

Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial

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ABSTRACT

Objective To assess the effect of a multimodal group exercise intervention, as an adjunct to conventional care, on fatigue, physical capacity, general wellbeing, physical activity, and quality of life in patients with cancer who were undergoing adjuvant chemotherapy or treatment for advanced disease.

Design Randomised controlled trial.

Setting Two university hospitals in Copenhagen, Denmark.

Participants 269 patients with cancer; 73 men, 196 women, mean age 47 years (range 20-65) representing 21 diagnoses. Main exclusion criteria were brain or bone metastases. 235 patients completed follow-up.

Intervention Supervised exercise comprising high intensity cardiovascular and resistance training, relaxation and body awareness training, massage, nine hours weekly for six weeks in addition to conventional care, compared with conventional care.

Main outcome measures European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), Medical Outcomes Study Short Form (MOS SF-36), Leisure Time Physical Activity Questionnaire, muscular strength (one repetition maximum), maximum oxygen consumption (Vo_2max).

Statistical methods The general linear model was used for continuous outcome while analysis of associates between categorical outcomes was performed as analysis of marginal homogeneity in contingency tables.

Results Adjusted for baseline score, disease, and demographic covariates, the intervention group showed an estimated improvement at six weeks for the primary outcome, fatigue, of -6.6 points (95% confidence interval -12.3 to -0.9, $P=0.02$; effect size=0.33, 0.04 to 0.61). Significant effects were seen on vitality (effect size 0.55, 95% CI 0.27 to 0.82), physical functioning (0.37, 0.09 to 0.65), role physical (0.37, 0.10 to 0.64), role emotional (0.32, 0.05 to 0.59), and mental health (0.28, 0.02 to 0.56) scores. Improvement was noted in physical capacity: estimated mean difference between groups for

maximum oxygen consumption was 0.16 l/min (95% CI 0.1 to 0.2, $P<0.0001$) and for muscular strength (leg press) was 29.7 kg (23.4 to 34.9, $P<0.0001$). No significant effect was seen on global health status/quality of life.

Conclusion A supervised multimodal exercise intervention including high and low intensity components was feasible and could safely be used in patients with various cancers who were receiving adjuvant chemotherapy or treatment for advanced disease. The intervention reduced fatigue and improved vitality, aerobic capacity, muscular strength, and physical and functional activity, and emotional wellbeing, but not quality of life.

Trial registration Current Controlled trials ISRCTN05322922.

INTRODUCTION

An increasing number of patients with cancer are offered chemotherapy given either alone or in combination with radiotherapy, surgery, or both as neoadjuvant, concomitant, or adjuvant treatment. Improved treatments have resulted in prolonged survival and better control of disease and treatment related complications. The majority of patients will, however, still face a range of symptoms and side effects such as nausea, vomiting, pain, insomnia, appetite loss, and fatigue. Surveys have shown that fatigue is among the most frequent and burdensome side effect of chemotherapy and results in impaired or diminished physical activity.¹ Whereas most side effects are drug specific, fatigue is associated not only with most anti-neoplastic drugs but also with the disease itself.² Prevention and treatment of fatigue are complicated; treatment with drugs alone is rarely adequate. In addition, psychosocial problems often follow the diagnosis of cancer and subsequent chemotherapy.³ For some patients, diagnosis and treatment are synonymous with an inactive daily life,⁴ resulting in loss of muscle mass and strength.^{5,6} Exercise training has been introduced to improve physical capacity and quality of life

and to reduce fatigue. Few intervention studies have included patients who were undergoing chemotherapy and the evidence is modest.⁷⁻⁹

Exercise studies have included predominantly women with breast cancer after cytostatic treatment and the interventions provided improved physical fitness and psychological benefits.⁷⁻⁹ Typically studies investigated the effects of a single activity of moderate intensity, such as cardiovascular training on stationary bicycles, rather than resistance training. Additional studies are needed to provide evidence on whether patients with different cancer diagnoses, stages of disease, and symptoms can benefit from combined resistance and cardiovascular training when undergoing chemotherapy. Moreover, high intensity exercise might further improve the patients' physical capacity, as recorded in sports science studies including healthy adults.^{5,10}

A wide range of low intensity interventions comprising psychosocial activities (relaxation and massage) are recommended as adjuvants to pharmacological therapies, to relieve nausea, pain, and fatigue and to increase the patient's perception of self control.^{11,12}

This body of research provides evidence that exercise and psychosocial interventions might be beneficial when tested as separate components. We developed a multimodal intervention consisting of high and low intensity components to achieve a broad spectrum of effects. The intervention was designed to appeal to male and female patients with cancer, irrespective of diagnosis and stage of disease.

The objective of the present study was to investigate the effect of a six week supervised structured group intervention comprising high intensity physical training and low intensity training in an intervention group compared with a control group. We tested the hypothesis that the intervention, as an adjunct to conventional care, could reduce fatigue (primary outcome), and improve other side effects, general physical and emotional wellbeing, global health status or quality of life, physical capacity, and physical activity in men and women with cancer who were undergoing adjuvant chemotherapy or treatment for advanced disease.

METHODS

Recruitment and assignment

Participants were recruited from the departments of oncology and haematology at Rigshospitalet and Herlev Hospital (Copenhagen University Hospitals) from March 2004 to March 2007. Participants were eligible if they had a diagnosis of cancer, had received at least one cycle of chemotherapy for advanced disease or as adjuvant treatment, had a WHO performance status of 0 or 1, and were aged 18-65 years. Exclusion criteria were brain or bone metastases, thrombocytopenia ($<50 \times 10^9/l$), myocardial infarction within the past three months, or uncontrolled hypertension (diastolic pressure >95 mm Hg). The patients were approached and enrolled by research nurses or by physicians and nurses from eight treatment departments. Furthermore, the participants could contact the project team

directly; information was accessible on posters and pamphlets in the hospitals' inpatient and outpatient departments.

After written informed consent, the baseline measures were obtained from the participants, who were randomly allocated to an intervention or a control group. The patients were stratified by sex, diagnosis category (breast, bowel, other oncological malignancies, haematological malignancies), and disease status (no evidence of disease or evidence of disease). Patients with no evidence of disease received adjuvant treatment after radical local treatment for their cancer disease, while patients with evidence of disease had residual or advanced disease after the initial diagnosis of cancer was made by biopsy or local treatment. Randomisation was done by computer (Clinical Internet Trial Management System: CITMAS). The allocation sequence was executed by the clinical research unit and concealed from the project team. The data were collected by a physiotherapist and a trained nurse specialist, who also conducted the daily training sessions. Data were anonymised by use of an identification code; administrative data were kept in a separate database. Blinding the participants to group assignment was not possible. Outcome measures were keyed in and analysed by research assistants who were not involved with the participants.

Intervention: exercise programme

Participants assigned to the intervention group received standard medical care while participating in a group based multimodal high and low intensity exercise intervention (supervised by trained nurse specialists and physiotherapists). There were seven to 10 participants per group, each group including individuals of both sexes and with various diagnoses and disease statuses.

On Mondays, Wednesdays, and Fridays, the patients participated in high intensity physical training for 90 minutes followed by 30 minutes relaxation training. On Tuesdays the programme included 90 minutes of body awareness training followed by 30 minutes of relaxation training. Mondays and Fridays were reserved for the patients to receive 30 minutes of massage. The intervention took place in a fitness facility at Rigshospitalet, and was undertaken over a six week period for nine hours per week. The multimodal intervention constituted a total package; the participants could not select one activity in preference over another. The intervention consisted of high and low intensity activities equivalent to a total of 43 metabolic equivalent of task (MET) hours per week.¹³ The high intensity physical training sessions comprised three components: 30 minutes of warm-up exercises, 45 minutes of resistance training, and 15 minutes of cardiovascular training. The warm-up consisted of dynamic exercises with the large muscle groups, along with balance and coordination training, and had an estimated average intensity of 9 METs (4.5 MET hours per training session). Six machines were used for resistance training: a leg press, a chest

press, a pull down, an abdominal crunch, a lower back, and a knee extension (Technogym, Gambettola, Italy). The one repetition maximum test was used to measure the weight a patient could lift once on any specific machine. The weight was expressed as 100% of the patient's strength and a training programme was then developed based on that measure. The aim of the resistance training component was to accomplish three continuous series of five to eight repetitions at 70-100% of the one repetition maximum test.¹⁴ To ensure progression, all patients performed one repetition maximum test every other week, with subsequent adjustments made to their training programmes. Resistance training was estimated to have an intensity of 5.5 METs (4 MET hours per training session). Cardiovascular training involved interval training on stationary bicycles with a workload of 70-250 W, equivalent to 85-95% of each participant's maximum heart rate. This training was estimated to have an intensity of 1.5 METs (3.75 MET hours per training session).

Low intensity physical training comprised three psychosocial components: relaxation (30 minutes four times a week), body awareness and restorative training (90 minutes once a week), and massage (30 min twice a week). In relaxation sessions, the participants lay on mats with pillows and blankets and were instructed in the use of relaxation mechanisms, using principles of progressive muscle relaxation. Participants were instructed in tensing and relaxing major muscle groups, working from head to foot.¹⁵ They were asked to focus on the contrast in sensations between muscle tension and relaxation. Audiotape progressive muscle relaxation was used to enhance treatment integrity by assuring that all participants were exposed to the same instructions. Body awareness and restorative training adopted various themes that focused on the participants' awareness, recognition, and control of their bodies. The first session was dedicated to stretching, which can contribute to reducing discomfort and pain.¹⁶ The theme selected for weeks 2 and 3 was respiration, inspired by yoga, which aims to increase mental and physical energy.¹⁷ The remaining weeks (weeks 4-6) focused on postural awareness and movement re-education, based on Pilates techniques.¹⁸ Massage was relaxing, facilitative, or therapeutic, including scar tissue massage. A few patients requested venous pump massage or ultrasound therapy.¹⁹ Relaxation training and massage were each estimated to have an intensity of 1 MET (total of 3 MET hours per week), while body awareness and restorative training were estimated to have an intensity of 2.5 METs (3.25 MET hours per week).¹³

Safety

Pre-exercise screening was performed before high intensity physical training. If one of the following criteria was met, the participant was excluded from the physical training component of the programme on that specific day: diastolic blood pressure <45 mm Hg or >95 mm Hg; pulse at rest >100 beats per minute; temperature >38°C; respiration frequency >20 per

minute; infections requiring treatment with antibiotics; ongoing bleeding; fresh petechiae; bruises; B thrombocytes <50×10⁹/l; B leucocytes <1.0×10⁹/l. During the training sessions the participants' heart rate was continuously monitored by means of a wireless heart rate transmitter, and the participants were advised to respect their own physical limitations.

Control group

Participants assigned to the control group received conventional medical care, and completed outcome measures in parallel with the intervention group. The control group was allowed to freely increase physical activity. They were invited to participate in the exercise programme after the six week assessments.

Primary and secondary outcome measures

Assessment included patient rated and objectively measured physiological outcomes. All outcomes were assessed at baseline and after intervention. The primary outcome, fatigue, was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30; 30 items).²⁰ The EORTC QLQ-C30 comprises five functional scales, nine symptom scales or items, and a global health status/quality of life scale. All scale/single item measures range in score from 0-100. A high score on the functional and global health status/quality of life scale represents a high or healthy level of functioning and high quality of life, while a high score for a symptom scale represents a high level of symptomatology. Secondary outcomes included all other scales on EORTC QLQ-C30, and general well-being was further assessed with the Medical Outcomes Study Short Form (MOS SF-36),²¹ which contains eight scales measuring general health concepts and two summary scales: physical component scale, and mental component scale.

Leisure time physical activity level was explored by questionnaire. The participants were classified as: sedentary (completely inactive); walking or cycling for pleasure; regular physical exercise at least 3 hours a week; or intense physical activity more than 4 hours a week.²²⁻²⁴

Other secondary outcomes included muscular strength stated in kilograms and aerobic capacity (V_O2max) stated in l/min. Muscular strength was ascertained using the one repetition maximum test to evaluate upper and lower body strength.²⁵ The tests were performed on Technogym (Gambettola, Italy) variable resistance equipment (chest press, leg press, and pull down) and targeted large muscular groups. Each patient started the test with three to four repetitions on each machine, on a low weight. The patient would increase the weight by 2.5 kg continuously. The test was complete when the patient reached maximum capacity (one repetition maximum). To obtain an overall score for improvement in muscular strength we used the mean of the relative changes in strength in chest press, leg press, and pull down.

$\dot{V}O_2\text{max}$ was indirectly estimated by use of a stepwise work capacity on a stationary exercise cycle (Monark Ergonomic 839E, Sweden). The steady rate test started with a workload of 67 W over 8 minutes with the patients' pulse rate being recorded during the final minute of the test. The watt max test started at 67 W, increasing by 20 W with each consecutive minute until the patient did not wish to continue cycling. $\dot{V}O_2\text{max}$ was estimated using the formula $\dot{V}O_2\text{max} = 0.16 + (0.0117 \times \text{MPO})$ where maximal power out (MPO) was measured in watts.²⁶

To compare estimated $\dot{V}O_2\text{max}$ with the maximum oxygen consumption both measurements were done in seven patients, and no significant difference was found between the tests.²⁷ We chose to use estimated $\dot{V}O_2\text{max}$ because this method was feasible for use in the study population.

Demographic and behavioural data were collected by self report, and medical data were drawn from records.

Sample size calculation and statistical analysis

According to the scoring manual for EORTC QLQ-C30 a change of 10 points or more is considered to be a moderate to large clinically significant change.²⁰ Based on this assumption and our pilot study ($n=82$)²⁸ the sample size was calculated on an 80% power to detect a difference in score of 10 points (SD 25) on the EORTC QLQ-30 fatigue scale (items 10, 12, and 18), using a type 1 error of 5%, a type 2 error of 20%, and univariate analysis (*t* test). This calculation resulted in 98 participants in each group. To accommodate expected dropout before study completion, because of inclusion of participants with present evidence of disease, a total of 135 participants were included in each group.

Baseline comparisons were done using univariate analyses of variance for continuous variables. For categorical measures likelihood ratio based χ^2 test for symmetry and marginal homogeneity was used to evaluate the potential changes.

The main analysis examined whether differences in outcome (mean differences) between baseline and six weeks existed between the control and intervention groups in all outcome measures (EORTC QLQ-C30, MOS SF-36, $\dot{V}O_2\text{max}$, and muscular strength). We performed a forward stepwise regression analysis using differences in outcome between baseline and six weeks (in all outcome measures) as the dependent variable in a general linear model. The stepwise procedure began by identifying the covariate that was most strongly related to the dependent variable. The next strongest related covariate was then selected after controlling for the first covariate, and so on. The variable intervention/control was fixed and the following covariates were tested: sex, age, cohabitation, educational level, baseline outcome score, relative change in β haemoglobin, $\dot{V}O_2\text{max}$, one repetition maximum knee extension, and the five disease related covariates—diagnosis, evidence of disease, relapse of disease, and

chemotherapy cycles before and during the study period. Potential effect modifications (interactions) of the five disease related covariates and their effect on the estimated mean difference were also tested.

All analyses were tested with a significance level of $P < 0.05$ by using the intention to treat principle. Available data for participants with missing data were included under the "missing at random" assumption.

Clinically important changes were estimated as effect sizes using Cohen's guidelines, whereby a value of 0.2 denotes a small, 0.5 a medium, and 0.8 a large effect size.²⁹⁻³¹ Effect size was calculated by the mean difference divided by the pooled standard deviation, the root mean square error estimated from the general linear model.

Participants classified as lost to follow-up ($n=34$) were compared with the study group ($n=235$) for baseline demographic data using ordinary *t* test and χ^2 test for homogeneity.

Data were entered into Excel using Microsoft Office 2000 Professional for Windows XP and SAS (version 9.1.3) software for statistical analysis.

RESULTS

Participants

During the study period (March 2004 to March 2007), 1956 patients with cancer aged 18-65 years were referred for chemotherapy (fig 1). Two hundred and sixty nine patients met the inclusion criteria and agreed to participate. For the primary outcome (fatigue) we obtained post-intervention data from 118 participants in the intervention group (87.4%) and 117 in the control group (87.3%). The intervention group adherence rate was 70.8% (17 of 24 training days, range 3-24) of their supervised exercise sessions.

The control and intervention groups were matched at baseline for demographic and medical characteristics (table 1). Participants were on average 47 years old (range 20-65 years), and 73% were female. The study included patients with 21 different cancer diagnoses: 17 with solid tumours and four with malignant haematological diseases. Forty eight per cent had evidence of disease and 52% no evidence of disease. The median number of days since diagnosis was 84.

The participants received a total of 59 different chemotherapy regimens during the study period. The most frequent chemotherapy regimen included cyclophosphamide, epirubicin, and 5-fluorouracil and was administered to 49 patients in each group. Also frequent were 5-fluorouracil based regimens in patients with colorectal cancer (12 in the control group and 14 in the intervention group) and platinum based regimens in women with ovarian cancer (10 *v* 15) and in men with testicular cancer (eight *v* six). All other regimens were given to fewer than five patients and regimens were balanced between groups. The intervention and control groups had received a mean of 2.5 and 2.6 cycles of chemotherapy, respectively, before the study period, and received a mean of 1.9 and 1.8 cycles, respectively, during the six week study period (table 2).

Main outcomes

Changes in patient rated outcomes

Tables 3 and 4 present the patient rated outcomes measured at baseline and after six weeks for the intervention and the control groups.

We found a significant effect in favour of the intervention group for the primary outcome, fatigue, in EORTC QLQ-C30. The fatigue score was reduced in the intervention group by an estimated mean difference of -6.6 points (95% CI -12.3 to -0.9) compared with the control group (P=0.02, effect size=0.33, 95% CI 0.04 to 0.61) (table 3).

We noted significant effects of the intervention on seven of 10 subscales on general wellbeing (MOS SF-36): physical functioning (effect size 0.37, 95% CI 0.09 to 0.65), role physical (0.37, 0.10 to 0.64), vitality (0.55, 0.27 to 0.82) role emotional (0.32, 0.05 to 0.59), mental health (0.28, 0.02 to 0.56), physical component scale (0.35, 0.06 to 0.63), and mental component scale (0.41, 0.14 to 0.69) (table 4). Significant interaction was seen for role physical, with greater improvement in patients with no evidence of disease than in those with evidence of disease.

Changes in objectively measured physiological outcomes

Vo₂max increased more in the intervention group than in the control group (table 5); the mean improvement in Vo₂max was 10.7% (SD 0.5) compared with no change in the control group. Significant improvements in muscular strength were seen in favour of the intervention group. The average improvement in muscular

strength was 29.6% (SD 36.4) for the intervention group (table 5). Significant interaction was seen for the muscular strength chest press, with more improvement in patients with no evidence of disease than in those with evidence of disease.

Changes in self reported physical activity level

Sixty-six per cent of the study population reported physical activity of at least 3 hours per week before their illness, whereas at baseline 18% had a sedentary lifestyle, when undergoing chemotherapy (table 1); only 33% of the population reported physical activity of at least 3 hours per week. Homogeneity of the marginal distribution was not fulfilled (P<0.0001); the level of self reported physical activity fell during the period from pre-illness to baseline for both the intervention and control group.

In the control group the joint distribution of baseline and post intervention physical activity satisfied symmetry (P=0.4) and as such homogeneity of the marginal distribution, indicating that the level of physical activity level had not changed during the period. By contrast, neither the hypothesis of symmetry nor marginal homogeneity was fulfilled (P<0.0001 for both hypotheses) for the intervention group. Post intervention, the patients increased their activity level. The mode changed from "walking or cycling for pleasure" (40%) at baseline to "regular physical exercise" (53%) after intervention.

DISCUSSION

Principal findings

Men and women with a broad range of ages, cancer diagnoses, disease statuses, and chemotherapy regimens participated in this study. The multimodal intervention of high intensity exercise, relaxation, body awareness training, and massage for patients undergoing chemotherapy showed broad effects. We noted significant effects on fatigue, vitality, physical functioning, role functioning, role emotional, mental health, physical component scale, and mental component scale, physical capacity (Vo₂max and muscular strength), and physical activity levels, while global health status/quality of life and symptom scales did not show improvements.

The intervention was offered as a package, and it must be viewed as an entity, whereby each component has had a role in the outcomes. Our findings confirmed that both men and women benefited from training in mixed groups, and no differences between men and women were observed in the dropout rate.

The primary outcome, fatigue, was the most frequently reported symptom; 65% of the study population reported a fatigue level greater than that of the general population (mean >20) at baseline³¹ and 29% reported severe fatigue (mean >60).

The effect size of the improvement in fatigue (0.33) suggests a small to medium clinically important change.^{29,30,32} Our result differs from findings of a meta-analysis which indicated that the magnitude of

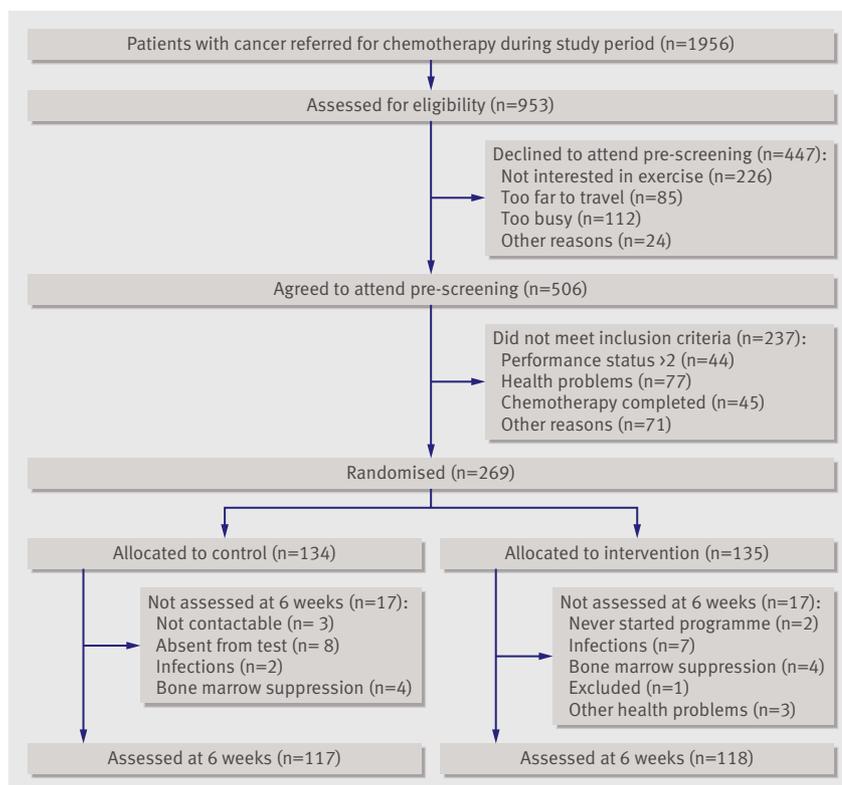


Fig 1 | Trial profile

Table 1 | Demographic and medical characteristics, and physical activity level for all patients and by group assignment. Values are numbers (percentages) of patients unless stated otherwise

	Control group (n=134)	Intervention group (n=135)
Demographic characteristics		
Age, years		
Mean (SD)	47.2 (10.6)	47.2 (10.7)
Range	20-65	21-65
Married, cohabiting, or in a relationship	89 (66.9)	95 (70.4)
Sex		
Male	39 (29.1)	34 (25.2)
Female	95 (70.9)	101 (74.8)
Completed secondary school or higher	106 (79.7)	104 (77.0)
Current smoker	19 (14.3)	26 (19.3)
Medical characteristics		
Median (range) days since diagnosis	89.5 (31-271)	83 (34-280)
No evidence of disease (NED) baseline	72 (53.7)	68 (50.4)
Evidence of disease (ED) baseline	62 (46.3)	67 (49.6)
Relapsed disease	26 (19.4)	17 (12.6)
Mean (SD) β haemoglobin, mmol/l	7.90 (0.8)	7.95 (0.8)
Cancer of breast (NED/ED)	59 (50/9)	60 (49/11)
Cancer of bowel (NED/ED)	17 (10/7)	18 (13/5)
Oncological malignancies (NED/ED)		
Cancer of ovaries	11 (3/8)	16 (5/11)
Cancer of testes	9 (0/9)	7 (0/7)
Cancer of oesophagus	3 (0/3)	2 (0/2)
Cancer of brain	4 (0/4)	1 (0/1)
Cancer of cervix	2 (0/2)	4 (0/4)
Cancer of pharynx	1 (0/1)	2 (0/2)
Cancer of pancreas	2 (0/2)	1 (0/1)
Cancer of stomach	2 (0/2)	1 (0/1)
Other diagnoses	9 (3/6)	10 (1/9)
Haematological malignancies (NED/ED)		
Hodgkin's	4	6
Non-Hodgkin's lymphoma	5	7
Acute leukaemia	5	0
Chronic leukaemia	1	0
physical activity level		
Pre-illness		
Sedentary	5 (4.0)	10 (7.5)
Walking or cycling for pleasure	34 (27.0)	40 (30.1)
Regular physical exercise, at least 3 h/week	75 (59.5)	74 (55.6)
Intense physical activity, more than 4 h/week	12 (9.5)	9 (6.8)
Baseline		
Sedentary	25 (19.8)	23 (17.4)
Walking or cycling for pleasure	48 (38.1)	75 (56.8)
Regular physical exercise, at least 3 h/week	47 (37.3)	30 (22.7)
Intense physical activity, more than 4 h/week	6 (4.8)	4 (3.0)

effect from exercise on cancer related fatigue might be too small to be clinically meaningful (effect size=0.13, 95% CI -0.06 to 0.33).⁷ A Cochrane meta-analysis found the association between exercise and fatigue to be insignificant and inconclusive owing to lack of studies.⁹ Likewise, two recent exercise studies of moderate intensity in women with breast cancer receiving adjuvant chemotherapy found no significant improvements in fatigue.^{33,34}

Table 2 | Chemotherapy cycles and surgery, by group assignment. Values are numbers of patients unless stated otherwise

	Control group (n=134)	Intervention group (n=135)	P value
Chemotherapy cycles			
Before study period			
1 cycle	33	41	0.75
2 cycles	43	37	
3 cycles	25	21	
4 cycles	16	19	
>4 cycles	17	17	
Mean	2.6	2.5	
During study period			
1 cycle	29	39	0.37
2 cycles	96	89	
>2 cycles	9	7	
Mean	1.8	1.9	
Advanced/adjuvant	72/62	73/62	
Surgery			
Mastectomy	39	33	
Lumpectomy	19	25	
Hysterectomy	11	16	
Ileo-colostomy	5	3	
Orchiectomy	8	6	
Other	27	26	

The cause of fatigue in cancer patients remains nebulous and multifactorial. Patients report fatigue as a state of physical disturbance and loss of function, with exhaustion being the lead factor in reduced physical activity. Severe fatigue results from extreme muscular de-conditioning caused by both the disease and treatment but can also be triggered by a sedentary lifestyle.³⁵ However, only 18% of the study population had a sedentary lifestyle at baseline, which may indicate that their fatigue burden was primarily due to the disease or to the chemotherapy. The patients' level of fatigue (mean 39.7, SD 25.8) corresponded to those obtained in other studies investigating cancer patients with the same WHO performance status and severity of disease (mean 40, SD 26).³²

Although the intervention reduced the patients' levels of fatigue after six weeks (mean 34.6, SD 24.3) the scores after intervention did not reach the level of the general population (mean 21).

Our qualitative research with participants from the pilot study showed that a reduction in fatigue could not be interpreted as an overall improvement in quality of life. However, a complete, partial, or periodic reduction in fatigue affected the patients' daily lives.³⁶

Consistent with recently published studies and meta-analyses on exercise interventions, including those in women receiving adjuvant therapy for breast cancer,^{7-9,33,34} we found no significant improvements in global health status/quality of life (EORTC QLQ-C30), which incorporates two questions: "How would

you rate your overall health during the past week?” and “How would you rate your overall quality of life during the past week?”

Table 3 | Health related Quality of Life (EORTC QLQ-C30) outcome variables and estimated differences

Outcome variable	Mean (SD)		Test (reference: control)	
	Baseline	6 weeks	Estimated mean difference (95% CI)	P*
Maximum number				
Control	134	117	NA	NA
Intervention	135	118	NA	NA
Global health status/quality of life				
Control	60.2 (22.4)	63.3 (22.4)		
Intervention	63.8 (21.1)	67.2 (20.3)	2.2 (-2.7 to 7.1)	0.4
Physical functioning				
Control	84.0 (15.7)	86.4 (14.5)		
Intervention	84.7 (14.5)	89.0 (12.4)	2.4 (-0.4 to 5.1)	0.09
Role functioning				
Control	65.6 (28.5)	68.9 (26.5)		
Intervention	68.7 (28.4)	74.8 (26.3)	4.6 (-1.7 to 10.9)	0.2
Emotional functioning				
Control	75.7 (19.3)	80.6 (17.8)		
Intervention	77.6 (12.2)	81.3 (17.2)	-0.3 (-4.0 to 3.4)	0.9
Cognitive functioning				
Control	81.9 (17.8)	81.3 (19.8)		
Intervention	84.4 (17.1)	83.8 (16.7)	1.7 (-2.6 to 6.0)	0.4
Social functioning				
Control	78.6 (21.2)	79.4 (20.8)		
Intervention	83.3 (20.6)	82.6 (20.5)	4.5 (-1.4 to 10.3)	0.1
Fatigue				
Control	43.0 (23.9)	41.0 (22.7)		
Intervention	39.7 (25.8)	34.6 (24.3)	-6.6 (-12.3 to -0.9)	0.02
Nausea and vomiting				
Control	17.3 (21.7)	13.7 (18.4)		
Intervention	16.0 (22.9)	13.4 (17.3)	-0.6 (-5.2 to 3.9)	0.8
Pain				
Control	15.4 (22.7)	16.8 (20.6)		
Intervention	17.4 (22.4)	14.6 (17.1)	-2.9 (-7.6 to 1.7)	0.2
Dyspnoea				
Control	18.2 (25.3)	18.2 (24.4)		
Intervention	15.3 (21.6)	14.3 (21.5)	-2.9 (-8.6 to 2.7)	0.3
Insomnia				
Control	32.7 (31.5)	26.4 (27.5)		
Intervention	22.7 (26.9)	18.4 (23.9)	-3.5 (-9.5 to 2.6)	0.3
Appetite loss				
Control	16.5 (26.6)	14.6 (22.1)		
Intervention	18.4 (27.6)	12.8 (22.3)	-3.4 (-8.9 to 2.0)	0.2
Constipation				
Control	22.2 (29.5)	18.4 (25.3)		
Intervention	16.7 (24.0)	20.8 (39.4)	4.5 (-4.0 to 13.1)	0.3
Diarrhoea				
Control	14.0 (23.5)	13.0 (21.9)		
Intervention	14.8 (28.0)	17.0 (26.1)	4.1 (-1.7 to 10.0)	0.2
Financial difficulties				
Control	14.3 (27.7)	13.0 (25.9)		
Intervention	11.1 (21.5)	10.8 (19.3)	-0.3 (-5.0 to 4.4)	0.9

*Adjusted general linear model.

Courneya et al tested resistance versus aerobic exercise for the duration of the patients' chemotherapy (17 weeks) in 242 patients with breast cancer. Neither aerobic exercise nor resistance training significantly improved cancer specific quality of life (as measured by functional assessment of cancer therapy questionnaire—anaemia).³⁴ Mutrie et al conducted a 12 week supervised group exercise programme during chemotherapy for early stage breast cancer in 203 women, and no significant effect was seen for general quality of life (functional assessment of cancer therapy questionnaire—general).³³

The failure of the intervention to significantly improve global health status/quality of life indicates that this type of short term intervention was not able to overcome the complexity of patients' overall negatively affected situation. Being diagnosed with cancer and exposed to chemotherapy disrupts the patient's life, affecting physiological and psychological functioning and contributing to negative effects on the global health status/quality of life.^{37,38} Improvements in this measure may have been too ambitious a goal in this short term clinical trial.

The intervention showed no significant effect on seven of eight somatic symptom scales in the EORTC QLQ-C30 questionnaire. This finding might be because many side effects induced by chemotherapy can be prevented or treated by supportive care drugs; for example, evidence based guidelines exist for the prevention and treatment of nausea, vomiting, and diarrhoea.³⁹

Supportive medical treatment may consequently have caused the observed floor effect where 50-70% of the study population were placed in the lowest quartiles on six of the symptom scales. Similarly we found a ceiling effect on three EORTC QLQ-C-30 functional scales.

By contrast, no such floor-ceiling effect was seen when applying the general wellbeing MOS SF-36 scale—which might be a more sensitive tool than the others for measuring effects of exercise in cancer patients—a finding confirmed in other exercise intervention studies.^{11,40}

Significant effects of the intervention were recorded for seven of 10 subscales for general wellbeing (MOS SF-36), with small to medium effect sizes for six of the scales. The present multimodal intervention showed greater significant effects and higher mean differences on several scales (MOS SF-36) compared to a 26 week supervised aerobic exercise programme in breast cancer patients receiving less toxic chemotherapy.⁴⁰ Particularly, vitality showed an effect size that was greater than medium (0.55). In existing meta-analyses regarding exercise based interventions, fatigue and quality of life are often highlighted, while measurement of vitality and its association with fatigue are not.⁷⁻⁹ In the present study an explorative general linear model analysis demonstrated that changes in fatigue were strongly affected by an increase in vitality. This finding may suggest that the multimodal intervention including a high intensity component generates vitality and

Table 4 | General wellbeing (MOS SF-36) outcome variables and estimated differences

Outcome variable	Mean (SD)		Test (reference: control)	
	Baseline	6 weeks	Estimated mean difference (95% CI)	P*
Maximum number				
Control	134	117	NA	NA
Intervention	135	118	NA	NA
Physical functioning				
Control	83.6 (14.8)	84.3 (16.2)		
Intervention	84.3 (13.7)	88.2 (13.2)	4.4 (1.1 to 7.7)	0.01
Role physical				
Control	27.1 (35.7)	31.8 (37.6)		
Intervention	30.5 (35.2)	46.1 (40.2)	12.4 (3.4 to 21.5)	0.007
Bodily pain				
Control	74.0 (24.6)	75.7 (22.7)		
Intervention	70.9 (27.6)	77.6 (20.0)	3.4 (-1.2 to 8.0)	0.2
General health perceptions				
Control	61.1 (22.9)	65.5 (22.4)		
Intervention	64.9 (18.4)	68.7 (19.7)	0.6 (-3.7 to 4.9)	0.8
Vitality				
Control	55.8 (21.1)	55.6 (21.6)		
Intervention	57.8 (20.2)	65.5 (18.1)	8.8 (4.4 to 13.1)	<0.0001
Social functioning				
Control	75.4 (21.8)	76.5 (22.0)		
Intervention	77.0 (21.1)	79.7 (22.2)	2.4 (-2.8 to 7.6)	0.4
Role emotional				
Control	58.6 (41.2)	58.7 (41.9)		
Intervention	56.1 (39.0)	69.6 (40.1)	12.0 (1.9 to 22.0)	0.02
Mental health				
Control	72.0 (16.7)	74.2 (16.1)		
Intervention	74.0 (16.3)	78.6 (15.0)	3.3 (0.2 to 6.4)	0.04
Physical component scale				
Control	44.3 (8.3)	45.1 (8.5)		
Intervention	44.2 (8.4)	47.4 (6.7)	1.9 (0.3 to 3.4)	0.02
Mental component scale				
Control	46.9 (10.2)	47.3 (10.0)		
Intervention	46.5 (9.7)	50.5 (9.4)	3.2 (1.1 to 5.4)	0.004

*Adjusted general linear model.

thereby reduces fatigue. The patients' perception of improved vitality is important especially during chemotherapy treatment periods.³⁶

At baseline, the patients had a mean score of 30.5 (SD 35.2) on the role physical scale, which was below that of the general Danish population range (mean 83.1, SD 31.7).⁴¹ By comparison with the control group the intervention group showed a lesser degree of limitation by their physical status when carrying out daily activities after intervention. Overall, they are ranked at a considerably lower level than the general population. By contrast, the patients in the intervention group scored high on the physical functioning scale at baseline (mean 84.3, SD 37.2) and after the six week intervention (mean 88.2, SD 13.2), their score was similar to that of the general Danish population (mean 87.6, SD 19.4).⁴¹ This finding confirms possibly the patient group's predisposition for doing physical activity and that the intervention group was prepared to partake in demanding activities without health

related constraints. With respect to the role emotional, mental health scales, and mental component scale, the patients in the intervention group showed significant improvement but had lower scores than their age equivalents in the general population.

In summary, our results in patient rated outcomes show small to medium effect sizes across a broad spectrum of physical and emotional wellbeing scales, including vitality and self reported physical activity levels. Furthermore, we found a reduction in fatigue, which we consider to be of importance to the patients' daily lives, even though no change was seen in the global health status/quality of life.

Objectively measured physiological outcomes also showed significant improvement in aerobic capacity and muscular strength. Studies in healthy adults and in people with cardiac and renal illnesses and with diabetes have shown that combined resistance and cardiovascular training programmes can have a range of beneficial effects such as increased physical function, aerobic capacity, and reduced muscular fatigue.⁴²⁻⁴⁶ Similarly, the results of the present study confirm that patients with cancer, even those undergoing chemotherapy, gain physiological benefits from combined resistance and cardiovascular training programmes.

According to a review of 26 studies by Galvao and Newton, the present study is the first of its kind to incorporate a high intensity design.⁴⁷ The results indicate that the high intensity design is an effective training programme as both muscle strength and overall fitness improved during a short time period. Patients with evidence of disease experienced the same improvement as patients with no evidence of disease. Improvements in muscle strength and fitness in this intervention are within the same range as in the exercise interventions that included patients with lesser burden of disease post-treatment and who showed improvement in specific areas despite longer training periods. The duration and frequency of the high intensity training sessions in the present study (270 minutes per week) imply a larger training volume than in single mode exercise interventions (120-135 minutes per week).^{7,9,47}

Improvement in the patients' self reported vitality and physical functioning were probably attributable to the high intensity component, since a connection exists between high intensity training and vitality in healthy athletes.⁴⁸

On days with high intensity exercise training, the sessions closed with low intensity relaxation training. The aim was to assist the patients to recognise and test their own physical reactions, such as dizziness, over-exertion, and cold sweat. The patients were advised to concentrate on breathing and muscle tension, and gain awareness of their physical and mental reactions. In this way the patients stabilised physically and emotionally before returning to their daily activities. These findings correspond to single intervention studies regarding patients' perception of self control.⁴⁹ On the other hand the intervention did not affect the

patients' levels of nausea, vomiting and pain suggesting non-effectiveness or simply that the patients in this study had a low level of symptoms at baseline.

Incorporating a heterogeneous group of cancer patients, each presenting different treatment related side effects, increases the need for daily pre-exercise screening by clinical nurse specialists. This has been of importance in preventing serious adverse events during high intensity programmes. Five participants were excluded from the high intensity physical training component (total of 25 times) during the study period because of leucopenia and/or increased blood pressure. Intermittent increase in heart rate and/or blood pressure were commonly observed in two or three patients weekly. In these cases, values for heart rate and blood pressure were retained after 10 minutes of recline, to meet pre-screening criteria and approval to enter the exercise room.

Five participants with breast cancer had lymphoedema at baseline; none experienced exacerbations during the intervention. One participant with a brain tumour experienced a grade 3 seizure after cardiovascular training. This participant was admitted to the hospital, recovered within 3 hours, and was discharged the same day. The participant was subsequently excluded from the intervention. We must therefore advise patients with brain tumours or brain metastases not to participate in high intensity exercise interventions. The inclusion and exclusion criteria, the daily screening procedures, the presence of the clinical nurse specialist during training, and training sphygmomanometer ensured the required level of safety. The combination of a training facility at the hospital and professional supervision was crucial and confirmed the patients' understanding that the training programme was a supplement to medical treatment. Despite the multimodal intervention being short term (six weeks) the volume of the intervention seemed adequate.

Strengths and weaknesses

The trial had a large sample size and included male and female patients with advanced cancer and different types of diagnoses. The strengths of the trial include supervised and structured exercise, combined high and low intensity components, use of validated objective physiological measurements, validated questionnaires, intention to treat analyses, and limited dropout rate of 12.7%. All participants were undergoing chemotherapy during the study period. Limitations included adherence rate of 70.8% and a 53% recruitment rate, which are comparable with other exercise interventions including cancer patients with lesser disease burden.^{33,34}

One weakness of the study is that while we were able to report the immediate effects of the intervention it was not possible to perform valid comparisons of the effect between the control and the intervention groups 3 months after intervention. The reason is that 59.7% of the control group patients subsequently elected to participate in the intervention following their six week participation in the study. Study allocation was not concealed, either to the patient or to the healthcare professionals, and the control group was allowed to freely increase physical activity.

Another weakness of the study is that the professionals conducting the daily exercise sessions also collected the data, which may have led to significant bias. However, research assistants who were not involved with the participants keyed in and analysed the data.

Self selection of participants in our study resulted in a sample of cancer patients who were overtly motivated to engage in group based physical activity.

Our findings suggest that population heterogeneity does not preclude use of this type of intervention. However, generalisation may be limited by the willingness of patients to allocate the necessary time to physical activity. Furthermore, all patients in the present study had a good performance status (WHO 0-1) and did not have brain or bone metastases. Our intervention may need to be modified in patients with a performance status of 2 or greater. Finally, we consider it a great challenge to motivate patients who are not interested in physical training in groups with mixed gender.

Meaning

There is a considerable rationale for promoting multimodal exercise interventions to improve physical capacity, vitality, and physical and mental wellbeing, and to relieve fatigue during chemotherapy; thereby supporting cancer patients' daily living activities. The range of exercise components used, from high intensity activity to relaxation, body awareness training, and massage has been shown to be feasible, safe, and beneficial to various patients with cancer during chemotherapy, even patients with advanced disease.

Very few exercise interventions include cancer patients with advanced disease and most of these involve patients with haematological disease during

Table 5 | Objective physiological outcome measure variables and estimated difference

	Mean (SD)		Test (reference control)	
	Baseline	6 weeks	Estimated mean difference (95% CI)	P*
Vo₂max (l/min)				
Control	1.90 (0.5)	1.88 (0.5)		
Intervention	1.82 (0.4)	1.96 (0.5)	0.16 (0.1 to 0.2)	<0.0001
Muscular strength (kg)				
Leg press				
Control	107.6 (33.3)	110.4 (36.0)		
Intervention	100.8 (30.5)	132.4 (42.3)	29.7 (23.4 to 34.9)	<0.0001
Chest press				
Control	40.2 (18.0)	39.7 (17.2)		
Intervention	37.9 (15.6)	45.2 (17.9)	7.5 (5.6 to 9.4)	<0.0001
Pull-down				
Control	42.0 (16.3)	42.8 (16.1)		
Intervention	39.6 (14.0)	47.2 (14.4)	6.4 (4.5 to 8.3)	<0.0001

*Adjusted general linear model.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Supervised cardiovascular exercise training of moderate intensity has shown benefits in patients with breast cancer during or after adjuvant chemotherapy

Supervised group exercise interventions including patients with different cancer diagnoses and with advanced disease undergoing chemotherapy have not been evaluated in randomised clinical trials

WHAT THIS PAPER ADDS

High intensity exercise can be undertaken safely by such patients and is associated with physiological, functional, and emotional benefits

Multimodal high and low intensity exercise interventions can be offered by interdisciplinary teams of clinicians

Innovative approaches to address men's needs for physical rehabilitation in this context are required

or after high dose chemotherapy and peripheral blood stem cell transplantation.⁵⁰⁻⁵¹ Patients with advanced solid cancers differ substantially from these patients—thus investigations including such patients are still needed. The present study had a clear majority of female patients (73%). However, the number of people with cancer each year is evenly distributed between the two sexes.⁵²⁻⁵⁶ We therefore recommend that interventions should be developed with greater appeal to male patients.

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