

STUDY PROTOCOL

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Evaluating the effects of a resistance exercise intervention for sarcopenia in patients receiving neoadjuvant chemotherapy for breast cancer: study protocol for a randomized controlled trial

Min Kyeong Jang^{1*}, Seho Park², Justine Y. Jeon^{3,4}, Min Jae Kang¹, Chang Park⁵, Ardith Z. Doorenbos^{6,7} and Sue Kim¹

Abstract

Background Sarcopenia is highly prevalent among people being treated for various types of cancers and is associated with adverse clinical impacts including postoperative complications, chemotherapy-related toxicities, and poor survival. These impacts highlight the need for early intervention to mitigate the progression of sarcopenia during treatment. To date, substantial evidence from clinical trials supports the effectiveness of resistance exercise for reducing sarcopenia, yet the specific effects of prehabilitation exercise during neoadjuvant chemotherapy among patients with breast cancer remain underexplored.

Methods This two-arm randomized controlled trial (RCT) aims to evaluate the effects of a supervised resistance exercise program in addressing sarcopenia, reducing treatment-related adverse effects, alleviating cancer-related symptoms, and improving quality of life (QOL) in patients with breast cancer undergoing neoadjuvant chemotherapy. Forty-six women (aged 20 years or older, diagnosed with breast cancer, and scheduled to start neoadjuvant chemotherapy) will be randomly assigned to either a resistance exercise group or a usual care control group. To overcome potential challenges related to geographic accessibility and treatment side effects, and to improve program completion, the exercise program offers a hybrid model with three expert-supervised exercise sessions per week available both on-site and online. Each supervised session lasts 60 min. Primary and secondary outcome measures include body composition (i.e., muscle mass), muscle strength, physical performance, treatment-related adverse effects, and self-reported cancer-related symptoms and QOL. Assessments will be conducted at baseline (pre-intervention), at 6 and 12 weeks during the intervention, and at completion of the intervention (18 weeks), using validated measures. The study was approved by the institutional review board of Yonsei University Health System's Severance Hospital.

*Correspondence:
Min Kyeong Jang
researchmkj0601@gmail.com

Full list of author information is available at the end of the article



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Discussion This proposed pragmatic RCT will provide meaningful insights into the role of resistance exercise in mitigating sarcopenia and its impact on the clinical outcomes of neoadjuvant chemotherapy for breast cancer. The trial is also expected to contribute to the development of evidence-based sarcopenia interventions tailored to patients with breast cancer and to help guide future directions for clinical practice and research.

Trial registration This trial was prospectively registered in the Clinical Research Information Service (reference number KCT0008961) in the Republic of Korea on November 16, 2023.

Keywords Sarcopenia, Resistance exercise, Muscle mass, Neoadjuvant chemotherapy, Breast cancer, Treatment adverse effect, Fatigue, Depression, Sleep quality, Quality of life

Background

Sarcopenia has received substantial research attention in oncology as well as gerontology because of its significant relationships to various adverse health outcomes [1, 2]. While sarcopenia is estimated to affect 10–16% of the older population globally [1], a recent meta-analysis reported a considerably higher prevalence—approximately 42%—in people being treated for different cancer types, where sarcopenia was also associated with an increased risk of mortality [3]. In the context of breast cancer, recent evidence from systematic reviews has shown that 33–45% of patients have experienced sarcopenia [4, 5], with resulting increases in chemotherapy toxicities and negative clinical outcomes [6]. Low muscle mass has been related to poor clinical outcomes in nonmetastatic breast cancer, including chemotherapy toxicities, dose reductions, treatment delays, and even treatment discontinuation [5]. Remarkably, 38.6% of patients with cancer already exhibit pre-therapeutic sarcopenia [7]. These findings indicate the importance of sarcopenia in patients with cancer, as well as a significant association of sarcopenia with adverse effects [2, 6] and mortality [3], suggesting the need for early intervention [3, 4].

A recent review aiming to determine optimal non-pharmacological interventions for sarcopenia found that resistance exercise, combinations of exercise and nutrition, and nutritional supplements may reduce the risk of sarcopenia. It also revealed that resistance exercise had a significant effect on increasing skeletal muscle mass and lean body mass [8]. A meta-analysis in the oncology setting that examined the effectiveness of sarcopenia interventions for patients receiving chemotherapy for cancer found that both resistance exercise and a combination of exercise plus nutrition effectively preserved muscle mass [9]. Meanwhile, resistance exercise is widely recognized as an effective approach for increasing muscle strength [10]. For patients with breast cancer specifically, a review analyzing pooled data from 11 randomized controlled trials (RCTs) found that resistance exercise had significant effects on improving lean body mass, handgrip strength, leg press strength, and overall physical performance, as well as on decreasing body fat [11]. To date, RCTs of

exercise interventions for sarcopenia in patients with breast cancer have been conducted with intervention periods ranging from 8 to 24 weeks, frequencies of two to four sessions per week, and session lengths varying from 20 to 90 min [11]. However, the review highlighted a need for future clinical trials to identify effective interventions tailored to different phases of chemotherapy.

Recently, prehabilitation exercise has been shown to meaningfully improve physical function [12] and cardiorespiratory fitness [13] in people with various types of cancer, as well as reduce the length of hospital stays [14] and enhance postoperative outcomes [15]. While there is comprehensive evidence to support the key role of exercise in cancer survivorship, the specific effects of prehabilitation exercise for people with breast cancer undergoing neoadjuvant chemotherapy remain underexplored [15]. In fact, while several RCTs have focused on exercise interventions during adjuvant chemotherapy for breast cancer, recent reviews highlight a critical need to examine the effects of exercise as prehabilitation in the neoadjuvant setting [11, 15].

Considering the current lack of evidence in this population, along with the prognostic importance of early interventions for patients undergoing neoadjuvant chemotherapy, we developed a tailored sarcopenia intervention specifically focusing on the neoadjuvant phase. This intervention, called SIGMA (Sarcopenia Intervention to Gain Muscle and Advance cancer treatment), is a supervised 18-week resistance exercise program intended to mitigate sarcopenia and its related effects. It uses a hybrid intervention model (available on-site and online) to enhance feasibility in a context where treatment-related side effects and geographic barriers to neoadjuvant chemotherapy pose potential challenges.

The pragmatic, hybrid RCT protocol described here aims to evaluate the effects of the SIGMA resistance exercise intervention on mitigating sarcopenia and treatment-related adverse effects, alleviating cancer-related symptoms, and improving QOL among patients receiving neoadjuvant chemotherapy for breast cancer.

Methods

Study design

This study is a parallel two-arm RCT designed to evaluate the effects of a supervised 18-week exercise program in patients with breast cancer during neoadjuvant chemotherapy. The study protocol was prospectively registered with the Clinical Research Information Service (CRIS) on November 16, 2023 (registration number KCT0008961) and approved by the institutional review board of Severance Hospital, Yonsei University Health System (protocol ID 4-2023-1128). This protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials 2025 Statement [16].

A flow diagram showing participant flow through the study can be found in Fig. 1. The intervention lasts for 18 weeks, with assessments conducted at baseline (pre-intervention), Week 6 (during the intervention), Week 12 (during the intervention), and Week 18 (at completion of the intervention).

Study participants and recruitment

Participants are currently being recruited from the outpatient breast cancer and oncology centers of Severance Hospital, a tertiary hospital in Seoul, Republic of Korea. Patients are eligible to participate in the study if they meet the following criteria: (1) woman 20 years of age or older at diagnosis; (2) verified diagnosis of breast cancer;

(3) scheduled for neoadjuvant chemotherapy; and (4) willing to sign a form indicating informed consent and desire to participate in this study. Patients are not eligible to participate if they (1) have been diagnosed with recurrent or metastatic breast cancer; (2) were 70 years of age or older at the time of cancer diagnosis; or (3) have physical conditions that would make it difficult to perform the exercise program according to consultation with a physician or exercise specialist.

Potential participants identified as eligible during breast cancer clinic visits are informed about the study by their physician or a research nurse and invited to participate. Additionally, recruitment notices have been placed in the Severance Hospital chemotherapy counseling room and breast cancer center, with information that allows interested patients to contact the research team directly. Before a patient is referred to the study team, their physician or research nurse screens them for any physical condition that might compromise safe participation in physical exercise. Once an interested patient is introduced to the study, the study team conducts eligibility screening based on the inclusion and exclusion criteria. Specifically, all potential participants are screened for cardiovascular conditions, arm/shoulder morbidity, musculoskeletal conditions, and other health risks. Informed consent is reviewed and obtained prior to study participation.

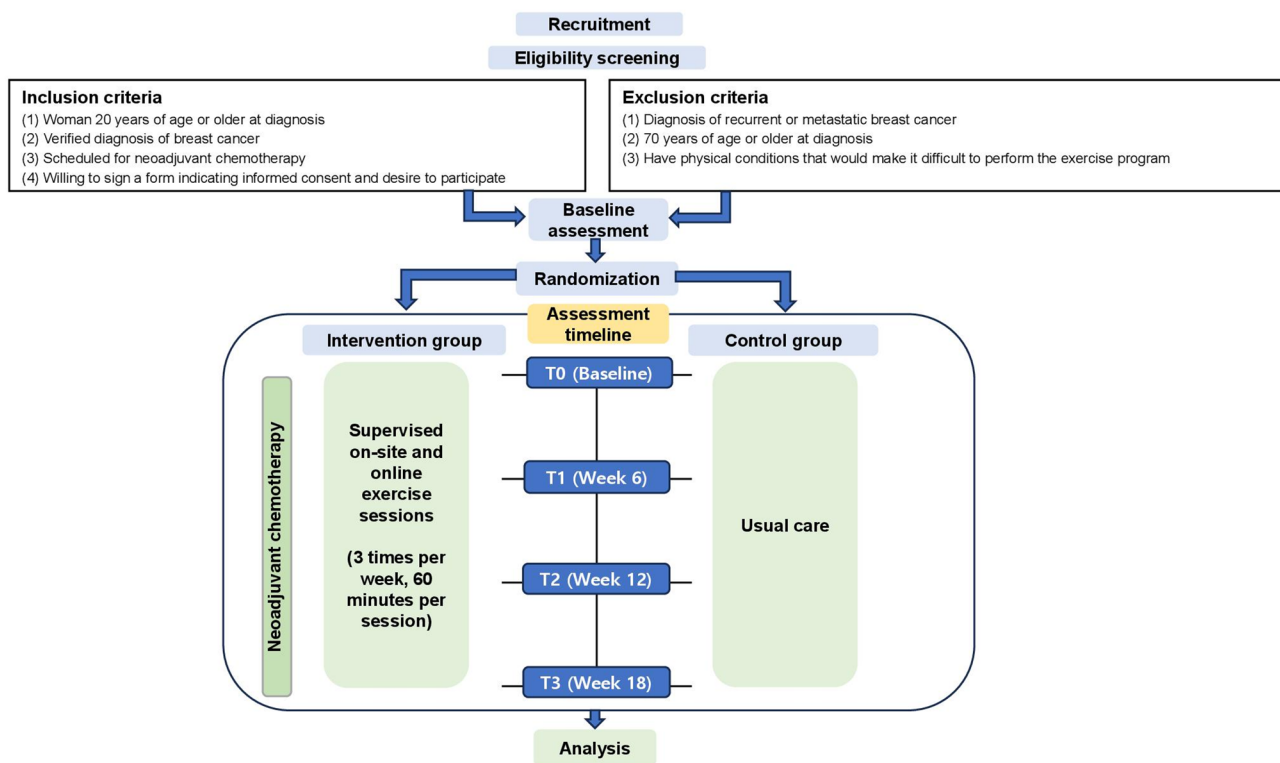


Fig. 1 Flow chart of the SIGMA study design. SIGMA Sarcopenia Intervention to Gain Muscle and Advance cancer treatment; T0, T1, T2, T3 time points for study assessments

Table 1 Participant timeline: Schedule of enrollment, interventions, and assessments

STUDY PERIOD	Enrollment	Baseline	Allocation	Post-allocation			Close-out
TIME POINT	Start of neoadjuvant chemotherapy	T0	T0	T1 (Week 6)	T2 (Week 12)	T3 (Week 18)	Completion of intervention
ENROLLMENT							
<i>Eligibility screening</i>	X						
<i>Informed consent</i>	X						
<i>Allocation</i>			X				
INTERVENTIONS							
<i>Exercise group</i>			X				
<i>Control group</i>			X				
ASSESSMENTS							
<i>Muscle mass</i>	X	X		X	X	X	
<i>Muscle strength</i>		X		X	X	X	
<i>Physical performance</i>		X		X	X	X	
<i>Physical activity</i>		X		X	X	X	
<i>Treatment-related adverse effects</i>		X		X	X	X	
<i>Cancer-specific and surgical outcomes</i>							X
<i>Cancer-related symptoms</i>		X		X	X	X	
<i>Quality of life and breast cancer-specific concerns</i>		X		X	X	X	
<i>Other measures (e.g., clinical data)</i>		X		X	X	X	
<i>Interview</i>							X

SPIRIT standard protocol items: recommendations for interventional trials; T0, T1, T2, T3 time points for study assessments

Randomization and blinding

Patients who fulfill the eligibility criteria and provide written informed consent are enrolled in this study and undergo a baseline assessment. Table 1 describes the

detailed schedule of enrollment, intervention duration, and assessments. After completing the baseline assessment, participants are randomly assigned either to a resistance exercise group or a usual care control group,

with an allocation ratio of 1:1. Randomization is conducted using a computer-generated random number to ensure allocation concealment. Any variable that identifies personal information is excluded from the randomization process, and the allocation number remains concealed from the treating physician, co-investigators, clinical research coordinator, and other research staff involved in recruitment. Due to the nature of the study design and the exercise intervention, concealing group assignment from the participants is not feasible. However, to minimize detection bias, data analysis is performed by a team member not involved in intervention delivery, using de-identified data to mask group allocation.

Intervention

The resistance exercise program is comprehensively designed as a prehabilitation intervention to mitigate muscle mass loss and improve physical function in patients undergoing neoadjuvant chemotherapy for breast cancer. A multidisciplinary team collaboratively developed the program. We adhered to the American College of Sports Medicine guidelines [17] during program development to ensure its safety and efficacy when tailored to participants' physical conditions. They then attend the supervised exercise program three times per week. Each session lasts 60 min and comprises a 5-minute warm-up, 50 min of resistance training, and a 5-minute cool-down.

This exercise program consists of two progressive phases, referred to as Version 1 and Version 2, which differ in progressive intensity and exercise complexity. Participants begin with Version 1 and move on to Version 2 as appropriate for their individual condition and abilities. Each exercise is performed for a set of 10 repetitions or 10 s, depending on the type of exercise, with a 10-second rest between exercises. Both versions are designed to progressively increase the number of sets (from one to three sets per session) over time. Exercise intensity gradually progresses using resistance bands based on each participant's physical condition and exercise adaptation. We selected a resistance band to provide safe muscular resistance during chemotherapy and allow participants to perform strength training independently at home. Resistance level is progressively increased through several strategies: adjusting the grip position on the elastic band (e.g., holding the band closer to where it is anchored), increasing movement complexity (e.g., from chair-assisted to free-standing squats), and adding light external loads (e.g., weights) when appropriate.

To mitigate potential challenges associated with treatment-related adverse effects, differing chemotherapy schedules, reduced immunity, and geographic accessibility, the program is offered in two supervised formats:

on-site supervised exercise sessions, and online supervised exercise sessions delivered via Zoom. The on-site sessions are provided one-on-one by a trainer who is an exercise expert at the Sports Science Center of Yonsei University, which is located next to the hospital. The expert trainer holds a graduate degree with a concentration in exercise medicine and has over 7 years of experience delivering supervised exercise interventions for clinical populations, including breast cancer patients; they are fully qualified to deliver exercise interventions.

The in-person exercise sessions are available to participants assigned to the exercise group who attend medical appointments, chemotherapy sessions, or examinations, as well as to those who live nearby or prefer in-person supervision. The online sessions allow participants to exercise from home, in small groups of at least one and up to four participants, while receiving real-time guidance from the expert trainer. These online sessions are suitable for participants experiencing treatment-related poor physical condition or those living in remote areas where long-distance travel to the hospital is challenging. We intentionally limit the online group size to a maximum of four to maintain the fidelity of exercise supervision and individualization, as real-time feedback is provided during each session.

Participants can choose their preferred mode of participation (on-site or online) based on their health status, treatment schedule (hospital visits), and personal circumstances. The program also offers flexibility, allowing participants to switch between formats weekly, as needed, to maintain the target of three supervised sessions per week. Depending on participants' neoadjuvant chemotherapy schedules, timing of surgery, or chemotherapy side effects, their individual assessment timelines can vary by ± 2 weeks. For example, the final study assessment may be conducted 1–2 weeks earlier than the scheduled 18-week timepoint for a participant with a shorter chemotherapy period or when surgery is planned prior to week 18, in order to align with their clinical treatment schedule.

To enhance intervention completion and accessibility, the exercise program provides several supportive strategies: To address potential technological barriers, the study provides tablets to participants who do not already have a suitable device for participating in the supervised online sessions during the intervention period. Participants also receive access to secure links to recorded exercise videos and a written exercise instruction manual, enabling them to easily follow the exercises at home. As part of the intervention and to ensure consistent implementation at home and on-site, all participants receive elastic bands prior to their first exercise session. Additionally, the study team sends weekly motivational text messages to participants, with reminders

and motivational information to encourage regular participation.

To ensure both intervention fidelity and participants' ability to successfully follow the exercise protocol across hybrid delivery formats, all participants in the exercise group receive standardized in-person instruction on proper exercise movement at baseline. All exercise sessions—both on-site and online—are conducted by the same trainer, who follows a standardized protocol to ensure intervention fidelity. During each session, the trainer monitors activity, records participant attendance and delivery mode (in-person or online), and ensures real-time feedback and correction. Participants are encouraged to wear form-fitting exercise clothing to facilitate form monitoring. Missed sessions due to medical appointments or reduced physical condition are rescheduled when possible. Protocol adherence data—including attendance rates, completion status, and format of delivery—are systematically tracked to account for variations in intervention exposure.

To ensure participant safety during the intervention, participants report their perceived physical condition and any discomfort or side effects at each assessment and each exercise session. This information guides the trainer in making real-time adjustments to ensure both safety and individualization of the exercise program. Additionally, program participation will be paused or discontinued in the event of any adverse event; clinically significant symptom, such as musculoskeletal disorder; or cancer treatment complication. Adverse events will be documented and classified by type and severity according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 [18]. Exercise sessions will be paused in cases of febrile neutropenia ($\geq$ grade 3), fatigue ($\geq$ grade 2), dizziness ($\geq$ grade 2), musculoskeletal disorders, or other severe symptoms. Exercise sessions will be reinitiated following symptom control or recovery; if necessary, the research team will consult with the participant's physician or oncologist prior to resuming the intervention. In cases of serious adverse events (e.g., life-threatening situations, prolonged hospitalization, persistent disability), study participation will be discontinued and the event reported to the institutional review board as soon as possible.

Control group participants receive their usual care during neoadjuvant chemotherapy, as prescribed by their clinic. In this trial, usual care refers to standard oncologic management without any structured or supervised exercise program provided by the research team. The control group along with the exercise group receives health education from the hospital's oncology team on chemotherapy-related symptom management, maintaining a balanced diet, and the importance of exercise before chemotherapy—which is standard practice. To ensure

methodological consistency [19], control group participants will receive outcome assessments at the same four time points as the intervention group, including assessments of body composition, physical performance, muscle strength, physical activity, and patient-reported symptoms. After this RCT is completed, the control group participants will be provided with a supervised exercise session with the study team's trainer in case they wish to engage.

Any participant in any group may choose to withdraw from the study at any stage.

Study outcomes

Participants are being assessed at four time points: baseline (pre-intervention), Week 6 and Week 12 during the intervention, and Week 18 (at completion of the intervention). Muscle mass, muscle strength, and physical performance are comprehensively assessed as key diagnostic components of primary sarcopenia, based on the Asian Working Group for Sarcopenia's 2019 updated consensus on sarcopenia diagnosis and treatment [20]. Given the characteristics of our study sample, the primary outcome is secondary sarcopenia, defined as muscle mass loss resulting from diseases such as cancer. Additional outcomes are muscle strength, physical performance, treatment-related adverse effects, cancer-related symptoms and QOL, which are assessed using validated questionnaires, measurement, and medical records.

Primary outcome

The primary outcome of this trial is muscle mass, which will be assessed through analysis of body composition at all four time points. Muscle mass is measured using bioelectrical impedance analysis with InBody. InBody provides segmental body composition data, including body fat mass, appendicular skeletal muscle mass (ASM), and lean balance across the trunk, arms, and legs. Based on the Asian Working Group for Sarcopenia guidelines for women, we are using a cutoff value of $<5.7 \text{ kg/m}^2$ as an indicator of sarcopenia [21].

To further validate the accuracy of muscle mass measurements, we will also analyze abdominal computed tomography (CT) scans of the third lumbar vertebra, which are routinely performed in clinical practice before and after neoadjuvant chemotherapy. The cross-sectional area of muscle (in cm^2) will be normalized to the square of the patient's height (in m^2), and the result will be reported as skeletal muscle index (SMI) (in cm^2/m^2) [22]. ASM is designated as the primary outcome due to its feasibility for repeated assessments, and SMI is included as an exploratory endpoint to complement these findings and inform future analyses on its clinical relevance and concordance with ASM.

Secondary outcomes

Muscle strength and physical performance Handgrip strength is measured for both arms with a digital hand dynamometer (TKK 5401, Japan). Before the test, participants receive standardized instructions regarding proper body position, which include avoiding bending the wrist and twisting the hands. Participants stand with their feet shoulder-width apart and hold the dynamometer, with their elbow fully extended, at their side. Measurements will be taken twice for each hand, and the highest value recorded for analysis. A low handgrip strength is defined as < 18.0 kg for women [21, 23].

For the 6-minute walk test, participants walk at a comfortable pace for 6 min along a 30-meter measuring tape placed on the floor, marked with cones. Given their potentially poor physical condition, participants will be advised that they can rest or stop on a fixed chair if they experience nausea, dizziness, fatigue, or shortness of breath. A 6-minute timer will run throughout the test, with periodic reminders of the remaining time. We will use a 6-minute walk test cutoff value of < 1.0 m/s [24, 25].

The chair stand test is conducted using a fixed chair, with the backrest secured against a wall to prevent movement. Before testing, participants will be instructed to sit slightly forward on the chair, with feet shoulder-width apart and arms crossed over the chest. After two to three practice trials, the participant will perform as many full sit-to-stand repetitions as possible within 30 s. For women, a score of ≤ 15 repetitions is considered predictive of sarcopenia [26, 27].

Self-reported physical activity Physical activity is assessed using the validated Korean version of the Global Physical Activity Questionnaire, which has demonstrated high reliability and validity in previous studies [28]. The Global Physical Activity Questionnaire assesses physical activity and sedentary behavior in three domains: work-related activity, travel to and from places, and leisure-time physical activity. It captures information on the intensity, frequency, and duration of physical activity, distinguishing between moderate- and vigorous-intensity activities. Additionally, it includes a measure of sedentary behavior, assessing the total time spent sitting per day [28].

Treatment-related adverse effects Adverse effects will be evaluated using the National Cancer Institute's CTCAE (V 5.0) [18]. Each adverse event will be classified and graded according to CTCAE severity guidelines. Participants' medical charts will be reviewed for chemotherapy completion or modifications and for occurrences of dose reductions, treatment delays, early treatment discontinuation, and other adverse events. Specifically, for hematologic toxicities, a research assistant will collect data from

routine complete blood count tests at four time points during intervention.

Cancer-specific clinical and surgical outcomes Breast cancer-specific outcomes and surgical outcomes will be evaluated using pathologic complete response, postoperative complications, length of hospitalization, readmission rates, and infection incidence. All data will be collected from participants' medical records following surgery and discharge.

Self-reported cancer-related symptoms and QOL Three cancer-related symptoms (fatigue, depression, sleep quality) and QOL are assessed at baseline, at Week 6 and Week 12, and at completion of the intervention, using psychometrically validated instruments. These instruments include the Center for Epidemiologic Studies Depression Scale (CES-D), the Functional Assessment of Chronic Illness Therapy–Fatigue Scale (FACIT–Fatigue), the Pittsburgh Sleep Quality Index (PSQI), and the Functional Assessment of Cancer Therapy–Breast (FACT–B).

Depression is assessed using the Korean version of the CES-D [29], which consists of 20 items in total. Each item is rated on a 4-point Likert scale, ranging from 0 to 3. A higher score indicates a higher level of depression. CES-D has good internal consistency, with a Cronbach's α of 0.89 in women undergoing treatment for breast cancer [30].

Fatigue is assessed using the Korean version of the FACIT–Fatigue [31], a validated instrument for measuring fatigue severity. The scale consists of 13 items, each rated on a 5-point Likert scale ranging from 0 (a lot) to 4 (not at all), with a possible range of 0–52. Lower scores indicate greater fatigue levels [32, 33]. This instrument has demonstrated high internal consistency, with a Cronbach's α of 0.93 in a Korean population [31].

Sleep quality is assessed using the Korean version of the PSQI [34], which consists of 19 items. Each item is rated on a 4-point Likert scale ranging from 0 (no difficulty) to 3 (severe difficulty), with higher scores indicating poorer sleep quality [35]. According to established guidelines for assessing sleep quality in cancer patients [36], a PSQI score of 8 or higher is considered indicative of poor sleep quality.

QOL and breast cancer-specific concerns are assessed using the Korean version of the FACT–B [37]. FACT–B consists of 37 items categorized into five subdomains: physical, social/family, emotional, functional well-being, and breast cancer-specific concerns [38]. Each item is rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (very much), with higher scores indicating better QOL.

Process evaluation

The RE-AIM framework [39], which stands for reach, effectiveness, adoption, implementation, and maintenance, will be used to evaluate the effects of this intervention on patients with breast cancer during neoadjuvant chemotherapy. We are using a qualitative approach to exploring the RE-AIM elements through interviews with participants in the exercise group [40]. Findings from the interviews will contribute to updating and improving this tailored exercise intervention for patients receiving neoadjuvant chemotherapy for cancer. In addition to qualitative interviews, feasibility assessment is collected throughout the intervention period. These data include session attendance, overall program completion, and compliance with exercise prescriptions. Attendance and compliance are documented by the expert trainer during each exercise session using a standardized tracking form. In this trial, compliance is defined as participation in at least 80% of the prescribed exercise sessions. Only participants meeting this threshold will be included in compliance-related analyses.

Sample size calculation

A power analysis was performed in G*Power 3.1.9.7 and RMASS to determine the sample size required for this trial [41]. The power analysis, which considered exercise and control groups that would have four repeated measures to assess changes in muscle mass over time, was conducted in collaboration with a senior statistician and co-investigator to ensure a robust estimate. The primary outcome for the sample size estimation was muscle mass, as it is the most relevant indicator for assessing sarcopenia. Due to limited available data on sarcopenia interventions among patients with breast cancer during neoadjuvant chemotherapy, we estimated the expected decrease in average muscle mass during neoadjuvant chemotherapy and the effect sizes related to exercise interventions based on several previous studies [42–44], which showed the effect sizes for exercise varying from 0.2 to 0.67.

Additionally, data from a previous RCT on sarcopenic obesity in older women, which compared the effects of elastic band resistance exercise on muscle mass and physical function [45], showed that the mean difference in muscle mass between exercise and control groups was 0.70 kg (95% confidence interval [CI], 0.12 to 1.28; $p < .05$) after 12 weeks of resistance exercise. This evidence indicates that even maintaining or slightly increasing muscle mass supports reduced treatment toxicity among cancer patients. Therefore, for this study, we conservatively selected an effect size of 0.20—classified as small by Cohen's criteria—to reflect realistic and clinically meaningful changes in muscle mass achievable during the limited duration of neoadjuvant chemotherapy.

The hybrid intervention model is fully supervised in real time, whether conducted in person or online, which will minimize variability in intervention fidelity. We applied a conservative approach to estimating the required sample size, and assumed a correlation of 0.5 for the repeated measure. By assuming an effect size of 0.20, a power of 80%, and an alpha level of 0.05, and incorporating a 30% allowance for attrition, we determined that a total of 46 participants (23 per group) would be sufficient to detect clinically meaningful changes in muscle mass.

Statistical analysis

All statistical analyses will be performed using Stata/IC 18.0 or IBM SPSS Statistics software. Descriptive analyses using means and standard deviations or frequencies and proportions will be used to summarize the demographic and clinical characteristics of the exercise and control groups. Baseline differences between the exercise and control groups will be examined using *t* tests or chi-square tests, as appropriate. Within-group comparisons to assess changes over time will be performed using a paired *t* test.

To analyze the effects of the exercise intervention, we will use mixed-effects models for repeated measures, including group (exercise vs. control), time (baseline, Week 6, Week 12, post-intervention), and their interaction, with a random intercept for each participant to account for between-subject variations. Clinically and theoretically relevant baseline covariates—including age, cancer stage, baseline body mass index, and the baseline value of the outcome variable—will be included as fixed effects control variables. Separate analyses will be conducted for each outcome measure to determine the outcome's specific intervention effects. For secondary outcomes, we will apply the Benjamini-Hochberg false discovery rate procedure to control for multiple comparisons. In case of missing values in covariates, we will consider using multiple imputation to address missing values in repeated measures. This decision will be based on the extent and pattern of missingness, and the imputation model will be constructed after reviewing the available data, including relevant time points and group assignments.

For all statistical analyses, $p < .05$ will be considered to be statistically significant.

Discussion

Sarcopenia has been recognized as a disease, with a diagnosis code included in the 2016 *International Classification of Diseases* [46]. Research on sarcopenia within populations with cancer has provided evidence of its prognostic significance related to treatment complications, poor functional performance, and poorer overall survival [4, 5, 47]. Considering the known impact of

preoperative sarcopenia on the entire cancer treatment process, further investigation into the effects of early interventions targeting sarcopenia within the context of prehabilitation is warranted. Early intervention may play a meaningful role in mitigating sarcopenia's negative impact across the cancer care continuum, particularly in the preoperative phase. In the context of neoadjuvant chemotherapy, a recent meta-analysis of high-quality studies found that patients with cancer have significant skeletal muscle loss during neoadjuvant chemotherapy, with a mean difference of $-1.13 \text{ cm}^2/\text{m}^2$ (95% CI, -1.65 to -0.62) in the SMI before and after neoadjuvant treatment [48]. This finding emphasizes the need to develop effective strategies to preserve skeletal muscle mass during neoadjuvant therapy.

Resistance exercise is a key approach to preserving muscle mass and reducing the risk of sarcopenia and associated poor clinical outcomes. Yet, according to a recent systematic review, few RCTs have assessed the effects of such an intervention specifically for patients with breast cancer undergoing neoadjuvant chemotherapy [15]. To fill this gap, this trial aims to evaluate the effects of resistance exercise on reducing the risk of sarcopenia and its impact on clinical outcomes in this population, thus offering valuable insights for both clinicians and researchers.

The potential impact is large: Breast cancer is the most common cancer diagnosis among women in most countries in the world [49]. Approximately one-third of patients with early breast cancer have sarcopenia [5], and this prevalence increases to over 40% when including patients with metastatic breast cancer [4, 6, 50]. From a prehabilitation perspective, should this trial demonstrate that exercise maintains or increases muscle mass during neoadjuvant chemotherapy, it may influence a wide range of clinical variables that are directly or indirectly associated with sarcopenia.

The potential outcomes of resistance exercise as a sarcopenia intervention are equally wide-ranging. Resistance exercise may be a safe, effective, and cost-effective strategy to allay that burden [51, 52] while enhancing therapeutic effect. A meta-analysis of RCTs in individuals with sarcopenia and frailty found that resistance exercise is effective in improving muscle strength and functional performance, increasing muscle mass, and reducing fat mass [53]. Furthermore, studies conducted across various cancer populations have shown that resistance exercise can both reduce the prevalence of sarcopenia and improve therapeutic outcomes [11, 54–56]. Hence, our resistance exercise intervention may provide beneficial physiological and psychological effects on outcomes such as fatigue, depression, poor sleep quality, and QOL, all of which are included as secondary outcomes for this trial.

In summary, this trial is expected to provide preliminary evidence that resistance exercise supports preserving muscle mass, reduces treatment-related adverse effects and cancer-related symptoms, and improves muscle strength, physical performance, and QOL in patients with breast cancer undergoing neoadjuvant chemotherapy. The findings may also contribute to developing patient-tailored prescriptions, such as exercise regimens with intensity, timing, duration, and frequency that are tailored to the specific needs of specific cancer populations during the preoperative phase. The resulting evidence and insights are likely to provide future directions for research and treatment, with important implications for people undergoing neoadjuvant chemotherapy.

Abbreviations

ASM	Appendicular skeletal muscle mass
CES-D	Center for epidemiologic studies depression scale
CI	Confidence interval
CRIS	Clinical research information service
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
FACIT-Fatigue	Functional assessment of chronic illness Therapy–fatigue scale
FACT-B	Functional assessment of cancer therapy–breast
PSQI	Pittsburgh sleep quality index
QOL	Quality of life
RCT	Randomized controlled trial
RE-AIM	Reach, effectiveness, adoption, implementation, and maintenance
SIGMA	Sarcopenia intervention to gain muscle and advance cancer treatment
SMI	skeletal muscle index

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Author contributions

MKJ, SP, SK, CP, and AD developed the initial trial concept. JJ, MJK, and MKJ further developed the trial concept and developed the exercise intervention. MKJ drafted the initial manuscript. All authors critically read and revised this manuscript. All authors approved the final version of this manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study is conducted in accordance with the World Medical Association Declaration of Helsinki. The protocol was approved by the institutional review board of the Yonsei University Health System's Severance Hospital (protocol ID 4-2023-1128). All participants gave informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹Mo-Im Kim Nursing Research Institute, Yonsei University College of Nursing, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea

²Division of Breast Surgery, Department of Surgery, Yonsei University College of Medicine, Seoul, Korea

³Department of Sport Industry Studies, Yonsei University, Seoul, Korea

⁴Exercise Medicine Center for Diabetes and Cancer Patients, Institute of Convergence Science, Yonsei University, Seoul, Korea

⁵Department of Population Health Nursing Science, Office of Research Facilitation, University of Illinois Chicago College of Nursing, Chicago, IL, USA

⁶Department of Biobehavioral Nursing Science, University of Illinois Chicago College of Nursing, Chicago, IL, USA

⁷University of Illinois Cancer Center, Chicago, IL, USA

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