

## Effects of Resistance Training on Cancer-Related Fatigue in Adult Persons with Breast Cancer - A Review of Randomized Controlled Trials

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### Abstract

Cancer-related fatigue (CRF) is the most common and distressing symptom in breast cancer patients. Approximately 40%-80% of cancer patients suffer from CRF. Evidence suggests that exercise improves CRF; however, the specific effects of training modalities are not well understood. This paper aims to analyze the effects of resistance training intervention on cancer-related fatigue in breast cancer patients. A systematic search of English articles was conducted using PubMed (2014-2019) to identify randomized control trials that evaluated the effects of resistance training on CRF in patients with breast cancer. One another were independently extracted by data for study characteristics; results were used to rate the methodological quality and description of the exercise intervention. Three randomized controlled trials (RCTs) met the inclusion criteria for this study. A significant improvement in cancer-related fatigue was observed for the exercise group in all three trials. Resistance training improves CRF in patients with breast cancer and could be considered a safe and effective adjunctive treatment in reducing CRF among breast cancer patients.

**Keywords:** Breast cancer, Cancer-related fatigue, Exercise, Randomized controlled trials, Resistance training

### Introduction

Breast cancer is the most commonly diagnosed invasive cancer in women (Anderson & Guttilla Reed, 2020) and (Konat-Bąska *et al.*, 2020). In 2012, approximately 1.7 million breast cancer cases were detected worldwide (Meneses-Echávez *et al.*, 2015) and (Schad *et al.*, 2020). The World Health Organization (WHO) <sup>1</sup> estimated that 627,000 women died from breast cancer, approximately 15% of all cancer deaths among women in 2018 (World Health Organization, 2019). Patients with breast cancer not only suffer from specific signs and symptoms but also suffer from cancer-related fatigue (CRF) as a general manifestation in cancer patients (Joly *et al.*, 2019), (Gandhi *et al.*, 2020) and (Mustian *et al.*, 2012). Accumulating evidence suggests that CRF may have been an important factor in lowering survival for cancer patients (Bower, 2014), (Invernizzi *et al.*, 2020) and (Kim *et al.*, 2020). CRF is the most common devastating symptom in all breast cancer patients, being present not only in inactive or advanced cancer but also in patients who have undergone treatment (Horneber *et al.*, 2012), (Horneber *et al.*, 2012) and (M *et al.*,

2020). A growing body of evidence indicates that exercise is an effective nonpharmacological adjuvant therapy for improving CRF in cancer patients (Mustian *et al.*, 2012), (American Cancer Society, 2020) and (Oei *et al.*, 2020). Some systematic review findings supported the effects of exercise interventions on CRF but, most of the interventions included combined exercise interventions (aerobic and resistance training), and the participants were from a different type of cancer (Meneses-Echávez *et al.*, 2015), (Inglis *et al.*, 2020) and (Hl *et al.*, 2020). Another systematic review about exercise and CRF concluded that aerobic exercise reduces CRF in cancer patients (Meneses-Echávez *et al.*, 2015), (Ikeuchi *et al.*, 2020) and (Mustian *et al.*, 2012). However, there is not enough evidence to date to support the benefits of resistance training for improving CRF in patients with breast cancer. This short narrative review aimed to determine the effect of resistance training on CRF in breast cancer patients. We reviewed randomized control trials that assessed the impact of resistance training on CRF in adult persons with breast cancer compared with a control group that received usual care or relaxation program but no exercise program.

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## Methods

### Eligibility criteria, in-/exclusion criteria

This review included randomized control trials examining the effect of resistance training on CRF in adult breast cancer patients. RCTs were included if they met the following criteria: adults 18 years of age and older who were breast cancer patients, resistance training (one group received supervised resistance training and the other group received the usual care or supervised muscle relaxation program without any physical activity program) and any measure of CRF as an outcome. RCTs were excluded based on any one of the following: inappropriate population such as pediatric and other types of cancers, combined intervention (aerobic exercise and resistance training) or non-

conventional exercise program (e.g., aqua aerobics, Tai Chi, and yoga) and non-supervised exercise program delivered via the internet or a DVD for a home program.

### Information sources and search strategy

A systematic literature searches of English articles published in the last five years was conducted in PubMed. Keywords, Medical Subject Headings, and other index terms were used to construct the search strategy, including breast cancer, cancer-related fatigue, exercise, resistance training, and all possible combination of the terms. Table 1 shows the search string and all filters which were applied.

Table 1. Search strategy, including search terms and limitations.

Database: PubMed Period: last five years Date of searching: 10.02.2019		
Search	Results	Queries
#1	3315	"Breast Cancer"
#2	2835	"Breast Cancer" [Mesh]
#3	<b>3315</b>	<b>#1 OR #2</b>
#4	829	"Cancer-related fatigue"
#5	294	"Fatigue in breast cancer"
#6	<b>988</b>	<b>#4 OR #5</b>
#7	8311	"Exercise" [MesH]
#8	5156	"Exercise therapy" [MesH]
#9	795	"Supervised exercise"
#10	2002	"Resistance training"
#11	1566	"Resistance training" [MesH]
#12	<b>10857</b>	<b>#7 OR #8 OR #9 OR #10 OR #11</b>
#13	<b>82</b>	<b>#3 AND #6 AND #12</b>
	44	Limitations: Only RCTs published in the last five years

A total of 44 RCTs were screened by one author. Titles and abstracts of articles were retrieved and screened to identify those that met the inclusion criteria, such as CRF assessment, supervised resistance training, and a control group with no exercise. A full-text screening evaluated the eligibility of the articles and led to exclusion if the specified criteria were not satisfied.

### Data extraction

Data from the RCTs, including the number of participants, description of resistance training (duration, intensity, frequency, and rest intervals), their inclusion/exclusion criteria, effect estimated, period and types of evaluation and assessment of CRF, and the study results and conclusion were extracted. The methodological quality of the trials was assessed using the Physiotherapy Evidence Database (PEDro) scale (0-10). This scale evaluates the risk of bias, random/concealed allocation, baseline comparability, the measure of key output, and blinded participants/therapist/assessors, etc. To rate the exercise intervention description, the Consensus on Exercise Reporting Template (CERT) was used to evaluate the characterization of the exercise intervention in three RCTs.

## Results

### Study selection

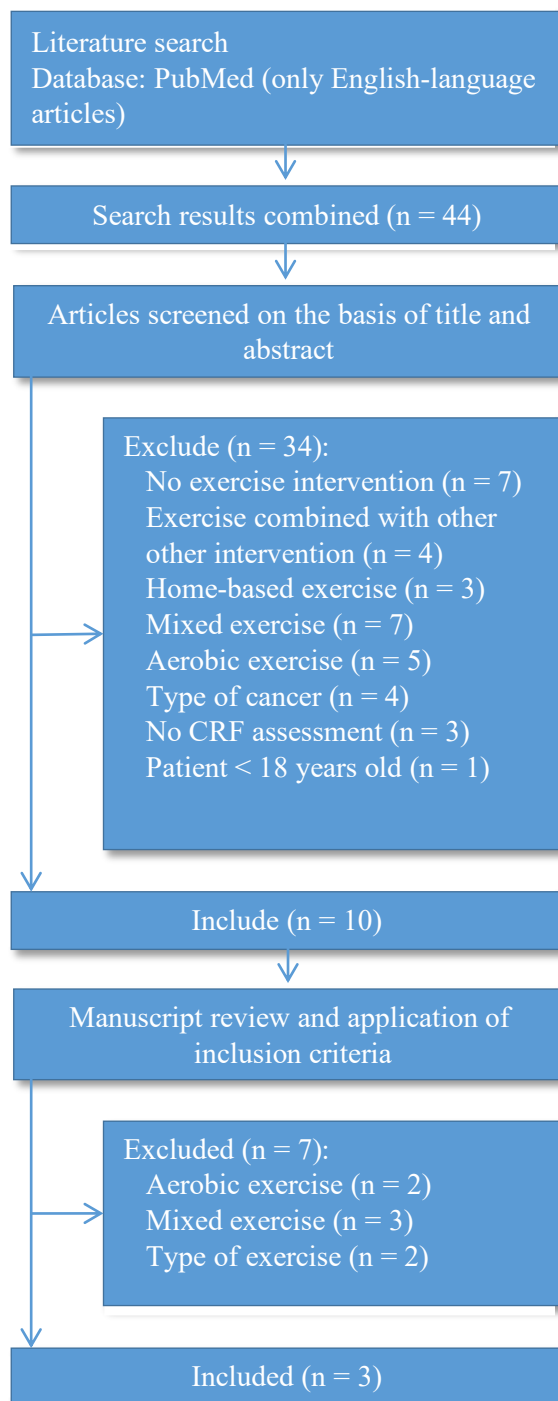


Figure 1. article selection

### Study characteristics and results

The three RCTs were conducted in Australia and Germany (one in Australia and two in Germany). Table 2 presents the number of patients, in-/exclusion criteria, and duration of the intervention. The participants of all RCTs had to be histologically diagnosed with breast cancer and aged more than 18 years. The duration of the two studies was 12 weeks and the other one 16 weeks /3 sessions per week. The duration of each session was 60 min for all trials.

Table 2. Summary of study characteristics

Source	No of patients	Inclusion criteria	Exclusion criteria	Duration
Steindorf <i>et al.</i> (2014)	160	Histologically confirmed primary BC, stage 0-III after lumpectomy or mastectomy, schedule for radiotherapy, age $\geq 18$ years, body mass index (BMI) $\geq 18$ kg/m <sup>2</sup> , ability to understand and follow the study protocol, and willingness to come to the exercise facilities.	Contraindication for resistance training (e.g. acute infectious disease, severe cardiac disease, severe respiratory insufficiency), patient with other concomitant malignant diseases (except carcinoma in situ of skin or cervix) and patients who were currently participating in systematic intense exercise training (at least 1 h twice/week) or who had previously participated in an exercise intervention trial.	12 weeks
Schmidt <i>et al.</i> (2014)	101	Histologically confirmed primary breast cancer after lumpectomy or mastectomy, scheduled for adjuvant chemotherapy, age $\geq 18$ years, body mass index (BMI) $\geq 18$ kg/m <sup>2</sup> , ability to understand and follow the study protocol, and willingness to come to Heidelberg exercise facilities.	Patients with contraindication for resistance training, with other concurrent malignant diseases (except carcinoma in situ of skin or cervix), or already participating in systematic intensive resistance or aerobic training (at least 1h twice/week).	12 weeks
Hagstrom <i>et al.</i> (2015)	39	History of histologically confirmed stage I-IIIa breast cancer with no evidence of recurrent disease, age 18-70 years, completed surgery, radiotherapy and/or chemotherapy, with or without current use of hormonal therapy (e.g. tamoxifen, aromatase inhibitor), sedentary (< 30 min of structured, continuous moderate-intensity exercise, three times per week and no current RT, stable underlying chronic diseases, ability to communicate in English, ability to provide written informed consent.	Acute or chronic medical conditions that would make exercise potentially hazardous or primary outcomes impossible to assess, high-risk individuals (after screened for participation using the Physical Activity Readiness Questionnaire (PAR-Q) and a standard health history questionnaire).	16 weeks

In two RCTs, the exercise group received the same duration and intensity of resistance training and the control group carried out progressive muscle relaxation without any aerobic or muscle-strengthening component. One trial (Hagstrom *et al.*, 2016) split the exercise prescription into two 8 weeks programs progressing from an introductory machine-based prescription to a more advanced free weight-style prescription. Program 1 exercises included leg extension, leg curl, or Romanian deadlift, lat pull down, machine bench press, seated

row, back extension, prone hold, or setups. Program 2 exercise included barbell squat, deadlift, free weight barbell bench press, leg press, barbell bent-over row, and assisted chin up. Both the exercise group and the control group receive usual medical care. The control group do not receive any specific instruction regarding physical activity and was not advised to change habitual activity levels. More details about the intervention and results can be found in table 3. The three RCTs assessed CRF with different questionnaires at baseline and post-

intervention. Two RCTs assessed CRF with the Fatigue Assessment Questionnaire (FAQ), a 20-item, multidimensional, and self-assessment questionnaire which covers the physical, affective, and cognitive fatigue dimensions. Scores are on a 0-100 scale, with higher scores indicating worse fatigue. One RCT (Hagstrom *et al.*, 2016) assessed fatigue with the Functional Assessment of Cancer

Therapy – Fatigue scale (FACIT – Fatigue) a 13-item scale and scoring ranges from 0 to 52 with a higher score indicating less fatigue. The three RCTs showed improvement in CRF after the intervention, particularly in the physical fatigue dimension, with an additional one-year follow-up in one RCT (Hagstrom *et al.*, 2016).

Table 3. Summary of results

Source	Intervention details	Assessment of CRF	Results
Steindorf <i>et al.</i> (2014)	The experimental group received about 60 minutes twice weekly over 12 week's RT, under the supervision of experienced physiotherapists. The progressive exercise intervention comprised eight different machine-based resistance exercises (3 sets, 8- 12 repetitions at 60 %-80 % of 1 repetition).	Fatigue Assessment Questionnaire (FAQ)	CRF decrease significantly in EX, while in RC there was no significant change. The effect was significant regarding physical fatigue ( $p = 0.013$ , $ES = 0.033$ ) but not for the affective ( $p = 0.91$ , $ES = 0.01$ ) or the cognitive ( $p = 0.65$ , $ES = 0.07$ ) dimensions
Schmidt <i>et al.</i> (2014)	60 min twice-weekly RT over 12 weeks under the supervision of experienced therapists. EX comprised 8 different machine-based resistance exercises (3 sets, 8- 12 repetitions at 60 %-80 % of 1 repetition maximum).	Fatigue Assessment Questionnaire (FAQ)	Improvement in CRF was significant in the EX group above the psychosocial effects. This benefit was mainly due to effects on the physical fatigue dimension ( $p = 0.052$ ).
Hagstrom <i>et al.</i> (2015)	16 weeks supervised RT program three times per week for approximately 60 min per session. Three sets of eight to ten repetitions were performed.	Functional Assessment of Cancer Therapy – Fatigue scale (FACIT – Fatigue)	The exercise intervention was associated with significant improvement in fatigue ( $P = 0.006$ , $ES = 0.20$ ).

RT, Resistance Training; CRF, Cancer-related fatigue; EX, Exercise group; RC, Relaxation Control group; ES, Effect Size.

The methodological quality and reporting of eligible studies are reported in table 4. The mean PEDro score for trials was 6.66 (range from 6 to 7).

Table 4. Methodological quality and reporting of eligible studies PEDro scale.

Study	PEDro Scale Items											PEDro Score (0 to 10)
	1 <sup>a</sup>	2	3	4	5	6	7	8	9	10	11	
Steindorf <i>et al.</i> (2014)	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Schmidt <i>et al.</i> (2014)	Y	Y	y	Y	N	N	N	Y	Y	Y	Y	7
Hagstrom <i>et al.</i> (2015)	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	6

All RCTs had a high methodological quality on the PEDro scale for cancer-related fatigue. Random and concealed allocation, baseline comparability, intention-to-treat analysis, comparison between the group, and calculation of point estimates and output variability were carried out in all three RCTs.

*Y = yes, N = no. <sup>a</sup>1 = Eligibility criteria, and score of participants, 2 = random allocation, 3 = concealed allocation, 4 = baseline comparability, 5 = blinded participants, 6 = blinded therapists, 7 = blinded assessors, 8 = adequate follow-up, 9 = intention-to-treat analysis, 10 = between-group comparisons, 11 = point estimates and variability. <sup>b</sup> Item 1 does not contribute to the total score.*

Table 5 presents the individual scores for each criterion of CERT evaluation in this review. A detailed data extraction method for each RCT is included in the appendix. CERT scores (expressed as a percentage of total possible points) ranged

from 42.1% to 73.6% for the three RCTs. None of the studies described how the adherence is measured, any motivation strategies, any home program component, and any non-exercise components. While all three RCTs reported the following criteria: exercise equipment, qualifications, expertise and/or training, group or individual exercise performance, supervision, adverse events that occur during the exercise, a detailed description of exercise intervention, and the extent to which the intervention was delivered as planned.

Table 5. Consensus on Exercise Reporting Template (CERT) Assessment

Item	Steindorf <i>et al.</i> (2014)	Schmidt <i>et al.</i> (2014)	Hagstrom <i>et al.</i> (2015)
1 A detailed description of the type of exercise equipment	1	1	1
2 Detailed description of the qualifications, expertise, and/or training	1	1	1
3 Describe whether exercises are performed individually or in a group	1	1	1
4 Describe whether exercise is supervised or unsupervised; how they are delivered	1	1	1
5 A detailed description of how adherence is the measure	0	0	0
6 A detailed description of motivation strategies	0	0	0
7a A detailed description of the decision rule(s) for determining exercise progression	0	0	1
7b A detailed description of how the exercise program was progressed	0	0	1
8 A detailed description of each exercise to enable replication	0	0	1
9 A detailed description of any home program component	0	0	0
10 Describe whether there are any non-exercise components	0	0	0
11 Describe the type and number of adverse events that occur during exercise	1	1	1
12 Describe the setting in which the exercises are performed	1	1	1
13 A detailed description of the exercise intervention	1	1	1
14a Describe whether the exercises are generic (one size fits all) or tailored	0	0	1

14b	A detailed description of how exercise is tailored to the individual	0	0	1
15	Describe the decision rule for determining the starting level	0	0	1
16a	Describe how adherence or fidelity is assessed/measured	0	0	0
16b	Describe the extent to which the intervention was delivered as planned	1	1	1
Total score		8 (42.1%)	8 (42.1%)	14 (73.6%)

1 = yes, 0 = no

## Discussion

### Summary of evidence

The reviewed RCTs estimated the effect of resistance training on cancer-related fatigue in patients with breast cancer. All three RCTs showed improvements in CRF in favor of the exercise group. However, in the trials from (Steindorf *et al.*, 2014) and (Schmidt *et al.*, 2015), this benefit was mainly due to the physical fatigue dimension at  $p < 0.05$  level. Besides, these two studies selected a group-based control intervention with psychosocial conditions similar to the exercise program. Thus, the results indicate pure resistance training effects beyond psychosocial effects induced by the group-based programs. The (Hagstrom *et al.*, 2015) study also showed that exercise intervention was associated with significant improvement in fatigue ( $p=0.006$ ,  $ES=0.20$ ) but, this study compared the exercise intervention with usual care; therefore, there is a possibility of psychosocial benefit related to the supervised group-based intervention. Furthermore, another interesting finding of (Hagstrom *et al.*, 2015), the study was a one-year follow up, which showed significant improvement in CRF in the exercise group. The findings are similar to studies that found significant improvement in CRF in patients with breast cancer after exercise intervention. It is worth noting that all three RCTs, besides CRF, assessed quality of life as a secondary end-point and found significant improvement in quality of life after exercise intervention. The RCT included in this study conducted the exercise intervention on breast cancer patients with a different stage of the disease and receiving different types of treatment like radiotherapy in (Steindorf *et al.*, 2014) study,

chemotherapy in (Schmidt *et al.*, 2014) study, and the participants of (Hagstrom *et al.*, 2015) study as breast cancer survivors. This indicates the application of resistance training as a safe, feasible, and efficacious adjunctive treatment in improving CRF and quality of life in a broad spectrum of breast cancer patients. Strength in the RCT from (Steindorf *et al.*, 2014) and (Schmidt *et al.*, 2014) was the group-based relaxation training as the control group.

### Limitations

The main limitation of this review was the small number of trials; the search only included English articles in the PubMed database. More eligible studies may exist in other languages and databases. Furthermore, like any other RCT of this nature, a fundamental limitation in all RCT included in this study was the inability to blind the participants in the receipt or assessment of the exercise program. Another limitation of the reviewed RCTs was long-term follow-up, which was not addressed so. Maintenance of the acquired benefits from the exercise group in breast cancer patients remains unknown. Further, (Hagstrom *et al.*, 2015) study did not compare the exercise group with the control group with similar psychosocial conditions to investigate the pure resistance training effects beyond the psychosocial benefits. Also, the study was designed around a primary immunological outcome. No power calculations for these secondary outcomes (CRF, quality of life) were conducted (Hagstrom *et al.*, 2015). Moreover, the information on non-participant patients were incomplete, which limit the generalization of the results in one study (Schmidt *et al.*, 2014).



## Conclusion

Based on this review, we conclude that resistance training effectively improves CRF in breast cancer patients. The findings of this review demonstrated that resistance training could be considered a safe, feasible, and effective adjunctive treatment in improving CRF among patients with breast cancer. This effect was over and above the psychosocial benefits associated with the group-based program in (Steindorf *et al.*, 2014) and (Schmidt *et al.*, 2014). Furthermore, resistance training improved CRF in breast cancer patients regardless of cancer stage and type of treatment, which shows the implication of this exercise intervention on a broad spectrum of breast cancer patients. Additionally, research with long-term follow-up is needed to examine whether the benefits of resistance training on CRF is long-lasting.

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