

The challenge of preserving cardiorespiratory fitness in physically inactive patients with colon or breast cancer during adjuvant chemotherapy: a randomised feasibility study

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ABSTRACT

Introduction: Anti-neoplastic treatment is synonymous with an inactive daily life for a substantial number of patients. It remains unclear what is the optimal setting, dosage and combination of exercise and health promoting components that best facilitate patient adherence and symptom management in order to support cardio-respiratory fitness and lifestyle changes in an at-risk population of pre-illness physically inactive cancer patients.

Methods: Patients with breast or colon cancer referred to adjuvant chemotherapy and by the oncologists pre-screening verified as physically inactive were eligible to enter a randomised three-armed feasibility study comparing a 12-week supervised hospital-based moderate to high intensity exercise intervention or alternate an instructive home-based 12-week pedometer intervention, with usual care.

Results: Using a recommendation based physical activity screening instrument in order to correspond with cardio-respiratory fitness (VO₂ peak) proved to be an applicable method to identify pre-illness physically inactive breast and colon cancer patients. The study demonstrated convincing recruitment (67%), safety and intervention adherence among breast cancer patients; while the attendance rate for colon cancer patients was notably lower (33%). VO₂-peak declined on average 12% across study groups from baseline to 12 weeks though indices towards sustaining watt performance and reduce fat mass favoured the hospital-based intervention. Pedometer use was well adapted in both breast and colon cancer patients.

Conclusions: Despite a fair adherence and safety, the current study calls into question whether aerobic exercise, regardless of intensity, is able to increase VO₂-peak during taxane-based chemotherapy in combination with Neulasta in physically inactive breast cancer patients.

Trial Registration: ISRCTN24901641

Strengths and limitations of this study

- The feasibility study demonstrated that prediagnostic physically inactive patients with breast or colon cancer may be identified by clinicians by using a simple screening instrument based on national recommendations for physical activity that associates with low cardiorespiratory capacity at onset of adjuvant chemotherapy.
- Physically inactive patients with breast cancer may be motivated to participate in supervised comprehensive or home-based exercise interventions of moderate-to-high intensity at onset of adjuvant chemotherapy. The low recruitment and high attrition of patients with colon cancer made it inadequate to raise a clear conclusion on feasibility.
- Both interventions were well timed and showed fair adherence and safety among patients with breast cancer but were partly inconclusive for patients with colon cancer regarding timing and volume of exercise components.
- The current feasibility study calls into question whether aerobic exercise, regardless of intensity, is able to increase cardiorespiratory capacity during taxane-based chemotherapy in combination with Neulasta among patients with breast cancer.

BACKGROUND

In Denmark, 4637 people were diagnosed with breast cancer and 2551 with colon cancer during 2011.¹ Improved treatment has increased the expected 5-year survival rate to 79% for breast cancer and 52% for colon cancer.^{1 2} A European survey among cancer survivors reported recently that <25% meet the current physical activity guidelines.³ Studies on exercise oncology are

predominantly performed following chemotherapy and few studies involve patients with colorectal cancer.^{4–7} Of relevance, Courneya *et al*⁸ found that symptoms and side effects from chemotherapy are dominant barriers to attending exercise sessions among survivors of breast cancer.

Regular leisure time physical activity among patients with breast or colon cancer may reduce the incidence and risk of relapse.^{9–12} Other studies have found an elevated prevalence of predisposing lifestyle factors (weight gain, hypertension, metabolic dysfunction, physical inactivity, smoking) and an increased risk of developing heart disease among patients with cancer.^{13–14} These findings necessitate the integration of lifestyle modifications in oncology rehabilitation^{15–18} and the promotion of increased physical activity specifically for physically inactive or sedentary cancer survivors. A review by Wahnefried *et al*,¹⁹ “Riding the crest of the teachable moment”, suggests that cancer survivors spontaneously adopt lifestyle changes in the hope of improving their health. A few clinical studies have documented this tendency towards lifestyle change,²⁰ but others have failed to confirm it.^{21–22} It remains unclear, though, what the optimal setting, timing during cancer treatment and survivorship, dosage and combination of exercise and health-promoting components best facilitate patient adherence and symptom management to support physiological improvements and sustainable lifestyle changes in this at-risk physically inactive cancer population. In general, there is a lack of powerful exercise studies examining physically inactive or sedentary cancer populations and during chemotherapy in particular.³

The objective of the present study is to investigate the capability of oncologists and nurses to evaluate physical activity among patients with breast or colon cancer during adjuvant chemotherapy and to recruit physical inactive patients for exercise intervention. The feasibility study examines adherence to one of two multimodal exercise interventions lasting 12 weeks, a hospital based, high intensity, group exercise intervention, and a home based, low intensity, individual pedometer intervention compared to a randomly selected control group and by targeting cardiorespiratory fitness (peak oxygen consumption; VO₂ peak) as the primary outcome of interest.

METHODS

Participants

Inclusion: Patients with breast or colon cancer referred to adjuvant chemotherapy, performance status 0–1 and verified during prescreening by oncologists or nurses as being physically inactive using guidelines from the Danish Health and Medicines Authority (150 min of regular and moderate recreational physical activity and at least 2×20 min of strenuous exercise per week)²³ were eligible. A clinical nurse specialist informed patients in depth about the study’s rationale, intervention and the

scientific tests to be conducted. The study protocol contains additional details on eligibility.²⁴

Exclusion: Patients with symptomatic heart disease (angina pectoris, acute coronary syndrome) within the past 6 months, and patients who were unable to read and understand Danish, were not eligible to enter the study.

Ethics

All patients provided informed written consent before entering the study. The Scientific Committee of the Capital Region (file no. H-1-2011-131) and the Danish Data Protection Agency (file no. 2011-41-6349) approved the study. Trial registration: Current Controlled Trials ISRCTN24901641.

Study design

The study was designed as a randomised controlled, three-armed feasibility study comparing a 12-week supervised, hospital-based moderate-to-high exercise intervention and a non-supervised instructive 12-week pedometer intervention with usual care (figure 1). The randomised controlled trial (RCT) design was chosen in order to examine barriers for recruitment, adherence, safety aspects and potential efficacy related to study group allocation. The scope of the feasibility study was not designed, however, to investigate significant effects in outcomes between groups.

Following baseline testing, patients were sequentially numbered, stratified by diagnosis and randomised (equal weight 1:1:1) by computer at the Copenhagen Trial Unit (CTU). To test feasibility, the goal was to include 45 patients undergoing adjuvant chemotherapy.

Setting

The present project was conducted at the Department of Oncology, Copenhagen University Hospital, Rigshospitalet and at the Center for Integrated Rehabilitation of Cancer Patients (CIRE), Copenhagen, Denmark, established and supported by the Danish Cancer Society and the Novo Nordic Foundation. CIRE adheres to three key intervention principles: (1) Early initiation of an intervention during cancer treatment; (2) EXercise/physical activity and (3) Patient ACTivation (EEX-ACT).^{25–26}

Intervention

Study arm 1 Supervised hospital-based group exercise intervention+health promotion counselling and symptom management (HIGH HOSP) (6 weeks; 9 h/week+6 weeks; 6 h/week)

Patients were offered a 12-week supervised exercise programme in groups of 10–14 patients by an exercise physiologist and a clinical nurse specialist (table 1). The first 6 weeks (part I, 9 h/week) included three training sessions per week comprising high-intensity/low-intensity components (cardiorespiratory training on stationary bikes, resistance training, relaxation training and massage), as well as one restorative session ‘Body

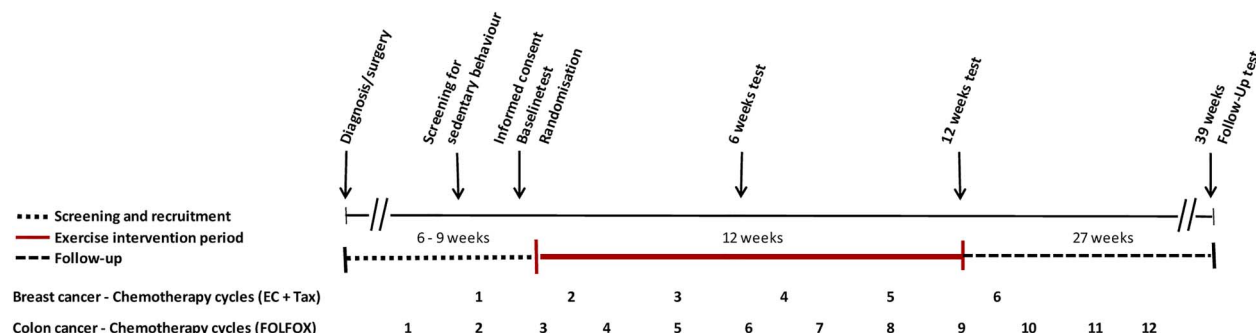


Figure 1 Global overview of study evaluation during chemotherapy (EC, epirubicin and cyclophosphamid FOLFOX, oxaliplatin and 5-FU (5-fluorouracil) and folinic acid; Tax, taxotere).

awareness' per week. The total training volume corresponded to approximately 43 metabolic equivalent of task (MET) hours per week.²⁷ An all-sports training element that included ball games, dance and circuit training was introduced during the last 6 weeks of the intervention (part II, 6 h/week) with a total training volume of 40 MET hours/week. Furthermore, patients received individual health promotion counselling and symptom management at baseline and at 6, 12 and 39 weeks. Pre-exercise screening took place before each session that involved moderate-to-high-intensity physical training^{27 28} (see study protocol²⁴).

Study arm 2 Home-based individual progressive pedometer intervention, health promotion counselling and symptom management (LOW PED)

The pedometer programme was individually organised and designed to progressively support increased physical activity during adjuvant chemotherapy (table 2). All pedometer data were delivered electronically by connecting the pedometers to Omron Health Management Software uploaded in study investigators' work station computers.

The individual pedometer instruction was provided by a clinical nurse specialist in cancer and exercise.

Patients were encouraged to enhance their physical activity levels and to avoid physical inactivity by integrating exercise into activities of daily living during chemotherapy. The overall goal was to achieve a low/moderate recreational physical activity level of 30 min/day and ultimately 10 000 steps/day, five times per week.²⁹ To enhance adherence in wearing and using pedometers, patients were instructed and supported with a tighter schedule at the beginning than at the end of the intervention. The patients were (1) issued an Omron Walking Style Pro pedometer with PC access capability that made it possible to visualise the patient's exercise achievements on a daily, weekly and monthly basis, as well as scheduled instruction and evaluation at baseline and at weeks 2, 4, 6, 9 and 12; (2) received similar individual face-to-face health promotion counselling as the HIGH HOSP group, including clinical advice concerning symptom management at baseline and at weeks 6 and 12 and later on at 39 weeks (see study protocol²⁴).

Study arm 3: CONTROL

The control group received standard care with no specific restrictions on participation in physical activity.

Table 1 Hospital-based supervised group exercise intervention

Weekly schedule				
Monday	Tuesday	Wednesday	Thursday	Friday
Part I: 6 weeks, 9 h/week				
Physical exercise (1.5 h)	Body awareness (1.5 h)	Physical exercise (2 h)		Physical exercise (1.5 h)
Relaxation (0.5 h)	Relaxation (0.5 h)	Relaxation (0.5 h)		Relaxation (0.5 h)
Massage(0.5 h)				Massage (0.5 h)
Part II: 6 weeks all-sport training, 6 h/week				
Physical exercise (2 h) eg, ball games, dancing, resistance and cardio training		Physical exercise (2 h) eg, ball games, dancing, resistance and cardio training		Physical exercise (2 h) eg, ball games, dancing, resistance and cardio training
Baseline	Week 6	Week 12	Week 39	
Health counselling and symptom management (1 h)	Health counselling and symptom management (1 h)	Health counselling and symptom management (1 h)	Health counselling and symptom management (1 h)	

Table 2 Home-based individual progressive pedometer intervention

Week 1	Week 2	Week 4	Week 6	Week 9	Week 12
Establish baseline level Pedometer instruction	Planning of pedometer use	Pedometer instruction and evaluation	Pedometer instruction and evaluation	Telephone: pedometer instruction and evaluation	Pedometer instruction and evaluation
Baseline	Week 6	Week 12	Week 39		
Health counselling and symptom management (1 h)	Health counselling and symptom management (1 h)	Health counselling and symptom management (1 h)	Health counselling and symptom management (1 h)		

Owing to ethical considerations and growing scientific evidence, control patients were in fact motivated and advised by their clinicians to be physically active.^{27–30} Following the control period, patients were offered participation in body and cancer,²⁷ an exercise programme provided by the Copenhagen Region hospitals after the 12-week study period.

Outcome measures

In accordance with the study protocol,²⁴ the primary outcome cardiorespiratory fitness/ VO_2 peak and secondary physiological and patient-reported outcomes (PRO) were measured at baseline (inclusion) and at 6 and 12 weeks (end of intervention).

Primary outcome: Cardiorespiratory fitness measured as the VO_2 peak and determined by an incremental test on a cycle ergometer (Monark Ergonomic 839E) and direct measures of respiratory gases.

Secondary outcomes: Physiological measures (respiratory exchange ratio (RER), maximum heart rate (HR_{max}), spirometry, test haemoglobin, fasting full body dual-energy X-ray absorptiometry (DXA) scan, digital pedometer steps, aerobic walking time and PRO, including the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C-30, the 36-Item Short Form (SF-36), the Hospital Anxiety and Depression Scale (HADS) and a supplemental questionnaire (physical activity/categorical, labour, disability, participation in local rehabilitation lifestyle factors (eg, smoking cessation, alcohol, physical activity)).²⁴

An oncology nurse specialist or project physiotherapist entered physiological variables, questionnaires and medical data gathered from patients' medical records into a database, OpenClinica, hosted by CTU, who exclusively had access to unblinded data while the trial was being conducted.

Statistics and analytic plan

The principal analysis employed the intention-to-treat approach. The explorative aspect includes descriptive statistical analysis across study groups to provide insight into mean values, SDs and the potential application of objective measurement tools and standardised PRO instruments.

RESULTS

Patient characteristics and feasibility analyses

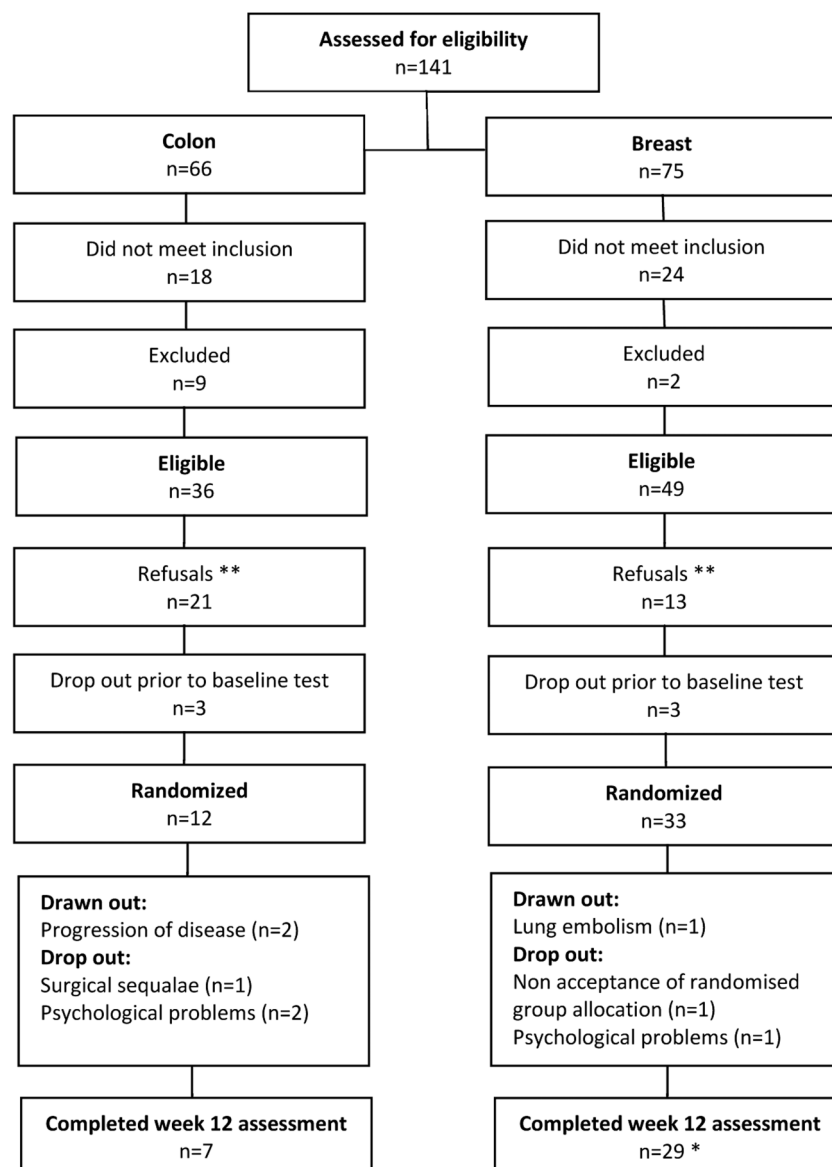
A total of 141 patients were assessed for eligibility, and this resulted in 45 patients being included, equalling an acceptance rate of 67% for breast cancers and 33% for colon cancers (figure 2). The number of refusals among patients with colon cancer was considerably high (58%). Compared with breast cancer, patients with colon cancer was older, had more postsurgical complaints (eg, prolonged tissue healing, ostomies and bowel problems) and accordingly were less prepared for a tight intervention programme schedule (9 h/week) during adjuvant chemotherapy. Six patients (3 with breast cancer and 3 with colon cancer) dropped out prior to the baseline test, mainly due to concerns about the level and amount of exercise in the hospital-based intervention regarding severe side effects, non-control of ostomy output and sequelae from surgery.

Table 3 presents the study population characteristics. All patients received adjuvant chemotherapy prior to and during the 12-week intervention or control period. On average, patients with breast cancer had received 1.3 chemotherapy cycles prior to study inclusion and patients with colon cancer 3.2 cycles supporting the feasibility of timing rehabilitation at this specific time point during the initial treatment. The time since diagnosis to baseline test was on average 77 days with an SD of 32. The majority 89% ($n=40$) had primary surgery within 0–20 days from the date of their initial diagnosis, whereas 11% ($n=5$) of participants were going through surgery 37–133 days after their initial diagnosis was established.

Using two superior physical activity screening criteria from the Danish Health and Medicines Authority²³ showed that *not* performing strenuous physical activity at least 20 min twice a week was the major patient-reported cause for study eligibility, whereas the majority (71%) reported an adequate performance of at least 150 min of moderate intensity recreational physical activity per week (figure 3). Accordingly, 67% fell into the low or very low group of VO_2 peak values at baseline when comparing individual VO_2 peak values with the Scandinavian background population.³¹

Adherence to the interventions and safety aspects: Thirty-seven of 45 patients (91% breast, 58% colon,

Figure 2 Flow chart.



* One patient missed 12 week assessment due to neutropenic fever

** Reasons for refusal to participate: Breast cancer HIGH HOSP: Intervention too excessive, transportation distance, no preference for physical activity, priorities work, psychological problems, other exercise option from local authorities. Colon cancer HIGH HOSP; Intervention too excessive, transportation distance, no preference for physical activity, priorities work, psychological problems

respectively) completed the study given an attrition rate of 18%. Patients with breast/colon cancer adhered to the HIGH HOSP intervention in 74%/50% of the total expected training days and with a tendency of falling adherence during the second half of the observational period. Patients wore the pedometer (breast/colon) in 75%/81% of the total expected days, respectively. The safety issues taken into consideration preceding maximum physiological tests and at daily attendance for the HIGH HOSP intervention followed a standardised and implemented procedure described previously.²⁷ No

serious adverse reactions related to the interventions were reported. On eight occasions, adverse events were reported during the high-intensity exercise or pedometer programme that led to discontinuation due to discomfort, for example, pain, neuropathies, nausea/vomiting, fatigue, neutropenia, fever, diarrhoea. Two patients in the HIGH HOSP intervention discontinued intermittently due to hospitalisation (lung embolism, anal fissure and infection). One patient with breast cancer completed the 12-week HIGH HOSP intervention but missed the 12-week assessment due to

Table 3 Patient characteristics by study groups

	Total n=45	Intervention HIGH HOSP n=15	Intervention LOW PED n=14	Control n=16
Gender: female/male	40/5	13/2	13/1	14/2
Age, mean (SD)	50.83 (10.29)	57.17 (10.51)	48.49 (8.41)	46.95 (9.19)
Diagnosis				
Breast/colon	33/12	11/4	11/3	11/5
Mastectomy/lumpectomy	17/16	6/5	7/4	4/7
Ostomy	4	1	1	2
Days since diagnosis, mean (SD)	77.09 (31.51)	71.33 (17.61)	73.64 (33.07)	85.50 (39.43)
Chemotherapy regimen				
Breast standard adj.	22	8	7	7
Breast READ protocol	11	3	4	4
Colon FOLFOX adj.	12	4	3	5
Chemotherapy cycles before study inclusion: mean (SD)	Br 1.33 (0.48) Co 3.17 (1.64)	Br 1.37 (0.50) Co 2.50 (1.29)	Br 1.45 (0.52) Co 3.33 (1.15)	Br 1.18 (0.40) Co 3.60 (2.19)
Chemotherapy cycles applied during interv./control mean (SD)	Br 4.00 (0.00) Co 7.11 (1.45)	Br 4.00 (0.00) Co 7.00 (2.00)	Br 4.00 (0.00) Co 8.00 (0.00)	Br 4.00 (0.00) Co 7.20 (1.10)
Educational level				
Lower	4	2	1	1
Secondary	14	4	5	5
Advanced	26	8	8	10
Missing value	1	1		
Physical activity prior to diagnosis				
<150 min moderate activity per week/>150 min week	13/32	4/11	6/8	3/13
<2x20 min strenuous activity per week/>2x20 min week	45/0	15/0	14/0	16/0
Weight mean (SD)	64.86 (23.03)	62.58 (21.77)	64.86 (19.32)	66.99 (27.93)
BMI mean (SD)	24.61 (4.42)	24.39 (5.27)	23.80 (2.59)	25.54 (4.90)
Smoking status				
Never/past*	19/19	5/7	8/5	6/7
Current	7	3	1	3
Alcohol intake/week mean (SD)	4.00 (4.57)	5.07 (4.92)	3.15 (3.63)	3.69 (5.00)

*Cessation >1 year.

BMI, body mass index; Br, breast; Breast READ protocol, six series of docetaxel plus cyclophosphamide; Breast standard adj., breast standard adjuvant; three series of epirubicin and cyclophosphamide followed by three series of docetaxel; Co, colon; Colon FOLFOX, oxaliplatin and 5-FU (5-fluorouracil) and folinic acid; interv, intervention.

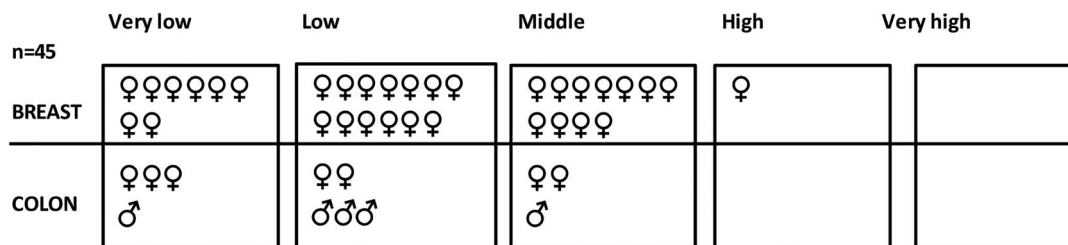
Days since diagnosis refers to the hospital system registered date of diagnosis.

neutropenic fever following taxane-based chemotherapy. The primary determinant for discontinuation in the pedometer group was severe taxane-induced pain (n=4) resulting in affected walking ability and decreasing the level of adherence in wearing pedometers.

Three patients were 'drawn out' by study investigators due to progression of underlying cancer (n=2) or lung embolism (n=1), while reasons for patients 'drop out'

were sequelae from surgical complication (n=1); non-acceptance of randomised group allocation (n=1); and psychological discomfort at this early stage of treatment (n=3).

Pedometer usability: Table 4 shows achievements and patient usability with the pedometer divided into four measurement points, each covering 3 weeks (T1, T2, T3 and T4). No progression in average of total steps,



Comment: Maximal oxygen uptake VO_2 peak at baseline test compared to the age-matched Scandinavian background population³²

Figure 3 Maximal oxygen uptake peak oxygen consumption.

aerobic walking time and days with >10 000 steps was observed during the intervention, though some heterogeneity was found between individuals (figure 4).

Health-related outcomes

Physiological test validity of primary outcome: Cardiorespiratory fitness VO_2 peak: The use of the gold standard for VO_2 peak and direct measures of respiratory gases demonstrated high validity judged on the RER, perceived exertion (Borg's Rating of Perceived Exertion (RPE)) and percentage of HR_{max} at peak exercise testing. There was no indication of improvements or declines in test habituation/performance at test time points (table 5), which supports the test applicability when measuring peak performance in patients with breast or colon cancer receiving adjuvant chemotherapy.

Table 6 shows the changes in cardiopulmonary capacity and performance capacity. By using analysis of variance (one-way ANOVA) did the primary outcome measure, mean VO_2 peak, decrease significantly within groups from baseline to postintervention (12 weeks) in breast cancer groups (high, low and control). There were minor changes within groups that potentially favoured the HIGH HOSP intervention in performance capacity (Watt max). Considering colon cancer, our tests suggested an improvement on the VO_2 peak and Watt performances in all study groups.

Table 7 shows muscle strength and results from the DXA scan at baseline and at weeks 6 and 12. In general, we found improvement in strength in all study groups. Results favoured the HIGH HOSP intervention by reducing fat mass and increasing lean body mass compared with LOW PED and Controls.

Secondary outcomes: Selected results from PROs: Selected PRO findings are presented, primarily among breast cancers, due to the relatively small group of colon cancers in the study. Table 8 provides an overview of selected PRO scales based on the given mean values and SD. A full analysis of the PROs may be available in online supplementary material. The patient-reported instruments were generally applicable to the breast or colon cancer population in this pilot study. Ceiling effects occurred in EORTC and SF-36 in relation to the physical functioning scales, whereas emotional scales (emotional functioning on EORTC and role emotional on SF-36) showed the potential functional effects of interventions. These results were supported by findings

on HADS, indicating that there was less anxiety related to the HIGH HOSP intervention. Notably, pain increased linearly on the EORTC from weeks 6 to 12, corresponding to the planned shift in the antineoplastic agent from cyclophosphamide to taxane. Sleeping problems and dyspnoea seemed to be of significant importance (see table 8 and the online supplementary material for the full EORTC and Medical Outcome Study SF-36 analyses).

DISCUSSION

Identifying physically inactive or sedentary cancer remains controversial due to the inconsistency in methods (patient reported and/or physiological measurements) for defining this target population in question.^{23 32–36} A consensus definition of sedentary behaviour has not yet been established, although agreement exists that sedentary behaviour is not classified as all behaviours separated from moderate-to-vigorous physical activity. A recent systematic review by Bourke *et al*³ on interventions to improve exercise behaviour in sedentary cancer survivors defines the term sedentary as cancer survivors not meeting recommended physical activity guidelines. Others have defined sedentary behaviour as the amount of activity ≤ 1.5 METs.³⁷ Based upon patient report at baseline 71% of participants did reach an activity level of approximately 30 min of light to moderate leisure time physical activity per day, which is equivalent to a MET intensity of 3.0.³⁸ We did not measure the amount of sedentary time spent on a daily or weekly basis, which is why a classification of the participants as sedentary may be biased. However, none of the participants reported that they were doing vigorous physical activities prior to their cancer diagnosis, why physically inactive not meeting recommended guidelines seem to be the most appropriate term. Accordingly, this study bridges the gap and approves the feasibility of using national guidelines as a threshold for patient-reported low physical activity assessment using national recommendations and a corresponding low VO_2 peak measure at baseline compared with the Scandinavian background population (figure 3).

Furthermore, our feasibility study demonstrated convincing recruitment, safety and intervention adherence among physically inactive patients with breast cancer at onset of adjuvant chemotherapy, while the attendance

Table 4 12 weeks pedometer achievements and adherence, n=14

	Total steps, mean % (SD)	Aerobic steps, mean % (SD)	Aerobic walking time, mean % (SD)	>10 000 steps days per 21 days (SD)	Adherence,* mean % (SD)
T1: weeks 1–3	6379 (2188)	1836 (1598)	16.24 (15.42)	3.93 (4.67)	91.50 (15.80)
T2: weeks 4–6	6175 (2969)	1671 (1667)	16.34 (15.53)	2.92 (4.92)	80.58 (26.41)
T3: weeks 7–9	6086 ((2591)	1674 (1432)	16.14 (14.65)	4.17 (4.95)	80.58 (27.75)
T4: weeks 10–12	5575 (4761)	1461 (1597)	13.34 (14.58)	3.18 (5.44)	75.36 (27.14)

*Percentage of days patients wore pedometers. T1 versus T4 p=0.0239.

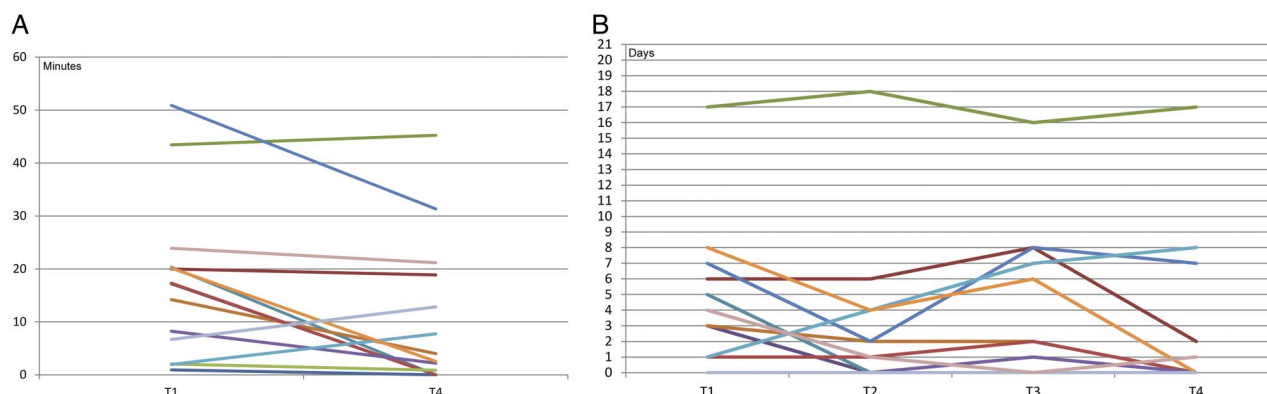


Figure 4 Average aerobic walking time (3 weeks average) at baseline (T1) versus intervention completion (T4) (A) and number of days with 10 000 steps achieved in cycles of 21 days measured four times (T1–T4) (B).

and acceptance rate for patients with colon cancer was notably lower and therefore insufficient to raise any clear conclusions for this subgroup. The major barriers for hindering attendance of patients with colon cancer involved the weekly volume and HIGH HOSP exercise components offered (9 h weekly) in relationship to the surgical sequelae the patients experienced and due to the higher frequency of hospitalisation and chemotherapy cycles. Consequently, the present study does not justify that the dose (volume) of exercise should be equal between these two physically inactive cancer populations and points to the need of exercise modifications for colon cancers in order to increase recruitment. Notably, five of seven patients with colon cancer who completed the 12 weeks test improved their VO_2 peak during adjuvant chemotherapy and 12-week follow-up assessment. However, owing to the limited inclusion and higher attrition among patients with colon cancer, we focused on recruitment and adherence results irrespective of the remarkable physiological improvements for some relatively younger men with colon cancer across group assignment. The challenge of designing an appropriate exercise interventional programme and broadening recruitment of patients with colon cancer therefore remains unsolved and as reflected in the limited scientific exercise literature during adjuvant chemotherapy for this specific subgroup.^{3 4}

Considering the included physically inactive patients with breast cancer, our findings correspond to a

meta-analysis by Husebo *et al*⁸⁹ predicting exercise adherence in moderate-to-vigorous programmes among cancer populations to vary between 42% and 92%. The test adherence of 84% is in line with the limited literature among screened physically inactive patients with breast cancer referred to exercise intervention during chemotherapy.^{40–42} We propose that the identification of patients and the oncologists' recommendation of physical exercise at time of onset for adjuvant chemotherapy are suitably timed to co-create opportunities for facilitating recruitment among these sedentary subgroups.⁴³ Moreover, we found that patient motivation and sustained participation may counteract the exercise barriers despite patients experiencing a range of escalating symptoms and side effects (fatigue, pain, sleeping problems and dyspnoea) from baseline to the 12-week assessment. However, severe symptoms and side effects decreased attendance in the interventions with, for example, perceived pain as the dominant cause affecting walking ability in the pedometer group. The landscape and experience of symptoms and side effects along with motivational factors need to be explored in larger RCT samples that allow stratification and subgroup analyses.

The clinical and public health rationale of promoting, enhancing and sustaining physical activity, especially among the physically inactive or sedentary risk populations, has pushed for the integration of practical, non-supervised interventions as the use of pedometers and accelerometers during treatment and cancer

Table 5 VO_2 peak test performance

	Breast			Colon		
	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks
N	33	24	29	12	8	7
RER, mean (SD)	1.21 (0.09)	1.22 (0.12)	1.22 (0.16)	1.23 (0.07)	1.20 (0.12)	1.21 (0.10)
RER>1.10 (>1.15)	88% (73%)	83% (71%)	86% (71%)	92% (92%)	75% (75%)	86% (86%)
BORG, mean (SD)	17.1 (1.3)	18.1 (1.1)	17.4 (1.8)	16.5 (1.8)	17.9 (1.1)	18.3 (1.4)
% of HR_{max} , mean (SD)	99.9 (8.4)	99.4 (9.1)	98.2 (9.8)	101.5 (6.9)	98.8 (9.7)	95.5 (7.5)

BORG, BORG Rating of Perceived Exertion; HR_{max} , heart rate maximum; RER, respiratory exchange ratio; VO_2 peak, peak oxygen consumption.

Table 6 Primary outcome VO₂ peak

	HIGH HOSP			LOW PED			Control		
	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks
Breast	n=11	n=9	n=9	n=11	n=9	n=10	n=11	n=9	n=10
VO ₂ peak (L/min)	1.8 (0.5)	1.7 (0.5)	1.6 (0.6)*	1.8 (0.4)	1.9 (0.4)	1.6 (0.5)*	2.1 (0.3)	2.0 (0.3)	1.9 (0.3)*
VO ₂ peak/BW (mL/min/kg)	29.4 (9.0)	29.4 (7.9)	27.3 (7.7)*	27.1 (6.4)	26.8 (6.6)	22.4 (6.5)*	30.5 (5.0)	28.8 (7.3)	27.7 (6.8)*
Watt max (w)	122 (52)	134 (56)	124 (53)	135 (45)	145 (43)	126 (44)	160 (30)	157 (31)	152 (29)
Colon	n=4	n=3	n=3	n=3	n=3	n=2	n=5	n=2	n=2
VO ₂ peak (L/min)	2.0 (0.4)	2.3 (0.6)	2.4 (0.6)	1.9 (0.4)	1.9 (0.4)	2.2 (0.4)	2.4 (1.0)	2.7 (1.1)	3.9 (0.5)
VO ₂ peak/BW (mL/min/kg)	24.9 (2.8)	26.4 (3.7)	26.9 (4.6)	27.4 (6.4)	27.2 (5.7)	31.0 (0.6)	27.6 (10.2)	31.6 (3.3)	41.1 (10.0)
Watt max (W)	148 (47)	160 (43)	170 (52)	125 (51)	138 (51)	154 (44)	200 (77)	194 (92)	289 (27)

Data are presented as means and SD.

*Baseline versus 12 weeks; p<0.05.

BW, body weight; VO₂ peak, peak oxygen consumption; Watt max, Watt power at the end of the incremental test.

survivorship.^{44–53} Patients allocated to pedometer use were not able to increase the number of walking steps during the present intervention and had, mainly due to a progression in the experience of taxane-related pain, a tendency of falling adherence in wearing their pedometers at the end of the intervention. However, the lowest quartile of adherence is still within a level >70% as found in sufficient studies incorporated in a systematic Cochrane review of exercise studies for women receiving adjuvant therapy for breast cancer.⁵⁴ Moreover, pedometer data included in our analysis solely comprise data from where pedometers were actually used. We assume that days on which patients did not wear their pedometers could reflect even lesser steps than on days with registered pedometer data. Our finding is in contrast to the majority of studies performed post chemotherapy^{44–53} and findings from a recent study by Backman *et al*⁴⁴ 2013 that found a high level of physical activity performance and goal achievement among a similar sedentary cancer population during adjuvant chemotherapy. We are unaware whether this discrepancy is due to pedometer measurement validity, the type and nature of the pedometer intervention or whether or not pedometer data are based on patient reports or electronically transferred to investigator computers.

On the basis of the existing evidence,^{4 27 55–57} we hypothesised that exercise in favour of moderate-to-vigorous intensity could increase the participants' physical capacity (ie, VO₂ peak, Watt performance, muscle strength and body composition).²⁴ The uniform maximum values of RER and HR_{max} at baseline and at 6 and 12 weeks of testing indicate that the maximal incremental cycle ergometry test is reproducible and valid for determination of the VO₂ peak in these specific sedentary cancer populations. The majority of patients reached the criteria for achieving a valid VO₂ max (RER>1.15; HR_{max}>expected HR_{max}—10 bpm).

The primary outcome, cardiorespiratory fitness (VO₂ peak), decreased significantly in study groups. In general, the use of test-blinded assessors, the application of an individualised incremental test protocol and the utilisation of gold standard methods for VO₂ peak measurement^{58 59} minimise test error, lending credibility to the results. Nonetheless, the aforementioned observation raises some concerns regarding the cardiorespiratory training potential in the intervention groups. From a physiological perspective, the HIGH HOSP intervention, with the combined aerobic and resistance components, could be affected by the use of two different exercise modalities that may reduce the other's effect.⁶⁰ The loss in VO₂ peak of 2.1 mL/kg min after 12 weeks in the HIGH HOSP intervention, however, is comparable to a study by Courneya *et al*⁶¹ in which the intervention group received aerobic training at an identical aerobic volume and lower intensity rate.

Our observation that neither the HIGH HOSP nor the LOW PED group could reverse expected declines in

Table 7 Muscle strength and body composition

	HIGH HOSP			LOW PED			Control		
	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks
Breast	n=11	n=9	n=9	n=11	n=9	n=10	n=10–11	n=8–9	n=9–10
Leg press	78.2 (25.2)	84.4 (25.1)	84.4 (30.0)	74.5 (22.5)	87.8 (34.6)	78.0 (34.6)	90.0 (20.5)	90.0 (21.8)	106.0 (13.5)
Chest press	25.9 (4.9)	33.3 (6.7)	33.3 (6.8)	27.3 (7.8)	30.8 (9.4)	28.0 (6.9)	25.8 (8.4)	31.3 (8.0)	29.4 (9.0)
Lean mass	38.0 (4.2)	–	38.7 (5.1)	40.8 (4.9)	–	41.2 (4.4)	41.7 (5.9)	–	42.9 (5.5)
Fat mass	21.9 (11.4)	–	17.1 (9.4)	25.9 (7.8)	–	25.4 (7.7)	25.0 (9.1)	–	25.3 (10.5)
Percentage of lean mass	62.8 (10.0)	–	68.1 (9.9)	59.9 (7.6)	–	60.2 (7.2)	61.0 (7.3)	–	61.6 (7.9)
Percentage of fat mass	33.2 (10.7)	–	27.8 (10.0)	36.7 (7.1)	–	36.1 (7.5)	35.2 (7.5)	–	34.5 (8.2)
BMI	22.6 (5.7)	20.4 (3.5)	20.5 (3.9)	23.6 (2.8)	23.8 (2.9)	24.1 (3.0)	24.3 (4.4)	25.1 (5.2)	24.8 (5.2)
Colon	n=4	n=3	n=3	n=3	n=3	n=2	n=5	n=2	n=2
Leg press	102.5 (49.9)	143.3 (73.7)	143.3 (63.5)	73.3 (32.1)	83.3 (32.1)	110.0 (28.3)	88.0 (43.3)	105.0 (49.5)	170.0 (42.4)
Chest press	47.5 (22.5)	50.8 (24.5)	53.3 (25.0)	36.7 (22.4)	35.8 (25.5)	43.8 (37.1)	41.0 (21.7)	53.8 (44.2)	85.0 (7.1)
Lean mass	50.8 (12.3)	–	56.4 (13.0)	41.0 (8.0)	–	48.5 (7.7)	50.6 (10.6)	–	62.4 (4.1)
Fat mass	26.3 (4.6)	–	26.8 (6.0)	24.2 (4.5)	–	27.2 (6.9)	32.9 (12.1)	–	30.1 (8.2)
Percentage of lean mass	62.9 (7.9)	–	64.9 (9.6)	60.4 (6.8)	–	61.7 (8.8)	59.0 (9.3)	–	65.3 (4.2)
Percentage of fat mass	33.5 (8.0)	–	31.6 (9.7)	33.3 (8.3)	–	34.8 (9.4)	37.5 (9.7)	–	31.1 (4.5)
BMI	27.9 (0.7)	28.6 (1.5)	29.0 (1.6)	24.6 (1.5)	25.0 (1.7)	24.9 (1.6)	29.3 (5.8)	27.3 (6.0)	29.1 (4.7)

BMI, body mass index.

Table 8 PRO breast (selected scales/results)

	HIGH HOSP			LOW PED			Control		
	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks
EORTC									
QLG C30	<i>n</i> =11	<i>n</i> =9	<i>n</i> =9	<i>n</i> =11	<i>n</i> =9	<i>n</i> =10	<i>n</i> =11	<i>n</i> =9	<i>n</i> =8
QL mean (SD)	56.8 (20.7)	63.0 (17.2)	55.6 (14.4)	52.3 (24.5)	60.2 (19.0)	48.3 (16.6)	54.5 (18.8)	59.3 (20.6)	52.1 (17.7)
PF mean (SD)	84.9 (16.6)	91.1 (6.7)	85.2 (12.8)	87.9 (7.2)	90.4 (7.5)	84.0 (13.8)	86.7 (10.8)	86.7 (6.7)	81.7 (12.7)
EF mean (SD)	76.5 (23.2)	87.0 (16.7)	85.2 (13.7)	76.5 (21.7)	82.4 (19.3)	81.7 (21.8)	84.1 (13.7)	74.1 (20.2)	73.0 (16.0)
FA mean (SD)	41.4 (29.9)	39.5 (29.0)	50.6 (32.0)	53.5 (32.1)	40.7 (26.6)	57.8 (18.7)	43.4 (16.1)	50.6 (28.4)	51.4 (21.4)
PA mean (SD)	10.6 (11.2)	20.4 (18.2)	31.5 (21.2)	24.2 (26.2)	20.4 (18.2)	35.0 (14.6)	34.8 (22.9)	25.9 (22.2)	33.3 (25.2)
SL mean (SD)	21.2 (30.8)	18.5 (24.2)	40.7 (36.4)	39.4 (44.3)	29.6 (35.1)	30.0 (18.9)	30.3 (27.7)	37.0 (42.3)	37.5 (37.5)
DY mean (SD)	6.1 (13.5)	11.1 (16.7)	25.9 (32.4)	12.1 (22.5)	18.5 (24.2)	20.0 (28.1)	6.1 (13.5)	18.5 (24.2)	33.3 (35.6)
HADS	<i>n</i> =11	<i>n</i> =9	<i>n</i> =9	<i>n</i> =11	<i>n</i> =9	<i>n</i> =9	<i>n</i> =11	<i>n</i> =9	<i>n</i> =9
Anx mean (SD)	4.54 (5.73)	3.44 (3.78)	3.33 (3.43)	6.64 (3.01)	5.78 (2.91)	5.44 (3.36)	5.18 (3.34)	5.89 (4.54)	5.44 (3.17)
Dep mean (SD)	3.2 (3.00)	3.7 (1.94)	3.0 (2.69)	4.09 (2.88)	2.44 (2.07)	4.55 (3.09)	4.09 (2.88)	4.78 (4.21)	5.55 (3.71)
MOS SF-36	<i>n</i> =11	<i>n</i> =9	<i>n</i> =9	<i>n</i> =11	<i>n</i> =8	<i>n</i> =10	<i>n</i> =11	<i>n</i> =9	<i>n</i> =9
RP mean (SD)	56.8 (43.4)	55.6 (41.0)	50.0 (45.1)	25.0 (40.3)	37.5 (42.3)	17.5 (31.3)	25.0 (31.6)	25.0 (37.5)	16.7 (35.4)
VT mean (SD)	52.9 (31.8)	56.7 (20.9)	48.9 (25.5)	49.1 (18.8)	54.4 (11.8)	41.5 (18.7)	50.5 (15.4)	41.7 (22.5)	37.8 (20.2)
MH mean (SD)	76.0 (21.6)	75.1 (20.4)	78.2 (14.3)	64.7 (14.3)	73.8 (11.0)	74.0 (14.9)	70.5 (19.3)	66.2 (20.6)	61.3 (23.0)
RE mean (SD)	63.6 (34.8)	62.5 (37.5)	88.9 (23.6)	69.7 (43.3)	70.4 (42.3)	60.0 (46.6)	51.5 (45.6)	51.8 (47.5)	55.6 (47.1)

Anx, anxiety; Dep, depression; DY, dyspnoea; EORTC, European Organisation for Research and Treatment of Cancer; EF, emotional functioning; FA, fatigue; HADS, Hospital Anxiety and Depression Scale; MH, mental health; MOS, Medical Outcome Study; PA, pain; PF, physical functioning; QLG C30, Quality of Life Core Questionnaire; QL, quality of life; PRO, patient-reported outcomes; RE, role emotional; RP, role physical; SF-36, 36-Item Short Form; SL, sleeping problems; VT, vitality.

the VO₂ peak is in striking contrast to the prevailing assumption in previous evidence that aerobic exercise in patients with breast cancer during chemotherapy promotes significant gains in cardiorespiratory fitness.^{4 27 57} A recent review of observational studies and two large RCTs using gold standard methods for the determination of cardiorespiratory fitness reported that the VO₂ peak decreases in patients with breast cancer during adjuvant chemotherapy.^{61–65} One possible explanation could be attributed to the use of taxane-based chemotherapy and is in line with two large RCTs.^{61 65} The causal relationship is unknown; however, we speculate that the muscular toxicity associated with taxane-based chemotherapy⁶⁶ could reduce aerobic exercise intensity due to pain,⁶⁷ thus leading to reductions in the cardiorespiratory response. There is not sufficient power in the present study to support this hypothesis. This central physiological question is explored in our ongoing larger trial, with the intention to clarify the possible harmful effects of adjuvant taxane-based chemotherapy on cardiorespiratory fitness and the potential preservative effects of aerobic exercise.

The HIGH HOSP group showed a positive response in Watt performance after 6 and 12 weeks and a tendency to experience the most favourable changes in body composition towards a higher proportion of lean body mass and a reduced proportion of fat mass. The higher proportion of lean mass was supported by gains in muscle strength. These favourable changes could potentially thwart expected increases in fat mass and reductions in lean mass in women undergoing adjuvant chemotherapy for breast cancer,⁶⁸ potentially leading to decreases in the risk of premature death associated with increased fat mass in the long run.⁶⁹

In summary

This study calls into question whether aerobic exercise, regardless of intensity, is able to increase cardiorespiratory capacity (VO₂ peak) during taxane-based chemotherapy in combination with Neulasta.^{61 63} Conversely, the study does not show whether the decline in VO₂ peak would have been greater without intervention due to the design, sample size, control group contamination and waiting list attendance.

The complexity of integrating exercise intervention within adjuvant chemotherapy for sedentary patients with breast cancer seems adequate in timing and dose (volume), while the comparative effects of different interventions are explored in an ongoing larger trial.

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REFERENCES

1. Statens Seruminstitut. Cancerregistret: tal og analyser 2011 The Danish Cancer Registry: figures and analysis 2011. Copenhagen: SSI, 2012.
2. Storm HH, Engholm G, Hakulinen T, *et al.* Survival of patients diagnosed with cancer in the Nordic countries up to 1999–2003 followed to the end of 2006: a critical overview of the results. *Acta Oncol* 2010;49:532–44.
3. Bourke L, Homer KE, Thaha MA, *et al.* Interventions to improve exercise behaviour in sedentary people living with and beyond cancer: a systematic review. *Br J Cancer* 2014;110:831–41.
4. Schmitz KH, Courneya KS, Matthews C, *et al.* American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc* 2010;42:1409–26.
5. Pinto BM, Eakin E, Maruyama NC. Health behavior changes after a cancer diagnosis: what do we know and where do we go from here? *Ann Behav Med* 2000;22:38–52.
6. Speck RM, Courneya KS, Masse LC, *et al.* An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv* 2010;4:87–100.
7. Jones LW, Alfano CM. Exercise-oncology research: past, present, and future. *Acta Oncol* 2013;52:195–215.
8. Courneya KS, McKenzie DC, Reid RD, *et al.* Barriers to supervised exercise training in a randomized controlled trial of breast cancer patients receiving chemotherapy. *Ann Behav Med* 2008;35:116–22.
9. Friedenreich CM, Gregory J, Kopciuk KA, *et al.* Prospective cohort study of lifetime physical activity and breast cancer survival. *Int J Cancer* 2009;124:1954–62.
10. Giovannucci E. Modifiable risk factors for colon cancer. *Gastroenterol Clin North Am* 2002;31:925–43.
11. Holmes MD, Chen WY, Feskanich D, *et al.* Physical activity and survival after breast cancer diagnosis. *JAMA* 2005;293:2479–86.
12. Meyerhardt JA, Giovannucci EL, Holmes MD, *et al.* Physical activity and survival after colorectal cancer diagnosis. *J Clin Oncol* 2006;24:3527–34.
13. Hawkes AL, Lynch BM, Owen N, *et al.* Lifestyle factors associated concurrently and prospectively with co-morbid cardiovascular disease in a population-based cohort of colorectal cancer survivors. *Eur J Cancer* 2011;47:267–76.

14. Herman DR, Ganz PA, Petersen L, *et al.* Obesity and cardiovascular risk factors in younger breast cancer survivors: the Cancer and Menopause Study (CAMS). *Breast Cancer Res Treat* 2005;93:13–23.
15. Jones LW, Haykowsky MJ, Swartz JJ, *et al.* Early breast cancer therapy and cardiovascular injury. *J Am Coll Cardiol* 2007;50: 1435–41.
16. Lenihan DJ, Cardinale D, Cipolla CM. The compelling need for a cardiology and oncology partnership and the birth of the International CardioOncology Society. *Prog Cardiovasc Dis* 2010;53:88–93.
17. Mann DL, Krone RJ. Cardiac disease in cancer patients: an overview. *Prog Cardiovasc Dis* 2010;53:80–7.
18. Schmitz KH, Prosnitz RG, Schwartz AL, *et al.* Prospective surveillance and management of cardiac toxicity and health in breast cancer survivors. *Cancer* 2012;118(8 Suppl):2270–6.
19. Demark-Wahnefried W, Aziz NM, Rowland JH, *et al.* Riding the crest of the teachable moment: promoting long-term health after the diagnosis of cancer. *J Clin Oncol* 2005;23:5814–30.
20. Jones LW, Courneya KS, Peddle C, *et al.* Oncologists' opinions towards recommending exercise to patients with cancer: a Canadian national survey. *Support Care Cancer* 2005;13:929–37.
21. Sabiston CM, Brunet J, Vallance JK, *et al.* Prospective examination of objectively assessed physical activity and sedentary time after breast cancer treatment: sitting on the crest of the teachable moment. *Cancer Epidemiol Biomarkers Prev* 2014;23:1324–30.
22. Broderick JM, Hussey J, Kennedy MJ, *et al.* Testing the 'teachable moment' premise: does physical activity increase in the early survivorship phase? *Support Care Cancer* 2014;22:989–97.
23. Danish Health and Medicines Authority. Physical activity: recommendations for adults (18–64 years old). 2013 cited 2013 Jul 3 http://www.sst.dk/English/Health_promotion/Physical_activity/Recommendations_for_adults.aspx
24. Møller T, Lillelund C, Andersen C, *et al.* At cancer diagnosis: a 'window of opportunity' for behavioural change towards physical activity. A randomised feasibility study in patients with colon and breast cancer. *BMJ Open* 2013;3:e003556.
25. Missel M, Pedersen JH, Hendriksen C, *et al.* A longitudinal exploration of 'Four Critical Moments' during treatment trajectory in patients with operable lung cancer and the feasibility of an exercise intervention: a research protocol. *J Adv Nurs* 2014;70:1915–25.
26. Quist M, Langer SW, Rorth M, *et al.* "EXHALE": exercise as a strategy for rehabilitation in advanced stage lung cancer patients: a randomized clinical trial comparing the effects of 12 weeks supervised exercise intervention versus usual care for advanced stage lung cancer patients. *BMC Cancer* 2013;13:477.
27. Adamsen L, Quist M, Andersen C, *et al.* Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. *BMJ* 2009;339:b3410.
28. Adamsen L, Midtgaard J, Rorth M, *et al.* Feasibility, physical capacity, and health benefits of a multidimensional exercise program for cancer patients undergoing chemotherapy. *Support Care Cancer* 2003;11:707–16.
29. Klarlund Petersen B. Skridttællerprogrammet The walk-up programme. 2008. <http://www.walk-up.dk/inspiration/skridttaelleren/13-skridttaellerprogrammet>
30. Midtgaard J, Christensen JF, Tolver A, *et al.* Efficacy of multimodal exercise-based rehabilitation on physical activity, cardiorespiratory fitness, and patient-reported outcomes in cancer survivors: a randomized, controlled trial. *Ann Oncol* 2013;24:2267–73.
31. ASTRAND I. Aerobic work capacity in men and women with special reference to age. *Acta Physiol Scand Suppl* 1960;49:1–92.
32. Forsythe LP, Alfano CM, George SM, *et al.* Pain in long-term breast cancer survivors: the role of body mass index, physical activity, and sedentary behavior. *Breast Cancer Res Treat* 2013;137:617–30.
33. Kim RB, Phillips A, Herrick K, *et al.* Physical activity and sedentary behavior of cancer survivors and non-cancer individuals: results from a national survey. *PLoS ONE* 2013;8:e57598.
34. Rogers LQ, Markwell SJ, Courneya KS, *et al.* Physical activity type and intensity among rural breast cancer survivors: patterns and associations with fatigue and depressive symptoms. *J Cancer Surviv* 2011;5:54–61.
35. Harvey JA, Chastin SF, Skelton DA. Prevalence of sedentary behavior in older adults: a systematic review. *Int J Environ Res Public Health* 2013;10:6645–61.
36. Curry WB, Thompson JL. Comparability of accelerometer- and IPAQ-derived physical activity and sedentary time in South Asian women: a cross-sectional study. *Eur J Sport Sci* 2014:1–8.
37. Gibbs BB, Hergenroeder AL, Katzmarzyk PT, *et al.* Definition, measurement, and health risks associated with sedentary behavior. *Med Sci Sports Exerc* 2015;47:1295–300.
38. Ainsworth BE, Haskell WL, Whitt MC, *et al.* Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000;32(9 Suppl):S498–504.
39. Husebo AM, Dyrstad SM, Soreide JA, *et al.* Predicting exercise adherence in cancer patients and survivors: a systematic review and meta-analysis of motivational and behavioural factors. *J Clin Nurs* 2013;22:4–21.
40. Mock V, Frangakis C, Davidson NE, *et al.* Exercise manages fatigue during breast cancer treatment: a randomized controlled trial. *Psychooncology* 2005;14:464–77.
41. Kolden GG, Strauman TJ, Ward A, *et al.* A pilot study of group exercise training (GET) for women with primary breast cancer: feasibility and health benefits. *Psychooncology* 2002;11:447–56.
42. Kim CJ, Kang DH, Smith BA, *et al.* Cardiopulmonary responses and adherence to exercise in women newly diagnosed with breast cancer undergoing adjuvant therapy. *Cancer Nurs* 2006;29: 156–65.
43. Jones LW, Courneya KS, Fairey AS, *et al.* Effects of an oncologist's recommendation to exercise on self-reported exercise behavior in newly diagnosed breast cancer survivors: a single-blind, randomized controlled trial. *Ann Behav Med* 2004;28:105–13.
44. Backman M, Wengstrom Y, Johansson B, *et al.* A randomized pilot study with daily walking during adjuvant chemotherapy for patients with breast and colorectal cancer. *Acta Oncol* 2014;53: 510–20.
45. Chevillat AL, Kollasch J, Vandenberg J, *et al.* A home-based exercise program to improve function, fatigue, and sleep quality in patients with Stage IV lung and colorectal cancer: a randomized controlled trial. *J Pain Symptom Manage* 2013;45:811–21.
46. Jones SB, Thomas GA, Hesselsweet SD, *et al.* Effect of exercise on markers of inflammation in breast cancer survivors: the Yale exercise and survivorship study. *Cancer Prev Res (Phila)* 2013;6:109–18.
47. Phillips SM, McAuley E. Physical activity and quality of life in breast cancer survivors: the role of self-efficacy and health status. *Psychooncology* 2014;23:27–34.
48. Pinto BM, Papandonatos GD, Goldstein MG, *et al.* Home-based physical activity intervention for colorectal cancer survivors. *Psychooncology* 2013;22:54–64.
49. Pinto BM, Stein K, Dunsiger S. Peers promoting physical activity among breast cancer survivors: a randomized controlled trial. *Health Psychol* 2015;34:463–72.
50. Rogers LQ, Hopkins-Price P, Vicari S, *et al.* A randomized trial to increase physical activity in breast cancer survivors. *Med Sci Sports Exerc* 2009;41:935–46.
51. Rogers LQ, Courneya KS, Anton PM, *et al.* Effects of the BEAT Cancer physical activity behavior change intervention on physical activity, aerobic fitness, and quality of life in breast cancer survivors: a multicenter randomized controlled trial. *Breast Cancer Res Treat* 2015;149:109–19.
52. Tonosaki A, Ishikawa M. Physical activity intensity and health status perception of breast cancer patients undergoing adjuvant chemotherapy. *Eur J Oncol Nurs* 2014;18:132–9.
53. Vallance JK, Courneya KS, Plotnikoff RC, *et al.* Randomized controlled trial of the effects of print materials and step pedometers on physical activity and quality of life in breast cancer survivors. *J Clin Oncol* 2007;25:2352–9.
54. Markes M, Brockow T, Resch KL. Exercise for women receiving adjuvant therapy for breast cancer. *Cochrane Database Syst Rev* 2006;(4):CD005001.
55. Courneya KS, Friedenreich CM, Quinney HA, *et al.* A randomized trial of exercise and quality of life in colorectal cancer survivors. *Eur J Cancer Care (Engl)* 2003;12:347–57.
56. Courneya KS, Segal RJ, Mackey JR, *et al.* Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J Clin Oncol* 2007;25:4396–404.
57. Mishra SI, Scherer RW, Snyder C, *et al.* Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev* 2012;8:CD008465.
58. Jones LW, Eves ND, Haykowsky M, *et al.* Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. *Lancet Oncol* 2008;9:757–65.
59. American Thoracic Society; American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167:211–77.
60. Coffey VG, Hawley JA. The molecular bases of training adaptation. *Sports Med* 2007;37:737–63.
61. Courneya KS, McKenzie DC, Mackey JR, *et al.* Effects of exercise dose and type during breast cancer chemotherapy: multicenter randomized trial. *J Natl Cancer Inst* 2013;105:1821–32.

62. Lakoski SG, Barlow CE, Koelwyn GJ, *et al.* The influence of adjuvant therapy on cardiorespiratory fitness in early-stage breast cancer seven years after diagnosis: the Cooper Center Longitudinal Study. *Breast Cancer Res Treat* 2013;138:909–16.
63. Peel AB, Thomas SM, Dittus K, *et al.* Cardiorespiratory fitness in breast cancer patients: a call for normative values. *J Am Heart Assoc* 2014;3:e000432.
64. Klassen O, Schmidt ME, Scharhag-Rosenberger F, *et al.* Cardiorespiratory fitness in breast cancer patients undergoing adjuvant therapy. *Acta Oncol* 2014;53:1356–65.
65. Courneya KS, McKenzie DC, Mackey JR, *et al.* Moderators of the effects of exercise training in breast cancer patients receiving chemotherapy: a randomized controlled trial. *Cancer* 2008;112:1845–53.
66. Kunitoh H, Saijo N, Furuse K, *et al.* Neuromuscular toxicities of paclitaxel 210 mg m⁻² by 3-hour infusion. *Br J Cancer* 1998;77:1686–8.
67. Andersen C, Rorth M, Ejlersen B, *et al.* Exercise despite pain—breast cancer patient experiences of muscle and joint pain during adjuvant chemotherapy and concurrent participation in an exercise intervention. *Eur J Cancer Care (Engl)* 2014;23:653–67.
68. Freedman RJ, Aziz N, Albanes D, *et al.* Weight and body composition changes during and after adjuvant chemotherapy in women with breast cancer. *J Clin Endocrinol Metab* 2004;89:2248–53.
69. Pischon T, Boeing H, Hoffmann K, *et al.* General and abdominal adiposity and risk of death in Europe. *N Engl J Med* 2008;359:2105–20.