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Exercise volume load in women with breast cancer: Study protocol for the ABRACE randomized clinical trial

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ABSTRACT

Background: An increased number of breast cancer patients are challenged by acute and persistent treatment side effects. Oncology guidelines have been establishing physical exercise to counteract several treatment-related toxicities throughout cancer care. However, evidence regarding the optimal dose-response, feasibility, and the minimal resistance exercise volume and/or intensity remains unclear. The ABRACE Study will assess the impact of different resistance training volumes (i.e., single or multiple sets) combined with aerobic exercise on physical and psychological outcomes of breast cancer patients undergoing primary treatment.

Methods: This study is a randomized, controlled, three-armed parallel trial. A total of 84 participants, aged ≥18 years, with breast cancer stages I-III, initiating adjuvant or neoadjuvant chemotherapy (≤50% of sessions completed) will be randomized to multiple sets resistance training plus aerobic training group, single set resistance training plus aerobic training group or control group. Neuromuscular and cancer-related fatigue (primary outcomes), muscle strength, muscle thickness, muscle quality by echo intensity, body composition, cardiorespiratory capacity, functional performance, upper-body endurance and quality of life will be measured before and after the 12-week intervention. Our analysis will follow the intention-to-treat approach and per-protocol criteria, with additional sub-group analysis.

Discussion: Findings support prescribing exercise during chemotherapy for breast cancer and elucidate the potential role of different resistance training volumes as a management strategy for physical and psychological impairments in women with early-stage breast cancer. Our main hypothesis is for superiority in physical and psychological outcomes for both training groups compared to the control group, with no difference between single or multiple sets groups.

Trial registration: Clinical trials NCT03314168.

1. Background

Breast cancer is the most prevalent cancer worldwide, accounting for ~2 million cases and ~700,000 deaths in 2020 [1]. Although advances in breast cancer therapies have been a determinant factor in improving 5-year survival rates, an increased number of individuals are burdened by physical and psychosocial consequences of treatment [2]. Individuals exposed to different cancer therapies may experience acute and

Abbreviations: ABRACE, Adaptations to Breast Cancer and Exercise; SS + AT, single set resistance training plus aerobic training; SM + AT, multiple sets resistance training plus aerobic training; CG, control group; QoL, quality of life; 1-RM, one-repetition maximum; 3-RM, three-repetition maximum; ES, effect size; MT, muscle thickness; MQ, muscle quality; EI, echo intensity; QF, quadriceps; VL, vastus lateralis; VM, vastus medialis; RF, rectus femoris; VT, vastus intermedius; DXA, Dual-energy X-ray absorptiometry; ITT, intent-to-treat analysis; PP, per-protocol analysis.

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persistent toxicities [3]. Treatment-related side effects include fatigue, musculoskeletal impairments, cardiovascular dysfunction, and body composition alterations, worsened by aging and physical inactivity [4–7]. These physiological impairments impact patient's quality of life (QoL) during and following breast cancer treatment as well as leading to a higher risk of cardiovascular and metabolic diseases increasing cancer-related and all-cause mortality [8–12].

Fortunately, exercise medicine research is increasingly acknowledged for establishing physical exercise as a complementary therapy to counteract several treatment-related toxicities throughout the cancer care continuum [13]. Previous studies demonstrated that resistance-based exercise programs could reduce cancer-related fatigue [14] and improve muscle strength, cardiorespiratory fitness, and body composition [14–16]. In addition, current exercise oncology guidelines [17] suggest that patients participate in at least 150 min of moderate aerobic physical activity per week (equivalent to 75 min of vigorous aerobic physical activity) and highlight that they should avoid inactivity [18], and return to normal daily activities as soon as possible following diagnosis [19,20]. Moreover, a prescription of two or more resistance training sessions per week, using at least two sets of 8–15 repetitions using 60% or more of one-repetition maximum (1-RM) is recommended [17] to improve a range of outcomes including fatigue, physical function, psychological distress and QoL. In 2018, the Clinical Oncology Society of Australia delivered a position statement on exercise in cancer care in which they encourage exercise should be "embedded as part of standard practice in cancer care and to be viewed as an adjunct therapy that helps counteract cancer and treatment adverse effects" [21]. This statement raised some concerns in the exercise oncology setting due to the paucity of evidence regarding the optimal dose-response, feasibility, and type of activity that should be prescribed for all cancer patients since the minimal resistance exercise volume and/or intensity required to achieve benefits in different outcomes of interest remains unclear.

Few investigations regarding resistance training dose-response were proposed in oncology patients [22,23]. Lopez et al. [22] have recently shown that low volume resistance training may be a suitable exercise recommendation for breast cancer patients undergoing primary treatment producing superior benefits for muscle strength compared to higher training volume, regardless of the intensity used. Nevertheless, it is still unknown if this lower dosage of resistance exercise improves different outcomes as physical function, body composition, and patient-reported outcomes in women with breast cancer. Thus, whether a lower dose of resistance training is found to be equally efficient compared to higher-doses, benefits such as decreasing cancer-related fatigue could improve adherence and minimize respective barriers in physical exercise interventions executed during active cancer treatment. This information has been considered clinically relevant to designing time-efficient exercise interventions beyond the *one-size-fits-all* approach and supporting exercise as an interception therapy for cancer [24].

We design of the "**A**daptations to **Bre**a**s**t **C**ancer and **E**xercise" (ABRACE) study, which will examine the effect of different resistance exercise volumes (i.e., single set or multiple-sets) combined with aerobic exercise on fatigue, muscle strength, muscle thickness, muscle quality, body composition cardiorespiratory capacity, functional performance, upper-body endurance and QoL compared with a control group, in breast cancer patients undergoing primary treatment. Our main hypothesis is for superiority in physical and psychological outcomes for both training groups compared to the control group, with no difference between single or multiple sets groups.

2. Methods

2.1. Protocol registration

The ABRACE study is a three-arm parallel, randomized controlled trial registered at ClinicalTrials.gov (NCT03314168) on October 2017, before first participant enrolment (i.e., on April 2018). This trial is designed according to the Consolidated Standards of Reporting Trials (CONSORT) statement [25] and reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [26].

2.2. Study setting and eligibility criteria

Participants will be recruited through a clinical referral from Hospital Moinhos de Vento and Clínica Oncotrata in Porto Alegre, southern Brazil. The research team and laboratories facilities necessary for all evaluations and training sessions will be from *Universidade Federal do Rio Grande do Sul*, Brazil. The inclusion criteria will be women aged ≥18 years diagnosed with breast cancer in stages I-III, undergoing adjuvant or neoadjuvant chemotherapy (with ≤50% of sessions completed). Exclusion criteria will be pregnancy, uncontrolled hypertension, cardiac or psychiatry illness, or any musculoskeletal, neurological, or cardiovascular disorder that could compromise their involvement in the training program or put participants at risk for exercising. The planned flow diagram of this trial is presented in Fig. 1.

2.3. Interventions

Participants will be randomly allocated to one of the three arms: 1) single set resistance training plus aerobic training (SS + AT), 2) multiple sets resistance training plus aerobic training (MS + AT), or 3) control group (CG), each lasting 12 weeks. Below is provided a detailed description of the interventions:

2.3.1. SS + AT and MS + AT

The exercise interventions will consist of resistance exercises performed with single (1 set per resistance exercise; SS + AT group) or multiple sets (3 sets per resistance exercise; MS + AT group) combined with an identical aerobic exercise program performed 2 sessions per week over 12 weeks. Both SS + AT and MS + AT groups will undertake similar resistance training program (except for sets number) comprising 8–12 repetitions at 60–80% of 1-RM for leg extension and chest press exercises (1-RM predicted will be reassessed every 4 weeks), and intensity of 6–8 OMNI scale [27] for the remaining exercises. A flexible prescription allowing patients to self-regulate each session's load or volume with supervision of the exercise physiologist according to their condition will be ensured, aiming to consider fluctuations in exercise tolerance, capacity, and self-efficacy during treatment [18]. Resistance exercises will include leg extension, chest press, leg curl, lat pull down, unilateral biceps curl, calf raises, triceps extension, external shoulder rotation, and curl-ups. The aerobic component of the training program will involve 20–25 min of cycling at 80–90% of heart rate at the second ventilatory threshold (obtained during the cycle ergometer test for cardiorespiratory fitness). All training sessions will be conducted in small groups of one to four participants under direct supervision of at least one exercise physiologist previously trained to carry out the intervention (1:4 supervision ratio). All participants will be instructed to report difficulties and limitations, and training variables (i.e., rate of perceived exertion, load, cadence, and total volume) or any protocol adaptation will be registered. In addition, adherence to interventions will be recorded as group attendance and compliance in the training groups. The periodization of resistance and aerobic training for SS and MS groups is presented in Table 1.

2.3.2. Control group

The CG participants will be recommended once, after baseline assessments, to avoid systematic physical exercise for three months while receiving usual care (e.g., general clinical recommendations such as nutritional intake and lifestyle issues in their respective hospitals). After the intervention, all volunteers in this group will be invited to participate in the supervised training program, performing the same protocol as the MS + AT.

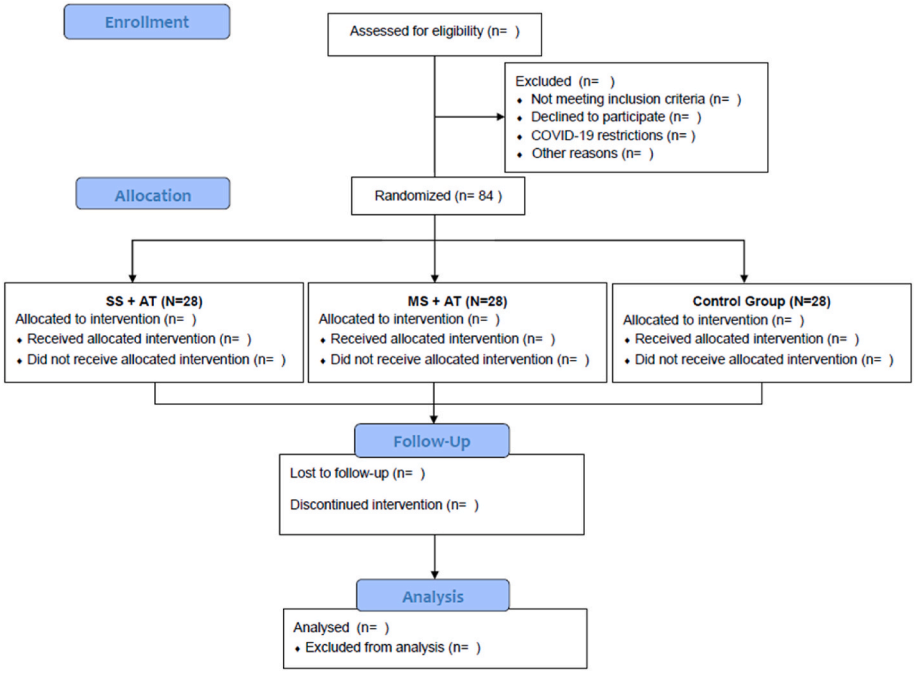

Fig. 1. The ABRACE flow diagram.

Table 1
Exercise periodization of resistance and aerobic training for SS + AT and MS + AT groups throughout 12 weeks of intervention.

Weeks	Resistance training					Aerobic training	
	SS + AT	MS + AT	Overall			Overall	
	Volume	Volume	Intensity	Volume Load[a]	Rest	Volume	Intensity
1-4w	1 set 10-12 reps	3 sets 10-12 reps	60%1-RM 6 OMNI's scale	SS + AT 6 to 7.2 a.u MS + AT 18 to 21.6 a.u.	~1min between sets and exercises	20min	80%HR of VT2
5-8w	1 set 8-10 reps	3 sets 8-10 reps	70%1-RM 7 OMNI's scale	SS + AT 5.6 to 7 a.u. MS + AT 16.8 to 21 a.u.	~1.5min between sets and exercises	25min	85%HR of VT2
9-12w	1 set 8 reps	3 sets 8 reps	80%1-RM 8 OMNI's scale	SS + AT 6.4 a.u. MS + AT 19.2 a.u.	~2min between sets and exercises	25min	90%HR of VT2

SS + AT: single set resistance training plus aerobic training; MS + AT: multiple sets resistance training plus aerobic training; Volume load: number of repetitions x sets x %intensity; %1-RM: percentage of 1-repetition maximum; a.u.: arbitrary units; HR: heart rate; VT2: second ventilatory threshold.
[a] Calculated as suggested by Nunes et al. (2021) [28].

2.4. Strategies for trial retention and criteria for discontinuing allocated interventions

We will use phone calls or WhatsApp messages to ask participants about their reasons for not attending each training session. Participants may be discontinued from the study for safety reasons or withdrawal of participant consent. Additionally, medical advice, disease complication, or a severe health event that precludes attendance to intervention sessions will be considered criteria for interrupting participation.

2.5. Outcomes

Randomized groups will be evaluated for the outcomes listed below by standardized methodological procedures for all participants, regardless of attendance or completion status (Table 2). For participants who drop out after randomization, research personnel will use contact information to invite such patients to undergo post-intervention outcome assessments.

2.5.1. Primary outcomes

Primary study outcomes will be neuromuscular fatigue assessed by fatigue index in an isokinetic machine and cancer-related fatigue assessed by the Piper fatigue scale. Fatigue will be chosen as the primary outcome because it is a widespread side effect caused by chemotherapy [13].

2.5.2. Secondary outcomes

Clinically relevant outcomes for breast cancer women will be established as secondary outcomes, including knee extension maximal strength, knee extensor muscle thickness and echo intensity, body composition, peak oxygen uptake, functional performance, upper-body endurance, and QoL.

2.6. Sample size

Sample size calculation was performed using G*Power software (version 3.1, Düsseldorf, Germany), assuming a significance level of 5%

Table 2
Time scheme for enrolment, interventions, and assessments of ABRACE study.

TIMEPOINT	Study period							
	Enrolment	Baseline measures	Allocation	Post-allocation		Close out		
	$-t_1$	t_0	t_1	t_2	t_3	t_4	t_5	t_6
Timepoint description	Interviews	Occurs 3 evaluation visits	–	Intervention start	Intervention end	Final evaluation visit 1	Final evaluation visit 2	Final evaluation visit 3
ENROLMENT								
Eligibility screening								
Informed consent	x							
Allocation			x					
INTERVENTIONS								
SS + AT				x	x			
MS + AT				x	x			
CG				x	x			
ASSESSMENTS								
Primary outcomes								
Cancer-related fatigue		x					x	
Fatigue index		x				x		
Secondary outcomes								
Isometric peak torque of knee extension		x				x		
Peak torque at 60°.s^{-1} of knee extension		x				x		
Predict 1-RM *knee extension*		x						x
Muscle thickness		x				x		
Echo intensity		x				x		
Body composition		x				x		
Peak oxygen uptake		x					x	
Functional performance		x						x
Upper-body endurance								x
Quality of life		x					x	

t: time; SS + AT: single set resistance training plus aerobic training; MS + AT: multiple sets resistance training plus aerobic training; CG: control group; %1-RM: percentage of 1-repetition maximum.

and power of 95%. The effect size (ES) of general cancer-related fatigue (ES = −0.22) reported in study by van Vulpen et al. [29] was used, and a sample of 23 participants per group was estimated. Considering potential dropouts, we exceeded the sample size by 20%. Therefore, 28 participants will be enrolled in each group (SS + AT, MS + AT, CG), resulting in 84 subjects.

2.7. Assignment of interventions and blinding

Participants included in the study will receive an internal number to be identified. Allocation sequence will be based on computer-generated random numbers (www.random.org; randomness via atmospheric noise) 1:1:1 ratio, with permuted blocks of random sizes that will not be disclosed to ensure concealment. Randomization requests follow the order in which participants complete baseline assessments. Allocation concealment will be implemented by researchers (J.S.H., R.P.F.) in charge of requesting randomization for one of the external investigators with access to the randomization list via email from the identifier number. Blinding of outcome assessors and participants receiving the intervention will not be applied due to research team internal logistics and the nature of exercise interventions, respectively.

2.8. Data collection

Study outcomes will be assessed at baseline (week 0) and after the intervention (week 13). An initial session will be held for the participants to read and sign the written informed consent and collect participants' sociodemographic and clinical characteristics. After that, the outcomes will be measured in three days, with an interval of at least 48 h. Body composition, muscle thickness, muscle quality, and peak torque measurements will be collected on the first day. Participants will perform a cardiorespiratory test and answer the cancer-related fatigue and QoL questionnaires on the second day. Lower limb maximal strength, functional performance and upper-body endurance will be measured using a three-repetition maximum (3-RM) test, a functional battery test, and the arm-curl test respectively, on the third day.

2.8.1. Cancer-related fatigue questionnaire

Cancer-related fatigue will be determined through an interview by scores from the Piper Fatigue Scale; the Portuguese validated version [30,31]. This is a comprehensive and multidimensional fatigue scale validated for cancer patients in Brazil, and one of the most used fatigue scales in studies in different countries [31]. The questionnaire consists of 22 items numerically scaled 0 (no fatigue) to 10 (severe fatigue) to assess four dimensions of fatigue (behavioral, affective, sensory and cognitive subescales), and total fatigue.

2.8.2. Peak torque and neuromuscular fatigue

Maximal isokinetic peak torque will be tested for the right knee extensors at angular velocity of 60°.s^{-1} on an isokinetic dynamometer (Cybex Norm, USA). Previous studies have demonstrated high reliability scores using isokinetic dynamometer, which have been considered the gold standard method in the literature to evaluate maximal peak torque [32,33]. Participants will be seated with hip flexed at 85° (0° = anatomic position) and the lateral femoral condyle of the right leg aligned with the dynamometer's axis of rotation. An initial warm-up of 10 submaximal isokinetic knee extension/flexion at 120°. s^{-1} will be performed, and 1 min after, participants perform one submaximal isometric voluntary contraction. Then, two 3-s knee extension maximal isometric voluntary contraction attempts at a knee angle of 60° (0° = knee fully extended) will be performed with rests periods of 120-s between attempts. After 3 min, a pre-test of 3 submaximal repetitions will be done, and the maximal isokinetic knee extension peak torque will be measured during one set of 10 repetitions at angular velocity of 60°.s^{-1} in a 90° range of motion.

Maximal isometric and dynamic peak torque will be defined as the

highest torque value (N. m) recorded during the maximal isometric voluntary contraction and maximal isokinetic knee extension, respectively. Fatigue index values will be determined by calculating the peak torque decline at $60^{\circ}.s^{-1}$ in knee extensors of the right leg. Therefore, we will use the muscular fatigue index: FI% = [(peak torque of 2, 3, and 4th repetitions – peak torque of 8, 9, and 10th)/peak torque of 2, 3, and 4th repetitions] x 100.

2.8.3. Muscle thickness and quality

Ultrasound images have been comprehensively used as a non-invasive technique for assessing muscle architecture and are considered a highly reliable method in measuring muscle thickness and quality [34,35]. B-mode ultrasound images will be obtained with a 38-mm, 9.0-MHz linear-array probe (image depth: 70 mm, 90-dB) using ultrasound (Logic P7, GE Healthcare, US). Participants will rest in the supine position with the lower limbs extended and relaxed for 5 min before image acquisition [36]. Whole quadriceps muscle thickness (QMFT) will be assessed through the sum of quadriceps femoris muscles (QFMT = RFMT + VIMT + VLMT + VMMT) as previously proposed [37]. The vastus lateralis (VL) measurement will be taken midway between the lateral condyle of the femur and the greater trochanter, whereas the measurement vastus medialis (VM) will be taken at 30% of the distance between the lateral condyle of the femur and the greater trochanter. Rectus femoris (RF) and vastus intermedius (VI) will be measured as 50% of the distance from the iliac crest to the upper edge of the patella.

Three images of the VL, RF-VI, and VM will be taken in that order, and images will be exported to a personal computer for further analyses performed by the same investigator. Image analyses will be performed using ImageJ 1.42q software (National Institutes of Health, Bethesda, MD, USA). Muscle thickness will be determined as the distance of the adipose tissue-muscle interface for VL, RF, and VM. For VI, muscle thickness will be determined as the distance between the bone and muscle interfaces [38].

Muscle quality (MQ) will be determined by echo intensity (EI) values, calculated by grayscale analysis performed using the standard function of the ImageJ software. For this purpose, a region of interest for each muscle (i.e., RF, VI, VL, and VM) will be selected, including the most significant amount of musculoskeletal tissue possible, avoiding other tissues and interference. The EI value will be determined using the mean of the grayscale histogram in ImageJ and it will be expressed as a value between 0 (black) and 255 (white) for each muscle in arbitrary units (a.u.). Higher EI values represent a more significant amount of non-contractile tissue within the muscle and, therefore, worse MQ [39].

2.8.4. Body composition

Percentage of fat, fat mass, and lean mass of the total body will be assessed by dual-energy X-ray absorptiometry (DXA) (GE Healthcare Lunar, model Lunar Prodigy Madison, USA). DXA is a widely used and a reliable method of body composition analysis, which presents high validity and reproducibility [40–42]. The participants will be instructed to wear light clothing, and they will be positioned in a supine position, lying still for approximately 8 min, while the arm of the equipment will scan the individual's body in the head-to-toe direction. The equipment will be calibrated before the evaluation, and the equipment's software will automatically calculate the present values (Encore version 14.1, Lunar Prodigy Madison, USA).

2.8.5. Cardiorespiratory test

VO_{2peak} will be determined by the breath-by-breath method using an open-circuit spirometry system (Quark CPET, Cosmed, Rome, Italy) on a cycle ergometer (ERGO- FIT, Pirmasens, Germany). The VO_{2peak} estimation using a cycle ergometer test has been considered accurate by previous studies in healthy and DM1 subjects, and will be applied with some adaptations due to different characteristics of the population [43–45]. The warm-up will consist of 3-min cycling at 60 rpm at 20W. Thereafter, the work rate will be increased to 20W/min until exhaustion, followed by a 3-min recovery at 20W. The heart rate will be measured continuously via chest belt telemetry (Cosmed, Rome, Italy). VO_{2peak} and second ventilatory threshold (used to prescribe the intensity of AT) data will be obtained through a visual inspection of the graphs. Participants will be verbally encouraged to perform at maximum effort during physical tests.

2.8.6. 3-RM test

Maximal strength will be measured using the bilateral leg extension 3-RM test (KonnenGym, China), with no more than five attempts, with a 3-min rest between attempts. Previous studies demonstrated that the 3-RM test presents high reliability and safety for untrained subjects [46,47]. Before the maximal test, participants will perform 10 sub-maximal repetitions as a warm-up. Thereafter, the resistance will be increased until no additional weight can be lifted through a full range of motion three times using proper technique and range of motion. The maximum weight and number of repetitions will be used to estimate the one-repetition maximum (1-RM) [48].

2.8.7. Functional performance and upper-body endurance

Following previous protocols, a validated and largely used worldwide functional battery test will be applied [49–51]. For all tests, the examiner will explain the instructions, demonstrate the tests, and start the chronometer immediately after the command "3,2,1, go". Moreover, it will be emphasized that tests should be performed as fast as possible without running, and standardized verbal encouragement will be given during the attempts. For the timed-up-and-go, sit-to-stand and stair climbing functional tests will be allowed one try as familiarization, and after, two attempts (with 90 s between them) will be performed, and only the shortest repetition will be considered. The timed-up-and-go test will require the individual to stand up from a seated position in a chair, walk 2.44 m, turn around a cone, walk back to the chair and sit down. For the 5-repetition sit-to-stand test, participants will be instructed to start the test in a seated position with arms folded across the chest. After the start command, participants will stand up until full knees extension and then back to a seated position. Time will be stopped when participants touch the seat after five complete repetitions. For the stair-climbing test, participants will be instructed to climb a 10-step staircase without skip steps or using the handrail (except in need of balance to prevent falls) [52]. The arm-curl test will be used to measure upper body endurance, through the maximal number of times a 2 kg dumbbell can be lifted with the dominant arm through elbow flexion in 30 s. It will be allowed a few repetitions to understanding, and the test will be executed in only one try. Participants will start the test seated in a chair, with arms extended and forearm maintained in supinated position during full range of motion.

2.8.8. QoL

QoL will be assessed using the validated Brazilian version of the 30-item European Organization for Research and Treatment of Cancer (EORTC QLQ-C30 version 3.0) and the 23-item breast cancer-specific module (EORTC QLQ-BR23) [53,54]. It is a multidimensional and self-administered questionnaire to assess oncology patients' QoL, which has been validated to a number of countries [55]. Scores will be derived and scaled from 0 to 100 according to the EORTC scoring manual. The EORTC QLQ-C30 includes global QoL scale and five multi-item functional scales (physical, emotional, role, cognitive, and social function), with higher scores indicating better QoL. Also, three multi-item and six single-item symptoms scales, with higher scores representing higher levels of complications. The QLQ-BR23 incorporates five multi-item scales to assess body image, sexual functioning, systemic therapy side effects, breast symptoms, and arm symptoms. Single items assess sexual enjoyment, future perspective, and hair loss. The scoring approach for this questionnaire is identical to that for the function and symptom scales of the QLQ-C30. Previous studies presented good rates of reliability in the different dimensions of both instruments, with the

exception of the functional scale of the C30 and the symptom scale of the BR23 [54].

2.9. Data management

All databases, including study outcomes and personal information collected by the investigators will be filed on an Excel Spreadsheet. Two investigators (J.S.H., R.P.F.) will carry data entry and the information will be stored under the confidentiality and responsibility of these investigators. Auditions for missing or inaccurate data will be conducted when necessary.

2.10. Statistical considerations

Generalized Estimating Equations (GEE) and Bonferroni post hoc tests will be used for comparison between time points (baseline and post-intervention) and groups (MS + AT, SS + AT, and CG) for both per-protocol and intention-to-treat analysis. All randomized women will be included in the analyses; there will be no exclusion due to low adherence to an intent-to-treat (ITT) analysis. In addition, an analysis per-protocol (PP) will be performed, in which after the training period, women with a training frequency of less than 70% during the 12-week will be excluded from the analysis. Moreover, we plan to carry out subgroup analysis stratifying both groups according to clinical characteristics of the tumor (staging and status of tumor receptors) and treatment (chemotherapy and radiotherapy protocols, when appropriate). Continuous variables will be summarized according to intervention groups at baseline, if applicable, and in the end of the trial using arithmetic or geometric means, standard deviations, ranges, and interquartile ranges. According to intervention groups, categorical variables at baseline and end of the trial (if applicable) will be summarized as the absolute number and proportion of subjects (%). Effect sizes based on the absolute difference (±SD) between baseline and post-intervention values will be calculated using Cohen's d. All tests will be processed in the SPSS version 26.0 software, adopting an alpha level of 5%.

3. Monitoring

3.1. Data monitoring and auditing

Due to limited resources, the ABRACE Study will not have a data monitoring committee or planned auditing trial conduct. We reason that this committee would not be mandatory due to the characteristics of interventions and outcomes, despite its high value for the overall quality of the trial.

3.2. Harms, ancillary and post-trial care

Adverse events will be managed according to the National Institute of Aging [56]. Such events will be classified according to their severity (i.e., mild, moderate, severe), predictability (i.e., expected or unexpected), and potential relationship with study procedures (i.e., definitely related, possibly related, or unrelated) [56]. The identification, possible solutions, and documentation of adverse events will be based on discussion and analysis between the principal investigators (R.S.P., S.S.P.), study manager (J.S,H.), and medical team (D.D.R., A.M.M, M.C.). For harms suffered during trial enrollment related to the study, we will plan contingency actions to provide participants with primary health care and guidance. Every effort will be made to prevent any unwanted events.

4. Discussion

This study will examine the effects of different volumes (i.e., single set or multiple sets) of resistance training combined with aerobic exercise on physical and psychological outcomes, compared with a control group, in breast cancer patients receiving adjuvant or neoadjuvant chemotherapy. Relevant studies have highlighted that the poor description [57] of exercise programs and the scarce application of training principles [58] in breast cancer clinical trials might explain the inconclusive results in several outcomes related to common side-effects of breast cancer treatment [17]. This study aims to collaborate with this relevant issue by presenting a comprehensive description of the supervised combined training intervention, using different volume of resistance exercises that can be replicated and applied in clinical or other settings. This trial will determine the extent to which supervised combined training twice per week improves physical and psychological outcomes in breast cancer patients. In addition, the rationale for conducting the study is that those women are undergoing breast cancer treatment present high levels of fatigue, which represent a barrier to the practice of physical exercise [59]. Thus, a lower volume of resistance training could be more bearable for women undergoing chemotherapy for breast cancer. The results of this trial will likely contribute to the development of future exercise prescriptions for breast cancer patients receiving primary treatment.

This study has limitations that must be noted. First, adherence to the exercise programs is a challenge. External validity will not be ensured due to potential selection bias (i.e., patients who volunteer to participate may also be the most motivated to exercise). However, the reasons for non-participation and abandonment will be collected and reported. Among the registered trials investigating physical exercise in the breast cancer setting, this is the first to engage patients undergoing primary treatment in Brazil. It is important to underline that this study was interrupted due to the COVID-19 pandemic in 2020. However, the disclosure of this protocol is important for methodological detail (and future reference) about the trial.

5. Trial status

The recruitment period for the ABRACE study was planned to range from October 2017 to July 2021. However, the study paused the recruitment phase in March 2020 until March 2022 due to the COVID-19 pandemic. We resumed the recruitment phase and study execution in April 2022. We have already screened 232 individuals, and the total enrollment comprised 28 participants. This is the first version of the manuscript and is accompanied by a description of existing amendments (Additional file 01).

Ethics approval and consent to participate

This trial received ethical approval from Hospital Moinhos de Vento (CAAE: 72983017.3.3001.5330; protocol number: 3.101.253) and Universidade Federal do Rio Grande do Sul (CAAE: 72983017.3.0000.5347; protocol number: 3.064.366). All patients have been informed about the research procedures, including the objectives of the study, a description of the testing procedures, an explanation of interventions and their randomized allocation process, the potential risks and benefits involved in the study, the costs to the participants (none), and information on anonymized data sharing. The participants must provide written informed consent prior to participation and medical clearance from their physician. Any protocol modifications that may impact changes to study procedures (e.g., changes in eligibility criteria, or assessments) or administrative routine require a formal amendment approved by the Ethics Committee berofe implementation.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable. This manuscript does not contain any data.

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Author's contribuition

J.S.H.: methodology, formal analysis, investigation, data curation, writing - original draft, supervision; D.D.A.: resources, writing - review & editing; A.M.M.: resources, writing - review & editing; M.C.: resources, writing - review & editing; S.S.P: methodology, formal analysis, investigation, writing - original draft, supervision; R.S.P: conceptualization, methodology, resources, writing - review & editing, project administration.

Declaration of competing interest

The authors declare that they have no competing interests.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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