Title page

Title

DOES PARTICIPATION IN THERAPEUTIC EXERCISE PROGRAMS AFTER FINISHING ONCOLOGY TREATMENT STILL ENSURE AN ADEQUATE HEALTH STATUS FOR LONG-TERM BREAST CANCER SURVIVORS? A ≥ 5 *YEARS FOLLOW-UP STUDY*

Short running title

HEALTH STATUS AMONG LONG-TERM BREAST CANCER SURVIVORS ≥ 5 *YEARS LATER AFTER COMPLETION OF THERAPEUTIC EXERCISE PROGRAMS*

Authors

Francisco ÁLVAREZ-SALVAGO[a,b], José Daniel JIMÉNEZ-GARCÍA[b,*], Clara PUJOL-FUENTES[a], Sandra ATIENZAR-AROCA[c], Cristina MOLINA-GARCÍA[d], Agustín AIBAR-ALMAZÁN[b]

Affiliations

[a]Department of Physiotherapy, Faculty of Health Sciences, European University of Valencia, Valencia, Spain

[b]Department of Health Sciences, Faculty of Health Sciences, University of Jaén, Jaén, Spain

[c]Department of Dentistry, Faculty of Health Sciences, European University of Valencia, Valencia, Spain

[d]Health Sciences PhD Program, Catholic University of Murcia, Murcia, Spain

Corresponding Author

José Daniel Jiménez-García, PhD

E-mail address

Josedanieljimenezgarcia@gmail.com

Full postal address

Faculty of Health Sciences, Department of Physiotherapy, University of Jaén, Jaén, Spain

Campus Las Lagunillas s/n, 23071, Jaén (Spain)

Acknowledgements

We gratefully acknowledge the contribution of long-term breast cancer survivors who wanted to participate in this project. This work was supported by the Spanish Ministry of Economy and Competitiveness [Plan Estatal de I+D+I 2013-2016]; Fondo de Investigación Sanitaria del Instituto de Salud Carlos III [PI14/01627]; Fondos Estructurales de la Unión Europea (FEDER). This study took place thanks to the additional funding from the University of Granada, Plan Propio de Investigación 2016. Excellence actions: Units of Excellence; Scientific Excellence Unit on Exercise and Health (UCEES).

Declaration of interest statement

The authors report no conflict of interest.

Availability of data and material: All authors certify that they have no affiliations or involvement with any organization or entity with financial or nonfinancial interests in the subject matter or materials discussed in this manuscript.

Code availability: (N/A)

Ethics approval: "*This study was performed in the line with the principles of The Declaration of Helsinki. Approval was granted by the Biomedical Research Ethical Committee of Granada (CEIm) (1038-N-16 I.P).*"

Consent to participate: *"Originally, participants were welcomed for assessments by a physiotherapist, who gave detailed information about the study. Once they signed written informed consent, a blinded researcher carried out the first assessment (baseline data), the reassessment at the end of the 8-week program and a new reassessment 6 months after completion of the program, all between September 2009 and September 2012".*

Consent for publication: (N/A)

Orcids

Francisco ÁLVAREZ-SALVAGO[a,b] https://orcid.org/0000-0002-1108-2174

José Daniel JIMÉNEZ-GARCÍA[b,*] https://orcid.org/0000-0002-4219-3993

Clara PUJOL-FUENTES[a] d https://orcid.org/0000-0002-1736-3209

Sandra ATIENZAR-AROCA[c] https://orcid.org/0000-0002-8164-3846

Cristina MOLINA-GARCÍA[d] https://orcid.org/0000-0003-4965-5721

Agustín AIBAR-ALMAZÁN[b] https://orcid.org/0000-0002-9386-9199

Abstract

Purpose: The aims of this study were to evaluate whether the effects of two therapeutic exercise programs are sustained over time (≥ 5 years) in long-term breast cancer survivors (LTBCS). Second, to determine the influence of the current level of physical activity (PA) performed on cancer-related fatigue (CRF) that these patients may present ≥5 years later.

Methods: A prospective observational study was conducted with a cohort of 80 LTBCS in Granada during 2018. Firstly, considering their participation in one of the programs, they were allocated into two groups: usual care and therapeutic exercise program, to assess CRF, pain and pressure pain sensitivity, muscle strength, functional capacity, and quality of life. Secondly, they were also classified into 3 groups according to current level of weekly PA performed: ≤ 3, 3.1-7.4, and ≥ 7.5 (MET-hour/week) respectively, to assess its impact over CRF.

Results: Although the positive effects of the programs are not sustained over time, a trend toward significance can be observed for a greater reduction in overall CRF levels, lower intensity of pain in the affected arm and cervical region, and greater functional capacity and quality of life in the group that underwent therapeutic exercise. Additionally, 66.25% of LTBCS are inactive ≥ 5 years after completion of the program and furthermore, such inactivity is accompanied by higher CRF levels (*P* .013 to .046).

Conclusion: The positive effects of therapeutic exercise programs are not maintained over time for LTBCS. Additionally, more than half of these women (66.25%) are inactive ≥ 5 years after completion of the program, this inactivity being accompanied by higher levels of CRF.

Keywords

Long-term survivorship, Breast cancer, Fatigue, Quality of life, Physical activity, Rehabilitation

Main text

Introduction

The most common malignancy among women worldwide is breast cancer. The likelihood of surviving the disease has significantly increased thanks to advancements in diagnosis, treatment, accessibility to health care systems, and screening programs [1]. According to recent research, breast cancer survivorship rates for women range from 85.5% at 5 years to 70% at 10 years [2, 3] after diagnosis. As a result, the number of long-term breast cancer survivors (LTBCS), or women who have survived the disease for at least 5 years, is rising [4]. Although the risks of recurrence and adverse effects are higher in the first few years after diagnosis [5], LTBCS continue to have uncovered new health issues and interruptions to their social lives decades after diagnosis. The main concerns include cancer-related fatigue (CRF), which is the most frequent and disabling symptom across the breast cancer continuum, apart from skin disorders, lymphedema, cardiotoxicity, cognitive impairment, bone and musculoskeletal health, pain and neuropathy, sexual health, depression, and anxiety, return to work, and daily activities [6, 7], which translates into a highly considerable impact on the quality of life at this stage of long survival [8].

In this sense, although different therapeutic modalities have been studied to date for the treatment and management of the sequelae of not only breast cancer patients but also LTBCS [9-11], the effects of physical activity (PA) and exercise regarded as the best non-pharmacological treatment option for several side-effect cancer-related therapies [12]. Furthermore, emerging observational data suggest that regular PA can reduce cancer recurrence and increase overall survival [13]. Despite the aforementioned evidence, most of the studies on exercise in breast cancer survivors are almost always focused on the initial stage of cancer treatment or on brief post-cancer follow-ups covering relatively short periods of time (ranged from 8 weeks to 2 years) [14-16]. Thus, not only there is little scientific evidence on whether the effects of therapeutic exercise programs last in the long term (when it comes to LTBCS), but also, among the few studies carried out, there is still controversy because these studies differ in their duration, in the type of intervention (some not only carried out therapeutic exercise, but also incorporated other therapies or even mix different types of cancers such as breast and colon), in the variables analyzed and, in the results achieved among different variables after follow-up [17-24]. Given this lack of consensus, one of the main reasons that has become more important as a justification for the fact that the benefits of the programs do

not last over time and that the patients even show physical and emotional deterioration is the lack of adherence on the part of the patients to continue being active once their participation in the exercise programs has ended [25].

This lack of adherence would translate into lower levels of PA performed, which is known to eventually lead to the appearance or persistence of symptoms such as CRF and pain [26], and hence, to a deterioration in the general health and quality of life of these patients [27]. Thus, assessing not only the long-term effectiveness of such interventions, but also the role of adherence rate over time, remains imperative because of the amount of relevant information we could extract to properly plan the long-term ongoing approach these patients need.

Therefore, the aims of this study were to evaluate whether the effects of the therapeutic exercise programs are sustained over time (≥ 5 years) in LTBCS, and furthermore, to determine the influence of the current level of PA performed on CRF that these patients may present ≥5 years later.

Materials and methods

Design and participants

A prospective observational study was conducted with a cohort of 80 LTBCS. Participants were recruited from therapeutic exercise programs conducted in Granada at the both Clinical laboratory of Faculty of Health Sciences and the Oncology Patient Support Unit (UAPO). LTBCS survivors had to meet the following inclusion criteria: (1) being above the age of 18; (2) being diagnosed with stage I-IIIa BC; (3) having finished oncology treatment; (4) having participating in previous studies of therapeutic exercise [28, 29] either in the control group (usual care recommendations by an oncologist in relation to a healthy lifestyle) or in the intervention group (therapeutic exercise program under the recommendation of the American College of Sports Medicine for cancer survivors) [30]; (5) having completed regardless of the type of participation, the two reassessments at the end of the program (week 8) and also in the long term (month 6); and (6) not having participated in any other therapeutic exercise program during the entire follow-up period. The participants who presented any medical condition or other reasons that did not allow them to understand the ≥ 5 years reassessment were excluded from the study.

Originally, participants were welcomed for assessments by a physiotherapist, who gave detailed information about the study. In both studies, participants were randomly assigned to the exercise group or the control group using computer-generated random numbers. These numbers were provided in numbered, opaque envelopes by an external member to ensure that research member responsible for outcome assessments was blind to treatment group assignment. The envelopes were opened after the baseline assessment. Once they signed written informed consent, a blinded researcher carried out the first assessment (baseline data), the reassessment at the end of the 8-week program and a new reassessment 6 months after completion of the program, all between September 2009 and September 2012 as previously mentioned and described in the Aquatic exercise study [28] and the Telerehabilitation exercise study [29] with its secondary analysis [31]. In this regard, the required sample size for the Aquatic exercise study was based on detecting between-group differences of 11 mm at a 100 mm in the Visual Analogue Scale (VAS), assuming a standard deviation of 9 (i.e., minimum clinically important difference) [28], whereas in the telerehabilitation exercise study, the calculation was based on detecting differences of at least 5% in health-related quality of life (i.e., global health status) using the European Organization for Research and Treatment of Cancer Core 30 Quality of Life Questionnaire (EORTC QLQ-C30) [29].

In relation to both exercise programs and although these are described in detail in their respective publications [28, 29], the Aquatic exercise program consisted of 1-hour session that included a 10-minute warm-up involving slow aerobic, mobility, and stretching exercise; 35 minutes of aerobic, low-intensity endurance, and core stability training; and a 15-minute cool-down period including stretching and relaxation exercises focusing on the neck/shoulder region. Progression in the aerobic training was individualized and performed throughout the 8 weeks by gradually increasing the intensity and the duration. The program was supervised by two physical therapists with clinical experience in the management of patients with different cancer conditions, and there were 10–12 participants per group [28]. As for the Telerehabilitation exercise program, it was implemented using the e-CUIDATE system, an online system that facilities the development of remote rehabilitation. The e-CUIDATE system consists of a public interface and a separate private interface. The public area is the home page, which has updated information about breast cancer. After completing the baseline assessment, the participants received in person instructions on how to access and use the private area on their own (usernames and passwords were provided). The CUIDATE research staff designed the most adequate tailored exercise program for each

participant. Each session was delivered online and contained a battery of specific exercises that were divided into 3 sections: 1) warm-up, 2) resistance and aerobic exercise training, and 3) cool-down. Participants had a space available to write questions or suggestions regarding their performance [29]. In both studies, the intensity and volume of the physical exercise training were established following the recommendations of the American College of Sports Medicine for cancer survivors [30].

Between January and April 2018, participants from both studies were again contacted for a reassessment (at least ≥ 5 years after completion of the therapeutic exercise program). Firstly, and considering their participation in one of the programs, were allocated into two groups: usual care and therapeutic exercise program under the recommendation of the American College of Sports Medicine for cancer survivors [30]. Subsequently, and also considering previously published cut-off points [32, 33], they were also classified into 3 groups according to the level of weekly PA performed ≥ 5 years after completion of the therapeutic exercise program: ≤ 3 (MET-hour/week), 3.1-7.4 (MET-hour/week) and ≥ 7.5 (MET-hour/week). This last reassessment was also blinded to the participant allocation and lasted approximately 1 hour. The flow diagram for study participants is presented in Figure 1.

[Figure 1 near here]

This study was performed in the line with the principles of The Declaration of Helsinki. Approval was granted by the Biomedical Research Ethical Committee of Granada (CEIm) (1038-N-16 I.P).

Variables

Cancer related-fatigue and its domains

The Spanish version of the Piper Fatigue Scale (PFS), which has shown high reliability in breast cancer survivors (Cronbach's α .86), is a validated self-reported scale to assess CRF [34]. It contains 22 items, and the scores range from 0 to 10 (0 = none, 1–3 = mild, 4–6 = moderate, 7–10 = severe) including four dimensions of subjective fatigue: "behavioral/severity", "affective", "sensory", and "cognitive/mood" [35]. A total fatigue score is also calculated and higher scores indicate greater fatigue. A minimally important difference (i.e., a change of 2 points) on the PFS total score represents a clinically significant improvement in fatigue [35].

Pain

The VAS is a linear scale with a length of 10 cm for subjective pain estimation. It ranges from 0 at one end (no pain) to 10 at the other end of the scale (the worst possible pain imaginable). Participants marked the level of pain that they felt on the arm homolateral to the affected breast. With an intraclass correlation coefficient (ICC) of 0.97, the VAS has previously demonstrated that it is a valid and reliable tool for assessing pain [36].

Pressure pain sensitivity

The pressure pain threshold (PPT) is the lowest level of pressure at which a pressure sensation initially transforms into pain [37]. It was assessed with an electronic algometer (Somedic AB, Farsta, Sweden). The pressure was applied at approximately a rate of 30 kPa/seconds by a 1-cm2 probe. Participants were told to press the button as soon as the pressure turned into discomfort. For each point, the analysis was conducted using the mean of three trials (intraexaminer reliability). Each trial was followed by a 30-second rest interval. The reliability of pressure algometry has been found to be high ICC 0.91 [38]. As previously mentioned [39], PPT was evaluated bilaterally over the C5-C6 zygapophyseal joints, deltoid muscles, and tibialis anterior muscles.

Upper limb muscular strength

Measurement of upper body muscular strength (handgrip strength) was determined using digital dynamometer (TKK 5101 Grip-D; Takey, Tokyo, Japan). The precision was 0.1 kg. For dynamometry measurement, patients had to maintain the standard bipedal position during the entire test with the arm in complete extension. The determination of optimal grip span according to hand size was obtained through a simple algorithm which allowing the grip span to adapt to the hand size in women before the test [40]. Each subject had to do three tests for each hand (alternating both hands) with 1 min of delay between measures. The final result will be the mean score for each hand. This test has shown to be valid and reliable [41].

Functional capacity

The 6-min walk test (6MWT) using a treadmill is a valid and reliable test [42] in breast cancer patients [43], which determines the maximum distance (meters) that a person can walk in 6 minutes. All participants were familiarized with the treadmill exercise protocol. They were instructed to set their own pace, to "walk as far as you can in 6 minutes", and to volitionally increase or decrease the speed of the treadmill. During the task standardized phrases of encouragement were given.

Quality of life

The European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23) is a breast cancer module of EORTC QLQ-C30, and it contains 23 items assessing functional and symptom scales. All of the items are rated on a four-point scale from 1 (not at all) to 4 (very much). The scores are transformed linearly to obtain a range of score from 0 to 100, with higher scores meaning a great response level. The test has shown to be reliable [44].

Physical activity level

The validated Spanish version of the Minnesota Leisure Time Physical Activity Questionnaire (MLTPAQ) [45] was administered by a trained interviewer who had detailed instructions and a list of clearly defined physical activities. The assessor asked the participants about what type of leisure-time physical activities they had been doing during last year. Then, the participants estimated the duration of the activities performed in min/week for each season. To be able to calculate energy expenditure for leisure-time PA, the time reported for each activity was multiplied by a Metabolic Equivalent of Task (MET) value [46]. For the main analysis, the duration of the activities performed in min/week were transformed into hour/week.

Statistical analyses

A statistical analysis was performed to examine differences in sociodemographic, medical, and clinical features using t student tests for continuous variables and Chi-square for categorical variables. The Kolmogorov-Smirnov test was used to check the hypothesis of normality for all variables ($P > .05$). Intergroup differences were compared using ANOVA, with usual care group or therapeutic exercise group under the recommendation of the American College of Sports Medicine for cancer survivors as the

independent variable and CRF, pain and pressure pain sensitivity, upper and lower body muscular strength, functional capacity, and quality of life at ≥ 5 years after completion of the therapeutic exercise program as dependent variables. The sexual functioning, sexual enjoyment, future perspective, and hair loss scales from the quality of life EORTC QLQ-BR23 questionnaire were excluded from the analysis because of a high proportion of missing data in both groups. The proportion of missing data for sexual functioning was 40% and 30% and for sexual enjoyment was 60% and 30% in both the usual care and exercise groups respectively. Likewise, the proportion of missing data for future perspective was 35% and 18%, and the proportion of missing data for upset by hair loss scale was 47% and 25% in both the usual care and exercise groups respectively.

Furthermore, intergroup differences were also analyzed using ANOVA, with the group performing ≤ 3 (MET-hour/week), 3.1-7.4 (MET-hour/week) and ≥ 7.5 (MET-hour/week) at ≥ 5 years after completion of the therapeutic exercise program as the independent variable and CRF level at ≥ 5 years as the dependent variable. Subsequently, a post-hoc multiple comparison of means was performed with Bonferroni adjustment.

The Statistical Package for the Social Sciences (IBM SPSS Statistic for Windows, Armonk, NY, USA version 27.0) was used for data analysis, and the significance level set at ($P < .05$) 95% confidence interval (CI).

Results

Characteristics measure scores

No significant differences were found for sociodemographic and clinical data between participants who received usual care (n = 38) and those who underwent therapeutic exercise (n = 42), who completed follow-up at ≥ 5 years. In the usual care group, the mean age was 49.74 ± 8.73 years, while in the therapeutic exercise group it was 48.81 ± 7.68 years. Regarding the usual care group, 31.58% were smokers, 52.63% had stage II breast cancer and 92.11% had received radiotherapy and chemotherapy. In contrast, in the therapeutic exercise group, 21.43% were smokers, 54.76% had stage II breast cancer and 85.71% had received radiotherapy and chemotherapy. The characteristics of the groups can be observed in Table 1.

[Table 1 near here]

Cancer related-fatigue

The ANOVA found no significant differences between groups for any of the domains of CRF in the PFS: "severity" (F = 0.15; *P* = 0.698), "affective" (F = 0.79; *P* = 0.377), "sensory" (F = 0.01; *P* = 0.938), "cognitive" (F = 0.89; *P* = 0.347) and "global" (F = 0.01; *P* = 0.920). Although there were no significant differences, LTBCS who performed therapeutic exercise presented a greater reduction in "affective" (mean difference for therapeutic exercise: -2.37 ± 3.26 vs. usual care: -2.73 ± 3.20) and "global" fatigue (-1.77 ± 2.73 vs. -1.71 ± 2.57, respectively) after ≥ 5 years follow-up, compared to the group that only received usual care Table 2.

[Table 2 near here]

Pain and pressure pain sensitivity

Regarding pain, the ANOVA results showed no significant differences between groups for pain intensity of the affected arm (F = 1.25; *P* = 0.267) nor for PPTs in: C5-C6 zygapophyseal joint on the affected (F = 3.42; *P* = 0.068) and unaffected side (F = 0.84; *P* = 0.362), the Deltoid muscle on the affected side (F = 0.31; *P* = 0.579) and nonaffected (F = 1.14; *P* = 0.289), and the Anterior Tibialis muscle on the affected (F = 1.33; *P* = 0.251) and nonaffected (F = 1.82; *P* = 0.182) sides. Although no significant differences were found between the groups, it could be observed on the one hand, how those LTBCS who performed therapeutic exercise presented lower pain intensity of the affected arm in the VAS (-1.60 ± 3.19 vs -0.82 ± 3.02, respectively) and higher PPT in the C5-C6 zygapophyseal joint on both the affected side (46, 67 ± 80.76 vs 12.29 ± 84.41, respectively) (trending toward significance *P* = 0.068) and unaffected side (13.88 ± 87.66 vs -2.21 ± 64.61, respectively) at ≥ 5 years follow-up, compared to those who only received usual care Table 3. On the other hand, the results also showed how those who received usual care were the ones who presented higher PPTs for the Deltoid muscle on both the affected and unaffected side, and for the Anterior Tibial muscle on the affected and unaffected side in the long term, compared to those who performed therapeutic exercise Table 3.

[Table 3 near here]

Upper limb muscular strength, functional capacity and quality of life

In relation to upper limb muscular strength, the ANOVA revealed no significant differences between groups for handgrip isometric strength on the affected (F = 0.03; *P* = 0.861) and unaffected (F = 0.12; *P* = 0.735) sides. Although there were no significant differences, it was the LTBCS who received usual care who showed the greatest improvement of strength assessed after ≥ 5 years follow-up compared to those who underwent therapeutic exercise Table 4**.**

[Table 4 near here]

With respect to functional capacity, the ANOVA did not reveal significant differences between the groups (F = 0.10; *P* = 0.751). However, and in a non-significant manner, we were able to contemplate how the LTBCS who performed therapeutic exercise were those who showed greater functional capacity after ≥ 5 years follow-up (mean difference for therapeutic exercise: 162.97 ± 167.69 vs usual care: 150.12 ± 180.47), compared to those who only received usual care Table 4.

Regarding quality of life, the ANOVA results showed no significant differences between groups for the following subscales of the QLQ-BR23: "body image" (F = 2.07, *P* = 0.154), "systemic therapy side effects" (F = 0.08, *P* = 0.773), "breast symptoms" (F = 0.56, *P* = 0.458) and "arm symptoms" (F = 2.31, *P* = 0.133). Although there were no significant differences, we could observe not only how the "systemic therapy side effects", "breast symptoms", and "arm symptoms" were more reduced after ≥ 5 years in the LTBCS who performed therapeutic exercise, compared to those who only received usual care, but also, how LTBCS from usual care exhibited, not significantly, a more impaired view of their body image along with higher levels of pain in the arm of the affected breast.

Physical activity level and its impact over cancer-related fatigue

Considering PA level, the ANOVA revealed significant differences between groups for all CRF domains: "severity" (F = 6.27; *P* = 0.003), "affective" (F = 3.51; *P* = 0.035), "sensory" (F = 4.46; *P* = 0.015), "cognitive" (F = 3.11; *P* = 0.050) and "global" (F = 4.91; *P* = 0.010) Table 5.

[Table 5 near here]

However, it was necessary to perform multiple comparisons using the Bonferroni test for adjustment, in order to determine between which groups there were significant differences.

Behavioral/Severity

The two groups performing less PA had significantly greater severity of CRF than those LTBCS performing more PA at ≥ 5 years of follow-up (≤ 3 MET-hour/week vs ≥ 7.5 MET-hour/week; *P* = 0.005) and (3.1-7.4 MET-hour/week vs ≥ 7.5 MET-hour/week *P* = 0.017) Table 6.

[Table 6 near here]

Affective

Only the group performing less PA showed significantly more affective CRF than those LTBCS performing more PA after ≥ 5 years follow-up (≤ 3 MET-hour/week vs ≥ 7.5 MET-hour/week; *P* = 0.046) Table 6.

Sensory

Only the group performing less PA significantly exhibited more sensory CRF than those LTBCS performing more PA at ≥ 5 years follow-up (≤ 3 MET-hour/week vs ≥ 7.5 MET-hour/week; *P* = 0.018) Table 6.

Cognitive/Mood

Despite there being no significant differences, we could observe a trend towards significance on how those LTBCS who performed less PA after ≥ 5 follow-up, still presented higher levels of cognitive CRF with respect to those LTBCS who performed more PA (≤ 3 MET-hour/week vs ≥ 7.5 MET-hour/week; $P = 0.051$) Table 6.

Global

Only the group performing less PA presented significantly more total CRF than those LTBCS performing more PA at ≥ 5 years follow-up (≤ 3 MET-hour/week vs ≥ 7.5 MET-hour/week; $P = 0.013$). Furthermore, a trend towards significance could be observed on how those LTBCS performing between (3.1-7.4 MET-hour/week), still presented higher levels of total CRF with respect to those LTBCS performing more PA in the long term (3.1-7.4 MET-hour/week vs ≥ 7.5 MET-hour/week; $P = 0.060$) Table 6.

Discussion

The purpose of this study was to evaluate whether the effects of two therapeutic exercise programs are sustained over time (≥ 5 years after completion of the program) in LTBCS, and furthermore, to determine the influence of the current level of PA performed on CRF that these patients may present ≥5 years later. The main findings of this study showed on the first hand, only a trend toward significance in all the variables (except for some algometry points and upper limb strength) in the group that underwent therapeutic exercise, so that it should be noted that the effects of therapeutic exercise programs are not maintained over time after follow-up, and additionally, how more than half of these women (66.25%) are inactive ≥ 5 years after completion of the program, this inactivity being accompanied by higher levels of CRF.

Although the therapeutic exercise programs in which our LTBCS participated showed both physical and psychological improvements that lasted even up to 24 weeks [28, 29, 31], the benefits obtained were not significantly maintained after our long follow-up period in none of the variables assessed, which seems to be in line not only with the results obtained by other studies of a similar nature [8, 24, 47], but also with other studies with shorter follow-up periods ranged between 1 to 4 years [18, 48-51].

In this regard, Witlox et al. carried out an 18-week program with colon and breast cancer survivors with positive effects on fatigue after finishing the program. However, and despite cancer patients in the intervention group tended to experience less physical fatigue at 4 years post-baseline compared to the usual care group (fact also observed in our LTBCS), the result was not statistically significant [48]. These authors justify that, as in our study (43.24%), their high number of losses (41.7%) could have influenced the results obtained [48].

In the same line, we found the results proposed by Roine et al. (BREX-study) in their 1-year exercise intervention with 573 breast cancer survivors. Thus, these authors observed how pain and quality of life improved with respect to the baseline data in the experimental group at 5 years although not significantly (fact also observed in our results) [24]. Interestingly, when these authors decided to continue their follow-up up to 10 years, it could be observed that the trend towards significance that could be observed at 5 years had been almost completely lost at 10 years of follow-up [8]. In view of these results, we also believe that a possible reason for the absence of long-term benefits could also be the same one as proposed by these authors, highlighting that although it is known that quality of life appears to improve in the first few years after the end of exercise programs, a delayed decline in quality of life might reflect late effects resulting from cancer and its treatment, such as cardiac, respiratory, or musculoskeletal problems that may appear more than five years after treatment [7, 52]. Unfortunately, the fact that many patients did not want to answer questions regarding hair loss, future perspective or both sexual function and enjoyment has meant that these data could not be analyzed in the long term in our LTBCS. This fact has been reflected in previous research as questionnaires concerning sexual health issues have a special risk of reporting bias [53, 54], making patients tend not to answer these types of questions because they are more sensitive for oncology patients [19]. Therefore, future research is still needed to provide more data on the long-term impact of exercise programs on these sensitive aspects for LTBCS.

In the case of functional capacity and upper limb muscle strength, the only ones who seem to have shed light on this issue are Penttinen et al. and Bolam et al. One the one hand, Penttinen et al. also failed to find significant differences in functional capacity (using the 2-km walk test) and quality of life after 5 years of follow-up in LTBCS [47], although in contrast to their results, in our experimental group their functional capacity does increase, although not significantly. As for upper limb muscle strength, no study

to date has directly assessed this variable using dynamometry in the same sample of LSCM more than five years after treatment, since the only significantly positive evidence that provides data using this instrument has only been evaluated till 2 years of follow-up [55]. At this point, it is necessary to mention how our LTBCS in the control group are the ones who showed greater upper limb muscle strength after follow-up. We believe that a possible explanation could be due to the fact that 73.3% of the controls claim to have attended physiotherapy sessions, from the time they finished the therapeutic exercise program until they were re-evaluated, to treat some of their sequels, which could have influenced the results not only in this respect but also in relation to some goniometry points such as the deltoid or tibialis anterior in our LTBCS. Therefore, future research evaluating the effectiveness of therapeutic exercise programs should consider longer intervention periods and the use of more specific instruments adapted to the needs of these patients during the long survival phase in order to establish more solid conclusions.

In contrast to the aforementioned findings, several programs carried out by Mutrie et al. and Schmidt et al. (this last one including patients also from two different exercise programs) demonstrated after 5 years of follow-up, physical and psychological benefits (including CRF and pain) [17, 19] and a level of quality of life comparable to that of age-matched healthy subjects, with the exception of cognitive function and sleep which were still significantly affected in LSCM [19]. Thus, we believe that the difference between these findings and our results after follow-up may be due to different reasons.

On the one hand, the sample size and loss rate described in our flow chart, since both studies evaluate almost twice as many participants [17, 19], which could have influenced the results obtained. On the other hand, the fact that the significantly better rating of global quality of life, physical function, and pain at follow-up might be a consequence of a response shift, i.e., survivors score better because there may have been a “recalibration” of their internal standards with respect to good or bad quality of life aspects due to poor functioning or worse pain during cancer treatment [56]. Likewise, another possible explanation is that the participants of Mutrie et al. followed a behavioral change model to promote an independent exercise habit after the end of the intervention [57], which is known to improve patients' adherence to remain active over time [58]. Something similar occurs in the Schmidt et al. trial, as at the end of the program patients were offered psycho-oncological support and access to different resources that could promote adherence to remain active during this period of time [19]. In contrast, when our

LTBCS completed the programs, they were only encouraged to continue performing the exercises carried out during the program once they had completed their participation, no specific intervention having been used to promote higher levels of adherence after the experimental phase [28, 29], which could explain not only the absence of benefits, but also the high rate of inactivity (66.25%) recorded in our participants in the long term.

Today, the strong evidence [15, 59] that exists on how PA is related to a shorter life expectancy and may cause or exacerbate symptoms such as CRF leading to a worse quality of life, seems not to be sufficient compelling reason to maintain an exercise habit in line with current recommendations, as the vast majority of our LTBCS can still be considered as inactive after 5 years of follow-up. This situation has also been reflected by Mason et al. and by Tollosa et al. between 10 to 15 years after diagnosis [60, 61]. Even, Hartman et al. a considerable tendency to inactivity monitored with a a Fitbit tracker for up to 2 years after the end of a randomized controlled trial to examine patterns of Fitbit use and activity over time [62], highlighting the challenges faced by cancer survivors to continue practicing PA on their own following a supervised therapeutic exercise program [60-62]. Furthermore, it is known that the benefits of exercise may cease if exercise is practiced discontinuously [63].

Likewise, recent research with breast cancer patients has shown that women who increased their level of PA after diagnosis or remained active after completing an exercise program (regardless of their experimental or control participation) had better physical fitness and mood, less CRF, and better quality of life 3 to 13 years later [17, 64, 65]. Suggesting that being active and maintaining a long-term PA habit was associated with greater health benefits [17, 64, 65]. All these results reinforce our findings, as 33.75% of our LTBCS can be considered physically active (≥ 7.5 (MET-hour/week), presenting in turn significantly lower CRF levels after 5 years of follow-up.

Thus, and taking into account the chronic nature of this disease and its long-lasting side effects, health care personnel should change their own paradigm when designing therapeutic exercise programs and take into account that, if the long-term health status of these patients is to be safeguarded, other tools should also be included, such as seminars, support plans and individualized monitoring of the level of PA beyond the end of the exercise programs. This could help not only to incorporate exercise in everyday

routine in the long term, but also to encourage adherence to a healthier lifestyle and prevent the benefits of exercise programs from disappearing over time and diminishing quality of life as a result of inactivity in LTBCS.

This study has several limitations that must be considered. Firstly, the PA cut-off points used in our study are accepted criteria [32, 33], but the inclusion of other cut-off points could modify our results. Likewise, PA measures in this study were self-reported and future studies should attempt objective monitoring of PA patterns including sedentary time. Therefore, future studies are needed to support our findings. Secondly, having used more objective variables (although all the tests have been previously validated) could have strengthened our results. In this sense, despite the fact the QLQ-BR23 questionnaire is a reliable tool for assessing quality of life in breast cancer patients [44], some research has pointed out that it may present certain difficulties in long-term assessments since most of the questions are focused on shorter follow-up periods [66]. Thirdly, the fact that many patients did not want to answer questions regarding hair loss, future perspective or both sexual function and enjoyment has meant that these data could not be analyzed in the long term in our LTBCS. Finally, and considering this is a long follow-up study, it is practically inevitable that participants go to physiotherapy treatments to address some of their sequelae meanwhile, so our results proposed here should be interpreted with caution.

Despite the aforementioned weaknesses, this is one of the few studies that follows up, in the same sample, the effects of therapeutic exercise programs on several variables that are determinant in the health status of LTBCS, since most of the studies performed do not usually provide such a broad approach (generally focusing on quality of life) or if they assess other variables such as pain or CRF, they usually do so even through questionnaires on quality of life and not with other instruments independently such as algometry or dynamometry as in our case. Moreover, an added value is that it provides the level of PA performed 5 years after completion of the exercise intervention and its relationship with the most disabling symptom in these patients such as CRF [6, 7], which makes it possible to observe the level of adherence to exercise of these patients over time and thus, be a point of reference so that future research does not forget that the health status of these patients should not be neglected despite the end of the exercise programs.

Conclusions

The results of this study, despite a trend toward significance in some variables, showed that the positive effects of therapeutic exercise programs are not maintained over time for LTBCS. Additionally, more than half of these women (66.25%) are inactive ≥ 5 years after completion of the program, this inactivity being accompanied by higher levels of CRF. Therefore, future researchers should take into account that simply participating in therapeutic exercise programs does not appear to be a guarantee of long-term health unless adherence and motivational strategies are encouraged in LTBCS between reassessment periods and/or consistently in their day-to-day lives.

References

1. Carioli G, Malvezzi M, Rodriguez T, et al (2017) Trends and predictions to 2020 in breast cancer mortality in Europe. Breast 36:89–95. https://doi.org/10.1016/j.breast.2017.06.003
2. Allemani C, Minicozzi P, Berrino F, et al (2013) Predictions of survival up to 10 years after diagnosis for European women with breast cancer in 2000-2002. Int J Cancer 132:2404–2412. https://doi.org/10.1002/ijc.27895
3. Sociedad Española de Oncología Médica (SEOM) Las cifras del cáncer en España 2022. In: https://seom.org/images/LAS_CIFRAS_DEL_CANCER_EN_ESPANA_2022.pdf. Accessed 19 ene 2023
4. Deimling GT, Bowman KF, Wagner LJ (2007) Cancer survivorship and identity among long-term survivors. Cancer Invest 25:758–765. https://doi.org/10.1080/07357900600896323
5. Demicheli R, Biganzoli E, Boracchi P, et al (2008) Recurrence dynamics does not depend on the recurrence site. Breast Cancer Res 10:R83. https://doi.org/10.1186/bcr2152
6. Cardoso F, Kyriakides S, Ohno S, et al (2019) Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 30:1194–1220. https://doi.org/10.1093/annonc/mdz173
7. Runowicz CD, Leach CR, Henry NL, et al (2016) American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. J Clin Oncol 34:611–635. https://doi.org/10.1200/JCO.2015.64.3809

8. Roine E, Sintonen H, Kellokumpu-Lehtinen P-L, et al (2021) Long-term health-related quality of life of breast cancer survivors remains impaired compared to the age-matched general population especially in young women. Results from the prospective controlled BREX exercise study. Breast 59:110–116. https://doi.org/10.1016/j.breast.2021.06.012

9. Lara-Palomo IC, Castro-Sánchez AM, Córdoba-Peláez MM, et al (2021) Effect of myofascial therapy on pain and functionality of the upper extremities in breast cancer survivors: A systematic review and meta-analysis. Int J Environ Res Public Health 18:4420. https://doi.org/10.3390/ijerph18094420

10. Hsueh E-J, Loh E-W, Lin JJ-A, Tam K-W (2021) Effects of yoga on improving quality of life in patients with breast cancer: a meta-analysis of randomized controlled trials. Breast Cancer 28:264–276. https://doi.org/10.1007/s12282-020-01209-6

11. Yan X, Wei S, Liu Q (2023) Effect of cognitive training on patients with breast cancer reporting cognitive changes: a systematic review and meta-analysis. BMJ Open 13:e058088. https://doi.org/10.1136/bmjopen-2021-058088

12. Ehlers DK, DuBois K, Salerno EA (2020) The effects of exercise on cancer-related fatigue in breast cancer patients during primary treatment: a meta-analysis and systematic review. Expert Rev Anticancer Ther 20:865–877. https://doi.org/10.1080/14737140.2020.1813028

13. Miyamoto T, Nagao A, Okumura N, Hosaka M (2022) Effect of post-diagnosis physical activity on breast cancer recurrence: A systematic review and meta-analysis. Curr Oncol Rep 24:1645–1659. https://doi.org/10.1007/s11912-022-01287-z

14. Hong F, Ye W, Kuo C-H, et al (2019) Exercise intervention improves clinical outcomes, but the "time of session" is crucial for better quality of life in breast cancer survivors: A systematic review and meta-analysis. Cancers (Basel) 11:706. https://doi.org/10.3390/cancers11050706

15. Joaquim A, Leão I, Antunes P, et al (2022) Impact of physical exercise programs in breast cancer survivors on health-related quality of life, physical fitness, and body composition: Evidence from systematic reviews and meta-analyses. Front Oncol 12:955505. https://doi.org/10.3389/fonc.2022.955505

16. Ficarra S, Thomas E, Bianco A, et al (2022) Impact of exercise interventions on physical fitness in breast cancer patients and survivors: a systematic review. Breast Cancer 29:402–418. https://doi.org/10.1007/s12282-022-01347-z

17. Mutrie N, Campbell A, Barry S, et al (2012) Five-year follow-up of participants in a randomised controlled trial showing benefits from exercise for breast cancer survivors during adjuvant treatment. Are there lasting effects? J Cancer Surviv 6:420–430. https://doi.org/10.1007/s11764-012-0233-y

18. De Backer IC, Vreugdenhil G, Nijziel MR, et al (2008) Long-term follow-up after cancer rehabilitation using high-intensity resistance training: persistent improvement of physical performance and quality of life. Br J Cancer 99:30–36. https://doi.org/10.1038/sj.bjc.6604433

19. Schmidt ME, Wiskemann J, Steindorf K (2018) Quality of life, problems, and needs of disease-free breast cancer survivors 5 years after diagnosis. Qual Life Res 27:2077–2086. https://doi.org/10.1007/s11136-018-1866-8

20. Kwiatkowski F, Mouret-Reynier M-A, Duclos M, et al (2017) Long-term improvement of breast cancer survivors' quality of life by a 2-week group physical and educational intervention: 5-year update of the 'PACThe' trial. Br J Cancer 116:1389–1393. https://doi.org/10.1038/bjc.2017.112

21. Vehmanen L, Sievänen H, Kellokumpu-Lehtinen P, et al (2021) Five-year follow-up results of aerobic and impact training on bone mineral density in early breast cancer patients. Osteoporos Int 32:473–482. https://doi.org/10.1007/s00198-020-05611-w

22. Hiensch AE, Peeters PHM, Jansen M, et al (2020) Socio-ecological correlates of physical activity in breast and colon cancer survivors 4 years after participation in a randomized controlled exercise trial (PACT study). PLoS One 15:e0231663. https://doi.org/10.1371/journal.pone.0231663

23. Kokkonen K, Kellokumpu-Lehtinen P-L, Kankaanpää M, et al (2022) Factors predicting long-term physical activity of breast cancer survivors. 5-year-follow-up of the BREX exercise intervention study. Acta Oncol 61:1200–1208. https://doi.org/10.1080/0284186X.2022.2103388

24. Roine E, Sintonen H, Kellokumpu-Lehtinen P-L, et al (2020) Health-related quality of life of breast cancer survivors attending an exercise intervention study: A five-year follow-up. In Vivo 34:667–674. https://doi.org/10.21873/invivo.11821

25. Fassier P, Zelek L, Partula V, et al (2016) Variations of physical activity and sedentary behavior between before and after cancer diagnosis: Results from the prospective population-based NutriNet-Santé cohort: Results from the prospective population-based NutriNet-Santé cohort. Medicine (Baltimore) 95:e4629. https://doi.org/10.1097/md.0000000000004629

26. Bower JE (2014) Cancer-related fatigue--mechanisms, risk factors, and treatments. Nat Rev Clin Oncol 11:597–609. https://doi.org/10.1038/nrclinonc.2014.127

27. Nurnazahiah A, Shahril MR, Nor Syamimi Z, et al (2020) Relationship of objectively measured physical activity and sedentary behaviour with health-related quality of life among breast cancer survivors. Health Qual Life Outcomes 18:222. https://doi.org/10.1186/s12955-020-01478-x

28. Cantarero-Villanueva I, Fernández-Lao C, Cuesta-Vargas AI, et al (2013) The effectiveness of a deep water aquatic exercise program in cancer-related fatigue in breast cancer survivors: a randomized controlled trial. Arch Phys Med Rehabil 94:221–230. https://doi.org/10.1016/j.apmr.2012.09.008

29. Galiano-Castillo N, Cantarero-Villanueva I, Fernández-Lao C, et al (2016) Telehealth system: A randomized controlled trial evaluating the impact of an internet-based exercise intervention on quality of life, pain, muscle strength, and fatigue in breast cancer survivors: Telehealth System in Breast Cancer. Cancer 122:3166–3174. https://doi.org/10.1002/cncr.30172

30. Schmitz KH, Courneya KS, Matthews C, et al (2010) American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 42:1409–1426. https://doi.org/10.1249/MSS.0b013e3181e0c112

31. Galiano-Castillo N, Arroyo-Morales M, Lozano-Lozano M, et al (2017) Effect of an Internet-based telehealth system on functional capacity and cognition in breast cancer survivors: a secondary analysis of a randomized controlled trial. Support Care Cancer 25:3551–3559. https://doi.org/10.1007/s00520-017-3782-9

32. Norton K, Norton L, Sadgrove D (2010) Position statement on physical activity and exercise intensity terminology. J Sci Med Sport 13:496–502. https://doi.org/10.1016/j.jsams.2009.09.008

33. Guthold R, Stevens GA, Riley LM, Bull FC (2018) Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1·9 million participants. Lancet Glob Health 6:e1077–e1086. https://doi.org/10.1016/S2214-109X(18)30357-7

34. Cantarero-Villanueva I, Fernández-Lao C, Díaz-Rodríguez L, et al (2014) The Piper Fatigue Scale-Revised: translation and psychometric evaluation in Spanish-speaking breast cancer survivors. Qual Life Res 23:271–276. https://doi.org/10.1007/s11136-013-0434-5

35. Piper BF, Dibble SL, Dodd MJ, et al (1998) The revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. Oncol Nurs Forum 25:677–684

36. Bijur PE, Silver W, Gallagher EJ (2001) Reliability of the visual analog scale for measurement of acute pain. Acad Emerg Med 8:1153–1157. https://doi.org/10.1111/j.1553-2712.2001.tb01132.x

37. Vanderweeën L, Oostendorp RAB, Vaes P, Duquet W (1996) Pressure algometry in manual therapy. Man Ther 1:258–265. https://doi.org/10.1054/math.1996.0276

38. Chesterton LS, Sim J, Wright CC, Foster NE (2007) Interrater reliability of algometry in measuring pressure pain thresholds in healthy humans, using multiple raters. Clin J Pain 23:760–766. https://doi.org/10.1097/AJP.0b013e318154b6ae

39. Fernández-Lao C, Cantarero-Villanueva I, Fernández-de-Las-Peñas C, et al (2010) Myofascial trigger points in neck and shoulder muscles and widespread pressure pain hypersensitivtiy in patients with postmastectomy pain: evidence of peripheral and central sensitization: Evidence of peripheral and central sensitization. Clin J Pain 26:798–806. https://doi.org/10.1097/AJP.0b013e3181f18c36

40. Ruiz-Ruiz J, Mesa JLM, Gutiérrez A, Castillo MJ (2002) Hand size influences optimal grip span in women but not in men. J Hand Surg Am 27:897–901. https://doi.org/10.1053/jhsu.2002.34315

41. España-Romero V, Ortega FB, Vicente-Rodríguez G, et al (2010) Elbow position affects handgrip strength in adolescents: validity and reliability of Jamar, DynEx, and TKK dynamometers. J Strength Cond Res 24:272–277. https://doi.org/10.1519/JSC.0b013e3181b296a5

42. Laskin JJ, Bundy S, Marron H, et al (2007) Using a treadmill for the 6-minute walk test: reliability and validity: Reliability and validity. J Cardiopulm Rehabil Prev 27:407–410. https://doi.org/10.1097/01.HCR.0000300270.45881.d0

43. Galiano-Castillo N, Arroyo-Morales M, Ariza-Garcia A, et al (2016) The six-minute walk test as a measure of health in breast cancer patients. J Aging Phys Act 24:508–515. https://doi.org/10.1123/japa.2015-0056

44. El Fakir S, Abda N, Bendahhou K, et al (2014) The European Organization for Research and Treatment of Cancer quality of life questionnaire-BR23 Breast Cancer-Specific Quality of Life

Questionnaire: psychometric properties in a Moroccan sample of breast cancer patients. BMC Res Notes 7:53. https://doi.org/10.1186/1756-0500-7-53

45. Elosua R, Garcia M, Aguilar A, et al (2000) Validation of the Minnesota leisure time physical activity questionnaire in Spanish women. Investigators of the MARATDON group. Med Sci Sports Exerc 32:1431–1437. https://doi.org/10.1097/00005768-200008000-00011

46. Ainsworth BE, Haskell WL, Herrmann SD, et al (2011) 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc 43:1575–1581. https://doi.org/10.1249/MSS.0b013e31821ece12Penttinen H, Utriainen M, Kellokumpu-Lehtinen P-L, et al (2019) Effectiveness of a 12-month exercise intervention on physical activity and quality of life of breast cancer survivors; Five-year results of the BREX-study. In Vivo 33:881–888. https://doi.org/10.21873/invivo.11554

47. Witlox L, Hiensch AE, Velthuis MJ, et al (2018) Four-year effects of exercise on fatigue and physical activity in patients with cancer. BMC Med 16:. https://doi.org/10.1186/s12916-018-1075-x

48. Thorsen L, Dahl AA, Skovlund E, et al (2007) Effectiveness after 1 year of a short-term physical activity intervention on cardiorespiratory fitness in cancer patients. J Clin Oncol 25:1301–1302. https://doi.org/10.1200/JCO.2007.10.6682

49. Saarto T, Penttinen HM, Sievänen H, et al (2012) Effectiveness of a 12-month exercise program on physical performance and quality of life of breast cancer survivors. Anticancer Res 32:3875–3884

50. Demark-Wahnefried W, Clipp EC, Morey MC, et al (2006) Lifestyle intervention development study to improve physical function in older adults with cancer: Outcomes from project LEAD. J Clin Oncol 24:3465–3473. https://doi.org/10.1200/jco.2006.05.7224

51. Stein KD, Syrjala KL, Andrykowski MA (2008) Physical and psychological long-term and late effects of cancer. Cancer 112:2577–2592. https://doi.org/10.1002/cncr.23448

52. Tourangeau R, Yan T (2007) Sensitive questions in surveys. Psychol Bull 133:859–883. https://doi.org/10.1037/0033-2909.133.5.859

53. Smedsland SK, Vandraas KF, Bøhn SK, et al (2022) Sexual activity and functioning in long-term breast cancer survivors; exploring associated factors in a nationwide survey. Breast Cancer Res Treat 193:139–149. https://doi.org/10.1007/s10549-022-06544-0

54. Bolam KA, Mijwel S, Rundqvist H, Wengström Y (2019) Two-year follow-up of the OptiTrain randomised controlled exercise trial. Breast Cancer Res Treat 175:637–648. https://doi.org/10.1007/s10549-019-05204-0

55. Ousmen A, Conroy T, Guillemin F, et al (2016) Impact of the occurrence of a response shift on the determination of the minimal important difference in a health-related quality of life score over time. Health Qual Life Outcomes 14:167. https://doi.org/10.1186/s12955-016-0569-5

56. Mutrie N, Campbell AM, Whyte F, et al (2007) Benefits of supervised group exercise programme for women being treated for early stage breast cancer: pragmatic randomised controlled trial. BMJ 334:517. https://doi.org/10.1136/bmj.39094.648553.AE

57. Pudkasam S, Polman R, Pitcher M, et al (2018) Physical activity and breast cancer survivors: Importance of adherence, motivational interviewing and psychological health. Maturitas 116:66–72. https://doi.org/10.1016/j.maturitas.2018.07.010

58. Spei M-E, Samoli E, Bravi F, et al (2019) Physical activity in breast cancer survivors: A systematic review and meta-analysis on overall and breast cancer survival. Breast 44:144–152. https://doi.org/10.1016/j.breast.2019.02.001

59. Mason C, Alfano CM, Smith AW, et al (2013) Long-term physical activity trends in breast cancer survivors. Cancer Epidemiol Biomarkers Prev 22:1153–1161. https://doi.org/10.1158/1055-9965.EPI-13-0141

60. Tollosa DN, Holliday E, Hure A, et al (2020) A 15-year follow-up study on long-term adherence to health behaviour recommendations in women diagnosed with breast cancer. Breast Cancer Res Treat 182:727–738. https://doi.org/10.1007/s10549-020-05704-4

61. Hartman SJ, Chen R, Tam RM, et al (2022) Fitbit use and activity levels from intervention to 2 years after: Secondary analysis of a randomized controlled trial. JMIR MHealth UHealth 10:e37086. https://doi.org/10.2196/37086

62. Banerjee S, Manley K, Thomas L, et al (2013) O2 Preoperative exercise protocol to aid recovery of radical cystectomy: Results of a feasibility study. Eur Urol Suppl 12:125. https://doi.org/10.1016/s1569-9056(13)62320-9

63. Kendall AR, Mahue-Giangreco M, Carpenter CL, et al (2005) Influence of exercise activity on quality of life in long-term breast cancer survivors. Qual Life Res 14:361–371. https://doi.org/10.1007/s11136-004-1468-5

64. Alfano CM, Smith AW, Irwin ML, et al (2007) Physical activity, long-term symptoms, and physical health-related quality of life among breast cancer survivors: A prospective analysis. J Cancer Surviv 1:116–128. https://doi.org/10.1007/s11764-007-0014-1

65. van Leeuwen M, on behalf of the EORTC QLG, Husson O, et al (2018) Understanding the quality of life (QOL) issues in survivors of cancer: towards the development of an EORTC QOL cancer survivorship questionnaire. Health Qual Life Outcomes 16:. https://doi.org/10.1186/s12955-018-0920-0

Statements and Declarations

Funding

This work was supported by the Spanish Ministry of Economy and Competitiveness [Plan Estatal de I+D+I 2013-2016]; Fondo de Investigación Sanitaria del Instituto de Salud Carlos III [PI14/01627]; Fondos Estructurales de la Unión Europea (FEDER). This study took place thanks to the additional funding from the University of Granada, Plan Propio de Investigación 2016. Excellence actions: Units of Excellence; Scientific Excellence Unit on Exercise and Health (UCEES).

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Authors contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Francisco Álvarez Salvago], [José Daniel Jimenez García], [Agustín Aibar Almazán]. The first draft of the manuscript was written by [Francisco Álvarez Salvago], [Sandra Atienzar Aroca], [Clara Pujol Fuentes] and [Cristina Molina García] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declaration of interest statement

The authors report no conflict of interest.

Table 1. Demographic, clinical, and medical characteristics of the groups ≥ 5 years after completion of the therapeutic exercise program

CHARACTERISTICS	TYPE OF PARTICIPATION		*P*
	USUAL CARE (*n*=38)	THERAPEUTIC EXERCISE UNDER THE RECOMMENDATIONS OF THE ACSM (*n*=42)	
Mean age ± SD, years	49.74 ± 8.73	48.81 ± 7.68	.560
Mean time since diagnosis ± SD, months	85.50 ± 34.73	94.20 ± 17.73	.857
Marital Status, *n* (%)			
Unmarried	4 (10.5)	8 (19.0)	
Married	27 (71.1)	29 (69.0)	
Divorced	4 (10.5)	4 (9.5)	
Widowed	3 (7.9)	1 (2.4)	.735
Educational level, *n* (%)			
Primary school	16 (42.1)	18 (42.9)	
Secondary school	11 (28.9)	7 (16.7)	
University	11 (28.9)	17 (40.5)	.605
Employment Status, *n* (%)			
Housewife	15 (39.5)	10 (23.8)	
Currently working	8 (21.1)	9 (21.4)	
Work leave	13 (34.2)	17 (40.5)	
Cannot work because of disability	2 (5.3)	6 (14.3)	
Retired	0 (0)	0 (0)	
Unemployed	0 (0)	0 (0)	.672
Tumor stage, *n* (%)			
I	13 (34.2)	9 (21.4)	
II	20 (52.6)	23 (54.8)	
IIIa	5 (13.2)	10 (23.8)	.347
Tobacco consumption, *n* (%)			
Non-consumption	18 (47.4)	20 (47.6)	
Smoker	12 (31.6)	9 (21.4)	
Ex-smoker	8 (21.1)	13 (31.0)	.384
Alcohol consumption, *n* (%)			
Non-consumption	16 (42.1)	13 (31.0)	
Monthly	7 (18.4)	13 (31.0)	
Weekly	11 (28.9)	16 (38.1)	
Daily	4 (10.5)	0 (0)	.250
Family history of breast cancer, *n* (%)			
No	19 (50)	21 (50.0)	
Yes	19 (50)	21 (50.0)	.769
Type of treatment, *n* (%)			
None	0 (0)	0 (0)	
Radiotherapy	1 (2.6)	1 (2.4)	
Chemotherapy	2 (5.3)	5 (11.9)	
Radiotherapy and Chemotherapy	35 (92.1)	36 (85.7)	.378
Surgery, *n* (%)			
Lumpectomy	7 (18.4)	10 (23.8)	
Quadrantectomy	18 (47.4)	17 (40.5)	
Unilateral mastectomy	10 (26.3)	14 (33.3)	
Bilateral mastectomy	3 (7.9)	1 (2.4)	.348
Type of medication, *n* (%)			
None	6 (15.8)	9 (21.4)	
Tamoxifen	17 (44.7)	21 (50.0)	
Other types	15 (39.5)	12 (28.6)	.861
Physiotherapy treatment for possible sequelae between the 6 months assessment and the ≥ 5 years reassessment, *n* (%)			
No	10 (26.3)	30 (71.4)	
Yes	28 (73.7)	16 (28.6)	.354

Psychological support between the 6 months assessment and the ≥ 5 years reassessment, *n* (%)			
No	25	22	
Yes	13	20	.345

P<.05*

NOTE. P values for between-groups differences were calculated using the *t* test for continuous variables and X^2 for categorical variables.

Abbreviations: n: Sample size; SD: Standard deviation; ACSM: American College of Sports Medicine.

Table 2. Inter-subject effects for mean cancer-related fatigue difference at baseline and follow-up at ≥ 5 years

OUTCOME ≥ 5 YEARS AFTER COMPLETION OF THE THERAPEUTIC EXERCISE PROGRAM		TYPE OF PARTICIPATION		*P*
		USUAL CARE (*n*=38)	THERAPEUTIC EXERCISE UNDER THE RECOMMENDATIONS OF THE ACSM (*n*=42)	
PFS, mean ± SD (95% CI)				
Behavioral/Severity	Baseline	5.36 ± 2.82 (95% CI 4.43 – 6.29)	4.31 ± 2.57 (95% CI 3.51 – 5.11)	
	≥5 years	3.68 ± 3.32 (95% CI 2.59 – 4.78)	2.37 ± 2.24 (95% CI 1.67 – 3.06)	
	Difference ≥5 years – Baseline	-1.67 ± 2.78 (95% CI -2.59 – -.76)	-1.94 ± 3.36 (95% CI -2.99 – -.90)	.698
Affective	Baseline	5.64 ± 2.81 (95% CI 4.71 – 6.56)	5.17 ± 2.79 (95% CI 4.29 – 6.03)	
	≥5 years	3.91 ± 3.59 (95% CI 2.73 – 5.09)	2.79 ± 2.67 (95% CI 1.96 – 3.62)	
	Difference ≥5 years – Baseline	-1.73 ± 3.20 (95% CI -2.78 – -.68)	-2.37 ± 3.26 (95% CI -3.39 – -1.35)	.377
Sensory	Baseline	5.42 ± 2.39 (95% CI 4.63 – 6.20)	4.84 ± 2.47 (95% CI 4.07 – 5.61)	
	≥5 years	3.75 ± 3.41 (95% CI 2.63 – 4.88)	3.22 ± 2.76 (95% CI 2.36 – 4.08)	
	Difference ≥5 years – Baseline	-1.67 ± 2.79 (95% CI -2.59 – -.75)	-1.62 ± 3.12 (95% CI -2.59 – -.65)	.938
Cognitive/Mood	Baseline	5.20 ± 2.61 (95% CI 4.34 – 6.06)	4.37 ± 2.54 (95% CI 3.58 – 5.16)	
	≥5 years	3.30 ± 3.33 (95% CI 2.21 – 4.40)	3.12 ± 2.60 (95% CI 2.31 – 3.92)	
	Difference ≥5 years – Baseline	-1.90 ± 2.92 (95% CI -2.86 – -.94)	-1.26 ± 3.14 (95% CI -2.24 – -.28)	.347
Global	Baseline	5.39 ± 2.41 (95% CI 4.59 – 6.18)	4.63 ± 2.20 (95% CI 3.94 – 5.32)	
	≥5 years	3.68 ± 3.23 (95% CI 2.62 – 4.74)	2.86 ± 2.37 (95% CI 2.13 – 3.60)	
	Difference ≥5 years – Baseline	-1.71 ± 2.57 (95% CI -2.55 – -.86)	-1.77 ± 2.73 (95% CI -2.62 – -.92)	.920

P<.05* / P<.001**
Data are shown as mean ± SD (95%CI) for baseline and ≥5 years and for time difference.
Analysis of variance (ANOVA).
Abbreviations: n: Sample size; SD: Standard deviation; CI: Confidence interval; PFS: Piper Fatigue Scale; ACSM: American College of Sports Medicine.

Table 3. Inter-subject effects for mean pain and pressure pain sensitivity difference at baseline and follow-up at ≥ 5 years

OUTCOME ≥ 5 YEARS AFTER COMPLETION OF THE THERAPEUTIC EXERCISE PROGRAM		TYPE OF PARTICIPATION		*P*
		USUAL CARE (*n*=38)	THERAPEUTIC EXERCISE UNDER THE RECOMMENDATIONS OF THE ACSM (*n*=42)	
VAS (Cm), mean ± SD (95% CI)				
Pain intensity of the affected arm	Baseline	3.13 ± 3.22 (95% CI 2.07 – 4.19)	3.86 ± 3.57 (95% CI 2.74 – 4.97)	
	≥5 years	2.32 ± 2.51 (95% CI 1.49 – 3.14)	2.26 ± 2.62 (95% CI 1.44 – 3.08)	
	Difference ≥5 years – Baseline	-.82 ± 3.02 (95% CI -1.81 – .18)	-1.60 ± 3.19 (95% CI -2.59 – -.60)	.267
Algometry (kPa/s), mean ± SD (95% CI)				
PPT C5-C6 Zygapohyseal joint affected	Baseline	166.92 ± 70.45 (95% CI 143.43 – 190.41)	160.10 ± 69.24 (95% CI 138.52 – 181.68)	
	≥5 years	179.21 ± 68.71 (95% CI 156.30 – 202.12)	206.77 ± 88.53 (95% CI 179.18 – 234.36)	
	Difference ≥5 years – Baseline	12.29 ± 84.31 (95% CI -15.82 – 40.40)	46.67 ± 80.76 (95% CI 21.51 – 71.84)	.068
PPT C5-C6 Zygapohyseal joint unaffected	Baseline	161.54 ± 55.47 (95% CI 143.04 – 180.03)	165.00 ± 70.19 (95% CI 143.13 – 186.87)	
	≥5 years	159.33 ± 39.27 (95% CI 146.24 – 172.43)	178.88 ± 68.33 (95% CI 157.59 – 200.17)	
	Difference ≥5 years – Baseline	-2.21 ± 64.61 (95% CI -23.75 – 19.33)	13.88 ± 87.66 (95% CI -13.44 – 41.20)	.362
PPT Deltoid muscle affected	Baseline	181.09 ± 82.78 (95% CI 153.49 – 208.69)	186.95 ± 78.02 (95% CI 162.64 – 211.26)	
	≥5 years	258.84 ± 115.09 (95% CI 220.47 – 297.21)	247.36 ± 108.00 (95% CI 213.70 – 281.01)	
	Difference ≥5 years – Baseline	77.75 ± 151.84 (95% CI 27.12 – 128.38)	60.40 ± 124.38 (95% CI 21.65 – 99.16)	.579
PPT Deltoid muscle unaffected	Baseline	181.91 ± 63.03 (95% CI 160.89 – 202.92)	199.59 ± 74.73 (95% CI 176.31 – 222.88)	
	≥5 years	289.15 ± 92.42 (95% CI 258.34 – 319.96)	280.34 ± 106.45 (95% CI 247.17 – 313.51)	
	Difference ≥5 years – Baseline	107.24 ± 96.74 (95% CI 74.99 – 139.49)	80.75 ± 120.46 (95% CI 43.21 – 118.28)	.289
PPT Tibialis Anterior muscle affected	Baseline	259.67 ± 111.73 (95% CI 222.42 – 296.93)	297.08 ± 102.24 (95% CI 265.22 – 328.94)	
	≥5 years	380.28 ± 111.00 (95% CI 343.27 – 417.29)	379.59 ± 117.58 (95% CI 342.96 – 416.23)	
	Difference ≥5 years – Baseline	120.60 ± 159.39 (95% CI 67.46 – 173.75)	82.51 ± 133.16 (95% CI 41.02 – 124.01)	.251

PPT Tibialis Anterior muscle affected	Baseline	254.60 ± 97.10 (95% CI 222.23 – 286.98)	297.61 ± 125.59 (95% CI 258.48 – 336.75)	
	≥5 years	386.52 ± 147.47 (95% CI 337.35 – 435.69)	382.51 ± 131.90 (95% CI 341.40 – 423.61)	
	Difference ≥5 years – Baseline	131.92 ± 131.15 (95% CI 88.19 – 175.64)	84.89 ± 172.85 (95% CI 31.03 – 138.76)	.182

P<.05* / P<.001**
Data are shown as mean ± SD (95%CI) for baseline and ≥5 years and for time difference.
Analysis of variance (ANOVA).
Abbreviations: n: Sample size; SD: Standard deviation; CI: Confidence interval; VAS: Visual Analogue Scale; ACSM: American College of Sports Medicine; PPT: Pressure Pain Threshold.

Table 4. Inter-subject effects for mean upper and lower body muscular strength, functional capacity, and quality of life difference at baseline and follow-up at ≥ 5 years

OUTCOME ≥ 5 YEARS AFTER COMPLETION OF THE THERAPEUTIC EXERCISE PROGRAM		TYPE OF PARTICIPATION		*P*
		USUAL CARE (*n*=38)	THERAPEUTIC EXERCISE UNDER THE RECOMMENDATIONS OF THE ACSM (*n*=42)	
Upper body muscular strength, mean ± SD (95% CI)				
Isometric handgrip strength affected side (kg)	Baseline	17.34 ± 7.61 (95% CI 14.84 – 19.84)	20.41 ± 6.59 (95% CI 18.36 - 22.46)	
	≥5 years	22.10 ± 6.62 (95% CI 19.93 – 24.28)	24.84 ± 6.07 (95% CI 22.96 - 26.74)	
	Difference ≥5 years – Baseline	4.76 ± 9.08 (95% CI 1.78 – 7.75)	4.43 ± 7.55 (95% CI 2.09 - 6.79)	.861
Isometric handgrip strength unaffected side (kg)	Baseline	18.52 ± 6.13 (95% CI 16.48 – 20.56)	20.52 ± 5.90 (95% CI 18.68 - 22.36)	
	≥5 years	23.24 ± 6.25 (95% CI 21.16 – 25.33)	24.78 ± 5.04 (95% CI 23.20 - 26.35)	
	Difference ≥5 years – Baseline	4.72 ± 7.16 (95% CI 2.34 – 7.11)	4.26 ± 4.98 (95% CI 2.71 - 5.81)	.735
Functional capacity, mean ± SD (95% CI)				
6-min walk test (m)	Baseline	309.89 ± 156.62 (95% CI 254.35 – 365.42)	330.42 ± 165.32 (95% CI 278.90 – 381.93)	
	≥5 years	460.00 ± 106.95 (95% CI 422.08 – 497.92)	493.39 ± 47.00 (95% CI 478.74 – 508.04)	
	Difference ≥5 years – Baseline	150.12 ± 180.47 (95% CI 86.13 – 214.11)	162.97 ± 167.69 (95% CI 110.72 – 215.23)	.751
Quality of life - EORTC QLQ-BR23, mean ± SD (95% CI)				
Body image	Baseline	55.70 ± 34.77 (95% CI 44.27 – 67.13)	71.43 ± 26.55 (95% CI 63.15 – 79.70)	
	≥5 years	54.12 ± 31.41 (95% CI 63.80 – 84.45)	79.96 ± 24.63 (95% CI 72.29 – 87.64)	
	Difference ≥5 years – Baseline	-1.58 ± 29.31 (95% CI 7.80 – 29.04)	8.53 ± 29.19 (95% CI -.56 – 17.63)	.154
Systemic therapy side effects	Baseline	37.73 ± 24.06 (95% CI 29.82 – 45.63)	32.94 ± 17.57 (95% CI 27.46 – 38.41)	
	≥5 years	31.83 ± 24.51 (95% CI 23.77 – 39.89)	25.71 ± 20.29 (95% CI 19.38 – 32.03)	
	Difference ≥5 years – Baseline	-5.90 ± 21.97 (95% CI -13.12 – 1.32)	-7.23 ± 19.20 (95% CI -13.21 – -1.24)	.773
Breast symptoms	Baseline	35.75 ± 28.00 (95% CI 26.54 – 44.95)	32.34 ± 20.84 (95% CI 25.85 – 38.84)	
	≥5 years	30.92 ± 32.18 (95% CI 20.34 – 41.50)	21.83 ± 21.70 (95% CI 15.06 – 28.59)	
	Difference ≥5 years – Baseline	-4.82 ± 38.44 (95% CI -17.46 – 7.81)	-10.52 ± 29.57 (95% CI -19.73 – -1.30)	.458

Arm symptoms	Baseline	28.07 ± 24.47 (95% CI 20.03 – 36.11)	30.69 ± 21.51 (95% CI 23.99 – 37.39)	
	≥5 years	35.38 ± 32.97 (95% CI 24.54 – 46.22)	28.57 ± 28.84 (95% CI 19.58 – 37.56)	
	Difference ≥5 years – Baseline	7.31 ± 29.93 (95% CI -2.53 – 17.15)	-2.12 ± 25.53 (95% CI -10.07 – 5.84)	.133

P<.05* / P<.001**
Data are shown as mean ± SD (95%CI) for baseline and ≥5 years and for time difference.
Analysis of variance (ANOVA).
Abbreviations: n: Sample size; SD: Standard deviation; CI: Confidence interval; ACSM: American College of Sports Medicine; kg: Kilograms; s: seconds; m: meters; EORTC QLQ-BR23: The European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23).

Table 5. Inter-subject effects for mean cancer-related fatigue and subscales according to physical activity level

CANCER RELATED-FATIGUE ≥ 5 YEARS AFTER COMPLETION OF THE THERAPEUTIC EXERCISE PROGRAM	PHYSICAL ACTIVITY LEVEL ≥ 5 YEARS AFTER COMPLETION OF THE THERAPEUTIC EXERCISE PROGRAM			*P*
	≤3 (MET-hour/week) (*n*=21)	**3.1 – 7.4 (MET-hour/week) (*n*=32)**	**≥7.5 (MET-hour/week) (*n*=27)**	
Cancer-related fatigue domains PFS, mean ± SD (95% CI)				
Behavioral/Severity	4.06 ± 3.49 (95% CI 2.47 – 5.65)	3.53 ± 2.66 (95% CI 2.57 – 4.49)	1.53 ± 1.90 (95% CI 1.78 – 2.28)	**.003***
Affective	4.31 ± 3.52 (95% CI 2.71 – 5.91)	3.71 ± 3.19 (95% CI 2.56 – 4.86)	2.09 ± 2.52 (95% CI 1.09 – 3.09)	**.035***
Sensory	4.57 ± 3.26 (95% CI 3.09 – 6.06)	3.88 ± 3.11 (95% CI 2.75 – 4.50)	2.15 ± 2.47 (95% CI 1.17 – 3.13)	**.015***
Cognitive/mood	4.21 ± 3.19 (95% CI 2.76 – 5.67)	3.41 ± 3.07 (95% CI 2.31 – 4.52)	2.17 ± 2.34 (95% CI 1.25 – 3.10)	**.050***
Global	4.28 ± 3.04 (95% CI 2.90 – 5.66)	3.65 ± 2.88 (95% CI 2.61 – 4.69)	1.98 ± 2.12 (95% CI 1.14 – 2.81)	**.010***

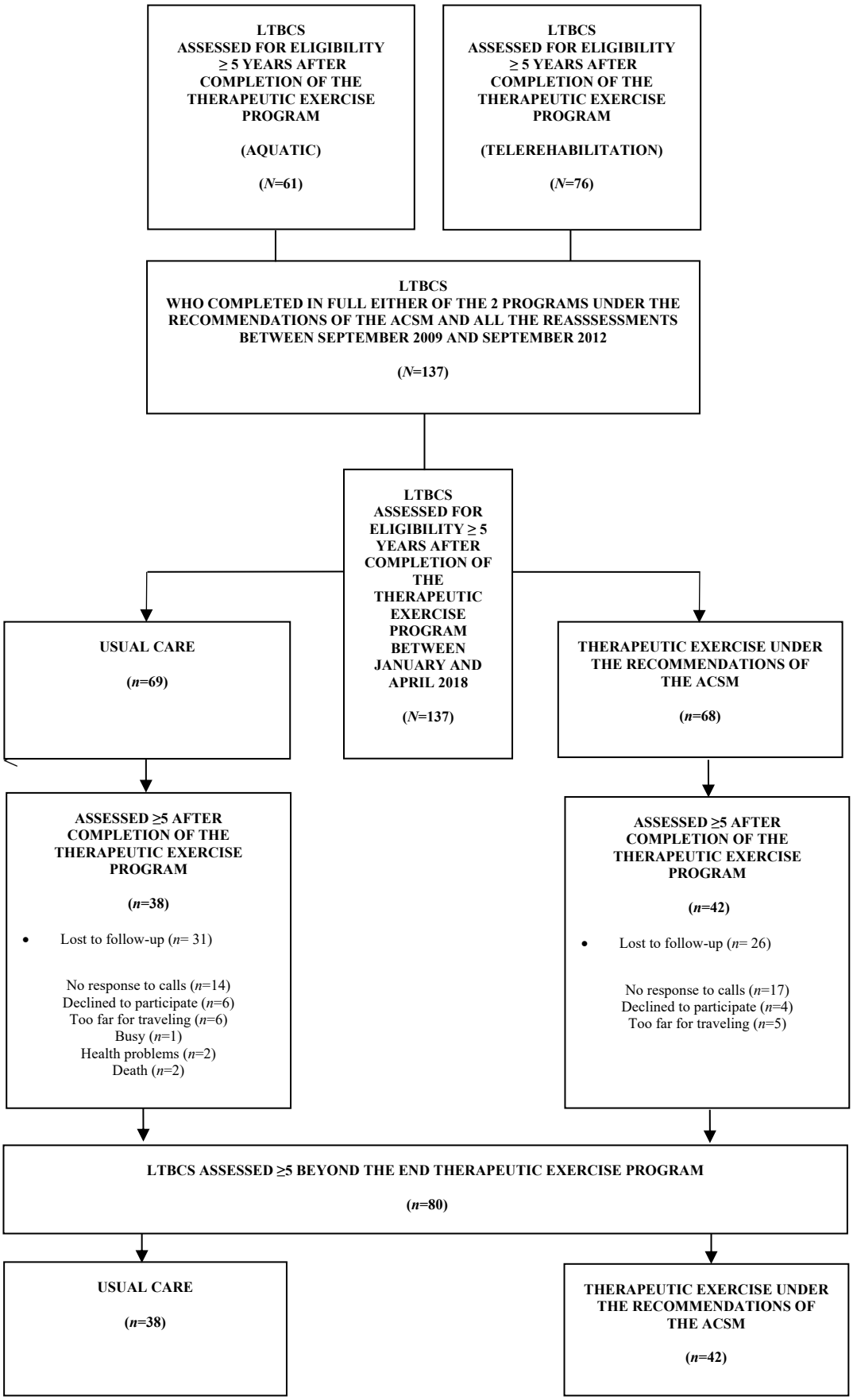
P<.05* / P<.001**
Analysis of variance (ANOVA).
Abbreviations: n: Sample size; SD: Standard deviation; CI: Confidence interval; PFS: Piper Fatigue Scale; MET: Metabolic equivalent of task.

Table 6. Inter-subject effects for the difference in means of cancer related-fatigue subscales according to physical activity level with Bonferroni adjustment

DEPENDENT OUTCOME ≥ 5 YEARS AFTER COMPLETION OF THE THERAPEUTIC EXERCISE PROGRAM	PHYSICAL ACTIVITY LEVEL ≥ 5 YEARS AFTER COMPLETION OF THE THERAPEUTIC EXERCISE PROGRAM		MEAN DIFFERENCE ± SD (95%CI)	*P*
Cancer-related fatigue domains, PFS	**(MET-hour/week)**	**(MET-hour/week)**		
Behavioral/Severity	3.1 – 7.4	≤3	-.53 ± .76 (95% CI -2.38 – 1.32)	1.00
	≥7.5	≤3	-2.53 ± .78 (95% CI -4.45 – -.61)	**.005***
	≥7.5	3.1 – 7.4	-1.20 ± .70 (95% CI -3.72 – -.28)	**.017***
Affective	3.1 – 7.4	≤3	-.60 ± .86 (95% CI -2.71 – 1.52)	1.00
	≥7.5	≤3	-2.22 ± .89 (95% CI -4.41 – -.03)	**.046***
	≥7.5	3.1 – 7.4	-1.62 ± .80 (95% CI -3.59 – .34)	.140
Sensory	3.1 – 7.4	≤3	-.70 ± .83 (95% CI -2.73 – 1.33)	1.00
	≥7.5	≤3	-2.42 ± .86 (95% CI -4.53 – -.32)	**.018***
	≥7.5	3.1 – 7.4	-1.73 ± .77 (95% CI -3.62 – .16)	.085
Cognitive/Mood	3.1 – 7.4	≤3	-.80 ± .81 (95% CI -2.78 – 1.18)	.973
	≥7.5	≤3	-2.04 ± .84 (95% CI -4.09 – .01)	.051
	≥7.5	3.1 – 7.4	-1.24 ± .75 (95% CI -3.08 – .60)	.311
Global	3.1 – 7.4	≤3	-.63 ± .76 (95% CI -2.48 – 1.22)	1.00
	≥7.5	≤3	-2.31 ± .78 (95% CI -4.22 – -.39)	**.013***
	≥7.5	3.1 – 7.4	-1.67 ± .70 (95% CI -3.40 – .05)	.060

P<.05* / P<.001**
Analysis of variance (ANOVA), multiple comparisons by Bonferroni adjustment.
Abbreviations: n: Sample size; SD: Standard deviation; CI: Confidence interval; PFS: Piper Fatigue Scale; MET: Metabolic equivalent of task.

Figure 1. Flow diagram for study participants.



Abbreviations: *N*/*n:* simple size; LTBCS: Long-term breast cancer survivors; ACSM: American College of Sports Medicine.