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Exercise interventions before and during active cancer treatment. A systematic review

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Summary. *Background:* Poor initial physical health in cancer patients is associated with a higher risk of treatment-related complications and poorer health outcomes. Physical functioning is amenable to interventions, such as exercise focusing on maintaining or building strength and endurance. This systematic review focuses on the effect of prehabilitation in patients undergoing or due to undergo cancer treatment on the course of treatment, quality of life, physical functioning and fatigue. *Materials and methods:* A systematic Medline and Embase search for randomised controlled trials addressing the effect of exercise interventions prior to or during active cancer treatment with radiotherapy, chemotherapy or surgery. *Results:* The search yielded 21,663 publications of which 33 publications from 28 studies were included in this review. Exercise interventions had the most consistent effect on functional tests (positive effect reported in 69%), followed by the ability to perform daily activities (positive effect in 53%), fatigue (41%) and overall quality of life (38%). Three studies also reported a positive effect on other outcomes such as chemotherapy completion, treatment-related complications and duration of hospitalisation. For improving physical functioning, endurance training appears to be most beneficial, while for maintaining overall quality of life, combined endurance-resistance exercise appeared superior to endurance or resistance exercise only. *Conclusion:* Although prehabilitative exercise interventions increase results on endurance tests, no benefit for quality of life, fatigue or daily functioning was ascertained. It is questionable whether these findings justify the investments that prehabilitation interventions require from both health care providers and patients.

Key words: prehabilitation, cancer treatment, exercise intervention

Introduction

In the past decades, multiple improvements have been seen in the treatment of malignancies, resulting in greater chances of cure as well as prolonged survival and better disease control. For example, although the number of people newly diagnosed with cancer in the Netherlands has nearly doubled over the past 25 years, the number of cancer-related deaths has risen by only 25% (1). However, these advances come at a price, as physical functioning and quality of life can decrease during oncological treatment (2, 3), sometimes temporarily, sometimes irreversibly.

This may be partly due to the direct impact of the cancer itself or the oncological treatment. However, other factors also contribute. For some patients, diag-

nosis and treatment of cancer are synonymous with an inactive daily life, (4), resulting in further loss of physical capacity, muscle mass and strength (4-6). Furthermore, poorer initial physical health and performance status are associated with a higher risk of treatment-related complications and poorer post-treatment health outcomes (7).

However, physical functioning is not a static state but can be amenable to intervention, such as exercise interventions focusing on maintaining or building strength and endurance. Given prior to or during active cancer treatment, exercise interventions could aid in stimulating an active lifestyle, potentially improving or maintaining physical reserves and overall health, leaving the patient less susceptible to complications or functional decline. For vulnerable or unfit patients, exercise interventions may improve weakness, even in very elderly people (8). Improving baseline functioning may even make specific oncological treatment styles feasible that at first appeared to be too aggressive for that particular patient.

The aim of this systematic review was to identify randomised controlled trials addressing what effect exercise interventions prior to or during active cancer treatment with radiotherapy, chemotherapy or surgery had on the course of cancer treatment, quality of life, physical functioning and fatigue.

Methods

Search strategy and article selection

For this review, exercise was defined as physical activity causing an increase in energy expenditure and involving a planned or structured movement of the body, performed in a systematic manner in terms of frequency, intensity and duration; interventions could consist of strength or endurance training, or a combination of both.

Possible outcomes were: physical functioning either assessed from the ability to perform daily activities or measured objectively using one or more physical performance tests; overall quality of life; fatigue; treatment completion, treatment-related complications and health care utilisation. Outcome measures were only included if they consisted of an objective measurement or were assessed using a validated assessment tool.

On May 29th 2014, a search was performed in both Medline and Embase using synonyms of 'exercise' and 'cancer' and 'treatment'. Details of the search can be found in Appendix 1.

The titles and abstracts of all studies retrieved by the search were assessed by one investigator (MH) to determine which were eligible for further investigation. All potentially relevant articles were subsequently screened as full text by two authors (MH and KA). Only full text manuscripts were included. Studies were excluded if: they had a single arm or non-randomised study design; did not include a care-as-usual or placebo arm; the study population included patients with benign disease; patients were not undergoing or due to undergo surgery, radiotherapy or chemotherapy; or patients were included who had already completed their cancer treatment, or the focus was only on pediatric patients. The same went for studies addressing the feasibility of or adherence to the exercise intervention or if exercise was only one component in a multimode intervention. In addition, studies using exercises focusing on a specific part of the body – such as swallowing exercises or pelvic floor exercises – were not included. Finally, studies were excluded if they were not written in English, German, French, Dutch or Spanish.

Where only an abstract was available, we attempted to find a final report of the study by searching Embase and Medline using the names of first, second and/or final authors as well as key words from the title. Also, in case of insufficient data in the original manuscript, the authors were contacted for additional information.

Finally, citations of publications included were cross-referenced to retrieve any additional relevant studies.

Data extraction

Data regarding study design and results were independently extracted by two investigators (MH and KA) for each eligible study. The following items were extracted: study setting, study population (number of patients, median age, sex, type of malignancy, type of cancer treatment), type of exercise intervention (en-

durance, resistance or both; home-based or supervised; intensity of exercise intervention, duration of intervention), adherence to intervention as well as the results of the intervention in terms of physical functioning, quality of life, fatigue and the course of treatment.

Quality assessment

The methodological quality of each of the studies was independently assessed by two reviewers (MH, KA), using a nine-item instrument adopted from the Cochrane guidelines for the methodological assessment of randomised trials (Appendix 2a) (9, 10). Disagreement among the reviewers was discussed during a consensus meeting and in case of persisting disagreement, the assistance of a third reviewer (FvdB) was enlisted.

Data synthesis and analysis

As a result of heterogeneity in study designs, diversity of patient populations and the wide variety in content of exercise interventions, a formal meta-analysis was not possible. We thus summarised the study results to describe our main outcomes of interest for all studies combined, as well as for several subgroups based on type of exercise, type of intervention, type of cancer and type of cancer treatment. For group comparisons, the chi-square test was used; a p-value ≤0.05 was considered statistically significant. Analyses were made using the SPSS (Statistical Package for the Social Sciences) version 21.0.

Results

Search and study selection

The search yielded 21,663 publications (Medline 8,921; Embase 12,742) of which 3,488 were duplicates. After exclusion of another 18,143 publications for other reasons (Figure 1), 32 publications from 28 studies were selected for this review (11-42). Cross-referencing yielded one more publication (43) from one of the 28 studies already included.

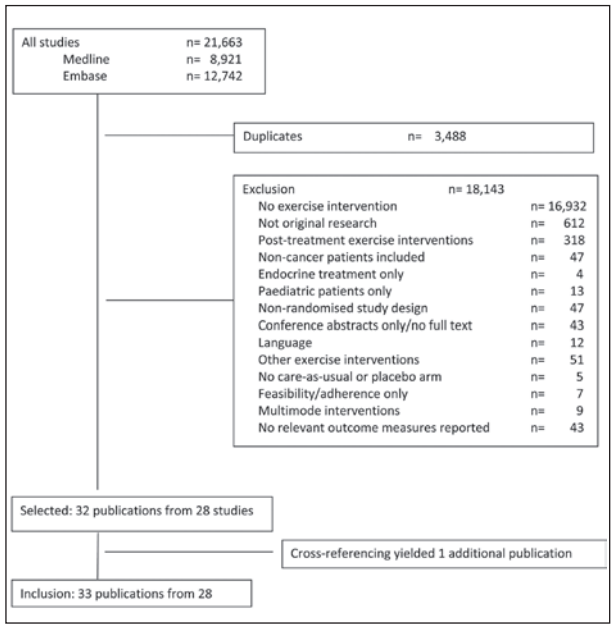

Figure 1. Search results and study selection

Baseline characteristics of studies included can be found in Table 1. Thirteen studies focussed on breast cancer(15, 16, 19, 20, 24, 26-30, 32, 34-36, 40); other malignancies were haematological (n=3) (17, 18, 37), prostate (n=3) (31, 41, 42), head and neck (n=2) (38, 39), lung (n=2) (14, 26) and various (n=5) (11-13, 21-23, 33, 43). Most studies focussed on chemotherapy (n=13) (11-13, 17-21, 24-27, 32, 36, 37) or a combination of chemotherapy and/or radiotherapy (n=7) (15, 16, 29, 30, 34, 35, 39, 40); six studies included only patients undergoing radiotherapy (28, 31, 33, 38, 41-43), one related to surgery (14) and one study included various treatment modalities (22, 23). The median number of patients was 48 (range 15-269). Median ages per study varied from 40 to 71 years with a median of 52 years. Due to the predominance of breast cancer studies, the vast majority of patients included were female.

Details on the interventions can be found in Table 2. In thirteen studies, the exercise intervention consisted of endurance training (13, 15, 17, 21-24, 26, 29-31, 36, 40, 42); one study focused exclusively on resistance training (38), two studies had an endurance training arm as well as a resistance training arm (19, 20, 41) and the remaining twelve studies used a

Table 1. Baseline characteristics of studies included

	Patients and setting						Outcome measures*				
	Cancer type	Treatment mode	n=	Age	% Female	Type of exercise Intervention	Physical functioning	Functional tests	Global quality of life	Fatigue	Others
Adamsen (2009, 2013)(11;12)	Various	CT	269	47.2 (SD 10.7)	73%	RE	+		+	+	
Backman (2014)(13)	Breast, colorectal	CT	77	54 (?)	90%	E	+		+	+	
Benzo (2011)(14)	Lung	S	19	71 (?)	53%	RE		+			Health care utilisation, treatment complications
Cadmus (2009)(15)	Breast	CT/RT	50	54 (9)	100%	E	+		+		
Campbell (2005)(16)	Breast	CT/RT	22	48 (?)	100%	RE	+	+	+	+	
Chang (2008)(17)	Haematological	CT	22	51 (?)	45%	E		+		+	
Coleman (2003)(18)	MM	CT	24	55 (?)	42%	RE		+		+	
Couneya (2007, 2008)(19;20)	Breast	CT	242	49 (25-78)	100%	E/R			+	+	Treatment completion measured as relative dose intensity
Dimeo (1997)(21)	Various	CT	70	40 (11)	73%	E		+			Health care utilisation and chemotherapy toxicity
Griffith (2009, 2013)(22;23)	Various	Various	126	60.2 (10.6)	61%	E	+			+	
Headley (2004)(24)	Breast	CT	38	51 (?)	100%	E	+			+	
Henke (2014)(25)	Lung	CT	46	?	?	RE	+	+	+	+	
Hornsby (2014)(26)	Breast	CT	20	49 (?)	100%	E	+		+	+	
Husebo (2014)(27)	Breast	CT	67	52.2 (9.3)	100%	RE		+		+	
Hwang (2008)(28)	Breast	RT	40	46.3 (?)	100%	RE	+		+	+	
Mock (2001)(29)	Breast	CT/RT	52	48.0 (11.1)	100%	E	+	+		+	
Mock (2004)(30)	Breast	CT/RT	119	52 (30-69)	100%	E		+		+	
Monga (2007)(31)	Prostate	RT	21	69 (?)	0%	E	+		+	+	
Moros (2010)(32)	Breast	CT	17	49 (38-61)	100%	RE			+		
Mustian (2009, 2010)(33;43)	Breast, prostate	RT	38	60.0 (12.1)	71%	RE			+	+	
Mutrie (2007, 2012)(34;35)	Breast	CT/RT	203	51.6 (9.5)	100%	RE	+	+	+	+	
Naraphong (2014)(36)	Breast	CT	23	47 (?)	100%	E		+		+	
Oechsle (2014)(37)	Haematological	CT	48	52 (?)	31%	RE	+			+	
Rogers (2013)(38)	Head and neck	RT	15	60.5 (12.5)	20%	R	+		+	+	
Samuel (2013)(39)	Head and neck	CT/RT	48	52 (?)	13%	RE		+			
Segal (2001)(40)	Breast	CT/RT	123	51 (8.7)	100%	E	+		+		
Segal (2009)(41)	Prostate	RT	121	66.3 (7.0)	0%	E/R			+	+	
Windsor (2004)(42)	Prostate	RT	66	68.8 (52-82)	0%	E				+	

MM multiple myeloma CT chemotherapy; RT radiotherapy CT/RT chemotherapy and/or radiotherapy S surgery; E endurance; R resistance; RE both endurance and resistance components; E/R endurance and resistance in separate arms * Details of assessments used can be found in Appendix 3.

Table 2. Exercise intervention per study

	Control arm	Intervention type	Description of intervention	Intensity per week	Duration	Place	Adherence
Adamsen (2009, 2013)(11;12)	Usual care	RE	High intensity cardiovascular and resistance training	9 hrs	6 weeks	S	71%
Backman (2014)(13)	Usual care	E	Daily walks of 10,000 steps and a weekly supervised group walk	11.5 hrs	10 weeks	SH	91%
Benzo (2011)(14)	Usual care	RE	Upper and lower extremity strength and endurance training and inspiratory muscle training	10 hrs	1 week	S	100%
Cadmus (2009)(15)	Usual care	E	Endurance training; majority used walking as activity of choice	2.5 hrs	26 weeks	H	64%
Campbell (2005)(16)	Usual care	RE	A variety of strength and endurance exercises	2 hrs	12 weeks	S	70%
Chang (2008)(17)	Usual care	E	Walking intervention	1 hrs	3 weeks	S	-
Coleman (2003)(18)	Usual care	RE	Aerobic and strength/endurance training	*	26 weeks	H	-
Couneya (2007, 2008)(19;20)	Usual care	E/R	Endurance OR strength training	3 hrs	26 weeks	S	E 72% R 68%
Dimeo (1997)(21)	Usual care	E	Biking on an ergometer in a supine position with interval training	3.5 hrs	while in hospital	S	82%
Griffith (2009, 2013)(22;23)	Usual care	E	Walking intervention	2.5 hrs	during treatment	H	68%
Headley (2004)(24)	Usual care	E	20 min of seated moderate-intensity repetitive motion exercises	1.5 hrs	12 weeks	H	75%
Henke (2014)(25)	Usual care	RE	Resistance and endurance (walking and stair walking) training	5 times	3 cycles	S	-
Hornsby (2014)(26)	Usual care	E	Aerobic exercise training	3 hrs	12 weeks	S	66%
Husebo (2014)(27)	Usual care	RE	Exercise programme combining strength and aerobic training	5 hrs	during treatment	H	17%
Hwang (2008)(28)	Placebo	RE	Stretching, aerobic and strengthening exercises	2.5 hrs	5 weeks	S	-
Mock (2001)(29)	Usual care	E	Walking intervention	1.5-3 hrs	during treatment	H	70%
Mock (2004)(30)	Usual care	E	Moderate intensity walking exercise programme	1.5-3 hrs	during treatment	H	72%
Monga (2007)(31)	Usual care	E	Aerobic exercise programme	1.5 hrs	8 weeks	S	-
Moros (2010)(32)	Usual care	RE	Individualised aerobic and strengthening exercise programme	3 hrs	18-22 weeks	S	-
Mustian (2009, 2010)(33;43)	Usual care	RE	Walking and progressive resistance exercise intervention	daily	4 weeks	H	-
Mutrie (2007, 2012)(34;35)	Usual care	RE	Aerobic and strengthening exercises	2 hrs	12 weeks	SH	-
Naraphong (2014)(36)	Usual care	E	Individually tailored programme using a progressive low- to moderate-intensity walking programme	2.5 hrs	12 weeks	H	-
Oechsle (2014)(37)	Usual care	RE	Exercise programme with ergometer endurance training and resistance exercises	3.5 hrs	while in hospital	S	-
Rogers (2013)(38)	Usual care	R	Resistance exercise intervention	2 hrs	12 weeks	SH	53%
Samuel (2013)(39)	Usual care	RE	Brisk walking and tailored resistance training of upper and lower limb	2-3 hrs	6 weeks	S	-
Segal (2001)(40)	Usual care	E	Walking intervention	3-5 hrs	26 weeks	S/H	-
Segal (2009)(41)	Usual care	E/R	Trunk, lower limb and upper limb resistance training OR progressive ergometer endurance training	2-3 hrs	24 weeks	S	R 88% E 83%
Windsor (2004)(42)	Usual care	E	Moderate-intensity walking intervention	1.5 hrs	4 weeks	H	

E endurance; R resistance; RE both endurance and resistance components; E/R endurance and resistance in separate arms

S supervised H home-based SH Both supervised and home-based components; S/H Study consisted of one supervised and one home-based arm; * individualised; - not reported

combination of both types of exercise (11, 12, 14, 16, 18, 25, 27, 28 32-35, 37, 39, 43). Exercise was home-based in ten studies (15, 18, 22-24, 27, 29, 30, 33, 36, 43), supervised in 14 studies (11, 12, 14, 16, 17, 19-21, 25, 26, 28, 31, 32, 37, 39, 41) and a combination of home-based and supervised in three (13, 34, 35, 38, 42); (in all this passage, check the numbers of studies cited vs the number mentioned in the text) one study had a separate arm for home-based exercise and for the supervised training programme (40). The exercise intervention took a median of 2.5 hours per week (range 1-11.5 hours) and lasted a median of 12 weeks (range 1-26 weeks). Most studies used care-as-usual as the control arm; one study used a placebo exercise intervention (28).

Quality assessment

The results of the quality assessment for included studies are summarised in Figure 2; full details can be found in Appendix 2b. Reviewer agreement was >95% for all items. Many studies did not clearly describe the randomisation process or method of allocation concealment, rendering it impossible to determine the risk of bias for these items. While all but one study had shortcomings in the blinding of participants and personnel, it was generally unclear whether outcome assessment was free from bias. Handling of attrition presented issues in 18% of studies; for another 25% this aspect could not be evaluated.

Most studies provided clearly defined primary outcomes (93%), demonstrated good baseline group comparability (89%) and performed intention-to-treat analyses (82%). However, 46% did not report a sample size calculation; in addition nine studies had sample sizes lower than 25 and fourteen studies lower than 50, potentially affecting the ability of these studies to detect differences between study arms.

Effect of the exercise intervention on physical functioning

Results of the exercise intervention can be found in Table 3; an overall summary as well as subgroup analyses are reported in Table 4. Eight out of the 28 studies (29%) did not find any positive effects from the exercise intervention.

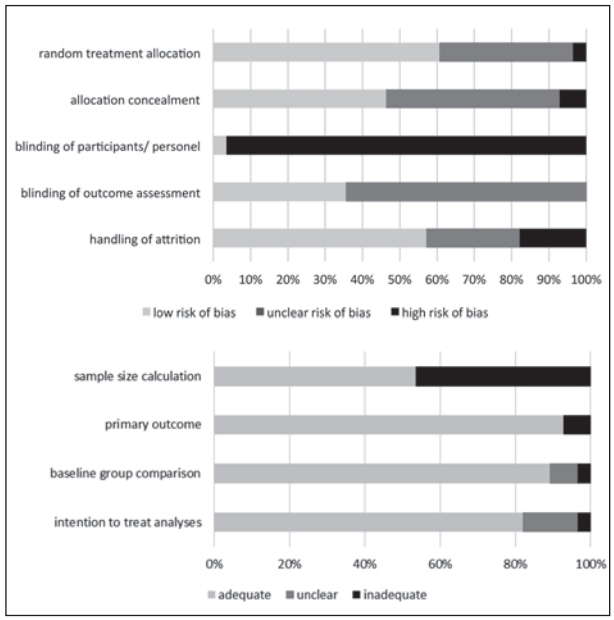

Figure 2. Quality assessment

Physical functioning was assessed in two ways: either based on the ability to carry out daily activities, assessed by the physical functioning subscale of various quality of life assessment tools, or objectively measured using functional or exercise tests. Of the fifteen studies that addressed ability to carry out daily activities (11-13, 15, 16, 22-26, 28, 29, 31, 34, 35, 37, 38, 40), eight found a positive effect brought by the exercise intervention (53%). Nine out of the thirteen studies (14, 16-18, 21, 25, 27, 29, 30, 34-36, 39) (69%) using objective physical performance measurements reported a statistically significant benefit from the exercise intervention. No differences were seen when subgroups were made according to type of cancer, type of treatment or the type or location of the intervention (Table 4).

Inconsistency in results could not be explained by sample size, intensity of the intervention or adherence; when comparing studies above and below the median for each of these items, no differences were seen in the proportion of studies reporting a positive effect from the intervention. However, 89% of the studies in which the intervention took twelve weeks or less found a positive effect in functional tests compared to 25% of longer interventions (p=0.02, Table 4). Of note, shorter studies less often focussed on breast cancer patients

Table 3. Effect of exercise intervention on outcome

	n=	Type of exercise Intervention	Place	Cancer type	Treatment modality	Physical functioning	Functional tests	Global quality of life	Fatigue	Adherence
Adamsen (2009, 2013)(11;12)	269	RE	S	Various	CT/RT	±		-	+	71%
Backman (2014)(13)	77	E	SH	Breast, colorectal	CT	-		-	-	91%
Benzo (2011)(14)	19	RE	S	Lung	RT		-			100%
Cadmus (2009)(15)	50	E	H	Breast	CT	+		-		64%
Campbell (2005)(16)	22	RE	S	Breast	CT	-	+	+	-	70%
Chang (2008)(17)	22	E	S	Haematological	Surg		+		+	-
Coleman (2003)(18)	24	RE	H	MM	RT		-		-	-
Couneya (2007, 2008)(19;20)	242	E/R	S	Breast	CT			E- R-	E- R-	E 72% R 68%
Dimeo (1997)(21)	70	E	S	Various	CT/RT		+			82%
Griffith (2009, 2013)(22;23)	126	E	H	Various	CT/RT	-			-	68%
Headley (2004)(24)	38	E	H	Breast	CT	+			+	75%
Henke (2014)(25)	46	RE	S	Lung	CT/RT	+	+	-	-	-
Hornsby (2014)(26)	20	E	S	Breast	CT	-		-	-	66%
Husebo (2014)(27)	67	RE	H	Breast	CT		-		-	17%
Hwang (2008)(28)	40	RE	S	Breast	CT	+		+	+	-
Mock (2001)(29)	119	E	H	Breast	CT	+	+		+	72%
Mock (2004)(30)	52	E	H	Breast	CT		-		-	70%
Monga (2007)(31)	21	E	S	Prostate	Various	+		+	+	-
Moros (2010)(32)	17	RE	S	Breast	RT			+		-
Mustian (2009, 2010)(33;43)	38	RE	H	Breast, prostate	CT/RT			+	+	-
Mutrie (2007, 2012)(34;35)	203	RE	SH	Breast	CT/RT	-	+	+	-	-
Naraphong (2014)(36)	23	E	H	Breast	CT		+		-	-
Oechsle (2014)(37)	48	RE	S	Haematological	RT	+			+	-
Rogers (2013)(38)	15	R	SH	Head and neck	CT/RT	-		-	-	53%
Samuel (2013)(39)	48	RE	S	Head and neck	RT		+			-
Segal (2001)(40)	121	E	S/H	Breast	CT	S+ H+		S- H-		R 88% E 83%
Segal (2009)(41)	123	E/R	S	Prostate	RT			R+ E-	R+ E+	-
Windsor (2004)(42)	66	E	H	Prostate	CT		+	-	-	

MM multiple myeloma; CT chemotherapy; RT radiotherapy CT/RT chemotherapy and/or radiotherapy Surg surgery; E endurance; R resistance; RE both endurance and resistance components; E/R endurance and resistance in separate arms * S supervised H home-based SH Both supervised and home-based components; S/H Study consisted of one supervised and one home-based arm Details of assessments used can be found in Appendix 3.

+ Positive effect of exercise intervention; - no effect of exercise intervention; ± inconsistent results across assessment

Table 4. Summary and subgroup analyses; data presented as proportion of studies that reported a positive effect of the exercise intervention on specified outcome measures

	Performing daily activities	Functional tests	Global quality of life	Fatigue
Overall	53%	69%	38%	41%
Type of exercise				
Endurance interventions	63%	83%	**17%**	40%
Resistance interventions	0%	-	**33%**	0%
Combined interventions	50%	57%	**71%**	44%
Type of intervention				
Home-based	75%	50%	33%	33%
Supervised	57%	83%	44%	60%
Type of cancer				
Breast cancer	63%	67%	50%	30%
Other malignancies	43%	71%	25%	40%
Type of treatment				
Chemotherapy	50%	67%	17%	36%
Radiotherapy	67%	100%	50%	77%
Chemotherapy and/or radiotherapy	60%	80%	50%	25%
Number of patients in study*				
n≤48 patients	63%	71%	**63%**	50%
n>48 patients	43%	67%	**13%**	30%
Intensity of intervention*				
≤2.5 hours per week	56%	88%	50%	46%
>2.5 hours per week	50%	50%	25%	38%
Duration of intervention*				
≤12 weeks	46%	**89%**	46%	47%
>12 weeks	75%	**25%**	20%	29%
Adherence to intervention*				
≤70%	33%	33%	20%	14%
>70%	33%	67%	0%	60%

* Groups were split according to the median value for each study characteristic

Bold print: p-value ≤ 0.05

(33% vs. 70% of longer studies; p=0.06), were generally smaller (p=0.008) and were more often fully or partially supervised (78% vs 30% of longer studies, p=0.06).

Effect of the exercise intervention on overall quality of life and fatigue

Sixteen studies addressed the impact of exercise on overall quality of life (11-13, 15, 16, 19, 20, 25, 26, 28, 31-35, 38, 40, 41, 43), of which six found a positive effect (38%). Combined resistance-endurance exercise interventions appear to be most effective, as 71% of these studies found that quality of life was better post-intervention when compared to the care-as-usual group; by comparison, only 17% of the endurance exercise only studies reported this result and 33% of the resistance training only (Table 4, p=0.05). Smaller studies more often reported a positive effect (63% in studies with a sample size equal to or below the median, compared to 13% in larger studies; p=0.02). Other subgroup comparisons did not reveal any differences.

Of the 22 studies focussing on the impact of exercise on fatigue (11-13, 16-20, 22-31, 33-38, 41-43), nine reported a positive effect (41%). Subgroup comparison showed no significant differences.

Effect of the exercise intervention on the course of treatment and health care utilisation

One study (19, 20) addressed the effect of exercise on chemotherapy completion by comparing the relative dose intensity (i.e. the proportion of the planned chemotherapy dose the patient actually received) of patients in the exercise group to those receiving usual care. This study included both a resistance training and an endurance training group. For the latter, no significant difference in the relative dose intensity was seen (p=0.27) but for patients in the resistance training group, the mean relative dose intensity was 5.7% higher when compared to usual care (p=0.03).

Two studies addressed the effect of exercise on treatment-related complications and duration of hospitalisation. In the first, patients receiving chemotherapy for various types of cancer were offered endurance training while in hospital.(21) Patients randomised to the training group had a shorter duration of neutropenia (p=0.01) and a borderline significant decrease in thrombocytopenia (p=0.06) and the need for platelet transfusion (p=0.06). Patients in the training group also experienced a significantly shorter duration of hospitalisation (p=0.03). The second study (14), which examined a combination of strength and endurance training as well as inspiratory muscle training in patients undergoing surgery for lung cancer, found that patients in the exercise group experienced fewer days of needing a chest tube (4.7 vs. 9.0 days in the care-as-usual group, p=0.03), a lower incidence of prolonged chest tubes (11% vs. 63% respectively, p=0.03), and the need for fewer days in hospital (6.4 vs. 11.1 days for usual care, p=0.06). There was no difference in the incidence of respiratory failure or pneumonia.

No other studies reported on the course of treatment or health care utilisation. A reporting bias cannot be excluded.

Discussion

In this systematic review of randomised controlled trials addressing the effect of exercise interventions prior to or during active cancer treatment with radiotherapy, chemotherapy and/or surgery, exercise appeared to have the most consistent effect on physical performance tests (positive effect reported in 69% of studies addressing this outcome), followed by the ability to perform daily activities (positive effect in 53%), fatigue (41%) and overall quality of life (38%). Three studies also reported a positive effect on other outcomes such as chemotherapy completion, treatment-related complications and duration of hospitalisation. For improving physical functioning, endurance training appears to be most beneficial while for maintaining overall quality of life, combined endurance-resistance exercise appeared superior to endurance or resistance exercise only.

There have been several prior reviews addressing prehabilitation, each with their own approach (44-50): some focussed only on surgery (44-46, 48), included patients undergoing non-cancer treatment (45, 46) or included studies on post-treatment exercise interventions(46-48, 50). This is the first systematic review

focussing exclusively on randomised controlled trials comparing exercise interventions to usual care before or during active cancer treatment with chemotherapy, radiotherapy and surgery. However, this review also has some limitations. First of all, although many quality of life questionnaires use comparable questions to explore similar subscales, they ultimately are not the same; this also applies to physical performance tests. Furthermore, given the heterogeneity in study populations, type of intervention and outcome measurements, no formal meta-analysis was considered feasible. Instead, we performed crude subgroup comparisons (Table 4), to enable some cursory comparisons. As a result, the data should be interpreted cautiously. In addition, many studies had methodological flaws or were too brief in their reporting of methodology to adequately assess their quality. Adherence to intervention was low in some studies. Again, patient numbers were relatively small, potentially limiting the ability of these studies to detect differences in outcome between groups. However, when only the larger studies were examined (Table 4), the proportion of studies finding positive results was similar or in some cases lower. Thus, the small sample size does not explain the lack of effect seen in our review.

Following cancer treatment, patients may be faced with a variety of cancer-related or cancer-treatment-related problems, including pain, fatigue, deconditioning, and difficulty with gait (51). They may also have problems resuming their previous level of functioning, which can impact on activities of daily living, instrumental activities of daily living, return to previous home and community activity levels, and return to work (51). Prior research has demonstrated that for cancer survivors, health-related quality of life is more often influenced by these physical issues than by emotional issues. For instance, one study found that one in four cancer survivors reported poor physical health whereas only one in ten reported poor mental health (52). Furthermore, a leading cause or perhaps *the* leading cause of emotional distress in cancer survivors is physical disability (53, 54). In fact, the risk of psychological distress in individuals with cancer is more strongly related to their level of disability than to the cancer diagnosis itself (54). Thus, interventions that can prevent loss of functional capacity could potentially be an important method of improving quality of life in cancer survivors.

Several studies have demonstrated that exercise interventions in patients due to undergo or undergoing cancer treatment can aid in improving or maintaining muscle strength, body composition and cardiopulmonary function (44, 47). Our review supports these findings, by demonstrating that exercise interventions result in better physical functioning when measured with endurance tests such as a shuttle walk or six minute walking test; improvements for the intervention group compared to care-as-usual were recorded for 69% of studies, with the strongest effect in studies using endurance exercise as the intervention (83%). The fact that endurance exercise will improve or help maintain endurance when compared to no exercise is not unexpected. However, our review also demonstrates that the benefit in terms of quality of life or daily functioning is limited. At the same time, the logistic requirements for such interventions are significant, as are both the motivation and efforts of the patient. Most studies required exercising many times a week – with some adding up to over 10 hours per week of actual exercise - in addition to whatever time is required to travel to the exercise venue in case of supervised exercise programmes, while the interventions often lasted for extended periods of time. The current review suggests that such investments may not be justifiable for many patients, given the lack of actual, generalised benefit.

The balance between investment and benefit may be different in situations where improvements in control or strength of specific muscles directly translate into improved functionality, as can be seen in studies using pelvic floor exercises prior to prostate surgery to preserve urinary continence, or swallowing exercises as prehabilitation prior to head and neck surgery (44). These types of exercise intervention fell outside the scope of this review but have each proved successful in several studies (55-57). Similarly, while improving or maintaining pulmonary condition with endurance exercise - during for instance adjuvant radiotherapy for breast cancer - may not measurably impact on quality of life or daily functioning, a positive effect from such interventions prior to lung surgery (which directly compromises pulmonary functioning) is much more likely (48).

In addition, comparisons between the methodology of the studies included in our review show that shorter interventions appear to be of greater benefit in functional testing than longer interventions (≤12 weeks 89% vs. >12 weeks 25%). This difference could not be explained by differences in adherence. However, shorter studies were generally smaller, supervised and focussing on malignancies other than breast cancer. These factors themselves did not achieve statistical significance in the univariate analyses (Table 4); however, a formal meta-analysis was not possible. Potentially, it is a combination of these factors that determines the success of the intervention. Thus, judicious application of pre-treatment exercise in specific situations does appear able to generate benefit in functionality and quality of life where a more generalised application does not. Future research should focus on a more precise identification of combinations of intervention and setting in which prehabilitation does result in direct benefit for the individual patient. In addition, explorations of multimode prehabilitation programmes, for example combining exercise with nutritional psychological interventions (58, 59). are warranted.

Conclusion

This review demonstrates that exercise interventions, particularly using endurance training, are successful in improving physical functioning compared to usual care when measured with endurance tests. However, this effect does not appear to translate into benefit for overall quality of life, fatigue or daily functioning. Because exercise interventions within prehabilitation programmes require major investments by both health care providers and patients, some reservation must be expressed about their broad implementation in cancer care. Future research should focus on a more precise identification of combinations of interventions, cancer treatments and settings in which prehabilitation will yield the greatest benefit for patients.

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Appendix

Appendix 1. Search syntax

(((((((exercise*[tiab] OR walking[tiab] OR rehabilitation[tiab] OR "Rehabilitation"[Mesh] OR training[tiab] OR physiotherapy[tiab])) OR physiotherapy techniques[MeSH Terms])) AND (((((((active AND cancer AND treatment) OR ((chemotherapy[tiab] OR radiotherapy[tiab] OR chemoradiotherapy[tiab] OR chemoradiation[tiab] OR (adjuvant[tiab] AND treatment[tiab])) OR pretreatment[tiab] OR pretreatment[tiab] OR preoperative[tiab] OR pre-operative[tiab] OR presurgery[tiab] OR pre-surgery[tiab]) OR ("Preoperative Care"[Mesh]))))) OR (care, perioperative[MeSH Terms])) OR (prophylactic[tiab] OR perioperative[tiab] OR peri-operative[tiab]))))) OR prehabilitation) AND (((((("Neoplasms"[Mesh]) OR (neoplasm*[tiab] OR cancer*[tiab] OR tumour[tiab] OR tumours[tiab] OR tumor[tiab] OR tumors[tiab] OR oncolog*[tiab] OR malignan*[tiab])))))))

Appendix 2a. Items for assessment of methodological quality of studies included

	Low risk of bias	High risk of bias	Unclear risk of bias
Random treatment allocation	- Method for sequence generation process stated and considered truly at random (e.g. referring to a random number table, using a computer random number generator, shuffling cards or envelopes;	- Sequence generated by inadequate process (e.g. odd or even date of birth, sequence generated by some rule based on date (or day) of admission	- Insufficient information about the sequence generation process to permit evaluation of 'Low risk' or 'High risk'.
Allocation concealment	- Central allocation (including telephone, web-based and pharmacy-controlled randomisation); - Sequentially numbered, opaque, sealed envelopes.	- Using an open random allocation schedule (e.g. a list of random numbers); - Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); - Any other explicitly unconcealed procedure.	- Insufficient information to permit evaluation of 'Low risk' or 'High risk'.
Blinding of participants and personnel	- No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; - Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.	- No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; - Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.	- Insufficient information to permit evaluation of 'Low risk' or 'High risk'; - The study did not address this outcome.
Blinding of outcome assessment	- No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; - Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.	- No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; - Blinding of outcome assessment, but likely that the blinding could have been broken and the outcome measurement is likely to be influenced by lack of blinding.	- Insufficient information to permit evaluation of 'Low risk' or 'High risk'; - The study did not address this outcome.
Handling of attrition	- Loss to follow-up less than 10% for short-term results - Reasons for missing outcome data unlikely to be related to true outcome - Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;	- Loss to follow-up more than 10% for short-term results - Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;	- Insufficient reporting of attrition/exclusions to permit evaluation of 'Low risk' or 'High risk'; - The study did not address this outcome.
	Adequate	**Inadequate**	**Unclear**
Sample size calculation	- Adequate if stated to have been undertaken and achieved	- No sample size calculation is provided or the study did not achieve the initial inclusion.	
Primary outcome	- Adequate if defined explicitly or used in sample size calculation	- No primary outcome is defined	
Baseline group comparison	- Adequate if groups were comparable for age, tumour type and stage, type of treatment	- Significant differences in patient demographics were observed	- Insufficient information to permit evaluation of adequacy - The study did not address this outcome.
Intention-to-treat analysis	- Adequate if intention-to-treat analysis was performed	- Inadequate if 'as-treated' analysis was done	- Insufficient information to permit evaluation of adequacy

This 9-item list was adopted from the Cochrane guidelines for methodological assessment of randomised trials(9) and the guidelines for critical appraisal of randomised controlled trials supplied by the Oxford Centre for Evidence Based Medicine(10).

Appendix 2b. Quality assessment of studies included

	Random treatment allocation	Allocation concealment	Blinding of participants/personnel	Blinding of outcome assessment	Handling of attrition	Sample size calculation	Primary outcome	Baseline group comparison	Intention to treat analyses
Adamsen (2009, 2013)(11;12)	+	+	-	+	-	+	+	+	+
Backman (2014)(13)	?	?	-	+	-	-	+	+	+
Benzo (2011)(14)	?	?	-	+	+	-	+	+	+
Cadmus (2009)(15)	+	+	-	?	+	-	+	-	+
Campbell (2005)(16)	+	+	-	?	?	-	-	+	+
Chang (2008)(17)	?	?	-	?	+	-	+	+	+
Coleman (2003)(18)	?	+	-	?	?	-	+	?	?
Couneya (2007, 2008)(19;20)	+	+	-	+	+	-	+	+	+
Dimeo (1997)(21)	?	?	-	+	?	+	+	+	+
Griffith (2009, 2013)(22;23)	?	?	-	?	+	+	+	+	+
Headley (2004)(24)	+	?	-	?	+	+	+	+	+
Henke (2014)(25)	+	?	-	?	-	+	+	+	+
Hornsby (2014)(26)	+	+	-	+	+	+	+	+	+
Husebo (2014)(27)	+	+	-	?	+	+	+	+	+
Hwang (2008)(28)	?	?	+	?	-	-	+	+	?
Mock (2001)(29)	+	+	-	?	?	-	-	?	-
Mock (2004)(30)	+	+	-	+	+	+	+	+	+
Monga (2007)(31)	?	?	-	?	?	-	+	+	?
Moros (2010)(32)	?	?	-	?	?	-	+	+	?
Mustian (2009, 2010)(33;43)	-	-	-	+	+	-	+	+	+
Mutrie (2007, 2012)(34;35)	+	+	-	+	+	+	+	+	+
Naraphong (2014)(36)	+	?	-	?	+	+	+	+	+
Oechsle (2014)(37)	?	?	-	?	+	+	+	+	+
Rogers (2013)(38)	+	+	-	?	?	-	+	+	+
Samuel (2013)(39)	+	-	-	+	-	+	+	+	+
Segal (2001)(40)	+	?	-	?	+	+	+	+	+
Segal (2009)(41)	+	+	-	?	+	+	+	+	+
Windsor (2004)(42)	+	+	-	?	+	+	+	+	+

+ low risk of bias/adequately performed ; - high risk of bias/inadequately performed; ? unclear

Appendix 3. Outcome assessments per study

	Performing daily activities	Functional testing	Global quality of life	Fatigue
Adamsen (2009, 2013)(11;12)	QLQ-C30 PF; MOS PF; FACT PF	-	QLQ-C30 GF; MOS GH; FACT overall	QLQ-C30 F; FACT F
Backman (2014)(13)	QLQ-C30 PF	-	QLQ-C30 GF	QLQ-C30 F
Benzo (2011)(14)	-	Shuttle walk	-	-
Cadmus (2009)(15)	MOS PF	-	MOS GH	-
Campbell (2005)(16)	FACT PF	12 minutes walking	FACT overall	Piper fatigue scale
Chang (2008)(17)	-	12 minutes walking	-	BFI
Coleman (2003)(18)	-	treadmill minutes	-	POMS-F
Couneya (2007, 2008)(19;20)	-	-	FACT overall	FACT F
Dimeo (1997)(21)	-	treadmill stress test	-	-
Griffith (2009, 2013)(22;23)	MOS PF	-	-	Piper fatigue scale
Headley (2004)(24)	FACIT PF	-	-	FACIT F
Henke (2014)(25)	QLQ-C30 PF; Barthel index	6 minutes walking test; staircase walking test	QLQ-C30 GH	QLQ-C30 F
Hornsby (2014)(26)	FACT PF	-	FACT overall	FACIT F
Husebo (2014)(27)	-	6 minutes walking test	-	Schwartz cancer fatigue scale
Hwang (2008)(28)	WHO-QOL PF	-	WHO-QOL overall	BFI
Mock (2001)(29)	MOS PF	12 minutes walking test	-	Piper fatigue scale; POMS F
Mock (2004)(30)	-	12 minutes walking test	-	Piper fatigue scale
Monga (2007)(31)	FACT PF	-	FACT overall	Piper fatigue scale
Moros (2010)(32)	-	-	QLQ-C30 GH	-
Mustian (2009, 2010)(33;43)	-	-	FACIT-QoL	BFI; FACIT F;
Mutrie (2007, 2012)(34;35)	FACT PF	12 minutes walking test	FACT overall	FACT F
Naraphong (2014)(36)	-	12 minutes walking test	-	Piper fatigue scale
Oechsle (2014)(37)	QLQ-C30 PF	-	-	QLQ-C30 F; MFIS
Rogers (2013)(38)	FACT PF	-	FACT overall	FACT f
Samuel (2013)(39)	-	6 minutes walking test	-	-
Segal (2001)(40)	MOS PF	-	MOS GH; FACT overall	-
Segal (2009)(41)	-	-	FACT overall	FACT F
Windsor (2004)(42)	-	Shuttle walk	-	BFI

QLQ-C30 Quality of life questionnaire C30; MOS medical outcomes study; FACT functional assessment of cancer therapy; FACIT functional assessment of chronic illness therapy; WHO World Health Organisation; BFI brief fatigue inventory; POMS profiles of mood states;

PF physical functioning; GF general functioning; GH general health; F fatigue; QoL quality of life