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REVIEW ARTICLE

The effect of training interventions on physical performance, quality of life, and fatigue in patients receiving breast cancer treatment: a systematic review

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Abstract

Objectives The primary purpose of this systematic review is to structure the available evidence concerning physical exercise programs and their effects on (1) physical performance outcomes, (2) experienced fatigue, and (3) quality of life (QoL) in patients during the initial treatment for breast cancer.

Data sources A systematic literature search, based upon the PRISMA guideline, up to January 1, 2018, was performed using four databases (Web of Science, Cochrane Library for Clinical Trials, PubMed, and Medline).

Study selection Inclusion criteria were as follows: (1) adults > 18 years; (2) patients with breast cancer undergoing initial treatment; (3) interventions with the aim to influence the patient's physical activity, QoL, or fatigue; (4) randomized controlled trials (RCTs) of all ages. The selected studies were scored for methodological quality, and data concerning physical performance, QoL, and fatigue were extracted. Twenty-eight RCTs were included.

Data extraction Different treatment modalities during initial treatment were identified (radiation therapy, chemotherapy, and combination therapy), as well as different types of physical training interventions (cardiovascular endurance exercise, strengthening programs, or a combination of both). Therefore, the results were clustered with regard to the above-mentioned grouping; extracting every relevant outcome related to physical performance (6 MWT or VO_{2peak}; grip/muscle strength), QoL (questionnaires), and fatigue (questionnaires).

Data synthesis Different training programs (endurance, resistance, or a combination of both) were found. These programs were applied during different phases of initial treatment. Some programs were supervised while others were home based. Overall, most training interventions provided an improvement in physical performance and a decrease in perceived fatigue. QoL was the outcome variable least susceptible to improvement.

This material was not presented anywhere thus far.

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Conclusion Different types of exercise programs are available for rehabilitation purposes of breast cancer patients during adjuvant therapy. Overall resistance training or resistance training in combination with CV endurance training provides the best results, especially on physical performance and perceived fatigue.

Keywords Breast cancer · Breast neoplasm · Physical activity · QoL · Fatigue · Motor activity · Benefit

Abbreviations

QoL	quality of life
6 MWT	6-min walking test
12 MWT	12-min walking test
CT	chemotherapy
RT	radiation therapy
ADL	activities of daily living
VO_{2peak}	peak oxygen uptake
1 RM	one repetition maximum
CV	cardiovascular

Introduction

Breast cancer is a devastating disease and is the most frequent diagnosed cancer in women [1]. The lifetime risk of being diagnosed with breast cancer is 1:8 [2]. Due to improved screening and awareness programs, breast cancer survival rates have doubled during the last four decades [3]. In addition, novel and personalized treatment protocols have also contributed to the increase in overall survival [4–8]. To date, the late 5-year relative survival for breast cancer in Europe approximates 83% and is still rising [9–11].

Although initial therapeutic strategies such as surgery, whether or not preceded by neo-adjuvant chemotherapy (CT), adjuvant CT, and radiation therapy (RT), hormone and targeted therapies become more personalized to the patients' individual tumor pathology; breast cancer survivors represent a group of patients with complex and often multiple side effects. [12, 13] [14], Frequent reported side effects include cardiac toxicity [15], reproductive dysfunction, lymphedema [16], nausea [17, 18], vomiting [17, 18], pain [17, 19], insomnia [17], appetite loss [17], cognitive changes [20, 21], and fatigue [17–19, 22, 23]. Fatigue has been reported as the most frequent occurring side effect (70–100% of the treated patients experience feelings of fatigue on the long term) [3, 17, 18, 22, 24–26]. Cancer-related fatigue often elicits a vicious circle of fatigue-induced reductions in physical activity; which exaggerates the feelings of fatigue. Reductions in physical activity have also been shown to reduce muscle mass and muscle strength resulting in decreased ADL empowering feelings of fatigue [27]. In combination with the overall feelings of fatigue, diminished levels of physical activity also have a negative impact on other side effects like health-related quality of life (QoL) [12, 17, 19, 22, 23, 25, 27, 28]. A growing body of evidence has shown that regular physical activity improves ADL and QoL in patients with breast cancer [3, 29]. For instance, physical exercise has been shown to be effective for increasing ADL and reductions in the feelings of fatigue [30]. Additionally, there is ample evidence that physical exercise has beneficial effects on mortality [18, 19], perceived fatigue [31, 32], ADL [27, 33, 34], QoL [31, 34, 35], anxiety, and depression [35, 36]. Despite growing scientific evidence regarding the beneficial effects of physical exercise, many breast cancer patients are reluctant to implement physical exercise in their daily life [18].

A Cochrane review by Furmaniak et al. showed that there is conclusive evidence regarding the positive effects of exercise training during adjuvant therapy in breast cancer patients [37]. Unfortunately, no distinction between different exercise protocols regarding type of training (resistance training vs endurance vs combined protocols) as well as the type of adjuvant therapy (CT, RT, or both) has been made. Therefore, the aim of the present systematic review is to assess the available evidence regarding the effects of physical exercise programs on physical performance, levels of fatigue, and QoL in breast cancer patients during the initial treatment period with respect to the different training protocols (endurance, resistance, or combined) and the type of adjuvant therapy (CT, RT, or both).

Methods

Literature search and selection criteria

The current review was registered on PROSPERO (www.crd.york.ac.uk/PROSPERO); registration number CRD42017071940.

This systematic literature search has been based upon the PRISMA guidelines (http://www.prisma-statement.org) and was performed using four different electronic databases; Web of Science (WoS), Cochrane Library for Clinical Trials, PubMed, and Medline. The latest full online search was performed on January 1, 2018, for all databases. Relevant keywords and entry terms were defined using the PICO(S) methodology, which was implemented into a Boolean search to obtain eligible studies. The following keywords were combined; "breast cancer" (P), "breast neoplasms" (P), "Exercise therapy"

(I), "Physical Endurance" (I), "motor activity" (I), "physical activity" (O), "activity level" (O), "physical fitness" (O), "quality of life" (O), "fatigue" (O), "strength" (O), and "cardiopulmonary function" (O). No comparison (C) was defined and all studies had to be randomized controlled trials (S); written in English, Dutch, or French. The specific search strategies for the four different databases are shown in Table 1. In Medline and PubMed, a filter concerning "document types" was used to define "randomized controlled trials. " Using WoS, the advanced data search method was applied in combination with the filter "document type: articles." The selection was conducted by two independent raters (M.C. and F.T.) in two screening phases. In phase one, all citations were screened for eligibility based on the title and abstract; for the eligibility criteria used, see Table 2. In phase two, the full-text articles were screened using the same criteria as listed in Table 2. In case of disagreement in either of both screening phases, consensus was reached during a consensus meeting moderated by a third researcher (M.C., F.T., N.G).

Quality assessment and data extraction

The methodological quality as well as the data extraction of the selected studies was assessed by two independent researchers (M.C. and F.T.). Methodological quality was evaluated using the checklist for randomized controlled trials (10 items) provided by the Dutch Cochrane Centre (http://Netherlands.cochrane.org). Items could be rated as "?," "0," or "1." An item was rated by "?" if no sufficient information was available in the article. If a criterion was lacking, this item was scored "0." An item was rated "1" if sufficient information was provided and bias was unlikely. If disagreement occurred during the rating, a consensus meeting was held with a third researcher (NG) as moderator. The total quality score, as provided in Table 3, is the sum of all criteria rated "1." Data extraction was done for every outcome related to physical performance, QoL, and perceived fatigue.

Results

Selection of studies and study characteristics

The initial search yielded 1512 studies. After the removal of duplicates and a first screening, 68 full-text articles were retrieved for second screening. Finally, after the second screening, 28 RCTs were included in the current review, see Table 3. The selected studies represented a total of 2525 breast cancer patients. The literature search, study selection process, and reasons for exclusion are shown in Fig. 1. All characteristics as well as the methodological quality of the 28 RCTs are presented in Table 3.

Physical exercise programs

Significant heterogeneity in the physical exercise programs was found among the selected studies. Fourteen studies [18, 19, 23, 27, 32, 35, 41, 44, 45, 48–52] used a cardiovascular (CV) endurance training intervention. Five [18, 32, 35, 45, 51] of these were reported on a supervised training program whereas the other nine studies [19, 23, 27, 41, 44, 48–50, 52] were reported on home-based training programs. Ten studies [22, 24, 25, 33, 34, 36, 38–40, 42] used a combined

Table 1 Summary of the Boolean search strategies in different databases used

Database	Search strategy
PubMed	(((breast AND cancer) OR "breast neoplasms" [MeSh]) AND (("exercise therapy" [MeSh]) OR (exercise AND therapy) OR (physical AND endurance) OR "motor activity" [MeSh]) AND ("physical activity" OR (activity AND level) OR "physical fitness" OR "quality of life" OR fatigue OR cardiopulmonary function OR strength))
Web of Science	TS = (("breast cancer" OR "breast neoplasms") AND ("exercise therapy" OR "physical endurance" OR "motor activity" OR aerobic training OR resistance training) AND ("physical activity" OR "activity level" OR "physical fitness" OR "quality of life" OR fatigue OR cardiopulmonary function OR strength))
Cochrane Library for Clinical Trials	(("breast cancer" OR "breast neoplasms") AND ("exercise therapy" OR "physical endurance" OR "motor activity" OR aerobic training OR resistance training) AND ("physical activity" OR "activity level" OR "physical fitness" OR "quality of life" OR fatigue OR cardiopulmonary function OR strength))
Medline	((breast cancer OR breast neoplasms) AND (exercise therapy OR physical endurance OR motor activity OR aerobic training OR resistance training) AND (physical activity OR activity level OR physical fitness OR quality of life OR fatigue OR cardiopulmonary function OR strength))

TS, topic search

Table 2 Summary of inclusion and exclusion criteria used in both screenings

PICOS	Inclusion	Exclusion
P_1	Adults (> 18 years)	No data could be extracted for a sample of breast cancer patients
P_2	Patients with breast cancer undergoing initial treatment defined as surgery, chemo- and/or radiotherapy.	The training intervention was initiated after the end of initial therapy.
I	Intervention had to be a training/exercise treatment of all kind.	Too few details available concerning to define the intervention as a training or exercise treatment
C	Not specified	/
O	The outcome measure had to be an indicator of the patients' physical activity; physical fitness, physical performance, fatigue, quality of life (QoL).	/
S	Randomized controlled trial	/
Other	Language was Dutch, English, or French	All other languages were excluded

strength and CV endurance training intervention. Among these, four [24, 34, 36, 40] used a supervised training, whereas the other six [22, 25, 33, 38, 39, 42] were reported from a home-based program. Three studies [43, 46, 47] had a three-arm design. Two used supervised interventions [43, 46], whereas the other study [47] preferred home-based programs. In all three-arm studies, a comparison was made between a usual care group, a CV endurance training group, and a resistance training group. Only Wiskemann et al. used a sole progressive resistance protocol [53].

Details on the interventions, patients, and outcome measures used in the included studies are listed in Table 3.

Effects of the interventions

CV endurance training for patients receiving CT and RT; further referred to as "mixed treatment"

Four studies [18, 19, 27, 32] investigated physical fitness; of which, three studies [18, 27, 32] showed improvements in aerobic capacity and levels of physical fitness in the exercise groups. Significant improvements for the 12-min walking test (12 MWT; $p < 0.001$ [32], $p = 0.02$ [27]) and a significant increase in peak oxygen uptake (VO_{2peak}) [18] ($p < 0.001$) were determined. One study, of low methodological quality, showed no significant difference between the usual care group and exercise group regarding physical fitness and aerobic capacity in a home-based setting [19].

Both Mutrie et al. [32] and Ligibel et al. [19] found no significant differences regarding fatigue (FACT-G) between the supervised exercise group and the usual care group. In contrast to the latter findings are the findings of Mock et al. [27] who reported enhanced results (PFS) in the exercising group compared to the less-exercising group.

As far as QoL is concerned, no significant differences were reported for the mixed treatment groups after a supervised training program. [32] After a home-based training program, a significant positive effect on QoL was reported. [19]

CV endurance training during CT

Both supervised [45, 46] and home-based [23, 41, 44, 48, 49] CV endurance training programs were employed to improve the physical fitness of breast cancer patients receiving CT.

Hornsby et al. [45] found a significant difference for VO_{2peak}, peak power output, and oxygen pulse; all in favor of the aerobic supervised exercise group. Gokal et al. [44] also noted significant better results for physical fitness in the home-based CV endurance training group ($p = 0.001$). Yang et al. [49] showed significant differences over time ($p = 0.02$) regarding physical activity during CT. Vallance et al. [48] showed no significant difference for broad-reach behavior change intervention of low intensity compared to public health guidelines.

Both Schmidt et al. [46] and Chaoul et al. [41] showed that neither interventions nor usual care was able to improve feelings of fatigue symptoms, whereas Headley et al. [23] and Gokal et al. [44] found less increase in experienced feelings of fatigue in the home-based training group compared to the usual care group ($p = 0.02$). Gokal et al. [44] and Hornsby et al. [45] also showed no difference between a supervised training group and the usual care group concerning the experienced fatigue.

Four studies [23, 35, 45, 46] discussed the effects on QoL of breast cancer patients receiving CT. Schmidt et al. [46] showed a significant decrease in physical function during treatment ($p = 0.001$). Three other studies

Table 3 Data extraction of the 28 selected RCTs

Author and year [ref]	QA	Sample size	Population	Control	Intervention	Physical activity during intervention	Follow up	Outcome measures: results
Results of the studies reporting on patients receiving mixed (CT&RT) therapy								
Campbell et al. 2005 [36]	8/10	$n = 22$ $I = 12$ C = 10	♀ receiving adjuvant CT or RT	Standard information on physical activity	Standard information + supervised exercise 2 x/w.	Warm up, 10–20′ varying aerobic exercise (60–75% adjusted HR max), cool down, relaxation + muscle strengthening	12 w.	FACT-G: I > C SWLS: I = Cl PFS: I = C SPAQ: I > C 12 MWT: I > C
Eakin et al. (2012) [38]	7/10	$n = 143$ $I = 73$ C = 70	♀ receiving CT/RT/HT	Workbook and exercise tracker	Motivated by phone calls to do home-based aerobic training combined with strength-based exercise + workbook + activity tracker	Phone calls of 15–30′: - 1 x/w. for 2 m. - 1 x/2w. for 2 m. - 1 x/m. for 4 m. intervention target: 4 x/w., 45′ moderate to vigorous aerobic training + 2 x/w. strength training.	12 m.	Active Australian survey: C = I CHAMPS: C < I FACT-B + 4: C = I
Haines et al. 2010 [33]	10/10	$n = 73$ $I = 37$ C = 36	♀ receiving CT/RT/HT	Flexibility and relaxation activities without progression	Combination of home-based strength, balance, shoulder mobility, and cardiovascular program.	Progression of strength: every 2–4 w if muscles were not feeling tired after completing the second set.	12 m.	EQ-5D + VAS: C = I EORTC-C30 + BR23: C < I MFI: C = I 6 MWT: C = I Grip strength: C&I =Leg press: C&I =
Hayes et al. 2013 [39]	8/10	$n = 194$ $I = 134$ C = 60	♀ receiving CT/RT/HT	Advice provided through standard care	Home-based or supervised exercise intervention for 8 m.	4 x/w., 45′ aerobic exercises and 2 x/w. strength exercises	12 m.	FACT-B: tel > C, C = FtF 3-min step test (HR): Tel&FtF > C Strength: FtF = Tel = C
Heim et al. 2007 [22]	5/10	$n = 63$ $I = 32$ C = 31	♀ receiving CT/RT/HT	Individualized rehabilitation program including educational program, physiotherapy, group exercises, and psycho-oncological interventions	Same as control group + brochure + encouraged to protocol their daily training exercises, intensity, repetitions, and duration	Brochure = 9 muscle strength and 9 stretching exercises for all large muscle groups (intention: 3 x/w.) + instructions for aerobic exercises (walking program; intention: 2 x/w. for 30′), coordination and relaxation.	3 m.	MFI: I = C
Kim et al. 2006 [18]	8/10	$n = 41$ $I = 22$ C = 19	♀ receiving CT/RT/HT	Standard information (incl. general benefits exercise)	Supervised aerobic training for 8 w.	Training at moderate intensity (60–70% VO_2) supervised 3 x/w.	8 w.	VO_2peak: I > C
Ligibel et al. 2016 [19]	5/10	$n = 98$ $I = 47$ C = 51	♀ receiving CT/RT/HT	/	Supervised and home-based intervention for 16 w.	In person and telephone contact; target goal 150′ moderate intensity/w.	16 w.	EORTC-QLQ-C30: I > CBruce Ramp treadmill: I = C
Mock et al. 2005 [28]	7/10	$n = 119$ $I = 60$ C = 59	♀ undergoing adjuvant CT or RT	Encouraged to remain on regular activity level + diary	Booklet and video with exercise information + diary HW = 60′, 3 or more times/w. LW = less activity than HW/w.	Walk 5–6 x/w., 50–70% HF max, 15′ till 30′	6 w.	PFS: HW > LW 12 MWT: HW > LW
Mutrie et al. 2007 [32]	9/10	$n = 201$ $I = 99$ C = 102	♀ undergoing CT/RT/HT	Standard care + 30 pamphlet "Exercise after cancer	Standard care + 2 x/w. supervised group exercise + 1 x/w. home-based exercises.	Warm up 10′, 25′ exercises 50–75% HF max, 15′ cool down/relaxation + discussion (1 theme/w. for 6 w); model	6 m.	FACT-G: I = C FACT-GP: I = C FACT-F: I = C PANAS positive: I > C. SPAQ leisure activity:

Table 3 (continued)

Author and year [ref]	QA	Sample size	Population	Control	Intervention	Physical activity during intervention	Follow up	Outcome measures: results
				diagnosis" = safety guidelines		behavior changes and promote independent exercise.		I > C 12 MWT: I > C Nights in hospital: I > C
Travier et al. 2015 [40]	8/10	n = 164 I = 87 C = 77	♀ receiving CT/RT/HT	Encouraged to remain on regular activity level	Supervised aerobic and strength exercise 2 x/w. for 18 w. + encouraged to be active for 3 other days 30′ + Bandura	60′ class: 5′ warm up, 25′ aerobic (interval), 25′ strength (arms, legs, trunk, shoulders), 5′ cooling down. 3 other days: min. 30′ aerobic component of moderate intensity.	36 w.	MFI + FQL: I > C EORTC-QLQ-C30: I = C SF-36: I > C Physical fitness VO_2peak, peak power output: I = C. VO2, power output at VT: I > C Strength flexion & extension at 60°: I > C Hand grip strength and legs at 180°: I = C
Results of the studies reporting on patients receiving chemotherapy								
Backman et al. 2014 [35]	8/10	n = 54 I = 27 C = 27	♀ receiving CT	Standard information on physical activity	Encouraged to walk 10,000 steps/day + 1 supervised group walk 1 h/w.	/	10 w.	EORTC-QLQ-BR: 2 I = C EORTC-QLQ-C30: I = C
Chaoul et al. 2018 [41]	5/10	I = 74 C1 = 68 C2 = 85	♀ receiving neo- OR adjuvant CT	C1 = usual care C2 = stretching program	Tibetan Yoga, 4 supervised session; stimulated to exercise at home at 2 session/week	4 main components: (1) mindfulness and focused attention through guided meditation with breathing and visualization; (2) an alternate nostril breathing and a breath retention exercise; (3) Tsa Lung movements; and (4) closing with a brief compassion-based meditation	12 m.	Non-significant between group interactions for BFI and PSQI
Courneya et al. 2007 [34]	7/10	n = 201 AT = 68 ST = 73 C = 60	♀ receiving adjuvant CT	Asked not to start an exercise program during the study	Home-based and supervised exercise (aerobic or strength) for the duration of CT.	AT: 3 x/w. cycle ergometer/ treadmill/elliptical trainer, 65% VO_2peak for 15′ till 80% VO_2peak for 45′. ST: 3 x/w., 2 x 8–12 rep. of 9 exercises at 60–70% of estimated 1 RM	6 m.	GLTEQ: I = AT = RT
Cornette et al. 2016 [42]	6/10	n = 30 I = 15 C = 15	♀ receiving CT	Encouraged to remain on a regular activity level	Home-based exercise min. 3 x/w.	2 x/w. aerobic training (cycle ergometer/walking), intensity based on CPET. 1 x/w. strength training 5 muscle groups using resistance bands 2 x 8–12 rep.	54 w.	VO_2max: I > C 6 MWT: I > C MFI-20: I = C EORTC-QLQ-C30: I = C
Dolan et al. 2010 [43]	7/10	n = 242 AT = 82 ST = 78 C = 82	♀ receiving CT	Asked not to start an exercise program during the study	Home-based and supervised exercise (aerobic or strength) for the duration of CT.	AT: 3 x/w. cycle ergometer/treadmill/elliptical trainer. 65% VO_2peak for 15′ till 80% VO_2peak for 45′. ST: 3 x/w., 2 x 8–12 rep. of 9 exercises at 60–70% of estimated 1 RM	17 w.	VO_2: AT =, C and RT ↓
Gokal et al. 2015 [44]	9/10	n = 50 I = 25 C = 25	♀ receiving CT	Usual care	Usual care + 12 w. self-management mod. Int. walking	Start 10′ walk increasing duration until 30′ walk 5 x/w.	12 w.	FACT-F: I > CGPPAQ: I > C

Table 3 (continued)

Author and year [ref]	QA	Sample size	Population	Control	Intervention	Physical activity during intervention	Follow up	Outcome measures: results
Headley et al. 2004 [23]	5/10	*n* = 32 *I* = 16 C = 16	♀ receiving CT	Encouraged to a remain on regular activity level	Home-based aerobic exercise through DVD for 3 x/w. with at least 1-day break between sessions.	Session = video. A seated exercise program 5′ warm up + 20′ moderate-intensity repetitive motion exercises + 5′ cool down.		FACIT-F: C = I both higher level of fatigue QoL: C = I
Hornsby et al. 2014 [45]	9/10	*n* = 20 *I* = 10 C = 10	♀ receiving adjuvant CT	Encouraged to remain on a regular activity level	3 supervised cycle ergometer sessions/week on non-consecutive days for 12 weeks.	w. 1: 60% of baseline peak workload for 15–20′ w. 2–4: 30′ at 65% peak workload w. 5–6: 60–65% peak workload for 30–45′ for 2 sessions + 1 session for 20–25′ at VT. w. 7–9: 2 sessions at 60–70% peak workload and 1 threshold workout for 20–30′ w. 10–12: 2 sessions at 60–70% peak workload and 1 interval session at 100% peak workload (30″ with 60″ of active recovery; 10–15 intervals)	12 w.	CPET: C < I in absolute VO_2peak, peak power output and oxygen pulse FACIT: C = I FACT-G total: C = I FACT-B total: C = I
Husebo et al. 2014 [25]	7/10	*n* = 67 *I* = 33 C = 34	♀ receiving adjuvant CT	Encouraged to remain on a regular activity level + 1 phone call during intervention period	Home-based exercise program that combined strength + aerobic exercise during adjuvant CT.	Strength training: exercises with resistance bands for UL and LL + upper body 3 x/w. Aerobic prescription: daily 30′ of brisk walking (could split in 10′ walks) at least at moderate intensity + encouraged by motivational phone calls every 2 w.	6 m.	SCFS-6: ↑ for both groups from baseline to end of CT IPAQ-SF: C = I 6 MWT: C = I Exercise diary: C = I
Schmidt et al. 2015 [46]	6/10	*n* = 67 ST = 20 AT = 20 C = 26	♀ receiving CT	Encouraged to remain on a regular activity level	ST: 2 x/w. supervised AT: 2 x/w. supervised	Resistance training: 20–50% 1 RM Aerobic training: Borg scale 11–14, 10′ warm up, 25–30′ exercises, 5′ cool down	12 w.	EORTC-QLQ: ↓R&E&CMFI-20: ↑ R&E&C
Schwartz et al. 2007 [47]	6/10	*n* = 66 AT = 22 ST = 21 C = 23	♀ receiving adjuvant CT	Encouraged to remain on a regular activity level	AT: 4 x/w. home-based aerobic exercise ST: 4 x/w. Thera band and tubing + workout logs	AT: 15–30′, 4 x/w., symptom-limited, moderate intensity. Instructed when to stop. Recording caloric expenditure. ST: 2 different 8–10 rep. Greater intensity Thera band over time.	6 m.	6 MWT: I > C 1 RM: seated row, leg press: I > C
Vallance et al. 2015 [48]	6/10	*n* = 95 *I* = 49 C = 46	♀ receiving CT	Usual care	Proactive PA resource kit with pedometer and recommendations	150′ per week moderate to intensive walking, cycling, dancing, hiking, golfing (brisk walking was recommended)	3–4 w.	Pedometer steps: I = C GELTEQ, LSI I = C
Yang et al. 2011 [49]	9/10	*n* = 40 *I* = 19 C = 21	♀ receiving adjuvant CT	Encouraged to remain on a regular activity level	Home-based aerobic exercise 3 x/w. for 12 w.	Each session 5′ warm up, 30′ moderate-intensity brisk walking (60–80% HF max adjusted for age), 5′ cool down + polar loop	12 w.	7-day PAR: I > C
Results of the studies reporting on patients receiving radiation therapy								
Drouin et al. 2005 [50]	6/10	*n* = 21 *I* = 13 C = 8	♀ receiving RT	Placebo stretching program 3–4 x/w.	Moderate-intensity aerobic exercise training. Weekly communication in person or by telephone.	Individual walking 20–40′, 3–5 x/w., 50–70% HRmax during SLGXT	9 w.	Vo2 peak: I > C
	4/10		♀ receiving RT				/	

Table 3 (continued)

Author and year [ref]	QA	Sample size	Population	Control	Intervention	Physical activity during intervention	Follow up	Outcome measures: results
Hwang et al. 2008 [24]		$n = 37$ $I = 17$ C = 20		Encouraged to remain on a regular activity level + shown how to perform shoulder ROM exercises	Supervised exercise program 3 x/w. for 5 w.	10′ warm up, 30′ exercise (incl. stretching focused on shoulder + aerobic exercise (treadmill walking/bicycling at 50–70% of age-adjusted HR max) + strengthening exercise and 10′ cool down (relaxation).		WHOOL-BREF: I > C BFI: I > C
Milecki et al. 2013 [51]	5/10	$n = 67$ $I = 35$ C = 32	♀ receiving RT	Irregular physical activity on their own	Supervised exercise program 5 x/w. for 6 w.	2′ warm up, 40′ cycling (65–70% HR max) 3′ relaxation before every RT session	6 w.	6 MWT: I > C
Reis et al. 2013 [52]	4/10	$n = 31$ $I = 22$ C = 19	♀ receiving RT	Encouraged to remain on a regular activity level + exercise log.	Meeting for instructions + DVD home based + exercise log	20–60′, 3 x/w. for 12 w.	12 w.	FACIT-F: I > C 6 MWT: I = C
Wiskemann et al. 2017 [53]	7/10	$I = 80$ C = 80	♀ receiving RT	Control group receives relaxation therapy	The intervention group receives a progressive resistance training; 2 sessions/week	Eight different machine-based resistance exercises with 12 repetitions: (1) leg extension; (2) leg curl; (3) leg press; (4) shoulder internal and external rotation; (5) seated row; (6) latissimus pull down; (7) shoulder flexion and extension; and (8) butterfly and butterfly reverse	12 w.	Progressive resistance training resulted in significant improvement of peak torque and isometric muscle contractions. Patients with previous CT had more gain in comparison to patients without CT. No difference on fatigue was demonstrated

QA quality assessment, *n* total number of participants, *I* number of participants in the intervention group, *C* number of participants in the control group, *CT* chemotherapy, *RT* radiation therapy, *HT* hormone therapy, ♀ women, ♂ men, *h/w.* hour(s) per week, *w.* week, *x/w.* times per week, *m.* months, *′* minutes, *HR* heart rate, *max* maximum, *min.* minimum, *rep.* repetition(s), *1 RM* one repetition maximum, *AT* aerobic training, *ST* strengthening training, *VT* ventilatory threshold, *$VO_2(max)$* (maximum) volume oxygen uptake, *UL* upper limbs, *LL* lower limbs, *incl.* inclusive, *HW* high walkers, *LW* low walkers, > significantly greater than, < significantly less than, = no significant difference, *EORTC-QLQ(-BR)* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire(-Breast Cancer module), *EORTC-QLQ-C30(+BR23)* EORTC-QLQ-for Cancer patients (breast cancer specific module), *FACT-G* Functional Assessment of Cancer Therapy—General, *SWLS* Satisfaction With Life Scale, *PFS* revised Piper Fatigue Scale, *SPAQ* Scottish Physical Activity Questionnaire, *12 MWT* 12-min walking test, *6 MWT* 6-min walking test, *GLTEQ* Godin Leisure Time Exercise Questionnaire, *CHAMPS* Community Healthy Activities Models Programs for Seniors, *FACT-F* fact-fatigue, *GPPAQ* General Practice Physical Activity Questionnaire, *FACT-B(+4)* FACT-Breast, *EQ-5D* EuroQol five-dimensions questionnaire, *VAS* Visual Analog Scale, *MFI(-20)* Multifactorial Fatigue Index (-20 item scale), *FACIT-F* functional assessment of chronic illness therapy fatigue, *QoL* quality of life, *CPET* Cardio Pulmonary Exercise Test, *SCFS-6* Schwartz Cancer Fatigue Scale-6, *IPAQ-SF* International Physical Activity Questionnaire-Short Form, *WHOOL-BREF* World Health Organization quality Of Life-short version, *BFI* brief fatigue inventory, *FACT-GP* FACT-General Population, *FACT-F* FACT-fatigue, *PANAS* Positive And Negative Affect Scale, *SPAQ leisure activity* Scottish Physical Activity Questionnaire for leisure activity, *FQL* Forensic inpatient Quality of Life questionnaire, *SF-36* Short Form-36 health survey, *7-day PAR* 7-day Physical Activity Recall, *SLGXT* symptom-limited graded exercise testing, *PSQI* Pittsburgh Sleep Quality Index

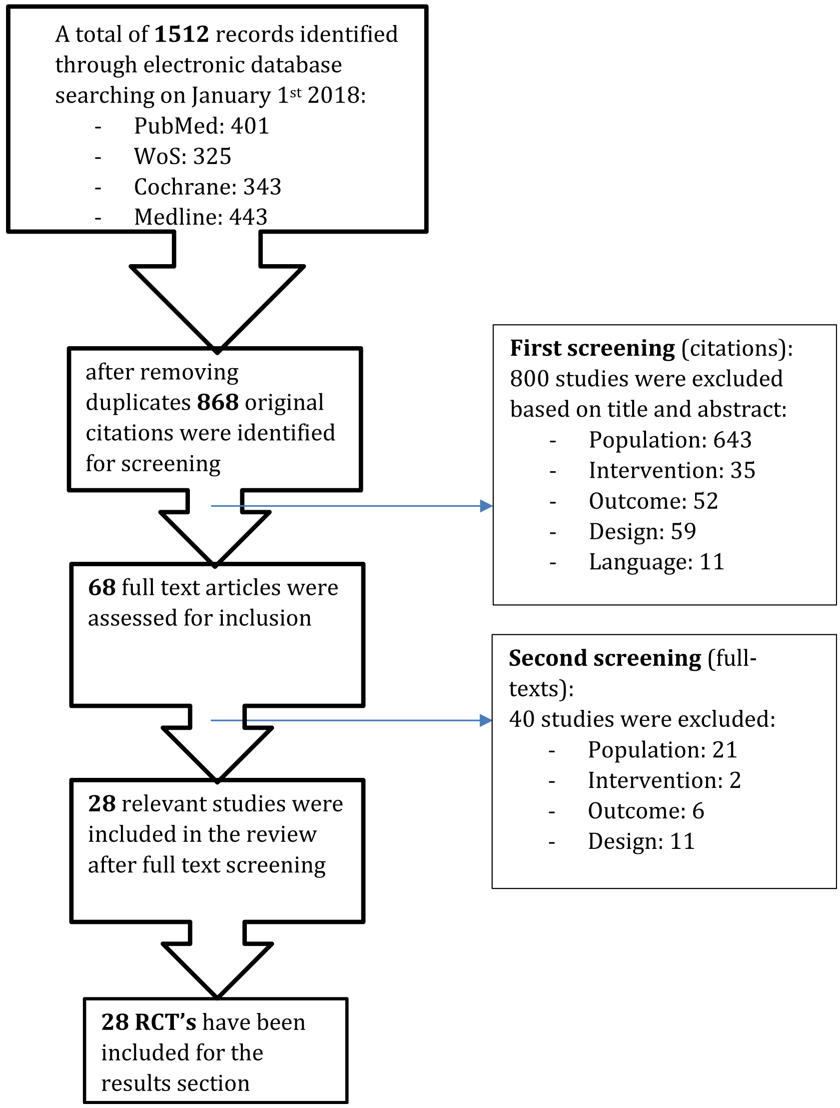

Fig. 1 Flow chart of the systematic search and selection process

[23, 35, 45] compared the exercising and usual care group and demonstrated no significant differences concerning QoL ($p > 0.05$). No differences in QoL (FACIT-F, FACT-G, EORTC-QLQ-C30) outcome could be detected for supervised [23, 46] and home-based training programs [35, 45].

CV endurance training during RT

Milecki et al. [51] showed that supervised CV endurance training significantly increased the result of the 6 MWT ($p = 0.00$). These findings were confirmed by Drouin et al. [50] who reported a significantly increased VO_{2peak} ($p > 0.001$) and improvement in physical fitness during a home-based CV endurance training.

Regarding experienced feelings of fatigue, Reis et al. [52] showed that a home-based Nia training (Nia is a cardiovascular and whole-body conditioning program based upon martial arts, dance arts, and healing arts) three times a week for 12 weeks had no significant effect ($p > 0.05$) over usual care.

Combined CV endurance and resistance training during mixed treatment

Concerning the outcome physical fitness, five [33, 36, 38–40] studies have been retrieved. In response to home-based interventions, two studies found no significant differences in physical fitness (active Australian survey, 6 MWT, grip strength, leg press) [33, 38]. One study reported greater improvements in the 3-min step test for the intervention group compared to usual care, whereas no differences in strength were observed [39]. In line with previous mentioned studies, Campbell et al. [36] and Travier et al. [40] showed improved physical fitness in the supervised training group compared to the usual care group for the 12 MWT ($p = 0.001$) [36], for the VO_{2peak}, and for power at ventilatory threshold (95% CI, 0.0 to 0.2, ES = 0.31) [40].

Five studies [22, 33, 36, 38, 40] have studied feelings of experienced fatigue following a combination training program. Haines et al. [33] showed a trend of lower fatigue in the home-based training group, whereas Travier et al. [40] showed lower physical fatigue in a supervised training group. Three other studies [22, 33, 36] showed no significant differences in experienced fatigue between a home-based [22, 33] or supervised [36] training group and usual care.

For QoL, Haines et al. [33] and Campbell et al. [36] showed significant improvement of QoL compared to control groups. However, one study [38], of low methodological quality, using a home-based intervention found no significant difference on QoL.

Combined CV endurance and resistance training during CT

Three studies [25, 34, 43] showed no significant differences between training groups and control groups on physical fitness, whereas two studies [42, 47] that were of less methodological quality showed significant improved results for physical fitness after a home-based training program.

We found only one study [47] that investigated the effect of home-based strength training. Enhanced results for one repetition maximum (1 RM) of the following exercises were found: seated row and leg press in the training group.

Courneya et al. [34] and Husebo et al. [25] demonstrated no differences of feelings of fatigue between supervised [34] and/or home-based [25] training programs. However, Husebo et al. [25] showed an increase in experienced fatigue during CT in both groups.

Cornette et al. [42] demonstrated no changes in QoL following a CV endurance and resistance training during CT.

Combined CV endurance and resistance training during RT

Only one study [24] investigated feelings of experienced fatigue and QoL in patients receiving RT. For both outcomes, significant changes were found between control and exercise groups, all in favor of the supervised training group.

Resistance training during RT

Only one study was found that investigated a progressive resistance training protocol during RT. [53] It was found that patients receiving the intervention training improved significantly on peak torque and isometric contractions of large muscle groups. No effect on perceived fatigue was found between patients receiving resistance training and patients in the relaxation group (control group).

Discussion

Selection of the studies and study characteristics

The present review assessed the available evidence regarding the effects of physical exercise and/or rehabilitation programs on physical performance, experienced feelings of fatigue, and QoL in patients with breast cancer during their initial treatment (defined as: surgery, CT, and/or RT). The results of this systematic review demonstrate the following:

1) Different types of exercise programs (CV endurance training, resistance training, or a combination of both, supervised or home-based) are available for rehabilitation purposes of breast cancer patients.
2) Many of the included studies found positive effects on physical performance [18, 24, 27, 32, 36, 39, 40, 42, 45, 47, 49–51, 53], but only few studies found significant results regarding the outcome measures for experienced fatigue and QoL.
3) Resistance training or resistance training in combination CV endurance seems to provide the best results, especially regarding physical performance outcomes and feelings of experienced fatigue.

Since physical training has become a corner stone in breast cancer rehabilitation, the above-mentioned findings show the importance of the current systematic review. A Cochrane review by Furmaniak et al. [37] concluded that exercise is beneficial for improving physical fitness, QoL, and perceived fatigue. As shown in their respective forest plots, all types of intervention (CV endurance, resistance training, or a combination of both) during all types of adjuvant therapy were analyzed jointly, resulting in favor of exercise in comparison to standard care. The current systematic review ennobles the findings of Furmaniak et al. by clearly demonstrating that not all types of intervention are able to produce the same significant results during the different adjuvant regimes. Our results warrant carefulness in interpreting the meta-analyses performed by Furmaniak et al. [37] For that reason, we will focus on the outcome measures with regard to the different exercise programs in the following sections of the discussion.

Physical performance

Physical performance in this review is regarded as the assessment of the level of physiological fitness or exercise capacity. From that perspective, VO_{2peak} and the 6 and 12 MWT were most often used in the literature reviewed. Grip strength and strength testing of large muscle groups were also commonly used for assessing physical performance. Studies using a supervised training program showed better results on physical performance outcomes than home-based approaches. This is especially true for studies during CT and RT [18, 19, 32, 36, 40, 53]. Although not substantiated by evidence, the majority of studies during CT alone used home-based approaches with conflicting results, i.e., no differences between the intervention and control group [25, 41, 43, 48] or significant improvements in the intervention group [42, 47, 49]. The only study that used a supervised protocol showed a significant improvement in VO_{2peak} for the intervention group [31].

As far as RT is concerned, only four studies were available. The best, from a methodological point of view, study [50] reported a significant improvement in physical performance for the intervention group over the control group during a home-based approach. A study [52] with a lower methodological score reported no differences in physical performance between the intervention and control group. Two studies [53] used a supervised program and demonstrated a significant improvement in favor of the intervention over the control group [51] during a supervised program.

Perceived fatigue

Perceived fatigued is extremely subjective and difficult to assess. Two studies that investigated physical activity interventions during RT showed an improvement in perceived fatigue [24, 52]. A striking finding, however, is that both studies, supervised and home-based, used strength training as intervention strategy. Similar observations were reported for interventions in patients receiving a mixed treatment of RT and CT. The two studies that used strength exercises during a supervised program found a significant improvement for perceived fatigue over the control group [36, 40]. Interestingly, the only study that used strength exercises in a home-based program did not show any differences between the intervention and control group. During CT, only one study [44] showed improvements in perceived feelings of fatigue for the intervention group. The intervention as used by Gokal et al. was a self-managed high-intensity walking program without any strength exercises [44]. All other studies were not able to find any differences between the intervention and control group [23, 25, 34, 42, 46]. Overall, we can conclude that incorporating resistance exercises in both the supervised as well as home-based programs was able to reduce the perceived fatigue.

QoL

Only one study that investigated QoL in a group of patients receiving RT only showed a significant increase in QoL for the intervention group receiving a supervised CV endurance and resistance exercises program [24]. None of the studies that studied the QoL in patients receiving CT were able to demonstrate improvements for any of the chosen interventions [23, 35, 45, 46]. Interestingly, three out of five studies in patients receiving both CT and RT found significantly improved QoL score in the intervention groups [19, 33, 40]. Although a reason for these differences is not easy to provide, the high level of heterogeneity in selected QoL questionnaires makes comparison between studies difficult and the selection of questionnaires could have an important effect on the final result. For instance, Travier et al. used both the EORTC-QLQ-C30 and SF-36, disease specific and generic questionnaires and reported significant improvements for the intervention group using the SF-36 but not for the EORTC-QLQ-C30. [40]

Breast cancer is a complex disease, and more and more patients receive, based on the characteristics of their tumor (TNM-classification), an individual tailored treatment plan. Regarding the fact that different treatment protocols cause different side effects [17–19, 22, 23], it is reasonable to assume that a variety in outcome measures and an overall range in daily activities make it difficult to compare results between the selected studies.

Limitations of the incorporated studies and current review

A major drawback that we observed in the selected studies is the wide range in the duration of the training intervention, i.e., from 5 weeks till 6 months and from 9 weeks till 8 months for supervised and home-based programs, respectively (see Table 3). Due to the heterogeneity in the duration of the different training interventions, it is impossible to make an unambiguous statement which training intervention, short or long, is advantageous in breast cancer rehabilitation. A second drawback is the wide range of different exercise workouts that have been used in the resistance training programs which makes comparison at least challenging. Based on the included studies, conclusions can only be drawn based on the methodological quality of all individual studies. A third limitation is the information concerning the medical treatment (type of surgery, chemotherapy scheme, radiation scheme) making it impossible to link medical treatment, adherence to exercise therapy, and beneficial effects of training. Fourth, a broad range of eligibility criteria was found among the selected RCTs, hampering comparison and conclusion forming. Finally, physical fitness itself is a very broad concept and we can only reflect on the outcome measures reported in the selected studies.

Limitations of the current review are as follows: (1) no meta-analysis was performed based upon the heterogeneity among the selected RCTs; (2) only information is provided on patients able to engage in exercise programs; (3) although personalization in exercise programs is probably warranted, we did not find any information concerning this item.

Recommendations for further research are multiple and need to be addressed with care, i.e.:

1) For patients undergoing RT, more high-quality studies are required. In addition, more differentiation of the different effects of the training interventions is necessary.
2) Further research is also indicated to determine which exercises/training is beneficial to use in clinical practice and to achieve the best effects on physical performance outcomes. Also, the use of studies with a high methodological quality is mandatory to distinguish between the effects of different exercise drills and programs during the initial treatment period.
3) It is recommendable that studies on the topic addressed in this review should include more details including information on treatment plans (e.g., neo-adjuvant vs adjuvant, CT or RT), type of surgery (important for possible limb use or disuse effects), and description of the exact physical activity plans.
4) Finally, responder analysis was lacking in most of the included studies. Such analysis could shed more light on the deficiencies of training modalities and give way to therapists to provide optimal and personalized training programs for their patients.

It can carefully be stated that the addition of a physical exercise program containing both CV endurance training and resistance exercises is beneficial in improving physical performance, reducing experienced fatigue, and affecting QoL positively for patients undergoing breast cancer treatment. The optimal (personalized) program has yet to be developed.

Conclusion

We conclude that based on the heterogeneity among the selected study's; conclusions regarding the type of physical rehabilitation programs as well as the chosen type of sypervision need to be formulated with caution.

To date, ambiguous evidence is present regarding the enhancement of the QoL by different training programs. This needs further attention since QoL is one of the most often used outcome measures in cancer research.

Overall, we must conclude that there is evidence that exercise programs during the initial treatment period provide hopeful results, but there is a need for high-quality studies.

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Compliance with ethical standards

Conflicts of interest The authors did not receive any funding for any of the steps taken to write this systematic review.

None of the authors have any conflict of interest to declare.

The data table created for this systematic review is under the control of Prof. Dr. Nick Gebruers and is available on request.

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