MLS - SPORT RESEARCH

https://www.mlsjournals.com/Sport-Research

ISSN: 2792-7156

How to cite this article:
Sánchez Calderón, R., Pulgar, S., & Lago Fuentes, C. (2023). Beneficios del ejercicio físico en mujeres diagnosticadas de cáncer de seno invasivo. Una revisión sistemática. *MLS Sport Research, 3*(2), 7-19. doi: 10.54716/mlssr.v3i2.1745.

BENEFITS OF PHYSICAL EXERCISE IN WOMEN DIAGNOSED WITH INVASIVE BREAST CANCER. A SYSTEMATIC REVIEW

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Abstract. The aim of the study was to analyze the benefits that physical exercise produces in women diagnosed with invasive breast cancer and are between stages I to IIIA, receiving chemotherapy, radiotherapy, or both simultaneously. The PubMed and Google Scholar databases were consulted until April 2022, yielding a total of 29,410 results. After applying the exclusion criteria, the number of selected articles that provided relevant data for the study was reduced to seven. The authors suggest that practicing aerobic training for a period of twelve to sixteen weeks at a rate of two days a week, in sessions lasting less than one hour and intensities of between 60%-80% of the HRmax generated beneficial adaptations. Similarly, practicing strength training at intensities between 60%-80% of 1RM, generated improvements in health status, psychological parameters and decreased pain symptoms and fatigue, among others. The study concludes that the practice of physical exercise by these patients, in the modalities of aerobic or strength training in a supervised and personalized manner, was beneficial, totally safe, and generated benefits such as the reduction of the sensation of fatigue, the reinforcement of the musculature, or the contribution to the daily physical activity did not decrease, which implicitly led to an improvement in the quality of life.

Keywords: breast cancer, aerobic training, strength training, health, chemotherapy, radiotherapy and side effects.

BENEFICIOS DEL EJERCICIO FÍSICO EN MUJERES DIAGNOSTICADAS DE CÁNCER DE SENO INVASIVO. UNA REVISIÓN SISTEMÁTICA

Resumen. El objetivo del estudio fue analizar los beneficios que el ejercicio físico produce en mujeres diagnosticadas de cáncer de seno invasivo y se encuentran entre las fases I a IIIA, recibiendo tratamiento de quimioterapia, radioterapia o ambos simultáneamente. Las bases de datos de PubMed y Google Académico fueron consultadas hasta abril de 2022 arrojando un total de 29.410 resultados. Tras aplicar los criterios de exclusión fijados, el número de artículos seleccionados que aportaban datos relevantes para el desarrollo del estudio se redujeron a siete. Los autores demostraron que practicar ejercicio aeróbico durante un periodo de entre doce y

dieciséis semanas a razón de dos días semanales, en sesiones inferiores a la hora de duración y en las que se realicen ejercicios a intensidades entre el 60%-80% de la FCmáx generaba adaptaciones beneficiosas. De igual manera, practicar entrenamiento de fuerza a intensidades entre el 60%-80% de la 1RM, generó mejoras en el estado de salud, los parámetros psicológicos y disminuyó los síntomas de dolor y la fatiga, entre otros. El estudio concluyó que la práctica de ejercicio físico en estas pacientes, incluyendo las modalidades de entrenamiento aeróbico o de fuerza de manera supervisada y personalizada, resultaba beneficioso, totalmente seguro y generaba beneficios tales como: la disminución de la sensación de fatiga, el refuerzo de la musculatura o la contribución a la adherencia de actividad física diaria, lo que resultó en una mejora en su calidad de vida.

Palabras clave: Cáncer de mama, entrenamiento, quimioterapia, radioterapia y efectos secundarios.

Introduction

Cancer is known as the disease that is generated in any cell of the body as a result of suffering some alteration originated by internal or external causes such as genes inherited from parents (Solidoro, 2006), exposure to certain carcinogenic agents (Walker et al., 2020) or even the food ingested throughout life (Cummings and Bingham, 1998). These changes cause the altered cells, which are called "cancerous", to multiply uncontrollably and may even spread to other parts of the body if the disease is not detected in time (Chaffer and Weinberg, 2011). Mutations usually affect three different types of genes: proto-oncogene, tumor suppressor gene and DNA repair gene. When modifications occur in these structures they are known as oncoinitiators (Martinez, 2011).

The normal cycle through which a cell passes during its lifetime consists of formation and multiplication through cell division. When they age or are damaged, their cycle ends, giving way to the birth of new ones (Weinberg, 1996). However, there are occasions when the cell ages or is damaged, instead of dying, it multiplies uncontrollably, generating the appearance of lumps in the tissues called tumors, which can be malignant or benign. In the case of cancerous tumors, they usually invade nearby tissues and if not treated in time, the damaged cells can spread to other parts of the body through the bloodstream or lymphatic vessels, thus forming new tumors (Aznar et al., 2005). This process is known as metastasis. On the other hand, non-cancerous tumors do not spread to nearby tissues and do not usually recur after removal. However, tumors of this type, in some cases, can reach large dimensions and can even cause death in some cases (INC, 2022; MedlinePlus, 2022)

The most common cancers in our country, according to the Spanish Society of Medical Oncology (SEOM), which puts the total number of cases diagnosed in 2021 at 276,239, were, in this order of incidence, the following: colorectal cancer with 43,581 cases, prostate cancer with 33,764, breast cancer with 33,375 and lung cancer with 29,549 cases. It should be considered that these figures may be biased because of the incidence of Covid-19, since, during the pandemic state, medical oncology consultations and tests were greatly affected (Al-Quteimat and Amer, 2020). Even so, the data obtained are very similar to the number of cases diagnosed in 2020 (REDECAN, 2020). Globally, and during 2020, the types of cancer with the highest incidence were in this order breast, lung, colorectal, prostate and stomach, all with values above one million cases (Ferlay, 2018).

This study focuses specifically on breast cancer, more specifically on invasive breast cancer, differentiating within these several types and the most common being invasive ductal carcinoma and invasive lobular carcinoma (Ramirez, 2018). Typically, within the glandular breast tissue, breast cancer occurs in 80% of cases due to a change in the epithelium lining the ducts, while in 10% of cases it develops in the lobules (Klijn, 2001). The remaining percentage of cases correspond to other less common subtypes (ACS, 2010). Initially, the cancerous tumor is usually confined to one of these two areas, being practically undetectable, asymptomatic and

with little capacity for dissemination, at this point being called stage 0. If the cancerous material is not detected in time, it can invade the surrounding breast tissue and become known as invasive breast cancer, spreading to the lymph nodes and thus initiating a metastasis called regional metastasis, and if the spread of cancer cells continues to advance it will be called distant metastasis (ACS, 2010).

Currently, the treatment of this type of cancer is usually very effective, especially when the disease is detected in early stages (Ginsburg et al., 2020). The most common approach to eradication is usually to combine surgical removal with radiotherapy, targeted biological medication, chemotherapy or hormonal therapy, all with the aim of eradicating cancerous particles that have managed to spread from the breast tumor through the blood (Mutebi et al., 2020).

Breast cancer is a non-communicable disease in which there are certain common behavioral patterns. Changing these behavioral patterns over the years has been shown to reduce the chances of becoming ill by about 30% (Boffetta and Nyberg, 2003). These patterns include a series of recommendations regarding lifestyle habits such as prolonged breastfeeding, avoidance of alcohol consumption, non-exposure to tobacco smoke, prolonged use of hormones, excessive radiation exposures, and regular physical exercise (PE) (Wild et al., 2020).

It is in this last recommendation that this work is based. Over time, numerous studies have been conducted to try to obtain a training program with guidelines that are proven beneficial in the treatment of this disease (Leach et al., 2019). To date, the common conclusion of the studies carried out to date is that both aerobic exercise and strength exercise practiced regularly during the treatment period report clear benefits (Prado et al., 2004). Aerobic exercise is a safe and effective exercise modality that has a positive impact on such common symptoms of breast cancer as fatigue, loss of aerobic capacity, decreased strength and endurance, reduced increase in body mass index, weight and pain, thus improving patients' quality of life and quality of sleep (Batista-Martínez et al., 2019).

In these patients diagnosed with breast cancer, strength training, performed both with external loads and self-loads, improves health status, psychological parameters, pain symptoms, physical functionality, sexual functionality and enjoyment, fatigue, mood, emotional health, cognitive health, body composition and physical capacity. (Santos Durán et al., 2021). According to the ACS (2010) when talking about the benefits of PE during treatment for any type of cancer, it can be highlighted that it reduces the feeling of tiredness or fatigue, helps to reduce pressure and anxiety, improves physical ability to be independent, improves muscle strength, bone health and range of motion, and reduces the side effects of treatment.

Currently, there is not much scientific evidence on the benefits of the EF in women diagnosed with invasive breast cancer stages I to IIIA. Therefore, the aim of this review is to provide an updated overview on the effectiveness of treatments based on FE interventions in patients with invasive breast cancer between stages I to IIIA. Once the existing information has been studied, the aim is to arrive at some kind of conclusive result, which will make it possible to objectify the importance of the EF as part of a therapeutic intervention in the fight against breast cancer.

Method

The search for articles to prepare the paper was carried out during the first four months of the year 2022, between January and March, consulting the Google academic and Pubmed databases. For the selection of the articles to be reviewed, we have used searches with combined words and Boolean markers to filter the information and thus be able to reach the largest number of articles under study, the words used were "breast cancer" "physical exercise" "physical

activity" "breast cancer" "physical exercise" "physical activity" "aerobic training" and "strength training".

All articles on the subject to be reviewed were selected, regardless of language, year of publication and age of the sample. All the selected articles contain the variable invasive breast cancer and the variable physical exercise, regardless of which type was used in the study methodology.

We excluded all articles that were outside the scope of the study, those focused on more than one pathology, articles whose objective was not to study the improvement of the disease by means of PE, and those that did not provide clear results or detailed conclusions.

Results

The Prisma flowchart below shows graphically and schematically the selection criteria used to sift through the more than twenty-nine thousand articles found that deal with physical exercise and breast cancer, being finally seven the only ones that meet all the criteria and therefore those chosen for this review.

Figure 1

PRISMA flowchart for the identification of studies through systematic reviews

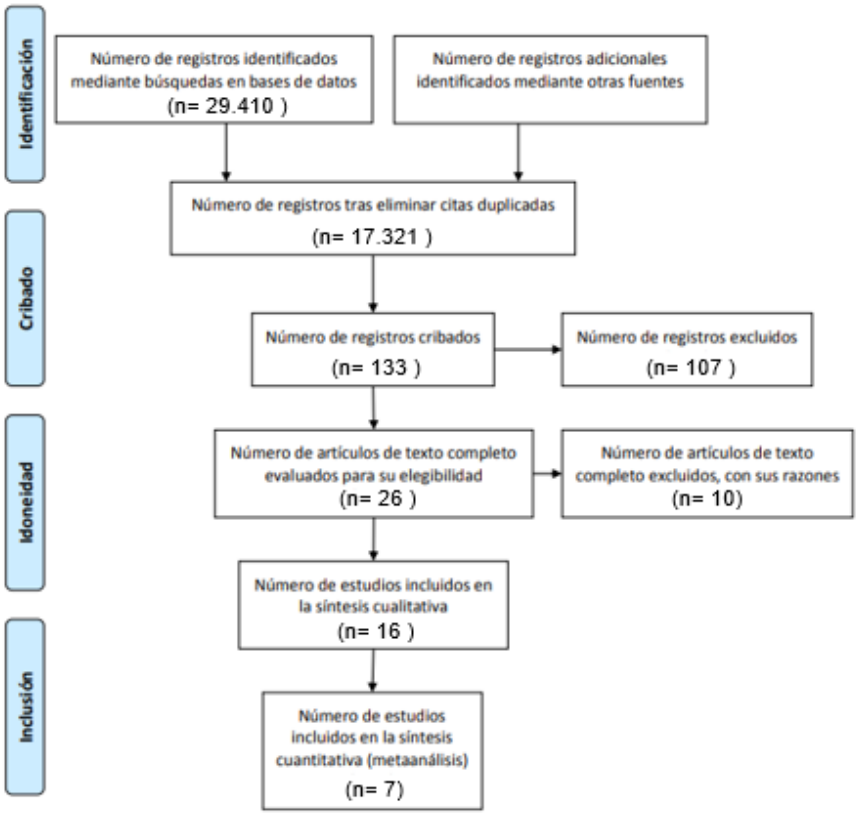

Table 1
*SEQ Illustration * ARABIC 2 Summary selected articles*

Title	Participants	Methodology	Intervention time	Method of evaluation	Results
Campbell et., al (2005)	22 women in stage I and II CM, receiving QT, RT or both	EA and EF. Intensity 60%-75% 1RM.	2 sessions of 20 minutes, per week for 12 weeks	Walking test for 12 minutes ACT-G ACT-B WLS FS PAQ	A structured group exercise program during adjuvant treatment is a safe, well-tolerated and effective way to provide psychological health benefits for women during early-stage breast cancer treatment.
Dieli-Conwright et al., (2018)	418 women with MC whose mean age was 53.5 years receiving QT and RT.	EA and EF	2/3 days a week for 16 weeks + 12 weeks non face-to-face training. G1: control group G2: days 1 and 3 aerobic exercise + strength (80') Day 2 aerobic exercise (50')	-Physical condition tests. -Biomarkers. -Quality of life questionnaires.	The patients' quality of life, depression and fatigue improved, and they were able to maintain their physical condition after 3 months. Significant increase in physical fitness and cardiorespiratory fitness
Ergun et al., (2013)	60 women with CM with mastectomy, and receiving QT, RT or both.	EA and EF. Intensity 60%-80% 1RM.	3 sessions per week of 45 minutes during 12 weeks	RayBio Human Cytokine Antibody array 3 -EORTC QLQ-C30 -BFI -BDI -ELISA kit.	Aerobic and strength exercises, alone or in combination, can be effective in improving quality of life and alleviating depression in breast cancer patients. It is important to schedule training sessions and to monitor patients. Changes in molecules related to angiogenesis and apoptosis are observed. More similar studies on exercise will be useful to raise awareness among both patients and health professionals.
Pereira-Rodríguez et al. (2020)	216 women in stage II disease and receive QT.	Supervised exercise included: high intensity cardiovascular and resistance training, relaxation training and body awareness. They were divided into 3 groups: **G1:** MICT **G2:** HIIT **G3:** control	3 days per week for 70' for 36 weeks. **G1:** 30' EA at 60%-80% FCmax and 20 min of EF at 40%.60% of 1 RM **G2:** the 30' of EA followed a 30-30	-Anthropometric measurements -Vital signs, cardiovascular function and stress test (6-minute walk). -Fatigue (FACT-Fatigue Scale)	Both HIIT and MICT training generate significant adaptations in the parameters evaluated. The first method is the most beneficial at the end of the intervention period. Both methods have been shown to be safe and

			protocol, i.e. 30 seconds at moderate intensity (60%-80% FCmax) and 30 seconds at high intensity (80%-90%) The EF phase was the same as G1.	-EORTC QLQ C-30.	beneficial for this type of patients affected by stage II breast cancer, also reducing fatigue levels, improving quality of life and increasing in parallel the indices of exercise tolerance, vo2 and MET.
Schmidt et al., (2015)	101 women over 18 years of age who have undergone mastectomy and are receiving QT.	EA and EF. Intensities 60%-80% 1 RM.	G1: 60-minute sessions 2 times a week. G2: 60-minute sessions twice a week. Both lasted 12 weeks	Fatigue is assessed with the Fatigue Assessment Questionnaire (FAQ) scale	The study demonstrates that practicing progressive and supervised strength exercises during chemotherapy treatment develops very important clinical benefits on fatigue and QoL. Starting to exercise coinciding with the first treatment sessions helps to prevent the spiral of deterioration that begins with loss of muscle strength, followed by a gradual decrease in physical activity and increased feelings of fatigue, all of which, even if the treatment is successfully completed, inevitably leads to health problems.
Travier et al., (2015)	204 women between 25 and 75 years of age with CM, without metastases and receiving QT.	EA and EF. **EA:** 25' per session **EF:** 2x10 reps at 65% 1RM, 1x10 reps at 75% 1RM, 1x20 reps at 45% 1RM.	**G1:** does not exercise. **G2:** 2 sessions per week for 18 weeks. 30' of unsupervised exercise 3 days a week was recommended	Multidimensional Fatigue Inventory (MFI) Fatigue Quality List (FQL) Dynamometries.	An 18-week supervised exercise program offered early in routine care during adjuvant breast cancer treatment showed positive effects on physical fatigue, submaximal cardiorespiratory fitness and muscle strength. At 36 weeks, these effects were no longer statistically significant. This could have been due to the high levels of physical activity of the participants in the control group during follow-up.
Winters-Stone et al., (2012)	106 women with stage I-IIIA CM, who are receiving QT, RT or both	EF. Intensity 60%-80% 1 RM.	2 sessions per week of 60 minutes during 1 year	1-RM measurement. SCFS.	Strength training along with impact-generating exercises are a

		PPB. Hand dynamometry.	good option for exercise adherence in addition to producing physical improvement. Elderly patients with CM can also participate in strength exercises to improve upper and lower body strength, reducing the risk of falls and future mobility problems.

Note. CM - Breast cancer PPB - Women's health questionnaire
QT - Chemotherapy MFI - Multidimensional Fatigue Inventory
RT - Radiotherapy Elisa Kit - antibody detection
AE - Aerobic Exercise SPAQ - Scottish Physical Activity Questionnaire
EF - Strength Training BDI - Beck Depression Inventory
SWLS - Satisfaction with Life Satisfaction Scale QoL - Quality of life
Fact-G - Functional assessment of general cancer treatment. EORTC QLQ-C30 - European Organization for Research and Treatment of Cancer.
Fact-B - Functional assessment of breast cancer treatment. MICT - Moderate Intensity Continuous Training
SCFS - Schwartz Cancer Fatigue Scale HIIT - High-Intensity Interval Training

Discussion and conclusions

The purpose of this research study is based on analyzing with tangible data whether the practice of PE in a guided and continued manner, whether aerobic or strength training, generates some type of benefit or help in minimizing the side effects produced by both the disease and the aggressive treatments that these patients have to face, such as tiredness or fatigue, weight loss, decreased cognitive function, loss of appetite or vomiting. This screening is framed for women who are diagnosed with invasive breast cancer and are between stages I to IIIA, and are receiving chemotherapy, radiotherapy or both at the same time, in any of the scheduled cycles.

In order to analyze the information in the most detailed and comprehensible way possible, a system has been used that consists of dividing this information into blocks, resulting in three clearly differentiated results: results referring to the benefits after strength training, aerobic training or combined training.

Regarding strength training, Schmidt et al., (2015) conclude that strength training in early stages of the disease can prevent muscle deterioration and alleviate the feeling of fatigue. In the study elaborated by Travier et al., (2015), the patients analyzed obtained improvements in the values of fatigue, submaximal cardiorespiratory capacity and muscle strength. These data are in agreement with those obtained by Battaglini et al. (2006), who examined the effects of a program with emphasis on individualized strength work in a group of women with breast cancer. In this study, the group of participants who underwent the intervention program significantly decreased their perception of fatigue and increased their muscle strength. Ergun et al., (2013) refers to the improvement in quality of life experienced by these patients when performing this type of training, as in a study by Soriano-Maldonado et al., (2019), which aimed to evaluate the effects on quality of life and muscle strength of a 12-week supervised strength exercise program with home aerobic exercise compared to home aerobic exercise alone. The increase in strength in both the lower and upper body automatically ensures that balance is not disturbed by the loss of muscle mass.

The improvements proposed by the aforementioned authors are all in line with each other. All the adaptations achieved took place in a time span of 12 weeks to one year. Ergun et al., (2013) themselves refer in their study to the fact that the action times were limited to 12 weeks, thus stating that the results cannot be considered conclusive in terms of the patients' life expectancy, but they can be considered conclusive in terms of improvement of body parameters. In the results obtained by Battaglini et al., (2006) and Soriano-Maldonado et al., (2019), and the results obtained in our review referring to improved quality of life, decreased fatigue and increased muscle strength, the durations of the interventions also ranged between those periods, respectively at 21 and 12 weeks.

To conclude this section, it should be emphasized that the intensities at which we worked in practically all the interventions ranged between 60%-80% of the 1RM, a range in which the stimulus received by the patient is optimal for obtaining improvements. If the intensity of the work is below 60%, it would be a stimulus with very little load, so we would not achieve significant adaptations. If, on the other hand, it were higher than 80%, it would be considered excessive, since we have to take into account that we are dealing with people with a complicated pathology (Pereira-Rodríguez et al., (2020a), Pereira-Rodríguez et al, (2020b), Winters-Stone et al., (2012), Schmidt et al., (2015), Campbell et., al (2005) and Ergun et al., (2013)) Travier et al., (2015) is the only one who deviates from this pattern, proposing to perform 4 series with the following structure: 2x10 repetitions at 65% 1RM, 1x10 repetitions at 75% 1RM and lastly 1x20 repetitions at 45% 1RM. In a review conducted by Lopez et al. (2020) that aimed to know the dose-response of strength exercise in breast cancer patients, after 10 articles analyzed, it was concluded that low-volume strength training could provide a conservative and appropriate approach in this type of patients, in addition to allowing a safer and more effective progression with the aim of producing the desired adaptations. The data obtained in this review are in agreement with those obtained in the present one, except for the one carried out by Traver et al. (2015).

In the results concerning aerobic training, Pereira-Rodriguez et al. (2020b) differ from conventional methods. The aim of the study is to analyze whether high-intensity interval training, known as HIIT, is really beneficial and can be safely practiced by breast cancer patients. The intensities at which we worked in this study were between 60%-80% of the FCmax for the MICT group, a range also proposed by other studies such as those published by Pereira-Rodriguez et al., (2020a), Winters-Stone et al., (2012). Schmidt et al., (2015), Campbell et., al (2005) and Ergun et al., (2013), and between 80%-90% of HRmax for those who trained HIIT. After 36 weeks of intervention, both the conventional and high-intensity interval training groups showed physical and biological improvements. If we look only at the women who trained HIIT, the improvements obtained were more significant. This study also included within the training session a part of strength exercises, which was identical for both the control group and the experimental group, so it can be concluded that the differences observed in the results were exclusively due to training with the HIIT method. In a study by Schmitt et al., (2016) the effects on quality of life and fatigue were compared in 2 groups of women with cancer. Each group of women underwent an exercise program, one based on combined strength and endurance exercise and the other with high intensity intervals. Both groups improved to a similar degree, however, they concluded that the HIIT strategy could be beneficial for this type of patient, since, in addition to reporting similar benefits, HIIT training took less time, which may be beneficial in this population.

Finally, it should be noted that most authors opt for combined training with sessions in which aerobic work and strength training are performed. Pereira-Rodríguez et al. (2020b) opted for a high intensity method for the aerobic work. Winters-Stone et al., (2012) opted for exercises that generate impact with the intention of improving balance and muscle strength, being the

improvement of these two aspects a contribution to reduce the risk of falls that usually suffer this type of patients throughout the disease. Pagola et al. (2020) analyzed the effects of a combined aerobic and strength exercise program for 24 weeks on psychological and physiological parameters in a group of women with breast cancer, compared to a control group without any type of physical exercise intervention. The results of this study concluded the importance of early inclusion of structured physical activity in cancer patients due to the improvements observed in the intervention group.

Dieli-Conwright et al., (2018) is the only one who after performing a sixteen-week intervention during chemotherapy treatment, proposed to the patients to continue for another twelve weeks performing physical exercise in an unsupervised manner and with the consequent lack of knowledge of the frequency of training that the patients performed during this period. The patients took advantage of the training and habits obtained during the first phase of the intervention to ingrain a training routine. Tests performed at the end of this period showed that the adaptations generated during the first phase did not diminish. However, these data are not in line with those obtained by Hwang et al. (2008), in which 40 women were randomized into 2 training groups: the first, which consisted of an exercise intervention at moderate intensity and supervised for 50 minutes 3 days per week. This intervention included shoulder-focused stretching exercises, aerobic exercise and strengthening exercise. The second, the control group, was composed of women who had to perform shoulder stretching exercises autonomously. The results showed that the control group showed decreased range of motion in all directions and a higher pain score. In contrast, the supervised exercise intervention group showed increased range of motion in all directions and lower pain scores. In addition, the structured exercise program was shown to produce better results. Although these improvements may be due to the fact that the supervised exercise group includes strength and endurance work in addition to flexibility, the results show that supervised, structured, multi-exercise physical exercise would produce greater benefits in these patients. Mutrie et al. (2207) also reported that the supervised exercise group showed improved physical and psychological functioning compared to the group performing unsupervised physical exercise at home, which is also similar to the study by Hwang et al., (2008) and contradicts our results. Therefore, supervised exercise guided by professionals may be more effective than home exercise.

The main limitation in preparing this study was the difficulty in selecting published articles that met all the eligibility criteria. For this reason, the final number of articles to be reviewed was only seven. Among those selected, although both the variability of the intervention periods and the variability of the evaluation tests used were heterogeneous, the conclusions were practically unanimous.

Once the review is completed, it can be concluded without a doubt that the practice of physical exercise in the modalities of aerobic or strength training on a continuous basis in women who have been diagnosed with some type of breast cancer and are undergoing treatment with chemotherapy or radiotherapy, is, from the clinical point of view, beneficial and totally safe, as long as it is performed in a supervised and personalized manner. It should be taken into account that on many occasions the physical activity to be performed must be adapted to the mood, sensations and particular needs of each of the patients, knowing that, depending on the moment of the cycle in which they are, these sensations will vary significantly.

It can also be concluded that, in women affected by this type of pathology, the habit of doing PE in a regular and controlled manner, apart from bringing psychological benefits, has other benefits such as: the reduction of the sensation of fatigue, the reinforcement of the muscles or the contribution to the daily physical activity does not decrease, with the objective of improving the quality of life.

Finally, it has also been shown that practicing aerobic exercise for twelve to sixteen weeks at a rate of two days a week, in sessions that do not exceed one hour in duration and in which exercise is performed on a treadmill or bicycle at intensities of between 60%-80% of the HRmax generates beneficial adaptations in women affected by invasive breast cancer who are between stages I to IIIA and who are receiving chemotherapy, radiotherapy or both. Similarly, practicing strength exercise independently or combined with aerobic exercise during the same period of time in which strengthening exercises are performed for both upper and lower body at intensities between 60%-80% of 1RM generates improvements in health status, psychological parameters, decreases pain symptoms, increases physical functionality, improves sexual functionality and enjoyment, decreases fatigue, improves mood, emotional health, cognitive health, body composition and physical capacity.

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Date received: 14/12/2022
Revision date: 03/03/2023
Date of acceptance: 22/03/2023