Physical activity in oncology patients with breast cancer: non-pharmacological sports-based medical therapy? Systematic review

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Summary

Introduction: Breast cancer (BC) remains the leading cause of cancer in women with nearly 1.4 million new cases worldwide annually and 27.000 in Spain. Increasingly effective oncology therapies, however, have numerous adverse effects such as muscle degeneration, fatigue, decreased physical function and aerobic capacity, along with deteriorating quality of life. In this sense physical activity (PA) seems to be an interesting non-pharmacological strategy to alleviate these serious complications and with potential benefits for women with BC.
Objective: To examine whether PA interventions are effective on the physical and psychological fitness of patients with post-surgical BC in early stages of disease (I-III) and also to identify the most appropriate component of physical activity.
Methods: Systematic review, based on PRISMA guidelines, using a structured search of electronic databases: Medline (PubMed), SciELO and Cochrane Library Plus. Results relating PA and BC were included until 30 september 2019, while a search restriction was applied to publications to be in the last 10 years. The methodological quality of articles evaluated using the McMaster critical review form.
Results: We found 8 articles that have described the benefits of PA, highlighting physical, psychological and quality of life improvements, as well as decreased fatigue and lymphedema. The exercise routines used are aerobic component work and muscle strength.
Conclusion: The performance of AF, with aerobic and muscular strength routines, stimulate the improvement of the physical, psychological state and the quality of life of the patients of BC patients.

Key words:
Breast cancer. Physical activity. Women. Fatigue. Quality of life. Lymphedema.

Actividad física en pacientes oncológicos de cáncer de mama: ¿Terapia médica deportiva no farmacológica? Revisión sistemática

Resumen

Introducción: El cáncer de mama (CM) sigue siendo la causa principal de cáncer en las mujeres con casi 1,4 millones de casos nuevos en todo el mundo anualmente y 27.000 en España. Las terapias oncológicas, cada vez más eficaces, sin embargo, tienen numerosos efectos adversos como el degaste muscular, la fatiga, la disminución de la función física y la capacidad aeróbica, conjuntamente con el deterioro de la calidad de vida. En este sentido la actividad física (AF) parece ser una estrategia no farmacológica interesante para aliviar estas graves complicaciones y con potenciales beneficios para mujeres con CM.
Objetivo: Examinar si las intervenciones de AF son efectivas sobre estado físico y psicológico de los pacientes de CM postquirúrgicos en estadíos tempranos de enfermedad (I-III) y además identificar el componente de la AF más adecuado.
Material y método: Revisión sistemática, basada en las guías PRISMA, realizando una búsqueda estructurada en las bases de datos electrónicas: Medline (PubMed), SciELO y Cochrane Library Plus. Se incluyeron los resultados que relacionaran las AF y CM hasta el 30 de septiembre de 2019, mientras que se aplicó una restricción de búsqueda en las publicaciones para que fueran en los últimos 10 años. La calidad metodológica de los artículos se evaluó mediante el formulario de revisión crítica de McMaster.
Resultados: Se encontraron 8 artículos que han descrito los beneficios de la AF en los que destacan las mejoras físicas, psicológicas y en la calidad de vida, así como la disminución de la fatiga y linfedema. Las rutinas de ejercicio empleadas son de trabajo de componente aeróbico y de fuerza muscular.
Conclusión: La realización de AF, con rutinas de aeróbicas y de fuerza muscular, estimulan la mejora del estado físico, psicológico y la calidad de vida de los pacientes de CM.

Palabras clave:
Cáncer de mama. Actividad física. Mujeres. Fatiga. Calidad de vida. Linfedema.

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Introduction

Cancer is a process in which cells grow and spread without control which can appear almost anywhere in the body and invade the surrounding tissue, causing metastases in distant parts of the body[1]. Cancer is a major epidemiological problem because it is one of the leading causes of death everywhere in the world[2]. Breast cancer (BC) is the most common type of cancer in women, with nearly 1.4 million new cases each year worldwide and 27,000 in Spain. Approximately 6-10% of these cases are stage IV cancer (de novo metastatic cancer) and the metastatic recurrence rate ranges from 20 to 30% of all existing cases of breast tumour[3].

BC is a systemic disease at the time of diagnosis. Consequently, hormone therapy, chemotherapy and/or radiotherapy are normally administered to eliminate any possible presence of hidden micrometastases following radical surgery, thereby reducing the risk of relapse and improving overall survival rates, as the clinically validated prognostic factors establish[4]. Despite the local, regional and systemic treatment applied, between 30% and 50% of patients with negative and positive axillary lymph nodes, respectively, relapse after five years of surgery[4].

Unfortunately, the disease itself, the adjuvant chemotherapy and the radiotherapy administered are associated with serious complications such as muscle wasting and weakness[5]. With BC, neoplastic cachexia causes great muscle mass and body weight loss, and neoplastic fatigue characterised by very extreme tiredness which does not improve with anything and gets worse with rest also appears[6]. These adverse effects are due not only to the therapy (chemotherapy and radiotherapy) but also to the physical inactivity of cancer patients[7], which exacerbates decline in their physical function and aerobic capacity, and further impairs their quality of life (QoL). Other potential side effects of treating BC include lymphedema, chronic inflammation, reduced bone mineral density, reduced cognitive function, vomiting, nausea, loss of appetite, insomnia, and peripheral neuropathy[8,9].

Physical activity (PA) plays an important role in alleviating many of the adverse effects of BC therapy. Clinic-based PA programmes have been shown to improve physical performance and reduce fatigue in BC patients. PA requires a set of intense and repetitive actions that give rise to a high level of metabolic and mechanical stress in the body that leads to adaptations of the different body systems of those who perform them[10]. PA stimulates a battery of intracellular processes which underlie these adaptations, including catabolic systems, such as autophagolysosome, the ubiquitin-proteasome and inflammation, and anabolic systems, such as protein synthesis. The activation and/or repression of specific signalling cascades which regulate these processes link the metabolic and mechanical stress to the regulation of cellular enzymes that lead to changes: myocellular changes in the mitochondria, the metabolic function, insulin-stimulated glucose uptake, intracellular signalling and transcriptional/translational regulation. PA also stimulates the proliferation and differentiation of muscle stem cells (satellite cells) as part of the adaptive response to training involving exercises to help patients recover from muscle wasting and weakness[11-14].

Moreover, some of the consequences of cancer or its adjuvant treatment cause states of chronic inflammation which play a crucial role in the development, progression and risk of cancer recurrence due to their effects on carcinogenesis and the development of the tumour microenvironment[1]. We know that a combination of aerobic and muscle resistance training stimulates the production and secretion of pro-inflammatory cytokines (IL-6, IL-2, IL-8, IL-10, TNF- α, IL-1 ß, IL-12, IFN-γ), which subsequently exert their effects locally in the skeletal muscle or their target organs. This initial pro-inflammatory response is controlled by anti-inflammatory molecules like the IL-1 receptor antagonist (IL-1ra), transforming growth factor beta (TGF-ß), interleukins 4, 6, 10, 11 and 13 and the specific IL-1, TNF α and interleukin 18 receptors. The immunomodulatory action of all these molecules limits the harmful effect of the inflammatory reaction in cancer[12,15]. Another neoplastic inflammatory process control mechanism could be established because the cytokine cascade induced by exercise differs from the cytokine cascade (TNF- α and IL-1) induced by cancer, which has been associated with a therapeutic action of PA by reducing the likelihood of tumour reactivation and progression. The ability of PA, therefore, to reduce chronic inflammation and favourably affect health makes it a crucial mechanism for BC survivors[15,16]. However, acute exposure to training only has a short-lived effect on the inflammatory profile and it is unlikely that a single exercise session will bring about adaptive changes. Repetition of the exercise would seem to be necessary for any long-term health benefits[15,16].

Another potential benefit of PA as a form of non-pharmacological intervention in cancer patients is the enhanced mental and social well-being resulting from taking part in PA programmes, leading to a reduction in the symptoms associated with the disease or its treatment[9].

The recommendation of moderate-intensity physical activity at least five days a week or 75 minutes of more vigorous exercise, together with two to three sessions per week of strength training, including exercises for the major muscle groups, has been approved by both the Canadian Cancer Society and the American Cancer Society to reduce the risk of breast cancer recurrence and lessen the symptoms associated with the disease or its treatment[17]. However, more hours of exercise and more exercise at a more vigorous intensity could potentially increase the benefits. In this sense, this study reviewed the articles published to date to examine whether PA interventions are effective in increasing physical fitness and improving other results (physical, psychological, muscular and biological) for postsurgical early-stage (I-III) BC patients and sought to identify the most suitable component of the physical activity carried out.

Materials and methods

Search strategy

This article is a systematic review focussing on the impact of performing physical activity on patients with BC. It was conducted following the specific methodological guidelines Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) and the PICOS question framework to define the inclusion criteria: P (population): "women with breast cancer," I (intervention): "impact of physical activity on patients with breast cancer", C (comparison): "same conditions with/without physical activity", O (outcomes): "Physical, biological, psychological, muscle and quality of life modifications induced following physical activity programmes", S (study type): "randomised design without placebo"[18].

A structured search was conducted in the following electronic databases: Medline (PubMed), SciELO and Cochrane Library Plus. Results until 30 August 2019 were included, while a search restriction was applied to publications so they were from the last 10 years due to constant developments in oncology. The search terms included a mix of medical subject headings (MeSH) and free text words for key concepts related to BC and physical activity: physical activity, neoplasms, breast cancer, exercise, benefits, prescription, physiotherapy and rehabilitation (Table 1). Through this search, relevant articles in the field of physical activity in patients with BC were obtained applying the snowball method. All the titles and abstracts from the search were crossed-checked to identify duplicates and studies which were potentially missing. The titles and abstracts were then examined for later review of the full text. Two authors (DFL and CIFL) independently performed the search for published studies and disagreements regarding the physical parameters were resolved by discussion.

Table 1. Databases, search terms, articles selected.

Search number	Database used	Search term	Number of articles after removing duplicates	Number of articles evaluated with full text
1	Medline (PubMed)	Physical activity AND cancer	77	8
2	Medline (PubMed)	Physical activity AND breast cancer	63	10
3	Medline (PubMed)	Physical activity AND breast cancer AND benefits	57	4
4	Medline (PubMed)	Physical activity AND breast cancer AND physiotherapy	20	4
5	Medline (PubMed)	Physical activity AND breast cancer AND prescription	23	4
6	Cochrane library plus	Cancer and physical activity	11	3
7	Cochrane library plus	Breast cancer AND physical activity	25	4
8	Cochrane library plus	Breast cancer AND physiotherapy	30	2
9	SciELO	Cáncer AND actividad física	6	1
10	SciELO	Cáncer de mama AND actividad física	27	0

Inclusion and exclusion criteria

The following inclusion criteria were applied to select the studies from the papers obtained in the search: 1) A well designed experiment involving physical activity in postsurgical early-stage (I-III) BC patients; 2) Not receiving chemotherapy or radiotherapy; 3) An identical situation of BC patients not doing physical activity; 4) Articles published in the last 10 years; 5) Publications on human female study subjects aged over 18; 6) Languages restricted to English, German, French, Italian, Spanish and Portuguese. The exclusion criteria applied were: 1) Publications not related to BC and physical activity; 2) Duplicated papers; 3) Studies more than 10 years old; 4) Not conducted on female humans; 5) No previous filters on fitness level or capacity to do physical activity; 6) Papers of poor methodological quality, ≤8 points according to the McMaster University critical review form[19] for quantitative studies; 7) Narrative or systematic reviews.

Data extraction and synthesis

After applying the inclusion/exclusion criteria to each study, the data on the source of the study (including authors and year of publication), BC patient status, study design, participant characteristics, PA protocol used with the patients, and the results and conclusions of the interventions were extracted independently by two authors (DFL and CFL) using a spreadsheet (Microsoft Inc., Seattle, WA, USA). Any disagreements were then resolved by discussion until consensus was reached..

Methodological quality assessment

The methodological quality of the articles assessed using the McMaster University critical review form19 attained scores ranging from 11 to 15 points, representing a minimum methodological quality of 68.8% and a maximum of 93.8% (Table 2). Of the 8 papers, 3 were considered to be of "very good" quality, 4 of "good" quality and 1 of "excellent" quality. No study was excluded for failing to meet the minimum quality threshold. Table 2 details the results of the criteria evaluated, where the main shortcomings found in terms of methodological quality were associated with items 5, 12 and 13 of the questionnaire, which cover detailed

Table 2. Methodological quality assessment

Reference	Ítems																T	%	MQ
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16			
Moros *el al.*[28] 2010	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	14	87.5	VG
Patsou *et al.*[24] 2018	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	14	87.5	VG
Dieli-Conwright *et al.*[20] 2018	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	15	93.8	E
Di Blasio *et al.*[22] 2016	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	0	13	81.3	VG
Musanti *et al.*[23] 2012	1	1	1	1	0	1	1	1	1	1	0	0	0	1	0	1	11	68.8	G
Speck, Gross, *et al.*[27] 2010	1	1	1	1	0	1	1	1	1	1	1	0	0	1	1	0	12	75	G
Rogers *et al.*[25] 2014	1	1	1	1	1	0	1	1	1	1	0	0	0	1	0	1	11	68.8	G
Saarto *et al.*[26] 2012	1	1	1	1	0	1	1	1	1	1	0	0	0	1	1	0	11	68.8	G
T	10	10	10	10	4	7	10	10	10	9	6	3	4	10	8	6			

T: total items met; MQ: Methodological quality (poor ≤8 points; acceptable 9-10 points; good 11-12 points; very good 13-14 points; excellent ≥15.
(1) Criterion met; (0) Criterion not met.

justification of the sample size, discussion of the clinical importance of the results and reporting drop-outs, respectively.

Results

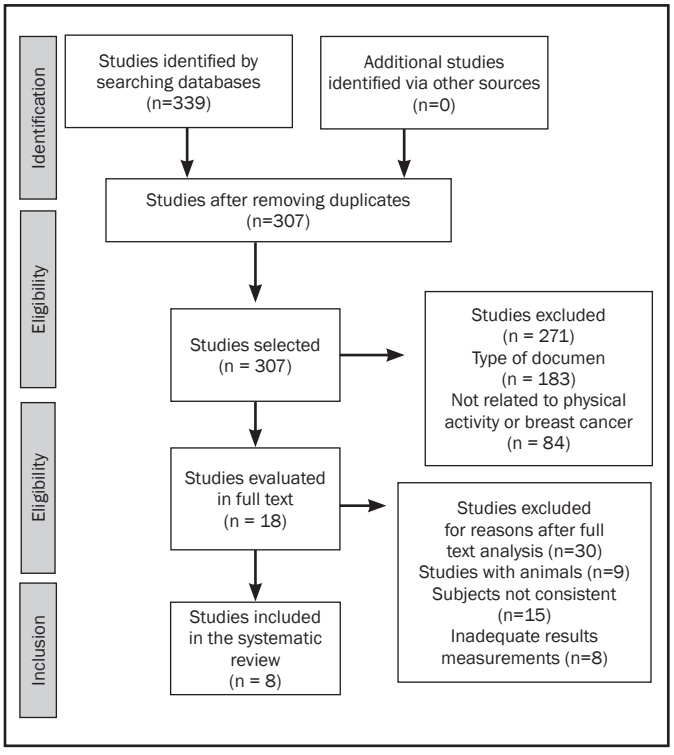
Selection of studies

The search yielded 389 articles, of which 339 were published after 2010. After removing the duplicate articles (n = 32), 307 articles were selected for examination by title and abstract, of which 183 were excluded because they did not involve any intervention and 84 because they were not related to the search subject. The full texts of the remaining 40 publications were evaluated according to the inclusion criteria, of which 9 studies were removed because they were conducted with animals, 15 because they involved subjects with comorbidities and 8 because they did not measure any of the variables included in this study. And so the eight articles included in this systematic review (Figure 1) were obtained.

Results measured

Table 3 includes data on the source of the study (including authors and year of publication), BC patient status, study design, participant characteristics, PA intervention protocol used with the BC patients and results and conclusions.

Figure 1. Flow chart of literature search and study selection.



Discussion

The health problems caused by BC are due both to the disease itself and to the action taken, such as: surgical resection and different treatments (hormonal therapy, adjuvant chemotherapy and radiotherapy). Additionally, these effects are exacerbated when the lifestyle of the BC patient is unsuitable because he/she is physically inactive, obese, has abnormal eating patterns (malnutrition or overeating) and has lost muscle mass. For these reasons, prescribing and performing PA could be an effective non-pharmacological strategy to mitigate all the effects of BC through which to modify the patient's lifestyle, stimulating potential physical, biological, psychological and muscle modifications leading to an improvement in the patient's quality of life[9,20].

This study aims to systematically review PA interventions for women with early stage BC who are not undergoing chemotherapy or radiation therapy to determine their effectiveness as a recovery strategy for patients and to provide some basic guidelines for the correct prescription of exercise in this population. The results provided could be considered

Table 3. Summary of the studies included in the review which investigate the impact of physical activity on patients with breast cancer.

Authors	Patient situation	Study	Intervention	Results	Conclusions
Moros *et al.*[28] 2010	22 ♀, 49±7 y.o. (40.9% were working prior to diagnosis) BC Post-SP Before chemotherapy	Randomised Controlled Trial Exclusion: condition preventing physical activity (heart disease, hypertension, anaemia, fracture risk, diabetes). Inclusion: DOES NOT exercise ♀> 65 y.o.	18-22 weeks of treatment, 3 sessions per week → 60 minutes per session. Warm-up (10´) Main part (45') – Exercise bike – Breathing exercises – Upper limb strength work, non-operated arm – Treadmill walking – Pelvic girdle and abdominal work Stretching / Relaxation (5')	↑*Quality of life (EORTC QLQ-C30). ↑ fatigue ↓ Functional capacity (Karnofsky performance status) ↓ Overall psychological well-being (General Health Questionnaire) ↓* Somatic / psychological ↓* Overall score	An exercise programme improves the quality of life of women with breast cancer undergoing chemotherapy.
Patsou *et al.*[24] 2018	171♀, 51.74±7.26 y.o. BC Post-SP Stage I-III: I: 31.5% II: 50.4% III: 28.1% 12-18 months after chemotherapy and/or radiotherapy ♀ 18-65 y.o	Randomised Controlled Trial G1 physically active group (n=82) G2 physically active group (n=89) The groups were established based on the IPAQ criteria: Types of PA, intensity, frequency and duration. Exclusion criteria: comorbidities or oncological processes which inhibit effects of physical activity	Exercise Vigorous: High-intensity aerobic exercises (running or cycling), lifting heavy weights Moderate: swimming, cycling at normal speed and walking quickly Mild: gentle walks Data on frequency (measured in days/week) and duration (time/day) were collected separately for each specific type of activity according to IPAQ Overall health assessed with EORTC QLQ-C30.	↑ Mood ↓* Anxiety ↑ * Self-esteem ↑ Psychological profile. ↑* Health ↑* Fitness ↑* Quality of life G1 significant positive correlations with self-esteem, overall health and quality of life (physical, role, emotional, cognitive and social).	Start carrying out physical activity as soon as possible after diagnosis, treatment to achieve greater self-esteem, better quality of life, lower anxiety, less symptoms of depression and better physical condition to achieve higher survival rate of BC patients.
Dieli-Conwright *et al.*[20] 2018	BC Post-SP Stage I-III: Stage I (40%) Stage II (38%) < 6 months after chemotherapy and/or radiotherapy	418 ♀ 56.3±10.4 y.o. Randomised Controlled Trial Assessment at start of the study, after the intervention (month 4) and 3-month follow-up period (exercise group only).	Intervention: 16 weeks, (3 per week) Aerobic 150 minutes Days 1-3: aerobic exercise + resistance (~ 80 minutes). Day 2: aerobic exercise (~ 50 minutes). Strength: * Circuit without rest periods between exercises 2-3 per week. Follow-up: The exercise group spent 12 weeks doing exercise on their own without intervention.	Intervention ↑* Quality of life (FACT; SF-36) ↑* Muscular strength ↑* VO_2max ↑* Bone formation (phosphatase and osteocalcin) ↓* fatigue ↓* depression Follow-up ↑* Physical fitness vs. start of study.	Intervention based on aerobic and resistance exercise designed to improve metabolic syndrome led to improvements in quality of life, depression, fatigue and physical fitness which were maintained after 3 months of follow-up. The first study to improve these outcomes significantly. Combined physical activity should be incorporated into the treatment and care plans for BC.
Di Blasio *et al.*[22] 2016	BC Post-SP with lymphedema type II Currently with hormonal treatment Without prior chemotherapy or radiotherapy	20 ♀, 50.6±3.6 Randomised Inclusion:>40 ≤55 y.o. No specific diet, no exercise <6 months at the start of study Randomly assigned to 4 groups	10 weeks, three sessions of 70 minutes at moderate intensity. Warm-up 15´ Central part 45' G1: Nordic walking (NW) G2: Walking (W) G3: ISA method (specific for BC survivors) +NW G4: ISA +W Cool-down 10'	*Group: 1, 3 and 4* ↓*Diameter arm/forearm homolateral SP ↑ Upper limb strength ↑ Lymphedema prevention Group: 1 and 4 ↓* Extracellular H2O; extracellular H2O/ Total H_2O ratio; wrist diameter, homolateral SP *Group:* 2 = Limb diameter and body H_2O	NW, NW+ISA, W+ISA are beneficial for reducing the arm and forearm circumference on the operated side and increasing upper limb muscular strength. However, just W does not produce any change in the upper limbs.

♀: Female; BC: Breast cancer: SP: Surgical procedure; ↑: Increase; ↑*: Statistically significant increase; ↓: Decrease; ↓*: Statistically significant decrease; ´: Minutes; VO_2max: Maximum oxygen uptake.

(continúa)

Authors	Patient situation	Study	Intervention	Results	Conclusions
Musanti *et al*.[23] 2012	BC Post-SP Stage I-III: ♀ 18+ y.o. Receiving hormonal therapy Post-chemotherapy 3 months + or Post-radiotherapy 6 weeks + before the start of the study and no more than 24 months beyond their last treatment.	42 ♀ in three randomly assigned groups: - Aerobic group (A): 13 women - Flexibility group (F): 12 women - Resistance group (R): 17 women - Aerobic and resistance group (AR): 18 women Exclusion criteria: comorbidities or oncological processes which inhibit effects of physical activity	Individualised home-based exercise programme *Aerobic exercise* Frequency: 3/5 per week. 15-30 min. per session. Progressive intensity: 40–85% *Resistance exercise.* Frequency: 2/3 per week Repeats per session: 10-12. Sets of exercises for major muscle groups with resistance band Intensity: 3-8 perceived exertion rating on a scale of 1 to 10. Aerobic + resistance exercise. Combination of the 2 protocols	R ↑ strength A ↑* VO_2max A-R ↑ physical and overall self-esteem. F ↑ body fat A-R ↑ overall self-esteem Long-term improvements ↑ physical fitness	The exercise model based on improving physical and overall self-esteem was beneficial for female survivors of breast cancer, especially for those who followed a protocol based on flexibility and resistance exercises followed by aerobic exercises, because they showed greater long-term adherence and maintenance. They all also improved their physical fitness and overall self-esteem.
Speck *et al*.[27] 2010	BC Post-SP Stage I-II: ♀ 18+ y.o. With or without lymphedema	234 [112 lymphedema] Two randomly assigned groups: Intervention Group (IG): physical activity 56±9 y.o. Control group (CG): no physical activity 58±9 y.o. Inclusion: 12 months of physical activity intervention Exclusion: comorbidities or oncological processes which inhibit effects of physical activity	IG: Strength training, upper and lower limbs, and core. 2 90-minute sessions per week. CG: Training without loads or with light weights. Warm-up and stretching added.	IG: ↓ incidence, ↓ severity ↓ exacerbation of lymphedema in the upper limbs. . ↑*Muscular strength ↑ Quality of life (SF-36) ↑ Self-perception appearance	Interventions with the potential to increase strength can improve body image in BC survivors Strength training positively influenced the self-perceptions of appearance, health, physical strength, sexuality, relationships, and social functioning.
Rogers *et al*.[25] 2014	Ductal BC *in situ* Post-SP Stage I-III: ♀ 118-70 y.o. Not receiving chemotherapy or radiotherapy ≥ 8 weeks post SP	222 women randomised into two groups: Intervention Group (IG): physical activity 54 y.o. Control Group (CG): no physical activity 55 y.o. Inclusion: 6 months of physical activity intervention Exclusion: comorbidities that prevent physical activity or its evaluation	IG: 3 months 12 sessions of supervised aerobic training + individual exercise at home and group physical activities. CG: received written information on physical activity	GI adherence to the treatment was 98% and ↑* CG ↑ Aerobic fitness ↑ 6-minute walk post-intervention. ↑*Physical activity in time and intensity ↑* Physical fitness ↑*Quality of life (FACT)	The intervention led to improved physical activity and aerobic capacity. In the short term, it was able to significantly improve quality of life several months after completion, representing an important and worthwhile finding.
Saarto *et al*.[26] 2012	BC Post-SP Stage I-II: ♀ 35-68 y.o. Treated with chemotherapy and/or adiotherapy ≥ 4 months Hormonal treatment no less than three months before.	500 women, mean age 52.3 randomised into two groups: *Intervention Group* (IG): activity n= 237 *Control Group* (CG): no activity n= 263 Exclusion: comorbidities that prevent physical activity or its evaluation	12 months of intervention. IG: Aerobic exercise Time = 48 weeks Duration = 60 min/session Frequency = 1 session/week Intensity = 86%-92%. CG: Encouraged to maintain their previous level of physical activity and exercise habits	Training group ↑ neuromuscular performance ↑ walking time ↑ physical fitness ↑* quality of life (EORTC QLQ-C30). ↑* time performing physical activity ↑ physical performance	Any increase in physical activity, whether triggered by the intervention or spontaneous, was related to improved quality of life in BC patients. Thus, even a motivation of BC survivors to exercise post-treatment could be sufficient to improve their physical activity and quality of life, at least among those who are inclined to be physically active.

♀: Female; BC: Breast cancer: SP: Surgical procedure; ↑: Increase; ↑*: Statistically significant increase; ↓: Decrease; ↓*: Statistically significant decrease; ´: Minutes; VO_2max: Maximum oxygen uptake.

of interest by professionals responsible for prescribing physical exercise as part of the treatment or rehabilitation process for this population. The studies included in this study are randomised controlled trials, considered the "gold standard" to examine whether there is a cause-and-effect relationship between PA and potential benefits for BR patients[21].

The most relevant results of this systematic review indicate that women who have received chemotherapy and/or radiotherapy for BR and do various forms of physical activity and exercise have improved in terms of physical health[20,22-27], psychological health[20,23,24,27], QoL[20,24-28] and fatigue[20]. Some studies have shown improvements in the specific physical capacity functions such as maximum oxygen uptake (VO_2max)[20,23], muscle strength[20,22,23,27] and muscular performance[26]. Other metabolic findings include possible positive effects on bone mineral density[20]. Two studies also report a decrease in upper-limb lymphedema[22,27].

The prescription of PA following the post-surgical procedure stage and chemotherapy and/or radiotherapy treatments took into account the limitations of these women. However, those women with BC-associated comorbidities (cardiovascular problems, respiratory problems, hypertension, anaemia, fracture risk, diabetes), in metastatic stage IV and with some kind of intrinsic impediment preventing them from performing PA were excluded. Primary breast tumours do not normally cause death; death in these cases is the result of the spread/metastasis of the cancer to secondary sites in the body. The 5-year survival rate stands at 99% for localised breast cancer, 84% for regional stage breast cancer (nearby lymph nodes) and 23% for metastases (distant organs) and lymph nodes[3,5]. For this reason, PA after surgery and chemotherapy and/or radiotherapy is justified because it reduces the levels of circulating oestrogen[29], which potentially slows down or halts the growth of hormone-sensitive tumours by blocking the body's ability to produce hormones or by interfering with the effects of hormones on breast cancer cells, which would reduce the risk of developing metastases[30]. It is also suggested[31] that regular PA so the women can reach an optimal physical condition helps keep oestrogen levels so low that they do not interact with the receptors in the breast cancer cells sensitive to the hormones, thus preventing changes in the expression of specific genes which can stimulate cell growth.

Physical activity

CWhen prescribing PA for BC patients, there are several ways of planning the type of training, seeking what is potentially the most beneficial type for the patient and adapting it to their condition[31]. In this review, seven studies included aerobic training (AT)[20,22-26,28] and in some[22,24-26] it was the only type of PA used. Doing PA which only involves AT[22,24-26] could be due to possible complications associated with the appearance of secondary lymphoedema caused by strength training (ST) of the upper limbs of these patients. However, Speck *et al.*[27] only used ST and observed that the symptoms and exacerbation of lymphoedema disappeared. Other studies performed work in which ST was combined with AT[20,23,28]. Musanti *et al.*[23] and Moros *et al.*[28] also included flexibility work at the end of the training sessions.

Aerobic training

Many varieties of AT establish specific routines: a) Impact activities, which besides serving as a warm-up to training, are widely used because they favour bone regeneration and prevent osteoporosis[28]. When performing exercise of this kind, the intensity is increased gradually over the session[20,22-24,28]; b) Exercises bikes can be combined with breathing exercises and even exercises to strengthen the upper limbs[28]; c) Nordic walking (NW) is a form of walking using walking poles to help you move along, thereby involving the trunk and upper limbs in the exercise[22]; d) Running or walking: this was the basic AT for the patients in the studies[20,23-26].

AT is prescribed in order to increase aerobic and functional capacity, which has diminished in patients with BC, generally after receiving cancer treatment[31]. Fitness assesses the level of physiological readiness or capacity for exercise. From this perspective, direct assessment by VO_2max[20,23] and the International Physical Activity Questionnaire (IPAQ)[24] or indirect methods which measure the time and intensity of the PA[25,26] performed have shown significant improvements in the specific physical capacity functions of patients with BC after following PA protocols.

Strength training

The aim of ST is to prevent the loss of muscle mass and strength produced by BC and oncological medical treatment. The most aggressive therapies are even associated with problems of malnutrition, resulting in anorexia or cachexia, which exacerbates muscle degeneration[31]. Increases have been observed[22,23] in muscle strength, some of which are significant[20,27], and also imply a better body image, thereby bringing in the psychological aspect, of particular importance when it comes to overcoming BC. These improvements in skeletal muscle associated with ST could result from the transcriptional deregulation of the MuRF-1 and atrogin-1 proteins which increase during BC and chemotherapy and/or radiotherapy[12]. MuRF-1 and atrogin-1 have been identified as ligases which participate in E3 ubiquitin-mediated muscle proteolysis, one of the chief pathways which regulates muscle protein breakdown, and this system plays a central role in controlling muscle size[32].

Doing PA also leads to the recovery of type II fibre, lost after chemotherapy and/or radiotherapy or due to neoplastic cachexia processes[31], producing an improvement in the contractile activity and speed of skeletal muscle, leading to improvements in strength[20,22,23,27].

Flexibility training

Flexibility training (FT) is prescribed together with other types of training[23,27,28] to increase joint mobility, especially in those patients who have undergone surgery and the area is quite retracted, the muscles improving the mobility and functional capacity of the affected area.

Control of lymphedema

The BC patients who engaged in an exclusive upper and lower limb ST programme[27] not only significantly increased their strength but

also had a lower incidence and severity of lymphedema. Di Blasio et al's study[22] reports that NW is effective in reducing lymphedema, significantly decreasing the diameter of the homolateral arm and forearm, as well as establishing a preventive mechanism against exacerbations. Probably the method of doing NW, which involves a cycle of opening and closing the hands, creating a pumping effect, promotes blood and lymphatic circulation by contraction of the upper limbs. NW is combined with the ISA method (specifically designed for breast cancer survivors), used to warm up the joints gently, lessen tensions and help reduce lymphedema. Reducing lymphedema leads to an increase in the effective contractile space which increases the strength of the upper limbs and improves MMSS and improves body image.

Improvement of fatigue

Interleukin 6 (IL-6) has been associated with symptoms of fatigue, which are the most common symptoms and their action among patients with BC is devastating because they are associated with chronic inflammatory processes. Besides being associated with fatigue, IL-6 is a predictive biomarker of survival in people with metastatic BC[12] because it plays a key role in the development, progression and risk of BC. Lahart *et al*.[31] claim that PA specifically reduces fatigue in people with BC and that this improvement could be associated with the reduction in IL-6 and other cytokines (IL-2, IL-8 and TNFα)[12,15]. This finding could contribute to the incorporation of PA routines which have been associated with a favourable tendency in survival through exercise in several populations with cancer[15]. In this regard, the direct measurement of fatigue by Dieli-Conwright *et al*.[20] saw a significant decrease which led to a significant improvement in the physical condition of BC patients compared to the start of the study. This decrease in fatigue is revealed indirectly[25,26] because these patients are able to significantly increase the time and intensity of PA, which supposes an improvement in physical fitness without the onset of fatigue.

Psychological aspects

At some point in the course of the disease, most BC survivors suffer psychological side effects related to the disease itself or the medical treatment received. Depression and low self-esteem are associated in part with the physical changes that the women experience and in part with loneliness[31]. To try to combat these psychological consequences, studies on PA in patients with BC[20,23,24,27] have reported improvements of such psychological factors as mood, anxiety and depression, self-esteem and self-perception of the appearance. In addition to the actual patients, these changes also benefit their families. These improvements in psychological profile affect QoL very favourably.

Quality of life of the patients

QoL can be related to all aspects of a person's life, but in the field of oncology the term focuses on the health of the patient[33]. At present, attention has been focused on the quality and not just the quantity of life. Non-pharmacological PA therapy should be assessed on whether it is more likely to provide a life worth living in social, psychological and physical terms, evaluating the health of the individual and the potential benefits and risks that may arise from PA[34].

Quality of life was assessed using validated questionnaires: the European Organisation for Research and Treatment of Cancer (EORTC) questionnaire (EORTC QLQC30)[24,26,28], the Functional Assessment of Cancer Therapy (FACT)[20,25] and the Short Form-36 Health Survey (SF-36)[20,27]. All the studies[20,24-28] showed a significant improvement in QoL compared with the control group. These results are consistent with others published[9,16,31,34]. Generally, QoL is influenced by the beneficial evolution obtained in perceptions of body image, self-esteem and mood after doing PA programmes. Additionally, adherence to PA therapy is favoured by improvements in QoL, which should encourage the implementation of PA as a continuous habit in patients with BC, resulting in all the long-term health benefits described[15,16].

Conclusion

Doing PA with AT and ST routines stimulates improvements of the physical and psychological condition of patients with BC. Doing PA gives rise to increases in muscle strength and VO_2max, decreases in fatigue and lymphedema, and improvements in self-esteem and body image which have a direct beneficial effect on the QoL of BC patients.

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Conflict of interest

The authors declare that they are not subject to any type of conflict of interest.

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