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EVALUATION OF THE EFFECTS OF PHYSICAL EXERCISE IN PATIENTS WITH BREAST CANCER: A SYSTEMATIC REVIEW

Marta Victoria Santiago García
European University of the Atlantic (Spain)
marta.santiago@alumnos.uneatlantico.es - https://orcid.org/0009-0004-0767-6377
Andrea Charda Colina
European University of the Atlantic (Spain)
andrea.charda@alumnos.uneatlantico.es · https://orcid.org/0009-0004-8716-8806
Susana Pulgar Muñoz
European University of the Atlantic (Spain)
susana.pulgar@uneatlantico.es · https://orcid.org/0000-0002-6845-248X

Abstract. The main aim of this review was to evaluate the effectiveness of a physical exercise (PE) program in breast cancer (BC) patients and its effects on their life's quality, perceived fatigue, depression and physical condition A systematic search, based on PRISMA guidelines, was performed using three databases: Medline, Pubmed and Google Scholar. Inclusion criteria were; adults (>18 years), BC patients during adjuvant therapy, PE interventions with the capability of influencing quality of life, fatigue and physical fitness.In addition, the exclusion criteria were; performing the PE intervention after the disease, articles published before 2010, as well as any written in languages that were not English, Spanish and/or French. The results five articles were included for review and all studies showed improvements in quality of life, physical fitness and/or body composition, as well as perceived fatigue and depression. It can be concluded that the complementary incorporation of systematized PE programs during adjuvant therapy for women with BC offers both improvements in quality of life and physical fitness and decreased fatigue and depression, whatever the type of training program (resistance, strength or the both of them combined).

Keywords: Breast cancer, physical exercise, physical condition, quality of life and fatigue.

EVALUACIÓN DE LOS EFECTOS DEL EJERCICIO FÍSICO EN PACIENTES CON CÁNCER DE MAMA: UNA REVISIÓN SISTEMÁTICA

Resumen. El objetivo principal de esta revisión fue evaluar la eficacia de un programa de ejercicio físico (EF) en pacientes con cáncer de mama (CM) y sus efectos sobre la calidad de vida, la fatiga percibida, la depresión y la condición física. Se realizó una búsqueda sistemática, basada en las directrices PRISMA, utilizando tres bases de datos diferentes: Medline, Pubmed y Google Académico. Los criterios de inclusión fueron; adultos (>18 años), pacientes con CM durante la terapia adyuvante, intervenciones de EF con el efecto de influir en la calidad de vida,

la fatiga y la condición física. Así mismo, los criterios de exclusión fueron; realizar la intervención de EF después de la enfermedad, artículos publicados antes del 2010 o en idiomas que no fueran inglés, castellano y/o francés.Los resultados incluyeron cinco artículos para la revisión y todos los estudios mostraron mejoras en la calidad de vida, la condición física y/o en la composición corporal, además de en la percepción de fatiga percibida y de la depresión.Se puede llegar a la conclusión de que las incorporaciones complementarias de programas de EF sistematizado durante la terapia adyuvante a mujeres con CM ofrece tanto mejoras en la calidad de vida, como en la condición física y una disminución de la fatiga y la depresión, sea cual sea el tipo de programa de entrenamiento (resistencia, fuerza o combinación de ambas)

Palabras clave: cáncer de mama, ejercicio físico, condición física, calidad de vida y fatiga

Introduction

CM is the most diagnosed in women worldwide (Ferlay et al.,2015), likewise, the risk of being diagnosed with CM is 1:8 (Kootstra et al., 2010), causing survivors a multitude of side effects (Diaby et al.,2015), including cardiac toxicity (Martin et al., 2013), vomiting (Adamsen et al.,2009) and fatigue (Heim et al., 2007), this being one of the most frequent.

Fatigue is the most common side effect in people with CM, with 70-100% of patients experiencing long-term feelings of fatigue (Lipsett et al., 2017). Cancer-related fatigue typically causes a vicious cycle, because reduced physical activity levels caused by the presence of fatigue exaggerate the feeling of tiredness (Gebruers et al., 2019).

During adjuvant treatments is where the greatest consequences are observed at the cardiovascular level, this affects the effects at the cardiac level and its consequences on aerobic capacity (Roca-Alonso et al.,2012). Due to fatigue, PA practice is abandoned, resulting in a loss of muscle and bone mass (Demark-Wahnefried et al, 2001). These losses, apart from the abandonment of PA and immobility, can also be triggered by decalcification and the effects of certain treatments (Winer et al., 2005).

In relation to the reduction in physical activity levels, the lack of physical activity triggers some consequences, such as a reduction in muscle mass and muscle strength (Demark -Wahnefried et al., 2001), as well as other side effects such as a decrease in quality of life (Ligibel et al., 2016), resulting in a decrease in activities of daily living, which again increases the feeling/perception of fatigue (Berger et al., 2018).

This feeling of fatigue may be more pronounced in those patients who are undergoing treatment compared to those who are not (Font et al., 2002).

Likewise, the World Health Organization (1997) defines quality of life as "the way in which the individual perceives his or her life, the place he or she occupies in the cultural context and value system in which he or she lives, the relationship with his or her goals, expectations, standards, criteria and concerns, all of which are permeated by daily activities, physical health, psychological state, degree of independence, social relationships, environmental factors and personal beliefs".

It has been shown that those patients who exercise have a greater tolerance of fatigue, as well as an increase in quality of life (Pereira et al., 2020). In addition to the various beneficial effects of EF in cancer patients, demonstrating a positive association between physical activity during and after antineoplastic treatments, resulting in improved quality of life and functional capacity (Tejada-Medina et al.,2020).

Therefore, the aim of this systematic review is to assess the efficacy of PE programs in women with MC during adjuvant therapy according to their effects on quality of life, fatigue, and physical fitness.

Method

This systematic search was carried out between October and December, was based on PRISMA guidelines and was performed using three different electronic databases; Google Scholar, PubMed and Medline. Relevant keywords and input terms were defined using the PICO(S) methodology, implementing a Boolean search to obtain eligible studies. The following keywords were combined: "CM", "EF", "physical activity", "quality of life", "adjuvant therapy" and fatigue.

Table 1
Searching strategies with Boolean operators in different databases

Database	**Search strategy**
Pubmed	"breast cancer" AND "physical exercise" AND benefits OR "quality of life" OR fatigue "breast cancer" AND "physical exercise" NOT "Physical activity" AND benefits OR "quality of life OR fatigue "breast cancer" and "adjuvant therapy" and "benefits" and "physical exercise"
Google Scholar	"CM" AND "EF" AND benefits OR "quality of life" OR fatigue "CM" AND "EF" NOT "physical activity" AND benefits OR "quality of life" OR fatigue
Medline	"breast cancer" AND "physical exercise" AND benefits "breast cancer" AND "physical exercise" NOT "Physical activity" AND benefits OR "quality of life OR fatigue

Table 2
Inclusion and exclusion criteria

PICO	INCLUSION	EXCLUSION
P1	Adults (>18 years old)	
P2	Women with CM during adjuvant therapy.	Post-illness FE intervention.
I	The intervention should be a training program that works on muscular strength and/or cardiorespiratory capacity.	
C		
O	The result should be an indicator of fitness level, quality of life and/or fatigue.	
Others	The language must be Spanish, English or French. Published from 2010 onwards	

Results

Figure 1 shows the flow chart of the systematic review

Figure 1
Flow diagram

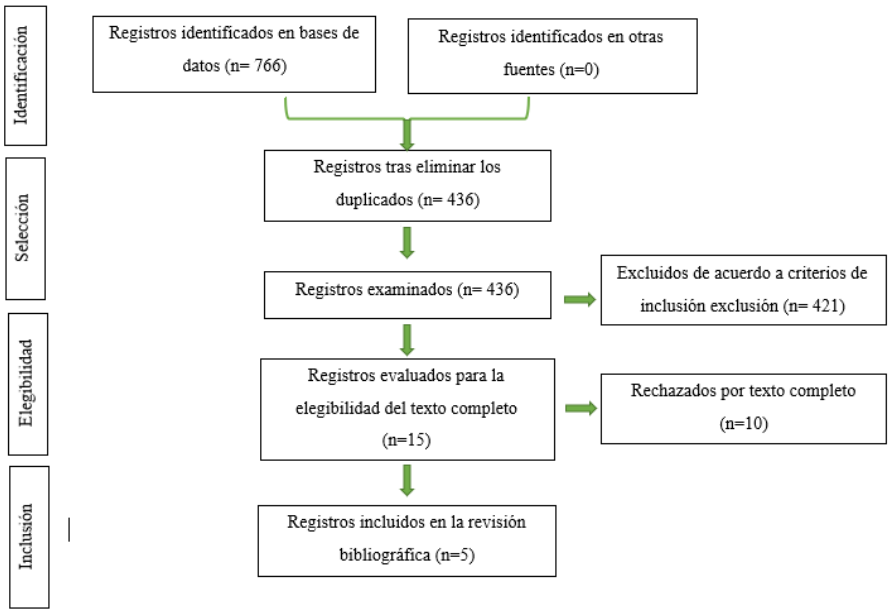

Table 3
Description of intervention studies

Authors	Type of study	Sample	Instrument	Intervention
Antunes et al, (2019)	Quantitative/qualitative	19 women (11 recent term and 8 late)	Balke's test *Test sit to stand* Manual dynamometer Questionnaire QLQ-C30	Aerobic training (<40% of the heart rate of the patient) reserve) Training strength (3 sets, 12-15 reps)
Casla et al., (2015)	Quantitative/ Qualitative	94 women (In early stage from 1 to 36 months after radiotherapy and chemotherapy)	Questionnaires Bruce Protocol (modified) TKK 5401 AND TKK 5402 Grip-D MRI test using the Mayhew formula	Combined aerobic and strength training (85% of heart rate reserve, 50% and 70% of 1RM)

			Electrical bioimpedance (BC-6001F) SF-36 Questionnaire	
Evigor el atl., (2010)	Quantitative/ Qualitative	Experimental group 27 women Control group: 15 women	6MWT Test sit and reach (modified) The brief fatigue inventory Beck depression inventory EORTC Questionnaire QLQ-C30 EORTC Questionnaire BR23	Rehabilitation training based on specific Pilates exercises, progressively increasing intensity over 8 weeks

Spartoo et al., (2012)	Quantitative/ qualitative	Experimental group: 236 women Control group: 237 women	UKK walking test 8-way race test EORTC Questionnaire QLQ-C30 FACIT-F Questionnaire Physical activity levels questionnaire Prospective journal	Aerobic exercise with an RPE between 14 and 16, which corresponds to 86-92% of HRmax, 76-85% of VO2max and 5-7 METs
Schmidt et al., (2015)	Quantitative/ qualitative	122 women in total, of which 101 passed the selection criteria	Fatigue Questionnaire (FAQ) Quality of Life EORTC QLQ-C30 Depression Questionnaire Trail making test Isomed 2000VR	Strength exercises (8 exercises performing 3 sets of 8-12 reps at 60-80% of RM)

	Vo2Max spiroergometry

The first article selected, was Antunes et al., (2019), where the main objective of this study was to evaluate the impact on health-related quality of life and physical fitness in patients with CM.

In that article, the women with MC were stage I to III and aged between 30 and 75 years.

The study included 19 women (52 ± 9.7 years of age) divided into group A (GA) and group B 79 (GB) according to follow-up time since CM diagnosis. The AG (n = 11) consisted of patients who had a recent term diagnosis of MC (23.5 ± 5.9 months; min-max: 14-30 months) and GB (N= 11) by patients with late term diagnosis (83.3 ± 5.7 months, 82 min-max: 74-92 months).

Study outcomes were assessed at baseline (M1), after 8 weeks (M2) and 16 (M3) weeks of M1. The following variables were evaluated: physical fitness and quality of life.

Aerobic capacity was assessed by a maximal treadmill exercise tolerance test using a modified Balke protocol. Maximal oxygen consumption (VO2max) was estimated indirectly using the Multi-Stage Submaximal Model.

Lower limb functionality was assessed by the sit-stand test, where the score was determined by the number of sit-to-stands performed in 30 seconds.

Grip strength was evaluated using a hand-held dynamometer, where each subject performed 3 trials for each arm with an alternating bilateral sequence. The average of the 3 trials was considered for the grip strength of the operated and non-operated limbs.

Quality of life was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30). Scale scores for physical function, fatigue and global health status were taken into account for the analysis.

The GA women performed an exercise program with 3 sessions per week for 16 weeks, combining strength and aerobic training.

Aerobic training included aerobic circuits, treadmill and exercise bike.

During the first two weeks, they performed 5 minutes of all these exercises at light intensity (<40% of reserve heart rate, <11 on the Borg scale). After this time, 3 min were added every two weeks until a volume of 30 min of aerobic training was reached.

Eleven exercises were included in the strength training sessions. During the first two weeks, they performed 2 sets of 10 repetitions with no load. After this period, the resistance was adjusted according to the individual differences of each person, so that they could complete 3 sets of between 12-15 repetitions. When the patients reached the capacity to perform the volume mentioned above, the lowest load (5-10%) was added.

At the end of treatment, a significant effect was observed in all fitness scores. In addition, a medium effect size was found in the grip strength of the operated and non-operated limb and a large increase in VO2max and sit-stand test. Post-intervention analysis revealed that only GA significantly improved these outcomes.

Regarding the results in the quality of life questionnaire, a significant increase on physical function and global health status and a significant reduction in the fatigue scale score for GA were observed.

On the other hand, another selected article, is the one by Soraya-Calsa et al 2015, where the main objective was to evaluate the respiratory fitness of breast cancer patients after primary treatment by means of an FE intervention. For this purpose, they recruited 235 women of whom 94 with early stage (I-III) breast cancer 1 to 36 months after radiotherapy and chemotherapy

were enrolled. These in turn, were randomly assigned to two groups, one composed of 44 people, who performed the intervention program combining aerobic and strength exercises (EX) and another of the same number who continued with the usual care (CON), both lasting 12 weeks.

A baseline test was performed at the beginning of the 12 weeks, a post-treatment test and a follow-up test at 6 months after the end of the intervention.

For this purpose, they evaluated Vo2Max as the primary endpoint and secondary criteria such as: muscle strength, shoulder range of motion, body composition and quality of life.

Prior to evaluating the aforementioned criteria, demographic and descriptive data were collected by means of questionnaires, including the level of physical activity.

Vo2max was assessed by a submaximal test at 85% of the reserve heart rate, using the modified (treadmill) Bruce protocol. They also applied the Canadian Society of Exercise Physiology equation to predict VO2max.

As for secondary assessments, isometric muscle strength and shoulder range of motion were evaluated using isometric dynamometers (TKK 5401 and TKK 5402) in hand, leg and back grip. Once obtained, they added up all the strength values and divided the result by the participant's body weight to obtain the strength index.

In relation to dynamic muscular strength, they performed chest press and leg extension exercises following a protocol of 8 repetitions maximum according to Mayhew's formulas (RM test using Mayhew's formula) and the indications of the

National Strength and Conditioning Association.

Muscle strength was evaluated following the test mentioned above so that the maximum number of repetitions at 50% of 1RM for the chest press and 70% of repetitions for the leg extension.

Regarding body composition and anthropometry, data on body composition were collected on the percentage of body fat and lean mass using electrical bioimpedance (BC-601F) and anthropometric values were obtained for weight, height, body mass index, waist-hip circumference and their relationship.

Finally, in reference to the secondary criteria, quality of life (QoL) was assessed through the SF-36 questionnaire, which consists of 36 items, including eight domains referring to physical functioning, role limitation due to physical health, bodily pain, general perception of health, vitality, social functioning, role limitation due to emotional health and mental health. Higher scores indicate higher levels of health.

At the conclusion, 87.7% of the patients completed the intervention, 86% of whom completed the follow-up evaluations at 6 months after the end of treatment.

According to the data reflected in this study, 91% of the women in the EX group met the guidelines for minutes of physical activity recommended by the ASCM guidelines at the end of the intervention, and at 6 months, 79% continued to meet these guidelines. On the other hand, as for the CON group, after 12 weeks only 49% were compliant.

As for the result of the primary assessment of Vo2Max, this was considerably higher in the women of the EX program than the CON. It should be noted that at 6 months the EX group maintained its Vo2max.

Regarding the results of the secondary evaluation, the index of isometric strength and maximal strength (chest press and leg extension) and muscle strength increased in the women

of the EX program compared to those of the NOC. At the 6-month follow-up, EX improved or maintained these.

In reference to body composition, the women in the EX program reduced the percentage of fat mass with a consequent increase in lean body mass. However, these changes were not maintained at the 6-month follow-up.

Regarding quality of life, participants in the EX group had higher levels with respect to mental and physical dimensions in SF36 compared to the group of CON women. Again, these changes were maintained for the EX group in those 6 months.

Finally, it was concluded that the EF is beneficial both psychologically, physiologically and a clear survival factor for this type of patients. Similarly, it is found that after such an intervention there is a significant improvement in Vo2Max capacity levels, which has been observed in different studies to be related to the reduction of cancer-specific mortality, as well as favorable effects on muscle strength, body composition and quality of life.

Another article on CM was conducted by Eyigor el al., (2010). This study consisted of a randomized controlled trial on the multidimensional effects of Pilates on physical performance, flexibility, fatigue, depression and quality of life in women with MC.

The program was carried out for eight weeks, performing the exercises three times a week. The sample consisted of 52 patients between 18 and 75 years old with CM, not recurrent or progressive, finishing treatment with surgery, radiotherapies and/or chemotherapy, with or without hormonal treatment at that time. However, 10 patients did not complete the treatment, ending with 27 patients in the experimental group and 15 in the control group performing general PE at home.

The workouts were structured in a warm-up where ten repetitions of different pilates postures where the whole body is involved are performed; and a main part with more specific pilates exercises, progressively increasing the intensity each week.

An analysis of the subjects before, during and after the intervention was performed. The tests performed were: Six-minutes walk test, modified sit and reach test, the brief fatigue inventory and finally beck depression inventory. To measure patients' global quality of life, the EORTC QLQ-C30 scale was used, specifically the EORTC BR23 specialized in cancer.

In the measurements taken before the program, no significant differences were observed between patients. However, at the end of treatment and assessment, changes were observed that positively affected the Pilates group in tests for functional capacity, depression, global quality of life and tumors. As for the control group, there was a significant decrease in the functional capacity test.

The results of this study revealed significant changes in the following parameters: functional capacity, depression, quality of life and, to a lesser extent, flexibility. However, the control group did not obtain significant changes in the different parameters evaluated.

In the article by Spartoo et al. where the aim was to determine whether physical training improves the quality of life (QoL) and physical fitness of MC survivors.

Patients were randomly assigned to a 1-year training or control group. The inclusion criteria for the study were: Histologically proven invasive CM, patient with premenopausal or postmenopausal CM treated with adjuvant chemotherapy or radiotherapy within 4 months, or patient who has initiated adjuvant endocrine therapy no less than 4 months prior and aged 35-68 years. The main reasons for exclusion were age over 68 years and the existence of health problems that contraindicated physical training.

Medical history was reviewed and physical examinations were performed at baseline and at 1-year follow-up. Patients completed the quality of life questionnaire, a questionnaire covering basic demographic and lifestyle issues, and an exercise diary two weeks before the intervention and after 6 and 12 months. Physical performance tests (2 km walking test and 8 km running test) were performed immediately before the start of the intervention and at 12 months follow-up.

The intervention focused on physical training at home, although, in turn, weekly supervised training sessions were held. Supervised group exercise training was organized once a week in groups of 5 to 15 people.

The supervised group exercise training consisted of two weekly classes with a duration of 60' each, where they alternated aerobic exercise training and circuit training. The intensity of the training program was based on the Rating of Perceived Exertion (RPE) scale. The target RPE of the training group was 14-16, a level of exercise that feels "somewhat hard" or "hard" and coincides with approximately 86-92 % of maximum heart rate, 76-85 % of VO2Max and 5-7 metabolic equivalents (METs).

The type of home training was optional but intended to be similar to supervised training, this consisted primarily of resistance training such as walking, Nordic walking or aerobic training, but also included jumping and hopping similar to step aerobics to promote bone health. Warm-up and cool-down exercises, such as walking or climbing stairs, were recommended before and after the home training session.

In addition, resistance training (walking, cycling, swimming, etc.) was recommended to the same RPE to meet the amount of weekly physical activity. It was intended that home training would be performed at least twice a week (but three times a week was recommended) so that total training would comprise a minimum of three training sessions per week. The control group was encouraged to maintain their previous level of physical activity and exercise habits throughout the study without any supervised or home training program.

Questionnaires were also conducted on leisure time physical activity levels prior to CM diagnosis, where activities were classified as low intensity, moderate intensity, high intensity or very high intensity activities.

In addition, information on the amount and intensity of current physical activity immediately prior to the start of the exercise intervention and at the follow-ups after 6 and 12 months was collected through a prospective physical activity diary, where patients reported the amount (minimum duration of 10 min) and type of physical activity.

As for the evaluation tests, cardiorespiratory capacity was assessed by a 2 km walking test (UKK walking test), neuromuscular performance was assessed by the 8-shape running test.

Quality of life was assessed using the European Organization for Research and Treatment of Cancer Questionnaire (EORTC QLQ-C30) with the addition of the CM module (BR-23). and finally, fatigue symptoms were assessed using the Functional Assessment of Chronic Illness Therapy (FACIT) questionnaire for fatigue (FACIT-F).

The amount of physical activity increased from baseline to 12 months in the exercise group and in the control group, with these increases being similar between groups. Neuromuscular performance improved significantly in the training group, while no improvement was observed in the control group. As for cardiorespiratory fitness, no significant effect was observed.

No significant differences were found between the experimental group and the control group in changes in quality of life during the intervention as measured by the EORTC-QLQ-

C30 or BR-23 module, and no significant differences were observed between the groups in depression or fatigue.

The last article selected in this review is the study conducted by Schmidt et al. in 2015, where the main objective was to investigate whether strength exercise during chemotherapy provides benefits on fatigue and quality of life beyond the possible psychosocial effects of group interventions. To do so, they recruited a sample of 101 women who passed the eligibility criteria for the study, which were to be over 18 years of age, have histologically confirmed primary breast cancer or after lumpectomy or mastectomy, be scheduled for adjuvant chemotherapy, have a body mass index (BMI) equal to or greater than 18/kgm2 and be able to follow and understand the study and be willing to participate in the study.

Once the sample was available, two groups were randomly formed where 49 women went to the exercise group (EX) and 46 to the relaxation control group (RC).

Regarding the EX group, they performed 8 different strength exercises on machines in a progressive manner, where they performed 3 sets of 8-12 repetitions at 60-80% of RM. On the other hand, the RC group performed progressive muscle relaxation using Jacobson's technique without any type of aerobic or strength exercise.

For this study, they will use several variables such as fatigue, through a fatigue assessment questionnaire (FAQ), which covers dimensions of both cognitive and physical fatigue. Quality of life (QoL), which was analyzed using a questionnaire (EORTC QLQ-C30). Another variable to be analyzed was depression, which was analyzed using the scale provided by the Center for Epidemiological Studies (CES-D), where high scales indicate greater depression, and within these, a scale greater than 38 from 0 to 100 indicates possible serious depressive disorders.

Cognitive function was assessed using a trail-making-test, which measures the time it takes the individual to connect numbers in a logical sequence.

Again, higher levels indicate worse cognitive function.

The last factors to be analyzed were medical history, BMI, weight and physical condition. Isometric muscle strength and cardiorespiratory capacity were assessed using tools such as IsoMed 2000VR, Vo2Max and spiroergometry.

The results of this intervention show a clear positive effect of strength exercise during chemotherapy in reducing physical fatigue, which is considered the most overwhelming side effect of chemotherapy, increasing quality of life and having psychosocial benefits, especially in the EX group. However, in the RC group, during chemotherapy physical fatigue worsened along with physical function. On the other hand, no significant difference was obtained over the EX and RC group in terms of cognitive fatigue.

Therefore, we conclude that the benefits observed in this study are not simply statistical, but are also clinically relevant.

Discussion and conclusions

In this systematic review, we examined the effectiveness of a PE program in patients with MS with the aim of looking at the potential benefits of PE.

Improvements have been found after a regular PE intervention in breast cancer patients, such as improved quality of life, decreased perceived fatigue and depression, improved body composition and physical fitness. The results found are in line with a study by Gebruers (2019) in which it was shown that EF is effective in increasing activities of daily living and reducing

the feeling of fatigue. In addition, a review by Furmaniak et al. (2016) showed that there is conclusive evidence regarding the positive effects of EF during adjuvant therapy in patients with CM.

It has been considered that EF during adjuvant treatment for MC can be considered as a supportive self-care intervention that is likely to result in lower levels of fatigue, improved physical fitness, and little or no difference in quality of life and cancer-specific depression (Mutrie et al., 2007). In addition, there is ample evidence that EF has beneficial effects on mortality, perceived fatigue, quality of life, anxiety, and depression (Carayol et al., 2017; Palesh et al., 2018).

Several studies have proven the various beneficial effects of PE in cancer patients, demonstrating a positive association between physical activity during and after antineoplastic treatments, resulting in improved quality of life and functional capacity (Tejada-Medina et al.,2020).

According to Courneya (2003), EF may be an effective treatment to improve quality of life in patients with MC, although more scientific evidence is still needed to know the effects of exercise on cancer relapse, biomarkers, other diseases and overall survival.

We conclude that systemized PE performed on a regular basis during adjuvant therapy has numerous benefits such as improved quality of life, decreased perceived fatigue and depression, improved body composition and physical condition, regardless of the type of training program performed (endurance, strength or a combination of both).

As limitations, future lines of research are recommended, where more emphasis can be placed on the intensity of training, as well as on the principles of training adaptation and adaptations according to the state of health of the patients depending on the evolution of the disease.

Similarly, there is no distinction between different training protocols (resistance training, strength training or combined protocols of both), as well as the type of adjuvant therapy (chemotherapy, radiotherapy or both) that has been performed.

Likewise, it would be of great interest to be able to record the evaluations and comments given by the women who take part in these studies, as well as to record the type of analgesics they take and how these affect different variables such as fatigue or depression.

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