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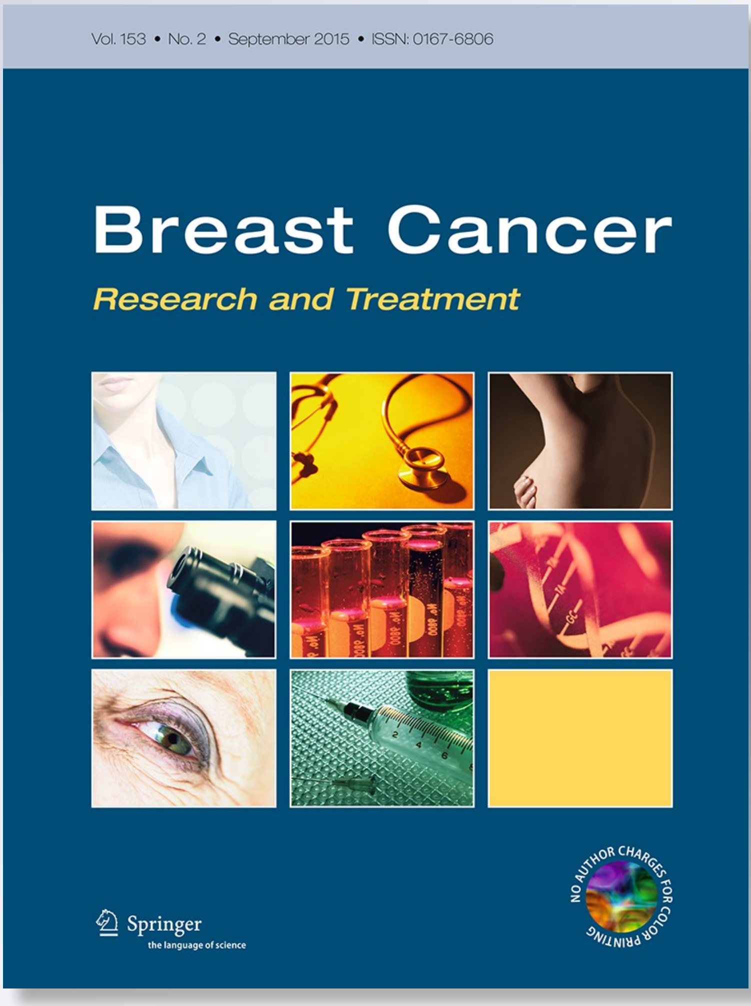

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CLINICAL TRIAL

Supervised physical exercise improves VO_{2max}, quality of life, and health in early stage breast cancer patients: a randomized controlled trial

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Abstract Breast cancer patients suffer impairment in cardiorespiratory fitness after treatment for primary disease, affecting patients' health and survival. The aim of this study was to evaluate the ability of a pragmatic exercise intervention to improve cardiorespiratory fitness of breast cancer patients after primary treatment. Between February 2013 and December 2014, 94 women with early stage (I–III) breast cancer, 1–36 months post-chemotherapy, and radiotherapy were randomly assigned to an intervention program (EX) combining supervised aerobic and resistance exercise ($n = 44$) or usual care (CON) ($n = 45$) for 12 weeks. Primary study endpoint was VO_{2max}. Secondary endpoints were muscle strength, shoulder range of motion, body composition, and quality of life (QoL). Assessments were undertaken at baseline, 12-week, and 6-month follow-ups. Eighty-nine patients aged 29–69 years were assessed at baseline and 12 weeks. The EX group showed significant improvements in VO_{2max}, muscle strength, percent fat, and lean mass ($p \leq 0.001$ in all cases) and QoL compared with usual care (CON). Apart from body composition, improvements were maintained for the EX at 6-month follow-up. There were no adverse events during the testing or exercise intervention program. A combined exercise intervention produced considerable improvement in cardiorespiratory fitness, physical function, and quality of life in breast cancer patients previously treated with chemotherapy and radiation therapy. Importantly, most of these benefits were maintained 6 months after ceasing the supervised exercise intervention.

Keywords Breast cancer · Exercise · Physical capacity · Lifestyle change · Quality of life

Trial registration number: NCT01990430.

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Introduction

Breast cancer is one of the most common cancers and a leading cause of cancer death in western women [1]. Fortunately, thanks to both mammogram screening campaigns and adjuvant therapies, breast cancer survival rates are increasing, and approximately, 80 % of patients remain cancer survivors at 5 years [2].

However, breast cancer treatments have serious implications to health and quality of life [3] with high incidence of comorbidities following treatments [4]. In addition, breast cancer patients show lower levels of physical capacity and mobility compared to women without cancer of similar age [5]. These impairments to physical capacity, assessed by maximum oxygen consumption (VO_{2max}) [6], and changes in body composition (muscle mass loss and fat mass gain) have been related to poorer survival and higher risk of metabolic diseases [7].

It has been reported that exercise is an integrative intervention that could eliminate, prevent, or reduce these side effects [8]. However, very few patients are aware of and follow the exercise recommendations [9, 10] possibly because clinical oncologists, during early treatment of breast cancer, may not place emphasis on exercise with this therapy being relegated to a low priority in the (neo) adjuvant treatments. Further, access and pragmatic implementation of exercise for this patient group may be difficult depending on available facilities and expertise. Finally, the persistence of benefits of exercise interventions in cancer survivors has been questioned [11] necessitating trials with longer term follow-up.

Therefore, the purpose of this study was to examine the effects of a combined exercise program highly transferable into best practice supportive care, incorporating aerobic and resistance exercises, on physical capacity of women with breast cancer following curative treatments and to evaluate the maintenance of any benefits at 6-month follow-up.

We hypothesized that a specific exercise intervention could restore physical capacity of breast cancer patients who have recently finished adjuvant chemotherapy and radiotherapy. We designed a randomized controlled trial to examine the effects of a combined exercise program on the physical capacity of these patients.

Materials and methods

This was a prospective randomized controlled trial (RCT) with participants randomly allocated in a 1:1 ratio to one of two study arms: supervised exercise plus dietary counseling (EX) or non-intervention control group (CON). Eligible patients that signed informed consent were randomly allocated to EX or CON groups by means of a random number table by an external person not involved in testing or training the participants [12]. The study was developed by collaboration between different institutions (Universidad Politécnica de Madrid (UPM), Spanish Group of Cancer Patients (GEPAC), Hospital General Universitario Gregorio Marañón, Hospital Universitario Puerta de Hierro-Majadahonda, and Hospital Madrid Norte-Sanchinarro). The intervention was carried out at facilities of the Physical and Sport Science Institute-INEF (INEF), and the study was approved by the Human Ethics Committee of UPM. Prior to any exercise testing or training, each participant's general health and readiness were evaluated using the PAR-Q [13].

GEPAC staff and medical oncologists from the 4 different institutions undertook patient identification and recruitment. Inclusion criteria were (1) previously confirmed diagnosis of stage I to III breast cancer; (2) age between 18 and 70 years; (3) at least 1 month and at most 3 years from completion of radiotherapy and chemotherapy, although they could have been under hormonal or biological treatments; (4) oncologist approval; and (5) willing to participate and sign the informed consent. Exclusion criteria were any other illness or disability incompatible with exercise (e.g., cardiac condition, uncontrolled hypertension, severe pulmonary disease, mental illness, or anticoagulant treatments).

Intervention group

The exercise program was designed and supervised by an oncologic exercise specialist based on the ACSM guidelines [14]. The exercise program consisted of twice-weekly supervised exercise sessions combining aerobic and resistance exercise that was increased in intensity over 12 weeks in a familiar and trusted environment, which promoted socialization between participants. Program characteristics are presented in Table 1. The intervention was developed as a pragmatic, nonclinical intervention, implemented with minimal cost and equipment increasing the transferability into the clinical environment. It was also complemented with an education program about exercise and nutrition guidelines. An initial orientation session on exercise was conducted outlining current exercise recommendations and the importance of adopting lifestyle changes to improve outcomes for breast cancer survivors.

The nutrition program consisted of three workshops, where specific concepts of nutrition and diet were explained. The first class was on the topic of different groups of nutrients. The second class was a practical session about interpreting food labels and relating measurements of food portions with recommendations for a healthy diet. The final session addressed the ten best (i.e., rich in antioxidants) and the ten worst (i.e., rich in animal fat) dietary components, which might prevent or promote cancer. The study dieticians 'recommended patients try to adopt the Mediterranean diet [15].

Non-intervention group

CON participants were asked to maintain their usual behavior, without changes in their physical activity levels or diet. At the end of the twelve weeks, patients in the CON group were offered to participate in the exercise classes for ethical considerations and to reduce attrition and contamination.

Study endpoints

All clinical and patient-reported outcomes were assessed at baseline and 12 weeks. EX participants were also assessed

Table 1 Intervention characteristics

	Warm-up				Aerobic exercise				Resistance exercise				Cool-down	
	Activities	Intensity	Control	Duration	Activities	Intensity	Control	Duration	Activities	Intensity	Control	Duration	Activities	Duration
1st month	Articular mobilization Walking exercises Running	50–60 % HRR 10–13 BORG scale	Heart-rate monitor	10′	Dance classes Power circuits Walking–running	55–70 % HRR 9–14 BORG scale	Heart-rate monitor BORG scale	30′	Shoulder circles, dorsal and chest exercises with elastic bands	10 reps, 2 sets 10–12 BORG scale	Reps and sets BORG scale	10′	Whole body stretching	10′
2nd month	Articular mobilization Walking exercises Running	60–70 % HRR 12–14 BORG scale	Heart-rate monitor	10′	Step and aerobic classes Power circuit Walking–running	70–80 % HRR 12–16 BORG scale	Heart-rate monitor BORG scale	25′	Shoulder circles, dorsal and chest exercises with elastic bands	15 reps, 2 sets 13–15 BORG scale	Reps and sets BORG scale	15′	Whole body stretching	10′
3rd month	Articular mobilization Walking exercises Running	60–70 % HRR 12–14 BORG scale	Heart-rate monitor	10′	Step-aerobic classes Power circuit Running	70–85 % HRR 12–17 BORG Scale	Heart-rate monitor BORG Scale	25′	Shoulder circles, dorsal and chest exercises with elastic bands	8 reps, 2 sets 17–20 BORG scale	Reps and sets BORG scale	15′	Whole body stretching	10′

6 months following completion of the 12-week supervised intervention to determine if benefits were maintained.

Demographic and descriptive data

Age, marital status, profession, subtype of tumor, type of resection, lymph node resection, type of endocrine medication, menopausal status, and physical activity level (sedentary, defined as less than 30 min of activity per week; low defined as between 30 and 150 min of activity per week; moderate defined as between 150 and 300 min of activity per week; or high defined as over 300 min of activity per week) [14] were recorded using questionnaires. Patients were asked not to include the exercise intervention time in the questionnaires at final assessments to be able to compare these assessments with the baseline and the follow-up measurements or changes in habitual physical activity.

Primary outcome: cardiorespiratory capacity

Cardiorespiratory capacity was assessed by estimating the VO_{2max} of each individual at each test occasion [16]. Each participant completed a submaximal test using the modified Bruce protocol performed on a treadmill (PANATA, Italy) at 85 % of heart rate-reserve (HRR). The Canadian Society for Exercise Physiology Equation Can [16] was then applied to predict VO_{2max}.

Secondary outcomes

Muscle strength and shoulder range of motion *Isometric muscle strength* was assessed using isometric dynamometers for hand-grip (TKK 5401, Grip-D, Japan) and legs and back (TKK 5402, Grip-D, Japan) strength. The Strength Index was obtained by adding all isometric strength values and dividing the result by the participant's body weight [17].

Dynamic muscle strength was assessed using the 8-repetition maximum (RM) test protocol for chest press and leg extension exercises with subsequent prediction of 1-RM strength following the National Strength and Conditioning Association guidelines [14] and Mayhew formulae [18]. *Muscular endurance* was determined as maximal number of repetitions performed at 50 % of 1RM for the chest press and 70 % of 1RM for the leg extension. All strength and endurance tests were performed using pin-loaded resistance machines (PANATA, Italy).

Body composition and anthropometrics Body fat and lean mass percentage were assessed by electrical bioimpedance (BC-601F, Tanita, Japan) [19]. Anthropometric assessments included weight, height, body mass index

(BMI), waist and hip circumferences, and waist–hip ratio [17]. Arm circumferences were measured in both limbs every 10 cm from the metacarpal-phalangeal joints to 15 cm proximal to the lateral epicondyles to assess arm volume and potential lymphedema [20, 21].

Quality of life (QoL) QoL was assessed using the SF-36 questionnaire which consists of 36 items divided into eight dimensions that have been interpreted together and separately with higher scores on this scale indicating higher levels of health [22, 23]. The eight subdomains include physical functioning, role limitation due to physical health, bodily pain, general health perception, vitality, social functioning, role limitation due to emotional health and mental health.

Statistical analysis

Based on the previous work by Jones et al. [6], a difference in VO_{2max} change of 0.306 (ml/kg*min) between the two groups is considered clinically relevant and used to estimate the required sample size. Using an alpha level of 0.05, a final sample size of 86 patients was required to obtain a statistical power of 80 %. Allowing for 10 % attrition, the target recruitment was set at 95 patients.

Data were analyzed using SPSS Version 20.0 (IBM, New York). Confidence interval was set at 95 %, and criteria for significance at $p \leq 0.05$ and tailed comparison to determine significance of the results. Continuous data are presented as mean ± standard deviation (mean ± SD) and categorical data as frequencies and percentages in the tables. Significant differences are presented as standardized mean difference (SMD), confidence interval of the difference (CI), and p value (SMD; 95 % CI; p). Groups were compared in terms of demographic variables by Chi-squared analysis, if they were categorical, and by ANOVA if they were continuous. For the other measures, ANCOVA adjusted for age and baseline values was used to analyse continuous data and Chi Square for nominal data. ANOVA was used to compare the 6-month follow-up assessments for EX participants.

Results

Two hundred and thirty-five women were screened and 94 were enrolled. Women were recruited from February 2013 to December 2014 and randomly assigned to the two study arms (Fig. 1). No differences in baseline measures were found between groups, except for age (Table 2).

Eighty-nine women ($n = 47$ in EX group and $n = 47$ in CON group, respectively) completed all of the testing protocol baseline and 12 weeks (Table 3) and 36 women from the EX group completed measurements at 6 months follow-up (Table 4).

Adherence and level of physical activity

The adherence to the program was 87.7 % defined as the percentage of patients that finally ending the whole program, and 86 % of the EX participants returned to perform the follow-up assessments at 6 months. Participant attendance for the exercise and diet sessions was over 80 % with 82 % attending all scheduled sessions. With respect to the number of minutes of physical activity performed per week, there were significant differences between groups ($\chi^2 = 30.78$; $p < 0.001$). At baseline, only 36 % of women in both groups were meeting the recommended 150 min of physical activity per week as per ASCM guidelines. Following 12 weeks, 91 % of women in EX and only 49 % in CON were meeting these guidelines ($p = 0.001$). At 6-month follow-up, 79 % of women in EX were still meeting the guidelines.

Primary outcome: cardiorespiratory capacity

Following the intervention, VO_{2max} was significantly higher for EX compared to CON ($p < 0.001$). Changes in VO_{2max} in both groups are presented in Fig. 2. At 6-month follow-up, EX maintained their VO_{2max} showing no significant decline.

Secondary outcomes

Muscle strength and shoulder range of motion

Isometric strength index increased significantly in women allocated to EX compared with those allocated to CON ($p = 0.004$). Further, EX improved *maximal strength* significantly more than CON for chest press ($p < 0.001$) and leg extension ($p = 0.001$). These differences were also significant when expressed relative to body weight in both the chest press ($p < 0.001$) and leg extension ($p < 0.001$). *Muscle endurance* was significantly lower in CON than EX participants for the chest press ($p < 0.001$) and leg extension ($p < 0.001$) at 12 weeks. At 6 months follow-up EX maintained or improved both (Table 4).

Body composition

EX showed significant reductions in fat mass percentage ($p < 0.001$) and significant increases in lean body mass ($p = 0.001$). These changes in body composition were not maintained by EX during the subsequent 6 months, presenting a significant rise in fat mass ($p = 0.001$) and a reduction in lean mass ($p = 0.74$). No differences between

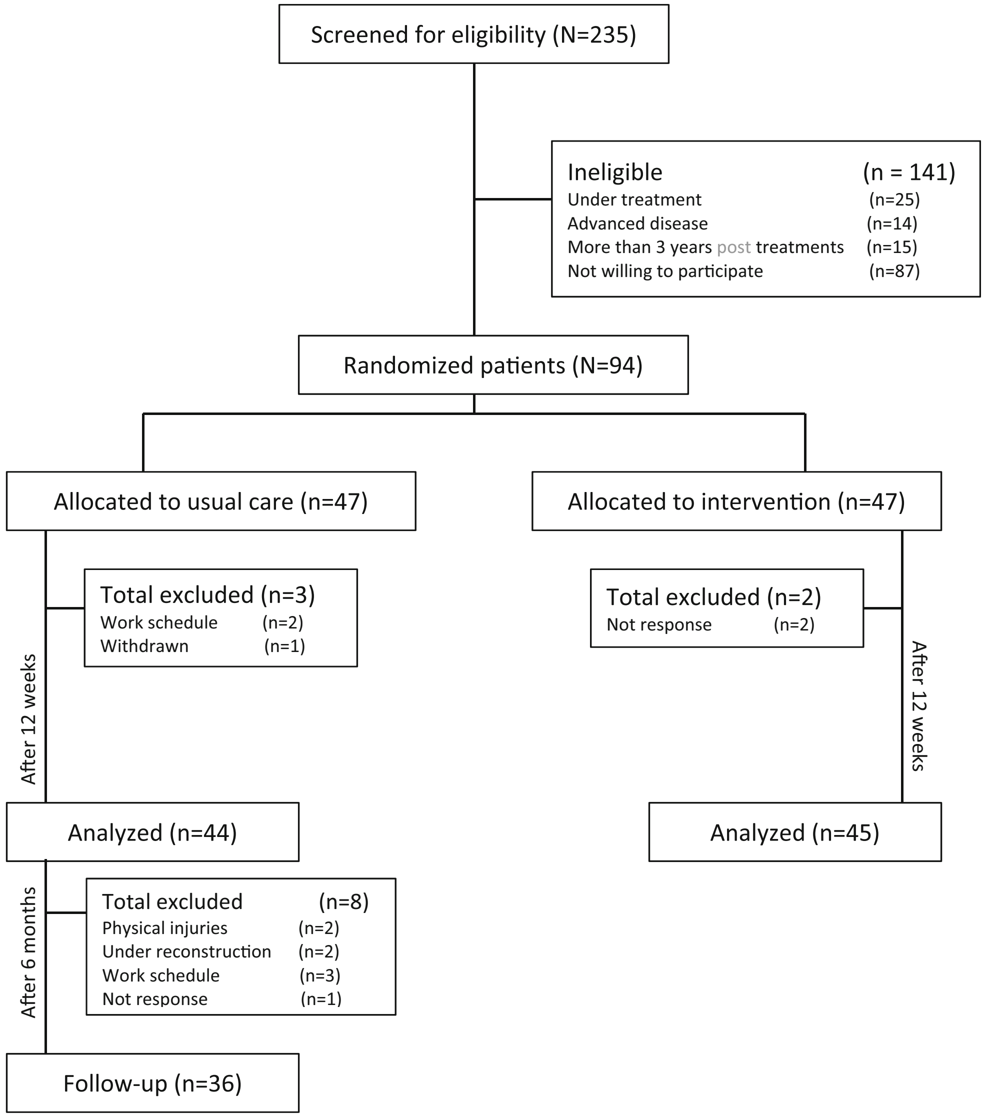

Fig. 1 CONSORT diagram

groups in affected arm volume were observed ($p > 0.05$) (results not presented).

Quality of life

EX participants showed significantly higher SF36 scores in mental and physical dimensions ($p = 0.002$; $p = 0.001$, respectively) and significant improvements in all SF36 subdomains, compared with CON, except for the role limitation due to emotional health. These changes were maintained for the EX group at 6-month follow-up.

Discussion

There can be no contention that appropriate exercise is of physiological, psychological, and survival benefit for breast cancer patients. However, pragmatic implementation of exercise into patient support and the longer-term benefits are much less understood. We found that a low-cost and specific intervention of combined exercise and dietary counseling can improve the cardiorespiratory performance of breast cancer patients, as shown by significant increase in VO_{2max} capacity. We also examined the effects of the intervention on muscle strength, body composition, and quality of life with similar beneficial outcomes.

Previous reviews, including meta-analysis, have reported results in accord to our VO_{2max} improvements [6, 24]. VO_{2max} has been established as an important predictor of anthracycline and trastuzumab-induced left ventricular dysfunction [25, 26], and improvement in VO_{2max} capacity has been related to reductions in all cause of mortality and cancer specific mortality [27, 28]. However, this study has some different and noteworthy points compared with previous research. First and foremost, our study was developed and designed as an easy to follow and a low-cost

Table 2 Participant characteristics

Variables	Frequency N (%)	EX frequency	CON frequency	χ^2_{gl}	P value
Number	94	47	47		
Age (years)	49.06 ± 8.75	45.91 ± 8.21	51.87 ± 8.21		0.01
With children	63 (67 %)	32	31		
Without children	31 (33 %)	15	16		
Marital status				$\chi^2_4 = 7.81$	0.1
Married	60 (64 %)	35	25		
Single with partner	18 (19 %)	8	10		
Divorced with partner	6 (6.4 %)	2	4		
Widow with partner	0 (0 %)	0	0		
Single without partner	7 (7.5 %)	2	5		
Divorced without partner	3 (3.1 %)	0	3		
Widow without partner	0 (0 %)	0	0		
Professional activity				$\chi^2_3 = 0.6$	0.9
Inactive (≤3 h stand)	68 (72.3 %)	35	33		
Active (>3 h stand)	20 (21.3 %)	9	11		
Housewife	6 (6.4 %)	3	3		
Educational level				$\chi^2_4 = 4.14$	0.39
Basic	8 (8.5 %)	6	2		
High school	31 (32.9 %)	17	14		
Bachelor	50 (53.2 %)	23	27		
Master	3 (3.2 %)	1	2		
Ph.D.	2 (2.2 %)	0	2		
Type of tumor				$\chi^2_3 = 3.94$	0.27
Hormon receptor (HR) positive/HER2−negative	53 (56.4 %)	22	31		
HR positive/HER2 positive	13 (13.8 %)	7	6		
HR negative/HER2 positive	19 (20.2 %)	12	7		
Triple negative (HR/HER2negative)	9 (9.6 %)	6	3		
Surgery				$\chi^2_1 = 0.76$	0.38
Lumpectomy	42 (44.6 %)	22	20		
Mastectomy	52 (55.4 %)	25	27		
Lymph node resection				$\chi^2_1 = 0.01$	0.93
Yes	57 (60.6 %)	28	29		
No	37 (39.4 %)	19	18		
General treatment received				$\chi^2_3 = 3.13$	0.37
Chemotherapy	6 (6.4 %)	2	4		
Radiotherapy	12 (12.8 %)	8	4		
Chemo + radio	69 (73.4 %)	32	37		
None	7 (7.4 %)	5	2		
Specific treatment received				$\chi^2_3 = 3.94$	0.27
Endocrine therapy	53 (56.4 %)	21	28		
Endocrine therapy +Anti-HER2	13 (13.8 %)	7	6		
Anti-HER2	19 (20.2 %)	12	7		
None	9 (9.6 %)	6	2		
Time since the end of chemo/radio therapy treatments (months)	10.44 ± 8.17	9.63 ± 7.66	11.16 ± 8.58		
Receiving at the moment of the study				$\chi^2_4 = 3.78$	0.44
Anti-estrogen	62 (65.9 %)	34	28		
Aromatase inhibitors	13 (13.8 %)	4	9		
Herceptin	2 (2.2 %)	1	1		

Table 2 continued

Variables	Frequency *N* (%)	EX frequency	CON frequency	χ^2_{gl}	*P* value
Others	13 (13.8 %)	6	7		
None	4 (4.3 %)	2	2		
Menstruation				$\chi^2_2 = 4.33$	0.11
Yes, regular	8 (8.50 %)	2	6		
Yes, irregular	3 (3.20 %)	3	0		
No	83 (88.30 %)	42	41		
Physical activity at baseline				$\chi^2_3 = 5.19$	0.16
Sedentary (<30)	22 (23.4 %)	10	12		
Low physical activity (30–150)	38 (40.4 %)	20	18		
Medium physical activity (150–300)	31 (33 %)	15	16		
High physical activity (>300)	3 (3.2 %)	2	1		

N number of participants, % percentage, *EX* exercise group, *CON* control group

intervention, which translated into high adherence and attendance. Second, the proposed intervention used in our study is highly transferable to pragmatic implementation in clinical settings due to the capacity to personalize exercise sessions and activities, something that has been observed as an important factor to increase exercise adherence [11, 29]. Other previous studies have carried out controlled intervention developed in lab conditions, which are usually planed as one to one and low motivation activities [30]. These interventions look for high-quality data but are not transferable and reproducible in clinical environment. However, our intervention shows that variables can be controlled using a motivating methodology based on the participant necessities [11], mixing resistance, and endurance activities with low-cost material and creating a transferable and reproducible methodology in the hospitals and medical centers.

Of high importance, at 6-month follow-up, approximately 80 % of patients were still performing 150 min of moderate exercise per week, which meets the ACSM recommendation at least for aerobic exercise. This can be considered as an effective change in patiećts lifestyle, which should provide longer-term health benefit.

Muscle strength was also significantly increased as a result of the intervention, particularly maximal strength of the chest muscles that are usually affected by local treatments [31]. Improving or preserving muscle strength is important because of increased resilience to musculoskeletal injury and muscular strength, playing a fundamental role in reducing joint pain and physical limitation, thus increasing QoL [32, 33]. These results are complemented with a significant improvement in affected shoulder range of motion. It is estimated that around 60 % of patients present one upper-body symptom, which affects breast cancer patients' daily activities and reduces significantly their quality of life [31]. Others have previously shown similar results to ours [34–40], despite the fact that most of these studies involved longer interventions. We are encouraged that shorter interventions of even 12 weeks appear effective to reduce such treatment side effects achieving similar improvements.

We also found a significant reduction in body fat mass percentage and increase in lean mass, changing body composition toward a more healthy balance, despite the fact that body weight and BMI did not change significantly. These are important findings as higher levels of fat mass and lower levels of muscle mass have been related to poorer survival [41, 42] and high risk of metabolic diseases [42–44] indicating the need to restore body composition of breast cancer survivors after treatments. Previous reviews have indicated that it is insufficient evidence for the effect of exercise on body composition in cancer patients [14, 45], but the few studies addressing this topic have found similar results to ours, suggesting that exercise may be an efficient tool to restore energy balance and thus improve body composition [43, 46]. The positive changes in body composition seen in our study after the 12-week intervention program suggests that such a program could be of great interest if introduced as a critical component of patient management, in concordance with the findings of other studies.

As has been reported in several previous studies [34, 47, 48], women in the exercise group did not present significant swelling in the affected arm, further demonstrating that combined exercise interventions do not increase the risk of developing or exacerbating lymphedema [49, 50]. It is hoped that this growing research evidence finally dismisses reticence to prescribe resistance training for patients with lymphoedema.

Apart from improvements in objectively measured outcomes of physical capacity, the exercise group also showed significant changes in all subdomains of the SF-36 and in

Table 3 Comparison between groups for study outcomes at baseline and 12 weeks presented as mean ± SD, standardized mean difference (SMD; 95 % CI; p), and size effect

Measure	Baseline		12 weeks		Adjusted difference*		p value	Size effect[+] Cohen d
	Exercise Mean ± SD	Control Mean ± SD	Exercise Mean ± SD	Control Mean ± SD	SMD	95 %CI		
Physical activity at baseline							<0.001	
Sedentary (<30 min/week, m/w)	10 (21.28 %)	12 (25.53 %)	0 (0 %)	9 (20.00 %)				
Low physical activity (30–150 m/w)	20 (42.55 %)	18 (38.30 %)	4 (9.10 %)	14 (31.10 %)				
Medium physical activity (150–300 m/w)	15 (31.92 %)	16 (34.04 %)	34 (77.30 %)	22 (48.90 %)				
High level (>300 m/w)	2 (4.25 %)	1 (2.13 %)	6 (13.60 %)	0 (0 %)				
Physical variables								
Physical capacity (mL/kg per min.)	26.97 ± 4.94	29.18 ± 5.51	32.32 ± 6.22	27.66 ± 4.33	5.32	3.99–6.64	0.001	0.94
IGS (Kp/kg)	2.31 ± 0.94	2.04 ± 0.68	2.60 ± 0.82	2.12 ± 0.68	0.27	0.088–0.446	0.004	1.52
Maximal strength chest (kg)	35.15 ± 10.14	32.51 ± 11.89	47.60 ± 9.40	29.79 ± 10.19	14.63	12.58–16.68	<0.001	1.69
Maximal strength legs (kg)	72.80 ± 20.96	69.56 ± 31.32	100.47 ± 26.77	65.46 ± 24.33	30.98	24.66–37.31	0.001	1.55
Resistance strength chest (kg)	429.79 ± 157.32	389.34 ± 204.53	601.51 ± 233.98	364.14 ± 170.28	195.02	139.69–250.34	<0.001	1.58
Resistance strength legs (kg)	977.26 ± 445.14	932.63 ± 619.18	1552.00 ± 679.01	909.66 ± 609.11	472	307.97–636.58	<0.001	1.52
Maximal strength chest/Weight	0.55 ± 0.19	0.49 ± 0.17	0.72 ± 0.15	0.45 ± 0.13	0.22	0.19–0.45	<0.001	
Maximal strength legs/Weight	1.11 ± 0.36	1.016 ± 0.43	1.5 ± 0.47	0.99 ± 0.29	0.48	0.38–0.57	<0.001	
Body composition								
BMI (kg/cm^2)	25.97 ± 3.65	25.10 ± 5.85	25.86 ± 3.33	25.66 ± 4.72	−0.236	−1.101–0.574	0.536	
Weight (kg)	66.62 ± 9.13	65.75 ± 12.49	66.78 ± 8.64	65.49 ± 12.29	0.31	−0.13–0.75	0.161	
Hip–waist ratio	0.75 ± 0.06	0.78 ± 0.60	0.74 ± 0.05	0.77 ± 0.07	0.007	−0.002–0.016	0.140	
Body fat mass (percentage)	35.17 ± 6.16	34.45 ± 7.59	34.53 ± 6.18	35.05 ± 7.56	−1.42	−2.08–0.75	<0.001	−0.08
Lean body mass (kg)	40.35 ± 3.90	40.11 ± 3.83	41.15 ± 3.42	38.42 ± 7.30	2.61	1.068–4.16	0.001	0.48
Quality of life								
SF36 mental	45.07 ± 5.14	44.84 ± 6.03	49.02 ± 4.18	46.06 ± 5.15	4.25	1.61–6.91	0.002	0.53
SF36 physical	38.81 ± 9.19	37.44 ± 9.53	42.57 ± 7.47	37.42 ± 11.70	2.48	1.084–3.89	0.001	0.64
Physical functioning	51.49 ± 66.61	40.41 ± 17.25	53.11 ± 3.49	49.69 ± 6.96	3.05	1.31–180	0.001	0.63
Role limitation—physical health	20.30 ± 8.37	19.87 ± 8.75	26.61 ± 2.24	25.18 ± 3.74	1.79	0.83–2.73	<0.001	0.47
Bodily pain	40.27 ± 16.97	38.42 ± 18.75	52.79 ± 6.87	49.25 ± 9.72	3.93	1.65–6.20	0.001	0.46
General health perception	39.00 ± 17.54	38.55 ± 17.36	51.11 ± 9.93	46.37 ± 9.70	5.44	2.52–8.37	<0.001	0.49
Vitality	42.58 ± 19.31	42.79 ± 20.03	58.19 ± 9.68	53.56 ± 12.88	5.79	2.35–9.25	0.001	0.41
Social functioning	36.71 ± 15.30	33.81 ± 15.18	46.29 ± 3.93	42.42 ± 6.93	4.62	2.97–6.27	<0.001	0.69
Role limitation—emotional health	13.77 ± 6.07	13.83 ± 6.25	18.02 ± 2.19	18.54 ± 10.79	−1.31	−3.77–1.14	0.29	
Mental health	51.59 ± 57.69	40.33 ± 19.61	57.51 ± 10.11	52.06 ± 14.13	7.36	3.59–11.12	<0.001	0.45

* Adjusted by baseline values of outcomes and age. [+] Size Effect presented by Cohen d: small effect $d = 0.20$, medium effect $d = 0.5$, large effect $d = 0.8$

Table 4 Results for EX group only for follow-up assessment at 6 months presented as mean ± SD, and standardized mean difference (SMD; 95 % CI; *p*) and size effect

Measure	Follow-up		Baseline-final		Baseline-follow-up		Final-follow-up	
	Mean ± SD	*p*	SMD (95 %CI)	*p*	SMD (95 %CI)	*p*	SMD (95 %CI)	*p*
Physical activity at baseline		<0.001	Range = 1.63	<0.05	Range = 2.38	>0.05	Range = 1.99	>0.05
Sedentary (<30 min/week, m/w)	5 %							
Low physical activity (30–150 m/w)	16 %							
Medium physical activity (150–300 m/w)	68 %							
High level (>300 m/w)	11 %							
Physical variables								
Physical capacity (mL/kg per min.)	33.01 ± 6.45	<0.001	−6.24 (−7.53 to −4.95)	<0.001	−5.89 (−7.87 to −3.90)	<0.001	0.36 (−1.39–2.13)	0.714
IGS (Kp/kg)	2.76 ± 0.74	0.007	−0.21 (−0.39 to −0.0023)	0.028	−0.23 (−0.38 to −0.0056)	0.010	−0.02 (−0.12–0.008)	0.682
Maximal strength chest (kg)	52.51 ± 9.06	<0.001	−11.25 (−13.09 to −9.40)	<0.001	−16.08 (−18.09 to −14.00)	<0.001	−4.83 (−6.41 to −3.23)	<0.001
Maximal strength legs (kg)	117.84 ± 22.07	<0.001	−27.22 (−32.35 to −22.09)	<0.001	−43.13 (−48.27 to −37.99)	<0.001	−15.90 (−21.83 to −9.98)	<0.001
Resistance strength chest (kg)	672.54 ± 168	<0.001	−166.30 (−221.67–110.95)	<0.001	−230.7 (−278 to −181.21)	<0.001	−63.77 (−123.37 to −5.17)	0.033
Resistance strength legs (kg)	1784.21 ± 785	<0.001	−592.14 (−751.85 to −432.43)	<0.001	−753.96 (−916.07 to −590.06)	<0.001	−160.92 (−351.48 to −29.64)	0.096
Maximal strength chest/weight	0.81 ± 0.16	<0.001	−017 (−0.21 to −0.14)	<0.001	−0.2 (−0.29 to −0.21)	<0.001	−0.08 (−0.11 to −0.05)	<0.001
Maximal strength legs/weight	1.85 ± 0.46	<0.001	−0.44 (−0.55 to −0.34)	<0.001	−0.70 (−0.81 to −0.60)	<0.001	−0.25 (−0.38 to −0.13)	<0.001
Body composition								
BMI (kg/cm^2)	25.40 ± 3.08	0.150	0.21 (0.05–0.37)	0.012	0.12 (−0.14–0.37)	0.374	0.092 (−0.30–0.11)	0.377
Weight (kg)	65.55 ± 8.59	0.179	0.52 (0.92–0.94)	0.018	0.29 (−0.40–0.98)	0.400	−0.23 (−0.75–0.29)	0.380
Hip–waist ratio	0.76 ± 0.076	0.004	0.006 (0.001–0.012)	0.017	0.013 (−0.03–0.002)	0.089	−0.019 (0.031 to −0.007)	0.003
Body fat mass (percentage)	34.77 ± 6.20	0.001	0.86 (0.23–1.50)	0.008	−0.23 (−0.80–0.35)	0.43	−1.09 (−1.69 to −0.48)	0.001
Lean body mass (kg)	40.02 ± 3.82	0.004	−0.53 (−7.80–4.59)	0.05	0.24 (−0.16–0.63)	0.23	0.76 (0.30–1.22)	0.74
Quality of life								
SF36 mental	42.15 ± 3.54	<0.001	−4.13 (−6.12 to −2.14)	<0.001	−2.93 (−5.14 to −0.71)	0.010	1.20 (−0.29–2.70)	0.113
SF36 physical	49.48 ± 7.58	<0.001	−2.54 (−3.83 to −1.24)	<0.001	−2.86 (−3.92 to −1.79)	<0.001	−0.31 (−1.28–0.64)	0.500
Physical functioning	53.47 ± 2.79	<0.001	−11.05 (−15.54 to −6.57)	0.001	−10.94 (−15.42 to −6.47)	0.001	0.11 (−0.61–0.84)	1.000
Role limitation—physical health	26.42 ± 2.58	<0.001	−5.89 (−8.34 to −3.44)	<0.001	−5.63 (−7.90 to −3.36)	<0.001	0.26 (−0.72–1.24)	0.261
Bodily pain	53.64 ± 6.27	<0.001	−12.43 (−16.86 to −7.99)	<0.001	−13.00 (−17.99 to −8.01)	<0.001	−0.57 (−2.44–1.29)	1.000
General health perception	51.10 ± 7.34	<0.001	−10.71 (−15.67 to −5.77)	<0.001	−10.64 (−15.68 to −5.59)	<0.001	0.083 (−1.71–1.88)	1.000
Vitality	57.96 ± 9.28	<0.001	−15.19 (−20.98 to −9.04)	<0.001	−14.73 (−20.51 to −8.95)	<0.001	0.46 (−1.69–2.61)	1.000
Social functioning	45.38 ± 40.04	<0.001	−9.19 (−13.38 to −5.01)	<0.001	−7.86 (−12.26 to −3.45)	<0.001	1.34 (0.071–2.60)	0.035
Role limitation—emotional health	17.85 ± 1.81	<0.001	−4.38 (−6.08 to −2.68)	<0.001	−3.80 (−5.47 to −2.12)	<0.001	0.58 (0.15–1.01)	0.004
Mental health	57.55 ± 10.62	0.850	−3.25 (−22.33–15.84)	1.000	−2.95 (−21.44–15.55)	1.000	0.30 (−2.33–2.93)	1.000

* Adjusted by baseline values of outcomes and age. + Size Effect presented by Cohen *d*: small effect $d = 0.20$, medium effect $d = 0.5$, large effect $d = 0.8$

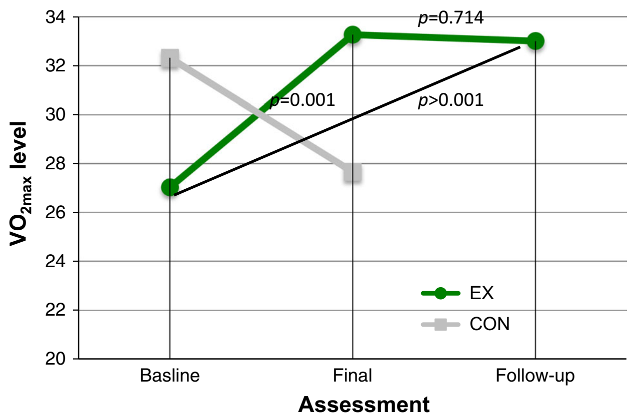

Fig. 2 Cardiorespiratory fitness at baseline, 12-week, and 6-month follow-ups for the intervention and control participants

general QoL compared with usual care, demonstrating the potential of this intervention to improve patient-reported outcomes (PROs). Our results are similar to previous studies and meta-analysis [8, 36, 51–56]. However, this is a post-treatment study, which may lead to greater changes than previous studies developed during chemotherapy [57], suggesting that the best opportunity to modify PROs should be after cancer (neo) adjuvant treatments.

With regard to longer-term maintenance of adaptations and benefit, EX retained the improvements in VO_{2max} and significantly improved muscle strength at 6-month follow-up. However, body fat mass percentage and lean mass returned to baseline, which suggests that high levels of physical activity or high intensity exercise may be necessary to maintain body composition improvements. Only a small number of studies have followed up exercise intervention achievements in cancer patients [11], suggesting that more follow-up studies are needed to design effective interventions to restore physical status of breast cancer survivors after treatments. In addition, changes in QoL were maintained after 6-month follow-up, which suggest that an integrative intervention could be effective to reduce physical and psychological side effects in a lasting way.

This study had some limitations, and the results have to be interpreted in this light. Our integrative program included not only an exercise program but nutritional recommendations as well. The impact of the dietary recommendations on the variables measured in our study cannot be established and separated from the benefits provided by the exercise program. However, a previous review has suggested that dietary intervention is insufficient to restore body composition [58]. It is unlikely, then that the dietary recommendations by themselves could have played a major role in the observed changes. In addition, self-reported assessments of questionnaires are normally inferior to objective measures. However, the used questionnaires have been extensively validated. Regarding the long-term maintenance of the benefit, our study follows patients only for 6 months. Additional studies with longer follow-up are necessary to establish the maintenance of benefit over multiple years. Lastly, our patients were well-functioning individuals mostly motivated to undertake the training program and may not be representative of all breast cancer patients recently completing adjuvant chemotherapy and radiotherapy.

Among the strengths of our study, we can mention the relatively large proportion of patients retained at 12 week and 6 month assessments, the high compliance to the intervention, and a very pragmatic, integrative group-based intervention that was implemented. Further, to our knowledge, this is the largest exercise intervention in breast cancer patients ever conducted in Spain.

In conclusion, we report that a combined aerobic and resistance exercise intervention results in statistically and clinically significant improvement in VO_{2max} in breast cancer survivors, as well as improvements in muscle strength, body composition, quality of life, and fatigue. Much of this benefit is retained at 6 month post-intervention. Future studies are needed to establish the ability of this integrative intervention to maintain the benefits beyond 6 months.

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Compliance with ethical standards

Conflict of interest Authors declare no conflict of interest.

Disclaimers Authors have nothing to disclaim.

References

1. Ferlay J, Soerjomataram I, Ervik M et al (2012) GLOBOCAN. In: CIaMWICNI (ed) GLOBOCAN 2012 v1.0 . International Agency for Research on Cancer, Lyon, France. http://globocan.iarc.fr/
2. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, Baili P, Rachet B, Gatta G, Hakulinen T et al (2008) Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol 9(8):730–756
3. Casla S, Hojman P, Marquez-Rodas I, Lopez-Tarruella S, Jerez Y, Barakat R, Martin M (2015) Running away from side effects: physical exercise as a complementary intervention for breast cancer patients. Clin Transl Oncol 17:180–196
4. Kumar M, Nagpal R, Hemalatha R, Verma V, Kumar A, Singh S, Marotta F, Jain S, Yadav H (2012) Targeted cancer therapies: the future of cancer treatment. Acta Biomed 83(3):220–233
5. Neil-Sztramko SE, Kirkham AA, Hung SH, Niksirat N, Nishikawa K, Campbell KL (2014) Aerobic capacity and upper limb strength are reduced in women diagnosed with breast cancer: a systematic review. J Physiother 60(4):189–200
6. Jones LW, Liang Y, Pituskin EN, Battaglini CL, Scott JM, Hornsby WE, Haykowsky M (2011) Effect of exercise training on peak oxygen consumption in patients with cancer: a meta-analysis. Oncologist 16(1):112–120

7. Vance V, Mourtzakis M, McCargar L, Hanning R (2011) Weight gain in breast cancer survivors: prevalence, pattern and health consequences. Obes Rev 12(4):282–294
8. Mishra SI, Scherer RW, Geigle PM, Berlanstein, Topaloglu O, Gotay CC, Snyder C (2012) Exercise interventions on health-related quality of life for cancer survivors. Cochrane Database Syst Rev 8:CD007566
9. Ibrahim EM, Al-Homaidh A (2011) Physical activity and survival after breast cancer diagnosis: meta-analysis of published studies. Med Oncol 28(3):753–765
10. CDC: A National Action Plan for Cancer Survivorship: Advancing Public Health Strategies (2014) In: Servise-USA Dohah (ed). Lance Amstrong Foundation. http://www.cdc.gov/cancer/survivorship/pdf/plan.pdf
11. Bourke L, Homer KE, Thaha MA, Steed L, Rosario DJ, Robb KA, Saxton JM, Taylor SJ (2013) Interventions for promoting habitual exercise in people living with and beyond cancer. Cochrane Database Syst Rev 9:CD010192
12. Thomas JR, Nelson JK (2007) Métodos de investigación en actividad física. Editorial Paidotribo, Badalona
13. Balady GJ, Berra KA, Golding LA, Gordon NF, Mahler DA, Myers JN, Sheldahl LM (2000) ACSM's guidelines for exercise testing and prescription, 6th edn. Lippincott Williams & Wilkins, Baltimore
14. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, Irwin ML, Wolin KY, Segal RJ, Lucia A et al (2010) American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 42(7):1409–1426
15. Castello A, Pollan M, Buijsse B, Ruiz A, Casas AM, Baena-Canada JM, Lope V, Antolin S, Ramos M, Munoz M et al (2014) Spanish Mediterranean diet and other dietary patterns and breast cancer risk: case–control EpiGEICAM study. Br J Cancer 111(7):1454–1462
16. CSEP (2010) The Canadian physical activity, fitness and lifestyle approach, 3rd edn. Canadian Society for Exercise Physiology, Ottawa
17. López-Silvarrey FJ, Segovia JC, Belinchón F (1996) Valoración morfológica I: metodología. In: Manual de Valoración Funcional Aspectos clínicos y fisiológicos, Segunda edn. Elselvier, Madrid
18. Mayhew J, Ball T, Arnold MD, Bowen J (1992) Relative muscular endurance performance as a predictor of bench press in college men and women. J Appl Sport Sci Res 6(4):6
19. Guinan EM, Connolly EM, Kennedy MJ, Hussey J (2013) The presentation of metabolic dysfunction and the relationship with energy output in breast cancer survivors: a cross-sectional study. Nutr J 12(1):99
20. Brorson H, Hoijer P (2012) Standardised measurements used to order compression garments can be used to calculate arm volumes to evaluate lymphoedema treatment. J Plast Surg Hand Surg 46(6):410–415
21. Harris S (2001) Clinical practice guidelines for the care and treatment of breast cancer. Can Med Assoc 23:191–196
22. Hays RD, Sherbourne CD, Mazel RM (1993) The RAND 36-item health survey 1.0. Health Econ 2(3):217–227
23. Ware JE, Snow KK, Kosinski M, Gandek B (1993) SF-36 health survey. Manual and interpretation guide. The Health Institute, New England Medical Center, Boston:
24. McNeely C, Rowe, Klassen, Mckey, Courneya (2006) Effects of exercise on breast cancer patients and surviviors: a systematic reviey and meta-analysis. CMAJ 5:34–41
25. Jones LW, Haykowsky M, Peddle CJ, Joy AA, Pituskin EN, Tkachuk LM, Courneya KS, Slamon DJ, Mackey JR (2007) Cardiovascular risk profile of patients with HER2/neu-positive breast cancer treated with anthracycline-taxane-containing adjuvant chemotherapy and/or trastuzumab. Cancer Epidemiol Biomark Prev 16(5):1026–1031
26. Jones LW, Haykowsky M, Pituskin EN, Jendzjowsky NG, Tomczak CR, Haennel RG, Mackey JR (2007) Cardiovascular reserve and risk profile of postmenopausal women after chemoendocrine therapy for hormone receptor–positive operable breast cancer. Oncologist 12(10):1156–1164
27. Betof AS, Dewhirst MW, Jones LW (2012) Effects and potential mechanisms of exercise training on cancer progression: a translational perspective. Brain Behav Immun 30:S75–S87
28. Warburton DE, Nicol CW, Bredin SS (2006) Health benefits of physical activity: the evidence. CMAJ 174(6):801–809
29. Husebo AM, Karlsen B, Allan H, Soreide JA, Bru E (2014) Factors perceived to influence exercise adherence in women with breast cancer participating in an exercise programme during adjuvant chemotherapy: a focus group study. J Clin Nurs 24:500–510
30. Jones LW, Fels DR, West M, Allen JD, Broadwater G, Barry WT, Wilke LG, Masko E, Douglas PS, Dash RC et al (2013) Modulation of circulating angiogenic factors and tumor biology by aerobic training in breast cancer patients receiving neoadjuvant chemotherapy. Cancer Prev Res (Phila) 6(9):925–937
31. Rietman JS, Dijkstra PU, Hoekstra HJ, Eisma WH, Szabo BG, Groothoff JW, Geertzen JH (2003) Late morbidity after treatment of breast cancer in relation to daily activities and quality of life: a systematic review. Eur J Surg Oncol 29(3):229–238
32. DeNysschen CA, Burton H, Ademuyiwa F, Levine E, Tetewsky S, O'Connor T (2014) Exercise intervention in breast cancer patients with aromatase inhibitor-associated arthralgia: a pilot study. Eur J Cancer Care 23(4):493–501
33. Irwin ML, Cartmel B, Gross C, Ercolano E, Fiellin M, Capozza S, Rothbard M, Zhou Y, Harrigan M, Snaft T et al. (2013) Randomized trial of exercise vs usual care on aromatase inhibitor-associated arthralgias in women with breast cancer. In: 2013 San Antonio Breast Cancer Symposium, USA
34. Cormie P, Pumpa K, Galvao DA, Turner E, Spry N, Saunders C, Zissiadis Y, Newton RU (2013) Is it safe and efficacious for women with lymphedema secondary to breast cancer to lift heavy weights during exercise: a randomised controlled trial. J Canc Surviv 7(3):413–424
35. Culos-Reed SN, Carlson LE, Daroux LM, Hately-Aldous S (2006) A pilot study of yoga for breast cancer survivors: physical and psychological benefits. Psycho-oncology 15(10):891–897
36. Heim ME, v d Malsburg ML, Niklas A (2007) Randomized controlled trial of a structured training program in breast cancer patients with tumor-related chronic fatigue. Onkologie 30(8–9):429–434
37. Allgayer H, Nicolaus S, Schreiber S (2004) Decreased interleukin-1 receptor antagonist response following moderate exercise in patients with colorectal carcinoma after primary treatment. Cancer Detect Prev 28(3):208–213
38. Ohira T, Schmitz KH, Ahmed RL, Yee D (2006) Effects of weight training on quality of life in recent breast cancer survivors: the weight training for breast cancer survivors (WTBS) study. Cancer 106(9):2076–2083
39. Schmitz KH, Ahmed RL, Hannan PJ, Yee D (2005) Safety and efficacy of weight training in recent breast cancer survivors to alter body composition, insulin, and insulin-like growth factor axis proteins. Cancer Epidemiol Biomark Prev 14(7):1672–1680
40. Winters-Stone KM, Dobek J, Nail LM et al (2012) Impact + resistance training improves bone health and body composition in prematurely menopausal breast cancer survivors: a randomized controlled trial. Osteoporos Int 24(5):1637–1646
41. Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Madarnas Y, Hartwick W, Hoffman B, Hood N (2002) Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. J Clin Oncol 20(1):42–51

42. Irwin ML, McTiernan A, Baumgartner RN, Baumgartner KB, Bernstein L, Gilliland FD, Ballard-Barbash R (2005) Changes in body fat and weight after a breast cancer diagnosis: influence of demographic, prognostic, and lifestyle factors. J Clin Oncol 23(4):774–782
43. Demark-Wahnefried W, Peterson BL, Winer EP, Marks L, Aziz N, Marcom PK, Blackwell K, Rimer BK (2001) Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. J Clin Oncol 19(9):2381–2389
44. Azrad M, Demark-Wahnefried W (2014) The association between adiposity and breast cancer recurrence and survival: a review of the recent literature. Curr Nutr Rep 3(1):9–15
45. Brown JC, Winters-Stone K, Lee A, Schmitz KH (2012) Cancer, physical activity, and exercise. Compr Physiol 2(4):2775–2809
46. Irwin ML, Alvarez-Reeves M, Cadmus L, Mierzejewski E, Mayne ST, Yu H, Chung GG, Jones B, Knobf MT, DiPietro L (2009) Exercise improves body fat, lean mass, and bone mass in breast cancer survivors. Obesity 17(8):1534–1541
47. McKenzie DC, Kalda AL (2003) Effect of upper extremity exercise on secondary lymphedema in breast cancer patients: a pilot study. J Clin Oncol 21(3):463–466
48. McKenzie DC, Lane KN (2007) Upper extremity lymphatic function at rest and during exercise in breast cancer survivors with and without lymphedema compares with health controls. Am Physiol Soc 21:917–925
49. Schmitz KH, Ahmed RL, Troxel AB, Cheville A, Lewis-Grant L, Smith R, Bryan CJ, Williams-Smith CT, Chittams J (2010) Weight lifting for women at risk for breast cancer-related lymphedema: a randomized trial. JAMA 304(24):2699–2705
50. Schmitz KH, Ahmed RL, Troxel A, Cheville A, Smith R, Lewis-Grant L, Bryan CJ, Williams-Smith CT, Greene QP (2009) Weight lifting in women with breast-cancer-related lymphedema. N Engl J Med 361(7):664–673
51. McNeely ML, Campbell KL, Rowe BH, Klassen TP, Mackey JR, Courneya KS (2006) Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. CMAJ 175(1):34–41
52. Daley AJ, Crank H, Saxton JM, Mutrie N, Coleman R, Roalfe A (2007) Randomized trial of exercise therapy in women treated for breast cancer. J Clin Oncol 25(13):1713–1721
53. Musanti R (2012) A study of exercise modality and physical self-esteem in breast cancer survivors. Med Sci Sports Exerc 44(2):352–361
54. Penttinen H, Nikander R, Blomqvist C, Luoto R, Saarto T (2009) Recruitment of breast cancer survivors into a 12-month supervised exercise intervention is feasible. Contemp Clin Trials 30(5):457–463
55. Collaborative Group on Hormonal Factors in Breast Cancer (1996) Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Lancet 347(9017):1713–1727
56. Saxton JM, Scott EJ, Daley AJ, Woodroofe M, Mutrie N, Crank H, Powers HJ, Coleman RE (2014) Effects of an exercise and hypocaloric healthy eating intervention on indices of psychological health status, hypothalamic-pituitary-adrenal axis regulation and immune function after early-stage breast cancer: a randomised controlled trial. Breast Cancer Res 16(2):R39
57. Courneya KS, Segal RJ, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, Ladha AB, Proulx C, Vallance JK, Lane K et al (2007) Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. J Clin Oncol 25(28):4396–4404
58. Kampman E, Vrieling A, van Duijnhoven FJ, Winkels RM (2012) Iimpact of diet, body mass index, and physical activity on cancer survival. Curr Nutr Rep 1:30–36