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The Effect of Non-Supervised Physical Activity before and after Breast Cancer Surgery on Quality of Life, Results from a Randomized Controlled Trial (PhysSURG-B)

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Abstract

Purpose: The trial PhysSURG-B examined prehabilitation before breast cancer surgery by randomizing patients to a non-supervised physical activity or a control group. Within the trial, the effects on both short and long-term Quality of Life (QoL) was examined, with a pre-specified subgroup analysis of patients receiving adjuvant chemotherapy.

Methods: Female patients planned for surgery were randomly assigned to either an intervention of 30 min of self-administered physical aerobic activity daily 2 weeks before and 4 weeks after surgery, or control. QoL was assessed with questionnaires at baseline, 4 weeks and 12 months post-op using the instruments FACT-B, RAND-36 and EQ-VAS.

Results: Out of 354 included participants at 12 months after surgery, 287 were available for QoL analysis. FACT-B scores at 4 weeks and 12 months showed no differences between intervention compared to control, Odds Ratio (OR) of 0.975 and 0.883, respectively. There was no difference in EQ-VAS seen comparing intervention to control at 4 weeks and 12 months, respectively, OR=1.163 and 0.817. RAND-36 domains "role limitations due to physical health" and "pain" showed a decrease at 4 weeks in both groups, returning towards baseline at 12 months follow-up. The subgroup of patients receiving adjuvant chemotherapy had significantly lower QoL measured using FACT-B at 12 months compared to patients not receiving chemotherapy (OR=0.475).

Conclusion: An intervention of non-supervised physical activity before and after surgery for breast cancer had no effect on short or long-term QoL, neither in the subgroup of patients receiving adjuvant chemotherapy.

Trial Registration: ClinicalTrials.gov registration number: NCT 02560662. Registered 25 September, 2015.

Keywords Breast cancer; Surgery; Physical activity; Prehabilitation; Quality of life

Abbreviations

ASA: American Society of Anesthesiologists; AUDIT-C: Alcohol Use Disorders Identification Test-Consumption; BMI: Body Mass Index; CI: Confidence Interval; EQ-VAS: EuroQol-Visual Analogue Scale; FACT-B: Functional Assessment of Cancer Therapy-Breast; FACT-G: Functional Assessment of Cancer Therapy-General; FACT-GP: Functional Assessment of Cancer Therapy-General Population; MID: Minimally Important Difference; OR: Odds Ratio; PRO: Patient-Reported Outcome; QoL: Quality of Life; RAND-36: RAND 36-Item Health Survey 1.0; SGPALS: Saltin Grimby Physical Activity Level Scale; SD: Standard Deviation; TOI: Trial Outcome Index

Introduction

Breast cancer affects more than 2 million women worldwide every year [1]. Patient reported

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outcomes [2-4], such as quality of life, are important when evaluating the effect of breast cancer treatment on survivorship [3-6], where common side-effects of treatment, such as fatigue [6], musculoskeletal pain and stiffness [5] are known to have negative impact on quality of life. In observational studies [7-9], regular physical activity after a breast cancer diagnosis has been associated with an increased breast cancer-specific and overall survival. In patients undergoing adjuvant treatment for breast cancer, interventions with physical exercise during or after treatment have been reported to reduce fatigue [10-12] and to increase quality of life [13-16]. Supervised exercise trials are likely more effective but have the disadvantage of sampling bias, higher cost and limited outreach potential [17]. A systematic review showed that home and center-based interventions for cardiac rehabilitation were comparable [18], and another review showed a small to moderate positive effect on physical activity levels even from counseling [19]. Prehabilitation with physical activity before breast surgery have the potential to improve resilience against the negative impact of breast cancer treatment, and two studies have been published regarding the feasibility of prehabilitation in this setting [20,21]. To our knowledge, there are no reports of any randomized trials of prehabilitation, consisting of physical activity before breast cancer surgery, and which address short- and long-term QoL. We have previously published the results of the PhysSURG-B trial, which randomized patients to either a self-administered intervention with pre- and postoperative physical activity or a control group. In short, the intervention did not improve the primary endpoint of recovery, neither was there any effect on complications. However, the effects on quality of life could potentially be more important and the aim of this study was to evaluate the potential effect of this intervention on the pre-specified secondary outcomes of short- and long-term quality of life.

Patients and Methods

Study design and setting

We report 4 weeks and 12 months follow-up data from the PhysSURG-B randomized, controlled, prospective interventional trial evaluating an intervention of added aerobic physical activity before and after breast cancer surgery. The study protocol and primary outcome of self-reported physical recovery at 4 weeks after surgery have been published previously [22]. Participants were recruited from three surgical departments in the Western Region of Sweden between November 2016 and December 2018. Participants were randomized to intervention with non-supervised physical activity, or control.

Participants and randomization

Female patient's ≥ 18 years, diagnosed with stage I-III breast cancer, scheduled for primary surgery were randomized into two groups, intervention and control. Exclusion criteria were male sex, stage IV disease, neoadjuvant treatment and inability to understand the study information or perform the intervention. Neither research nurses nor participants were blinded, due to the nature of the intervention, but patient allocation was not actively briefed to healthcare personnel involved in the routine care of the patient.

Intervention and control

The intervention in the PhysSURG-B trial has been described in detail previously [22]. In summary, patients in the intervention group received an individual consultation with a physiotherapist and were instructed to add 30 min of daily aerobic physical activity, 2 weeks ± 1 week before and 4 weeks after breast cancer surgery. The intervention was instructed to be of medium intensity resulting in shortness of breath but with ability to talk, of the participant's own choice after suggestions from the physiotherapist, and to be performed without supervision. In addition, two follow-up telephone calls were made during the intervention period. Added physical activity was registered in a diary. Adherence to the intervention was considered if added physical activity was registered >10 days preoperatively and >20 postoperatively. This cut-off was chosen being in accordance with international guidelines for recommended physical activity [23]. The participants in the control group received brief information regarding the study aim, being to examine if physical activity before and after surgery improves outcome, in order to make informed consent. However, the control groups were not aware of the amount or duration of the intervention and were not advised regarding physical activity. All patients received standard information regarding early mobilization and shoulder movement after surgery according to routine care. The baseline level of physical activity was measured with the Saltin Grimby Physical Activity Level Scale (SGPALS) [24].

Outcome measures

Patient-reported outcome measures of quality of life was a secondary outcome in the PhysSURG-B-trial, reported at three time points from which change from baseline to 4 weeks and 12 months respectively after surgery was calculated. The following validated instruments were used (Swedish versions):

Functional Assessment of Cancer Therapy-Breast (FACT-B) [25], including FACT-B Total Score, FACT General (FACT-G) Total Score and FACT-B Trial Outcome Index (TOI).

RAND36-Item Health Survey 1.0 [26].

EuroQol- visual analogue scale (EQ-VAS) [27].

A single-item QoL question validated and used previously [28-30] asking "How would you describe your quality of life the last month?" Answering alternatives on a scale from "0" (worst possible quality of life) to "6" (best possible quality of life).

Sample size and statistical analysis

The sample size calculation for PhysSurg-B was performed for the primary outcome measure of physical recovery 4 weeks after surgery. No sample size calculation was performed for the secondary outcome quality of life. A statistical analysis plan was written before any of the analyses were performed. The analyses were according to randomization (intention-to-treat analysis). Baseline demographic data (patient and tumour characteristics and type of surgery) were described per allocated group. Total scores and subscale scores of the QoL instruments were calculated. The scores (total score for FACT-B, EQ-VAS) had skewed and multi-modal distribution making a Gaussian linear model invalid. Therefore, the effect of the intervention was estimated using an ordinal regression model [31]. The baseline measurements were included as a covariate along with fixed factors for study group, time and their interaction. The single item QoL question was dichotomized into "low QoL" (scale option 1-4) and "high QoL" (scale option 5-6) before analysis. For all instruments, the primary analysis was the unadjusted. Adjuvant chemotherapy was imbalanced across the study groups and therefore, as an additional analysis adjuvant chemotherapy was adjusted for. Also, a subgroup analysis of patients given adjuvant chemotherapy was conducted. The results are presented as Odds Ratios (OR) for intervention scoring higher than the control with 95% Confidence Intervals (CIs). All tests were two-sided and a statistical significance level of 5% was used.

We made no adjustments for multiple comparisons. No imputations were made. All statistical analyses were performed with SAS® 9.4.

Ethics

The Regional ethical review board in Gothenburg, Sweden approved the trial (registration numbers 522-15, T1152-16, T700-17, T160-18). The procedures used in this study adhere to the tenets of the 1964 Helsinki declaration with amendments. Informed consent was obtained from all individual participants included in the study. PhysSURG-B was registered at ClinicalTrials.gov (NCT 02560662) September 25, 2015.

Results

The participant flow throughout the trial is visualized in Figure 1. At 12 months after surgery 354/400 participants (88.5%) remained in the trial, 44 patients withdrew informed consent (18 in the control group and 26 in the intervention group) and one participant in each group had died. 297/354 (84%) returned their questionnaires (return rate 83% to 90% for the different time points), with no difference between the study groups. Complete data for QoL assessment at all three time-points was reported by 81% (287/354 participants), 148 in the control group and 139 in the intervention group respectively. Baseline patient demographics, tumour characteristics and type of surgery were similar in the two study groups (Table 1, 2). Median age was 63 years (mean 62 years, range 30 to 89 years). More than thirty percent of the participants reported a risk consumption of alcohol according to Alcohol Use Disorders Identification Test (AUDIT-C), and two thirds of the patients had at least one comorbidity where cardio-vascular disease was the most frequent. The majority of patients underwent breast-conserving surgery (79%) and sentinel lymph node biopsy (95%) (Table 2). To 94% of the participants, adjuvant treatment was given. Endocrine therapy was received by 76% in the control and 79% the intervention group, respectively. Radiotherapy was administered to 75% in the control and 83% in the intervention group, respectively. Adjuvant chemotherapy was given to 26% in the control compared to 37% in the intervention group. No severe adverse events related to the intervention were reported. Adherence to the intervention was less than 60% according to the physical activity diary. Physical activity level measured with SGPALS, at baseline and at the end of the intervention period, showed an increased physical activity in 18% of the patients in the intervention group, compared to 11% in the control group.

FACT-B

At baseline, 4 weeks and 12 months the median FACT-B scores were 116.8, 121.5 and 121.9 in the control group, compared

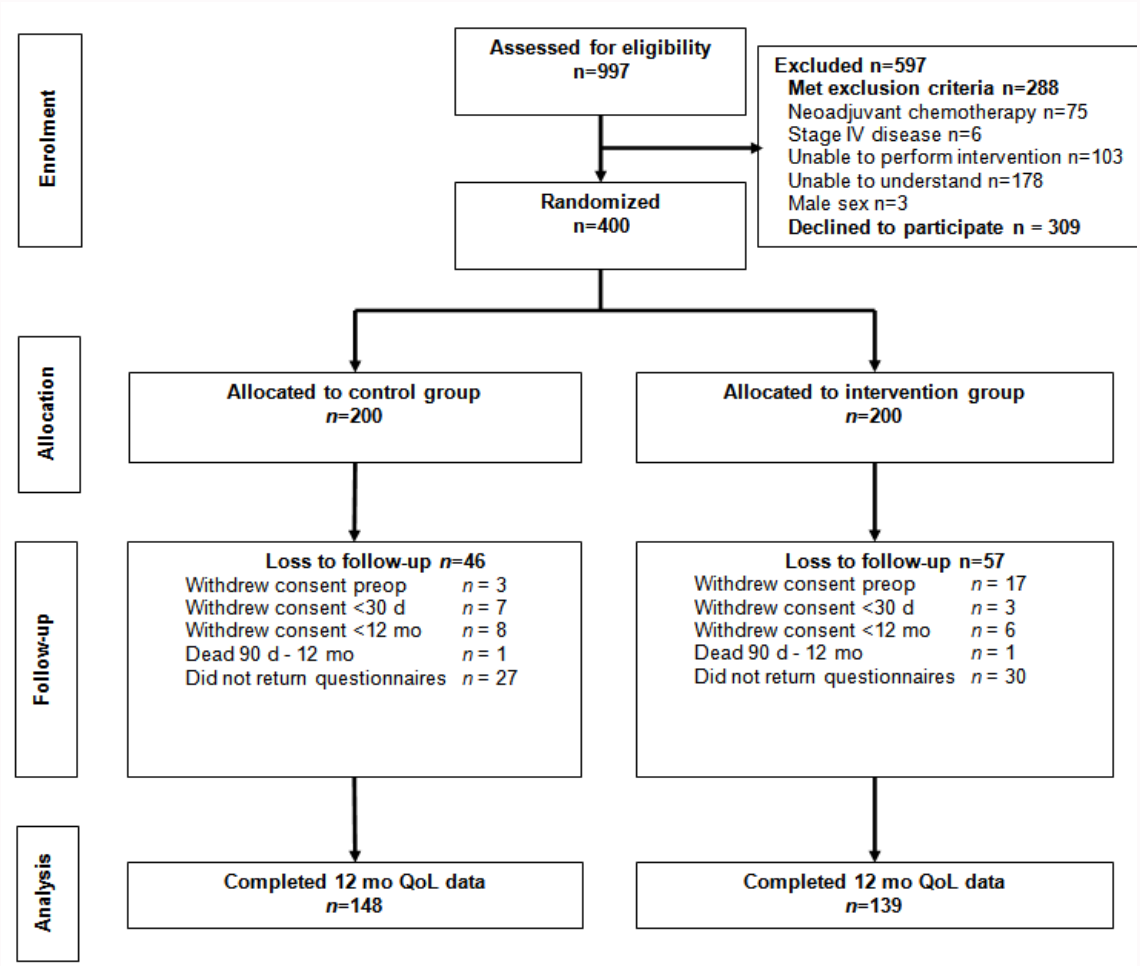

Figure 1: CONSORT flow diagram for the PhysSURG-B trial.
At baseline, 340/380 patients (90 %) returned the baseline questionnaire. At 4 weeks after surgery, 370/400 patients (93 %) remained in the trial, of these 318/370 (86 %) returned the 4 week questionnaire, 89% in control and 83% in intervention. At 12 months, the questionnaire was returned by 297/354 patients (84 %), 154/181 (85%) in control and 143/173 (83%) in intervention.

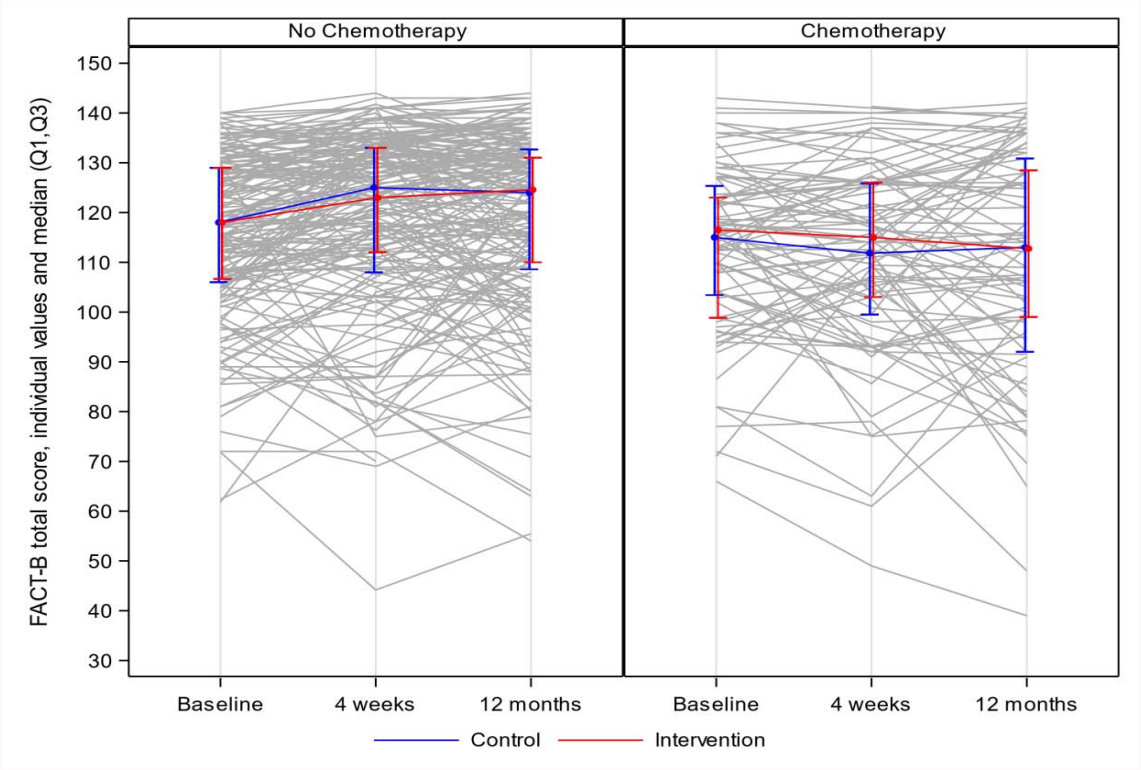

Figure 2: FACT-B spaghetti plot at baseline, 4 weeks and 12 months for patients receiving chemotherapy compared to no chemotherapy. Participants (both intervention and control) with adjuvant chemotherapy had significantly lower FACT-B total score, with OR 0.418 (95% CI 0.260-0.670) at 4 weeks and OR 0.475 (95% CI 0.300-0.753) at 12 months, compared to no chemotherapy.

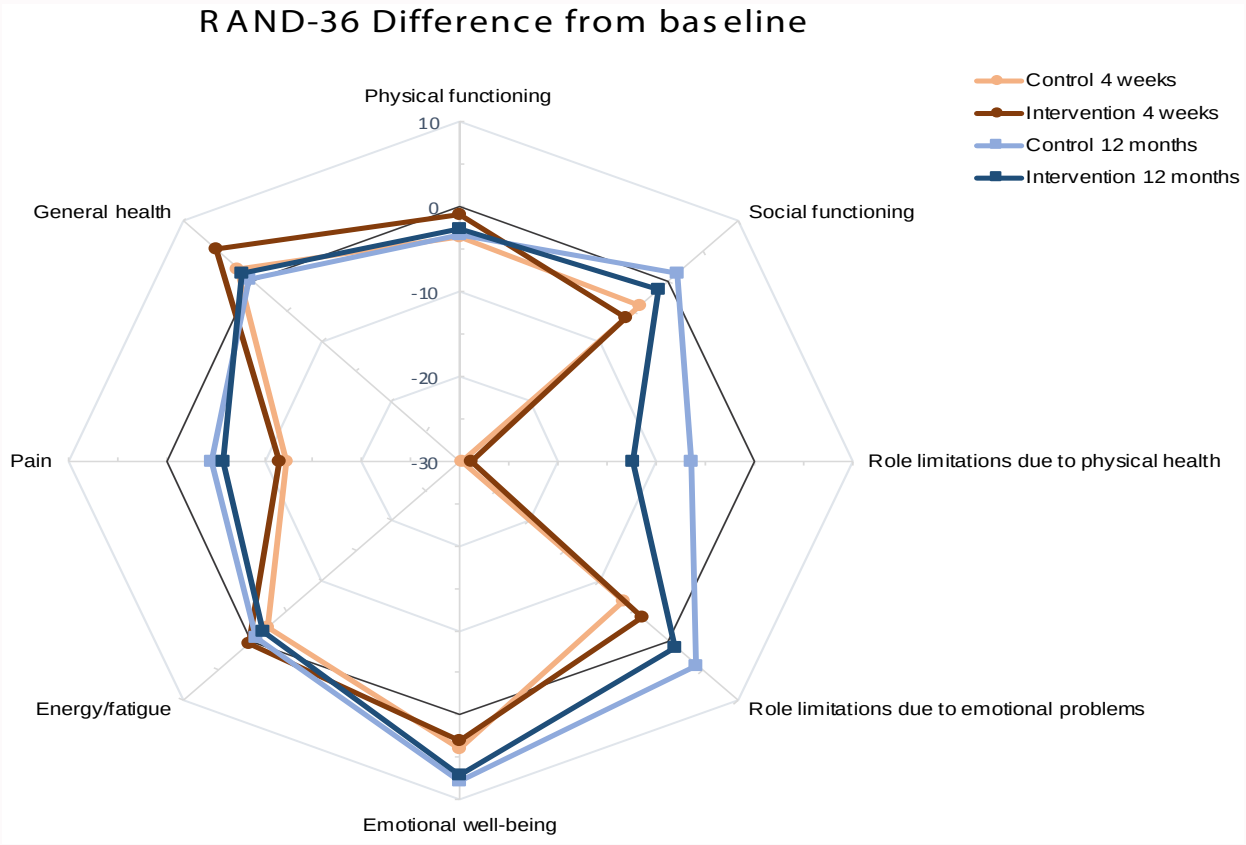

Figure 3: Difference from baseline to 4 weeks and 12 months as randomized for the eight domains of RAND-36.

Table 1: Baseline characteristics of study participants.

	Control n=148	Intervention n=139
Age, years		
median (IQR)	64 (54-72)	62 (51-68)
range	38-89	30-84
BMI, kg/m²		
median (IQR)	25	24.6
range	19.0-38.5	17.7-47.6
missing	8	11
ASA		
I	58/148 (39%)	73/137 (53%)
II	82/148 (55%)	62/137 (45%)
III	8/148 (5%)	2/137 (1%)
IV	0	0
Missing	0	2
Comorbidities		
None	52/142 (37%)	46/135 (34%)
Diabetes	10/147 (7%)	8/139 (6%)
Cardiovascular disease	48/142 (34%)	33/135 (24%)
Pulmonary disease	5/142 (4%)	10/135 (7%)
Psychiatric illness	25/142 (18%)	21/135 (16%)
Chronic pain	13/142 (9%)	11/135 (8%)
Active smoking		
Yes	10/145 (7%)	3/138 (2%)
No	135/145 (93%)	135/138 (98%)
Missing	3	1
Alcohol consumption		
AUDIT-C score <4	94/143 (66%)	93/137 (68%)
AUDIT-C score ≥ 4[1]	49/143 (34%)	44/137 (32%)
Missing	5	2
Physical activity at baseline[2]		
1 (inactive)	23/147 (16%)	18/137 (13%)
2 (low)	97/147 (66%)	85/137 (62%)
3-4 (moderate-vigorous)	27/147 (18%)	34/137 (25%)
Missing	1	2
Residence		
Rural	13/147 (9%)	13/138 (9%)
Urban	134/147 (91%)	125/138 (91%)
Missing	1	1
Educational level		
University education or higher	72/147 (49%)	89/138 (64%)
12 years or less	75/147 (51%)	49/138 (36%)
Missing	1	1

ASA: American Society of Anesthesiologists; BMI: Body Mass Index; SGPALS: Saltin Grimby Physical Activity Level Scale Valid percent given
[1]Risk consumption level defined as AUDIT-C-score ≥ 4
[2]Measured using SGPALS at baseline

Table 2: Tumour characteristics and treatment.

	Control n=148	Intervention n=139
Type of breast surgery		
Breast conserving surgery	114/148 (77%)	113/139 (81%)
Mastectomy	34/148 (23%)	26/139 (19%)
Missing	0	0
Type of axillary surgery		
non-ALND[1]	142/148 (96%)	131/139 (94%)
ALND	6/148 (4%)	8/139 (6%)
Missing	0	0
Tumour type		
Invasive cancer	137/148 (93%)	129/139 (93%)
Cancer *in-situ*	11/148 (7%)	10/139 (7%)
Other	0	0
Missing	0	0
Tumour size (mm), median (IQR)	16 (11-23)	17 (11-25)
Estrogen receptor positive (ER+)	118/148 (86%)	114/139 (89%)
Progesterone receptor positive (PR+)	103/148 (75%)	97/139 (76%)
Her2-positive (HER2+)	16/148 (12%)	10/139 (8%)
Nodal metastasis (N+)	26/148 (19%)	36/139 (27%)
Adjuvant treatment, *any*	140/148 (95%)	129/137 (93%)
Radiotherapy	111/148 (75%)	113/137 (83%)
Chemotherapy	39/148 (26%)	50/137 (37%)
Endocrine therapy	113/148 (76%)	108/137 (79%)
Bisphosphonates	17/148 (12%)	24/137 (18%)
Anti-Her-2-therapy	12/148 (8%)	10/137 (7%)
Missing	0	2

ALND: Axillary Lymph Node Dissection, SGPALS: Saltin Grimby Physical Activity Level Scale
[1]Non-ALND includes Sentinel Lymph Node Biopsy and no axillary surgery

Table 3: Results for FACT-B total score, EQ-VAS and General QoL question as randomized at 4 weeks and 12 months.

	Odds Ratio Intervention/Control (95% CI)		
	Baseline	**4 weeks**	**12 months**
FACT-B			
Crude	1.023 (0.676-1.550)	0.975 (0.636-1.495)	0.883 (0.581-1.342)
Adjusted[1]		1.073 (0.697-1.651)	0.997 (0.654-1.520)
EQ-VAS			
Crude	0.869 (0.576-1.312)	1.163 (0.760-1.779)	0.817 (0.536-1.244)
Adjusted[1]		1.254 (0.816-1.926)	0.852 (0.559-1.300)
QoL question[2]			
Crude		0.91 (0.25-3.32)	1.07 (0.30-3.86)

FACT-B: Functional Assessment of Cancer Therapy-Breast, total score; CI: Confidence Interval
[1]adjusted for adjuvant chemotherapy
[2]Dichotomised into "low QoL" and "high QoL"

to 117.5, 121.0, 119.1 in the control group (Table 4). Comparing the intervention to the control group, the odds ratio for FACT-B score at 4 weeks was 0.975 (95% CI 0.636-1.495) and at 12 months 0.883 (95% CI 0.581-1.342) (Table 3). When adjusted for adjuvant chemotherapy, the odds ratio at 12 months was 0.997 (95% CI 0.654-1.520). For the subset of patients who received adjuvant chemotherapy, a significantly lower FACT-B score at 4 weeks and 12 months was seen, with an odds ratio of 0.418 (95% CI 0.260-0.670)

Table 4: FACT-B score as randomized at baseline, 4 weeks and 12 months.

		Control n=148				Intervention n=139			
		Mean	Median	± SD	Missing	Mean	Median	± SD	Missing
FACT-B (0-148)	Baseline	115.3	116.8	16.6	11	114.7	117.5	16.7	8
	4 weeks	117	121.5	18.2	8	116.3	121	20	10
	Change[1] to 4 weeks	1.8	3	13.1		2.5	2	12.5	
	12 months	116.3	121.9	20.3	2	115.8	119.1	19.9	3
	Change[1] to 12 months	1.3	3.5	16.2		0.9	2.8	14.6	
FACT-G (0-108)	Baseline	86.2	87.8	13.7	7	85.7	87.6	13.8	5
	4 weeks	88.5	93	14.6	8	87.2	92	16.4	10
	12 months	88.4	93	16.3	0	87.8	92	15.6	2
Breast cancer Subscale (0-40)	Baseline	28.8	29	4.5	5	28.9	30	4.5	5
	4 weeks	28.5	29	5	5	29.2	30	4.8	8
	12 months	27.9	29	5.5	0	28.1	29	5.4	1
Physical well-being (0-28)	Baseline	24.8	26	3.7	3	24.7	25.8	3.3	1
	4 weeks	24.1	25	3.8	6	24	26	4.5	8
	12 months	23.8	25	4.6	0	23.4	24.8	4.6	1
Emotional well-being (0-24)	Baseline	16.5	17	4.9	2	16.8	18	4.8	1
	4 weeks	19.3	20	4.6	6	18.7	20	5.2	9
	12 months	20	21	4	1	20.1	21	3.9	2
Social well-being (0-28)	Baseline	24.2	25.7	3.8	5	23.7	25	4.4	1
	4 weeks	24.7	25.8	3.9	6	23.9	25	4.3	9
	12 months	23.2	24.3	5.1	2	22.8	24	4.6	1
Functional well-being (0-28)	Baseline	20.5	21	5.1	2	20.4	21	5.5	0
	4 weeks	20.4	21	5.7	6	20.8	22	5.6	8
	12 months	21.4	22	5.6	0	21.6	22.5	5.3	1
FACT-B TOI	Baseline	74.2	76.5	10.9	8	73.9	76	11.3	6
	4 weeks	73	75	12.7	7	73.9	78	13.4	8
	12 months	73.1	77	13.6	0	73	77	13.8	2

FACT-B: Functional Assessment of Cancer Therapy-Breast; FACT-G: Functional Assessment of Cancer Therapy- General; TOI: Trial Outcome Index; SD: Standard deviation

[1]Change from baseline

Table 5: EQ-VAS at baseline, 4 weeks and 12 months, as randomized.

	Control N=148			Intervention N=139		
	Mean (Min - Max)	Median	± SD	Mean (Min - Max)	Median	± SD
Baseline	76 (5-100)	80	18	73 (0-100)	80	20
4 weeks	76 (20-100)	80	18	75 (20-100)	80	19
Change[1] to 4 weeks	-0.0 (-50-40)	± 0	15.8	+3.2 (-60-90)	± 0	18.2
12 months	79 (30-100)	80	17	76 (27-100)	80	19
Change[1] to 12 months	+2.5 (-55-45)	± 0	16	+2.8 (-40-98)	± 0	20.2

SD: Standard Deviation

[1]from baseline

and 0.475 (95% CI 0.300-0.753), respectively when compared to those who did not receive chemotherapy (Figure 2), but with no significant difference based on study group. The FACT-G scores and the breast cancer subscales showed no difference over time or between the study groups (Table 4). FACT-G mean baseline scores were 86.2 for control and 85.7 for intervention (median 87.8 and 87.6, respectively).

EQ-VAS

EQ-VAS median score was 80 at all time points, and there were no differences seen between the study groups (Table 5). During the active part of the intervention (from baseline to 4 weeks post-op), the odds ratio was 1.163 (95% CI 0.760-1.779) for the intervention compared to the control group. At 12 months the odds ratio was 0.817 (95% CI 0.536-1.244), and adjusted for chemotherapy 0.852 (95% CI 0.559-1.300) (Table 3). For all participants, regardless of study group, EQ-VAS at 4 weeks had an odds ratio of 0.557 (95% CI 0.350-0.886), and at 12 months an odds ratio of 0.656 (95% CI 0.417-1.032) for chemotherapy compared to no chemotherapy.

RAND-36

Supplementary Table 1: RAND 36 at baseline, 4 weeks and 12 months postoperatively as randomized. Mean values for the eight domains in RAND-36.

	CONTROL						INTERVENTION					
	Baseline		4 weeks		12 months		Baseline		4 weeks		12 months	
DOMAIN	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Physical functioning	85.64	18.8	82.25	19.2	82.81	20.4	87.73	15.2	86.91	14.2	85.04	16.9
Social functioning	82.4	21.5	78.58	23	83.87	22.8	82.73	23.2	76.81	26.1	81.3	24.7
Role limitations due to physical health	76.19	37.3	47.46	44.6	70.21	40.2	82.97	31.4	54.77	42.4	71.11	38
Role limitations due to emotional problems	73.02	36.2	65.21	41.4	76.87	35.2	74.45	36.2	70.48	40.4	75.98	37.6
Emotional well-being	68.05	19.3	71.8	19.1	75.92	18.4	69.17	20.1	72	21.5	76.12	19.4
Energy/fatigue	65.54	19.4	62.9	21.5	65.14	23.5	65.18	22.9	65.69	23.6	63.69	23.5
Pain	81.95	23.3	69.5	23.6	76.86	27.9	82.02	21.8	70.49	24.8	74.66	27.5
General health	67.28	19.8	69.4	69.4	67.65	23	65.22	19.4	71.19	20.4	66.57	22.4

SD: Standard Deviation

When analyzing the RAND-36 questionnaire, there was a decline in the domains "role limitations due to physical health" and "pain" at 4 weeks postoperatively, with no difference between the study groups. At 12 months participants had to a large extent resumed their baseline QoL (Figure 3 and Supplementary Table 1).

General QoL question

Analysis of the dichotomized QoL question, "How would you describe your quality of life the last month?" resulted in no difference between the intervention and control group, neither at 4 weeks (OR=0.91, 95% CI 0.25-3.32) nor at 12 months (OR=1.07, 95% CI 0.30-3.86) (Table 3).

Discussion

The results from this randomized trial examining the effect of moderate physical activity as prehabilitation in women undergoing breast cancer surgery did not show any effect on quality of life at 4 weeks or 12 months after surgery. Very reassuring is the fact that after 12 months most patients returned to their baseline QoL, even after receiving adjuvant treatments. This may in part be explained by a high baseline level of QoL in breast cancer patients, as also seen in our trial, and difficulties to detect and/or discriminate improvements from this level. Previous studies on quality of life during adjuvant treatment [16] have primarily investigated effects following supervised, high intensity exercise interventions for a longer period of time [12]. Even with such intense exercise interventions, significant improvements in quality of life have not been reported [12]. The aim of our trial was to investigate the effect of a simple non-supervised intervention, in keeping with national and international recommendations regarding physical activity for the general population [23]. The intervention was designed based on two major assumptions. The first was to design an intervention with a potential for high external validity, being easily implementable in the care pathway for breast cancer treatment with a minimum of economic and organizational impact. Most studies so far have used extensive supervised physical exercise programs with limited possibility of implementation in routine health care, where specifically organizational matters have been identified as main barriers [32]. Secondly, we wanted to investigate the effect of introducing the intervention at the time of diagnosis, as this has been reported to increase the possibility that a patient actually increases their physical activity. We considered the interval between diagnosis and treatment a window-of-opportunity for changes in habits [33]. However, the results showed a very modest increase in physical activity, 18% of the patients in the intervention group compared to 11% in the control group. This is important information when designing future trials, where even more research is needed on how to motivate patients to increase their levels of physical activity. The duration of physical activity is another important factor to consider. Ideally a phase of prehabilitation should probably be longer than 2 to 3 weeks; however this is less feasible in patients scheduled for cancer treatment where waiting time to treatment should be kept short. Also, the intensity of physical activity, and whether it is supervised or not, are important factors. However, previous studies showed that higher volume of exercise did not necessarily give a greater effect. Aerobic training for 300 min per week did not lead to a better result than the public health recommendation of 150 min/week, the same recommendation that is the base for the intervention in this trial [34]. Yet another trial showed that there was no difference between a higher volume of combined aerobic and resistance training for 50 min to 60 min and a lower volume of only aerobic training for 25 min to 30 min in a general breast cancer population [35]. The FACT-G score in our trial cohort revealed a higher level of QoL, with a mean baseline score of 86, compared to 77 in the normative data for the general Swedish female population sample (pro-rated mean FACT-GP scores) [36]. The FACT-G Minimally Important Difference (MID) is considered to be approximately 5-6 in a breast cancer population, with a MID 7-8 for the total FACT-B score [37]. The higher FACT-G score in our sample of breast cancer patients could suggest a sampling bias, where individuals with lower QoL declined participation. Another possible explanation is the difference in age distribution in our study sample (mean 62 years) compared to the previously published population sample with a manage of 49 years [36], as a higher age was positively correlated to higher FACT-GP score. Moreover, the FACT-G and FACT-B scores we present are similar to previously published results for breast cancer patients [38-40]. Over time, the FACT-B scores were stable regardless of study group and treatment factors, except for the subgroup of patient receiving adjuvant chemotherapy, where a significant decline was seen. Interestingly, this was not only seen at 12 months but also at 4 weeks, when the participants had not yet started their adjuvant chemotherapy but had gained information about the projected start of treatment. EQ-VAS median score was stable regardless of study group and time for assessment and all changes seen in mean scores were less than the MID of 8 for EQ-VAS [41]. RAND-36 showed a temporary decline in the domains "Pain" and "Role limitations due to physical health" at 4 weeks, these changes were not seen at 12 months where participants had resumed their QoL. Interestingly, the domain "Emotional well-being" showed even better results at 12 months compared to baseline, possibly as a result

of improved adaptive strategies and response shift over time. The domain "General health" improved during the active intervention period at 4 weeks after surgery, but at 12 months returned to baseline. The consistency in FACT-B and EQ-VAS score from baseline to 4 weeks after surgery could indicate an inability of the instruments to encompass or discriminate changes resulting from the surgical insult, or that breast cancer diagnosis and surgery alone in fact has low impact on QoL. A significant difference was only seen for patients receiving adjuvant chemotherapy, compared to patients not receiving adjuvant chemotherapy, suggesting that this is a subgroup of patients that may benefit more from interventions aimed at improving QoL. The strengths of the current study include the randomized controlled design, the use of several validated QoL instruments, both generic and disease specific, as well as both short- and long-term follow-up. Limitations include the lack of objective measures of physical activity, regarding type, duration and/or intensity of physical activity. Low adherence to the intervention, confine the effects of this non-supervised intervention and point to the draw-backs of recommendations regarding exercise, in line with previous studies [12,42]. Our results, in accordance with previous findings seem to suggest the need for improved strategies and additional support in order to achieve the recommended physical activity level for patients with breast cancer. Based on our presented results and previously presented outcomes of this trial we cannot advocate for including unsupervised physical activity into prehabilitation guidelines for patients awaiting surgery for breast cancer. Based on the findings from this trial, one of the most important aims for future prehabilitation research is to identify implementable interventions that will increase the possibility for improved outcome. Also, the knowledge gained from this trial concerning quality of life before and after breast cancer treatment, using different questionnaires, gives additional support for future research.

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