Title: An online home-based combined exercise intervention with self-selected intensity for women with breast cancer: Design and rationale of the Home-Combo randomized controlled trial.

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Trial registration: submitted to clinicaltrials.gov, 16/04/2024
Version 1: April 29th, 2024

Funding

There are no foreseen funding sources. However, some partnerships might be made to acquire some expenses that might exist (e.g., participants' insurance) and resources (i.e., equipment or human resources) needed to conduct the study.

Roles and responsibilities

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ABSTRACT

Background. Chemotherapy drugs carry many side effects that may hinder the functional performance of women with breast cancer (BC). Chemoresistance can lead to treatment failure. A relative dose intensity of chemotherapy <85% is associated with a worse diagnosis and lower treatment efficacy. Exercise may modulate treatment response through its effects on the tumor microenvironment and treatment tolerability. The need for a pleasant and sustainable exercise practice is important, considering the psychological and physiological stress that accompanies women with a BC diagnosis during treatment. Studies investigating the effects of exercise interventions on chemotherapy completion rates are needed.

Purpose. This study aims to investigate the effects of a self-selected intensity structured supervised home-based combined exercise intervention on the chemotherapy completion rates of women with BC. Secondly, we intend to analyze the impact of this intervention on functional performance, quality of life, body composition, and physical activity levels. A 3-month follow-up will investigate if physically active behavior is sustained post-intervention.

Methods. A 2-arm randomized controlled trial will be implemented in a real-world exercise setting to compare an online structured and supervised group aerobic and strength exercise intervention with an active control group during chemotherapy treatments. The study recruitment goal is 122 women with a BC diagnosis stage I-III who are scheduled to have neoadjuvant or adjuvant chemotherapy. Outcome measures will be obtained at baseline, mid-treatment (≈3 months), post-intervention (≈6 months), and 3-month follow-up. A mediation analysis will also be conducted.

Key-words: Breast cancer; Home-based exercise; Chemotherapy; Functional performance; Body composition; Physical activity; Quality of life

Introduction

Background and rationale

Breast cancer (BC) is the most diagnosed cancer type, with high levels of incidence, prevalence, and cancer-related deaths among women worldwide [1,2].

Chemotherapy is commonly used as an anticancer therapy, consisting of the intravenous administration of a combination of cytotoxic drugs to delay cancer growth or, in some cases, eradicate the tumor and prevent cancer cell multiplication, invasion, and metastasizing [3,4]. However, since chemotherapy drugs are not selective to tumor cells or normal cells, many side effects hinder functional performance (i.e., a person's ability to perform daily activities involving physical effort with vigor and without excessive fatigue) of women with BC [5,3,6]. Another problem that may arise during treatment is the development of tumor cells' resistance to chemotherapy, ultimately leading to treatment failure [7,8]. A relative dose intensity (RDI) (i.e., the dose of drugs delivered to a person with cancer each week of treatment) <85% is associated with a worse disease prognosis and lower treatment efficacy [9–12].

Exercise appears to be a safe and effective cancer co-therapy that improves functional performance in women with BC during treatments and may potentially enhance treatment efficacy [12–15]. Despite the very well-known benefits of exercise for women with BC, this population often fails to adhere to a more active lifestyle and comply with the recommended physical activity (PA) guidelines due to fatigue, conflicting scheduled commitments, sickness, forgetting appointments, pain, procrastination, and lack of self-discipline, enjoyment or interest [16–18].

Some evidence has shown that exercise may modulate treatment response through its effects on the tumor and may also improve the tolerability of chemotherapy, making it a potential tool to enhance chemotherapy completion rate (i.e., reception of the planned treatment doses) [12]. So far, evidence shows that exercise does not disrupt chemotherapy delivery, but failed to demonstrate that exercise may increase chemotherapy completion rates [12,19]. For instance, Mijwel et al. (2020) randomized 240 women to either a resistance and high-interval training group, aerobic and high-interval training group, or usual care groups and found no effects of exercise on chemotherapy completion rate. Sanft et al. (2023) conducted a home-based exercise and nutrition counseling intervention on 173 women with BC undergoing chemotherapy, reporting no intervention effects in RDI compared to the usual care group.

Home-based exercise interventions (i.e., programs performed inside or in the immediate surroundings of one's home [21]) are a convenient and flexible strategy with high adherence and proven to be effective and beneficial to improve functional

performance, raising activity levels, reducing symptoms, and improving overall quality of life in women with a BC diagnosis [22-24].

The need for a pleasant and sustainable exercise practice may be a relevant topic when considering the psychological and physiological burden and stress that often accompanies women after a BC diagnosis and during the treatment phase when dealing with therapy side effects [25,26]. Even though some evidence suggests that allowing self-selection of exercise intensity may not be optimal to maximize health or fitness, increasing enjoyment and adherence to exercise practice and creating sustained lifestyle changes can be more beneficial [27]. Although some exercise methods might be highly efficient in potentiating physiological outcomes in women with BC (e.g., high-intensity interval training), they may fail to meet this population's preferences and hinder the sustainability of active lifestyle behaviors after the studies' interventions [28-30].

Bolam et al. (2019) performed a 2-year follow-up on 206 women with a BC diagnosis who participated in either a concurrent high-intensity interval and progressive resistance training or a concurrent high-intensity interval training and continuous moderate-intensity aerobic exercise to analyze the PA levels of the participants post-intervention. Results showed that none of the participants in the intervention significantly changed their PA levels compared to the usual care group. Ramírez-Parada et al. (2019) conducted a questionnaire-based study on a sample of 112 women with BC to investigate the exercise preferences among this population, reporting that most participants preferred to perform the exercise in a group with other BC survivors at moderate intensity in a supervised setting. Studies have shown that participants can achieve adequate intensity and improve functional performance with exercise interventions where they self-select their training intensity in the general population [33,34]. Evidence suggests that self-selected intensities seem higher when the participants are supervised by a qualified professional [34,35]. Ratamess et al. (2008) investigated women's responses and the resistance training intensity selected, with and without professional supervision, in a healthy population. Findings in this study showed that women selected higher intensities, loads, and ratings of perceived exertion when supervised compared to unsupervised settings.

Also, evidence has shown that developing a program that is tailored and sensitive to the participants' needs and consider their preferences is essential to promoting continued engagement and long-term behavior changes [36]. Gildea et al. [37] Schleicher et al.[28] stated that to maximize adherence to an exercise program and lifelong active lifestyles, the participants' preferences, facilitators, and perceived barriers must be considered.

Studies investigating the effects of exercise interventions on chemotherapy completion rates as a primary outcome are still needed to substantiate further findings [12]. Also, to the authors' knowledge, no study has conducted and analyzed the effects of a structured and supervised home-based [21] self-selected intensity exercise program in women with a BC diagnosis.

Objectives

This study will investigate the effects of a structured, supervised, home-based combined exercise intervention with self-selected intensity on the chemotherapy completion rates of women with BC. We also intend to analyze the impact of this intervention on functional performance, body composition, PA levels, and quality of life. A 3-month follow-up will be performed to investigate short-term outcomes and active lifestyle sustainability post-intervention.

Hypothesis 1: Women in the intervention will have a better completion rate than those in the control group.

Hypothesis 2: Women in the intervention will present better functional performance, body composition, PA levels, and quality of life than the control group.

Hypothesis 3: In the post-intervention period, women in the intervention group will maintain a more physically active lifestyle than women in the control group.

Trial design

This study will be a 2-arm pragmatic and superiority randomized controlled trial with an intervention and an active control group, with a 1:1 allocation ratio. It will comprise a structured, supervised, home-based combined exercise intervention that will start 1-2 weeks after chemotherapy treatments begin and continue until 3-4 weeks post-treatment. Additionally, a 3-month follow-up will be performed. This protocol followed the Spirit guidelines [38].

Methods

Study setting

The Home-Combo study will take place in the Algarve, and the sample will be recruited by medical referral from various public and private hospitals, and oncologic organizations across the region.

The intervention design will consider the PA/exercise preferences, perceived barriers, and facilitators of women with BC. This information will be collected before the intervention through a mixed-methods qualitative study that will include a survey and focus groups. The intervention will be conducted online to ensure the participants' safety during the chemotherapy treatment phase, as they may have compromised immunity. Also, this option was made to attenuate participants' burden caused by commuting requirements [17,39,40]. Due to the specific timings between the first contact and study enrolment, participants will be enrolled continuously for one year. Recruitment will continue for each cohort until the number of participants per group is achieved. A scheme of the study timeline is presented in Table 1.

Eligibility criteria

Women aged ≥18 years with a BC stage I-III diagnosis, scheduled to receive neoadjuvant or adjuvant chemotherapy, and who have access to a computer will be considered eligible to participate in the study. Women already at the mid-stage of the chemotherapy treatments, with medical counterindication to perform the exercise intervention or physical assessments due to concomitant comorbidity, non-controlled health conditions or diseases, or psychological illness, currently enrolled in a structured exercise program, or women unable to complete the entire program (e.g., due to scheduled surgery or personal commitments) will be considered ineligible. Participants who get pregnant or have a worsening in their clinical condition during the intervention will be discounted from the program.

The exercise professionals who will perform the interventions and assessments must have an academic degree in Exercise Sciences and a specialization in exercise with cancer populations or receive education sessions with an exercise professional specialized in exercise for BC populations to acquire knowledge and skills to conduct exercise sessions online. Also, professionals who conduct the interventions will have to perform at least three simulated sessions among each other, supervised by a qualified peer, to guarantee consistency in the intervention application.

Interventions

Combined home-based exercise group. Participants in this group will exercise throughout their chemotherapy treatments, starting within 1-2 weeks of its start and ending within 3-4 weeks post-treatment completion [41].

The exercise intervention will be led by qualified exercise professionals, comprising two weekly 60-minute online exercise group sessions with a 5-minute warm-

up, a 30-minute resistance training, and a 20-minute aerobic exercise component, finishing with a 5-minute cooldown [42]. The warm-up will be composed of mobility and activation movements, such as cat-camels, butterfly chest stretch, overhead reach, floor angels, spine twist in sitting and alternated all fours position, doorway chest stretch, wall slides, scissors, pointer, and single leg stances. The resistance training component will consist of 9 different exercises, performed either with body weight or free weights, completing 2-3 sets of 10-15 repetitions, and will involve movements such as chair sit-to-stand, multi-directional lunges, calf, and toe raises, double-arm and one-arm rows, push-ups, glute bridges, clams, chest press, multi-directional shoulder raises, leg curls, and abdominal exercises (i.e., crunches, leg raises, crisscross) [41,42]. The aerobic component will consist of low-impact dance exercises, moving large muscle groups to increase heart rate, involving marching, side steps, knee raises, leg curls, multi-directional arm movements, and dance movements [42]. The cooldown will consist of breathing exercises and light stretches. Every exercise professional will follow a written protocol to ensure consistency in the intervention program's application [42].

Before the beginning of the exercise program, participants will receive an education session on how to use Borg's Perceived Rate of Exertion Scale (RPE) to monitor their effort during aerobic and resistance training and tips on when they may increase the exercise intensity [43,44]. During the training sessions, participants in the intervention group will be asked to choose their preferred load to execute each exercise in the resistance component, told to perform the aerobic exercises at their preferred speed, and informed that they can stop exercising whenever they need to rest. The exercise professional may suggest increasing loads in specific exercises, but these increases will not be imposed on the participants. Attendance to the sessions in the intervention and control groups will be registered. Additionally, women in this group will be encouraged to perform brisk walking at their preferred intensity and receive a pedometer to increase walking motivation [45–47,42].

Control group. Women randomized to the control group will receive weekly 30-minute supervised sessions with breathing, stretching, relaxation exercises, and meditation during the intervention period [42]. Women in this group will not be forbidden to perform PA but will not receive any incentives or advice from the supervising exercise professional.

Criteria for discontinuing or modifying allocated interventions

Participants will be informed in the pre-study initial meeting that they may leave the study anytime. Participants will be asked to refrain from continuing the intervention if a worsening clinical condition prevents them from exercising and performing the

assessments safely. The exercise program might be reviewed and tailored to the participants' condition across the intervention.

Strategies to improve adherence

Before implementing this study, a survey and focus-group-based study will be performed to adjust the exercise program to the preferences, perceived barriers, and facilitators of women with a breast cancer diagnosis, considering the environmental and cultural context from where the intervention will be conducted. The supervising professional will monitor adherence to the supervised sessions through presence registration. This study will also consider the participants' adherence to the control group. To attempt dropout minimization, we will have an active control group.

Concomitant care

Physiotherapy treatments prescribed by the participant's primary physician and any exercises prescribed to be performed at home prescribed by the physiotherapist will be allowed during the intervention. Participants in the study will be asked not to engage in other exercise and PA programs or activities outside the program. Participants in the control group will not be prohibited from performing physical activities like brisk walking.

Outcomes

Assessments will be performed at four-time points: baseline (T_0, 1-2 weeks post-chemotherapy start), mid-treatment (T_1, planned mid-cycle), post-intervention (T_2, 3-4 weeks post-chemotherapy finishing), and 3 months post-intervention finishing (T_3, follow-up). The primary outcome of this study will be the chemotherapy completion rates. Secondary outcomes will include functional performance, body composition, PA levels, sedentary behavior (SB) (i.e., behaviors with energy expenditure ≤1.5 METs while sitting, or lying [48]), and quality of life. Demographical information (age, education level, marital status, socioeconomic status), PA history, and clinical history data (disease and treatment history, concomitant comorbidities, and other existing health problems besides BC) will also be collected as covariates in the data analysis.

Participant timeline

*** Table 1***

Sample size

Considering this study design, sample size calculations were made for the primary outcome with a factorial variance analysis with repeated measures as reference statistical analysis, giving an initial estimation of 82 participants. Based on previous findings and considering a 20% dropout, the sample size was estimated at 98 participants with a moderate effect size (α=0.05; statistical power=0.80) according to Cohen's D calculations, using G* Power 3.1 [49,50].

Recruitment

Recruitment will occur through medical referrals from primary physicians of several public and private hospitals in the Algarve region. Additionally, the project will be presented at breast cancer-themed congresses and events, and digital flyers with information about the study will be made to assist in disseminating the project and the recruitment process. A research team member will then contact patients referred by the doctors to receive detailed information about the study. Optionally, patients can call the research team directly or contact them through email if they prefer. After confirming eligibility criteria and interest in participating in the study, patients will be asked to attend an initial session where more information will be given, and the informed consent will be signed. During that session, participants will be told they are not obliged to participate in the study and may decide to leave the project. Consent for data collection or sharing will also be obtained.

Assignment of interventions

Allocation

Sequence generation

After signing the informed consent form, participants will be given a number, randomly generated through Excel and emailed by a non-interventionist team member, which will be their participant number throughout the study. Participants will be instructed not to reveal their number to the research team or the other participants and to keep it with them until the end of the study. After all baseline assessments, participants will be randomly assigned to either the intervention or control arm through an online program (https://www.graphpad.com/quickcalcs/randomize1/). If recruitment takes longer than expected, adjustments in allocation may be made.

Allocation concealment mechanism

Participants and research team members will be unaware of group allocation during recruitment and baseline assessments. A non-interventionist research team member will fill in the measurements' results during the field tests. This team member will be the only person, besides the participant, who will know the participant's number. The participants will identify the questionnaires with their numbers.

Implementation

After all questionnaires have been received, the random allocation will be performed. The non-interventionist team member will email all participants the numbers allocated in each group (intervention or control).

Blinding (masking)

Participants will be told they are part of an exercise intervention without any mention of a control group. The healthcare professionals responsible for the chemotherapy prescription and administration and registering all clinical information will be blinded to the participants' groups. None of the research team members will know the number of participants, so data analysis will be performed in a blinded setting. The exercise professional conducting the assessments will be blinded to the participant's number but not to which group the participant belongs. If, at any given moment, a participant reveals her number to a research team member, all posterior data from that participant will be disregarded. If a participant decides to leave the study or must abandon it due to health complications, the team member with the number information will be informed, and all further data will be disregarded from the analysis.

Data collection, management, and analysis

Data collection methods

Assessments will be conducted in standardized conditions, in a clinical setting, in a calm and comfortable environment, in small groups, and performed by a qualified exercise professional. The assessments will be conducted in the morning, starting with the body composition measurements, followed by a 15-minute pause so participants can eat (since they will be weighted while fasting), preceded by a 10-minute warm-up with general movements to mobilize big muscle groups and the physical tests, that will be performed in the following order: shoulder angular measurements, strength, mobility, and aerobic endurance. Participants will be divided into small groups to facilitate instruction and conduction of the tests. Participants will receive the accelerometers one week before

the field tests and return them on the physical assessment day. After the field measurements, all questionnaires will be delivered and answered through email (Google Forms). Summarized information regarding assessment time points and tools can be found in Table 1.

Primary outcome

Chemotherapy completion rates. Chemotherapy completion rates will be assessed at T_0, T_1, and T_2. This outcome will be reported as the mean RDI ($mg.m^{-2}/wk^{-1}$), which corresponds to a fraction of the planned chemotherapy dose intensity, by dividing the dose of chemotherapy per square meter (of surface area where the drug is related) in each cycle by the number of weeks in a cycle [52,9,19]. Information regarding the planned chemotherapy treatment and the effectively received treatment (i.e., dose, type, and duration) will be acquired from medical records after signing the informed consent [53,19]. A successful chemotherapy completion rate will be considered if the RDI is ≥85% of the planned treatment, as an RDI below this cut-off is associated with a worse disease prognosis and lower treatment efficacy [12]. Calculations to compare the actual chemotherapy dose intensity received and the initially planned dose intensity will be calculated as total milligrams of chemotherapy divided by the product of the body surface (in square meters) and total weeks of treatment [19]. The RDI results from the actual dose intensity received are divided by the planned dose intensity [9,19].

Secondary outcomes

Functional performance. Functional performance will be assessed at T_0, T_1, T_2, and T_3. The test battery will consider aerobic capacity, upper and lower body strength, grip strength, shoulder mobility, and overall mobility. Aerobic endurance will be assessed using the 6-minute walk test, a standardized field test performed indoors in a 30-meter corridor with two turning points marked every 3 meters along the course, that has been considered valid and reliable for evaluating aerobic capacity in cancer patients [54–56]. In this test, participants will be asked to walk the maximum distance possible in 6 minutes on a flat and hard surface, whereas the distance walked is the outcome [54–56]. The arm curl and sit-to-stand tests will be used to test the lower and upper body strength, respectively, since they are valid and reliable in these populations [57,58]. Handgrip strength will be measured using the JAMAR dynamometer since it has shown reasonable validity and reliability in measuring this variable among adults ≥50 years old and used in oncologic samples [59–61]. While performing the handgrip test for each hand, participants will be instructed to stand upright with feet at hip width and elbows completely stretched while applying the maximum grip continuously for more than 3 seconds, and 30 seconds

of rest will be given between measurements [62–64]. Handgrip strength will be considered to the nearest 0.1 kilograms, with each participant performing 2 attempts in each hand, and a best value will be considered [64]. The timed up-and-go test will assess participants' overall mobility. Participants will be instructed to rise from a chair, walk 2.44 meters, turn around, walk back to the chair, and sit down [65,57]. Shoulder flexion and abduction angular measures will be performed on both sides using a validated and reliable goniometer to measure this variable [66,51]. Upper limb flexibility will be assessed using the back scratch test [65,57].

Body composition. Body composition will be measured through bioelectrical impedance (Impedimed Australia) at T_0, T_1, T_2, and T_3 at the beginning of each assessment [67]. Data regarding weight, fat mass, lean mass, water percentage, bone mass, visceral fat, and phase angle will be collected from the scale [67]. Participants will be asked to maintain their dietary patterns before the test and refrain from intense exercise the day before [68]. The measurement will be performed under standardized conditions (i.e., in the morning, 8-hour fasting, bladder voiding before the assessment, controlled room temperature, and no exercise before the measurement) [69,70,51]. The height measurement will be considered to the nearest 0.1 cm of the participants and will be performed using a balance-mounted stadiometer (SECA, Germany), with the participants standing and bare-footed [71,51]. Body weight will be measured to the nearest 0.1kg with a digital scale (SECA, Germany) [51]. BMI (kg/m2) will be calculated from weight (kg) and height (m). Participants will be asked to maintain their dietary patterns before the test and refrain from intense exercise the day before [68]. The measurement will be performed under standardized conditions (i.e., in the morning, 8-hour fasting, bladder voiding before the assessment, controlled room temperature, and no exercise before the measurement) [69,70,51].

Physical Activity and Sedentary Behavior. PA levels and SB will be assessed at T_0, T_1, T_2, and T_3 using a motion sensor (GT9 link, Actigraph) and the International Physical Activity Questionnaire Short-Form (IPAQ-SF) [72,73,51,74]. Accelerometers have been previously reported as valid and reliable tools to objectively measure PA levels in general and clinical populations [75,72,76,74]. Participants will be instructed to wear the device on an elastic belt on the non-dominant hip for 7 days during all waking hours, removing only to sleep [77,51]. The sampling units (epochs) will be settled to 1s to ease data analysis and ensure the appropriate sensitivity of the device during low-intensity activities. The accelerometer counts will be categorized into sedentary, light, moderate, and vigorous activity levels according to specific established thresholds [78,79]. Any interval of 60 or

more minutes with continuous zero counts, will be considered as non-wear time [78]. The IPAQ-SF comprises 9 items that measure the weekly time spent on all intensities PA (i.e., light, moderate, and vigorous) and time spent sitting on week and weekend days. Total PA scores are calculated from the collected data and discriminated by intensity [73].

Quality of life. Quality of life will be assessed at T_0, T_1, T_2, and T_3, using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). The specific module EORTC QLQ-BR45 will measure breast cancer-related quality of life. Both tools demonstrated adequate validity and reliability, specifically for cancer patients [80,81]. The EORT QLQ-C30 questionnaire consists of 30 items, grouped into 8 multi-item scales (i.e., functional: physical, role, emotional, cognitive, and social; symptom: fatigue, pain, and nausea), one global health status and quality of life subscale, and 6 single-item questions (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) [51,80]. The breast cancer module QLQ-BR45 comprises 5 functional sub-scales (body image, future perspective, sexual functioning, sexual enjoyment, breast satisfaction) and 7 symptoms sub-scales (arm symptoms, breast symptoms, endocrine therapy, skin mucositis, endocrine sexual symptoms, systemic therapy side effects, and upset hair loss), for a total of 45 items (the previous 23 items found in QLQ-BR23 plus 22 new items) [82,81,83]. High scores on the functional scales determine better functioning, and high scores on the symptoms scale and body image mean higher issues [80,84]. Because the QLQ-BR45 algorithm has not yet been validated, the QLQ-BR23 algorithm will be used to score the questionnaire [85].

Covariates

Demographics, physical activity and medical history. Participants' demographic information (e.g., age, education, marital status, and economic status) and PA history will be collected through a general information questionnaire, and clinical history data will be retrieved from their medical records after they sign the informed consent form.

Plans to promote retention

The conducting exercise professional will control participants' adherence to the exercise program through a presence registry collected by the research team member with access to the list of participants' numbers. After the session, the non-interventionist research team member will pass the presence list to the respective numbers of the participants for program adherence analysis. If a participant fails to attend a session, contact will be made to ensure the participant's welfare and motivate them to participate

in the next session. The data analysis will not consider participants who fail to attend 50% or more sessions. Positive feedback will be given to the participants during the sessions, as positive feedback is proven to enhance feelings of competence, enjoyment, and interest in the activity [86]. Additionally, participants will be encouraged to keep an activity diary where they may register all activities performed autonomously. Participants will be contacted one week before the assessment to confirm their availability and presence. Data from participants who fail to perform the assessments during the intervention period will be excluded from data analysis. After the intervention, participants will be contacted monthly to check their well-being and keep their interest and motivation in engaging in the follow-up assessment.

*** Table 2***

Data management

All the data collected in this study will be kept confidential, computerized, and encrypted in a database without any elements that may allow identification of the participants. After the participants have expressed interest and written informed consent, a number corresponding to the participant ID during the study will be provided. When the participant receives her ID number, all data inserted in the databases will not be directly linked to the participant's personal identification. A dataset will be created for each assessment time point. All datasets will be maintained by the members responsible for the investigation on a secure server of CIDEFES-UL for ten years and will be used exclusively for research purposes. Datasets used for specific analyses or to develop sub-studies will contain only the necessary variables and the demographical indicators provided to the research team members upon request to the leading investigator.

Statistical methods

All data will be analyzed using IBM SPSS (version 29.0). Factorial ANCOVAS with repeated measures will be used for the primary and secondary outcomes, adjusted for potential covariates (e.g., concomitant treatments, BC diagnosis, neo-adjuvant/ adjuvant chemotherapy). Independent sample T-tests will be used to compare results between groups at each time point, considering chemotherapy completers versus non-completers [19]. A Fisher's exact test will compare the proportion of participants who needed chemotherapy adjustments from those who did not [19]. The intention-to-treat analysis will be conducted to ensure that all participants are included in the overall assessment, considering their compliance with the study protocol. The Last Observation

Carried Forward method will be used to input missing data values. A per-protocol analysis will also be conducted without participants who failed to complete at least 50% of the training sessions. Normality plots and Kolmogorov-Smirnov tests will be performed to test the normality of outcome variables. If normality is not satisfied, non-parametric tests will be applied (e.g., Krustal-Wallis). Mediators of change (i.e., mechanisms by which RDI) will be explored using structural equation modeling (AMOS 18.0) and multiple mediation analysis (PROCESS macro for SPSS) [51]. Putative candidates will include treatment (e.g., dose planned vs. given dose, planned cycles minimum/maximum, treatment interruption ratios, response to treatment, percentage of participants who needed dose adjustments, and the mean value of dose adjustment), and physiological (e.g., body composition, functional performance, handgrip strength, PA levels) variables. Mediation occurs when a causal effect of an independent variable occurs on a dependent variable, partly or entirely explained by a mediator [87]. Indirect effects testing will be performed using Preacher and Hayes' procedures [88].

Monitoring

Data monitoring

A data monitoring committee will not be required for this trial as the interventions pose minimal risk, and participants will be protected by personal insurance throughout the study.

Harms

All participants will have their adverse events monitored throughout the study, whether directly related to the intervention or not (if applicable). This monitoring will be done through self-reporting at the start of each session, registered for analysis and report purposes, or by their primary care physicians. Participants will be advised to contact the clinical team if they have difficulties.

Auditing

Two authors will supervise all trial procedures and cross-check the interventionist actions and study processes. Additionally, an independent person external to the project will review the protocol.

Ethics and dissemination

Research ethics approval

This study has received ethical approval from the collaborating hospital (UAIF 069/2024). This trial will follow the World Medical Association's Declaration of Helsinki for Human Studies [89].

Protocol amendments

Any changes to the protocol will be promptly communicated to all participants involved in the study or data manipulation. The lead investigator will inform all cooperating institutions, sponsors, or funding agencies. Modifications to the protocol will be submitted for approval to all the Ethics committees involved in the project. The published protocol or the informed consent form will be amended, and updated, if necessary.

Consent or assent

Healthcare professionals will approach potential participants to determine if they are interested in participating. If they express interest, they will be referred to a research team member who will contact them. Additionally, interested participants will be allowed to share the study information with other women who have been diagnosed with breast cancer. If any of these women express interest in participating, they will also be considered after obtaining medical clearance. Once the eligibility criteria for the study are confirmed and the women express their interest in participating, they will receive the Informed Consent through email. In the informational session, women will be asked to digitally fill out and sign the Informed Consent. It will be clear to the participants that they can withdraw their consent anytime. After the informational session, a PDF copy of the signed Informed Consent will be emailed to each participant. The research team will also take additional measures to collect and share the participants' data.

Confidentiality

The responsible members of the investigation will maintain all datasets on a secure server of CIDEFES-UL for ten years. These datasets will be used solely for research purposes. Datasets utilized for specific analyses or sub-studies will only contain the necessary variables and the demographic indicators provided to the research team members upon request by the leading investigator.

Declaration of interests

The authors declare no competing interests.

Access to data

The corresponding author will make anonymized trial data available for non-commercial research purposes upon reasonable request.

Ancillary and post-trial care

Post-trial care is unnecessary as no harm is expected during the trial. However, an insurance policy will cover participants if needed during the study.

Dissemination policy

This trial's findings will be disseminated through publication in leading international oncology scientific journals and presentations at national and international conferences. In addition. the results and mediation analysis will be produced and published. As this is a pragmatic trial with highly applicable outcomes for participants and decision-makers, it presents potential for future widespread implementation through relevant stakeholders [90].

Authors' contributions

Pedro G.F. Ramos conceived the project and wrote the manuscript. Nuno Dias revised and edited the manuscript and will randomly assign participants' numbers and random allocation. Eliana V. Carraça and Pedro B. Júdice assisted in project refinement and revised and edited the manuscript. Also, the former authors will supervise the entire trial.

Acknowledgements

We thank Doctor Gabriela Valadas for facilitating open communication between the Hospitals and the research team. Without the action of this medical professional, the successful implementation of this study would be compromised.

Declaration of Generative AI and AI-assisted technologies in the writing process

While preparing this work, the authors utilized Grammarly's AI-powered writing assistance to enhance the manuscript's language and readability. Subsequently, the authors reviewed and edited the resulting content as necessary, taking full responsibility for the publication's final version.

Discussion

The Home-Combo study aims to expand the knowledge regarding the effects of a supervised home-based combined exercise program for women undergoing neo-adjuvant and adjuvant chemotherapy for breast cancer. The incidence of breast cancer has been increasing steadily over the years, particularly among women. [2,1]. In specific home-based exercise training programs, exercise training programs have already been proven safe for women with BC during the treatment phase [24,91]. Studies conducting structured and supervised home-based exercise programs in women with BC during the treatment phase are still scarce [24]. Furthermore, since this study also includes participants performing neo-adjuvant chemotherapy, it will be possible to verify the effects of the intervention in a prehabilitation (i.e., pre-operative) context [92]. Also, according to Júdice et al. [12], there is a need for more studies that analyze the effects of exercise on chemotherapy completion rates. Lastly, to the authors' knowledge and according to the research, no studies have conducted an exercise intervention where the intensity of the performed exercise is self-selected by the participants in a sample with a diagnosis of BC during treatments. Therefore, this study may give a significant contribution to robust knowledge regarding home-based exercise programs in women with BC diagnosis undergoing chemotherapy treatment. Also, this study is expected to have immediate benefits to all women with BC enrolling in this study and a potential impact on improving interventions designed to promote higher adherence to the study and active lifestyle behaviors. The online alternative and the dissemination of an easy-access exercise program that can be performed at home might be particularly important for the region where the study will be conducted, since public transportation is not very effective, and many people live in remote areas with little to no access to a nearby sports or exercise facilities. If the hypothesis are confirmed, or if at least results show that women with a BC diagnosis can stick to the planned chemotherapy sessions and doses, with little to no interruptions and no dose adjustments, the results will potentially represent less time to treatment exposure, quicker return to everyday life, fewer side effects, and better overall and disease-related quality of life.

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