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ORIGINAL REPORT

Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial

Hanna van Waart, Martijn M. Stuiver, Wim H. van Harten, Edwin Geleijn, Jacobien M. Kieffer, Laurien M. Buffart, Marianne de Maaker-Berkhof, Epie Boven, Jolanda Schrama, Maud M. Geenen, Jetske M. Meerum Terwogt, Aart van Bochove, Vera Lustig, Simone M. van den Heiligenberg, Carolien H. Smorenburg, Jeannette A.J.H. Hellendoorn-van Vreeswijk, Gabe S. Sonke, and Neil K. Aaronson

Hanna van Waart, Martijn M. Stuiver, Wim H. van Harten, Jacobien M. Kieffer, Marianne de Maaker-Berkhof, Gabe S. Sonke, Neil K. Aaronson, The Netherlands Cancer Institute; Edwin Geleijn, Laurien M. Buffart, and Epie Boven, VU University Medical Center; Laurien M. Buffart, EMGO Institute for Health and Care Research; Maud M. Geenen, Sint Lucas Andreas Hospital; Jetske M. Meerum Terwogt, Onze Lieve Vrouwe Gasthuis; Jeanette A.J.H. Hellendoorn-van Vreeswijk, Comprehensive Cancer Centre of the Netherlands, Amsterdam; Jolanda Schrama, Spaarne Hospital, Hoofddorp; Aart van Bochove and Simone M. van den Heiligenberg, Esperanz, North Holland; Aart van Bochove, Zaans Medisch Centrum, Zaandam; Vera Lustig, Flevohospital, Almere; Simone M. van den Heiligenberg, Westfries Gasthuis, Hoorn; and Carolien H. Smorenburg, Medical Center Alkmaar, Alkmaar, the Netherlands.

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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Corresponding author: Neil K. Aaronson, PhD, Division of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands; e-mail: n.aaronson@nki.nl.

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ABSTRACT

Purpose
We evaluated the effectiveness of a low-intensity, home-based physical activity program (Onco-Move) and a moderate- to high-intensity, combined supervised resistance and aerobic exercise program (OnTrack) versus usual care (UC) in maintaining or enhancing physical fitness, minimizing fatigue, enhancing health-related quality of life, and optimizing chemotherapy completion rates in patients undergoing adjuvant chemotherapy for breast cancer.

Patients and Methods
We randomly assigned patients who were scheduled to undergo adjuvant chemotherapy (N = 230) to Onco-Move, OnTrack, or UC. Performance-based and self-reported outcomes were assessed before random assignment, at the end of chemotherapy, and at the 6-month follow-up. We used generalized estimating equations to compare the groups over time.

Results
Onco-Move and OnTrack resulted in less decline in cardiorespiratory fitness ($P < .001$), better physical functioning ($P \leq .001$), less nausea and vomiting ($P = .029$ and .031, respectively) and less pain ($P = .003$ and .011, respectively) compared with UC. OnTrack also resulted in better outcomes for muscle strength ($P = .002$) and physical fatigue ($P < .001$). At the 6-month follow-up, most outcomes returned to baseline levels for all three groups. A smaller percentage of participants in OnTrack required chemotherapy dose adjustments than those in the UC or Onco-Move groups ($P = .002$). Both intervention groups returned earlier ($P = .012$), as well as for more hours per week ($P = .014$), to work than the control group.

Conclusion
A supervised, moderate- to high-intensity, combined resistance and aerobic exercise program is most effective for patients with breast cancer undergoing adjuvant chemotherapy. A home-based, low-intensity physical activity program represents a viable alternative for women who are unable or unwilling to follow the higher intensity program.

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INTRODUCTION

Adjuvant chemotherapy improves breast cancer survival[1] but can also lead to fatigue, muscle wasting, and reduced physical fitness.[2] This, in turn, can have a negative impact on activities of daily living, social interaction, and health-related quality of life (HRQoL).[3] Previous studies have demonstrated that exercise programs can have a salutary effect on cardiorespiratory fitness, muscle strength, fatigue, mood, HRQoL, and immune function,[4-10] and possibly on chemotherapy completion rates.[11]

Previous studies have used a wide range of exercise types and intensities.[10] It has been hypothesized that home-based, low-intensity programs may be easier for patients to follow during chemotherapy,[12] whereas higher intensity, supervised exercise programs that incorporate resistance training and aerobic exercise may be most effective.[4,13] To our

knowledge, no study has yet made a head-to-head comparison of these two types of programs.

The primary aim of our study was to evaluate the effectiveness of a home-based, low-intensity physical activity program (Onco-Move) and a supervised, moderate- to high-intensity, combined resistance and aerobic exercise program (OnTrack) in maintaining or enhancing physical fitness and minimizing fatigue in patients undergoing adjuvant chemotherapy. In addition, we hypothesized that both interventions would result in higher levels of physical activity and functioning in daily life, less psychological distress, and better HRQoL. We expected greater gains in cardiorespiratory fitness and muscle strength for participants in the OnTrack versus the Onco-Move program. Finally, we hypothesized a positive effect of both interventions on chemotherapy completion rates (ie, the percentage of patients who would complete chemotherapy without dose adjustments).

PATIENTS AND METHODS

Research Design and Study Sample

The Physical Exercise During Adjuvant Chemotherapy Effectiveness Study (PACES) was a randomized, controlled, multicenter trial with two intervention groups and a usual care (UC) control group. Patients were eligible for the trial if they had histologically confirmed primary breast or colon cancer and were scheduled to undergo adjuvant chemotherapy at one of 12 hospitals in the Amsterdam region of the Netherlands.[14] Patients were excluded if they had serious orthopedic, cardiovascular, or cardiopulmonary conditions, were suffering from malnutrition, had serious psychiatric or cognitive problems, or did not have basic fluency in Dutch. There was no upper age limit. Institutional review boards of all participating hospitals approved the study.

Procedure

Potentially eligible patients with breast cancer were identified through hospital records, whereas patients with colon cancer were identified by their treating physicians. After providing informed consent and completing baseline assessments, patients were randomly assigned to Onco-Move, OnTrack, or UC using the minimization method,[15] which balanced groups with respect to age, primary diagnosis, treating hospital, and use of trastuzumab.

Interventions

Onco-Move is a home-based, low-intensity, individualized, self-managed physical activity program, as proposed by Mock,[12] to which behavioral reinforcement techniques were added in this study. These comprised written information that was tailored to the individual's preparedness to exercise according to the Transtheoretical model,[16] and an activity diary that was discussed at each chemotherapy cycle. Specially trained nurses encouraged participants to engage in at least 30 minutes of physical activity per day, 5 days per week, with an intensity level of 12 to 14 on the Borg Scale of perceived exertion.[17]

OnTrack is a moderate- to high-intensity, combined resistance and aerobic exercise program and was supervised by specially trained physical therapists.[18] The participants attended two sessions per week. Six large muscle groups were trained for 20 minutes per session, with two series of eight repetitions at 80% of the one repetition maximum. One repetition maximum testing was repeated every 3 weeks. Each session incorporated 30 minutes of aerobic exercises, with an intensity of 50% to 80% of the maximal workload as estimated by the Steep Ramp Test.[19] The intensity was adjusted using the Borg Scale, with a threshold of less than 12 for increase and more than 16 for decrease of intensity.[17] Participants in this group were also encouraged to be physically active 5 days each week for 30 minutes per session and to keep an activity diary. Both interventions started with the first cycle of chemotherapy and continued until 3 weeks after the last cycle.

UC varied according to hospital guidelines and preferences, but did not involve routine exercise.

Timing of Assessments and Study Measures

Patients underwent performance-based tests and completed questionnaires at three points in time: before random assignment and start of chemotherapy (T0), at completion of chemotherapy (T1), and 6 months after completion of chemotherapy (T2).

Primary outcomes were cardiorespiratory fitness, muscle strength, and fatigue. Cardiorespiratory fitness was assessed with the Steep Ramp Test[19] and an endurance test at 70% of the estimated maximal workload,[14] muscle strength with the microFET handheld dynamometer (Hoggan Health, Salt Lake City, UT) for elbow flexion[20] and knee extension,[21] and the JAMAR grip strength dynamometer (Lafayette Instrument, Lafayette, IN),[22] and lower-limb muscle endurance with the 30-second chair stand test.[23] Fatigue was measured with the Multidimensional Fatigue Inventory[24] and the Fatigue Quality List.[25]

The secondary outcomes included self-reported physical activity level, functioning in daily life, psychological distress, HRQoL, return to work, and chemotherapy completion rates[14,26] (Table 1).

Statistical Analyses

With more than 64 participants per group, the study had 80% power to detect an effect size of 0.5, with a two-tailed *P* value set at .05.[27] Scores on the Multidimensional Fatigue Inventory, Fatigue Quality List, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), Hospital Anxiety and Depression Scale, Sleep Quality Inventory, Impact on Participation and Autonomy, and Physical Activity Scale for the Elderly were calculated according to published scoring algorithms.

Table 1. Outcome Measures

Assessment	Measurement Instrument
Primary outcome measures	
Cardiorespiratory fitness	Steep Ramp Test: maximal short exercise capacity
	Endurance test, endurance time
Upper muscle strength	MicroFET† handheld dynamometer elbow flexion, Nm
	JAMAR* grip strength dynamometer, kg
Lower muscle strength	MicroFET† handheld dynamometer knee extension, Nm
	30-second chair stand test: No. of times to rise
Fatigue	Multidimensional Fatigue Inventory
	Fatigue Quality List
Secondary outcome measures	
Health-related quality of life	EORTC QLQ-C30
Psychological distress	Hospital Anxiety and Depression Scale
Self-reported physical activity level	Physical Activity Scale for the Elderly
Functioning in daily life	Impact on Participation and Autonomy
Quality of sleep	Sleep Quality Inventory
Return to work	Return to work questionnaire (study specific)
Chemotherapy regimen, dose, and adverse effects of chemotherapy	Medical records
Compliance with exercise programs	No. of sessions attended
	Activity diary
Other measures	
Clinical characteristics	Tumor stage and type (medical records)
	Radiotherapy (yes *v* no; medical records)
	Comorbidity (questionnaire)

Abbreviation: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30.
*Lafayette Instrument, Lafayette, IN.
†Hoggan Health, Salt Lake City, UT.

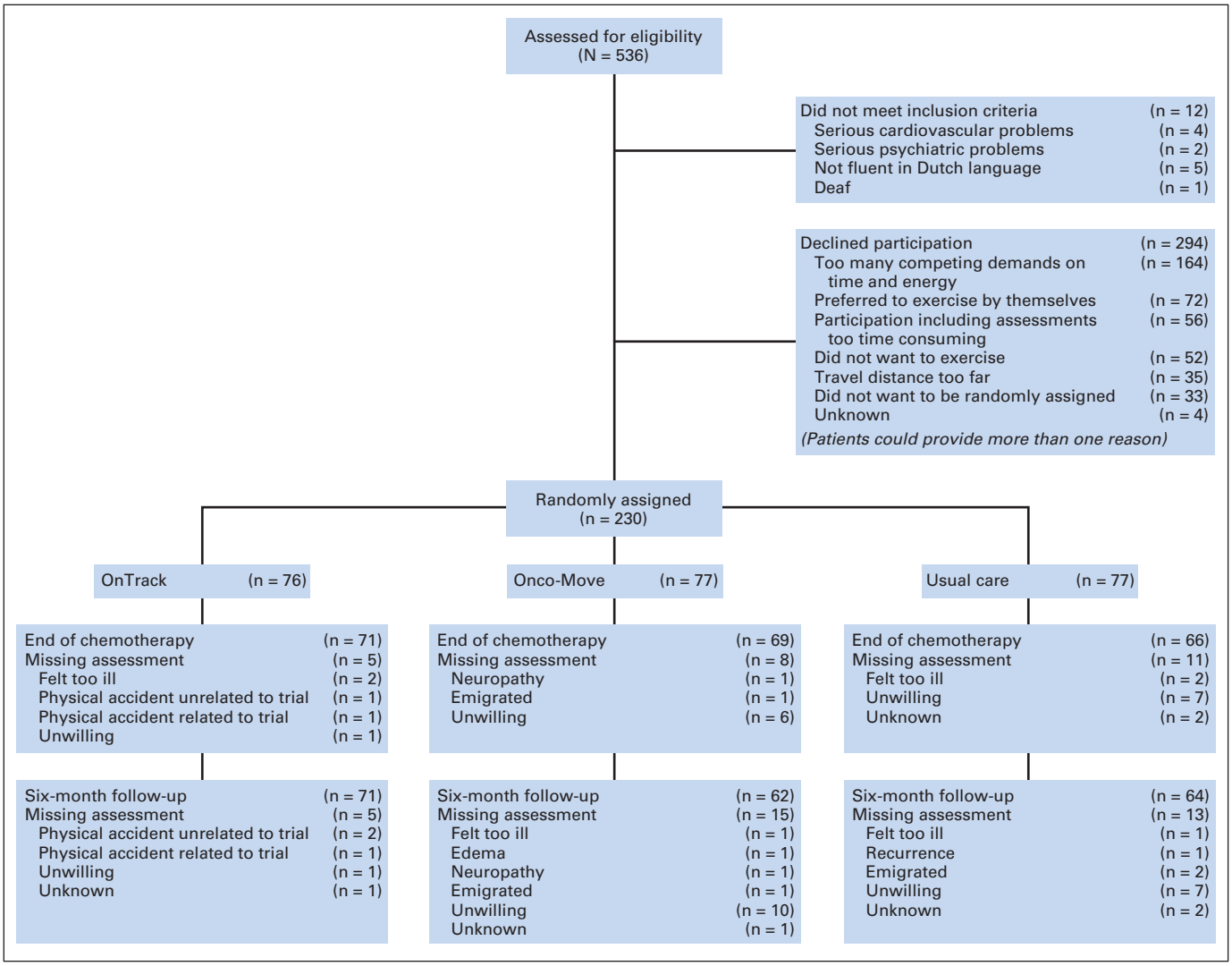

Fig 1. CONSORT diagram of patients with breast cancer participating in the Physical Exercise During Adjuvant Chemotherapy Effectiveness Study (PACES). The No. of missing assessments at the end of chemotherapy and 6-month follow-up were not necessarily cumulative.

Generalized estimating equations analysis with an exchangeable correlation structure was used to simultaneously evaluate the effects of the interventions at T1 and T2. This statistical technique adjusts for the non-independence of observations over time. We entered group, time, and the interaction of group × time as independent variables into the regression model, adjusting for baseline values.[28] Mean differences and 95% CIs were accompanied by effect sizes (ESs).[29] ESs of 0.2 were considered small, of 0.5 were considered moderate and clinically relevant, and of 0.8 were considered large.[27,30]

Group differences in chemotherapy completion rates were analyzed with binary logistic regression analysis; dose reduction during the period of chemotherapy treatment (the period between T0 and T1) was the dependent variable.

We provide descriptive data and 95% CIs for all comparisons, and significance tests (*P* values) for hypothesized comparisons only. All analyses were conducted on an intention-to-treat basis.

RESULTS

Between March 2010 and December 2012, 230 of 524 eligible patients with breast cancer (44%) were recruited for the study. Reasons for nonparticipation are shown in Figure 1. During the study period, only 63 patients with colon cancer were referred to the study, 23 of whom were successfully recruited. As a result of the small number of patients with colon cancer, this analysis is restricted to patients with breast cancer. Because we stratified by primary diagnosis, the success of the random assignment process was not affected by the exclusion of patients with colon cancer.

Study nonparticipants had a significantly lower educational level ($P = .006$) and were significantly less likely to be working ($P < .001$) than participants. There were no other significant differences in background characteristics between participants and nonparticipants.

Participants had a mean age of 51 years, 55% had a college or university degree, and 68% were employed. Most participants had stage II (47%) or III breast cancer (46%). Approximately three fourths of the participants underwent breast-conserving surgery, approximately 30% had an axillary lymph node dissection, and approximately 75% received radiotherapy. Baseline characteristics were balanced across groups (Table 2).

Table 2. Baseline Sociodemographic and Clinical Characteristics

Characteristic	Total (N = 230)	OnTrack (n = 76)	Onco-Move (n = 77)	Usual Care (n = 77)
Age, years				
Mean (SD)	50.7 (9.1)	49.9 (8.4)	50.5 (10.1)	51.6 (8.8)
Female sex, No. (%)	228 (99)	74 (97)	77 (100)	77 (100)
Marital status, No. (%)				
Single/divorced/widowed	50 (22)	18 (24)	17 (22)	15 (19)
Married/living together	180 (78)	58 (76)	60 (78)	62 (81)
Education, No. (%)				
Primary/middle school	43 (19)	13 (17)	12 (16)	18 (23)
High school	61 (26)	17 (22)	23 (30)	21 (27)
College/university	126 (55)	46 (61)	42 (54)	38 (50)
Work, No. (%)				
Full time	63 (27)	22 (29)	19 (25)	22 (29)
Part time	95 (42)	31 (41)	32 (41)	32 (41)
Other*	72 (31)	23 (30)	26 (34)	23 (30)
Cancer stage, No. (%)				
Stage I	12 (6)	5 (7)	2 (3)	5 (6)
Stage II	109 (47)	32 (42)	40 (52)	37 (48)
Stage III	109 (47)	39 (51)	35 (45)	35 (46)
Locoregional treatment, No. (%)				
Breast-conserving surgery	178 (77)	56 (74)	62 (81)	60 (78)
Axillary lymph node dissection	71 (31)	24 (32)	18 (23)	29 (38)
Radiotherapy	180 (78)	60 (79)	60 (78)	60 (78)
Breast cancer subtype, No. (%)				
Triple negative	42 (18)	13 (17)	12 (16)	17 (22)
HER2+, ER+, and/or PR+	44 (19)	15 (20)	14 (19)	15 (19)
HER2+, ER−, and PR−	11 (5)	2 (3)	6 (8)	3 (4)
HER2−, ER+, and/or PR+	133 (58)	46 (60)	45 (57)	42 (55)
Comorbidity, No. (%)	125 (54)	40 (53)	38 (49)	47 (61)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor, SD, standard deviation.
*Other work group comprised students, homemakers, and retired and unemployed individuals.

On average, participants in OnTrack attended 71% of the planned sessions. On the basis of the exercise diary, 48% of the OnTrack group and 55% of the Onco-Move group followed the recommendations regarding daily activity levels at least 75% of the time. Outcome data were available for 204 participants (89%) directly after chemotherapy, and for 196 (85%) at the 6-month follow-up. In the remainder of the article we will use the terms OnTrack, Onco-Move, and UC to denote the participants in those groups.

Cardiorespiratory Fitness, Muscle Strength, and Fatigue

Data on cardiorespiratory fitness, muscle strength, and fatigue are shown in Tables 3 and 4. At T1, OnTrack had a significantly higher maximal short exercise capacity than UC (ES, 0.45) and Onco-Move (ES, 0.32). Both OnTrack and Onco-Move had significantly longer mean endurance time than UC (8 and 4 minutes longer; ES, 0.90 and 0.45, respectively). OnTrack had significantly longer mean endurance time than Onco-Move (4 minutes longer; ES, 0.45). Muscle strength of the arms (elbow flexion: ES, 0.54 and 0.36; grip strength: ES, 0.29 and 0.26) and legs (knee extension: ES, 0.38 and 0.27) was significantly greater in OnTrack than UC and Onco-Move, respectively. In general, physical fitness levels were maintained immediately after completion of chemotherapy in OnTrack but declined in UC and Onco-Move.

At T1, OnTrack reported significantly less physical (ES, 0.63) and general fatigue (ES, 0.29), reduced activity (ES, 0.31), and reduced motivation (ES, 0.34) than UC and significantly less physical fatigue (ES, 0.42) than Onco-Move. OnTrack perceived fatigue as significantly less frustrating (ES, 0.47), frightening (ES, 0.41), and more pleasant (ES, 0.39) than UC and less frightening (ES, 0.27) than Onco-Move.

At T2, no significant between-group differences were observed for any of the performance-based measures of physical fitness or in self-reported fatigue.

HRQoL, Symptom Burden, Activities in Daily Living, and Return to Work

At T1, both OnTrack and Onco-Move reported significantly better physical functioning (ES, 0.81 and 0.68, respectively), less nausea and vomiting (ES, 0.89 and 1.00), and less pain (ES, 0.46 and 0.60) than UC. In addition, OnTrack reported significantly better cognitive functioning (ES, 0.32) than UC and less constipation compared with UC and Onco-Move (ES, 0.98 and 0.61, respectively). Onco-Move reported significantly less fatigue on the basis of the EORTC QLQ-C30 scale (ES, 0.51) than UC (Table 5).

At T2, OnTrack and Onco-Move reported significantly better social functioning (ES, 0.42 and 0.35), whereas only OnTrack reported significantly less pain (ES, 0.36) than UC. There were no other significant group differences at T1 or T2 for the remaining EORTC QLQ-C30 scales or the measures of psychological distress (Hospital Anxiety

Table 3. Mean Values at Baseline, End of Chemotherapy, and 6-Month Follow-Up, and Between-Group Differences for Objective Performance Measures

Measure	T0: Mean (SD)	T1: Mean (SD)	T2: Mean (SD)	Between-Group Difference at T1			Between-Group Difference at T2		
				AMD (95% CI)	ES	*P*	AMD (95% CI)	ES	*P*
Maximal short exercise capacity, watts									
OnTrack	263.7 (49.3)	239.3 (57.3)	254.1 (56.6)						
Onco-Move	256.1 (48.2)	221.0 (63.4)	253.6 (52.2)						
UC	245.0 (48.9)	202.4 (66.5)	234.9 (53.9)						
OnTrack *v* UC				**22.1 (8.5 to 35.6)**	**0.45**	**.001**	6.3 (−6.2 to 18.9)	0.13	.32
Onco-Move *v* UC				6.7 (−7.0 to 20.4)	0.14	.34	4.0 (−6.9 to 14.9)	0.08	.47
OnTrack *v* Onco-Move				**15.4 (3.0 to 27.7)**	**0.32**	**.015**	2.3 (−7.8 to 12.4)	0.05	.66
Endurance time, minutes									
OnTrack	13.5 (9.2)	13.7 (9.0)	13.7 (10.0)						
Onco-Move	12.3 (8.7)	9.0 (9.0)	11.8 (9.4)						
UC	11.4 (8.6)	5.1 (5.4)	11.7 (9.8)						
OnTrack *v* UC				**8.0 (5.7 to 10.2)**	**0.90**	**< .001**	1.2 (−1.4 to 3.7)	0.13	.38
Onco-Move *v* UC				**3.9 (2.0 to 5.9)**	**0.45**	**< .001**	−0.1 (−2.6 to 2.3)	0.01	.92
OnTrack *v* Onco-Move				**4.1 (1.6 to 6.5)**	**0.45**	**.001**	1.3 (−1.0 to 3.6)	0.14	.28
HHD elbow flexion, Nm									
OnTrack	31.7 (12.5)	32.0 (13.7)	32.7 (14.1)						
Onco-Move	30.2 (11.6)	27.4 (11.9)	31.3 (13.5)						
UC	29.1 (13.0)	25.2 (12.1)	30.1 (14.9)						
OnTrack *v* UC				**7.0 (2.6 to 11.3)**	**0.54**	**.002**	1.5 (−3.4 to 6.5)	0.12	.55
Onco-Move *v* UC				2.6 (−1.5 to 6.7)	0.21	.22	0.9 (−3.9 to 5.8)	0.08	.71
OnTrack *v* Onco-Move				**4.4 (0.1 to 8.7)**	**0.36**	**.046**	0.6 (−4.0 to 5.2)	0.05	.81
HHD knee extension, Nm									
OnTrack	70.2 (18.6)	71.4 (17.6)	67.2 (17.7)						
Onco-Move	70.3 (20.9)	66.3 (20.6)	65.9 (19.1)						
UC	65.7 (20.8)	62.3 (22.0)	63.7 (22.9)						
OnTrack *v* UC				**7.6 (2.1 to 13.0)**	**0.38**	**.007**	1.1 (−4.8 to 7.0)	0.06	.71
Onco-Move *v* UC				2.1 (−3.4 to 7.7)	0.10	.45	−0.4 (−6.2 to 5.5)	0.02	.91
OnTrack *v* Onco-Move				**5.4 (0.3 to 10.5)**	**0.27**	**.038**	1.5 (−3.7 to 6.7)	0.07	.58
Grip strength, kg									
OnTrack	31.8 (6.4)	30.6 (5.3)	29.7 (5.7)						
Onco-Move	29.9 (5.8)	28.2 (6.0)	27.6 (6.7)						
UC	29.4 (5.9)	27.5 (5.6)	27.5 (5.5)						
OnTrack *v* UC				**1.8 (0.4 to 3.1)**	**0.29**	**.012**	0.8 (−0.8 to 2.4)	0.13	.32
Onco-Move *v* UC				0.1 (−1.1 to 1.3)	0.02	.82	−0.6 (−2.1 to 1.0)	0.10	.46
OnTrack *v* Onco-Move				**1.6 (0.3 to 3.0)**	**0.26**	**.019**	1.4 (−0.3 to 3.1)	0.23	.11
30-second chair stand, No. of times									
OnTrack	19.3 (5.5)	19.1 (5.0)	20.7 (6.6)						
Onco-Move	18.8 (6.4)	18.8 (7.0)	19.5 (6.4)						
UC	17.7 (4.3)	16.9 (5.3)	18.0 (5.7)						
OnTrack *v* UC				0.5 (−0.6 to 1.6)	0.11	.35	0.7 (−0.7 to 2.2)	0.15	.33
Onco-Move *v* UC				0.7 (−0.5 to 2.0)	0.14	.23	0.5 (−0.9 to 1.9)	0.10	.47
OnTrack *v* Onco-Move				−0.2 (−1.4 to 1.0)	0.04	.72	0.2 (−1.2 to 1.7)	0.04	.77

NOTE. Bold font indicates significant difference.
Abbreviations: AMD, adjusted mean difference between groups; ES, effect size of difference between groups; HHD, handheld dynamometer; SD, standard deviation; T0, baseline before chemotherapy; T1, at completion of chemotherapy; T2, 6 months after completion of chemotherapy; UC, usual care.

and Depression Scale), functioning in daily life (Impact on Participation and Autonomy instrument), or self-reported activity level (Physical Activity Scale for the Elderly; data not shown).

At T1, significantly more patients in OnTrack (34%) and Onco-Move (40%) were working than in UC (15%; $P = .010$). At T2, both intervention groups had significantly higher return to work rates than UC (83% and 79% *v* 61%; $P = .012$ for both comparisons), and worked a significantly higher percentage of the preillness hours on the job than UC (59% and 60% *v* 42%; $P = .014$ for both comparisons). Physical health limitations were reported more frequently as the reason for not returning to work by UC (41%) than either OnTrack (25%) or Onco-Move (27%).

Chemotherapy and Trastuzumab Completion Rates

Information on chemotherapy and trastuzumab completion rates is shown in Table 6. The planned chemotherapy regimens and schedules of the three groups were similar and included combinations of anthracyclines, taxanes, alkylating agents, and antimetabolites. In total, 61 patients required chemotherapy dose adjustments. The main reason for adjustment was neuropathy (31%; Table 6).

A significantly smaller percentage of OnTrack (12%) required dose adjustments in the prescribed chemotherapy regimen than UC (34%) or Onco-Move (34%; odds ratio [OR], 0.26; $P = .002$), indicating about a fourfold lower likelihood of dose adjustment; 95% CI, 0.11 to 0.61 for both comparisons). The average dose reduction

Table 4. Mean Values at Baseline, End of Chemotherapy, and 6-Month Follow-Up, and Adjusted Between-Group Differences for Fatigue

Measure	T0:Mean (SD)	T1:Mean (SD)	T2: Mean (SD)	Between-Group Difference at T1			Between-Group Difference at T2		
				AMD (95% CI)	ES	*P*	AMD (95% CI)	ES	*P*
MFI, physical fatigue*									
OnTrack	10.0 (4.0)	11.7 (4.2)	9.0 (4.7)						
Onco-Move	9.9 (3.5)	13.3 (4.7)	9.9 (4.3)						
UC	11.1 (4.5)	14.7 (4.4)	10.3 (4.3)						
OnTrack *v* UC				**−2.7 (−4.0 to −1.4)**	**0.63**	**< .001**	−0.8 (−2.1 to 0.6)	0.18	.27
Onco-Move *v* UC				−1.1 (−2.4 to 0.2)	0.28	.10	0.0 (−1.3 to 1.3)	0.01	.97
OnTrack *v* Onco-Move				**−1.6 (−2.9 to −0.2)**	**0.42**	**.021**	−0.7 (−2.2 to 0.7)	0.20	.32
MFI, general fatigue*									
OnTrack	10.6 (4.1)	13.1 (3.9)	10.0 (4.6)						
Onco-Move	10.6 (3.8)	13.7 (3.9)	10.6 (4.2)						
UC	11.7 (4.4)	14.7 (4.2)	11.7 (4.1)						
OnTrack *v* UC				**−1.3 (−2.5 to −0.1)**	**0.29**	**.041**	−1.2 (−2.5 to 0.1)	0.28	.08
Onco-Move *v* UC				−0.7 (−1.8 to 0.5)	0.17	.25	−0.6 (−1.9 to 0.6)	0.16	.32
OnTrack *v* Onco-Move				−0.6 (−1.7 to 0.6)	0.15	.32	−0.5 (−1.9 to 0.8)	0.14	.42
MFI, reduced activity*									
OnTrack	10.2 (3.7)	11.1 (3.7)	8.1 (4.1)						
Onco-Move	10.2 (4.1)	11.7 (4.5)	9.3 (4.0)						
UC	11.3 (4.7)	12.8 (4.8)	9.0 (4.1)						
OnTrack *v* UC				**−1.3 (−2.6 to 0.0)**	**0.31**	**.045**	−0.6 (−1.8 to 0.7)	0.13	.38
Onco-Move *v* UC				−0.9 (−2.3 to 0.4)	0.21	.16	0.4 (−0.8 to 1.6)	0.09	.50
OnTrack *v* Onco-Move				−0.4 (−1.6 to 0.9)	0.09	.56	−1.0 (−2.3 to 0.3)	0.25	.14
MFI, reduced motivation*									
OnTrack	8.5 (3.1)	8.7 (3.1)	7.9 (4.1)						
Onco-Move	8.1 (3.4)	9.1 (3.8)	7.4 (3.2)						
UC	9.5 (3.7)	10.2 (4.6)	7.8 (3.5)						
OnTrack *v* UC				**−1.2 (−2.3 to 0.0)**	**0.34**	**.049**	0.4 (−0.7 to 1.6)	0.13	.47
Onco-Move *v* UC				−0.7 (−1.9 to 0.5)	0.19	.26	0.0 (−1.0 to 1.0)	0.01	.95
OnTrack *v* Onco-Move				−0.5 (−1.4 to 0.5)	0.15	.34	0.4 (−0.7 to 1.5)	0.12	.48
MFI, mental fatigue*									
OnTrack	9.3 (4.3)	10.5 (4.0)	9.7 (4.2)						
Onco-Move	9.7 (4.0)	11.3 (4.6)	10.9 (4.1)						
UC	10.8 (4.9)	11.8 (4.8)	10.2 (4.8)						
OnTrack *v* UC				−0.4 (−1.6 to 0.7)	0.10	.44	0.4 (−0.7 to 1.5)	0.09	.49
Onco-Move *v* UC				0.0 (−1.2 to 1.2)	0.01	.95	1.0 (−0.2 to 2.2)	0.21	.12
OnTrack *v* Onco-Move				−0.4 (−1.5 to 0.7)	0.10	.47	−0.6 (−1.8 to 0.7)	0.13	.37
FQL, frustrating†									
OnTrack	18.9 (21.1)	28.7 (25.0)	22.8 (28.5)						
Onco-Move	16.6 (23.9)	32.5 (31.1)	21.0 (25.9)						
UC	21.3 (26.2)	40.6 (30.0)	30.0 (33.6)						
OnTrack *v* UC				**−11.2 (−19.8 to −2.7)**	**0.47**	**.010**	−6.5 (−15.6 to 2.7)	0.27	.17
Onco-Move *v* UC				−5.7 (−14.8 to 3.4)	0.23	.22	−6.4 (−15.5 to 2.7)	0.26	.17
OnTrack *v* Onco-Move				−5.6 (−14.3 to 3.2)	0.25	.21	0.0 (−8.4 to 8.3)	0.00	1.00
FQL, exhausting†									
OnTrack	8.6 (17.1)	13.7 (21.0)	7.4 (18.6)						
Onco-Move	2.9 (10.7)	12.7 (22.3)	4.5 (11.6)						
UC	6.8 (17.0)	19.3 (27.0)	10.2 (18.8)						
OnTrack *v* UC				−7.4 (−15.1 to 0.3)	0.43	.06	−3.9 (−9.8 to 1.9)	0.23	.19
Onco-Move *v* UC				−5.8 (−13.8 to 2.2)	0.41	.15	−4.6 (−9.8 to 0.7)	0.32	.09
OnTrack *v* Onco-Move				−1.6 (−8.4 to 5.3)	0.11	.66	0.6 (−4.4 to 5.6)	0.04	.81
FQL, pleasant†									
OnTrack	30.3 (22.0)	27.3 (21.7)	31.0 (28.4)						
Onco-Move	31.4 (17.9)	23.3 (19.6)	27.5 (23.4)						
UC	25.7 (22.2)	16.7 (17.4)	24.1 (22.9)						
OnTrack *v* UC				**8.6 (2.4 to 14.9)**	**0.39**	**.007**	4.9 (−2.8 to 12.6)	0.22	.21
Onco-Move *v* UC				4.8 (−1.4 to 10.9)	0.24	.13	0.9 (−6.7 to 8.6)	0.05	.81
OnTrack *v* Onco-Move				3.9 (−2.8 to 10.6)	0.19	.25	4.0 (−4.3 to 12.2)	0.20	.35

(continued on following page)

Table 4. Mean Values at Baseline, End of Chemotherapy, and 6-Month Follow-Up, and Adjusted Between-Group Differences for Fatigue (continued)

Measure	T0:Mean (SD)	T1:Mean (SD)	T2: Mean (SD)	Between-Group Difference at T1			Between-Group Difference at T2		
				AMD (95% CI)	ES	*P*	AMD (95% CI)	ES	*P*
FQL, frightening†									
OnTrack	12.2 (18.9)	5.3 (13.3)	6.7 (15.8)						
Onco-Move	7.5 (16.8)	8.2 (17.1)	4.9 (13.6)						
UC	10.7 (17.9)	12.1 (20.2)	7.8 (14.7)						
OnTrack *v* UC				**−7.5 (−12.9 to −2.2)**	**0.41**	**.005**	−1.5 (−6.3 to 3.3)	0.08	.55
Onco-Move *v* UC				−2.7 (−8.2 to 2.9)	0.15	.35	−1.2 (−5.7 to 3.3)	0.07	.61
OnTrack *v* Onco-Move				**−4.9 (−9.7 to −0.1)**	**0.27**	**.046**	−0.3 (−5.1 to 4.5)	0.02	.90

NOTE. Bold font indicates significant difference.
Abbreviations: AMD, adjusted mean difference between groups; ES, effect size of difference between groups; FQL, Fatigue Quality List; MFI, Multidimensional Fatigue Inventory; SD, standard deviation; T0, baseline before chemotherapy; T1, at completion of chemotherapy; T2, 6 months after completion of chemotherapy; UC, usual care.
*MFI scores range from 4 to 20; high scores indicate more fatigue.
†FQL scores range from 0 to 100; higher scores in each category indicate fatigue is frustrating, exhausting, pleasant, or frightening to a higher degree.

among those who required chemotherapy adjustment in OnTrack and Onco-Move was 10%, compared with 25% in UC (mean difference, −0.15; 95% CI, −2.96 to −0.01; $P = .014$).

In an exploratory analysis, we examined trastuzumab completion rates and left ventricular ejection fractions. Sixty-five patients, distributed equally across the study groups, received trastuzumab during and after their chemotherapy. There were no statistically significant differences between the groups ($P = .16$). Six percent of the patients in OnTrack required delay or discontinuation of trastuzumab treatment because of reduced left ventricular ejection fraction, compared with 28% in UC (OR, 0.16; 95% CI, 0.02 to 1.57) and 24% in Onco-Move (OR, 0.20; 95% CI, 0.02 to 1.91).

DISCUSSION

The results of this trial support our hypothesis that moderate- to high-intensity exercise during chemotherapy (OnTrack) has a beneficial effect on cardiorespiratory fitness, muscle strength, fatigue, and chemotherapy completion rates. Salutary effects were also found for symptom burden (eg, nausea and vomiting, pain, constipation) and return to work. The effects of low-intensity physical activity were less pronounced (except for nausea) and were limited to measures of endurance, symptom burden, and return to work.

The observed intervention effects did not reflect improvement in physical fitness levels or fatigue during chemotherapy, but rather a less steep decline or a stable situation. Similar results have been reported in earlier exercise trials in breast cancer,[9,11,31,32] with only one trial of high-intensity resistance training reporting improvement over time in muscle strength.[9]

Most of the positive effects of the interventions were limited to the period during which the patients were receiving chemotherapy. At 6-month follow-up, all groups had returned to approximately their baseline (ie, prechemotherapy) levels of physical fitness and fatigue. This does not detract from the efficacy of the interventions in that they were designed primarily to minimize decline in, if not enhance, fitness and to reduce symptom burden during the period of active treatment. We would emphasize that a return to baseline levels at 6-month follow-up does not necessarily imply that the patients had returned to their preillness fitness levels. Our baseline assessments took place after patients had undergone surgery and, in most cases, radiotherapy. Previous studies have reported a decline in physical fitness and functioning levels after surgery and/or radiotherapy.[33] Thus, it is likely that participants in our study had not returned to their preillness levels of physical health, and therefore might still benefit from participating in physical rehabilitation programs after completion of treatment.

Patients who participated in a physical exercise or activity program were more likely to have returned to work at 6-month follow-up than those in UC. This not only has financial implications, but also carries meaning in terms of quality of life and a sense of return to normalcy.[34]

To the best of our knowledge, our study is the first to replicate the previously observed positive effect of moderate- to high-intensity exercise on chemotherapy completion rates. We also observed a potential dose-response relationship for exercise on chemotherapy completion rates.[11] OnTrack had substantially higher chemotherapy completion rates than both Onco-Move and UC. However, the amount of dose reduction required among those whose chemotherapy regimen was modified was lower in both intervention groups as compared with UC. We did not have sufficient statistical power for this subgroup analysis; thus, future trials are needed to confirm this finding. These findings have potentially important clinical implications, in that higher chemotherapy completion rates may improve disease-free and overall survival.[1] An exploratory follow-up of the exercise trial by Courneya et al[11] lends preliminary support to this hypothesis.[35]

An interesting finding, albeit one that is based on exploratory analyses, was the trend toward less delay or discontinuation of trastuzumab treatment in the OnTrack group. This might indicate a potential protective effect of exercise against cardiotoxicity.[36] However, we would note that the percentage of patients in OnTrack with delayed or discontinued trastuzumab use was comparable to that reported by de Azambuja et al,[37] whereas the percentage in Onco-Move and UC groups was much higher. Thus, we cannot rule out that our observed differences may reflect a chance finding.

Our study had several limitations that should be noted. First, we were unable to determine peak oxygen uptake directly as a result of

Table 5. Mean Values at Baseline, End of Chemotherapy, and 6-Month Follow-Up, and Adjusted Between-Group Differences Secondary Outcome Measures

EORTC QLQ-C30 Measure*	T0:Mean (SD)	T1:Mean (SD)	T2:Mean (SD)	Between-Group Difference at T1			Between-Group Difference at T2		
				AMD (95% CI)	ES	*P*	AMD (95% CI)	ES	*P*
Physical functioning									
OnTrack	89.4 (10.2)	80.3 (14.1)	87.7 (12.2)						
Onco-Move	87.0 (13.4)	77.8 (17.2)	87.5 (13.4)						
UC	84.8 (13.8)	68.1 (17.6)	83.1 (14.2)						
OnTrack *v* UC				**9.9 (4.9 to 14.9)**	**0.81**	**< .001**	1.5 (−2.4 to 5.5)	0.13	.44
Onco-Move *v* UC				**9.2 (3.9 to 14.5)**	**0.68**	**.001**	3.2 (−0.6 to 7.0)	0.23	.10
OnTrack *v* Onco-Move				0.7 (−3.9 to 5.3)	0.06	.76	−1.6 (−5.4 to 2.1)	0.14	.39
Cognitive functioning									
OnTrack	83.6 (20.5)	78.2 (19.0)	79.8 (20.1)						
Onco-Move	83.5 (20.5)	73.6 (24.8)	74.9 (19.9)						
UC	80.5 (22.2)	70.2 (23.1)	75.3 (23.9)						
OnTrack *v* UC				**6.8 (0.5 to 13.1)**	**0.32**	**.033**	1.9 (−4.4 to 8.1)	0.09	.56
Onco-Move *v* UC				2.5 (−4.7 to 9.6)	0.11	.50	−1.9 (−8.7 to 4.8)	0.09	.58
OnTrack *v* Onco-Move				4.4 (−2.3 to 11.1)	0.21	.20	3.8 (−2.4 to 9.9)	0.18	.23
Social functioning									
OnTrack	79.8 (19.9)	73.5 (21.6)	87.1 (17.9)						
Onco-Move	83.3 (19.5)	74.6 (22.7)	86.9 (16.8)						
UC	80.5 (23.2)	67.9 (29.1)	78.1 (22.2)						
OnTrack *v* UC				6.4 (−1.8 to 14.6)	0.30	.13	**9.1 (2.7 to 15.6)**	**0.42**	**.006**
Onco-Move *v* UC				6.1 (−2.2 to 14.4)	0.29	.15	**7.6 (1.2 to 13.9)**	**0.35**	**.019**
OnTrack *v* Onco-Move				0.3 (−6.8 to 7.4)	0.01	.94	1.5 (−4.3 to 7.4)	0.08	.60
Fatigue									
OnTrack	30.3 (19.6)	46.0 (23.7)	29.2 (25.1)						
Onco-Move	29.6 (21.0)	42.3 (24.7)	27.5 (19.6)						
UC	31.2 (20.8)	51.3 (23.7)	32.8 (20.3)						
OnTrack *v* UC				−6.2 (−13.3 to 0.8)	0.31	.08	−3.0 (−9.8 to 3.9)	0.15	.39
Onco-Move *v* UC				**−10.6 (−17.6 to −3.5)**	**0.51**	**.003**	−6.0 (−12.3 to 0.4)	0.29	.07
OnTrack *v* Onco-Move				4.3 (−2.6 to 11.3)	0.21	.22	3.0 (−3.9 to 9.9)	0.15	.40
Nausea and vomiting									
OnTrack	3.1 (7.1)	4.2 (9.6)	3.5 (10.5)						
Onco-Move	1.9 (5.4)	3.7 (9.5)	1.9 (6.2)						
UC	3.0 (7.0)	10.4 (22.8)	2.1 (5.6)						
OnTrack *v* UC				**−6.2 (−11.9 to −0.6)**	**0.89**	**.031**	1.4 (−1.3 to 4.2)	0.21	.30
Onco-Move *v* UC				**−6.2 (−11.9 to −0.6)**	**1.00**	**.029**	0.3 (−1.9 to 2.5)	0.04	.81
OnTrack *v* Onco-Move				0.0 (−3.2 to 3.3)	0.00	.99	1.2 (−1.4 to 3.8)	0.19	.38
Pain									
OnTrack	18.2 (18.3)	22.3 (20.1)	18.3 (20.3)						
Onco-Move	21.0 (19.4)	19.9 (24.8)	19.4 (20.7)						
UC	23.2 (20.1)	31.8 (22.2)	26.6 (22.6)						
OnTrack *v* UC				**−8.9 (−15.8 to −2.0)**	**0.46**	**.011**	**−7.0 (−13.9 to −0.1)**	**0.36**	**.047**
Onco-Move *v* UC				**−11.9 (−19.6 to −4.2)**	**0.60**	**.003**	−7.0 (−14.2 to 0.2)	0.36	.06
OnTrack *v* Onco-Move				3.0 (−4.5 to 10.5)	0.16	.44	0.0 (−6.8 to 6.9)	0.00	.99
Constipation									
OnTrack	6.1 (17.0)	3.3 (14.0)	8.9 (17.8)						
Onco-Move	4.3 (11.3)	10.9 (18.7)	6.6 (13.4)						
UC	6.1 (12.9)	17.7 (26.3)	9.4 (17.3)						
OnTrack *v* UC				**−14.7 (−21.1 to −8.3)**	**0.98**	**< .001**	0.1 (−5.5 to 5.6)	0.00	.98
Onco-Move *v* UC				−6.0 (−13.3 to 1.3)	0.49	.11	−1.1 (−6.1 to 3.9)	0.09	.66
OnTrack *v* Onco-Move				**−8.7 (−13.1 to −4.3)**	**0.61**	**< .001**	1.2 (−4.0 to 6.4)	0.08	.65

NOTE. Bold font indicates significant difference.
Abbreviations: AMD, adjusted mean difference between groups; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; ES, effect size of difference between groups; SD, standard deviation; T0, baseline before chemotherapy; T1, at completion of chemotherapy; T2, 6 months after completion of chemotherapy; UC, usual care.
*EORTC CQL-C30 scores range from 0 to 100; high scores indicate high global health status, high level of functioning, and high level of symptomatology/problems.

limited testing facilities and the small time-window between referral to the trial and start of chemotherapy. Instead, we used the maximal short exercise capacity on the Steep Ramp Test to evaluate changes in cardiorespiratory fitness. The Steep Ramp Test has been shown to be reliable (intraclass correlation coefficient, 0.996) and valid for this purpose.[19] We also added an endurance test, which may be more clinically relevant than maximal short exercise capacity, given that activities in daily living are not performed at peak levels.[38]

Table 6. Rates of and Reasons for Chemotherapy Dose Reduction

Characteristic	Total (N = 230)	OnTrack (n = 76)	Onco-Move (n = 77)	Usual Care (n = 77)
Patients requiring dose adjustments, No. (%)	61 (26)	9 (12)	26 (34)	26 (34)
Mean prescribed length of chemotherapy, days	118.6	119.2	119.9	116.7
Reasons for chemotherapy adjustment, No. (%)				
Neuropathy	19 (31)	3	10	6
Myelosuppression	7 (11)	2	2	3
Febrile neutropenia	7 (11)	0	1	6
Nausea and vomiting	7 (11)	2	2	3
Pain	6 (10)	1	2	3
Infection	4 (7)	0	1	3
Dyspnea	4 (7)	0	2	2
Edema	3 (5)	0	3	0
Cardiac signs or symptoms	2 (3)	0	2	0
Obstipation/diarrhea	2 (3)	1	1	0
Average % dose reduction*		9.8	9.7	25.2

*Average dose reductions per group among participants needing a dose adjustment.

Second, our study was limited to the effect of exercise during adjuvant chemotherapy. We anticipate that exercise would be equally if not more effective in patients receiving neoadjuvant chemotherapy, because they will not have yet experienced the functional limitations associated with surgery (eg, on shoulder function). A recent phase II trial showed improved physical fitness and decreased fatigue after aerobic exercise during neoadjuvant chemotherapy.[39]

Third, although our recruitment rate was much higher than the anticipated 25%,[14] slightly more than half of the eligible patients declined to participate in the trial. This is a common finding in exercise oncology trials[40-42] and raises issues regarding the generalizability of results to the larger target population. Those who chose to participate in the trial were more highly educated and more likely to be working than those who did not. This is not unexpected, in that education is correlated positively with health literacy, and those who are health literate may be more open to advice about being physically active during treatment.[43] Future studies are needed to better understand the practical and attitudinal barriers to being physically active both during and after cancer treatment, and to develop appropriate, tailored approaches to encourage reluctant patients to become more active.

Finally, although we intended to recruit both patients with breast cancer and colon cancer into our trial, we experienced significant problems in recruiting the latter group. More patients with colon cancer than anticipated were receiving palliative rather than adjuvant chemotherapy, and patients who had undergone major abdominal surgery were typically advised to refrain from intensive physical activity for 6 weeks after surgery. Clinicians were also more hesitant to refer patients with colon cancer to our study. Others have also reported difficulty in recruiting patients with colon cancer into exercise oncology trials,[44] and thus more research is needed to better understand how to modify existing exercise programs to meet the needs of this patient population.

Our study also had a number of strengths, including a direct comparison of home-based, low-intensity and supervised, moderate- to high-intensity exercise programs versus UC, a large sample size, multicenter participation, limited loss to follow-up, and the use of both objective and self-reported outcomes.

In conclusion, our findings indicate that both a moderate- to high-intensity physical exercise program and a low-intensity physical activity program are safe and feasible during adjuvant chemotherapy for breast cancer. The moderate- to high-intensity program was most effective in minimizing decline in cardiorespiratory fitness and muscle strength, limiting fatigue and symptom burden, avoiding the need for chemotherapy dose reduction, and facilitating return to work. The low-intensity program also had significant, positive effects, albeit of a lesser scope and magnitude. In general, we would recommend that women who are able and willing to participate be offered a supervised, moderate- to high-intensity exercise program during adjuvant chemotherapy. For other women, the home-based, low-intensity physical activity program represents a viable alternative.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Hanna van Waart, Martijn M. Stuiver, Wim H. van Harten, Edwin Geleijn, Laurien M. Buffart, Jeannette A.J.H. Hellendoorn-van Vreeswijk, Gabe S. Sonke, Neil K. Aaronson
Provision of study materials or patients: Epie Boven, Jolanda Schrama, Maud M. Geenen, Jetske M. Meerum Terwogt, Aart van Bochove, Vera Lustig, Simone M. van den Heiligenberg, Carolien H. Smorenburg, Gabe S. Sonke
Collection and assembly of data: Hanna van Waart, Marianne de Maaker-Berkhof, Epie Boven, Jolanda Schrama, Maud M. Geenen, Jetske M. Meerum Terwogt, Aart van Bochove, Vera Lustig, Simone M. van den Heiligenberg, Carolien H. Smorenburg
Data analysis and interpretation: Hanna van Waart, Martijn M. Stuiver, Jacobien M. Kieffer, Laurien M. Buffart, Gabe S. Sonke, Neil K. Aaronson
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group, Peto R, Davies C, et al: Comparisons between different polychemotherapy regimens for early breast cancer: Meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 379:432-444, 2012
2. Courneya KS: Exercise in cancer survivors: An overview of research. Med Sci Sports Exerc 35: 1846-1852, 2003
3. Hartvig P, Aulin J, Hugerth M, et al: Fatigue in cancer patients treated with cytotoxic drugs. J Oncol Pharm Pract 12:155-164, 2006
4. Cheema B, Gaul CA, Lane K, et al: Progressive resistance training in breast cancer: A systematic review of clinical trials. Breast Cancer Res Treat 109:9-26, 2008
5. Galvão DA, Newton RU: Review of exercise intervention studies in cancer patients. J Clin Oncol 23:899-909, 2005
6. Knols R, Aaronson NK, Uebelhart D, et al: Physical exercise in cancer patients during and after medical treatment: A systematic review of randomized and controlled clinical trials. J Clin Oncol 23: 3830-3842, 2005
7. Kuchinski AM, Reading M, Lash AA: Treatment-related fatigue and exercise in patients with cancer: A systematic review. Medsurg Nurs 18:174-180, 2009
8. 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 8:CD008465, 2012
9. 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 105:1821-1832, 2013
10. Baumann FT, Bloch W, Weissen A, et al: Physical activity in breast cancer patients during medical treatment and in the aftercare: A review. Breast Care (Basel) 8:330-334, 2013
11. 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 25:4396-4404, 2007
12. Mock V, Cameron L, Tompkins C, et al: Every Step Counts: A Walking Exercise Program for Persons With Cancer. Baltimore, MD, John Hopkins University, 1997
13. Velthuis MJ, Agasi-Idenburg SC, Aufdemkampe G, et al: The effect of physical exercise on cancer-related fatigue during cancer treatment: A meta-analysis of randomised controlled trials. Clin Oncol (R Coll Radiol) 22:208-221, 2010
14. Van Waart H, Stuiver MM, van Harten WH, et al: Design of the Physical exercise during Adjuvant Chemotherapy Effectiveness Study (PACES): A randomized controlled trial to evaluate effectiveness and cost-effectiveness of physical exercise in improving physical fitness and reducing fatigue. BMC Cancer 10:673, 2010
15. Scott NW, McPherson GC, Ramsay CR, et al: The method of minimization for allocation to clinical trials: A review. Control Clin Trials 23:662-674, 2002
16. van der Ploeg HP, Streppel KR, van der Beek a J, et al: Counselling increases physical activity behaviour nine weeks after rehabilitation. Br J Sports Med 40:223-229, 2006
17. Borg G: Borg's Perceived Exertion and Pain Scales. Champaign, IL, Human Kinetics, 1998
18. Geleijn E, Smeets C, Vrijman M, et al: CytoFys, behoud van kracht en uithoudingsvermogen tijdens chemotherapie. Ned Tijdschr voor Oncol 8:80-86, 2011
19. De Backer IC, Schep G, Hoogeveen A, et al: Exercise testing and training in a cancer rehabilitation program: The advantage of the steep ramp test. Arch Phys Med Rehabil 88:610-616, 2007
20. van der Ploeg RJ, Fidler V, Oosterhuis HJ: Hand-held myometry: Reference values. J Neurol Neurosurg Psychiatry 54:244-247, 1991
21. Knols RH, Aufdemkampe G, de Bruin ED, et al: Hand-held dynamometry in patients with haematological malignancies: Measurement error in the clinical assessment of knee extension strength. BMC Musculoskelet Disord 10:31, 2009
22. Trutschnigg B, Kilgour RD, Reinglas J, et al: Precision and reliability of strength (Jamar vs. Biodex handgrip) and body composition (dual-energy X-ray absorptiometry vs. bioimpedance analysis) measurements in advanced cancer patients. Appl Physiol Nutr Metab 33:1232-1239, 2008
23. Jones C, Rikli R, Beam W: A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. Res Q Exerc Sport 70:113-119, 1999
24. Smets EM, Garssen B, Bonke B, et al: The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 39:315-325, 1995
25. Gielissen MF, Knoop H, Servaes P, et al: Differences in the experience of fatigue in patients and healthy controls: Patients' descriptions. Health Qual Life Outcomes 5:36, 2007
26. Chinapaw MJ, Buffart LM, van Mechelen W, et al: Alpe d'HuZes cancer rehabilitation (A-CaRe) research: Four randomized controlled exercise trials and economic evaluations in cancer patients and survivors. Int J Behav Med 19:143-156, 2012
27. Cohen J: Statistical Power Analysis for the Behavioral Sciences (ed 2). London, UK, Routledge, 1988
28. Twisk JWR: Applied Longitudinal Data Analysis for Epidemiology: A Practical Guide (ed 2). Cambridge, UK, Cambridge University Press, 2013
29. Morris S: Estimating effect sizes from pretest-posttest-control group designs. Organ Res Meth 11:364-386, 2008
30. Norman GR, Sloan JA, Wyrwich KW: Interpretation of changes in health-related quality of life: The remarkable universality of half a standard deviation. Med Care 41:582-592, 2003
31. Segal R, Evans W, Johnson D, et al: Structured exercise improves physical functioning in women with stages I and II breast cancer: Results of a randomized controlled trial. J Clin Oncol 19:657-665, 2001
32. Kim CJ, Kang D-H, Smith BA, et al: Cardiopulmonary responses and adherence to exercise in women newly diagnosed with breast cancer undergoing adjuvant therapy. Cancer Nurs 29:156-165, 2006
33. Lakoski SG, Eves ND, Douglas PS, et al: Exercise rehabilitation in patients with cancer. Nat Rev Clin Oncol 9:288-296, 2013
34. Peteet JR: Cancer and the meaning of work. Gen Hosp Psychiatry 22:200-205, 2000
35. Courneya KS, Segal RJ, McKenzie DC, et al: Effects of exercise during adjuvant chemotherapy on breast cancer outcomes. Med Sci Sports Exerc 46:1744-1751, 2014
36. Wonders KY, Reigle BS: Trastuzumab and doxorubicin-related cardiotoxicity and the cardioprotective role of exercise. Integr Cancer Ther 8:17-21, 2009
37. de Azambuja E, Procter MJ, van Veldhuisen DJ, et al: Trastuzumab-associated cardiac events at 8 years of median follow-up in the Herceptin Adjuvant trial (BIG 1-01). J Clin Oncol 32:2159-2165, 2014
38. Ong KC, Chong WF, Soh C, et al: Comparison of different exercise tests in assessing outcomes of pulmonary rehabilitation. Respir Care 49:1498-1503, 2004
39. Hornsby WE, Douglas PS, West MJ, et al: Safety and efficacy of aerobic training in operable breast cancer patients receiving neoadjuvant chemotherapy: A phase II randomized trial. Acta Oncol 53:65-74, 2014
40. Sears SR, Stanton AL, Kwan L, et al: Recruitment and retention challenges in breast cancer survivorship research: Results from a multisite, randomized intervention trial in women with early stage breast cancer. Cancer Epidemiol Biomarkers Prev 12:1087-1090, 2003
41. Würtzen H, Dalton SO, Andersen KK, et al: Who participates in a randomized trial of mindfulness-based stress reduction (MBSR) after breast cancer? A study of factors associated with enrollment among Danish breast cancer patients. Psychooncology 22:1180-1185, 2013
42. Chinn DJ, White M, Howel D, et al: Factors associated with non-participation in a physical activity promotion trial. Public Health 120:309-319, 2006
43. von Wagner C, Knight K, Steptoe A, et al: Functional health literacy and health-promoting behaviour in a national sample of British adults. J Epidemiol Community Health 61:1086-1090, 2007
44. Courneya KS, Vardy J, Gill S, et al: Update on the Colon Health and Life-Long Exercise Change trial: A phase III study of the impact of an exercise program on disease-free survival in colon cancer survivors. Curr Colorectal Cancer Rep 2014

GLOSSARY TERM

health-related quality of life (HRQoL): a broad multidimensional concept that usually includes self-reported measures of physical and mental health.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial

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Hanna van Waart
No relationship to disclose

Martijn M. Stuiver
No relationship to disclose

Wim H. van Harten
No relationship to disclose

Edwin Geleijn
No relationship to disclose

Jacobien M. Kieffer
No relationship to disclose

Laurien M. Buffart
No relationship to disclose

Marianne de Maaker-Berkhof
No relationship to disclose

Epie Boven
Research Funding: Novartis (Inst)

Jolanda Schrama
No relationship to disclose

Maud M. Geenen
No relationship to disclose

Jetske M. Meerum Terwogt
No relationship to disclose

Aart van Bochove
No relationship to disclose

Vera Lustig
No relationship to disclose

Simone M. van den Heiligenberg
No relationship to disclose

Carolien H. Smorenburg
No relationship to disclose

Jeannette A.J.H. Hellendoorn-van Vreeswijk
No relationship to disclose

Gabe S. Sonke
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