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Exercise effects on lean body mass, muscle strength and functional performance in patients with metastatic breast cancer: the randomized controlled PREFERABLE-EFFECT study

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Abstract

Background Low skeletal muscle mass and strength are common in patients with metastatic breast cancer (mBC) and have been associated with treatment toxicities and poor prognosis. The PREFERABLE-EFFECT study (NCT04120298) investigated exercise effects on body composition, muscle strength, and functional performance (secondary outcomes) in patients with mBC.

Methods Patients with mBC (n = 357) were randomized to a 9-month supervised aerobic, resistance and balance exercise program (EX) or control. Body composition (subset n = 66), lower body strength (subset n = 126), handgrip strength and functional performance were assessed at baseline, 3 and 6 months. Changes between groups were compared using linear mixed models for repeated measures.

Results EX significantly increased whole body lean mass at 3 months (between-group difference = 0.79 kg, 95%CI [0.14; 1.44], effect size = 0.14), appendicular skeletal muscle mass at 3 months (0.60 kg, [0.22; 0.97], ES = 0.19) and 6 months (0.48kg, [0.09; 0.87], ES = 0.15), and lower body strength at 3 months (18.32 kg, [7.58; 29.06], ES = 0.44) and 6 months (34.22 kg, [23.0; 45.45], ES = 0.83) compared to control. EX also improved functional performance, including balance, compared to control.

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Conclusions The results support the promotion of supervised exercise for patients with mBC, with beneficial effects on skeletal muscle mass, muscle strength and physical performance.

Trial registration The PREFERABLE-EFFECT study was registered on ClinicalTrials.gov on October 9, 2019 (NCT04120298).

Keywords Metastatic breast cancer, Exercise, Body composition, Lean body mass, Skeletal muscle mass, Muscle strength

Background

Globally, breast cancer accounts for almost 24% of all cancer cases in females, making it the most commonly diagnosed cancer and the leading cause of cancer deaths in women worldwide [1]. In high and upper-middle income countries, approximately 5–10% of breast cancer cases are metastatic at initial diagnosis and 20–30% of patients with early stage breast cancer develop metastatic disease [2–5]. While survival rates have improved and more people are living longer with metastatic breast cancer (mBC), mBC is still considered incurable and patients often undergo several lines of systemic treatment [6, 7]. These treatments impact patients' quality of life and cause debilitating side-effects such as fatigue, nausea and pain. Combined with the underlying disease itself and physical inactivity, they also negatively affect body composition, muscle strength and functional performance by causing a depletion of skeletal muscle mass [8–11].

Addressing skeletal muscle mass loss among people with cancer has become an important focus in oncology research as low skeletal muscle mass has been associated with worse clinical outcomes [12]. Skeletal muscle is the principal component of lean body mass. Hence, changes in lean body mass are mostly driven by an increase or decrease in skeletal muscle mass. Therefore the terms lean body mass and skeletal muscle mass are often used interchangeable, although the actual measure is usually lean body mass, which also includes fluids and viscera.

Low levels of skeletal muscle mass, muscle strength and physical performance are common in patients with mBC undergoing systemic treatments [9, 13–16]. In patients with localized and advanced disease receiving chemotherapy, low lean body mass and sarcopenia have been associated with increased treatment-related toxicities, more frequent dose reductions as well as poorer treatment outcomes and survival [14, 17–19]. Further, declines in skeletal muscle mass and muscle strength are generally associated with poorer physical performance, functional health and quality of life [20]. Low muscle strength of the lower extremities is also commonly associated with balance issues, which can be further exacerbated by therapy-induced peripheral neuropathy and increase the risk of falls. Falls prevention is particularly important in patients with bone metastases, who have an increased risk of fracture. Yet, static and dynamic balance has been reported to be poor in 42–81% of patients with advanced breast cancer, depending on age and type of balance test [15]. Hence, there is a need to maintain or improve skeletal muscle mass, muscle strength and physical performance in patients with (metastatic) cancer.

There is strong evidence in the curative setting that exercise can improve skeletal muscle mass, muscle strength and physical performance in patients with breast cancer. For example, a meta-analysis including 17 studies and involving 1,743 breast cancer survivors showed a significant benefit of exercise compared with control on lean body mass (0.58 kg, 95% confidence interval (CI) = 0.27 to 0.88). Positive effects were shown for both resistance training and aerobic training, and for exercise training conducted during and after cancer treatment [21]. In addition to improvements in body composition, a meta-analysis in patients with localized or locally advanced breast cancer undergoing chemotherapy also showed beneficial effects of resistance training on lower and upper body muscle strength and overall physical performance [22]. However, evidence on the effects of exercise on skeletal muscle mass, muscle strength and physical performance in patients with mBC is insufficient or lacking, in part because they have often been excluded from exercise-oncology trials [23]. Importantly, these patients differ from patients treated with curative disease as they have more extensive disease, often receive continuous treatments and experience greater symptom burden [7, 8]. This can contribute to a greater risk of malnutrition, physical inactivity, systemic inflammation and other dysregulations, exacerbating muscle dysfunction [11, 24, 25]. The two published trials in patients with mBC (n = 49 and n = 40, respectively) that involved a physical activity intervention and included body composition measures, did not find changes in lean body mass [9, 26]. Further, studies that found exercise effects on strength and physical performance outcomes have been small or single arm [10, 26–28].

The multinational randomized controlled PREFERABLE-EFFECT study (NCT04120298) is the largest randomized controlled trial in patients with mBC to date. It showed that a 9-month supervised exercise program significantly reduces fatigue and improves quality of life in patients with mBC [29]. Here we report on a secondary aim of the PREFERABLE-EFFECT study, which was

to evaluate the effects of the exercise program on body composition (incl. lean body mass and fat mass), muscle strength and physical performance.

Methods

Design and participants

The study protocol and primary results of the study have been published previously [29, 30]. In brief, patients with mBC from five European countries (Germany, Spain, Netherlands, Poland, Sweden) and Australia were eligible to take part in this study if they were ≥ 18 years of age, had an ECOG performance status ≤ 2 and were able and willing to participate in the exercise program. Exclusion criteria included: unstable bone metastases as determined by the treating clinician; untreated symptomatic brain metastases; estimated life expectancy < 6 months; serious active infection; being too physically active (> 210 min/week of moderate-to-vigorous intensity exercise) or already engaging in an exercise program comparable to the study intervention; any contraindication for exercising; any circumstances that would impede adherence to study requirements or ability to give informed consent; or pregnancy.

After baseline testing, participants were randomized to either a 9-month supervised and individualized exercise program or the control group using a computerized blocked randomization procedure stratified by study centre and therapy line (1st/2nd vs 3rd or higher). Due to the nature of the intervention, participants, study staff and clinical personnel were not blinded to group assignment at the follow-up assessments.

Intervention

Participants in the exercise group received two supervised exercise sessions per week for the first 6 months. Thereafter, one supervised exercise session was replaced by an unsupervised exercise session for the last 3 months. Supervision was provided by a qualified exercise specialist. All supervised exercise sessions lasted approx. 60 min and included balance exercises (~ 5 min), moderate-to-high intensity aerobic training (~ 15 min), and resistance training (~ 35 min) (Table 1). In addition, participants in the exercise group were encouraged to be physically active for at least 30 min per day on all remaining days of the week, which was supported by an exercise app.

Participants in both groups received standard medical care as well as the current exercise guidelines for people diagnosed with cancer (in written form at one time point) and a physical activity tracker (i.e., a Fitbit Inspire HR).

Outcome measures

At baseline, 3 months and 6 months, participants visited the study centre in person for body composition, physical fitness and performance assessments (secondary outcomes). Anthropometric data (i.e., body weight and height) were measured in light clothing without shoes. Body mass index (BMI) was assessed in all participants using the formula: BMI = weight (kg) / height^2 (m^2). In a subset of 66 participants, whole body and regional (arm and leg) lean mass and whole body fat (percentage) were derived from whole body dual-energy X-ray absorptiometry (DXA) scans using a Lunar iDXA ME scanner (GE Healthcare, Chicago, Illinois, USA). Scans were performed at two sites that had access to a DXA machine (Australia and Sweden) and based on standard procedures. Participants were instructed not to exercise vigorously or drink alcohol in the 24 h prior the DXA scan and to abstain from smoking, food and drinks in the 2 h prior to the scan. Appendicular skeletal muscle mass was calculated by summing the muscle mass of the four limbs. Appendicular skeletal muscle mass was indexed to height squared to determine the skeletal muscle mass index [31].

Lower body strength was assessed via hypothetical 1-repetition maximum (h1-RM) test on the leg press,

Table 1 The PREFERABLE EFFECT exercise program[a]

Week	Balance training (5 min)	Aerobic training (15 min)	Resistance training (35 min)
1–3	Variety of different balance tasks (e.g., tandem stand on a balance pad)	Moderate-intensity continuous training: 15 min at 50–60% of W_{peak}	Six exercises. Three sets per exercise[c]. The intensity was periodized, alternating between 10 and 12 reps with 70–75% of h1-RM and 6 and 8 reps with 80–85% of h1-RM every month
4–14		Interval training[b]: 8 × 1 min at W_{peak}, alternated with 1 min active rest at 30W	
15–25		Interval training[b]: 3 × 3 min at 70% of W_{peak}, alternated with 2 min active rest at 30W	
26–36		Interval training[b]: 8 × 30 s at 65% of MSEC, alternated with 1 min active rest at 30% of MSEC	

Abb. h1-RM, hypothetical 1-repetition maximum; MSEC, Maximal Short Exercise Capacity derived from a Steep Ramp Test; W_{peak}, peak Wattage estimated from a Steep Ramp Test

[a]The exercise program included two supervised, multimodal exercise sessions of 1 h per week for the first six months. Thereafter, one supervised session was replaced by one unsupervised session for three months

[b]All interval sessions started with a 3-min warm-up at 30 Watt and concluded with a 3-min cool-down. Interval training was introduced to provide some variation for participants, whilst ensuring new training stimuli are introduced over time

[c]Main exercises included the leg press, leg curl, leg extension, chest press, seated row, lat pulldown. Variations of these exercises were allowed and depended on the exercise modality

where deemed safe (i.e., in participants who did not have bone metastases in the body regions that were loaded). The test was not conducted in one centre due to logistical issues. While machines used for lower body muscle strength measures differed between centres, they did not within centres. For the h1-RM test, the highest weight that was successfully lifted for 12 repetitions and the corresponding h1-RM were recorded [28]. Handgrip strength was assessed in all participants using a handgrip dynamometer (hydraulic Jamar®). The test was conducted seated with elbows by the side and flexed to the right angle (70°), and a neutral wrist position. Three measurements were performed for each hand, and the best attempt of each hand was recorded.

The 5 times sit-to-stand test was used to assess functional strength of the lower limbs unless participants had spinal or pelvis metastases that made the test potentially unsafe to conduct, as determined by the assessor. The time (in seconds) required to perform 5 rises from a chair to an upright position as fast as possible was recorded [32]. The Short-Form Fullerton Advanced Balance (SF-FAB) scale was used to assess static and dynamic balance during four tasks, including the tandem walk, standing on one leg, standing on a foam pad with eyes closed, and stepping up onto and over a 6-inch bench. SF-FAB tasks are rated on a 0- (unable to complete task) to 4-point (independent task completion) ordinal scale with higher scores indicating better balance [33].

Statistical analysis

Descriptive statistics were used to characterize the study population at baseline. Changes from baseline to 3 and 6 months (i.e., primary time point) were compared between groups using mixed models for repeated measures. Models were adjusted for the baseline value of the outcome and stratification factors (i.e., study centre and therapy line). All analyses were performed according to the intention-to-treat principle and included all participants for whom a baseline measure and data from at least one additional time point were available. Missing outcome values were considered missing at random and dealt with using linear mixed-effect models. We report two-sided *p*-values. Cohen's standardized effect sizes (ES) were calculated by dividing the adjusted between-group differences of the 3-month and 6-month post-intervention means by the pooled standard deviation at baseline. All statistical analyses were performed in R (Version 4.3.2) using the tidyverse (data wrangling), lme4 and emmeans (statistics) and ggplot2 (visualisation) packages.

Results

In total, 357 patients were included in the PREFERABLE-EFFECT study, 178 in the exercise group and 179 in the control group. The baseline characteristics of all included participants as well as the subset of participants who completed the DXA scan (n = 66) and h-1RM leg press (n = 126) are outlined in Table 2. On average, participants were 55.4 ± 11.1 years of age and had a BMI of 26.2 ± 5.2kg/m^2. Most participants were on their 1st/2nd treatment line (74.8%) and had bone metastases (67.2%).

In the subset of participants who underwent DXA scans and those who completed h1-RM tests, some differences in sociodemographic and clinical characteristics between the exercise and control groups were observed. Regarding the subset who completed the DXA scans, the exercise group was slightly younger, had a higher percentage of participants who were still employed and had never smoked, compared to the control group. The exercise group also had a shorter time since mBC diagnosis, and a higher percentage of participants who were currently receiving chemotherapy. For the subset of participants who completed the h-1RM testing, the exercise group had a slightly lower percentage of patients with triple negative breast cancer.

As previously reported, the overall dropout rate from the study was 12.3% at 3 months and 18.5% at 6 months. The median attendance rate of the supervised exercise sessions was 77% and the median adherence rate with the exercise protocol was 70% for the balance component, 59–83% for the aerobic components and 63–100% for the resistance components. Two exercise-related serious adverse events (SAEs) were reported, a wrist fracture and a sacral stress fracture; however, neither was associated with bone metastases [29].

The following results are based on the model-based, between-group differences including participants for whom the outcome was available at baseline and at least one other time points. The percentage changes from baseline to 3 and 6 months are included in Additional File 1. The mean values (± SD) and number of participants who completed the assessments at each respective time point are provided in Additional File 2.

Body composition and BMI

The exercise program increased whole body lean mass, with statistically significant between-group differences at 3 months (between-group difference = 0.79kg, 95%CI [0.14; 1.44], effect size = 0.14) but not 6 months (0.32kg, [− 0.35; 0.99], ES = 0.06) (Table 3). Significant differences between groups at both 3 and 6 months were observed for appendicular skeletal muscle mass ((0.60kg, [0.22; 0.97], ES = 0.19) and (0.48kg, [0.09; 0.87], ES = 0.15), respectively) and skeletal muscle mass index ((0.22kg/m^2, [0.08; 0.36], ES = 0.24) and (0.18kg/m2, [0.04; 0.33],

Table 2 Baseline characteristics of the patients with metastatic breast cancer in the PREFERABLE EFFECT study

	Complete study population		Subset: DXA Scan present		Subset: h1-RM present	
	EX (*n* = 178)	**CON (*n* = 179)**	**EX (*n* = 32)**	**CON (*n* = 34)**	**EX (*n* = 62)**	**CON (*n* = 64)**
Sociodemographic characteristics						
Age, years	54.9 (11.6)	55.9 (10.7)	50.2 (10.9)	58.5 (12.1)	51.5 (11.3)	55.2 (11.0)
Sex						
Female	177 (99.4)	178 (99.4)	32 (100.0)	34 (100.0)	62 (100.0)	64 (100.0)
Male	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Marital status						
Married	121 (68.0)	117 (65.4)	19 (59.4)	20 (58.8)	41 (66.1)	43 (67.2)
Living alone	57 (32.0)	62 (34.6)	13 (40.6)	14 (41.2)	21 (33.9)	21 (32.8)
Education						
No or basic education	7 (3.9)	5 (2.8)	2 (6.3)	0 (0.0)	1 (1.6)	3 (4.7)
Middle education	35 (19.7)	40 (22.3)	1 (3.1)	4 (11.8)	9 (14.5)	16 (25.0)
Higher education	37 (20.8)	43 (42.0)	2 (6.3)	7 (20.6)	11 (17.7)	17 (26.6)
Academic education	99 (55.6)	90 (50.3)	27 (84.4)	23 (67.6)	41 (66.1)	28 (43.8)
Other	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Body Mass Index, kg/m^2	25.9 (5.1)	26.6 (5.3)	26.5 (5.5)	24.4 (4.3)	25.3 (4.7)	26.6 (5.3)
Smoking status						
Never smoked	93 (52.2)	92 (51.4)	24 (75.0)	18 (52.9)	32 (51.6)	36 (56.3)
Former smoker	76 (42.7)	67 (37.4)	7 (21.9)	14 (41.2)	27 (43.5)	22 (34.4)
Current smoker	9 (5.1)	20 (11.2)	1 (3.1)	2 (5.9)	3 (4.8)	6 (9.4)
Work status						
Employed	83 (46.6)	77 (43.0)	24 (75.0)	15 (44.1)	35 (56.5)	30 (46.9)
On sick leave	*34 (41.0)*	*43 (55.8)*	*8 (33.3)*	*7 (46.7)*	*12 (34.3)*	*13 (43.3)*
Permanently disabled	31 (17.4)	33 (18.4)	0 (0.0)	1 (2.9)	7 (11.3)	8 (12.5)
Unemployed	2 (1.1)	3 (1.7)	0 (0.0)	2 (5.9)	1 (1.6)	2 (3.1)
Retired	38 (21.3)	34 (19.0)	4 (12.5)	10 (29.4)	11 (17.7)	10 (15.6)
Home duties	12 (6.7)	14 (7.8)	1 (3.1)	0 (0.0)	2 (3.2)	8 (12.5)
Other[a]	11 (6.2)	28 (15.6)	3 (9.4)	6 (17.6)	5 (8.1)	6 (9.4)
Physical activity, median (IQR) min/week						
Aerobic exercise						
Vigorous intensity	*0 (0–0)*	*0 (0–0)*	*0 (0–1)*	*0 (0–0)*	*0 (0–0)*	*0 (0–0)*
Moderate intensity	*0 (0–58)*	*0 (0–60)*	*0.5 (0–1)*	*1 (0–33)*	*0 (0–49)*	*0 (0–33)*
Light intensity	*30 (0–150)*	*15 (0–132)*	*1 (0–90)*	*1 (0–146)*	*8 (0–120)*	*30 (0–150)*
Resistance exercises	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–1)	0 (0–0)	0 (0–0)
Clinical characteristics						
Disease presentation at the time of mBC diagnosis						
De-novo stage IV	58 (32.6)	59 (33.0)	9 (28.1)	8 (23.5)	22 (35.5)	22 (34.4)
Recurrent disease	116 (65.2)	111 (62.0)	22 (68.8)	24 (70.6)	40 (64.5)	39 (60.9)
Time since mBC diagnosis, median (IQR) months	23.1 (8.1–54.3)	22.5 (9.1–49.9)	36.8 (11.8–68.6)	53.5 (11.8–71.4)	17.3 (4.5–40.3)	21.0 (8.5–38.9)
Line of treatment						
1st line	98 (55.1)	91 (50.8)	12 (37.5)	10 (29.4)	42 (67.7)	38 (59.4)
2nd line	36 (20.2)	42 (23.5)	8 (25.0)	9 (26.5)	9 (14.5)	16 (25.0)
3rd or higher	44 (24.7)	46 (24.6)	12 (37.5)	13 (38.2)	10 (16.1)	8 (12.5)
Tumor subtype						
Triple negative	13 (7.3)	22 (12.3)	3 (9.4)	4 (11.8)	2 (3.2)	9 (14.1)
HER2 positive	42 (23.6)	41 (22.9)	7 (21.9)	11 (32.4)	22 (35.5)	20 (31.3)
HER2 negative and hormone receptor positive	108 (60.7)	106 (59.2)	17 (53.1)	14 (41.2)	35 (56.5)	31 (48.4)
Current treatment						
Endocrine treatment	94 (52.8)	93 (52.0)	12 (37.5)	12 (35.3)	31 (50.0)	34 (53.1)
Targeted therapy[b]	105 (59.0)	99 (55.3)	15 (46.9)	16 (47.1)	38 (61.3)	40 (62.5)
Chemotherapy	48 (27.0)	43 (24.0)	15 (46.9)	7 (20.6)	17 (27.4)	11 (17.2)
Bone-modifying agent	83 (46.6)	83 (46.4)	13 (40.6)	10 (29.4)	19 (30.6)	24 (37.5)

Table 2 (continued)

	Complete study population		Subset: DXA Scan present		Subset: h1-RM present	
	EX (*n* = 178)	CON (*n* = 179)	EX (*n* = 32)	CON (*n* = 34)	EX (*n* = 62)	CON (*n* = 64)
Prior cancer treatment						
Primary surgery	120 (67.4)	120 (67.0)	28 (87.5)	26 (76.5)	44 (71.0)	46 (71.9)
Surgery of metastases	21 (11.8)	17 (9.5)	0 (0.0)	2 (5.9)	9 (14.5)	8 (12.5)
Chemotherapy	115 (64.6)	114 (64.0)	24 (75.0)	22 (64.7)	43 (69.4)	46 (71.9)
Endocrine treatment	96 (53.9)	96 (53.6)	16 (50.0)	15 (44.1)	29 (46.8)	28 (43.8)
Radiotherapy	111 (62.4)	95 (53.1)	22 (68.8)	17 (50.0)	36 (58.1)	32 (50.0)
Location of metastases						
Bone metastases	116 (65.2)	124 (69.3)	18 (56.3)	20 (58.8)	29 (46.8)	29 (45.3)
Lung metastases	49 (27.5)	46 (25.7)	9 (28.1)	11 (32.4)	16 (25.8)	27 (42.2)
Liver metastases	67 (37.6)	57 (31.8)	7 (21.9)	7 (20.6)	23 (37.1)	15 (23.4)
Lymph node metastases	68 (38.2)	70 (39.1)	10 (31.3)	15 (44.1)	23 (37.1)	24 (37.5)
Comorbidities						
No comorbidities	104 (58.4)	104 (58.4)	26 (81.3)	28 (87.5)	42 (67.7)	39 (60.9)
1 comorbidity	37 (20.8)	33 (18.4)	4 (12.5)	3 (8.8)	11 (17.7)	13 (20.3)
>1 comorbidity	37 (20.8)	42 (23.5)	2 (6.3)	3 (8.8)	9 (14.5)	12 (18.8)

Continuous characteristics are presented as mean (± SD), whereas categorical characteristics are presented as n (%), unless stated otherwise.

Abb. CON, control group; DXA, dual-energy X-ray absorptiometry; EX, exercise group; mBC, metastatic breast cancer

[a]Includes caregiver, working on projects when health status allows.

[b]Includes both biologic agents, such as cyclin-dependent kinase 4 (CDK4) and CDK6 inhibitors, as well as human epidermal growth factor receptor 2 (HER2)-targeted therapy.

ES = 0.20), respectively), as well as leg lean mass and arm lean mass independently (Table 3 and Fig. 1), in favor of the exercise group. No significant differences between groups were observed for whole body fat percentage (– 0.28% [– 1.63; 1.08], ES = 0.04 at 6-months) or BMI (0.02 [– 0.22; 0.25], ES = 0.00 at 6-months) (Table 3).

Muscle strength

The exercise program improved lower body strength assessed via h1-RM leg press compared to control at 3 months (18.32kg, [7.58; 29.06], ES = 0.44) and 6 months (34.22kg, [23.0; 45.45], ES = 0.83) (Table 3). No significant differences were observed between groups for handgrip strength at either time point, although handgrip strength improved significantly within the exercise group from baseline to 6 months (Table 3).

Physical performance

Changes in physical performance outcomes are presented in Table 3. A statistically significant difference between groups was observed for functional strength of the lower limbs assessed via 5 times sit-to-stand test at 6 months (– 1.53s, [– 2.11; – 0.94], ES = 0.41) but not 3 months (– 0.52s, [– 1.10; 0.06], ES = 0.14). The exercise program significantly improved static and dynamic balance tasks of the SF-FAB, leading to significant between-group differences at 3 months (0.44, [0.12; 0.76], ES = 0.19) and 6 months (0.74, [0.41; 1.1], ES = 0.31).

Discussion

The PREFERABLE-EFFECT study was the first large-scale randomized controlled trial to demonstrate beneficial effects of supervised exercise on fatigue, quality of life (primary outcomes) and a number of other patient-reported health outcomes, such as pain, dyspnea and sexual health, in patients with mBC [29, 34]. Further a cost-utility analysis demonstrated that the intervention is cost-effective [35]. Our analysis of the study's secondary outcomes, body composition, muscle strength and physical performance, provides novel evidence that a supervised combined aerobic and resistance exercise program can also improve these objectively assessed outcomes in patients with mBC. Thereby, we address a significant research gap—the lack of robust evidence in patients with metastatic (breast) cancer—that has been highlighted in national and international exercise guidelines for patients with cancer [36–38] and in recent systematic reviews [23, 39].

Low skeletal muscle mass has been associated with increased treatment-related toxicities, increased dose reductions as well as poorer treatment outcomes and survival in patients with breast cancer [14, 17–19]. Hence preserving or even improving muscle mass during cancer treatment has become an important aim in exercise-oncology interventions. Yet, whether this is achievable in patients with mBC during ongoing treatment has been underexplored. Our study was able to demonstrate a significant increase in whole body lean mass after 3 months

Table 3 Effects of supervised exercise on body composition, muscle strength and physical performance outcomes in patients with metastatic breast cancer in the PREFERABLE EFFECT study

		Baseline	Within-group differences		Between-group differences			
			Baseline to 3 months	Baseline to 6 months	At 3 months		At 6 months	
		Mean (± SD)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	ES	Mean (95% CI)	ES
Weight (kg)	EX	71.13 (15.38)	- 0.13 (- 0.61–0.34)	- 0.29 (- 0.76–0.18)	- 0.01 (- 0.63–0.62)	0.00	0.02 (- 0.60–0.65)	0.00
	CON	72.45 (14.34)	- 0.18 (- 0.68–0.32)	- 0.33 (- 0.83–0.18)	Reference		Reference	
BMI (kg/m^2)	EX	25.88 (5.09)	- 0.05 (- 0.22–0.13)	- 0.10 (- 0.28–0.08)	0.00 (- 0.23–0.24)	0.00	0.02 (- 0.22–0.25)	0.00
	CON	26.57 (5.28)	- 0.07 (- 0.26–0.11)	- 0.13 (- 0.31–0.06)	Reference		Reference	
Whole Body Lean Mass (kg)	EX	40.93 (5.52)	0.45 (- 0.00–0.90)	0.32 (- 0.15–0.80)	**0.79 (0.14–1.44)***	0.14	0.32 (- 0.35–0.99)	0.06
	CON	39.67 (5.51)	- 0.32 (- 0.89–0.25)	- 0.03 (- 0.61–0.55)	Reference		Reference	
Arm Lean Mass (kg)	EX	4.32 (0.83)	0.03 (- 0.06–0.11)	0.01 (- 0.08–0.11)	**0.15 (0.02–0.27)***	0.19	**0.13 (0.00–0.26)***	0.16
	CON	4.27 (0.75)	**- 0.13 (- 0.24–- 0.01)***	**- 0.12 (- 0.23–0.00)***	Reference		Reference	
Leg Lean Mass (kg)	EX	14.25 (2.66)	**0.24 (0.00–0.47)***	0.19 (- 0.06–0.43)	**0.45 (0.15–0.75)****	0.18	**0.35 (0.04–0.66)***	0.14
	CON	13.32 (2.23)	- 0.21 (- 0.50–0.08)	- 0.17 (- 0.46–0.13)	Reference		Reference	
Appendicular Skeletal Muscle Mass (kg)	EX	18.57 (3.42)	0.26 (- 0.02–0.54)	0.20 (- 0.10–0.49)	**0.60 (0.22–0.97)****	0.19	**0.48 (0.09–0.87)***	0.15
	CON	17.59 (2.87)	- 0.34 (- 0.70–0.01)	- 0.28 (- 0.64–0.08)	Reference		Reference	
Skeletal Muscle Mass Index (kg/m^2)	EX	6.83 (1.01)	0.09 (- 0.02–0.20)	0.07 (- 0.04–0.18)	**0.22 (0.08–0.36)****	0.24	**0.18 (0.04–0.33)***	0.20
	CON	6.41 (0.83)	- 0.13 (- 0.26–0.01)	- 0.11 (- 0.24–0.03)	Reference		Reference	
Whole Body Fat (%)	EX	38.70 (8.00)	- 0.53 (- 1.43–0.37)	- 0.30 (- 1.24–0.65)	-0.76 (- 2.10–0.58)	0.10	- 0.28 (- 1.63–1.08)	0.04
	CON	36.79 (7.09)	- 0.04 (- 1.17–1.09)	- 0.14 (- 1.29–1.01)	Reference		Reference	
Hypothetical 1-RM (kg)	EX	102.92 (41.05)	**31.38 (23.29–39.46)****	**44.68 (36.27–53.09)****	**18.32 (7.58–29.06)****	0.44	**34.22 (23.00–45.45)****	0.83
	CON	96.33 (41.78)	**13.35 (3.65–23.05)****	**10.67 (0.67–20.68)***	Reference		Reference	
5-times Sit-to-Stand Test (s)	EX	10.42 (3.75)	**- 1.39 (- 1.93–-0.85)****	**- 1.20 (- 2.54–-1.45)****	- 0.52 (- 1.10–0.06)	0.14	**- 1.53 (- 2.11–-0.94)****	0.41
	CON	10.74 (3.68)	**- 0.88 (-1.45–-0.31)****	- 0.48 (- 1.06–0.10)	Reference		Reference	
SF-FAB	EX	14.90 (2.22)	**0.46 (0.15–0.76)****	**0.55 (0.24–0.86)****	**0.44 (0.12–0.76)****	0.19	**0.74 (0.41–1.1)****	0.31
	CON	14.50 (2.48)	0.12 (- 0.21–0.44)	- 0.11 (- 0.44–0.22)	Reference		Reference	
Handgrip Strength, right (kg)	EX	27.53 (6.74)	0.47 (- 0.25–1.19)	**1.07 (0.34–1.80)****	0.23 (- 0.67–1.13)	0.03	0.69 (- 0.23–1.60)	0.10
	CON	27.79 (6.77)	0.22 (- 0.44–1.03)	0.28 (- 0.51–0.97)	Reference		Reference	
Handgrip Strength, left (kg)	EX	26.55 (6.06)	0.36 (- 0.25–1.19)	**0.76 (0.34–1.80)***	0.00 (- 0.84–0.85)	0.00	0.47 (- 0.39–1.32)	0.07
	CON	26.42 (6.48)	0.30 (- 0.54–0.98)	0.23 (- 0.49–1.05)	Reference		Reference	

Models were adjusted for the baseline value of the outcome and stratification factors (i.e., center and therapy line) and included participants for whom the outcome was observed at two or more time points

Significant within-group and between-group differences are in bold (* $p < 0.05$; ** $p < 0.01$)

Abb. BMI, body mass index; CON, control group; ES, effect size; EX, exercise group; SF-FAB: Short-Form Fullerton Balance Scale; 1-RM, one-repetition maximum

of exercise training in the exercise group compared to the control group. The difference between groups of 0.79kg is comparable to the difference observed in studies in the curative setting that have included a resistance exercise component (0.83kg) [21]. Notably, the difference between groups becomes even more apparent and is also significant at 6 months for appendicular skeletal muscle mass, skeletal muscle mass index and leg lean mass and arm lean mass independently, two body regions that host major muscle groups that were targeted during the exercise intervention. The significant differences in lean mass between groups at 3 and 6 months were primarily driven by a significant decline in arm lean mass within the control group and a significant increase in leg lean mass within the exercise group.

Our findings are novel as previous, smaller scale studies with less supervision have been unable to detect exercise effects on lean body mass in patients with mBC. A randomized controlled lifestyle trial in patients with mBC (n = 40) found no effects on lean body mass as

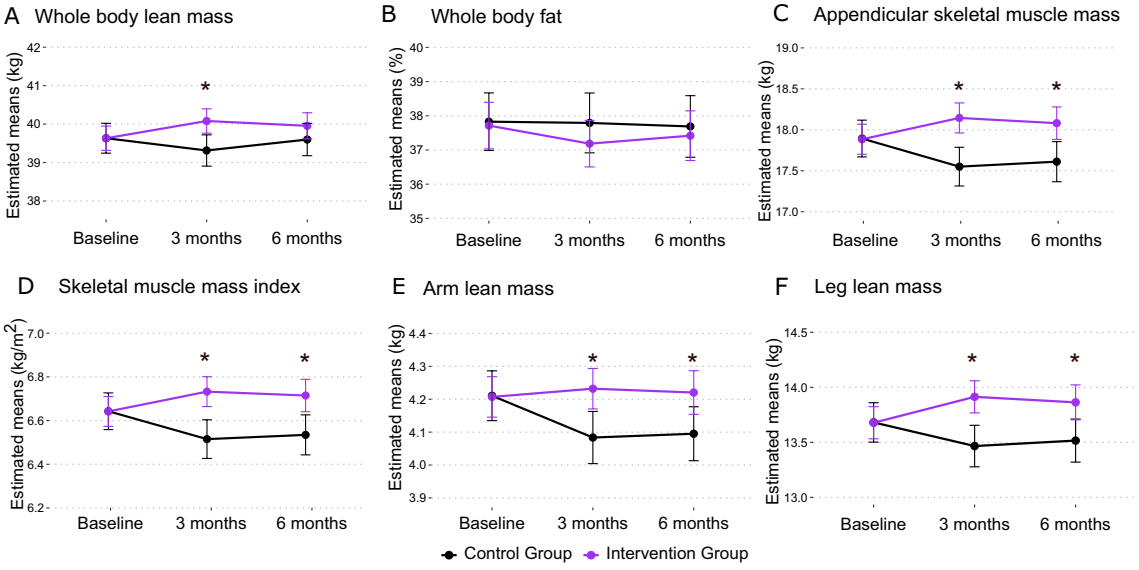

Fig. 1 Changes in body composition outcomes in a subset of patients with mBC included in the PREFERABLE-EFFECT exercise intervention. Estimated marginal means for whole body lean mass (**A**), whole body fat (**B**), appendicular skeletal muscle mass (**C**), appendicular skeletal mass index (**D**), arm lean mass (**E**) and leg lean mass (**F**) derived by DXA scan. Bars represent the 95% confidence interval and * represent significant between-group differences

measured by DXA scan [26]. The trial involved a 12-week multimodal intervention to promote adoption of physical activity (150 min of moderate intensity physical activity and 2 sessions of resistance training per week) and nutrition guidelines. In contrast to our trial, in-person support was limited to four supervised exercise sessions followed by weekly telephone sessions. Similarly, a single-arm feasibility study found that a 6-month unsupervised physical activity intervention with activity tracker maintained but did not improve lean body mass, calculated based on skeletal muscle area at L3 following computed tomography (CT) scan in 49 patients with mBC [9]. Patients in this study received a weekly goal of steps per day and weekly feedback by a physical activity instructor, but no supervised intervention and no resistance exercise advice. While aerobic exercise has also shown to improve lean body mass in people with breast cancer treated with curative intent, effects are larger for resistance exercise. Resistance exercise has been deemed the most effective intervention to improve lean body mass in women diagnosed with or at high-risk of breast cancer [21, 40]. Further, supervised exercise has been established to provide greater benefits than unsupervised exercise interventions for a range of health outcomes [41–43].

Importantly, we found no difference between groups in BMI. This underscores the emergent recognition that BMI can mask changes in body composition and hence is not a reliable marker for determining body composition [14]. Shachar et al. and others found, that BMI and body surface area (BSA), commonly used to dose chemotherapy, were not predictive of treatment-related toxicities in patients with mBC. However, sarcopenia and skeletal muscle measures, such as lean body mass and skeletal muscle gauge, were associated with clinical outcomes, such as toxicities, hospitalisations and time to treatment failure [14, 17]. While skeletal muscle measures appear to be clinically relevant factors that should possibly be considered when determining treatment doses and assessing the likelihood of toxicities, further research on the prognostic value of body composition measures, including lean mass and fat mass, in the metastatic setting is required, as disease and treatment types may play a role [16, 44].

Apart from improvements in lean body mass, we found beneficial effects of a combined aerobic and resistance training program on muscle strength. While both groups experienced improvements in lower body strength assessed via h1-RM leg press and the 5 times sit-to-stand test, the exercise program led to a greater improvement compared to control, with significant between-group differences at 6 months. This is in line with a meta-analysis on the effects of exercise in patients with advanced cancer undergoing palliative treatment (SMD = 0.48 (95% CI = 0.12, 0.84) [45] and has also been observed in a few small or single arm studies in patients with mBC [10, 27, 28]. Two single-arm studies that assessed a 3- and 6 month intervention aimed at increasing physical activity levels with weekly feedback [27] or weekly cognitive and behavioural skill focussed sessions [28], found improvements in isometric quadriceps strength (22%) and the 30 s sit-to-stand test (27.5%), respectively. Further, one small randomized controlled trial (n = 14) evaluating an 8-week aerobic (unsupervised) and resistance (supervised) exercise intervention also showed

improvements in lower limb strength, although with a smaller between group difference of 10.3 kg and assessed via back-leg dynamometer [10]. Importantly, a recent systematic review and meta-analysis found that, in studies with a high percentage of patients with advanced cancer, those with greater muscle strength had a significantly (23–46%) reduced risk of all-cause mortality compared to those patients with lower muscle strength [46]. Further, higher levels of physical function may also be associated with a reduction in overall-mortality in cancer survivors [47].

While we found significant improvements in handgrip strength within the exercise group, we did not observe a significant difference between groups. Delrieu et al. found no improvement in handgrip strength following a 6-month unsupervised physical activity intervention (without resistance training) [26]. However, Sheean et al. found a significant difference between groups in handgrip strength in favour of the intervention group, which received a 12-week multimodal intervention (including both aerobic and resistance training) to promote adoption of physical activity and nutrition guidelines [26, 27]. During adjuvant chemotherapy for breast cancer and in patients with sarcopenia, resistance training has also been shown to improve handgrip strength [22, 48]. Importantly, with an average handgrip strength of approx. 27 kg at baseline, and with a skeletal muscle mass index of approx. 6.6 kg/m^2, participants in our study exceeded the cut-off point for sarcopenia (< 16 kg or < 5.5 kg/m^2 in women, respectively) [24]. Further, it is important to consider the interventions that are offered and the muscles that are targeted when interpreting handgrip strength results (i.e., training specificity). Although the PREFERABLE-EFFECT intervention included upper body resistance training, it did not include exercises that specifically targeted the finger flexors. Nevertheless, the within-group changes in handgrip strength are consistent with the overall picture of improved muscle strength.

Balance is an important physical performance outcome for patients with mBC, particularly for those with bone metastases or treatment-induced osteoporosis where falls prevention is key to reducing the risk of fractures. However, the effects of exercise on balance have been understudied in this population. In the curative setting, and in particular in patients with chemotherapy-induced peripheral neuropathy, exercise that involves balance training has shown to improve stability [49]. In patients with metastatic colorectal cancer (n = 30), an eight-week supervised multimodal exercise program, including aerobic, resistance and balance training (2 × /week for 60 min) revealed no improvements in simple static and dynamic balance compared to control. However, significant differences between groups were observed for advanced static balance (including more challenging and complex tasks) [50]. Importantly, we had originally intended to use the Short Physical Performance Battery to assess physical performance [51]. However, we observed ceiling effects in our first participants in the simpler balance tasks. This led us to use the SF-FAB instead, which includes more challenging balance tasks. We found significant differences in balance assessed with the SF-FAB between groups at 3 and 6 months, despite only including approx. 5 min of balance exercises per session. This suggests that other components of the exercise program, such as the resistance training, may have contributed to these results. This is in line with a systematic review that found that a range of different exercise interventions can improve balance in women treated with breast cancer [52].

We attribute the beneficial effects that we observed on lean body mass, muscle strength and physical performance, but also on our previously reported primary outcomes, fatigue and quality of life, to the tailored nature of the exercise prescription (moderate-to-high intensity aerobic and resistance exercise), the duration of the program and the level of supervision. Supervision by a qualified exercise specialist is not only important to maximize the benefits of exercise, keeping in mind that the control group also received written exercise advice and a Fitbit activity tracker, but also to ensure safety. Skeletal complications (e.g., bone pain, pathological fractures, spinal cord compressions) related to bone metastases are a significant concern in this population, which has historically led to the exclusion of patients with bone metastases from exercise trials. Further, patients themselves have reported fear of falls or injury as barriers to exercise participation, which may result in patients exercising at lower intensities and avoiding resistance exercise when no supervision is provided [53]. In the PREFERABLE-EFFECT study, we sought medical clearance from the treating physicians and participants were asked before and after each exercise session if they experienced any new or increase in pain or symptoms. This close monitoring allowed the trainers to modify the program accordingly by alternating the exercise selection or load. This meant that in most situations participants could complete the exercise session. In line with the guidelines of the International Bone Metastases Exercise Working Group, trainers ensured exercises were conducted in a controlled manner and with the correct technique [54]. Further, trainers had the option to avoid loading affected bones or taking the 'start low, progress slow' approach during exercise sessions. Importantly, despite this cautious approach, which possibly limited progressive overload at times, participants were still able to maintain and even improve skeletal muscle mass, muscle strength and functional performance. Moreover, the two exercise-related SAEs that were reported—a wrist fracture and a sacral stress fracture—were not associated with bone

metastases. Following a temporary interruption and/or program adjustment, both participants continued the exercise program.

Limitations

Our study is not without limitations. CT and MRI scans are the gold standards for estimating muscle mass in research due to their precision. However, they are associated with higher costs, limited accessibility and higher radiation exposure, and hence DXA is the preferred alternative method. However, in our study, body composition via DXA scan was only assessed in a subgroup of participants as only two sites had (free) access to DXA machines. This reduced our sample size for the body composition outcomes significantly. While it is likely that a larger sample size would have led to similar effects on lean body mass, it is unclear how this would have influenced the body fat outcomes. While studies in the curative setting have demonstrated changes in body fat following an exercise intervention, and this may be relevant to improving prognosis and preventing other chronic diseases [55], this requires further investigation in the metastatic setting [44]. Patients that are intending to lose weight, for example, may benefit from a combined exercise and dietary intervention.

We cannot rule out that there was a higher learning effect in the exercise group compared to the control group for the h1-RM test, as some participants used the leg press during training. This may have led to an overestimation of the effect. A further limitation is that it was not possible or deemed safe to conduct the h1-RM leg press test in all participants. Despite doing a 12-RM instead of a true 1-RM test, to maximize safety, we decided to avoid loading bones that had bone lesions in participants with bone metastases in the testing environment. However, the 5 times sit-to-stand test was conducted in a larger sample size and supports the effects we observed in the h1-RM leg press test. Further, patient-reported physical functioning, measured with the EORTC QLQ-C30 and reported elsewhere, also significantly improved in the exercise group compared to the control group [29].

An important aspect to consider when interpreting our findings is that we included patients into the study at any time during their treatment for mBC, and the majority were on their 1st or 2nd line of treatment. While this contributed to a heterogeneous sample, it also increases the generalizability of our findings. Nevertheless, it would be interesting to further explore whether exercise responses differ based on treatment lines, tumour types and/or treatments received.

Lastly, there were some differences at baseline between the exercise and control groups in the subset of participants that completed the DXA scan and h1-RM. For example, with regard to the DXA subset, the exercise group had a higher percentage of participants who were currently receiving chemotherapy. This may have negatively affected their muscle mass outcomes and have led to an underestimation of the training effects. On the other hand, their time since mBC diagnosis was shorter.

Conclusion

In the PREFERABLE-EFFECT study, we were able to demonstrate that a supervised aerobic and resistance exercise program can improve lean body mass, muscle strength and physical performance in patients with mBC. There is growing recognition that skeletal muscle mass plays a pivotal role in treatment tolerance (i.e., reducing treatment-related toxicities), prognosis and overall health in patients with cancer. Further, greater muscle strength and physical functioning have been associated with better quality of life and reduced risk of mortality. Therefore, our novel evidence further supports the call for exercise, and specifically supervised exercise with a resistance exercise component, to be integrated as a standard component of cancer care and for this to be extended to patients with metastatic disease.

Abbreviations

mBC	Metastatic breast cancer
CI	Confidence interval
BMI	Body mass index
DXA	Dual-energy X-ray absorptiometry
h1-RM	Hypothetical 1-repetition maximum
SF-FAB	Short-Form Fullerton Advanced Balance scale
ES	Effect sizes
SAEs	Serious adverse events

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13058-026-02235-6.

Additional file 1.

Additional file 2.

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Author contributions

EMZ, MES, EMM, PZ, JB, KAB, EvdW, NKA, ES, AU, MMS, KS, WB, YW, AMM and HR designed the study. EMZ, JW, ES, AU, MMS, KS, WB, YW and AMM were principal investigators of the study at their local study center. AMM was the main principal investigator of the PREFERABLE project. RA, CM, EvdW, ES and AU recruited participants for the study. GJ, DC, MT, AEH, EMM, PZ, JB,

RFG, JM, KAB, MG and HR were involved in data acquisition. GJ, AEH and EH conducted the data analyses. EMZ wrote the first draft of the manuscript. All authors contributed to the interpretation of the findings and provided critical feedback and final approval of the manuscript.

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Data availability
The data that support the findings of this study are not yet openly available owing to reasons of confidentiality. Researchers can request current data from the principal investigator of the PREFERABLE-EFFECT study (a.m.may@umcutrecht.nl). Pseudonymized data (including data dictionaries) will be made available through the Digital Research Environment, which is a trusted platform that can be accessed at [https://mydre.org]. This will be carried out after the review and approval of a methodologically sound proposal by the General Assembly of PREFERABLE, with a signed data access agreement, which is in line with Ethics Committee requirements (The Ethics Committee of University Medical Center Utrecht, The Netherlands). Requests will be processed within 6 weeks. These files will be available from the date of publication until the date stated in the approved request. Once the PREFERABLE project has been fully completed, the database will be anonymized and shared using DataverseNL. The study protocol is available as an open access publication ([https://doi.org/10.1186/s13063-022-06556-7] (https://doi.org/10.1186/s13063-022-06556-7)).

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the standards of Good Clinical Practice and the Declaration of Helsinki. The conduct of the study was approved by the local ethical review boards of all participating institutions. Informed consent was obtained from all individual participants included in the study.

Consent for publication
The manuscript contains no individual person's data in any form.

Competing interests
AMM's institution, UMC Utrecht, have received fees from Eli Lilly and Company for the development of an e-learning tool on exercise and cancer. All other authors declare that they have no competing interests.

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References

1. Ferlay J EM, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F. Global Cancer Observatory: Cancer Today: Lyon, France: International Agency for Research on Cancer; 2024 [Available from: https://gco.iarc.who.int/today.
2. Dowsett M, Forbes J, Bradley R, Ingle J, Aihara T, Bliss J. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015;386(10001):1341–52.
3. Benitez Fuentes JD, Morgan E, de Luna Aguilar A, Mafra A, Shah R, Giusti F, et al. Global stage distribution of breast cancer at diagnosis: a systematic review and meta-analysis. JAMA Oncol. 2024;10(1):71–8.
4. Lobbezoo DJA, van Kampen RJW, Voogd AC, Dercksen MW, van den Berkmortel F, Smilde TJ, et al. Prognosis of metastatic breast cancer: are there differences between patients with de novo and recurrent metastatic breast cancer? Br J Cancer. 2015;112(9):1445–51.
5. Mariotto AB, Etzioni R, Hurlbert M, Penberthy L, Mayer M. Estimation of the number of women living with metastatic breast cancer in the United States. Cancer Epidemiol Biomarkers Prev. 2017;26(6):809–15.
6. Caswell-Jin JL, Plevritis SK, Tian L, Cadham CJ, Xu C, Stout NK, et al. Change in survival in metastatic breast cancer with treatment advances: meta-analysis and systematic review. JNCI Cancer Spectrum. 2018;2(4):pky062.
7. Cardoso F, Paluch-Shimon S, Schumacher-Wulf E, Matos L, Gelmon K, Aapro MS, et al. 6th and 7th International consensus guidelines for the management of advanced breast cancer (ABC guidelines 6 and 7). The Breast. 2024;76:103756.
8. Hamer J, McDonald R, Zhang L, Verma S, Leahey A, Ecclestone C, et al. Quality of life (QOL) and symptom burden (SB) in patients with breast cancer. Support Care Cancer. 2017;25(2):409–19.
9. Delrieu L, Martin A, Touillaud M, Pérol O, Morelle M, Febvey-Combes O, et al. Sarcopenia and serum biomarkers of oxidative stress after a 6-month physical activity intervention in women with metastatic breast cancer: results from the ABLE feasibility trial. Breast Cancer Res Treat. 2021;188(3):601–13.
10. Yee J, Davis GM, Beith JM, Wilcken N, Currow D, Emery J, et al. Physical activity and fitness in women with metastatic breast cancer. J Cancer Surviv. 2014;8(4):647–56.
11. Pin F, Couch ME, Bonetto A. Preservation of muscle mass as a strategy to reduce the toxic effects of cancer chemotherapy on body composition. Curr Opin Support Palliat Care. 2018;12(4):420–6.
12. Bland KA, Kouw IWK, van Loon LJC, Zopf EM, Fairman CM. Exercise-based interventions to counteract skeletal muscle mass loss in people with cancer: can we overcome the odds? Sports Med. 2022;52(5):1009–27.
13. Rier HN, Jager A, Sleijfer S, van Rosmalen J, Kock MCJM, Levin M-D. Low muscle attenuation is a prognostic factor for survival in metastatic breast cancer patients treated with first line palliative chemotherapy. Breast. 2017;31:9–15.
14. Shachar SS, Deal AM, Weinberg M, Nyrop KA, Williams GR, Nishijima TF, et al. Skeletal muscle measures as predictors of toxicity, hospitalization, and survival in patients with metastatic breast cancer receiving taxane-based chemotherapy. Clin Cancer Res. 2017;23(3):658–65.

15. Kokkonen K, Saarto T, Mäkinen T, Pohjola L, Kautio H, Järvenpää S, et al. The functional capacity and quality of life of women with advanced breast cancer. Breast Cancer. 2017;24(1):128–36.
16. Ballinger TJ, Marques HS, Xue G, Hoffman R, Gatsonis C, Zhao F, et al. Impact of muscle measures on outcome in patients receiving endocrine therapy for metastatic breast cancer: analysis of ECOG-ACRIN E2112. J Natl Compr Canc Netw. 2023;21(9):915-23.e1.
17. Wopat H, Harrod T, Brem RF, Kaltman R, Anderson K, Robien K. Body composition and chemotherapy toxicity among women treated for breast cancer: a systematic review. J Cancer Surviv. 2024;18(4):1356–69.
18. Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res. 2009;15(8):2920–6.
19. Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: a meta-analysis and systematic review. Eur J Cancer. 2016;57:58–67.
20. Adams SC, Segal RJ, McKenzie DC, Vallerand JR, Morielli AR, Mackey JR, et al. Impact of resistance and aerobic exercise on sarcopenia and dynapenia in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. Breast Cancer Res Treat. 2016;158(3):497–507.
21. Fraser SF, Gardner JR, Dalla Via J, Daly RM. The effect of exercise training on lean body mass in breast cancer patients: a systematic review and meta-analysis. Med Sci Sports Exerc. 2022;54(2):211–9.
22. Tan TW, Tan HL, Chung YC. Effectiveness of resistance training in preventing sarcopenia among breast cancer patients undergoing chemotherapy: a systematic review and meta-analysis. Worldviews Evid Based Nurs. 2024;21(6):687–94.
23. O' Riordan JMCV, McCullagh R, Murphy PJ, Sheill G, Horgan F, French HP. The effects of a prescribed exercise programme in people with metastatic breast cancer: a systematic review. Physiotherapy. 2024;125:101423.
24. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16–31.
25. Knowlton SE, Wardell AC, Bailey C, Connelly B, Carey LA, Wood WA, et al. Assessment of the functional and health-related needs of patients with metastatic breast cancer prior to initiation of cancer treatment. Breast Cancer Res Treat. 2025. https://doi.org/10.1007/s10549-024-07590-6.
26. Sheean P, Matthews L, Visotcky A, Banerjee A, Moosreiner A, Kelley K, et al. Every day counts: a randomized pilot lifestyle intervention for women with metastatic breast cancer. Breast Cancer Res Treat. 2021;187(3):729–41.
27. Delrieu L, Pialoux V, Pérol O, Morelle M, Martin A, Friedenreich C, et al. Feasibility and health benefits of an individualized physical activity intervention in women with metastatic breast cancer: intervention study. JMIR Mhealth Uhealth. 2020;8(1):e12306.
28. Lee CY, Laffoon K, Mama SK, Liao Y, Whisenant M, Brewster A, et al. Outcomes for breast cancer survivors with metastatic disease in a physical activity program for medically underserved cancer survivors. J Cancer Surviv. 2024. https://doi.org/10.1007/s11764-024-01600-8.
29. Hiensch AE, Depenbusch J, Schmidt ME, Monninkhof EM, Pelaez M, Clauss D, et al. Supervised, structured and individualized exercise in metastatic breast cancer: a randomized controlled trial. Nat Med. 2024;30(10):2957–66.
30. Hiensch AE, Monninkhof EM, Schmidt ME, Zopf EM, Bolam KA, Aaronson NK, et al. Design of a multinational randomized controlled trial to assess the effects of structured and individualized exercise in patients with metastatic breast cancer on fatigue and quality of life: the EFFECT study. Trials. 2022;23(1):610.
31. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998;147(8):755–63.
32. Muñoz-Bermejo L, Adsuar JC, Mendoza-Muñoz M, Barrios-Fernández S, Garcia-Gordillo MA, Pérez-Gómez J, et al. Test-retest reliability of five times sit to stand test (FTSST) in adults: a systematic review and meta-analysis. Biology. 2021. https://doi.org/10.3390/biology10060510.
33. Rose DJ, Lucchese N, Wiersma LD. Development of a multidimensional balance scale for use with functionally independent older adults. Arch Phys Med Rehabil. 2006;87(11):1478–85.
34. Schmidt ME, Hiensch AE, Depenbusch J, Monninkhof EM, Belloso J, Clauss D, et al. Impact of exercise on sexual health, body image, and therapy-related symptoms in women with metastatic breast cancer: the randomized controlled PREFERABLE-EFFECT trial. Int J Cancer. 2025;157(3):490–503.
35. Schouten AEM, Hiensch AE, Frederix GWJ, Monninkhof EM, Schmidt ME, Clauss D, et al. Supervised exercise for patients with metastatic breast cancer: a cost-utility analysis alongside the PREFERABLE-EFFECT randomized controlled trial. J Clin Oncol. 2025;43(11):1325–36.
36. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al. Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. Med Sci Sports Exerc. 2019;51(11):2375–90.
37. Ligibel JA, Bohlke K, May AM, Clinton SK, Demark-Wahnefried W, Gilchrist SC, et al. Exercise, diet, and weight management during cancer treatment: ASCO guideline. J Clin Oncol. 2022;40(22):2491–507.
38. Schmitz KH, Campbell AM, Stuiver MM, Pinto BM, Schwartz AL, Morris GS, et al. Exercise is medicine in oncology: engaging clinicians to help patients move through cancer. CA Cancer J Clin. 2019;69(6):468–84.
39. De Lazzari N, Niels T, Tewes M, Gotte M. A systematic review of the safety, feasibility and benefits of exercise for patients with advanced cancer. Cancers (Basel). 2021. https://doi.org/10.3390/cancers13174478.
40. Kudiarasu C, Lopez P, Galvão DA, Newton RU, Taaffe DR, Mansell L, et al. What are the most effective exercise, physical activity and dietary interventions to improve body composition in women diagnosed with or at high-risk of breast cancer? A systematic review and network meta-analysis. Cancer. 2023;129(23):3697–712.
41. Buffart LM, Kalter J, Sweegers MG, Courneya KS, Newton RU, Aaronson NK, et al. Effects and moderators of exercise on quality of life and physical function in patients with cancer: an individual patient data meta-analysis of 34 RCTs. Cancer Treat Rev. 2017;52:91–104.
42. Courneya KS, Karvinen KH, McNeely ML, Campbell KL, Brar S, Woolcott CG, et al. Predictors of adherence to supervised and unsupervised exercise in the Alberta physical activity and breast cancer prevention trial. J Phys Act Health. 2012;9(6):857–66.
43. Van Vulpen JK, Sweegers MG, Peeters PHM, Courneya KS, Newton RU, Aaronson NK, et al. Moderators of exercise effects on cancer-related fatigue: a meta-analysis of individual patient data. Med Sci Sports Exerc. 2020;52(2):303–14.
44. Trestini I, Carbognin L, Monteverdi S, Zanelli S, De Toma A, Bonaiuto C, et al. Clinical implication of changes in body composition and weight in patients with early-stage and metastatic breast cancer. Crit Rev Oncol Hematol. 2018;129:54–66.
45. Toohey K, Chapman M, Rushby AM, Urban K, Ingham G, Singh B. The effects of physical exercise in the palliative care phase for people with advanced cancer: a systematic review with meta-analysis. J Cancer Surviv. 2023;17(2):399–415.
46. Bettariga F, Galvao DA, Taaffe DR, Bishop C, Lopez P, Maestroni L, et al. Association of muscle strength and cardiorespiratory fitness with all-cause and cancer-specific mortality in patients diagnosed with cancer: a systematic review with meta-analysis. Br J Sports Med. 2025. https://doi.org/10.1136/bjsports-2024-108671.
47. Brown JC, Harhay MO, Harhay MN. Physical function as a prognostic biomarker among cancer survivors. Br J Cancer. 2015;112(1):194–8.
48. Cheng F, Li N, Yang J, Yang J, Yang W, Ran J, et al. The effect of resistance training on patients with secondary sarcopenia: a systematic review and meta-analysis. Sci Rep. 2024;14(1):28784.
49. Khemthong U, Hawsawi S, Schneider JK. Effects of exercise on balance in cancer survivors with chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. Cancer Nurs. 2024;49(1):52–66.
50. Zimmer P, Trebing S, Timmers-Trebing U, Schenk A, Paust R, Bloch W, et al. Eight-week, multimodal exercise counteracts a progress of chemotherapy-induced peripheral neuropathy and improves balance and strength in metastasized colorectal cancer patients: a randomized controlled trial. Support Care Cancer. 2018;26(2):615–24.
51. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994;49(2):M85-94.
52. Bula A, Tatar K, Wysocka R, Chyrek K, Piejko L, Nawrat-Szołtysik A, et al. Effect of physical activity on static and dynamic postural balance in women treated for breast cancer: a systematic review. Int J Environ Res Public Health. 2023;20(4):3722.
53. Sweegers MG, Depenbusch J, Kampshoff CS, Aaronson NK, Hiensch A, Wengström Y, et al. Perspectives of patients with metastatic breast cancer on

physical exercise programs: results from a survey in five European countries. Support Care Cancer. 2023;31(12):694.
54. Campbell KL, Cormie P, Weller S, Alibhai SMH, Bolam KA, Campbell A, et al. Exercise recommendation for people with bone metastases: expert consensus for health care providers and exercise professionals. JCO Oncol Pract. 2022;18(5):e697–709.
55. Bao C, Feng Y, Huang J, Wang Z, Wang X, Hou Y, et al. The efficacy of exercise training for improving body composition in patients with breast cancer: a systematic review and meta-analysis of randomized controlled trials. Clin Rehabil. 2024;38(9):1188–99.

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