Effectiveness of a 12-month Exercise Program on Physical Performance and Quality of Life of Breast Cancer Survivors

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Abstract. *Aim: The study aimed at determining whether physical exercise training improves the quality of life (QoL) and physical fitness of breast cancer survivors. Patients and Methods: A total of 573 breast cancer survivors were randomized into an exercise or a control group, 12-months after adjuvant treatments. EORTC QLQ-C30 and BR-23 questionnaires were used for evaluation of QoL, FACIT-F for fatigue and the Finnish modified version of Beck's 13-item depression scale (RBDI) for depression. Physical fitness was assessed by a 2-km walking test, and a figure-8 running test and physical activity (PA) by metabolic equivalent (MET) hours per week (MET-h/wk). Results: Figure-8 running time improved significantly among the patients of the intervention group compared with the controls (p<0.001). No significant between-group differences were observed in 2-km walking time, in PA, EORTC-QLQ-C30, BR-23, FACIT-F or BDI. However, there was a linear relationship between increased PA and improved QoL (p=0.006), irrespective of the intervention. Conclusion: Increase in physical activity was associated with improved QoL, but no effect of the exercise intervention was observed.*

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The prognosis of breast cancer has dramatically improved over the past decades. However, many of the survivors experience prolonged adverse physical and psychological effects such as fatigue, vasomotor symptoms and psychosocial distress (1, 2). Rehabilitation of this large survivor population has become necessary. Exercise seems to be a feasible and well-tolerated, promising strategy for ameliorating breast cancer survivor's physical and psychological problems (3-11). Meta-analyses have concluded that exercise positively influences the quality of life (QoL) of patients with breast cancer (7, 9, 10). There is some support for exercise improving fatigue (12-15), contradictory findings regarding depression (3, 9, 16, 17), and evidence from randomized controlled trials showing the lack of effectiveness of exercise as a treatment for hot-flashes (18-21). However, despite the quantity of the evidence on exercise

Table I. *Inclusion and exclusion criteria of the BREX study.*

Inclusion criteria
• Histologically-proven invasive breast cancer T1-4N0-3M0
• Pre- or post-menopausal breast cancer patient treated with adjuvant chemotherapy or radiotherapy within 4 months, or patient who has started adjuvant endocrine therapy (antiestrogens, aromatase inhibitors, LHRH agonists, or combinations) no less than 4 months earlier
• Age between 35 and 68 years
• Signed informed consent prior to beginning specific protocol procedures
Exclusion criteria
• Male gender
• Prior malignancy except basal cell carcinoma or *in situ* cervix carcinoma
• Haematogenous metastases (M1)
• No systemic adjuvant therapy
• Post-menopausal women with antiestrogens as the only adjuvant treatment (with/without radiotherapy)
• Pregnancy or recent lactation (<1 year)
• Severe cardiac disease (New York Heart Association class III or greater), myocardial infarction within 12 months, uncontrolled hypertension
• Verified osteoporosis (proximal femur or lumbar spine t-score ≥–2.5 or fracture without trauma)
• Concomitant medications affecting calcium and bone metabolism such as bisphosphonates, calcitonin, parathormone (PTH), selective estrogen receptor modulators (SERMs), oral corticosteroids (over 6 months), anticonvulsants (fenytoin, carbamatsebin) and prolonged heparin therapy
• Other diseases affecting calcium and bone metabolism, such as hyperthyroidism, newly diagnosed hypothyroidism, primary hyperparathyroidism, renal failure, chronic hepatic diseases, organ transplant
• Other serious illness or medical condition which could be contraindication for exercise
• Patient not capable of training (severe knee arthritis, severe ligament or cartilage injuries at lower extremities)
• Residence more than one hour from the exercise centre
• Competitive athlete

interventions improving the QoL of patients with breast cancer, further studies are needed (6, 22, 23). The previous trials have been relatively small and focused on different outcomes (6). The measures used, as well as the timing, type and duration of interventions, have also varied between the studies, which complicates comparison of the results in meta-analyses (7, 9, 24). In particular, there is a lack of large randomized controlled trials of long duration. Before physical activity interventions can be routinely integrated into *e.g.* general rehabilitation guidelines for breast cancer patients, definite evidence of QoL benefits, derived from a randomized controlled trial that evaluates the effectiveness of a physical activity intervention, are needed.

The period following initial treatment, ending with recurrence or death, is defined as survivorship. It can be divided into the rehabilitation period (the time from treatment completion to 3-6 months post-treatment) and the disease prevention/health promotion period, which describes longer-term survival (25, 26). Early reviews on exercise studies summarized the evidence from all exercise interventions, regardless of whether patients were in the treatment, rehabilitation or survival period (even 10 years after treatment), while subsequent reviews separated the results of treatment and post-treatment interventions. Only little is known about the rehabilitation period which can be seen as a focus for future research (26). This is particularly important in this context since survivors typically experience a relevant decline in their physical activity during the treatment (27, 28) and more than half of all cancer survivors would prefer to begin an exercise programme immediately or soon after rather than during-treatment (26, 29). On the other hand, completion of treatments can also serve as a motivator to improve lifestyle, *i.e.* increase the amount of physical activity (22, 25). During the period of 3-5 months post-treatment, the patients themselves feel fit enough to make behavioral changes, and may not yet have lost their motivation to change (30). Although the rehabilitation period thus seems particularly viable for starting exercise interventions, only a few physical exercise studies on patients with cancer have been carried out at this stage (8, 22).

The BREX (BReast cancer and EXercise) study is a large open prospective randomized clinical trial of breast cancer survivors participating in a 12-month physical exercise intervention, shortly after adjuvant treatment, *i.e.* during the rehabilitation period. One of the primary objectives of the BREX study, and the main objective of this article, is to investigate the effects of exercise intervention on QoL, fatigue, depression and menopausal symptoms; the secondary end-point was recording of the effects on physical fitness. We hypothesized that the exercise intervention would increase physical activity and physical performance of breast cancer survivors and consequently improve their QoL and reduce fatigue, depression and menopausal symptoms. An impact of exercise on bone health has been reported elsewhere (31).

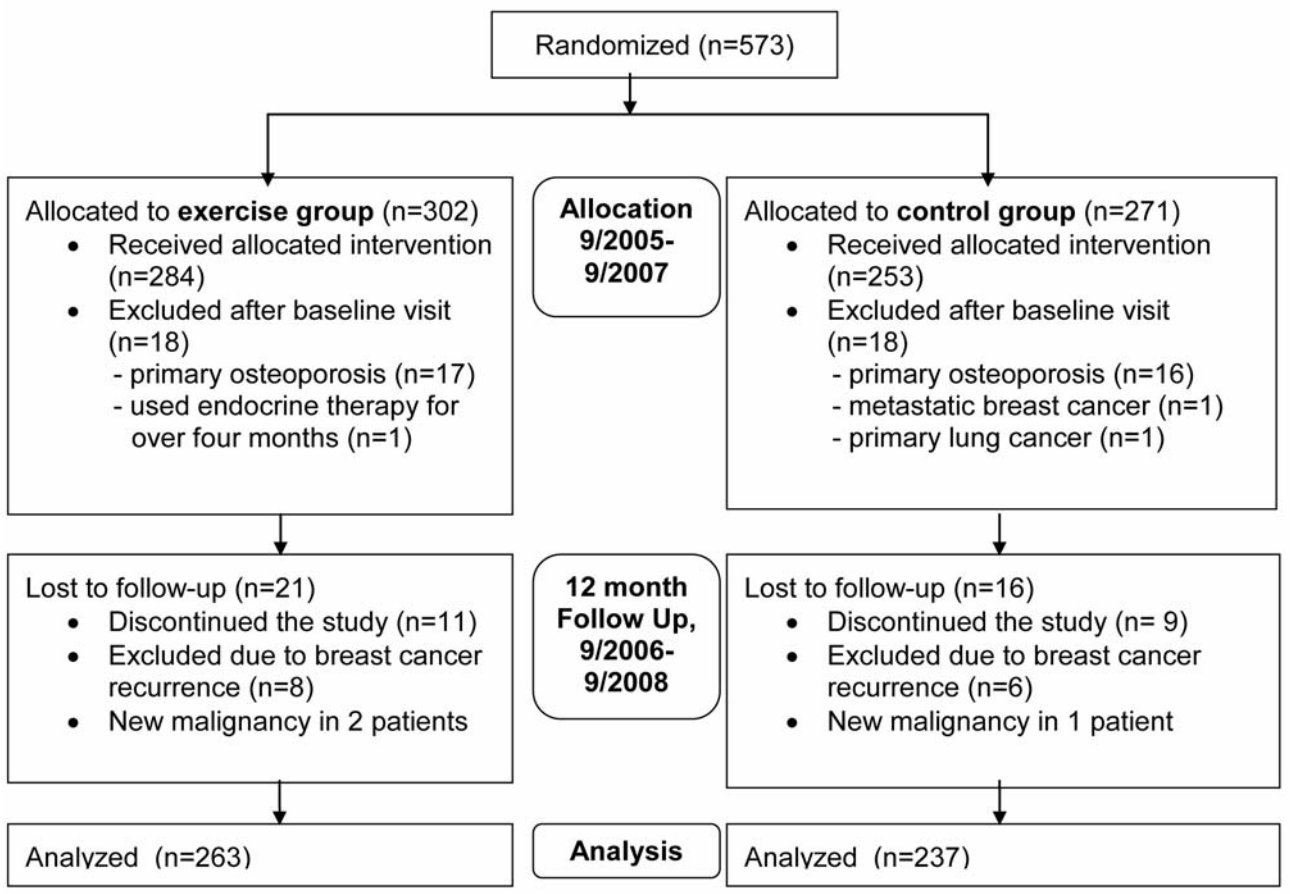

Figure 1. *Flow diagram of participants through the intervention.*

Patients and Methods

Patients. Five hundred and seventy-three pre- and post-menopausal women aged from 35 to 68 years with histologically proven newly diagnosed invasive breast cancer from the Departments of Oncology at Helsinki, Tampere and Turku University Hospitals were enrolled into the one-year aerobic exercise intervention study (BREX) between September 2005 and September 2007. The age range was set to harmonize the training groups and ensure participants' adherence to progressive vigorous exercise training (32). Patients were randomly allocated into a one-year exercise training or a control group. Inclusion and exclusion criteria of the study are shown in Table I. The QoL, physical performance and activity of the patients in the beginning of the trial as well as the screening process, have been reported in detail previously (32, 33). The recruitment rate of the patients considered eligible for the study was 78%:54% from the potentially eligible patients and 31% from all those screened. The main reasons for exclusion were age over 68 years and existence of health problems that contraindicated physical training, *e.g.* musculoskeletal disorders.

The flow diagram of the participants through the intervention is presented in Figure 1. Out of the 573 randomized patients, 500 were included in the final analyses: 263 in the exercise (124 pre-menopausal and 139 post-menopausal) and 237 in the control group (105 pre-menopausal and 132 post-menopausal). Seventy-three patients were excluded from the final analyses because 36 of them did not meet the inclusion criteria and thus did not start the intervention (the main reason was osteoporosis discovered at baseline screening). An additional 20 patients discontinued the intervention due to personal, unspecified reasons. Breast cancer recurrence was detected in 14 patients and a new malignancy was diagnosed in three patients during the 12-month intervention. Thus, complete data were not available from these 73 patients.

All patients were treated with adjuvant chemotherapy and/or endocrine therapy and also with radiotherapy, if needed. The treatments were completed (or in the case of endocrine therapy, started) no later than four months before recruitment into the exercise intervention. The adjuvant treatment was carried out according to clinical guidelines.

Randomization and approvals. This study is a prospective, non-blinded randomized two-arm phase III trial. A computer-generated randomization schedule was used to allocate the patients to either the exercise intervention or control arm. The study nurse performed the randomization after the baseline visit. Patients were blinded until the baseline physical performance tests were completed. Randomization was centralized and stratified for study centers,

endocrine treatments and menopausal status. The local Ethical Committee of Helsinki University Hospital approved the study protocol and written informed consent was obtained from all participants before entry into the study. The trial has been registered in the Helsinki and Uusimaa Hospital District Clinical Trials Register (www.hus.fi) (trial number 210590) and on the website http://www.clinicaltrials.gov/ (identifier number NCT00639210).

Clinical investigations. Medical history was examined and physical examinations were performed at baseline and at one-year follow-up. Patients completed the QoL questionnaire, a questionnaire covering basic demographics and lifestyle issues, and a two-week exercise diary before the intervention and after 6 and 12 months. The tests of physical performance (2-km walking test and figure-8 running test) were performed immediately before the start of the intervention and at 12 months follow-up.

Intervention. The duration of the exercise intervention was 12 months, aiming to attain permanent changes in lifestyle. The exercise intervention consisted of both supervised and home training, which were previously tested for feasibility in our pilot study (34). The focus of the intervention was on home-based exercise training, while the weekly supervised training sessions were included to motivate and educate participants, and to offer them peer support.

Supervised training was organized for the exercise group once a week in groups of 5 to 15 individuals and these sessions were led by an experienced physical therapist. The supervised training of the exercise group consisted of two different classes that alternated weekly, step aerobics class and circuit training class. The 60-minute aerobics and circuit training classes included warm-up and cool-down periods both lasting 10-15 min. The intensity of the training program was based on the Rating of Perceived Exertion (RPE) scale, which relies on self-estimated stress levels (35). The training group's target RPE was 14-16, a level of exercise that feels "somewhat hard" or "hard" and coincides with about 86-92% of maximal heart rate, 76-85% of maximal VO_2 and 5-7 metabolic equivalents (METs). One MET accounts for the amount of oxygen consumed when resting in a seated position, *i.e.* 3.5 ml oxygen consumption per kilogram per minute (35). During the first 6 weeks, the participants performed exercises at a lower level of RPE (approximately 11-13), in order to adapt to the training and so that newly-recruited participants could join the group without difficulty. A physical therapist constructed and tailored the home program together with each participant during the one-month run-in period.

The type of home training was optional but was intended to be similar to that of supervised training. It mainly consisted of endurance training such as walking, Nordic walking or aerobic training, but it also included jumps and leaps similar to step aerobics (96 jumps and leaps per home training session) to promote bone health (31). Warm-up and cool-down exercises, such as marching or climbing-up stairs were recommended before and after the home training session. In addition, brisk endurance training (walking, cycling, swimming *etc*.) at the same RPE was recommended to fulfill the amount of weekly physical activity. Home training was aimed to be carried out at least twice a week (but three times a week was recommended) so that the total training would comprise a minimum of three training sessions per week. The control group was encouraged to maintain their previous level of physical activity and exercise habits throughout the study without any supervised or home training programs.

Assessment of physical activity. Crude information on previous leisure time physical activity occurring before the breast cancer diagnosis was collected through a questionnaire, where leisure time activities were classified as low intensity (*e.g.* mostly watching TV, reading), moderate intensity (*e.g.* walking or cycling at least 4 h per week), high intensity (*e.g.* gym, ball games, swimming or jogging at least 3 h per week) or very high intensity activities (*e.g.* competitive athletics) (36).

Information on the amount and intensity of current physical activity immediately preceding the start of the exercise intervention, and at 6- and 12-month follow-ups was collected by a prospective two-week physical activity diary from all the patients. Patients reported the amount (minimum duration of 10 min) and the type of physical activity. The intensity of each reported activity was categorized as light (<3 METs), moderate (3 to 6 METs), hard (6 to 9 METs) or very hard (>9 METs), based on the compendium of physical activities (37). The total physical activity was expressed in MET hours per week (MET-h/wk) and was calculated by multiplying the intensity of the activity by the time spent on that activity.

Assessment of physical performance. Cardiorespiratory fitness was tested by a 2-km walk test (UKK walk test, Tampere, Finland) (38). Neuromuscular performance was evaluated by the figure-8 running test, where patients were asked to run two loops around a track that included two poles placed ten meters apart from each other, as fast as possible (39).

QoL. QoL was evaluated by the European Organisation for Research and Treatment of Cancer (EORTC) questionnaire (EORTC QLQ-C30) (version 3) (40) with the breast cancer module supplement (BR-23) (41). These questionnaires have been validated and cross-culturally tested in various cancer populations (41).

Symptoms of fatigue were assessed using the the Functional Assessment of Chronic Illness Therapy (FACIT) questionnaire for fatigue (FACIT-F). Values below 34 correspond to International Classification for Diseases (ICD-10) criteria for fatigue, thus 34 was used as a cut-off point (42). Depressive symptoms were assessed using the Finnish modified version of Beck's 13-item depression scale (RBDI) (43). The sum of point measures the depth of the depression symptoms: 0-4 points signifies no depressive symptoms, 5-7 mild, 8-15 moderate and 16-39 severe depressive symptoms. Menopausal symptoms were assessed by the Women's Health Questionnaire (WHQ) (44). The 37-item questionnaire includes different subscales for emotional and physical health. In the present study subscale for vasomotor symptoms was used.

Statistical analyses. Analyses were performed on an intention-to-treat basis for all participants who completed the baseline and at least one follow-up measurement. The original power calculation of the study was made to detect a 1% between-group difference in changes in bone mineral density at a significance level of 1% and a power of 90% with separate analyses in pre- and pos-tmenopausal patients. Moreover, a drop-out proportion of 30% was assumed. To detect clinically significant differences (10-point change in EORTC-C30 score) at a significance level of 5% and power of 80%, a sample of 140 patients per group in the QoL study was required (45). The results are given as means with standard deviation or the 95% confidence interval. The treatment effect was defined as mean between-group difference in changes from baseline to 12 months. The statistical comparisons between study groups were carried out by using either analysis of co-

Table II. *Patients' characteristics at baseline.*

Variable	Exercise group (n=263) n (%)	Control group (n=237) n (%)
General and socioeconomic characteristics		
Mean age, years, (range)	52.3 (36-68)	52.4 (35-68)
Menopausal status		
Pre-menopausal	124 (47.1%)	105 (44.3%)
Post-menopausal	139 (52.9%)	132 (55.7%)
BMI		
<25 (normal weight)	118 (41.1%)	111 (46.8%)
25-30 (overweight)	104 (39.5%)	88 (37.1%)
>30 (obese)	51 (19.4%)	38 (16.0%)
Any reported disease	141 (53.%)	131 (55.3%)
Smokers (daily smoking)	28 (10.6%)	31 (13.1%)
Marital status		
Married or common-law marriage	168 (63.9%)	151 (63.7%)
Unmarried	38 (14.4%)	29 (12.2%)
Widowed	6 (2.3%)	14 (5.9%)
Divorced	45 (17.1%)	34 (14.3%)
Missing information	6 (2.3%)	9 (3.8%)
Years of education, mean (SD*)	14 (3.5)	14 (3.3)
Employment status		
Self-employed	9 (3.4%)	10 (4.2%)
Upper-level employee	48 (18.3%)	49 (20.7%)
Lower-level employee	119 (45.2%)	93 (39.2%)
Manual worker	26 (9.9%)	19 (8.0%)
Student	3 (1.1%)	2 (0.8%)
Pensioner, housewife	43 (16.3%)	48 (20.3%)
Unemployed	8 (3.0%)	5 (2.1%)
Missing information	7 (2.7%)	11 (4.6%)
Breast cancer and treatment data		
Median tumor size, mm, (range)	19.0 (4-150)	20.0 (4-130)
Median number of metastatic lymph nodes (range)	1 (0-31)	1 (0-42)
Estrogen receptor-positive	223 (84.8%)	195 (82.3%)
Progesterone receptor-positive	183 (69.6%)	165 (69.6%)
Breast surgery, final		
Mastectomy	127 (48.3%)	129 (54.4%)
Resection	136 (51.7%)	108 (45.6%)
Axillary operation, final		
Dissection	190 (72.2%)	179 (75.5%)
Sentinel node biopsy	73 (27.8%)	58 (24.5%)
Mean time in weeks since surgery (SD*)	33.7 (8.8)	32.6 (9.0)
Since last chemotherapy cycle	12.2 (7.3)	11.0 (7.6)
Since last radiotherapy session	4.7 (7.1)	3.3 (7.2)
Since start of endocrine treatment	8.9 (7.5)	7.0 (7.8)
Adjuvant treatments		
Chemotherapy	236 (89.7%)	220 (92.8%)
Radiotherapy	206 (78.3%)	185 (78.1%)
Endocrine treatment	224 (85.2%)	195 (82.3%)
Aromatase inhibitor	78 (29.3%)	80 (33.8%)
Tamoxifen	146 (55.9%)	115 (48.5%)
Physical performance and activity		
Mean figure 8 running, s (SD*)	15.9 (2.9)	15.9 (2.8)
Mean 2-km walking test, min (SD*)	18.6 (2.0)	18.4 (1.8)
History of leisure time physical activity (before breast cancer diagnosis)		
Low	53 (22.2%)	34 (14.3%)
Moderate	134 (51.0%)	136 (57.4%)
High	68 (25.9%)	53 (22.4%)
Missing information	8 (3.0%)	14 (5.9%)
Mean self-reported physical activity, MET-h/wk# (SD*)	27.40 (16.54)	26.37 (15.69)

*SD: Standard deviation, #MET-h/wk: metabolic equivalent (MET) hours per week.

variance with baseline value as a co-variate, or linear mixed models for repeated measurements (baseline, 6 and 12 months). Statistical significance for the hypotheses of linear trend was obtained by analysis of co-variance with an appropriate contrast. All tests were two-sided. No adjustment was made for multiple testing.

Results

Patients' characteristics. The characteristics of the study groups are presented in Table II. There were no differences between groups at baseline. The response rate to the questionnaires at baseline, 6-month and 12-month follow-up were 94%, 96% and 93%, respectively.

Training attendance. Patients in the exercise group attended the supervised weekly training classes 32 times out of a total of 52 (62%) during the 12-month intervention. As regards to home training, 232 exercise group participants (88%) returned their training diaries reporting that they had accomplished the training on average three times (3.2 h/week) per week. The median total number of training sessions (supervised and home training together) was 3.8 per week (interquartile range 2.3-5.1).

Physical activity and performance. The amount of physical activity increased from baseline to 12 months by 3.10 (95% CI=0.46 to 5.74) MET-h/wk in the exercise group and by 3.57 (95% CI=0.71 to 6.42) MET-h/wk in the control group, and the increases were similar between groups [between-group training effect 0.47 (95% CI=–3.40 to 4.34) MET-h/wk; p=0.97].

Neuromuscular performance improved significantly in the training group. Among the trainees, the mean change in the figure-8 running time was –0.26 s (95% CI=–0.39 to –0.13 s), while no improvement was observed among the controls (0.07 s, 95% CI=–0.06 to 0.19 s). The between-group training effect was 0.32 s (95% CI=0.14 to 0.50 s, p<0.001).

No significant effect of the intervention was observed on cardiorespiratory fitness. The between-group effect on 2-

Table III. *Changes in quality of life (QoL) during the intervention in exercise and control groups measured by the EORTC QLQ-C30 and BR-23, FACIT-F and BDI questionnaires.*

Scale	Baseline [mean (SD)]		Change from baseline to 12-months in scores [mean (95% CI)]†		*p*-Value*
	Exercise	Control	Exercise	Control	
EORTC-QLQ-C30#					
Global health score	69.8 (17.8)	70.2 (19.9)	4.2 (1.9 to 6.6)	5.6 (3.1 to 8.1)	0.43
Physical functioning	83.5 (14.6)	80.9 (16.7)	1.9 (0.2 to 3.5)	3.4 (1.7 to 5.1)	0.21
Social functioning	88.1 (18.5)	86.2 (20.6)	5.0 (2.4 to 7.5)	8.8 (6.2 to 11.5)	0.039
Role functioning	86.9 (18.7)	86.4 (19.2)	2.4 (–0.2 to 5.0)	3.8 (1.0 to 6.5)	0.48
Emotional functioning	82.5 (16.6)	82.4 (18.4)	1.2 (–0.9 to 3.4)	1.9 (–0.4 to 4.3)	0.64
Cognitive functioning	85.4 (18.4)	83.4 (20.5)	–1.0 (–3.2 to 1.2)	2.2 (–0.1 to 4.6)	0.048
EORTC-QLQ-BR23&					
Body image	65.0 (25.8)	62.5 (28.9)	10.7 (8.1 to 13.3)	12.0 (9.2 to 14.8)	0.50
Sexual functioning	31.2 (26.2)	28.5 (26.0)	4.3 (1.5 to 7.2)	3.8 (0.7 to 6.9)	0.80
Sexual enjoyment	62.8 (25.7)	62.5 (23.2)	0.1 (–3.7 to 3.9)	1.0 (–3.2 to 5.3)	0.75
Future perspective	55.0 (27.6)	55.0 (30.0)	9.0 (5.9 to 12.2)	10.0 (6.6 to 13.4)	0.68
Adverse effects of systemic therapy	21.4 (12.2)	21.7 (15.3)	–4.2 (–5.7 to –2.6)	–6.2 (–7.9 to –4.5)	0.083
Breast symptoms	18.1 (16.1)	19.0 (16.3)	–6.2 (–8.1 to –4.3)	–7.4 (–9.4 to –5.4)	0.39
Arm symptoms	18.1 (19.0)	18.2 (17.7)	–0.04 (–2.4 to 2.3)	0.2 (–2.3 to 2.7)	0.89
FACIT-F£	40.5 (8.3)	40.9 (9.2)	2.4 (1.3 to 3.4)	2.4 (1.3 to 3.5)	0.95
RBDI§	3.5 (3.4)	3.5 (4.2)	–0.3 (–0.7 to 0.1)	–0.5 (–0.9 to –0.04)	0.50

†Model based least squares means. *Difference between exercise and control groups based on mixed effects models with measurements at baseline, 6 and 12 months. #EORTC-QLQ-C30: EORTC QoL questionnaire for cancer patients, & EORTC-QLQ-BR23: EORTC QoL questionnaire for breast cancer patients, £FACIT-F: FACIT questionnaire for fatigue, §RBDI: the Finnish modified version of Beck's 13-item depression scale.

km walk time was 0.18 min (95% CI=–0.02 to 0.37 min, p=0.15). However, it is noted that the walk time improved significantly in both groups during the intervention. In the exercise group, the mean change was –0.89 (95% CI=–1.03 to –0.76 min) min and in the control group –0.72 (–0.85 to –0.58) min.

QoL. No significant difference was found between the exercise and control groups in changes of QoL during the intervention measured by EORTC-QLQ-C30 or BR-23 module (Table III). Subgroup analyses are shown in Figure 2. No significant between-group differences were observed in depression or fatigue (Table III).

No difference was found in vasomotor symptoms between the groups [exercise group: baseline mean 0.75 (SD 0.40), mean change –0.01 (95% CI= –0.06 to 0.03; p=0.087 for treatment effect) and the control arm: baseline mean 0.75 (SD 0.39), mean change –0.07 (95% CI=–0.12 to –0.02)]. Neither was any difference detected in sleeping problems [exercise group: baseline mean 0.44 (SD 0.32), mean change –0.02 (95% CI=–0.07 to 0.01); control arm: baseline mean 0.43 (SD 0.32), mean change –0.05 (95% CI= –0.09 to –0.01), p=0.44 for between-group training effect].

Changed physical activity, performance and QoL. The relationship between changes in physical activity and physical performance and QoL, (global health score of EORTC-QLQ-C30), depression (BDI) and fatigue (FACIT-F) are shown in Figure 3. All the study participants were included in these secondary analyses irrespective of their study group. The pooled data was broken down by physical activity or performance tertiles. There was a significant linear trend between higher physical activity and improved QoL and recovery from fatigue. No significant relationship was detected between physical activity and depression or between physical performance (figure 8-running or 2-km walking test) and QoL, fatigue or depression.

Discussion

The BREX study is the largest randomized prospective physical exercise intervention trial of breast cancer survivors post-treatment and so far the only one being implemented immediately after adjuvant treatment. Both study groups increased their amount of physical activity throughout the 12-month period. The intervention had no effect on cardiorespiratory fitness or the QoL of the exercise group

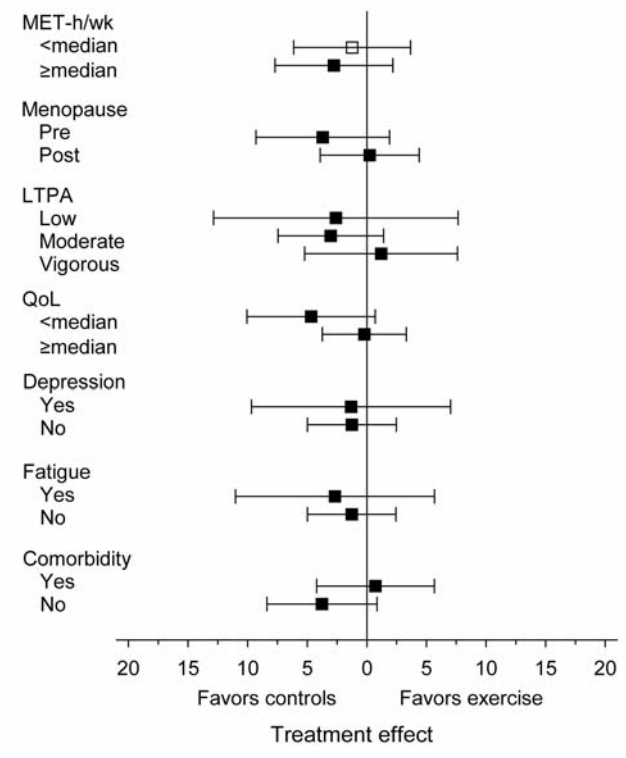

Figure 2. *The effect of exercise intervention on QoL measured by the EORTC-QLQ-C30 questionnaire in different subgoups. Univariate analyses. MET-h/wk: Metabolic equivalent (MET) hours per week, LTPA: leisure time physical activity.*

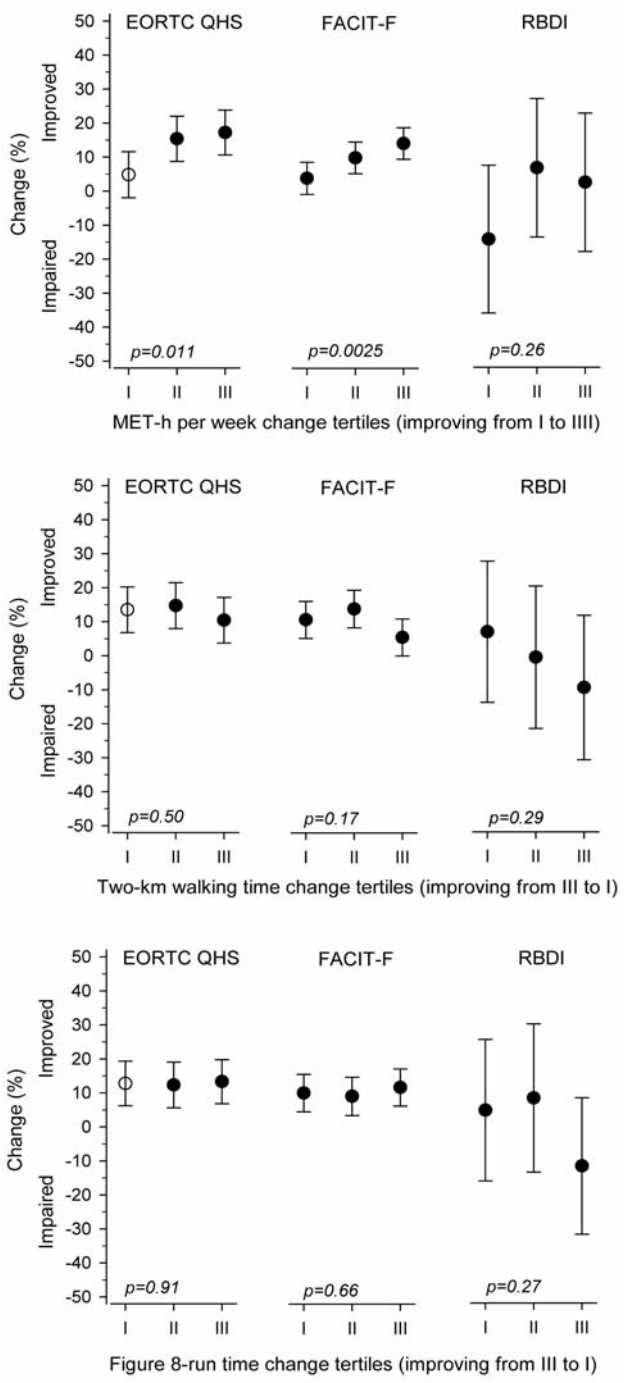

Figure 3. *Relationship between changes in physical activity and performance and in QoL. Values corresponding to MET-h per week change tertiles are: I ≤–3.58, II -3.54–7.04, III ≥7.06; 2-km walking time (min) change tertiles I ≤–1.22 , II –1.20–0.37, III ≥–0.35; and figure 8 run time (s) change I ≤–0.42, II –0.41–0.19, III ≥0.20, respectively. p-values for linearity are adjusted for age, menopausal status and body mass index (BMI) at baseline. EORTC QHS: Health score of EORTC-QLQ-C30 QoL questionnaire for cancer patients, FACIT-F: fatigue measured by FACIT questionnaire for fatigue, RBDI: depression measured by the Finnish modified version of Beck's 13-item depression scale.*

participants, even if the exercise intervention significantly improved their neuromuscular performance. Since the trial was not blinded we cannot rule out the possibility that the participation in the study itself could also have motivated the control participants and thus improved their QoL, given that the generally increased physical activity in both groups was observed to significantly correlate with improved QoL.

Previous literature indicates that physical exercise training is effective in improving cardiorespiratory fitness of breast cancer survivors (3-5). However, when considering the post-treatment period only, improvements have been seen particularly in muscle strength, while the effect on aerobic fitness has not been completely consistent (8). Correspondingly, our exercise intervention improved the neuromuscular performance of the exercise group of participants, but the effect on cardiorespiratory fitness was less evident. However, this could be related to significant activation of all study participants including the controls. After enrollment into the study, the weekly time spent in leisure-time physical activity increased by 17% (3 MET-h/wk) in both groups. The increase, corresponding to one extra hour of brisk walking per week, can be considered clinically relevant and it also appeared to account for the improved walking time.

Alfano *et al*. (46) showed that nearly 32% of long-term breast cancer survivors reported increasing physical activity after their breast cancer diagnosis. Our patients' physical activity was already relatively high at baseline, and as Alfano *et al*. indicated, it subsequently increased during the first year. Findings from previous interventions support the notion that the encouragement to exercise by a physician or telephone calls are sufficient to increase physical activity (47, 48). In our case, participation in the exercise intervention trial itself may have served as a motivator to further increase the amount of physical activity and thus lead to improved cardiorespiratory fitness. However, the supervised training boost by jumps and leaps significantly improved neuromuscular performance and hip bone density especially in pre-menopausal women, which is important in reducing fracture risk later in life (31).

In addition to the positive training effects on physical performance, several previous exercise interventions of breast cancer survivors have demonstrated some effects on QoL (6-11, 24). In the review by Spence et. al. who concentrated on post-treatment studies (22), only four out of 10 included studies were, however, randomized controlled trials. The largest study included in the review by Thorsen *et al*. (49) (111 participants), demonstrated an effect on cardiorespiratory fitness, but no effect on patients' experience of fatigue, mental distress, or health-related QoL. In their study, Cadmus *et al*. (50) also showed no impact of 6 months of exercise training on QoL in 112, either recently diagnosed or post-treatment breast cancer survivors, but as in our study, the baseline physical performance of participants was already relatively high. In our study, no intervention effect on QoL existed, but there was a significant spontaneous improvement in QoL and fatigue in both study groups. Moreover, the increased physical activity in both groups was observed to significantly correlate with improved QoL and fatigue, such that the control group motivation may have affected the result.

Another potential reason that we did not observe any effects on QoL may, at least partly, be the insensitivity of the chosen QoL questionnaires. The disease-specific QoL questionnaires such as EORTC-QLQ-C30 are designed to evaluate the QoL of cancer patients, not of cancer survivors. The items are intended to be delivered during illness and related treatment, and their relevance may diminish after the illness is conquered and the acute cancer treatment is finished. A diagnosis-independent measure of QoL might be more pertinent for intervention studies focusing on survivors. Indeed, Adamsen *et al*. (51) found that exercise did have a significant effect in 7 out of 10 subscales of general well-being of cancer survivors with different malignant diseases when measured by the Medical Outcome Study Short Form-36 health survey questionnaire (MOS SF-36), but the effect was found only in one out of eight subscales of QoL when measured by the EORTC-QLQ-30. Although our study patients' global health scores, and physical, cognitive and social functioning at baseline were slightly lower than in the general population (33), the QoL of the study patients at the start of the study was relatively high and they might have had little room to improve.

The main strength of the present study is its size, being by far the largest prospective randomized physical exercise intervention trial of breast cancer survivors published so far. The recruitment rate of the patients was also high: 78% from those considered eligible for the study and 31% from all those screened for the study (32). Furthermore, to facilitate the broad applicability of the exercise program among breast cancer survivors in general, the training was designed to be easily performed, without the need for extensive training equipment. The progression of the exercise program was based on perceived physical exertion of each patient, and the feasibility of the exercise program for breast cancer survivors was evaluated in our earlier pilot study (34).

The main limitation of this study is the considerable motivation of the control patients. In the following, we discuss problems related to selection, adherence, and non-blind study design that may have obscured the intervention effects. Despite the high recruitment rate of the eligible patients, the participation criteria selected populations that consist of mainly active persons. In our study, only a quarter of participants were clearly sedentary according to the physical activity questionnaire carried-out before the breast cancer diagnosis. This contributes to a ceiling effect in the ability to detect intervention effects; in other words, selected patients with an already healthy lifestyle and good performance have less capacity to benefit from the intervention. Such a selection also increases the risk of "contamination" of the control group. Courneya *et al*. found that past exercise was the strongest independent predictor of exercise contamination (52), and concluded that most active patients should be excluded from randomized exercise intervention studies. Secondly, the relatively low adherence to the supervised exercise training in our study may have impaired the anticipated effects of the intervention. Limited adherence is a well-known problem in lifestyle interventions, especially in those with a long duration. Thirdly, any study design, such as the present one, where the patients are randomly allocated to two groups of which one receives an intervention while the other does not, and both are monitored in terms of outcome variables, works reasonably well when the treatment is medical and given in a blinded fashion. However, the case is different when the treatment is largely behavioral. Clearly, from a psychological point of view, participation in the study is a behavioral intervention in itself. A more appropriate description of the study would be that we actually had two intervention groups of which one had an additional module, namely the actual exercise. This is also consistent with the observation that physical activity increased in both groups.

In summary, the present study of 500 breast cancer survivors failed to demonstrate superiority of the 12-month supervised vigorous aerobic exercise and home training over the control arm in improving QoL. This, however, seems to be related to the

significant motivation of the control patients and/or significant spontaneous recovery of the participants during the post-treatment period shortly after the adjuvant treatments. Nevertheless, any increase in physical activity, whether triggered by the intervention or spontaneous, was related to improved QoL. Thus, even a motivation of breast cancer survivors to exercise post-treatment could be sufficient to improve their physical activity and QoL, at least among survivors who are inclined to be physically active. Future studies comprising of more targeted interventions on a needs-based approach could offer a more effective way to study the role of physical exercise in the rehabilitation of cancer survivors.

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