on data from patients receiving adjuvant therapy)	• Moderate risk of bias • Allocation concealed • Analyses carried out on an ITT basis • No blinding of outcome assessment

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Wang 2011[58]	• Design: RCT-2 arms • Sources of funding: Mark Diamond Research Fund, Graduate Student Associate, University at Buffalo, the State University of New York • Setting: Home-based intervention with patients from Chang-Gung Memorial Hospital and National Taiwan University Hospital • Sample size: 72 • Duration: 6 weeks	• Eligibility Criteria: women 18 to 72 years, newly diagnosed with stage I or stage II breast cancer, expecting chemotherapy • following recovery from surgery, and able to read or write Chinese. Exclusion criteria: (1) obesity (body mass index Q30 kg/m2; excluded to avoid bone and joint problems); (2) • degenerative arthritis; (3) adverse effects or inability to exercise as • recommended by their physicians for example, women with leukopenia, anemia, thrombocytopenia, and high fever up to 102-F; (4) unsafe conditions to exercise; (5) limiting dyspnea with exertion; (6) bone pain; (7) severe nausea; (8) psychiatric problems; (9) contraindications to exercise; (10) recurrent breast cancer; and (11) a reported history of other types of cancer. • Average age; all=50.42 years, exercise=48.40	• Exercise intervention; 6-weeks, home-based walking program, low to moderate intensity measured by a heart rate maximum (HR max) from 40% to 60% or the modified Borg Scale between 0.5 and 2, • 3 to 5 sessions per week, and at least 30 minutes per session or the accumulation of 10-minute sessions to reach 30 minutes	• QOL (FACT-G, Chinese version): • Hierarchical linear model analysis: pattern • of change between the 2 groups was significantly different • at linear growth rate (t70=3.76, p<.001) and quadratic growth rate (t70=2.64, p=.011). (results provided in text and graphs only) • Fatigue (FACIT-F): • Significant differences between the 2 groups were detected only	• Not reported whether there were any adverse events	• High risk of bias • High contamination rate in usual care group (30.4%), • Missing logs from 17.7% in usual care group • No description of randomization process or allocation concealment

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
		years, usual care=52.3 years		• at the nadir (time 3=8.52, P<.001) and at the end of the • program (time 4=5.78, P<.001). • (results provided in text and graphs only)		

7.4.2 Prostate cancer

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Galvao 2010[46]	• Design: RCT-2 arms • Sources of funding: the Cancer Council of Western Australia • Setting: Sir Charles Gairdner Hospital (Perth, Western Australia) • Sample size: 57 • Duration: 12 weeks	• Inclusion criteria: historically documented prostate cancer, minimum prior exposure to AST no longer than 2 months, without PSA evidence of disease activity, and anticipated to remain hypogonadal for the subsequent 6 months. Medical clearance from physician. • Patients characteristics: Mean age; IG=69.5(SD 7.3), CG=70.1 (SD 7.3) • Previous radiation;	• Intervention: Combined progressive resistance and aerobic exercise 2 x weekly for 12 weeks. Resistance exercise included chest press, seated row, shoulder press, triceps extension, leg press, leg extension and leg	QOL (general): SF-36; General health: Adjusted group difference in mean changes over 12 weeks: MD=12.9 (CI; 1.9-23.9), p=0.022 Physical health composite: Adjusted group difference in mean changes	QOL (cancer specific): QLQ-C30; fatigue subscale: (p=0.021) No adverse events during testing or exercise	• Moderate risk of bias • • Low power • • Cardiopulmonary measures not aligned with project defined

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
		IG=37.9%, CG=39.3% • Current radiation; IG=27.6%, CG=21.4%	curl, with abdominal crunches. Resistance exercise was designed to progress from 12-to-6-repitition maximum for two to four sets per exercise. The aerobic component included 15-20 minutes of cardiovascular exercise (cycling, walking, jogging) at 65% to 85% maximum heart rate. • Comparator: • Usual care	over 12 weeks: MD=5.0(CI; 0.81-9.2), p=0.02 QOL (cancer specific): QLQ-C30; No significant difference for domain “physical”		
Windsor 2004[59]	• Design: RCT 2 arms • Sources of funding: none stated • Setting: home-based intervention, Dundee, Scotland • Sample size: 66 • Duration: 4 weeks	• Eligibility criteria: men on outpatient waiting list for radical conformal radiotherapy for localized prostate carcinoma. Exclusion criteria: physical frailty due to age and comorbidities e.g. unstable or severe angina, recent	• Intervention: home-based, moderate-intensity, continuous walking for 30 min at least 3 days per week during	Fatigue: No significant difference for mean BFI score btwn groups after radiotherapy (p=0.18) or at week 8 follow-up	Cardio-pulmonary functioning: No significant group difference in pre-post test resting HR or pre-to-posttest exercise HR.	• High risk of bias • No allocation concealment • Low power

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	(duration of radiotherapy)	myocardial infarction, or dementia. • Patients characteristics: • Mean age (+- standard error) • CG=69.3 (+-1.3) • IG=68.3 (+-0.9)	radiotherapy at HR 60-70% of calculated max HR. • Comparator: patients not discouraged from performing normal activities but advised to rest and take things easy if they became fatigue.	(p=0.197) In time a significant within group increase for fatigue scores in CG (p=0.013) but not a significant difference in fatigue scores for IG (p=0.203)		
Monga 2007[52]	• Design: RCT 2 arms • Sources of funding: not reported • Setting: Academic Medical Center , US • Sample size: 21 men with prostate cancer • Duration: 8 weeks	• Eligibility criteria: patients with first time cancer diagnosis, had to be ambulatory and able to complete self-report measures • Patients characteristics: • Exercise group, mean age: 68 (+-4.2) • Control group, mean age: 70.6 (+-5.3)	• Intervention: Supervised aerobic exercise program 3 x weekly for 8 weeks 30 min aerobic exercise at target heart rate (.65) x (max HR – rest HR) + rest HR • Comparator: standard care including education and radiotherapy	Cardiac fitness btwn group comparison METS:(MET=3.5 ml O2·kg−1·min−1) significant mean difference favoring exercise=2.8 (SD +- 1.8), p=0.006 Fatique btwn group comparison PFS significant mean difference favoring exercise= -4.3(SD +-2.1), p<0.001 QOL (FACT-P)	Significant within group improvement for exercise group pre-post intervention Cardiac fitness (METS): p<0.001 Fatique: p=0.02 FACT-P: p=0.04 Physical well-being: p=0.002 Significant within group decline for control group Increase in fatique score,	• High risk of bias • Low power • Possibly biased towards healthier prostate cancer patients • no description of allocation concealment

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
				btwn group comparison Significant mean difference favoring exercise=13.8 (SD +-10.1), p=0.006, subscale “physical well-being” (p<0.001)	p=0.004, decline in social well-being; p<0.05	
Segal 2009[57]	• Design: RCT 3 arms, Resistance exercise (RET), Aerobic exercise (AET) or usual care (UC) • Sources of funding: Supported by Grant from the Canadian Prostate Cancer Research Fund • Setting: Ottawa Hospital Regional Cancer Centre, Ottawa, Canada • Sample size: 121 men • Duration: 24 weeks	• Eligibility criteria: historically documented prostate cancer, scheduled to receive radiotherapy with or without ADT and approved by treating oncologist • Patient characteristics: • Mean age; 66.3 years (SD=7.0) • Married=82.6% • Completed University or College=51.2% • Employed full-time=23.9% • Cancer stage II=78.5%	• Intervention; • 1. arm: Resistance exercise training group (RET) exercising 3x pr week (2 x 8-12 rep of 10 diff exercises at 60-70% of 1RM) • 2. arm: Aerobic training group (AET) exercising 3 x pr week beginning at 50-60% of predetermined VO_2 peak for week 1-4, progressing to 70-75% for week 5-24 • 3.arm: Usual care	FACT-Fatique (unadjusted group differences): Significant effect for RET vs. UC at 12 weeks (midpoint); M=4.11 (CI=0.87-7.35), p=0 .010 Significant effect for AET vs. UC at 12 weeks (midpoint); M=4.64 (CI=1.47-7.80) P=0.004 Significant effect for RET vs. UC at 24 weeks (post-test); M=4.78 (CI=1.77-7.78) P=0.002 Not significant for	Objectively measured outcomes Group difference (baseline to post-test) Unadjusted VO_2 peak RET vs. UC; MD=1.5 (CI=0.06-3.0) P=0.041 AET vs. UC; MD=1.4 (CI=-0.1-2.8) P=0.52 (NS) Adjusted VO_2 peak RET vs. UC ; MD=1.6 (CI=1.0-3.1) P=0.037 AET vs. UC ; MD=1.4 (CI=0.08-2.8) P=0 .063	• Moderate risk of bias • Centralized with allocation concealment before assignment.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
			group (UC). UC was asked not to initiate exercise during trial	AET vs. UC at 24 wks MD=2.65(CI=-0.29-5.58),P=0.08 FACT-G significant for RET vs. UC at 12 weeks ; MD 4.76 (p=0;017) and at 24 weeks; MD 4.43 (p=0;015) FACT-G no effect for aerobic vs. UC No effect for FACT-P in any intervention arm	(NS) Adverse events : 3 adverse events of these one serious adverse event occurring in the group performing aerobic exercise on day 3 of training protocol (acute myocardial infarction, patients recovered but did not complete intervention)	

Results retrieved from a systematic review by M.J. Velthuis, 2010 [2]

7.4.3 Lung cancer

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Arbane 2011[27]	• Design: RCT, 2 arms • Sources of Funding: St Georges Hospital Therapies Charitable Funding and the Faculty of Health and Social Care Sciences • Setting: St George Healthcare, London, UK • Sample size: 53 patients attending thoractomy for lung cancer • Duration: 1-5 days post-operative and a further 12 weeks post-operative with supervised home exercises	• Eligibility criteria: Patients with NSCLC referred for lung resection via open thoractomy or visual assisted thoractomy • Patient characteristics: Mean age CG=62.6y (32-47), IG=65.4y (47-82), 28 males, 25 females	• Intervention group (n=22): usual care plus 2x/day strength and mobility training (walking, marching on the spot, recumbent bike exercises at bedside and seated leg raises with 2-4lb ankle weights) from day 1 to day 5 postoperative, at 60-80% of max heart rate + a 12-week program of home support • Comparator group (n=21): usual care, including routine physiotherapy treatments, airway clearance techniques, mobilizations as able and upper limb activities, (1x/day), monthly telephone calls providing education	QOL (EORTC-C30): non-significant difference both within groups and between groups EORTC-C30 (functional): IG: pre to post-op mean difference=2.0 (CI=-5.5-9.3) CG: pre to post-op mean difference=2.7 (-4.7-10.0)	Secondary outcomes not part of project outcomes	(+)moderate risk of bias randomization codes kept by independent team member

7.4.4 Colorectal cancer

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Courneya, 2003[32]	• Design: RCT, 2 arms assigned in a 2:1 ratio • Sources of funding: grant from the National Cancer institute of Canada • Setting: Cross Cancer Institute, Edmonton, Canada • Sample size: 102 colorectal cancer survivors • Duration: 16 weeks	• Eligibility criteria: Surgery for colorectal cancer within past 3 months, recovery from surgery as indicated by attending physician, ability to understand and provide written informed consent in English, passed the revised Physical Activity Readiness Questionnaire and no contraindications to exercise as determined by a sub maximal cardio respiratory fitness test. • Patients characteristics: • Age (mean, SD); IG=59.92(10.73) • CG=61.13(9.93) • Patients % on chemotherapy: IG=63.9%, CG=67.7% • Patients % on radiotherapy: IG=23.0%, CG=16.1%	• Intervention group (n=62): prescription of a home-based, personalized exercise program (cardiovascular and flexibility exercises, 3-5 times per week, for 20-30 minutes at 65-75% of predicted HR max.) + weekly phone calls from project director to report participants level of exercise and answer any questions. • Comparator group (n=31): were asked not to begin a structured exercise program and were not given an exercise prescription.	QOL (measured by FACT-C): mean change between groups=-1.3(95%CI -7.8-5.1), p=0.679 (Exploratory ancillary analysis of patients with increased cardiorespiratory fitness compared with patients with decreased cardiorespiratory fitness showed a significant effect for FACT-C, p=0.038) Difference between groups in change from baseline to post-intervention: FACT-C Scale (p=0.679) FACT-G scale (p=0.652)	Cardiopulmonary function Mean change in resting HR=-2.7 (95%CI 3.2 to -8.6) (p=0.361) Remaining outcomes not part of guideline outcomes	moderate risk of bias ITT analysis Blinding of assessors No allocation concealment Exercise group did not perform appreciably more moderate/strenuous exercise than control group

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
				Trial outcome index (p=0.903) physical well-being (p=0.898) functional well-being (p=0.987) emotional well-being (p=0.082), social/family well-being (p=0.933), colorectal cancer subscale (p=0.839)		
Houborg 2006[38]	• Design: RCT, 2 arms • Sources of funding: Danish Research Agency, Danish Cancer Society, Danish Health Insurance Foundation, Danish Cancer Society's Clinical Research Unit • Setting: Aarhus University Hospital, Denmark • Sample size: n=119 • Duration: until	• Eligibility criteria: patients >60y old when admitted for elective, abdominal colorectal surgery • Exclusion: patients with inflammatory bowel disease, disseminated cancer, significant psychiatric disease or dementia or other medical reason • • Patient characteristics: IG: 30 women, 30 men, mean age 72y (SD 7) CG: 29 women, 30 men, mean age 72y (SD 7)	• Intervention group (n=37): mobilizations, strength training of upper and lower extremities and aerobic training, 45 min/session (1/3 mobilization or aerobic training, 1/3 strength training upper extremity, 1/3 lower extremity), load of 50-80% of one repetition maximum.	Fatigue (VAS): Postoperative day 7: more increase in CG 2.3 (95%CI 1.8-2.9) (p=0.0007) Postoperative day 30 and 90: no significant differences between groups in change in fatigue score (no p-value mentioned)		Low risk of bias High number of drop-outs, no direct measurement of one repetition maximum, no monitoring of activities beside intervention

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	discharge		• Comparator group (n=48): turning and positioning in bed, stretching, relaxing neck and shoulders, tightening and relaxation exercises, hot wrappings, massage (45min/session)			

7.4.5 *Haematological cancers*

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Baumann 2011[28]	• Design: RCT 2-arm • Sources of funding: the German José Carreras Leukemia Foundation, the Stefan Morsch Foundation, Förderverein Transplantationszentrum • Setting: center for transplantation ,	• Eligibility criteria: patients with malignant disease, scheduled for HSCT, >18y, good German skills • Exclusion: severe cardiac disease, orthopedic illness of the legs, bone metastases, thrombopenia, acute bleedings, acute health or somatic complaints • Patient characteristics:	• Intervention group (n=17): aerobic endurance training (cycle ergometer, training intensity achieved watt load -20%, 10-20min without interruption) and ADL-training (during chemotherapy and	Quality of life (EORTC-QLQ-C30): Overall QOL difference over time IG: 63.7±19.7 vs. 68.6±11.2, +7.7%) CG: 62.5±23.9 vs. 56.3±17.6, -9.9%) (no p-values	Fatigue (EORTC-QLQ-C30) Difference over time IG: 41.8±25.3 vs. 43.8±22.7, +4.8%, no p-value mentioned CG: 36.1±24.5 vs. 52.8±27.1, +46.3%,	High risk of bias Contamination in control group, no ITT analysis, no reporting of allocation concealment

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	Germany • Sample size: n=47 • Duration: until discharge	• IG: n=17, 11 men, 6 women, mean age 41.41y (SD 11.75) • CG: n=16, 5 men, 11 women, mean age 42.81y (SD 14.04)	after engraftment, different exercises on strength, coordination, stretching, walking and stair climbing, 20-30min/day), twice a day, conducted by professional therapist, start 6 days prior to transplantation until discharge • Comparator group (n=16): clinic's standard physiotherapy program, consisting of individualized mobilization treatment (active and passive methods with low intensities), 20min/session, 5 days/week, conducted by physiotherapist, start one day after transplantation	mentioned) Physical functioning difference over time IG: 83.1±16.9 vs. 65.9±16.5, -20.7%, p=0.005 CG: 79.6±19.2 vs. 59.6±22.9, -25.1%, p=0.002	p=0.046	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
			until day before discharge			
Coleman 2003[31]	• Design: RCT 2-arm • Sources of funding: University of Arkansas for Medical Sciences Medical Endowment Research Fund, the Oncology Nursing Foundation, the Earl Knudsen Charitable Foundation • Setting: Arkansas Sample size: n=24 • Duration: duration of chemotherapy (+/- 6 months)	• Eligibility characteristics: patients receiving high-dose chemotherapy and randem peripheral blood stem cell transplantation for the treatment of multiple myeloma, >40y, not at high risk for pathologic fracture • Patient characteristics: mean age 55 years, age range 42-74 years, 10 women, 14 men, all white	• Intervention group (n=14): Home-based exercise program, combination of resistance and aerobic exercise, 3x weekly for 20 minutes • Comparator group (n=10): usual care and encouragement to remain active	Fatigue (POMS): no reduction over time (no changes and p-values mentioned)	Adverse events: a broken central venous catheter stick	Low sample size, study underpowered Unclear reporting (study split results of patients on or off thalidomide therapy thus only 10 patients are reported on exercise versus not exercise) No reporting of completion rate or adherence to exercise
Jarden 2009[39]	• Design: RCT, two-armed • Sources of funding: the Lundbeck Foundation, the Novo Nordic Foundation, the Danish Cancer Society, the Copenhagen Hospital Corporation and the Danish	• Eligibility criteria: 18-65y, scheduled for HDSCT • Exclusion: prior HSCT, recent cardiovascular or pulmonary disease, abnormal electrocardiogram, psychiatric disorder and motor, musculoskeletal or neurological dysfunction, bony metastasis, infection, anemia, neutropenia,	• Intervention group (n=21): usual care plus multimodal intervention, consisting of 4min warm-up (stationary cycling, 15-30min,<75% of max heart rate, 5 days/week), dynamic and	QOL-Physical functioning (EORTC-QLQ-C30): Difference pre-post between groups IG:82.9±16.3 vs 75.3±17.4 CG: 83.8±13.4 vs	Fatigue (EORTC-QLQ-C30): Difference pre-post between groups IG:33.9±28.2 vs 50.3±24.6 CG: 34.9±28.4 vs 58.8±26.0	High risk of bias Control group was free to increase physical activity Small sample size

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	Nursing Society • Setting: University Hospital of Copenhagen, Denmark • Sample size: n=42 • Duration: 4-6 week	thrombocytopenia • Patients characteristics: • IG: n=21, mean age 40.9y (SD 13.3) • CG: n=21, mean age 37.4y (SD 11.1)	stretching exercises (15-20min, 5 days/week), resistance training (15-20min, 3days/week), progressive relaxation (20min, 2days/week) and psycho-education • Comparator group (n=21): usual care (range of motion, resistance and massage)	63.5±22.6 (p=0.089) Difference pre-3months between groups IG: 82.9±16.3 vs 77.1±18.1 CG: 83.8±13.4 vs 67.7±23.1 (p=0.325) Difference pre-6months between groups IG: 82.9±16.3 vs 87.1±13.2 CG: 83.8±13.4 vs 74.4±23.1 (p=0.131) QOL-FACT-g: Difference pre-post between groups IG:87.0±10.9 vs 81.6±14.5 CG: 77.8±14.7 vs 69.0±11.5 (p=0.298)	(p=0.405) Difference pre-3months between groups IG:33.9±28.2 vs 44.4±25.0 CG: 34.9±28.4 vs 57.3±26.0 (p=0.302) Difference pre-6months between groups IG:33.9±28.2 vs 29.6±21.3 CG: 34.9±28.4 vs 49.6±34.1 (p=0.097) Fatigue (FACT-An) Difference pre-post between groups IG:39.6±6.7 vs 33.9±9.7 CG: 37.5±8.9 vs 27.8±9.0 (p=0.218)	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
				Difference pre-3months between groups IG:87.0±10.9 vs 85.6±9.9 CG: 77.8±14.7 vs 71.3±13.0 (p=0.241) 67.7±23.1 (p=0.241) Difference pre-6months between groups IG:87.0±10.9 vs 90.1±11.9 CG: 77.8±14.7 vs 78.1±18.0 (p=0.620) QOL-FACT-An: Difference pre-post between groups IG:149.2±18.0 vs 136.5±26.1 CG: 136.4±24.6 vs 115.8±21.6 (p=0.225)	Difference pre-3months between groups IG:39.6±6.7 vs 37.1±8.9 CG: 37.5±8.9 vs 31.2±11.9 (p=0.312) Difference pre-6months between groups IG:39.6±6.7 vs 40.1±10.6 CG: 37.5±8.9 vs 33.2±13.0 (p=0.325) Cardiopulmonary function (VO_2peak) Difference pre-post IG: 1.97±0.53 vs 2.03±0.59 (mean % change 0.01) CG: 2.03±0.58 vs 1.45±0.46 (mean %	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
				Difference pre-3months between groups IG:149.2±18.0 vs 145.6±19.9 CG: 136.4±24.6 vs 121.7±25.2 (p=0.167) Difference pre-6months between groups IG:149.2±18.0 vs 153.8±25.1 CG: 136.4±24.6 vs 131.7±34.6 (p=0.395)	change -27.68) p<0.0001	
Courneya 2009[34]	• Design: RCT, 2 arms • Sources of Funding: Lance Armstrong Foundation, the Canada Research Chair program, Health Student – ships, Senior Health Scholar Award, and Clinical Investigator Award from the Alberta Heritage Foundation for	• Eligibility criteria: English speaking, ≥18 years, historically confirmed HL or NHL, receiving chemotherapy or no treatment • Patient characteristics: Mean age: 53.2 (range 18-80) Cancer type: NHL indolent (42%), NHL aggressive (39.3%), Hodgkins lymphoma (18%) Treatment status: Chemotherapy	• Intervention group (n=60): aerobic exercise 3xweekly for 12 weeks, intensity at 60% of peak power output first week, increased by 5% each week to 75% (week 4), duration 15-20 min week 1-4, increased by 5 min pr week to 40-45min (week 9).	Cardiopulmonary function (VO_2peak (l/min)) Difference pre-post IG: mean change +0.40 (95%CI 0.34-0.47) CG: mean change -0.03 (95%CI -0.09-0.03) Unadjusted group difference in	Fatigue (FACT-An) Difference pre-post IG: mean change +4.5 (95%CI 1.9-7.1) CG: mean change -0.1 (95%CI -2.7-2.4) Unadjusted group difference in mean change	moderate risk of bias allocation sequence generated independently and concealed in opaque envelopes from the study coordinator who assigned participants to

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	Medical Research, grant from National Cancer institute of Canada, by Canadian Cancer Society and the NCIC/CCS Sociobehavioural Cancer Research Network • Setting: Cross Cancer institute, Edmonton, Alberta, Canada • Sample size: 122 lymphoma patients • Duration: 12 weeks	(44.3%) but stratified for treatment status Off treatment (55.7%)	Additionally one session of interval training above ventilator threshold (week 7) and one session of VO_2 peak interval training (week9) • Comparator group (n=62): usual care and asked not to increase exercise above baseline during trial	mean change +0.43 (95%CI 0.34-0.52) (p<.001) Adjusted group difference in mean change +0.43 (95%CI 0.34-0.52) (p<.001) QOL (FACT-An) Difference pre-post IG: mean change +10.6 (95%CI 4.9-16.3) CG: mean change +1.1 (95%CI -4.5-6.7) Unadjusted group difference in mean change +9.5 (95%CI 1.5-17.5) (p=0.021) Adjusted group difference in mean change +7.2 (95%CI 0.4-14.1)(p=0.039)	+4.6 (95%CI 1.0-8.3) (p=0.013) Adjusted group difference in mean change +4.0 (95%CI 0.9-7.0)(p=0.012) Treatment status (on or off chemo) did not moderate effect for any objectively measured outcomes: Adverse events No serious adverse event but 3 adverse event (back, hip and knee pain) related to exercise. Patients with knee pain withdrew. The two other patients continued with	groups

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
					modified exercise program	
Dimeo 1997[35]	• Design: RCT, 2arms • Sources of funding: the Nenad Keul Foundation Preventive Medicine, Freisburg in Breisgau, Germany • Setting: Freiburg University Medical Centre • Sample size: 70 • Duration: individual duration depending on hospitalization (11-18 days)	• Eligibility criteria: malignancy confirmed by biopsy, ECOG performance score 0-2, 18-60y, no evidence of impairment of cardiac, pulmonary, renal and hepatic function; absence of bony metastases in the lower extremities; and transplantation of CD 34+ peripheral blood stem cells. • Patients characteristics: mean age IG 39 years (+-10), mean age CG 40 years (+-11)	• Intervention group (n=33): aerobic exercises on bed ergometer, intervals of 1 min x 15 daily, intensity at min 50% of cardiac reserve • Comparator group (n=37): no exercise	Cardiopulmonary function (heart rate) Maximal heart rate at admission IG: 170±18 CG: 168±16 p=0.58 Maximal heart rate at discharge IG: 166±21 CG: 168±19 p=0.84 % of estimated maximal heart rate at admission IG: 94±7 CG: 94±8 p=0.89 % of estimated maximal heart rate at admission IG: 92±10	Adverse events less severity of complications in IG: Diarrhea: p=0.04 Pain: p=0.01 One severe adverse event in exercise group deemed to be highly unlikely related to exercise (patient died of hepatic hemorrhage)	high risk of bias multiple comparisons, increased risk of spurious findings randomization not well described no description of allocation concealment

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
				CG: 93±9 p=0.69		
Chang 2008[30]	• Design: RCT, 2 arms • Sources of funding: none stated • Setting: medical centre in central Taiwan • Sample size: 22 patients with AML • Duration: 3 weeks	• Eligibility criteria: > 18 years of age diagnosed with AML and aware of their diagnosis, prescribed chemotherapy, in satisfactory functional condition as determined by ECOG-PS (rating of 0-3.), willing to sign consent form • Patients characteristics: mean age IG=49.4 years (SD=15.3), CG=53.3 years (SD=13.6)	• Intervention group (n=11): 12 min walking in hospital hallway, five days per week for 3 weeks • Comparator group (n=11): non-invasive routine care	Fatigue Average fatigue intensity: difference between groups At day 7: -3.64 (95%CI -6.65 to -0.62) p=0.02 At day 14: -3.73 (95%CI -6.65 to -0.81) p=0.010 At day 21: -2.55 (95%CI -5.62 to -0.53) p=0.100 Worst fatigue intensity: difference between groups At day 7: -4.73 (95%CI -8.73 to -0.72) p=0.02 At day 14: -4.27 (95%CI -7.53 to -1.01) p=0.01 At day 21: -3.36 (95%CI -6.74 to	Secondary outcomes not part of project outcomes No adverse events	high risk of bias allocation concealment not described small sample size lacks patient similarity at baseline

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
				0.01) p=0.05 Fatigue interference difference between groups At day 7: -2.58 (95%CI -5.06 to -0.09) p=0.04 At day 14: -2.83 (95%CI -5.56 to -0.11) p=0.04 At day 21: -3.32 (95%CI -6.18 to -0.46) p=0.02		

7.4.6 Mixed cancers

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Rummans 2006[41]	• Design: RCT, two-arms • Sources of funding: the Linse Bock Foundation, Saint Marys Hospital Sponsorship Board • Setting: Mayo Clinic Cancer Center • Sample size: n=103 • Duration: 4 weeks	• Eligibility criteria: newly diagnosed with advanced cancer, estimated 5-year survival rate of 0-50% who planned to receive at least 2 weeks of radiation therapy. Exclusion: scored 20 or less on Folstein mini mental status examination, 3 or more on the Eastern Cooperative Oncology Group, active thought disorder or suicidality, ongoing alcohol or substance abuse, previous radiation therapy, recurrence of disease • Patient characteristics: IG: n=49, mean age 59.7y (SD 11.49), CG n=54, mean age 59.4y (SD 10.62)	• Intervention group (n=49): 8x90min-sessions, completed within 4 weeks after enrollment, led by psychiatrist or psychologist co facilitated by nurse, physical therapist, chaplain or social worker, 20min conditioning exercises, educational instruction and 20min relaxation exercises. • Comparator group (n=54): usual care	QOL (Spitzer QOL Uniscale + Linear Analogue Scales of Assessment (LASA) of QOL) Overall QOL at baseline IG: 70.0±21.89 CG: 73.0±20.80 p=0.4829 Overall QOL at week 4 IG: 72.8±20.62 CG: 64.1±22.53 p=0.0469 Overall QOL at week 8 IG: 71.9±19.41 CG: 68.4±23.48 p=0.4229 Overall QOL at week 27 IG: 72.1±19.49 CG: 72.1±18.97 p=0.9922 No significant difference in overall	Secondary outcomes not part of project outcomes	High risk of bias Small sample size Heterogeneity of study population

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
				QOL in intervention group, a significant decrease in QOL (no p-value mentioned)		
Adamsen 2009[26]	• Design: RCT 2 arms • Sources of funding: The Lundbeck Foundation, The Novo Nordisk, The Egmont Foundation, The Danish Cancer Society, The Svend Andersen Foundation, The Aase and Ejnar Danielsen Foundation, The Beckett Foundation, The Wedell-Wedellsborg Foundation, The Hede Nielsen Family Foundation, The Gangsted Foundation, Copenhagen University Hospital • Setting: Two University Hospitals in Copenhagen, Denmark	• Eligibility criteria: diagnosis of cancer, having received at least one cycle of chemotherapy for advanced disease or as adjuvant treatment, having a WHO performance status of 0 or 1, and 18-65 years • Patients characteristics: 73 men, 196 women, mean age 47 years (range 20-65), 21different cancer diagnosis, 59 different chemotherapy regimes	• Intervention group (n=118): Group based multimodal high and low intensity exercise intervention supervised by trained nurse specialist and physiotherapist, high intensity training for 90 minutes 3 x weekly for 6 weeks, activities equivalent to a total of 43 MET hours per week • Comparator group (n=117): conventional medical care + allowed freely to increase physical activity + exercise program after the six week	QOL (EORTC QLQ-C30) Global health status/QOL: difference baseline-6weeks IG: 63.8±21.1 vs 67.2±20.3 CG: 60.2±22.4 vs 63.3±22.4 Mean difference: 2.2 (95%CI -2.7-7.1), p=0.4 Physical functioning: difference baseline-6weeks IG: 84.7±14.5 vs 89.0±12.4 CG: 84.0±15.7 vs 86.4±14.5 Mean difference: 2.4 (95%CI -0.4-5.1), p=0.09	Fatigue (EORTC-QLQ-C30) Difference baseline-6weeks IG: 39.7±25.8 vs 34.6±24.3 CG: 43.0±23.9 vs 41.0±22.7 Mean difference: -6.6 (95%CI -12.3 to -0.9), p=0.02 Adverse events One patient with brain tumor experienced grade 3 seizure post cardiovascular training (recovered but subsequently excluded from trial)	Low risk of bias Randomization using CITMAS Allocation concealed Outcome measures keyed and analyzed by independent research assistant Analyses carried out on an ITT basis

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	• Sample size: 269 patients with cancer (mixed) • Duration: 6 weeks		assessment	Cardiopulmonary function (VO_2peak in l/min) Difference baseline-6weeks IG: 1.82±0.4 vs 1.96±0.5 CG: 1.90±0.5 vs 1.88±0.5 Mean difference: 0.16 (95%CI 0.1-0.2), p<0.0001		
Mustian 2009[40]	• Design: RCT 2-arms • Sources of funding: the National Cancer Institute • Setting: University of Rochester James P. Wilmot Cancer Center • Sample size: n=38 (breast and prostate cancer patients) • Duration: 4 weeks	• Eligibility criteria: women with breast cancer and men with prostate cancer beginning standard radiation therapy, no distant metastases, no recurrent disease, no contraindications, at least 30 scheduled radiation treatments, sedentary lifestyle • Patient characteristics: IG: n=19, 6 men, 13 women, CG: n=19, 5 men, 14 women	• Intervention group (n=19): radiation therapy+ individually tailored home-based, progressive walking (60-70% of heart rate, 7 days a week for 4 weeks) and therapeutic resistance band program (moderately intense progressive resistance exercise, 7 days a week for 4 weeks,	Fatigue (BFI) Difference baseline-post-intervention IG:1.85±1.87 vs 1.60±1.36 (-0.25±1.24) (Cohen's d=-0.15) CG: 2.62±2.14 vs 2.44±2.08 (-0.18±1.16) (Cohen's d=-0.08) Difference post-intervention-3months IG:1.60±1.36 vs 1.16±0.98 (-0.66±1.52)	Secondary outcomes not part of project outcomes	Low risk of bias Patients not blinded, risk of experimenter bias, participant expectancy effect or nonspecific treatment effects

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
			focused on upper body) • Comparator group: conventional medical care (radiation therapy)	(Cohen's d=-0.58) CG: 2.44±2.08 vs 2.73± 2.60 (0.12±1.95) (Cohen's d=0.04) Fatigue (FACIT-F) Difference baseline-post-intervention IG:38.68±11.66 vs 41.79±8.99 (3.11±8.69) (Cohen's d=0.29) CG: 36.89±11.73 vs 35.84±12.08 (-1.05±4.84) (Cohen's d=-0.09) Difference post-intervention-3months IG:41.79±8.99 vs 43.17±7.74 (3.89±7.77) (Cohen's d=0.45) CG: 35.84±12.08 vs 40.35±12.24 (3.88±6.97) (Cohen's d=0.29)		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
				Cardiopulmonary function (6MWT) Difference baseline-post-intervention IG:1894.37±296.78 vs 1937.95±261.99 (43.58±227.84) (Cohen's d=0.16) CG: 1478.21±401.02 vs 1425.28±438.27 (-28.44±303.75) (Cohen's d=-0.13) Difference post-intervention-3months IG:1937.95±261.99 vs 2020.59± 386.36 (133.53±396.79) (Cohen's d=0.37) CG: 1425.28±438.27 vs 1600.33±468.86 (78.73±484.12) (Cohen's d=0.28) QOL (FACIT-F) Difference baseline-post-intervention		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
				IG:124.19±25.12 vs 130.19±20.13 (6.00±18.31) (Cohen's d=0.26) CG: 117.59±29.65 vs 116.92±30.58 (-0.67±11.51) (Cohen's d=-0.02) Difference post-intervention-3months IG:130.19±20.13 vs 132.96± 16.41(8.76±16.51)(Cohen's d=0.41) CG: 116.92±30.58 vs 126.13±31.81 (8.55±11.28) (Cohen's d=0.28)		
Griffith 2009[37]	• Design: RCT 2-arms • Sources of funding: The National Institutes of Health, National Center for Research resources, NIH Roadmap for Medical Research • Setting: university teaching hospital and community cancer center in Baltimore	• Eligibility criteria: >21y, diagnosis of stage I to II cancer who were scheduled to receive chemotherapy, radiation therapy or both, exclusion: comorbidities, individuals exercising more than 120min per week • Patient characteristics: IG: n=68, mean age 59.8y (SD 10.8), CG: n=58, mean age 60.6y (SD 10.8)	• Intervention group (n=68): walking intervention, 50-70% of maximum heart rate, brisk 20-30 min walk followed by 5 min slower walking (cool down), 5 times per week + biweekly telephone call by study nurse	Cardiopulmonary function (VO_2peak) Difference pre-post IG: -2.9% CG: +5.6% p=0.26	Cardiopulmonary function (VO_2peak) Difference pre-post (dose-response analysis) Prostate group: +8% Nonprostate group:->9%	High risk of bias Adherence problems, small sample size, limited power for subset analysis, use of 2 methodologies for

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	• Sample size: n=126 • Duration: ?		• Comparator group (n=58): biweekly phone calls by study nurse + patients were encouraged to maintain their current level of activity		p=0.008	cardiorespiratory fitness assessment
Brown 2006[29]	• Design: RCT 2-arms • Sources of funding: the Linse Bock Foundation and the Saint Mary's Hospital Sponsorship Board • Setting: Division of Radiation Oncology Mayo Clinic, Rochester • Sample size: n=115 • Duration: 4weeks	• Eligibility criteria: cancer diagnosis within the past 12 months, expected survival of at least 6 months, 5-year survival probability of no more than 50%, treatment recommendation for at least 2 weeks, exclusion: MMSE less than 20, ECOG score 3 or more, active alcohol or substance abuse, active thought disorder, suicidal plans • Patient characteristics: IG: n=49, CG: n=54	• Intervention group (n=49): 8x90-min sessions over 4 weeks, seated range of motion exercises of upper and lower extremities, resistive exercises with elastic band, stretching exercises, functional lower extremity exercises to increase endurance, relaxation exercises and a individualized home program • Comparator group (n=54): standard medical care (not	Fatigue Difference between groups at baseline: POMS fatigue-inertia: p=0.3934 POMS vigor-activity: p=0.2495 SDS Fatigue: p=0.9887 LASA: p=0.7950 STAI: p=0.9302 Difference between groups at week 4: overall higher fatigue QOL-scores (p=0.047) in IG Difference between groups at week 8	Secondary outcomes not part of project outcomes	High risk of bias Compliance to exercise instructions unknown, amount of exercises not known in control group

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
			further described)	no significant differences, but trend towards better fatigue-score in CG (POMS Fatigue-inertia p=0.065 and SDS Fatigue p=0.098)		
Dodd 2010[36]	• Design: RCT 3-arms • Sources of funding: the National Cancer Institute, the Clinical and Translational Science Institute, Clinical Research Center • Setting: 6 outpatient settings in San Francisco Bay Area • Sample size: n=119 • Duration: 1y	• Eligibility criteria: women, >18y, confirmed diagnosis of breast, colorectal or ovarian cancer, beginning first chemotherapy, Karnofsky Performance Status score of 60 or greater, exclusion: concurrent radiation therapy, bone marrow transplantation, uncontrolled hypertension, diabetes mellitus, pain intensity score greater than 3, lytic bone lesion, orthopedic limitations, history of major depression, sleep disorders, chemotherapy within past year, diagnosis of AIDS-related malignancy, leukemia • Patient characteristics: IG: n=44, mean age 49.4y (SD 8.2); CG: n=39, mean age 52.0y (SD 10.8); Post-IG: n=36, mean age 50.4y (SD	• Intervention group (n=37): exercise prescription with weekly phone calls from exercise trainers, consisting of individualized cardiovascular/aerobic exercises, 3-5 times per week, heart rate at 60-80% VO_2peak, 20-30min of continuous exercises • Later-intervention group (n=32): similar exercise intervention after completion of cancer treatment • Comparator group (n=37): usual care (no exercise	Fatigue (PFS) Change over time p=0.084 Change over time per group No p-value mentioned	Adverse events Hip pain, sciatica (n=16), arm discomfort (n=4), knee discomfort (n=10), ankle discomfort (n=3), foot discomfort (n=8), asymptomatic ischemic changes electrocardiogram (n=10), asymptomatic bigeminy (n=6), premature ventricular complexes (n=9)	Moderate risk of bias Only 3 assessments in 1 year period to capture effect

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
		9.0)	prescription) + weekly phone calls by research nurse			
Courneya 2008[33]	• Design: RCT, 2 arms • Funding: funding and drug supply provided by Amgen, Canada, Inc. • Setting: Cross Cancer Institute, Edmonton, Canada • Sample size: 55 mild-to-moderately anemic cancer patients • Duration: 12 weeks	• Eligibility criteria: historically confirmed nonmyoloid cancer diagnosis, an Hb lever of 80-110 g/l, an Eastern Cooperative Oncology group performance status of 0-2, completed definitive surgery, expected survival ≥3 months, English speaking and ≥18 years of age, darbepoetin alfa therapy • Patient characteristics: mean age=56 (25-77), Female 45 (81.8%), Current chemotherapy=51 (92.7%), not stratified for chemo vs. non-chemo	• Intervention group (n=26):3 x cycle ergometry sessions pr week for 12 weeks at 60-100% of baseline peak power output • Comparator group (n=29):usual care, asked not to initiate a structured exercise program during intervention period	QOL (FACT-An) Mean change baseline-postintervention IG: +13.4 (95%CI 2.5-24.2) CG: +20.3 (95%CI 9.2-31.4) Unadjusted group difference: -6.9 (95%CI -22.1-8.3), p=0.363 Adjusted group difference: -3.2 (95%CI -16.7-10.4), p=0.637 Fatigue (FACT-An) Mean change baseline-postintervention IG: +7.8 (95%CI 2.8-12.8) CG: +9.1 (95%CI 4.4-13.8) Unadjusted group difference: -1.3	Cardiopulmonary function (VO_2peak) VO_2peak (ml/kg/min) Unadjusted group difference: +3.0 (95%CI -1.2-4.7), p=0.001 Adjusted group difference: +3.0 (95%CI 1.1-5.0), p=0.003 VO_2peak (l/min) Unadjusted group difference: +0.21 (95%CI 0.08-0.34), p=0.001 Adjusted group difference: +0.22 (95%CI 0.08-0.37), p=0.004	moderate risk of bias ITT analysis Appropriate allocation concealment

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
				(95%CI -8.0-5.4), p=0.694 Adjusted group difference: +2.1 (95%CI -2.8-7.1), p=0.388		
Schwartz 2009[42]	• Design: RCT 3 arms • Funding: National Institutes of Health grant • Setting: 3 major cancer centres and community medical oncology practices • Sample size: 101 women • Duration: 12months	• Eligibility criteria: women with histologically confirmed neoplasia, >18y, able to speak and read English, ambulatory, exercised<120min per week, chemotherapy and radiotherapy naïve, beginning chemotherapy with a steroid or as an antiemetic, exclusion: psychiatric illness, cardiovascular disease, movement-limiting arthritis, pulmonary diseases, steroids 6 months prior to start of study, Paget's disease, hyperparathyroidism, rheumatoid arthritis, ankylosing spondylitis, other metabolic bone diseases • Patient characteristics: AG: n=34, mean age 48y; RG: n=34, mean age 47y; CG: n=33, mean age 48y	• Intervention aerobic exercise group (AG)(n=34): 4days/week, 20-30min, low intensities, weight bearing aerobic activities + telephone follow-up • Intervention resistance exercise group (RG)(n=34): specific exercises with theraband or on weight equipment, at least 3 sets of 12 repetitions or 2 sets of 18-20 repetitions (based on subjects 1-repetition maximum)+ telephone follow-up	Cardiopulmonary function (12MWT) Change over time AG: baseline 1017.3 (SD 210), at 6 months 1219.2 (SD 178), at 12 months 1201 (SD 183) RG: baseline 1021.7 (SD 186), at 6 months 1174.7 (SD 191), at 12 months 1144 (SD 185) CG: baseline 1035.4 (SD 200), at 6 months 911.1 (SD 194), at 12 months 983 (SD 193) Difference between groups AG:+16%, mean 661±9ft at 6 and	Adherence rate: in AG 94% (79% at 12months), in RG 74% and 65% at 12 months	High risk of bias Problems with adherence rate in RG

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
			• Comparator group (n=33): only telephone call	12months RG:+11%, mean 401±28ft at 6 and 12months (p<0.05) CG: 12% decrease at 6 months, increase at 12months but 5% decline compared to baseline		

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