

# Comparing Endurance and Resistance Training with Standard Care during Chemotherapy for Patients with Primary Breast Cancer

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**Abstract.** *Background/Aim:* Previous findings suggest that physical activity during breast cancer treatment can reduce side-effects and improve clinical outcome. In the present study, endurance (ET) and resistance training (RT) in 67 patients with breast cancer undergoing chemotherapy were compared with standard-care (SC). *Patients and Methods:* Study end-points were muscular strength, endurance and subjective perceived exertion during the endurance stress test (Borg scale) and quality of life (QoL) measured by standardized report form of the European Organization for Research and Treatment of Cancer (EORTC QLQ C30+BR23) before and after 12 weeks of treatment. *Results:* The RT and ET groups improved significantly in muscular strength compared to the SC group. Endurance decreased in all groups after treatment ( $p>0.05$  for all groups); the maximum endurance loss occurred in the SC group ( $p=0.001$ ). The subjective perceived exertion at 100 W remained stable in the RT group ( $p=1.00$ ) decreased most in the SC group ( $p=0.3$ ) and to a lesser extent in the ET group ( $p=0.02$ ). In the RT group, QoL improved significantly ( $p=0.011$ ). There was also a trend for improvement of QoL in the ET group ( $p=0.09$ ) whereas that of the SC group decreased ( $p=0.8$ ). *Conclusion:* Results highlight improvements in strength, endurance and QoL from exercise training and support its implementation in standard of care during chemotherapy for patients with breast cancer.

After primary breast cancer diagnosis, patients with a moderate-to-high risk of disease recurrence often receive a

recommendation for adjuvant chemotherapy (1, 2). Chemotherapy improves disease-free and overall survival in these women, but it also induces common side-effects. Amongst other, patients suffer from fatigue (3, 4), loss of cognitive function (5), loss of physical fitness (6- 9) and a reduced quality of life (QoL) (10). Inactivity, related or not related to cancer treatment, can weaken the skeleton, cause muscle loss and lead to fat gain (11-14). These changes in body composition place breast cancer survivors at higher risk of obesity-related diseases, breast cancer recurrence, frailty and fractures (15). Previous findings suggest that physical activity during breast cancer treatment can reduce side-effects (11, 12, 16, 17) and improve clinical outcome (7, 13, 14, 17).

Currently, physical training in patients with breast cancer is not performed to the same degree as e.g. for patients with coronary heart disease. In part, this is due to the lack of studies comparing different forms of exercise according to their effectiveness, which hinders the development of exercise guidelines. Physical interventions such as endurance and resistance training have not been adequately compared prospectively in patients with early breast cancer during chemotherapy.

This clinical intervention study compares the effects of moderate endurance (ET) and moderate resistance (RT) training with standard care (SC) on physical fitness, fatigue, concentration and QoL in women with primary breast cancer during adjuvant chemotherapy.

## Patients and Methods

In this prospective, controlled and randomized intervention trial 12-week supervised RT, and ET, were compared with SC in women with primary moderate- or high-risk breast cancer during adjuvant chemotherapy. An overview of the study flow is shown in Figure 1. Patients were recruited at the University Hospital of Schleswig-Holstein, Campus Kiel in Germany. Interested women were screened to determine if they met the following eligibility

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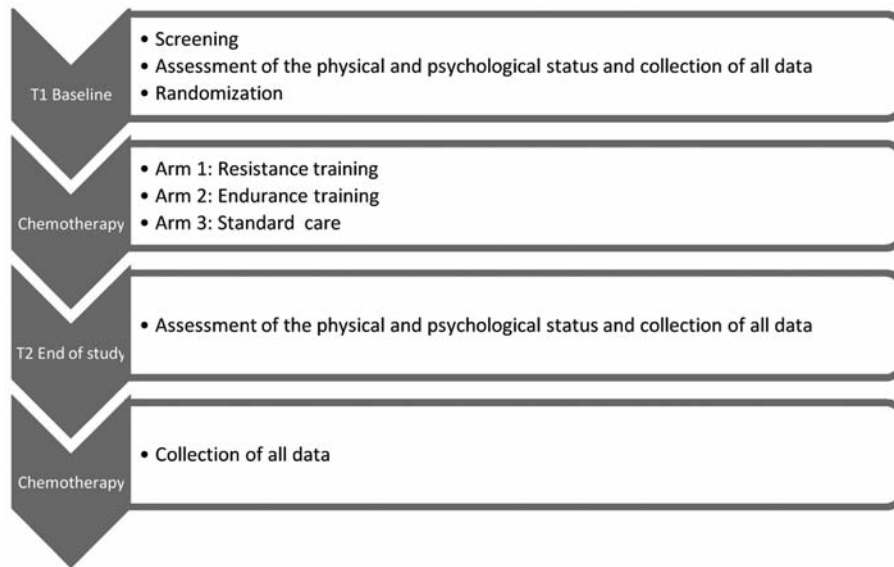


Figure 1. Study design.

criteria: primary moderate- or high-risk breast cancer, initiating adjuvant chemotherapy without taxane and Herceptin, 18-70 years old, and physician clearance to exercise. Exclusion criteria comprised acute infectious disease, severe cardiac disease (New York Heart Association functional class III; myocardial infarction <3 months), severe pulmonary or renal insufficiency (glomerular filtration rate <30%), serious neurological disorders, fewer than 10,000 platelets per ml, hemoglobin <8 g/dl and planned radiotherapy during the study.

All patients received the recommendation to participate from their oncologist, furthermore, there was information about the study design accessible from pamphlets in the hospital. The study was approved by the Local Review Board (registration number: AZ A 157/11). All participants gave their written informed consent prior to enrollment in the study.

After baseline assessments, the patients were assigned randomly (1:1:1) to RT, ET or SC using a computer-generated program. The allocation sequence was executed by the clinical research unit and concealed from the project team.

The analyses included data of patients who attended a minimum of 70% of the training sessions according to protocol. Performance was assessed at baseline (T1), and at 12 weeks after initiation of chemotherapy and physical intervention (T2). Primary end-points of this trial were muscular strength in newton meters at *latissimus* pull down, bench press and leg press, endurance, and subjective perceived exertion during endurance stress test (Borg scale) and QoL assessed using measured by standardized report form of the European Organization for Research and Treatment of Cancer (EORTC QLQ) C30+BR23 at T1 and T2. Results obtained at baseline were compared across the treatment and control groups using an independent *t*-test for continuous outcomes, with statistical significance set at the probability level of  $p < 0.05$ . The data are expressed as the mean and standard deviations. The analyses were performed using the SPSS system for windows (Version: PASW 18, IBM, Ehningen, Germany).

Out of 100 patients screened between February 2012 and October 2013, 81 were enrolled in the study and randomized before the start of chemotherapy into the intervention groups ET and RT, or SC. Nineteen patients did not enroll due to timing problems. Due to chemotherapy-related side-effects or withdrawal of consent, 14 out of 81 patients dropped out: three withdrew from the RT, nine from the ET and two from the SC groups. The data of 67 patients were fully evaluable (21 patients in the RT, 20 in the ET and 26 in the SC groups). An overview of the patient cohort is shown in Table I.

The muscular strength of upper (*latissimus dorsi* and *pectoralis* muscles) and lower (quadriceps femoris muscle) extremities was assessed by measuring isometric muscular capacity with M3 Diagnos (Schnell, Germany) combined with the computer program Diagnos Professional 2000. In order to test the maximum strength of the lower extremities, patients sat on a chair. The patients were requested to stretch their legs against a fixed bar for about 5 seconds. To test the maximum strength of the upper extremities, the patients were encouraged to stretch their arms against the fixed bar for about 5 seconds (*pectoralis* muscle), followed by pulling the fixed bar for about 5 seconds (*latissimus dorsi* muscle). Every test was repeated twice with appropriate breaks in between tests.

The endurance test was assessed with the "Physical Worker Capacity Test 150" (PWC 150) ramp test as a bicycle ergometer test. For the ramp test, the patient was instructed to cycle at a speed of 60 to 70 revolutions per minute (RPM). The test started at 25 W, after which the load was increased by 25 W every 2 min. At the end of each exercise level, the watt load, the subjective perceived exertion during the endurance stress test based on a numerical scale according to Borg (18, 19), the heart rate and the blood pressure were recorded.

The test ended if the patient had a heart rate of 150 beats per minute or cycling speed fell below 60 RPM. The maximum workload was recorded.

The European Organization for Research and Treatment of Cancer (EORTC) has developed several validated questionnaires to

Table I. Anamnestic and anthropometric parameters of the patients.

	Study group		
	RT	ET	SC
Number	21	20	26
Age (years) (mean±SD)	53 ±12.55	56±10.15	54 ±11.19
Height (cm) (mean±SD)	176±5.63	175±4.87	177±2.57
Weight (kg) (T1) (mean±SD)	74.8±15.83	72.1±12.35	76.3±15.40
Surgery			
Breast-preserving	16	15	20
Breast ablation	6	4	6

RT: Resistance training; ET: endurance training; SC: standard care.

assess the QoL of patients with cancer in a multidimensional approach. The questionnaire used was EORTC QoLQ C30, version 3 BR23, which was especially developed for patients with breast cancer. The results section of the questionnaire focuses on QoL and fatigue (20, 21). The fatigue symptoms were assessed by the Multidimensional Fatigue Inventory with 20 questions (MFI-20). The MFI-20 is an internationally frequently used questionnaire (22, 23). Cognitive function was estimated with the D2-Test. This is a standardized, reliable and valid measure. The D2-Test of attention measures processing speed, rule compliance, and quality of performance, allowing for a neuropsychological estimation of individual attention and concentration (24).

The RT and ET were performed during the period of chemotherapy. After initiation of chemotherapy, both physical interventions took place for 60 min twice weekly for 12 weeks. The training sessions of the RT and ET were supervised and documented by experienced exercise therapists. Before each training session, the intensity of levels were checked according to the exercise guidelines for cancer survivors of the American College of Sports Medicine (25).

In order to define the individual resistance for each exercise, the therapist carried out the hypothetic one-repetition maximum (h1RM) according to the Brzycki method (26) in the first training session of the RT group. The h1RM is a dynamic maximum force test and was performed according to the repetition method. Thereby, the therapist chose the weight so that the patient could not carry out more than 20 repeats (27). The h1RM test took place on all workout machines. At the beginning, patients of the RT group completed one training set of 20 repetitions, with a hypothetical 50% of the maximum weight. The training took place on the following devices: squat, chest press, leg curl, rowing, leg extension, upper arm curl, upper arm extensors, shoulder press, abdominal bench and *latissimus* pull down. Any further increase in intensity was based on the Borg scale (18, 19).

The ET took place on an indoor bike (Tomahawk; Indoorcycling Group, Nuremberg, Germany). As subjective reference point for the performance during the training, the Borg-scale was used. The patients were encouraged to be active at Borg level 11-14 (18, 19). During the training, patients exercised for 45 min. After a 10-minute warm-up, the patients exercised for 25-30 min followed by a 5-min cool-down.

## Results

The changes in muscular strength for *latissimus* pull down, bench press and leg press, of total force in endurance and subjective perceived exertion during endurance stress test are shown in Tables II and III. The muscular strength improved significantly in the RT group for *latissimus* pull down ( $p=0.014$ ) and bench press ( $p=0.021$ ), and in the ET groups for the bench press ( $p=0.023$ ). In the SC group, the muscular strength was maintained. Performance of all groups decreased in the endurance stress test after 12 weeks, however, the maximum endurance loss was greatest in the SC group (RT: 0.16 W/kg/bodyweight ( $p=0.01$ ); ET: 0.10 W/kg/bodyweight ( $p=0.006$ ), SC: 0.21 W/kg/bodyweight ( $p=0.001$ ). The subjectively perceived exertion at 100 W remained stable with RT ( $p=1.00$ ) and decreased most with SC ( $p=0.3$ ), and to a lesser extent with ET ( $p=0.02$ ). The subjectively perceived exertion at the maximum watt level in the RT and ET groups significantly increased after therapy (RT:  $p=0.002$ ; ET:  $p=0.02$ ). A significant decrease of the perceived exertion was found in the SC group ( $p=0.03$ ).

Neither intervention methods were associated with an improvement of fatigue symptoms from T1 to T2. All groups had a significant statistical improvement in cognitive function. Changes in cognitive function were favored in the exercise groups (RT:  $p=0.001$ , ET:  $p=0.001$ , SC:  $p=0.02$ ). However, both types of intervention were associated with improved QoL. In the RT group, QoL score improved significantly during 12 weeks of intervention ( $p=0.011$ ). There was also a trend for improvement of QoL in the ET group ( $p\geq 0.05$ ). The SC group experienced a decrease in QoL.

In the RT and ET group, a trend towards improvement from T1 to T2 was observed for pain (RT:  $p=0.54$ , ET:  $p=0.07$ ) and insomnia (RT:  $p=0.26$ , ET:  $p=0.21$ ), in contrast to a non-significant decrease in the SC (pain:  $p=0.78$ , insomnia:  $p=0.51$ ).

A non-significant improvement in emotional function (RT:  $p=0.29$  ET:  $p=0.10$ , SC:  $p=0.30$ ) and diarrhea (RT:  $p=0.45$  ET:  $p=0.33$ , SC:  $p=0.60$ ) from T1 to T2 was detected in all groups.

In all groups, a significant increase in chemotherapy-related side-effects from T1 to T2 was observed (RT:  $p=0.001$ ; ET:  $p=0.001$ ; SC:  $p=0.001$ ). For both intervention groups, patients with a low level of physical efficiency at T1 improved more than patients with a high efficiency at the start (Tables IV and V).

## Discussion

Previous studies performed during cancer therapy described an improvement in physical function, fatigue and QoL after interventional physical activity (12, 28-30). The primary

Table II. Changes in total force (NM) and percentage improvement of the intervention groups and the standard care (SC) group. Data are means±SD.

Group	Leg press				Bench press				Latissimus pull-down			
	T1 (NM)	T2 (NM)	p-Value	%	T1 (NM)	T2 (NM)	p-Value	%	T1 (NM)	T2 (NM)	p-Value	%
RT	85.62±33.01	90.06±29.2	0.615	4.47	113.0±54.5	148.5±37.5	0.021	31.41	111.5±48.5	146.97±38.0	0.014	31.81
ET	70.0±22.51	72.3±18.53	0.726	3.28	72.0±34.01	98.01±35.6	0.023	36.25	85.2±38.22	111.0±43.0	0.052	30.28
SC	79.71±24.5	80.03±26.5	0.969	0.4	85.3±36.5	91.32±29.0	0.567	7.05	94.17±42.27	96.50±32.83	0.847	2.47

T1: Baseline; T2: 12 weeks after the initiation of chemotherapy and intervention; RT: resistance training; ET: endurance training.

Table III. Weight and exercise capacity of the intervention groups and the standard care (SC) group at baseline (T1) vs. 12 weeks after the initiation of chemotherapy and intervention (T2). Data are means±SD.

Parameter	T1			T2			p-Value		
	RT	ET	SC	RT	ET	SC	RT	ET	SC
Weight (kg)	74.8±15.83	72.1±12.35	76.3±15.40	75.7±10.28	73.2±9.10	76.1±13.50	0.82	0.64	0.96
W/kg/bodyweight	1.70±0.51	1.66±0.38	1.48±0.47	1.54±0.51	1.43±0.47	1.27±0.39	0.01	0.006	0.001
Maximum watts	120.0±28.79	117.5±21.61	108.65±26.40	111.25±32.92	108.75±23.33	95.19±23.47	0.03	0.03	0.001
Subjective perceived exertion at 100 W	13.92±2.30	14.25±1.73	14.81±2.07	13.92±1.68	15.40±1.40	15.37±1.85	1.00	0.02	0.3
Subjective perceived exertion at maximum watts	15.85±1.66	16.6±2.3	15.11±3.05	15.05±1.84	15.87±2.37	16.00±2.59	0.002	0.02	0.03

RT: Resistance training; ET: endurance training.

objective of the present study was to determine the impact of RT and ET compared to SC in patients with breast cancer undergoing adjuvant chemotherapy. The vast majority of interventions in previous studies were in the form of aerobic exercise, whereas RT as intervention was under-represented.

There have been several randomized controlled trials (RCTs) during chemotherapy of patients with breast cancer that have compared various modes of physical activity (31-33). The multi-modal high-intensity exercise intervention in cancer patients undergoing chemotherapy and its effects were described by Adamsen *et al.* in 2009. Out of 269 patients with different cancer entities, 119 patients with breast cancer were enrolled. The training program resulted in significant improvements of vitality, physical function, role function, emotional function, fatigue and mental health. In addition, the physical capacity (maximum oxygen consumption and muscular strength) was significantly improved. No significant effect was seen in global health status and QoL (31). Battaglini *et al.* observed that after a 21-week exercise training, significant differences in lean body mass, body fat and strength occurred (32). In a multi-center RCT, 242 patients with breast cancer at initiation of adjuvant chemotherapy were subjected to SC, supervised resistance exercise or supervised aerobic exercise for the duration of their chemotherapy. There was an indication that resistance

exercise was superior to SC for improving self-esteem, muscular strength, lean body mass and chemotherapy completion rate. There were no significant changes in cancer-specific QoL, fatigue, depression and anxiety (33). Our results are similar to the results of these studies. The comparison of interventions showed that RT, as well as ET, lead to significantly improved total force. Additionally, the subjective perceived exertion during physical activity and the QoL were improved. The increment of total force was largest in the RT group and in comparison with SC, differences were statistical significant ( $p=0.015$ ). The comparison of the other groups did not show statistically significant differences (RT/ET:  $p\geq 0.05$ ; ET/SC:  $p\geq 0.05$ ).

In contrast to the results of the studies by Adamsen *et al.* (31) and Courneya *et al.* (33), in both intervention groups (RT and ET) an increase in QoL was seen, whereas a decrease in QoL in the SC group was observed. Several other studies used RT and ET without exact definition of techniques and applied intensities. Therefore a comparison of the different previous trial results is difficult. Moreover, it remains uncertain if both RT and ET could equally be used as supportive measures during adjuvant chemotherapy for patients with breast cancer. This is one of the first clinical trials systematically comparing different precisely specified physical interventions. Both RT and ET groups received a

Table IV. *Psychology parameters, quality of life (EORTC QLQ C30) fatigue (MFI20) and cognitive functioning (D2-test) of the intervention groups and the standard-care (SC) group. Data are means±SD.*

Parameter	T1			T2			<i>p</i> -Value (T1 vs. T2)		
	RT	ET	SC	RT	ET	SC	RT	ET	SC
Physical functioning	85.71±15.14	85.92±15.70	87.29±12.34	82.94±14.94	73.83±16.34	77.5±13.59	0.40	0.001	0.001
Role functioning	77.78±29.70	66.67±22.94	69.44±30.56	70.63±25.77	66.67±28.61	65.44±26.23	0.35	1.00	0.55
Emotional functioning	55.56±24.49	59.17±23.08	57.29±22.83	61.9±26.63	67.5±21.27	62.85±20.56	0.29	0.10	0.30
Cognitive functioning	83.33±19.00	83.33±19.50	86.11±19.45	73.02±25.47	75.0±23.88	86.11±18.98	0.02	0.06	0.01
Social functioning	59.52±31.43	70.83±25.29	65.28±31.44	65.08±28.34	64.17±23.12	56.94±30.26	0.36	0.33	0.13
Fatigue	22.22±21.94	31.11±26.39	30.56±17.72	38.62±17.43	48.00±21.77	43.52±21.46	0.001	0.02	0.001
Nausea and vomiting	3.91±14.82	2.50±6.11	2.08±5.63	14.29±16.06	10.0±17.44	8.33±13.00	0.20	0.07	0.05
Pain	24.60±31.89	43.17±28.34	22.92±22.42	20.63±28.34	20.83±24.11	24.31±25.05	0.54	0.07	0.78
Dyspnea	16.67±22.94	15.00±22.88	8.33±1.72	15.00±20.94	31.67±35.00	26.31±24.04	0.58	0.03	0.001
Insomnia	36.84±36.67	45.00±32.94	44.44±34.98	29.82±31.22	35.00±35.00	50.00±34.05	0.26	0.21	0.51
Appetite loss	4.76±1.94	10.00±19.04	8.33±17.72	19.05±29.00	23.33±28.82	18.66±24.04	0.07	0.12	0.11
Constipation	3.33±10.26	5.00±12.21	8.33±20.26	21.67±29.17	21.6±32.93	22.22±36.34	0.02	0.06	0.14
Diarrhea	21.67±27.09	1.67±7.45	13.89±19.45	15.00±27.52	0.00±0.00	11.11±25.38	0.45	0.33	0.60
Financial difficulties	26.98±38.90	26.67±29.81	20.83±29.17	31.75±41.47	23.33±28.87	37.50±34.49	0.38	0.54	0.03
Quality of life	24.83±14.04	30.36±18.23	31.14±19.76	31.29±15.88	36.79±17.99	30.95±15.29	0.011	0.09	0.8
General fatigue	9.25±3.09	8.76±4.31	9.54±3.35	10.55±3.22	12.35±4.37	12.38±3.50	0.03	0.02	0.001
Cognitive functioning	127.23±25.54	129.30±33.90	127.19±36.71	143.57±23.96	143.00±36.32	137.07±35.15	0.001	0.001	0.02

T1: Baseline; T2: 12 weeks after the initiation of chemotherapy and intervention; RT: resistance training; ET: endurance training.

Table V. *Psychological parameters (EORTC QLQ-BR23) of the intervention groups and the standard-care (SC) group. Data are means±SD.*

Parameter	T1			T2			<i>p</i> -Value		
	RT	ET	SG	RT	ET	SC	RT	ET	SC
Body image	72.37±30.60	81.02±23.54	74.62±25.26	60.0±32.70	62.96±30.14	59.72±	0.02	0.001	0.001
Sexual functioning	38.60±33.82	19.44±19.17	31.88±28.83	36.0±31.55	20.37±27.15	26.81±23.43	0.73	0.86	0.40
Sexual enjoyment	100±0.0	60.0±43.46	66.67±30.86	80.95±37.80	66.67±40.82	66.67±25.20	0.23	0.37	1.00
Future perspective	31.58±26.0	43.86±31.53	49.12±32.45	43.86±31.53	34.92±30.16	38.1±26.23	0.03	0.38	0.74
Systematic therapy side-effects	16.52±20.21	13.97±12.72	11.83±10.09	48.98±11.79	45.12±13.72	42.41±17.07	0.001	0.001	0.001
Breast symptoms	30.03±23.82	32.92±19.40	28.70±17.92	20.63±22.76	20.69±14.55	17.36±16.10	0.02	0.001	0.01
Arm symptoms	24.87±25.07	29.44±22.30	21.76±22.10	24.87±30.41	31.67±24.52	22.69±21.35	1.00	0.71	0.84

T1: Baseline; T2: 12 weeks after the initiation of chemotherapy and intervention; RT: resistance training; ET: endurance training.

defined training program, with moderate to accelerated individualized intensities. Intensities were defined using validated tests.

Adamsen *et al.* found a significantly positive effect in favor of the intervention groups for fatigue in a study with different cancer entities undergoing chemotherapy (31). Reduced fatigue in women with breast cancer during chemotherapy, with a home-based intervention, was also reported by Schwartz *et al.* (4). This single-arm study examined the relationship between fatigue and exercise. All 72 participants were instructed to keep a fatigue diary. All measures of fatigue were significantly reduced on the day of exercise

compared to non-exercise days. The amount of exercise, measured as the number of minutes trained, was significantly associated with fatigue levels. In our study, fatigue was not improved by any of the interventions, fatigue values deteriorated from T1 to T2. This can be explained by fatigue being one of the main unwanted side-effects of chemotherapy and the low frequency of measurements (two time points) and long periods of time between measurements (12 weeks).

Cognitive impairment is being acknowledged as an after-effect of cancer treatment. Chemotherapy-induced cognitive impairments occurred in 23% in women with breast cancer. Previous studies focused on the impact of psychoeducational

techniques or cognitive training to alleviate cognitive impairment. Studies have not yet considered physical activity as having potential for alleviating cognitive problems (34, 35). Cognitive function improved in all three of our groups from T1 to T2. This can be explained by T1 being a time point shortly after the patients learned about their breast cancer diagnosis. Compared to normal levels of cognitive function (24), at T1 of this trial, cognitive function already registered reduced levels. Obviously patients learned to cope with their breast cancer during chemotherapy and were psychologically less impaired than immediately before initiation of chemotherapy at T1. This may also explain the improved cognitive function at T2. Sub-group analysis was not performed due to small sample sizes. Different chemotherapy regimens and different surgical procedures were evenly distributed within the three groups.

The methods used, RT and ET, should not be regarded as competitors, but as a supplement of supportive therapeutic options. Both intervention methods can improve QoL and attenuate the loss of physical performance.

In their study, Courneya *et al.* found that patients with breast cancer may have preference for a particular training method and that this preference influences the effectiveness of the training program. Patients who preferred RT had improved QoL if they had participated in RT compared with SC or aerobic exercise training (29, 33).

## Conclusion

This clinical trial shows a combined intervention of ET and RT may be optimal and needs to be further evaluated. The beneficial results of this trial suggest that physical intervention (including a resistance intervention) should be implemented into standard-of-care during adjuvant chemotherapy for patients with breast cancer.

## Conflicts of Interests

The Authors declare that they have no competing interests with regard to this study.

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