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**Original Research**

# Nonlinear, Multicomponent Physical Exercise With Heart Rate Variability-Guided Prescription in Women With Breast Cancer During Treatment: Feasibility and Preliminary Results (ATOPE Study)

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## Abstract

**Objective.** The purpose of this study was to examine the feasibility, safety, adherence, and preliminary efficacy of the ATOPE program during radiotherapy (RT) or chemotherapy (CT) for women with breast cancer.

**Methods.** This single-blind, pretest–posttest feasibility study included 38 women with breast cancer at the beginning of their treatment. The ATOPE program consisted of 12 to 18 sessions of a multimodal physical exercise program, prescribed based on daily heart rate variability and clinimetric assessments using the ATOPE+ mHealth system. Overall health was assessed with quality of life, autonomous balance, and body composition, whereas health-related fitness was measured through functional capacity, physical activity levels, and upper and lower limb strength.

**Results.** The rates of recruitment, retention, and adherence were 52.35, 73.68, and 84.37%, respectively, and the satisfaction rating was 9.2 out of a possible 10 points. The perceived health status change score was 3.83 points, scored on a −5 to 5 point scale. No adverse effects were found. Compliance results showed that the ATOPE+ mHealth system was used on 73.38% of the days, and the Fitbit bracelet (Google, Mountain View, CA, USA) was used on 84.91% of the days. Women stayed physically active 55% of days. Regarding preliminary results, for overall health, the percentage of body fat in the RT group decreased by 1.93%, whereas it increased by 5.03% in the CT group. Lower limb strength increased in the RT group, specifically knee extensor isometric strength (6.07%), isokinetic knee flexors 180 degree/second (1.53%), and isokinetic knee extensors 300 degree/second (4.53%), in contrast with the reductions found in the CT group (11.07, 18.67, and 14.89%, respectively).

**Conclusion.** The ATOPE program, through nonlinear prescription based on daily monitoring with the ATOPE+ mHealth system, is feasible and safe for application during breast cancer treatment. The results suggest that the overall health can be maintained or even improved regarding most variables.

**Impact.** This study focused on the feasibility, safety, and completion of a physical therapist-led program at early diagnosis for adults with breast cancer. The multimodal, supervised, tailored, nonlinear physical exercise program is feasible and safe, showed a good completion rate, and was able to prevent the quality-of-life deficits that are often triggered by systemic breast cancer treatment. This study highlights the importance of daily morning assessments using the ATOPE+ mHealth system in patients with breast cancer to prescribe nonlinear physical exercise.

**Keywords:** Breast Neoplasms, Exercise Therapy, Mobile Applications, Quality of Life

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## Introduction

The impact of cancer and its treatments pose a threat to systemic homeostasis,[1] which can have negative consequences for overall health, particularly physical health. The mere presence of a tumor,[1,2] in combination with different risk factors prior to cancer diagnosis, such as age[3] or lifestyle factors,[4,5] leads to alterations in systemic homeostasis.[1,6] In fact, some of the physiological and clinical manifestations (ie, metabolite availability, hormone availability, immune composition, sleep problems, and distress) are already evident in people with cancer at the time of diagnosis.[6–10] These alterations are aggravated by cancer treatments, especially radiotherapy (RT) and chemotherapy (CT).[11] These alterations in systemic homeostasis are closely related to the process of tumor development in patients with breast cancer.[5,12,13]

This supports the theory of the "multiple hit," which could cause a less effective host response to different types of stressors in people with breast cancer.[14] A physical stimulus that can produce an easy and positive host response[1,6] in individuals in the healthy population could be challenging for people with breast cancer, entailing an allostatic load.[15] Therefore, cumulative physical stimulus could cause allostatic overload,[15] and hence people with breast cancer may need more time for adequate recovery. Thus, it is absolutely necessary to develop tools that help control the balance between physical stimuli and recovery status.[16–18]

In patients with cancer, this alteration in homeostasis and the low capacity to have a positive host response to a physical stimulus have been confirmed,[1,6,19] and it is usually measured as a predominance of the sympathetic nervous system (SNS). It can also be related to increased side effects from treatments,[20,21] especially an increased loss of muscle mass and functional capacity.[22] In contrast, parasympathetic nervous system (PNS) activation has been related to decreased tumor proliferation.[23] Through measurements of heart rate variability (HRV), among other outcome measurements, we are able to determine the balance between the SNS and PNS to understand the homeostasis state.[24]

It has been established that regular physical exercise influences the control of the mechanisms involved in physiological disturbances,[25] as well as the regulation and progression of cancer,[4] as it inhibits tumor growth across cancer histologies and at all stages of tumor development.[25] Many direct and indirect anticancer mechanisms of action have been described, and they are clearly interrelated, especially the inflammation, immunity, and insulin resistance pathways.[26] For these reasons, exercise has transitioned from a healthy to therapeutic, because of its whole-body effects, the alleviation of cancer-related adverse events, and the improvement of anticancer treatment efficacy.[25]

The current cancer guidelines[27] highlight the need for the frequency, intensity, time, and type[28] methodology; it must be emphasized that this methodology is safe[29] and specifies the volume (V) and, especially, the form of progression (P), according to the general physical exercise principles.[30] The vast majority of women with breast cancer experience a deterioration in their physical health during treatments, such as cardiovascular fitness and functionality,[31] and they experience health fluctuations during treatments. For these reasons, there is a need for flexible approaches,[32] such as nonlinear prescription, that consider the recovery state of each person.[27,33]

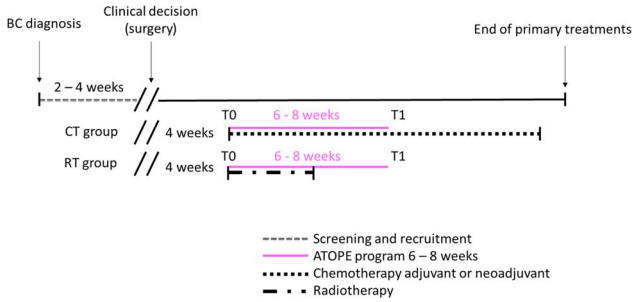


**Figure 1.** Schematic diagram of the study. BC = breast cancer.

Some studies have compared linear and nonlinear prescriptions in people with cancer, agreeing that the latter is well tolerated and useful, but this needs further investigation.[34] For sports performance, nonlinear prescription has been carried out for years based on HRV[35] and has also been considered in other clinimetric assessments.[36] This is a very interesting approach for people with cancer during treatments because they have ups and downs in regard to cancer-related side effects, which influence their capacity for physical recovery.[37,38]

The ATOPE+ mHealth system[39,40] is a novel tool that records HRV and clinimetric measurements (perception of recovery, sleep satisfaction, and emotional distress), allowing for an assessment of the daily recovery status of an individual, and then provides individualized daily physical activity or exercise recommendations. Therefore, the purpose of this study was to analyze the feasibility, safety, and compliance rate of the ATOPE program as well as examine the difference in associated changes in women undergoing RT and CT.

## Methods

### Study Design

This was a single-blind, prospective, 2-arm, pretest–posttest feasibility study that is part of a larger randomized controlled trial (ClinicalTrials.gov, NCT03787966). A schematic diagram of the study is presented in Figure 1. This study adhered to the STROBE guidelines.

### Setting

This study was conducted at the facilities provided to the Biosanitary (BIO277) group by the University of Granada, Spain. Recruitment took place between February 2019 and May 2022. In total, 38 women diagnosed with breast cancer were recruited to participate in the ATOPE program.[41] Baseline assessments were conducted before RT and CT treatments were started. Follow-up was conducted within 72 hours after the last physical exercise session of the ATOPE program.

### Participants

Patients from the Surgical Unit of the Hospital Universitario Clínico San Cecilio in Granada, Spain, who met the inclusion and exclusion criteria described in a previous protocol,[41] were screened. In brief, the included patients were women with newly diagnosed, histologically confirmed, unresected stages I–III breast cancer who were scheduled for surgery, RT, and/or CT. Women who had a previous history of malignancy, had undergone previous treatment for cancer, were pregnant, had a psychiatric or cognitive disorder that could prevent them

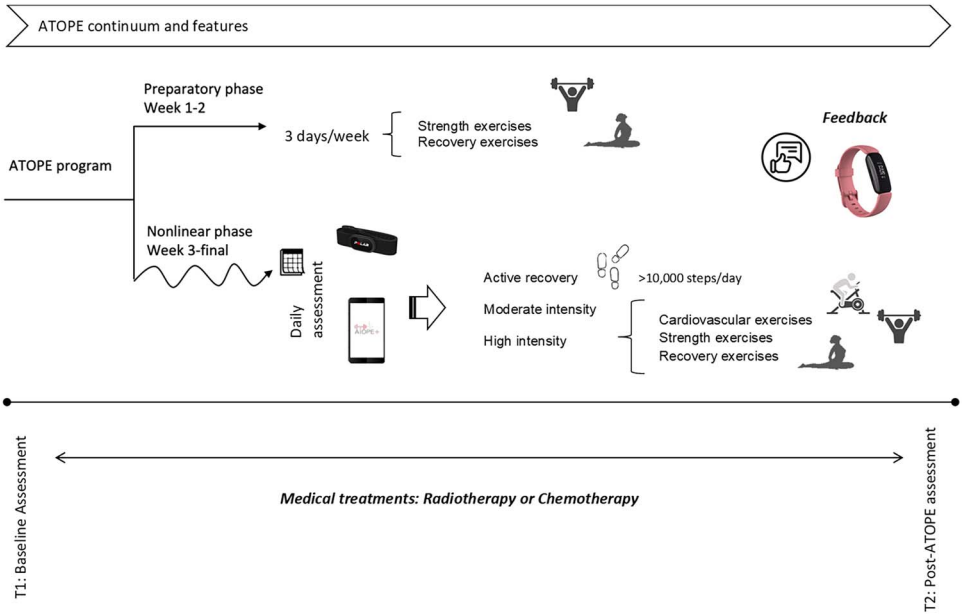


**Figure 2.** Continuum and features of the ATOPE program.

from performing the exercises correctly, had acute or chronic conditions that prevent exercises, and had any absolute contraindication for high-intensity exercise were excluded. A member of the BIO277 group contacted the patients, gave them verbal and written information about the study and scheduled an appointment, during which the patients signed informed consent forms and were assessed (baseline).

## Blinding

It was not possible to blind the participants or exercise staff. However, the assessments and statistical analysis were performed by the blinded researchers.

## Ethics Approval and Data Protection

The study was approved by the Ethics Committee of the Junta de Andalucía (0507-N-18, July 27, 2018) according to the Helsinki Declaration for biomedical research. Data from the participants were masked with a code that did not allow their identification.

For ethical reasons, participation in other physical activities outside the program was not limited but was monitored via an activity bracelet.

## The ATOPE Program

The full intervention details were described in a previous protocol[41] (Fig. 2). The training load of each session was determined by multiplying the training duration (minutes) by the session rate of perceived exertion (0–10) for each patient.[42]

In addition, physical activity promotion and avoiding sedentary behavior were proposed. Physical activity was monitored daily by Fitbit activity bracelets (Inspire model). During the first 2 weeks, the progression in physical activity time was determined by weekly increments,[43] according to the step count of each participant at baseline. Weekly progression was adjusted according to the perceived fatigue of the participants.[43] After this, every morning, the application reminded the participants to stay physically active, and following international guidelines, patients were asked to reach 10,000–12,500 steps per day.[44]

The ATOPE+ mHealth system[40] was designed to measure HRV with a heart rate chest band (Polar H10 Heart Rate Monitor, Finland) and self-reported responses with electronic patient-reported outcome measures (ePROMS) such as sleep (satisfaction and duration), physical exercise recovery, and distress. All ePROMS were validated in a previous study.[40] The ATOPE+ mHealth system has shown good reliability when assessed against gold standard tools.[40] During the ATOPE program, the women had to use the ATOPE + mHealth system each morning (7 days per week), which established a physical exercise intensity recommendation for the day through an algorithm that considers different cut-off points for HRV, recovery perception, sleep satisfaction, fatigue, and emotional distress.[40] The system sets recommendations for active rest (walking until daily goal steps are reached) or physical exercise sessions with moderate or vigorous intensity.

## Outcomes and Assessments

The outcomes and assessments are displayed in Table 1.

## Statistical Analysis

An adequate sample size was estimated as 12 participants,[45] and with a possible drop-out[46] rate of 25%, 15 patients per group would be enough to demonstrate feasibility. Data are summarized as the mean [standard deviation (SD)] or number and percentage according to the categorical or continuous nature of the variable. Chi-square tests, Fisher exact tests, Student *t*-tests, or Wilcoxon rank sum tests were used to test differences between the RT and CT arms, as appropriate. The differences between the groups in the variables mentioned above were tested using ANOVA with 1 factor (RT or CT group). To assess efficacy, multiple imputation was used for missing data. The IPAQ data were dichotomized into active versus nonactive according to a cutoff point of 7.5

**Table 1.** Outcomes and Assessments[a]

| Assessment | Instrument/Measure | Timepoint |
|---|---|---|
| *Feasibility* | | |
| Recruitment/acceptance | Percentage of participants who met the eligibility criteria out of the total number who provided consent and enrolled after completing the baseline assessment (spreadsheet). | T0 |
| Retention | Percentage of drop-outs and withdrawals throughout the program with recorded reasons (spreadsheet). The feasibility threshold for retention in both arms was 75%.[46] | T0, T1 |
| Adherence | The average proportion of the number of completed program sessions. The program was considered feasible if the adherence rate reached a minimum value of 79–83% in the RT group[73] and 71%–79% in the CT group.[46] | T0, T1 |
| Satisfaction (PROMs) | Individual satisfaction with (1) the program, (2) research team, and (3) activity bracelets, rated on a scale from 1 to 10, where 1 represented "very bad" and 10 represented "very good" (3 self-composed items in a questionnaire).[74] | T1 |
| Perceived health status change (PROMs) | Global Rating Changing scale,[75] scored from −5 to 5 points, where −5 means much worse and 5 means much better than before the program. | T1 |
| *Adherence to the program* | | |
| ATOPE+ mHealth system usage | Mean percentage of days the participants took measurements with the ATOPE+ program in the morning divided by the total number of days that they participated in the program. | T1 |
| Fitbit bracelet and mobile application usage | Mean percentage of days participants recorded their daily steps from the total number of days that they participated in the program. | T1 |
| Walking program compliance | The number of days the participants took more than 10,000 steps; mean percentage of days in which these participants reached at least 10,000 steps. | T1 |
| *Safety* | | |
| Adaptations | Physical exercise modifications made by researchers during exercise because of participant discomfort or pain (spreadsheet). | T1 |
| Adverse effects (PROMs) | The National Cancer Institute Common Terminology Criteria for Adverse Events (v.5.0) (periodic interviews). | T1 |
| Barriers (PROMs) | Possible barriers to assessment appointments (parking, distance to the center) and the exercise program (recorded with a questionnaire with open-ended questions).[76] | T1 |
| Facilitators (PROMs) | Possible facilitators of the physical exercise program (recorded with a questionnaire with open-ended questions).[76] | T1 |
| *Preliminary efficacy results* | | |
| Quality of life (PROMs) | European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), v 3.0.[77] | T0, T1 |
| Body composition | Weight, skeletal muscle mass, body mass index, percent body fat, waist-hip ratio, visceral fat area, obesity degree, bone mineral content, basal metabolic rate (InBody 720 impedanciometria; InBody Co. Ltd, Seoul, Republic of Korea).[78] | T0, T1 |
| Heart rate variability | Natural log of the square root of the mean of the sum of the squares of differences between adjacent normal to normal intervals (Norav DL800 Holter ECG monitor; Norav Medical Ltd, Delray Beach, FL, USA).[79] | T0, T1 |
| Physical activity level (PROMs) | Short form of the International Physical Activity Questionnaire (IPAQ) measuring physical activity level (MET/h/wk) and inactivity level (no. of sitting hours per day) in the last week.[80] | T0, T1 |
| Physical fitness | General physical functioning and mobility (6MWT); 6MWT prediction.[81] | T0, T1 |
| Upper limb strength | Handgrip strength in kg (Takei TKK 5101 Grip-D digital dynamometer; Takei Scientific Instruments Co. Ltd, Tokyo, Japan).[82] Both hands were evaluated 3 times, allowing 1 min of rest between sets. | T0, T1 |
| Lower limb strength | Isokinetic test dominant knee extension and flexion at different velocities, with 4 repetitions at 60°/s, 8 repetitions at 180°/s, and 15 repetitions at 300°/s and their ratios (Humac NORM isokinetic dynamometer; Computer Sports Medicine Inc, Stoughton, MA, USA). A warm-up was performed in each velocity, and 2 min of rest was allowed between sets.[83] | T0, T1 |

[a] 6MWT = 6-Minute Walk Test; CT = chemotherapy; HR = heart rate; PROMs = patient-reported outcome measures; RT = radiotherapy.

met/hour/week,[47] as well as nonsedentary versus sedentary with a cutoff point of 5 hours of sitting per day.[48] The percentage of women in each group was reported and analyzed using Fisher tests. IBM SPSS version 25 was used for the analyses (IBM SPSS Statistics Corp, Armonk, New York, USA).

## Results

The participant flow is presented in Supplementary Material Figure 1. A total of 38 eligible women agreed to participate in the study. Of these, 18 (47.37%) women were assigned to receive the RT regimen, and 20 (52.63%) were assigned to receive the CT regimen. The average age was 50.00 (10.29) years for the total sample. There were no differences in sociodemographic or clinical characteristics, except for overweight [body mass index (BMI) ≥25]; 66.7% of the RT group was overweight, whereas only 36.8% of the CT group was overweight ($P = .041$). Supplementary Material Table 1 shows the baseline sociodemographic and clinical characteristics of the participants in this study.

**Table 2.** Feasibility Data[a]

| Outcome | Total Sample ($n=28$) | Radiotherapy Group ($n=13$) | Chemotherapy Group ($n=15$) | *P* |
|---|---|---|---|---|
| **Feasibility** | | | | |
| Recruitment, % | 52.35 | | | |
| Retention, % | 73.68 | 72.22 | 75.00 | 1 |
| Adherence, %, mean (SD) | 84.37 (11.55) | 88.88 (8.54) | 78.44 (11.99) | .01 |
| Satisfaction, mean (SD) | | | | |
| With exercise program | 9.2 (2.02) | 8.82 (2.99) | 9.52 (0.66) | .98 |
| With equipment | 9.2 (1.80) | 8.73 (2.61) | 9.62 (0.65) | .27 |
| With activity bracelets | 8.8 (2.75) | 7.55 (3.86) | 9.85 (0.38) | .07 |
| Perceived health status change, mean (SD) | 3.83 (1.49) | 4.00 (1.55) | 3.67 (1.58) | .51 |
| **Safety** | | | | |
| Adaptations, % | 23.7 | 12.5 | 35 | .22 |
| Adverse effects, % | | | | |
| Yes | 0 | 0 | 0 | |
| No | 100 | 100 | 100 | |
| Barriers | | | | |
| Fatigue | 1 (3.6) | 0 | 1 (6.7) | 1[b] |
| Type of exercise | 1 (3.6) | 0 | 1 (6.7) | 1[b] |
| Pain | 1 (3.6) | 1 (7.7) | 0 | .48[b] |
| Timetable | 2 (7.1) | 0 | 2 (13.3) | .48[b] |
| Adverse effects of treatment | 5 (17.9) | 2 (15.4) | 3 (20.0) | 1[b] |
| Distance | 0 (0) | 0 | 0 | |
| Parking | 1 (3.6) | 1 (7.7) | 0 | .48[b] |
| Medical appointments | 2 (7.1) | 0 | 2 (13.3) | .48[b] |
| Facilitators | | | | |
| None | 20 (71.4) | 5 (38.5) | 5 (33.3) | 1[b] |
| Research group | 4 (14.3) | 2 (15.4) | 2 (13.3) | 1[b] |
| Perceived improvement after exercise | 3 (10.7) | 2 (15.4) | 2 (13.3) | 1[b] |
| Exercise intervention leader | 1 (3.6) | 1 (7.7) | 0 | 1[b] |
| Compliance with the ATOPE program | | | | |
| ATOPE+ mHealth system use, %, mean (SD) | 73.38 (15.01) | 74.77 (19.22) | 73.07 (18.36) | .72 |
| Fitbit use, %, mean (SD) | 84.91 (20.10) | 85.83 (16.87) | 78.45 (25.52) | .52 |
| 10,000 steps/d, %, mean (SD) | 55.00 (24.64) | 54.91 (33.46) | 55.93 (28.82) | .94 |

[a]Data are reported as numbers (percentages) of participants unless otherwise indicated. ATOPE program: the program in general; ATOPE+ mHealth system: mobile health application. [b]Fisher exact test.

## Feasibility Results

The areas of feasibility (recruitment, retention, adherence, satisfaction, and perceived health change) are described below and summarized in Table 2.

Of the 141 women who were referred for this study because they met the inclusion criteria, 70 agreed to participate, yielding a recruitment rate of 52.35%. Regarding the retention measurement, out of the 38 women who ultimately participated in the study, 28 completed the intervention, and 10 dropped out, leading to a retention rate of 73.68%. Supplementary Material Figure 1 shows the flowchart of participants throughout the study and their reasons for dropping out. The adherence rate was >75% for the total sample and for both groups, with a higher rate in the RT group (88.88% vs 78.44%; $P=.010$ difference between groups). Satisfaction ratings for the program were >8 points out of 10 for the total sample, although satisfaction was higher for the CT group. Regarding perceived health status changes after the ATOPE program, there were no significant differences between the groups, but the RT group had a slightly higher value. A schematic representation of the feasibility data of the ATOPE program is summarized in Figure 3.


**Figure 3.** Schematic representation of the feasibility of the ATOPE program.

## Safety Results

Adaptations made throughout the ATOPE program are summarized in Supplementary Material Figure 2. No adverse events were recorded during the ATOPE program for our sample. The most prevalent barrier for both groups (20%) was the presence of adverse effects of medical treatments (RT or CT), which were higher in the RT group (16.70%). Medical appointments and the timetable of the program were additional barriers perceived by the CT group (15.40%). Most participants did not mention the existence of a program facilitator (52.60% of the total sample). The research group (considered as the therapeutic alliance and closeness with patients) and the physical exercise benefits were the most

perceived facilitators of the ATOPE program for the total sample (21.10%), as well as for each group (20% for the RT group and 22.20% for the CT group), and 10% of the participants in the RT group identified the researcher leading the program as a facilitator (Suppl. Material Fig. 3). No significant differences in safety outcomes were found between the 2 study groups.

### Compliance With the Program

Regarding program usage, participants used the ATOPE+ mHealth system on a mean of 73.38% of the days. Reasons for not using the system were mainly related to the servers being down, being late to medical appointments, or not having enough time for the assessment. The ATOPE+ mHealth system stopped working for 1 of the participants, and it could not be fixed. Two of the participants had 1 missing week of data due to skin burns caused by RT.

Regarding Fitbit bracelet usage, participating women recorded their daily steps on a mean of 84.91% of the days. Reasons for not recording their daily steps were related to participants forgetting to synchronize and upload their progress to the mobile app (which should be done at least once a week). A total of 4 participants disconnected their device from the mobile app but did not notice due to low mobile phone capabilities.

The training loads for each patient are shown in Supplementary Material Figure 4. Using a threshold of 10,000 daily steps, patients were physically active on a mean of 55% of the days with a range of 5.17 to 95.65% (Suppl. Material Fig. 5).

### Preliminary Efficacy Results

Table 3 shows the within-group differences in overall health and HRF after the ATOPE program.

### Overall Health: Quality of Life

Physical function increased significantly (by 4.74%) in the RT group after the ATOPE program. Both the RT and CT groups showed significant increases in emotional function by 10.26% and 22.10%, respectively. For the symptom scales, only in the CT group were the scores for nausea and constipation significantly reduced (by approximately 65.57 and 44.36%, respectively) after the program.

### Health-Related Fitness: Physical Activity Level

Women in the RT and CT groups were classified as active (70% and 69.20%, respectively) or inactive (30 and 30.80%) (Suppl. Material Figs. 6a and 7a). After the ATOPE program, all women in the RT group were classified as active (100%), whereas the percentages of active or inactive women in the CT group were the same (Suppl. Material Figs. 6b and 7b). Fisher test showed no difference in the proportions in the cross-table for either of the groups ($P > .05$).

For sitting time, at baseline, the percentages of women classified as not sedentary were 70% and 61.50% in the RT and CT groups, respectively (Suppl. Material Figs. 6c and 7c). After completion of the ATOPE program, the percentage of nonsedentary women increased to 80% in the RT group and 69.20% in the CT group (Suppl. Material Figs. 6d and 7d). However, the change in percentages was not significant by Fisher test ($P < .05$).

### Health-Related Fitness: Functional Capacity

The score on the 6MWT was significantly higher (by 4.49%) in the RT group after the ATOPE program.

### Health-Related Fitness: Upper and Lower Limb Strength

In the intragroup analysis, only the CT group showed a lower limb strength score for 60 degree/second knee extension (by 15.02%) and for 180 degree/second knee extension and flexion (by 20.37% and 18.67%, respectively) after the ATOPE program. Finally, in the same direction, the CT group showed less strength in 300 degree/second knee extension and flexion isokinetic tests (14.89% and 19.51%, respectively).

## Discussion

The findings obtained in this study demonstrated that the ATOPE program, an adapted and individualized multimodal program with a nonlinear prescription physical exercise program, is feasible and safe for women with breast cancer during RT or CT treatments. The described approach could potentially maintain or even improve QoL as an indicator of overall health, with this effect being more pronounced in the RT group. Although evidence of the feasibility and efficacy of physical exercise with linear prescriptions has been widely described in patients with breast cancer during medical treatments,[49] data related to nonlinear prescriptions are scarce. In general, these findings are extremely important in the cancer rehabilitation area. The ATOPE program is based on the balance of individual homeostasis that allows safe and effective doses of physical exercise.

Regarding feasibility, our recruitment rate (52.35%) was lower than expected, so it took more time to reach the number of participants per group that we considered adequate for good feasibility ($n = 12$). After 38 months, we decided to check our data because of the pandemic situation, the implementation of various simultaneous research projects in the hospital, and above all, the complexity of life management that women experience on a personal level during treatments.[50] A few previous similar studies have shown recruitment ratios between 25% and 66%,[51–53] and our results are in line with these findings, although previous studies followed linear prescription.

Our retention rate was slightly lower, especially in the RT group, although it was close to the feasibility threshold (RT: 72.22%; CT: 75%). These results may be due to the presence of skin-related conditions as a consequence of RT treatment (up to 85% of patients experience skin symptoms ranging from local erythema to moist desquamation),[54] which require special care and could be perceived as an absolute contraindication to physical exercise. In addition, only approximately 20% of participants in the RT group felt they were experiencing any benefits from physical exercise; taken together with side effects, this could have been the reason for the high drop-out rate. However, previous studies of patients during RT showed good retention rates,[55–57] so these results led us to consider ways to achieve an improvement in the retention rate for the clinical trial.

The adherence rate for the ATOPE program was 84.37% for both groups. These results agree with the results of Kirkham et al[58] for the group with an exercise prescription during CT according to the cycles of CT and self-reports of

**Table 3.** Preliminary Efficacy Results Between and Within Groups in Overall Health and Health-Related Fitness After the ATOPE Program[a]

| Outcomes | Radiotherapy Group ($n = 13$) | | | Chemotherapy Group ($n = 15$) | | | ANOVA *P* |
|---|---|---|---|---|---|---|---|
| | Before Program | After Program | % Change | Before Program | After Program | % Change | |
| Overall health | | | | | | | |
| Quality of life | | | | | | | |
| Functionality | | | | | | | |
| Physical | 88.69 (8.96) | 92.89 (5.81) | 4.74[b] | 87.47 (13.12) | 85.12 (12.60) | 2.69 | .12 |
| Tasks | 79.65 (21.57) | 88.29 (14.88) | 10.85 | 80.35 (17.90) | 80.12 (14.16) | 0.29 | .06 |
| Emotional | 71.61 (15.32) | 78.96 (11.70) | 10.26[b] | 60.96 (19.67) | 74.43 (14.50) | 22.10[b] | .15 |
| Cognitive | 84.30 (14.30) | 84.83 (12.34) | 0.63 | 77.11 (24.32) | 76.95 (7.91) | 0.21 | .94 |
| Social | 85.18 (18.81) | 90.80 (10.66) | 6.60 | 75.81 (27.61) | 76.60 (16.73) | 1.04 | .35 |
| Symptoms | | | | | | | |
| Fatigue | 23.70 (18.58) | 25.42 (11.83) | 7.26 | 38.64 (25.08) | 36.23 (12.82) | −6.24 | .64 |
| Nausea | 4.59 (8.71) | 3.12 (7.89) | −32.03 | 14.00 (18.67) | 4.82 (8.60) | −65.57[b] | .25 |
| Pain | 16.45 (15.79) | 15.07 (14.57) | −8.38 | 26.43 (15.30) | 25.77 (21.02) | −2.50 | .82 |
| Dyspnea | 8.87 (24.11) | 9.58 (16.83) | 8 | 6.61 (12.07) | 11.65 (13.62) | 76.25 | .28 |
| Insomnia | 42.40 (30.95) | 35.31 (25.18) | −16.72 | 59.21 (23.04) | 52.84 (24.50) | −10.76 | .82 |
| Appetite | 5.63 (10.80) | 5.10 (8.79) | −9.41 | 16.45 (23.96) | 13.19 (14.26) | −24.24 | .90 |
| Constipation | 16.34 (19.03) | 11.92 (17.85) | −27.05 | 21.71 (25.59) | 12.08 (17.45) | −44.36[b] | .23 |
| Diarrhea | 1.02 (2.81) | 2.39 (3.97) | 134.31 | 7.97 (13.26) | 10.49 (17.87) | 31.62 | .87 |
| Global health | 71.08 (19.03) | 75.19 (9.78) | 5.78 | 64.33 (21.40) | 65.34 (8.30) | 1.57 | .65 |
| Autonomous balance | | | | | | | |
| LnrMSSD | 3.47 (0.52) | 3.63 (0.58) | 4.61 | 3.40 (0.61) | 3.59 (0.62) | 5.59 | .86 |
| Body composition | | | | | | | |
| Fat mass, % | 25.09 (8.53) | 23.35 (8.17) | 6.14 | 22.76 (9.36) | 24.13 (8.74) | 6.02 | .08 |
| SMM, kg | 22.62 (2.56) | 22.47 (2.14) | −0.66 | 22.18 (2.64) | 22.27 (2.10) | 0.41 | .16 |
| BMI, kg/m$^2$ | 26.56 (4.02) | 26.15 (3.64) | 1.54 | 24.65 (4.73) | 25.56 (4.49) | 3.69 | .06 |
| PBF, % | 36.22 (8.46) | 35.52 (8.93) | −1.93 | 34.19 (7.98) | 35.91 (6.97) | 5.03 | .02[b] |
| WHR | 0.92 (0.072) | 0.90 (0.07) | −2.17 | 0.89 (0.07) | 0.92 (0.07) | 3.37 | .60 |
| VFA | 106.30 (42.04) | 100.96 (36.44) | −5.02 | 95.86 (39.27) | 100.95 (36.41) | 5.31 | .25 |
| Obesity degree, % | 124.18 (18.27) | 121.92 (16.70) | −1.82 | 115.78 (21.75) | 118.78 (20.59) | 2.59 | .07 |
| Body cell mass, kg | 27.20 (2.74) | 26.65 (2.45) | −2.02 | 26.46 (2.79) | 26.90 (2.07) | 44 | .15 |
| BMC, kg | 2.60 (0.34) | 2.42 (0.30 | −6.92 | 2.51 (0.31) | 2.53 (0.33) | 0.80 | .14 |
| BMR, kcal | 1278.08 (92.17) | 1263.81 (77.71) | −1.12 | 1253.88 (92.51) | 1265.35 (66.68) | 88.64 | .09 |
| Health-related fitness | | | | | | | |
| Functional capacity | | | | | | | |
| 6MWT, m | 595.46 (73.09) | 622.22 (69.91) | 4.49[b] | 602.70 (59.40) | 616.66 (50.33) | 2.32 | .32 |
| Upper limb strength | | | | | | | |
| Handgrip, dominant, kg | 25.09 (4.12) | 25.15 (3.49) | 0.24 | 27.12 (6.07) | 25.82 (4.44) | −4.79 | .35 |
| Handgrip, nondominant, kg | 23.09 (3.70) | 24.09 (3.13) | 4.33 | 24.68 (5.21) | 24.33 (3.85) | −1.42 | .94 |
| Lower limb strength | | | | | | | |
| Maximum torque, N·m | 100.21 (32.36) | 106.29 (39.70) | 6.07 | 119.65 (31.03) | 106.41 (30.30) | −11.07 | .04[b] |
| Peak torque slope, N·m/s | 76.11 (47.19) | 63.66 (50.50) | −16.36 | 84.35 (45.89) | 64.70 (45.10) | −23.30 | .88 |
| Time to maximum torque, s | 3.15 (1.45) | 3.49 (1.18) | 10.79 | 3.02 (1.51) | 3.19 (1.03) | 5.63 | .35 |
| Peak torque at 60°/s, Ext, N·m | 87.14 (30.24) | 86.19 (24.76) | −1.09 | 100.45 (27.48) | 85.36 (28.72) | −15.02[b] | .23 |
| Peak torque at 60°/s, Flex, N·m | 61.25 (20.42) | 58.44 (12.75) | −4.59 | 72.30 (20.76) | 62.43 (20.96) | −13.65 | .39 |
| Peak torque at 180°/s, Ext, N·m | 55.06 (29.32) | 54.04 (15.97) | −1.85 | 66.56 (16.53) | 53.00 (12.53) | −20.37[b] | .07 |
| Peak torque at 180°/s, Flex, N·m | 43.12 (15.86) | 43.78 (13.05) | 1.53 | 52.64 (15.02) | 42.81 (10.23) | −18.67[b] | .03[b] |
| Peak torque at 300°/s, Ext, N·m | 38.17 (14.82) | 39.90 (12.47) | 4.53 | 48.03 (10.96) | 40.88 (10.78) | −14.89[b] | .03[b] |
| Peak torque at 300°/s, Flex, N·m | 35.21 (14.26) | 35.54 (11.34) | 0.94 | 44.81 (16.48) | 36.06 (16.39) | −19.51[b] | .13 |

[a]Data are reported as mean (SD) unless otherwise indicated. Preliminary results for both groups are shown. 6MWT = 6-Minute Walk Test; ANOVA = analysis of variance; BMC = bone mineral content; BMI = body mass index; BMR = basal metabolic rate; Ext = knee extensor muscles; Flex = knee flexor muscles; LnrMSSD = natural log of square root of the mean of the sum of squares of differences between adjacent normal-to-normal intervals; PBF = percentage of body fat; SMM = skeletal muscle mass; VFA = visceral fat area; WHR = waist-to-hip ratio. [b]Significant differences ($P < .05$) within groups as determined with Student *t*-tests or Wilcoxon rank sum tests as appropriate (column of % change), and between groups (ANOVA *P* column).

fatigue compared with a group that received linear prescription (78% vs 63%, respectively). Other studies conducted with patients during CT reported that hospitalization was the main cause of nonattendance at sessions,[34] but in our study, no women needed to be hospitalized. There was a high perception of satisfaction with the ATOPE program (9.2 out of 10 points), highlighting that these results could be attributed to the perception of health changes; the satisfaction rating was above 3.83 (out of −5 to 5 points) in both groups, despite being impacted by the cancer diagnosis and its treatment.[59] In addition, although participants in both groups reported being satisfied, they also identified barriers to participating in the ATOPE program, with the presence of adverse effects, scheduling problems, and a lack of time among the most frequent barriers, as described in previous studies.[60,61] Few facilitators were identified, but they were consistent with the previous literature on programs applied during medical treatment.[61]

The ATOPE program was safe, with no adverse effects recorded. The detailed baseline assessment allowed us to assess the participants' initial physical conditions; however, in addition to responding to our main challenge, the ATOPE program has a preparatory phase, in which the objective is to guarantee the correct execution of exercises, therefore adjusting an adequate baseline dose of training.[41] In addition, individual exercise adaptations were made if needed (Suppl. Material Fig. 2). The results of similar exercise prescriptions during CT treatment[34,58] and after treatments[49] have found similar results, even showing that they could be safer than linear prescriptions. That is why some studies have recently started to use nonlinear prescriptions, mainly adjusting the recommendations by the self-perception of fatigue,[34,58] even developing new methods to evaluate it[62], or adjusting the exercise doses according to the CT cycles.[34] However, to assess the response situation after a physical stimulus more safely, a more objective and broad assessment must be made, which allows greater safety of the exercise dose. That is why the ATOPE+ mHealth system collects different outcome measurements (HRV and clinimetric measurements) of the internal load, which guarantees participant safety by adjusting the dose to an individual's state of recovery.

Regarding compliance, adherence to the ATOPE+ mHealth system was high (74.77% and 73.07% in the RT and CT groups, respectively), with loss of use mainly due to technical issues and skin problems in the RT group, which made it difficult to use the chest band. Our usage data could be considered good if we compare them to a systematic review published in 2020,[63] which highlights the high heterogeneity in the use of this type of device during cancer treatments, with compliance rates of 45% to 94% for the wearable device. With these results, we can assume that this type of device is an effective tool to improve adherence to physical activity within our population by feedback, and it has been successful in some other studies.[64]

With the integration of strategies to promote physical activity and reduce sitting time in the ATOPE program in accordance with international guidelines,[65] there was an increase in physical activity (30%); at the end of the ATOPE program, all women in the RT group achieved at least 7.5 MET/hour/week. There was an increase in the percentage of nonsedentary women after the ATOPE program, with an increase of 10% in the RT group and 7.7% in the CT group (not statistically significant). This result is positive, especially considering that a recent meta-analysis found that following treatments, achieving more than 7.5 MET/hour/week would reduce the recurrence of breast cancer.[66] Moreover, considering physically active to be a mean of 10,000 steps per week, participants were above this threshold on 55% of the days, with a range of 5.17% to 95.65%.

Based on preliminary data, the ATOPE program has the potential to maintain or even increase overall health and HRF, especially when performed in a supervised format.[67] There are previous studies with nonlinear prescription that have found modest improvements in variables such as the patient-reported outcomes and cardiorespiratory fitness, with both linear and nonlinear prescription methods.[34,49] In this line, our preliminary results, although extracted from a very small sample, are promising, indicating the maintenance or even an improvement of QoL in both groups. Moreover, a recent study highlighted the importance of adherence, rather than intensity, to obtain benefits.[68] The ATOPE program assures a moderate-to-high intensity and facilitates adherence, allowing for higher intensities when each person has recovered and can experience benefits. However, the results show that perhaps the prescription provided to the CT group should be adjusted, as the ATOPE program could not counteract the reduction in limb strength in the CT group. It should also be noted that the ATOPE program was not able to improve or maintain the body fat mass percentage in the CT group. These results could be because of unavoidable weakness and muscle mass loss induced by CT.[69] Additionally, CT treatment causes a situation where fat gain is promoted.[70] This could also suggest that for our participants, a specific prehabilitation intervention is needed before the start of treatment, especially for patients receiving CT.

We are aware of the heterogeneity of the physical exercise dose, which was the main limitation of this study; paradoxically, this allowed the dose to be tailored and adjusted individually. There was a similar training load in the RT and CT groups (278.95 and 285.48 AUs, respectively); however, each woman worked at a different intensity and frequency, according to their ability to assimilate the physical load. An analysis with a larger sample size will allow us to improve the ATOPE+ mHealth system algorithm, establish profiles of patients who respond better to certain doses, and establish even more appropriate doses for certain outcomes. Additionally, this study does not contribute to the analysis of physical exercise as a multidisciplinary tool integrated into oncological rehabilitation, as defended by scientific evidence.[71,72] We did not incorporate a nonintervention control group, which was a weakness of this study, but we did this for ethical reasons. Finally, because of our small sample size and because the study was only conducted in 1 region, the extrapolation of our results should be performed carefully until larger studies can be conducted.

Although we consider our results to be preliminary, the ATOPE program is an optimal and safe option for tailoring and adjusting individual doses of physical exercise according to the dose-recovery cycle. The ATOPE+ mHealth system is established through a complex algorithm that collects different outcome measurements for the internal load, which guarantees participant safety by recommending doses that the individual is able to assimilate. The ATOPE program allows us to overcome some typical identified barriers of this delicate treatment phase for people with cancer, favoring high adherence to interventions. It is absolutely necessary to develop optimal systems for prescribing and controlling exercise doses, and the ATOPE+ mHealth system could be a way to achieve this.

## Conclusions

A tailored physical exercise program following nonlinear prescription based on daily monitoring with the ATOPE+ mHealth system is mostly feasible and safe during breast cancer treatments. The results suggested that overall health could be maintained or even improved during treatments with respect to its baseline value in each of the groups studied, except for lower limb strength in the CT group. This is a novel proposal that opens the door for a wide range of research in the area of physical exercise for the prehabilitation of people with cancer during treatments.

## Author Contributions

Ángela González-Santos (Formal analysis-Equal, Writing—original draft-Equal, Writing—review & editing-Equal), Maria Lopez-Garzon (Data curation-Equal, Writing—original draft-Equal, Writing—review & editing-Equal), Rocío Gil-Gutiérrez (Data curation-Equal, Writing—original draft-Equal), María del Mar Salinas-Asensio (Data curation-Equal, Writing—original draft-Equal), Paula Postigo-Martin (Conceptualization-Equal, Project administration-Equal, Writing—original draft-Equal, Writing—review & editing-Equal), Irene Cantarero Villanueva (Conceptualization-Equal, Formal analysis-Equal, Funding acquisition-Equal, Project administration-Equal, Writing—original draft-Equal, Writing—review & editing-Equal).

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## Data Availability

De-identified sections of the dataset will be available from the corresponding author upon reasonable request from the time of publication.

## Disclosures

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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