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REVIEW ARTICLE

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

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Abstract

Background: Obesity has been recognized as a risk factor in the development and recurrence of breast cancer and is also associated with poor prognostic outcomes. This systematic review and network meta-analysis aimed to identify the most effective exercise, physical activity, and dietary interventions to reduce fat mass, body fat percentage and body weight as well as potentially increase lean mass in women diagnosed with or at high risk of breast cancer.

Methods: A systematic search of databases was performed up to May 2022. Eligible randomized controlled trials examined the effects of exercise, physical activity and/or dietary interventions on fat mass and lean mass in women diagnosed with or at high risk of breast cancer. A random-effects network meta-analysis was conducted to determine the effects of different interventions across outcomes when sufficient studies were available.

Results: Eighty-four studies (n = 6428) were included in this review. Caloric restriction and combined exercise + caloric restriction significantly reduced fat mass (range, –3.9 to –3.7 kg) and body weight (range, –5.3 to –4.7 kg), whereas physical activity + caloric restriction significantly reduced body fat percentage (–2.4%; 95% confidence interval [CI], –3.4% to –13%) and body mass index (–2.2 kg $\times$ m^{-2}; 95% CI, –3.0 to –1.4 kg $\times$ m^{-2}) in breast cancer patients. Resistance exercise was the most effective intervention to increase lean mass (0.7 kg; 95% CI, 0.5–1.0 kg) in breast cancer patients.

Conclusion: Multimodal exercise and diet programs were the most effective interventions to reduce fat mass, body fat percentage, and body weight and increase and/or preserve lean mass.

KEYWORDS
body composition, breast cancer, diet, exercise, fat mass, lean mass

INTRODUCTION

Female breast cancer is the most commonly diagnosed cancer worldwide with ~2.3 million new cases and ~700,000 deaths in 2020.[1] Obesity has been recognized as a modifiable risk factor in the development[2] and recurrence of breast cancer[3] and is associated with increased surgical complications during treatment,[4–8] worse adverse cancer-related outcomes,[9] and breast cancer–specific survival.[10] Specifically, women with breast cancer who are overweight or obese during treatment experience ~20%–30% increased risk of cancer-related and all-cause mortality.[11,12] More recently, sarcopenia (i.e., loss of muscle mass) has been associated with poorer prognosis in patients with cancer[13] including poorer quality of life, physical function, and surgical outcomes, increased incidence of hospitalization, and longer length of hospital stay.[14] Studies in women with breast cancer found that low lean mass is associated with greater chemotherapy toxicities and shorter survival.[15–24] One study demonstrated that women with low levels of lean mass may have ~40% increased risk of mortality.[15]

Multicomponent allied health interventions, including nutrition and structured exercise programs, are widely used to counteract increases in body fat and fat mass and decreases in lean mass experienced during and following active cancer treatment.[25–29] This is crucial, because weight loss achieved through combined exercise and dietary interventions is associated with reductions in fasting insulin levels and improvements in inflammatory markers, potentially enhancing treatment outcomes and reducing the risk of cancer recurrence.[30–33] Current exercise guidelines recommend at least 20–30 minutes of moderate-intensity aerobic exercise most days of the week combined with two resistance training sessions per week for cancer patients and survivors to help reduce treatment toxicities and cancer-related fatigue, and improve physical function and quality of life.[34,35] Evidence shows that regular physical activity and a healthy diet based on increased consumption of vegetables, fruits, and whole grains is associated with reduced risk of breast cancer–specific and all-cause mortality,[36] although effects on fat mass, lean mass, and body weight are variable.[25–29] These current recommendations lack specificity on interventions to improve body composition components (e.g., fat mass, lean mass) and body weight in women diagnosed with breast cancer, whereas there is limited evidence for those at high risk of breast cancer. Therefore, a more comprehensive assessment of the literature is necessary to better target specific components of body composition and weight and achieve meaningful changes before, during, and following breast cancer diagnosis and treatment.

The aim of this systematic review and network meta-analysis was to identify the most effective physical activity (i.e., any bodily movement produced by skeletal muscles that results in energy expenditure),[37] exercise (i.e., a subset of physical activity that is planned, structured, and repetitive bodily movement),[37] and/or dietary interventions (e.g., healthy diet, caloric restriction, and low-fat diet), to reduce fat mass, body fat percentage, and body weight and increase lean mass in women diagnosed with or at high risk of breast cancer. In addition, we performed subgroup analyses to examine the effects of these interventions based on age, body mass index (BMI), and timing of treatment. The results of this review may be used to assist clinicians to provide specific information on fat mass, body fat percentage, body weight, and muscle mass management interventions for breast cancer care and inform future research.

MATERIALS AND METHODS

All procedures undertaken in this study are reported in accordance with the Cochrane Back Review Group,[38] the Implementing Prisma in Exercise, Rehabilitation, Sport Medicine and Sports Science,[39] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses (PRISMA-NMA) statement[40] including registration with the international prospective register of systematic reviewers (PROSPERO identifier: CRD42021250180).

Literature search strategy and study selection

A systematic search was conducted using CINAHL, Cochrane Library, Embase, PubMed, SPORTDiscus, and Web of Science databases from inception to May 21, 2021. An updated search was conducted on May 16, 2022, to identify the most recent studies. The search terms for this systematic review included a combination of keywords relating to breast cancer, exercise, physical activity, diet, nutrition, and body composition. The search strategy is described in Appendix S1.

Eligibility was assessed independently by three authors (C.K., L. M., and B.F.), with discrepancies resolved by consensus. In case of any disagreement, a fourth reviewer (P.L.) was consulted. Titles and abstracts were independently evaluated following the eligibility criteria assessment. Full-text articles that met the criteria were retrieved and read independently by all reviewers and assessed for inclusion in the study. A manual search of references in selected articles was performed to detect studies that were potentially eligible for inclusion.

Inclusion and exclusion criteria

The inclusion criteria for this systematic review followed the Population, Intervention, Comparator, Outcomes, Study design framework.[40] Studies were included if 1) participants were diagnosed with breast cancer or at high risk of developing breast cancer (i.e., BRCA1/BRCA2 genetic mutations); 2) the intervention included exercise, physical activity and/or dietary information; 3) outcome measures had one of the following variables: whole-body fat mass (kg), whole-body lean mass (kg) or body fat percentage (%); and 4) the study design was a randomized clinical trial (RCT).

The exclusion criteria were: 1) studies that included mixed cancers without specific results on breast cancer patients; 2) studies that did not report specific outcomes of interest for this review; 3) interventions less than 4 weeks; and 4) non-English publications.

Data extraction, risk of bias assessment, and certainty of evidence

Three authors (C.K., P.L., and F.S.) extracted publication information (authors, year of publication), demographic and clinical characteristics (age, BMI, disease stage and treatment), experimental design and sample size, prescription characteristics (delivery, modality, frequency, volume, and intensity for exercise interventions), exercise, physical activity, dietary recommendations (e.g., for low carbohydrate diet, reduce carbohydrate intake by 30 g per day), adherence, and retention rate and main outcomes from the studies using a standardized form. Information was extracted from baseline versus post-intervention assessment. For studies that did not provide dispersion values of change for the outcomes assessed such as standard deviation (SD), standard errors or 95% confidence intervals (95% CI), the SD of the change was calculated assuming a correlation of zero between the baseline and post-intervention assessment measures by the square root of $\left(SD^2_{Baseline} + SD^2_{Post-intervention}\right)$.[41]

Risk of bias assessment was conducted by two authors (C.K. and P.L.) and evaluated according to the second version of the Cochrane risk-of-bias tool for randomized trials (RoB 2) with each assessment focused on the outcome level. The certainty of evidence for the network intervention ranking was assessed using the Grading of Recommendations Assessment, Development and Evaluation approach for network meta-analysis.

Data synthesis and analysis

Continuous outcome data in both pairwise and network meta-analyses (NMA) were summarized as mean difference (MD) and 95% CI. Pairwise comparisons between interventions and control groups were conducted in R (R Development Core Team, Vienna, Austria) using the package “meta.”[42] The frequentist graph theoretical was performed following current PRISMA guidelines for NMA[43,44] and conducted using the R package “netmeta”[45] for studies involving women diagnosed with breast cancer. A random-effects model was undertaken as studies differed both clinically and methodologically (i.e., between-study variability). The between-study variability (i.e., heterogeneity) and variance of the intervention effects within each comparison was assessed by I^2 and τ^2, respectively.

For each NMA, we assessed a priori for transitivity and consistency assumptions using average age, BMI, and overall risk of bias as potential intervention effect modifiers,[46] with values reported for each study. We evaluated each network for inconsistency using the random-effects design-by-treatment interaction model[47] and locally by splitting the direct and indirect evidence.[48] For studies involving women at high risk of breast cancer, given the small number of studies, pairwise meta-analyses were used to investigate the effect of exercise, physical activity, and/or dietary interventions compared to control groups on outcomes of interest.

Significant intervention effects were ranked according to *p* scores, measuring the extent of certainty that an intervention was better than the other.[49] Comparisons were made when more than one study was included for each comparator and were considered statistically significant when the 95% CI did not include the value of zero. NMA with subgroup analyses were conducted for the primary outcomes considering potential intervention effect modifiers such as age (below 50 and equal to or over 50 years), BMI (overweight or obese), and timing of treatment status (during vs. following treatment).

RESULTS

A total of 3218 records were screened after removing 2859 duplicates. A total of 2106 records were excluded based on titles and abstracts due to their irrelevance to the research question, and 1112 records were deemed eligible for full-text review. After including six additional studies via other methods, a total of 84 randomized clinical trials[30–33,50–129] were included in this systematic review and network meta-analysis (Figure 1).

Study, participant, and intervention characteristics

A total of 6428 women with a median age of 53.1 years (interquartile range [IQR], 50.0–56.0 years) were included in this review. The median BMI was 28.5 kg $\times$ m^{-2} (IQR, 25.8–30.8 kg $\times$ m^{-2}); most participants were either overweight (k = 42, *n* = 3257, 50.7%) or obese (k = 25, *n* = 1724, 26.8%). Most participants (66%) in the studies completed active treatment, 25% were still undergoing active treatment, 9% were at high risk of breast cancer with no treatment, and 1% did not report any information regarding treatment status.

Eighty-four trials that included a total of 105 interventions were analyzed. The definition of interventions is presented in Table 1. For the purpose of this review, we elected to categorize activities as resistance and aerobic exercise based on definitions from Newton and Galvao[130] because these were the most common forms of exercise modality used in patients with cancer. All other activities not meeting these exercise-based definitions were categorized as physical activity (e.g., tai chi, yoga). The most common intervention modality was combined resistance and aerobic exercise (21.9%), followed by resistance exercise (14.3%), physical activity (14.3%), aerobic exercise (11.4%), physical activity + caloric restriction (6.7%),

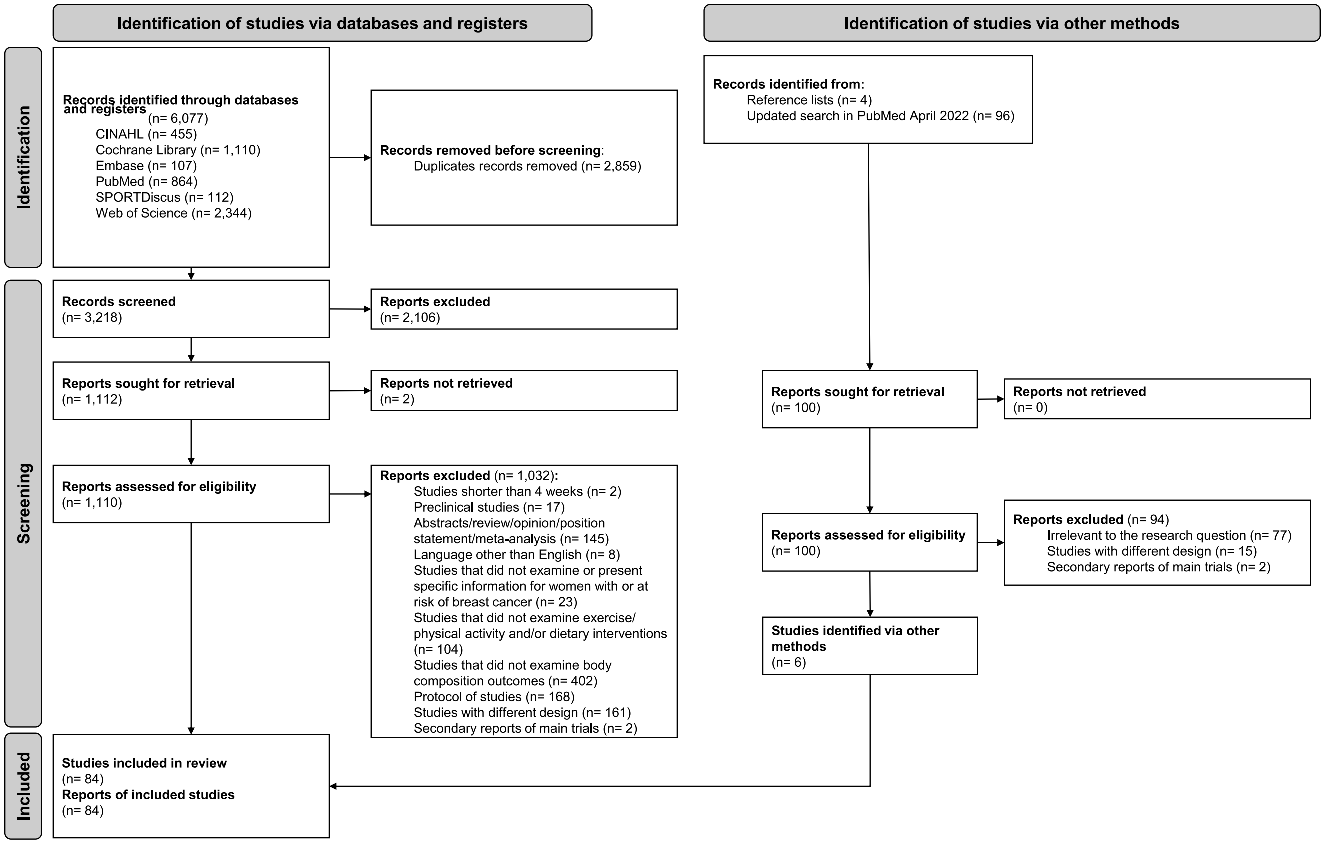

FIGURE 1 Flow chart of study selection process.

TABLE 1 List of interventions investigated.

Intervention	Definition
Physical activity	Nonplanned and nonstructured activities involving any bodily movement produced by skeletal muscles that require energy expenditure
Resistance exercise (or anabolic exercise)	Activity based on performing sets of repeated movements against a resistance with prominent effects observed on the musculoskeletal and neural systems
Aerobic exercise (or endurance exercise)	Activity involving large muscle groups and performed in a continuous or intermittent fashion over an extended period of time, with prominent effects observed on cardiorespiratory fitness and blood lipid profiles
Combined resistance and aerobic exercise (combined exercise training or concurrent training)	Combination of structured resistance and aerobic exercise within the same exercise program
Healthy diet	Diet high in fruits, vegetables, and fibers
Caloric restriction	Diet with restricted daily calorie intake to meet a specified energy goal
Low-carbohydrate diet	Diet with restricted daily intake from carbohydrate foods (e.g., starchy vegetables, rice, pasta)
Low-fat diet	Diet with restricted daily intake from high-fat food (e.g., oils, butter, greasy food)
High-protein diet	Supplementation of protein (e.g., whey protein) or a diet with increased intake of protein (e.g., fish, chicken, eggs, dairy) than normally required
Mediterranean diet	Diet with the eating patterns observed in countries around the Mediterranean Sea, that are low in saturated fats and high in vegetable oils (e.g., grains, legumes, beans, nuts)
Ketogenic diet	Diet focusing on high fat, low carbohydrate, and adequate levels of protein foods

caloric restriction (2.9%), combined resistance and aerobic exercise + caloric restriction (2.9%), healthy diet (2.9%), and Mediterranean diet (2.9%). The median duration of the exercise interventions was 17 weeks (IQR, 12–26 weeks) at a frequency of two to three sessions per week. Study characteristics and risk of bias assessment results are presented in Table S1 and Tables S2–S6, respectively.

Whole-body fat mass and lean mass

Forty-six intervention effects were included in the analyses for whole-body fat mass (Table S7 and Figure 2). The network geometry of studies examining whole-body fat mass and lean mass is presented in Figure S1. The median whole-body fat mass at baseline was 29.7 kg (IQR, 26.5–33.2 kg). Caloric restriction (*p* score = 85.3%) and combined resistance and aerobic exercise + caloric restriction (*p* score = 83.3%) were the most effective interventions to reduce fat mass with mean effects ranging from −3.9 to −3.7 kg (Table 2 and Table S8). Subgroup analyses for whole-body fat mass are presented in Figure 2. Aerobic exercise was only effective in participants below 50 years old (*p* score = 76.1%), whereas caloric restriction (*p* score = 87.9%) and combined resistance and aerobic exercise + caloric restriction (*p* score = 86.6%) were the most effective interventions for participants equal to or over 50 years. Combined resistance and aerobic exercise and combined resistance and aerobic exercise + caloric restriction were the most effective interventions for participants who were overweight (*p* score = 77.7%) or obese (*p* score = 69.0%), respectively. Caloric restriction (*p* score = 86.2%) and combined resistance and aerobic exercise + caloric restriction (*p* score = 85.3%) were most effective following primary treatment. For participants undergoing primary treatment, no significant interventions were found to reduce fat mass. For whole-body fat mass, the certainty of evidence was graded low (Table 2). For women at high risk of breast cancer, studies including a healthy diet,

Study or Subgroup	Mean Difference	SE	Experimental Total	Control Total	Mean Difference IV, Random, 95% CI
2.1.1 Below 50					
Physical activity + Low-fat diet	-1.9	3.94	29	27	-1.90 [-9.62, 5.82]
Aerobic exercise	-0.91	0.46	78	82	-0.91 [-1.81, -0.01]
Resistance exercise	-0.31	0.5	105	107	-0.31 [-1.29, 0.67]
Physical activity	-0.07	0.95	59	43	-0.07 [-1.93, 1.79]
2.1.2 50 and over					
Caloric restriction	-3.94	1.32	97	100	-3.94 [-6.53, -1.35]
Combined exercise + Caloric restriction	-3.74	1.04	119	120	-3.74 [-5.78, -1.70]
Physical activity + Caloric restriction	-2.91	1.09	156	128	-2.91 [-5.05, -0.77]
Combined exercise	-1.93	0.6	785	997	-1.93 [-3.11, -0.75]
Aerobic exercise	-1.11	0.95	250	146	-1.11 [-2.97, 0.75]
Physical activity	-0.74	0.81	150	122	-0.74 [-2.33, 0.85]
Resistance exercise	-0.32	0.83	248	249	-0.32 [-1.95, 1.31]
2.1.3 Overweight					
Physical activity + Low-fat diet	-2.16	3.9	29	27	-2.16 [-9.80, 5.48]
Combined exercise	-0.95	0.37	354	590	-0.95 [-1.68, -0.22]
Aerobic exercise	-0.67	0.24	284	195	-0.67 [-1.14, -0.20]
Resistance exercise	-0.66	0.09	298	302	-0.66 [-0.84, -0.48]
Physical activity	-0.49	0.4	200	155	-0.49 [-1.27, 0.29]
Combined exercise + Healthy diet	-0.05	0.67	33	30	-0.05 [-1.36, 1.26]
2.1.4 Obese					
Combined exercise + Caloric restriction	-4.44	2.22	119	117	-4.44 [-8.79, -0.09]
Caloric restriction	-4.38	2.82	97	100	-4.38 [-9.91, 1.15]
Combined exercise	-3.84	1.83	143	145	-3.84 [-7.43, -0.25]
Physical activity + Caloric restriction	-3.02	2.12	156	128	-3.02 [-7.18, 1.14]
2.1.5 During primary treatment					
Physical activity + Low-fat diet	-1.89	3.94	29	26	-1.89 [-9.61, 5.83]
Combined exercise	-0.91	0.58	185	279	-0.91 [-2.05, 0.23]
Aerobic exercise	-0.71	0.48	273	185	-0.71 [-1.65, 0.23]
Resistance exercise	-0.21	0.51	82	82	-0.21 [-1.21, 0.79]
Physical activity	-0.05	0.98	92	91	-0.05 [-1.97, 1.87]
2.1.6 Following primary treatment					
Caloric restriction	-4.03	1.49	97	100	-4.03 [-6.95, -1.11]
Combined exercise + Caloric restriction	-3.83	1.16	119	120	-3.83 [-6.10, -1.56]
Physical activity + Caloric restriction	-2.92	1.21	156	128	-2.92 [-5.29, -0.55]
Combined exercise	-2.22	0.75	600	718	-2.22 [-3.69, -0.75]
Aerobic exercise	-1.36	1.16	85	73	-1.36 [-3.63, 0.91]
Physical activity	-0.49	0.89	117	74	-0.49 [-2.23, 1.25]
Resistance exercise	-0.37	0.9	271	274	-0.37 [-2.13, 1.39]

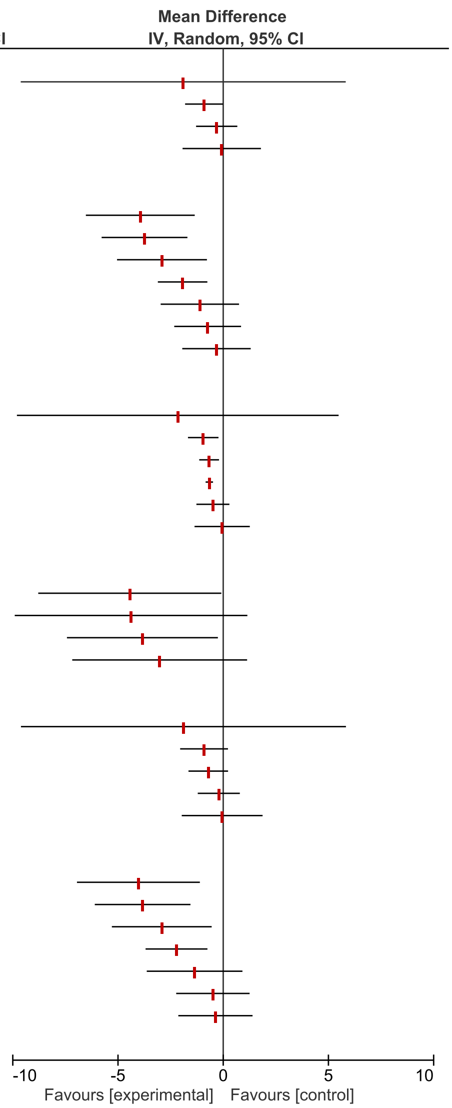

FIGURE 2 Estimated mean difference effects between exercise, physical activity, and/or dietary intervention modalities versus control group on whole-body fat mass based on subgroup analyses for age, body mass index and treatment status in women diagnosed with breast cancer.

TABLE 2 Network meta-analysis results for body composition outcomes in women diagnosed with breast cancer.

	Intervention modality	*n*	k	Comparison to control groups MD	95% CI	*p*	*p* score, %	Certainty
Whole-body fat mass, kg	Caloric restriction	271	4	−3.9	−6.2 to −1.7	<.001	85.3	⊕⊕⊖⊖[a,b] Low
	Combined resistance and aerobic exercise + caloric restriction	293	5	−3.7	−5.5 to −2.0	<.001	83.3	
	Mediterranean diet	73	2	−3.1	−8.5 to 2.3	.257	—	
	Physical activity + caloric restriction	156	3	−2.9	−4.8 to −1.0	.003	72.5	
	Physical activity + low-fat diet	58	2	−2.2	−10.1 to 5.7	.584	—	
	Combined resistance and aerobic exercise	872	11	−1.8	−2.8 to −0.8	<.001	56.3	
	Aerobic exercise	447	8	−1.2	−2.4 to 0.1	.060	—	
	Physical activity	235	8	−0.6	−1.8 to 0.7	.351	—	
	Resistance exercise	445	11	−0.4	−1.5 to 0.8	.558	—	
	Combined resistance and aerobic exercise + healthy diet	33	2	−0.2	−2.6 to 2.3	.887	—	
	τ2 = 1.25; I2 = 67.5%; design-by-treatment interaction random effects model, Q = 6.9, *p* = .650; publication bias, Egger's test, *p* = .098							
Whole-body lean mass, kg	Resistance exercise	476	13	0.7	0.5 to 1.0	<.001	94.3	⊕⊕⊕⊖[a] Moderate
	Combined resistance and aerobic exercise	965	14	0.5	0.2 to 0.8	<.001	84.1	
	Aerobic exercise	504	10	0.4	−0.0 to 0.7	.058	—	
	Physical activity	217	8	0.1	−0.4 to 0.6	.640	—	
	Combined resistance and aerobic exercise + healthy diet	100	3	−0.2	−0.7 to 0.4	.533	—	
	Physical activity + low-fat diet	58	2	−0.4	−4.6 to 3.9	.865	—	
	Physical activity + caloric restriction	240	5	−0.6	−1.1 to −0.0	.043	22.6	
	Caloric restriction	271	4	−0.7	−1.3 to 0.0	.060	—	
	Combined resistance and aerobic exercise + caloric restriction	293	5	−0.9	−1.5 to −0.3	.005	11.2	
	τ2 = 0.04; I2 = 14.9%; design-by-treatment interaction random effects model, Q = 16.4, *p* = .126; publication bias, Egger's test, *p* = .120							
Body fat percentage, %	Physical activity + caloric restriction	240	7	−2.4	−3.4 to −1.3	<.001	84.5	⊕⊕⊖⊖[a,b] Low
	Caloric restriction	28	3	−2.4	−4.6 to −0.3	.028	79.0	
	Physical activity + low-fat diet	71	3	−2.1	−6.4 to 2.2	.334	—	
	Combined resistance and aerobic exercise	549	21	−1.7	−2.3 to −1.1	<.001	68.4	
	Aerobic exercise	565	14	−1.5	−2.3 to −0.7	<.001	57.9	
	Healthy diet	40	2	−1.2	−3.9 to 1.5	.372	—	
	Resistance exercise	501	16	−1.1	−1.8 to −0.5	<.001	43.9	
	Combined resistance and aerobic exercise + caloric restriction	32	2	−1.0	−2.7 to 0.7	.235	—	
	Physical activity	284	11	−0.7	−1.7 to 0.3	.157	—	

TABLE 2 (Continued)

Intervention modality	n	k	Comparison to control groups MD	95% CI	p	p score, %	Certainty
Combined resistance and aerobic exercise + healthy diet	126	4	−0.5	−1.6 to 0.6	.365	—	
τ2 = 0.49; I2 = 38.6%; design-by-treatment interaction random effects model, Q = 7.2, p = .889; publication bias, Egger's test, p = .094							

Abbreviations: *n*, number of participants; k, number of studies; MD, mean difference.

[a]Certainty of evidence downgraded due to study limitations, with most studies presenting with high risk in the risk of bias assessment.

[b]Certainty of evidence downgraded due to imprecision, with confidence intervals from interventions crossing null values or including values favoring both interventions tested; certainty of evidence grading: ⊕⊝⊝⊝ = very low, ⊕⊕⊝⊝ = low, ⊕⊕⊕⊝ = moderate, ⊕⊕⊕⊕ = high.

Mediterranean diet and aerobic exercise resulted in a significant reduction of –3.8 kg (95% CI, –6.9 to –0.7 kg, $p = 0.02$) (Figure S5).

Fifty-two intervention effects were included in the analyses for whole-body lean mass (Table S9 and Figure 3). The median whole-body lean mass at baseline was 42.8 kg (IQR, 40.3–45.4 kg). Resistance training alone was the most effective intervention to increase lean mass (p score = 94.3%) with a mean effect of 0.7 kg (Table 2 and Table S10). Results were consistent across subgroup analyses as presented in Figure 3. Resistance training such as resistance exercise and/or combined resistance and aerobic exercise were the most effective interventions to increase lean mass in participants below 50 years of age (p score = 85.2%) and equal to or over 50 years (p score = 91.3% and 91.5%), participants who were overweight (p score = 94.3%) or obese (p score = 99.7%), and during (p score = 94.9%) or following primary treatment (p score = 83.3% and 91.9%). The certainty of evidence was graded moderate (Table 2). For women at high risk of breast cancer, interventions including a healthy diet, Mediterranean diet and aerobic exercise resulted in a significant reduction in whole body lean mass of –1.4 kg (95% CI, –2.3 to –0.6 kg, $p < .001$) (Figure S5).

Body fat percentage

The network geometry of studies examining body fat percentage is presented in Figure S2. Seventy intervention effects were included in the NMA body fat percentage (Table S11 and Figure 4). The median body fat percentage at baseline was 38.7% (IQR, 34.8%–42.0%). Physical activity + caloric restriction (p score = 84.5%) and caloric restriction (p score = 79.0%) were the most effective interventions to reduce body fat percentage with effects of –2.4% (Table 2 and Table S12). Subgroup analyses are presented in Figure 4. Aerobic exercise was the most effective intervention to reduce body fat percentage for participants below 50 years of age (p score = 73.6%), whereas physical activity + caloric restriction (p score = 86.2%) and combined resistance and aerobic exercise (p score = 81.7%) were most effective for participants equal to or over 50 years. For participants who were overweight or obese, combined resistance and aerobic exercise was the most effective intervention (p score = 72.1% and 77.7%, respectively). During primary treatment, only combined resistance and aerobic exercise was found to be effective (p score = 71.5%), whereas physical activity + caloric restriction (p score = 84.3%) and caloric restriction (p score = 74.4%) were the most effective following primary treatment. The certainty of evidence was graded low (Table 2). For women at high risk of breast cancer, interventions including a healthy diet, Mediterranean diet, fatty acids, low-fat diet, physical activity + healthy diet and aerobic exercise resulted in a significant reduction of –2.2% (95% CI, –2.8% to –1.6%, $p < .001$) in body fat percentage (Figure S5).

Body weight and BMI

The network geometry of studies examining body weight and BMI are presented in Figure S3. Seventy-four intervention effects were included for analyses (Table S13 and Figure S4). The median body weight value at baseline was 73.1 kg (IQR, 69.2–82.2). Caloric restriction (p score = 90.7%) and combined resistance and aerobic exercise + caloric restriction (p score = 84.6%) were the most effective interventions to reduce body weight with effects of –5.3 and –4.7 kg, respectively (Table S14 and Table S15). Fifty intervention effects were included for BMI (Table S16 and Figure S4). The median BMI at baseline was 28.4 kg $\times$ m^{-2} (IQR, 26.3–30.8 kg $\times$ m^{-2}). Physical activity + caloric restriction (p score = 89.7%) was the most effective intervention to reduce BMI with an effect of –2.2 kg $\times$ m^{-2} (Table S14 and Table S17). Subgroup analyses for body weight and BMI are presented in Figure S4. The certainty of evidence was graded very low for body weight and low for BMI (Table S14). For women at high risk of breast cancer, reductions in body weight (–4.0 kg; 95% CI, –7.0 to –1.0 kg, $p = 0.009$) and BMI (–1.2 kg $\times$ m^{-2}; 95% CI, –2.6 to 0.2, $p = .090$) were observed (Figure S5).

DISCUSSION

The present systematic review and network meta-analysis identified the most effective interventions to improve body composition and body weight outcomes in women diagnosed with or at high risk of breast cancer. The main findings were: 1) interventions based on

Study or Subgroup	Mean Difference	SE	Control Total	Experimental Total	Mean Difference IV, Random, 95% CI
3.1.1 Below 50					
Physical activity	-1.13	2.76	27	26	-1.13 [-6.54, 4.28]
Physical activity + Low-fat diet	-0.98	2.56	27	29	-0.98 [-6.00, 4.04]
Aerobic exercise	0.56	0.42	146	144	0.56 [-0.26, 1.38]
Resistance exercise	1.04	0.44	107	105	1.04 [0.18, 1.90]
3.1.2 50 and over					
Combined exercise + Caloric restriction	-0.79	0.32	117	119	-0.79 [-1.42, -0.16]
Caloric restriction	-0.59	0.37	100	97	-0.59 [-1.32, 0.14]
Physical activity + Caloric restriction	-0.56	0.29	176	240	-0.56 [-1.13, 0.01]
Combined exercise + Healthy diet	-0.17	0.31	70	84	-0.17 [-0.78, 0.44]
Physical activity	0.18	0.28	139	165	0.18 [-0.37, 0.73]
Aerobic exercise	0.37	0.24	166	271	0.37 [-0.10, 0.84]
Combined exercise	0.67	0.18	1071	859	0.67 [0.32, 1.02]
Resistance exercise	0.67	0.19	279	279	0.67 [0.30, 1.04]
3.1.3 Overweight					
Physical activity + Low-fat diet	-0.38	2.17	27	29	-0.38 [-4.63, 3.87]
Combined exercise + Healthy diet	-0.17	0.24	86	100	-0.17 [-0.64, 0.30]
Physical activity	0.09	0.26	141	167	0.09 [-0.42, 0.60]
Aerobic exercise	0.29	0.17	292	396	0.29 [-0.04, 0.62]
Combined exercise	0.41	0.2	610	373	0.41 [0.02, 0.80]
Resistance exercise	0.79	0.1	229	227	0.79 [0.59, 0.99]
3.1.4 Obese					
Physical activity + Caloric restriction	-0.54	0.41	176	240	-0.54 [-1.34, 0.26]
Combined exercise + Caloric restriction	-0.52	0.48	120	119	-0.52 [-1.46, 0.42]
Caloric restriction	-0.31	0.58	100	97	-0.31 [-1.45, 0.83]
Combined exercise	1.28	0.5	201	198	1.28 [0.30, 2.26]
3.1.5 During primary treatment					
Physical activity + Low-fat diet	-0.58	2.18	27	29	-0.58 [-4.85, 3.69]
Physical activity	-0.31	0.41	108	107	-0.31 [-1.11, 0.49]
Combined exercise + Healthy diet	-0.17	0.23	70	84	-0.17 [-0.62, 0.28]
Aerobic exercise	0.1	0.25	219	309	0.10 [-0.39, 0.59]
Combined exercise	0.19	0.25	335	241	0.19 [-0.30, 0.68]
Resistance exercise	0.87	0.32	82	82	0.87 [0.24, 1.50]
3.1.6 Following primary treatment					
Combined exercise + Caloric restriction	-0.69	0.65	120	119	-0.69 [-1.96, 0.58]
Physical activity + Caloric restriction	-0.57	0.36	161	223	-0.57 [-1.28, 0.14]
Caloric restriction	-0.5	0.47	100	97	-0.50 [-1.42, 0.42]
Physical activity	0.17	0.41	58	84	0.17 [-0.63, 0.97]
Aerobic exercise	0.43	0.36	93	106	0.43 [-0.28, 1.14]
Resistance exercise	0.65	0.26	294	292	0.65 [0.14, 1.16]
Combined exercise	0.84	0.27	756	637	0.84 [0.31, 1.37]

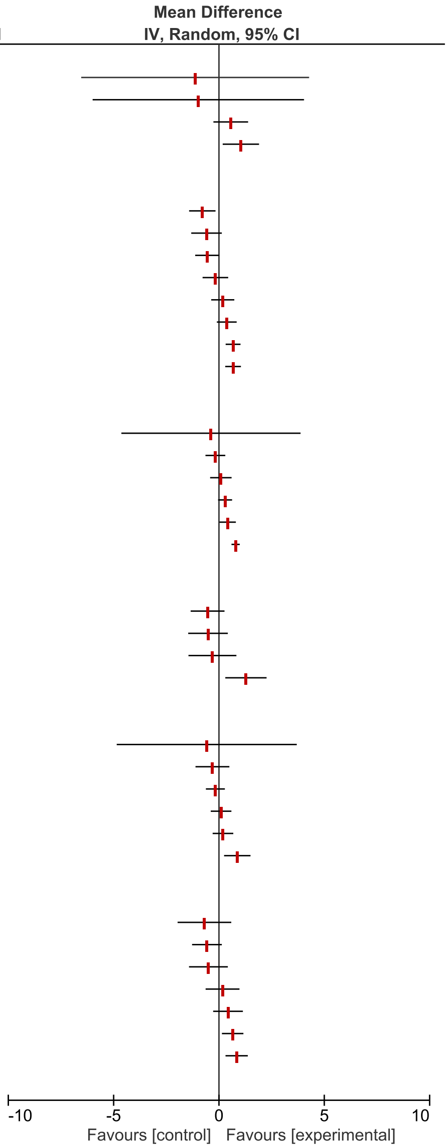

FIGURE 3 Estimated mean difference effects between exercise, physical activity, and/or dietary intervention modalities versus control group on whole-body lean mass based on subgroup analyses for age, body mass index, and treatment status in women diagnosed with breast cancer.

caloric restriction, or combined resistance and aerobic exercise + caloric restriction were the most effective interventions to reduce whole-body fat mass; 2) resistance exercise was the most effective intervention to increase whole-body lean mass; 3) physical activity + caloric restriction or caloric restriction were the most effective interventions to reduce body fat percentage; and 4) caloric restriction and physical activity + caloric restriction were the most effective interventions to reduce body weight and BMI, respectively. Our findings demonstrate that multimodal exercise and dietary intervention programs were most effective to improve body composition. Specifically, resistance training was beneficial for preserving and improving lean mass whereas caloric restriction in combination with resistance and aerobic exercise or physical activity was required to reduce fat mass, body fat percentage, body weight, and BMI during and following treatment in breast cancer patients.

Previous research showed that interventions with both exercise and dietary components were the most effective to achieve fat mass reductions[30,59,95,99,128] and weight loss in breast cancer survivors.[131] In contrast, our findings showed that caloric restriction (–3.9 kg) was as effective as combined resistance and aerobic exercise + caloric restriction (–3.7 kg) to reduce fat mass. This result concurs with another recent meta-analysis.[25] Additionally, the observed reduction of ~4.0 kg with 18 to 52 weeks of intervention could be considered clinically meaningful as patients' gains in weight and fat mass usually range from 2.0 to 6.0 kg during the first year following diagnosis.[132,133] Although we could not explore such features in women at high risk of breast cancer, these findings are important because it

Study or Subgroup	Mean Difference	SE	Experimental Total	Control Total	Mean Difference IV, Random, 95% CI
4.1.1 Below 50					
Physical activity + Low-fat diet	-1.72	2.84	29	27	-1.72 [-7.29, 3.85]
Aerobic exercise	-1.34	0.42	239	234	-1.34 [-2.16, -0.52]
Resistance exercise	-1.12	0.48	105	107	-1.12 [-2.06, -0.18]
Physical activity	-0.95	1.59	112	110	-0.95 [-4.07, 2.17]
Combined exercise	1.49	1.53	29	30	1.49 [-1.51, 4.49]
4.1.2 50 and over					
Physical activity + Caloric restriction	-2.18	0.62	220	146	-2.18 [-3.40, -0.96]
Combined exercise	-1.9	0.38	477	559	-1.90 [-2.64, -1.16]
Aerobic exercise	-1.54	0.61	327	213	-1.54 [-2.74, -0.34]
Healthy diet	-1.22	1.42	21	29	-1.22 [-4.00, 1.56]
Resistance exercise	-1.13	0.42	314	315	-1.13 [-1.95, -0.31]
Physical activity + Healthy diet	-0.85	3.18	27	26	-0.85 [-7.08, 5.38]
Physical activity	-0.74	0.59	152	145	-0.74 [-1.90, 0.42]
Combined exercise + Caloric restriction	-0.7	1.02	32	30	-0.70 [-2.70, 1.30]
Combined exercise + Healthy diet	-0.45	0.69	110	97	-0.45 [-1.80, 0.90]
Caloric restriction	2.9	3.66	10	10	2.90 [-4.27, 10.07]
4.1.3 Overweight					
Physical activity + Low-fat diet	-2.18	2.12	42	44	-2.18 [-6.34, 1.98]
Combined exercise	-1.35	0.3	239	327	-1.35 [-1.94, -0.76]
Resistance exercise	-1.32	0.09	317	313	-1.32 [-1.50, -1.14]
Aerobic exercise	-1.21	0.29	448	360	-1.21 [-1.78, -0.64]
Physical activity	-0.97	0.47	202	204	-0.97 [-1.89, -0.05]
Combined exercise + Healthy diet	-0.48	0.31	126	113	-0.48 [-1.09, 0.13]
4.1.4 Obese					
Combined exercise	-2.91	1.01	162	162	-2.91 [-4.89, -0.93]
Physical activity + Caloric restriction	-2.38	0.93	230	158	-2.38 [-4.20, -0.56]
Aerobic exercise	-2.16	1.79	47	36	-2.16 [-5.67, 1.35]
Caloric restriction	-1.85	1.79	28	32	-1.85 [-5.36, 1.66]
Combined exercise + Caloric restriction	-1.67	1.8	32	30	-1.67 [-5.20, 1.86]
Physical activity	0.33	1.78	60	59	0.33 [-3.16, 3.82]
4.1.5 During primary treatment					
Physical activity + Low-fat diet	-1.73	2.36	42	44	-1.73 [-6.36, 2.90]
Combined exercise	-1.27	0.53	203	295	-1.27 [-2.31, -0.23]
Aerobic exercise	-1.04	0.57	428	320	-1.04 [-2.16, 0.08]
Resistance exercise	-0.97	0.72	82	82	-0.97 [-2.38, 0.44]
Combined exercise + Healthy diet	-0.45	0.51	84	70	-0.45 [-1.45, 0.55]
Physical activity	0.36	2.95	52	56	0.36 [-5.42, 6.14]
4.1.6 Following primary treatment					
Physical activity + Caloric restriction	-2.45	0.61	213	143	-2.45 [-3.65, -1.25]
Caloric restriction	-2.33	1.21	28	32	-2.33 [-4.70, 0.04]
Combined exercise	-1.92	0.42	324	315	-1.92 [-2.74, -1.10]
Aerobic exercise	-1.68	0.65	138	127	-1.68 [-2.95, -0.41]
Resistance exercise	-1.16	0.44	318	319	-1.16 [-2.02, -0.30]
Combined exercise + Caloric restriction	-1.14	1.03	32	30	-1.14 [-3.16, 0.88]
Physical activity	-0.83	0.58	232	225	-0.83 [-1.97, 0.31]

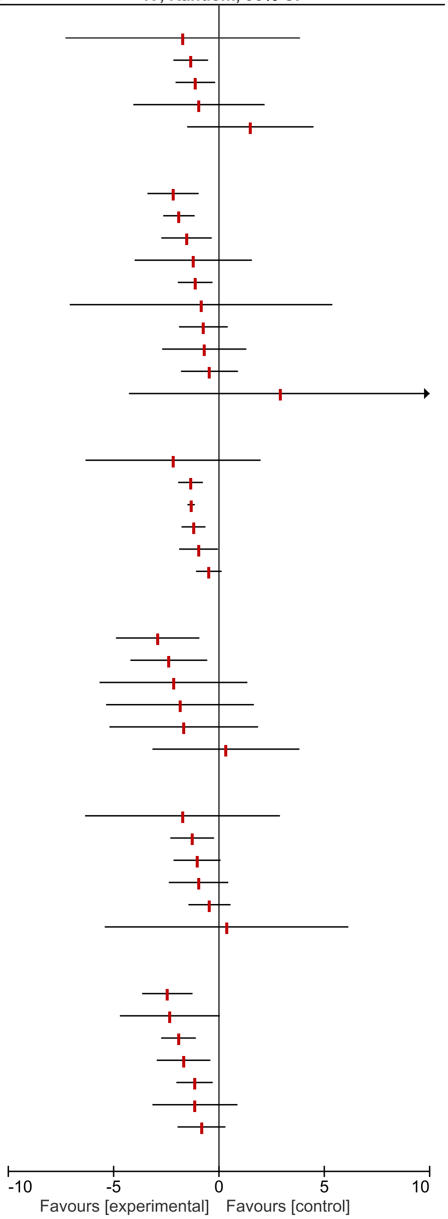

FIGURE 4 Estimated mean difference effects between exercise, physical activity and/or dietary intervention modalities versus control group on body fat percentage based on subgroup analyses for age, body mass index, and treatment status in women diagnosed with breast cancer.

is well established that changes in weight and fat could potentially reduce the risk of breast cancer, improve treatment outcomes, and decrease overall and cancer-related mortality.[27] Interestingly, we observed in the pairwise meta-analyses that diet and aerobic exercise interventions resulted in a reduction of ~4.0 kg in fat mass and body weight in women at high risk of breast cancer. Although we could not explore the most effective modality, these results highlight the importance of exercise and dietary interventions before a breast cancer diagnosis.

In our subgroup analyses, we found that breast cancer patients who are obese had significant reductions in whole-body fat mass (~4.4 kg) following combined resistance and aerobic exercise + caloric restriction. Women over the age of 50 and women who completed treatment also appeared to respond well to caloric restriction or combined resistance and aerobic exercise + caloric restriction, decreasing whole-body fat mass by ~4.0 kg. Adding combined resistance and aerobic exercise may be important to improve physical function[134] and cardiorespiratory fitness,[135] both critical for healthy aging,[136] and cardiometabolic protection[137] that may not be obtained through diet only interventions. Combined resistance and aerobic exercise + caloric restriction and caloric restriction alone were also associated with reductions between 4.7 to 5.3 kg in body weight.

Considering that patients who are older and obese are at a higher risk of treatment complications, our results are clinically meaningful, with weight and fat loss associated with significant reductions in fasting insulin levels and improvements in inflammatory markers[30–33,138] as well as cardiovascular and metabolic risk factors.[67]

Resistance exercise was the most effective intervention to improve lean mass, with effects of ~0.7 kg regardless of age and/or the timing of treatment. This effect, although modest, could be considered important as breast cancer patients undergoing chemotherapy experience losses in lean mass ranging from 0.4 to 1.7 kg even after therapy completion.[22,139] Additionally, increases in lean mass were achieved with short-duration programs (i.e., 12 weeks). In regard to patients who are overweight or obese, who may find aerobic exercise physically challenging, gradual progressive resistance exercise programs can be undertaken safely while also preserving and increasing lean mass.[53,64,66,80] In fact, low-volume resistance training was sufficient to induce significant improvements in muscle strength in breast cancer survivors; however, the specific dosage effect on body composition is yet to be determined.[140] There is evidence that excess fat and low lean mass (i.e., sarcopenic obesity) are common side-effects during and after breast cancer treatment[22,141] and are more prevalent in older cancer patients.[142] In addition, sarcopenic obesity is also strongly associated with increased treatment toxicity[143] and decreased survival rate.[15] The observed increases in lean mass following resistance exercise have clinical implications including counteracting treatment-related side-effects such as reducing the incidence of lymphedema,[64] preventing bone loss during hormone therapy,[47,49,50,56] and improving chemotherapy completion rate.[57] Our findings are supported by previous meta-analyses that stress the importance of including resistance exercise as part of cancer treatment, not only to increase lean mass during and after treatment to help combat sarcopenia[143] but also to improve muscle strength, physical function and overall quality of life in this population.[144–146] More recently, we reported that increased lean mass was associated with increased levels of myokines (released at rest and in response to exercise) post-exercise in men with advanced prostate cancer.[147] This may have the potential to suppress tumor growth and offer a protective effect against disease progression.[148] Further studies are required to investigate the mechanistic effect and clinical outcomes of resistance training on muscle mass and muscle function in individuals with breast cancer.

To the best of our knowledge, this is the first study that provides extensive and compelling evidence on the most effective interventions to improve body composition in women diagnosed with or at high risk of breast cancer. The strengths of this review include: 1) many randomized trials (n = 84) with up to 6428 patients; 2) a network meta-analysis involving simultaneous comparisons of exercise, physical activity, and dietary interventions; 3) investigation of the most effective interventions to improve body composition and body weight measures; and 4) subgroup analyses providing specific information based on age, BMI, and timing of treatment. However, there are limitations worthy of comment. First, we could not recommend specific exercise and/or dietary programs for women at high risk of breast cancer, given the limited number of studies in this population. Nevertheless, our exploratory pairwise meta-analysis indicates that aerobic exercise and/or dietary interventions could be useful to significantly reduce fat mass and body weight; however, this is accompanied by a reduction in lean mass in women at high risk of breast cancer. Previous exercise and dietary recommendations for adults who are overweight or obese may be useful to improve lean mass and fat mass in this specific subgroup[149–152] and potentially reduce the risk for future treatment/surgical complications. Second, most studies had a high risk of bias, and this likely affected the precision, magnitude, and certainty of the evidence. Third, most studies included in the review targeted participants following active treatment, whereas only ~25% included participants undergoing active adjuvant or neoadjuvant chemotherapy, reducing the ability to provide more specific information for these patient groups. Finally, our results need to be carefully interpreted given the challenge of comparing interventions with different structure and duration of programs.

In conclusion, this systematic review and network meta-analysis of 84 RCTs highlights the importance of multimodal exercise and dietary interventions to improve body composition and assist with weight management in women diagnosed with or at high risk of breast cancer regardless of age, BMI, or timing of treatment. These findings are important to assist health professionals to deliver best practices in breast cancer care and help achieve better patient and clinical outcomes. Clinicians should recommend and emphasize the benefits of incorporating regular resistance and aerobic exercise and caloric restriction to reduce fat mass and preserve or increase lean mass during or following primary treatment not only to improve body composition but to help reduce treatment-related side-effects, risk of other comorbidities, cancer recurrence, and mortality.

AUTHOR CONTRIBUTIONS

Christine Kudiarasu: Conception and design, acquisition of data, analysis and/or interpretation of data, writing–original draft, and writing–review and editing. **Pedro Lopez:** Conception and design, acquisition of data, analysis and/or interpretation of data, and writing–review and editing. **Daniel A. Galvão:** Conception and design and writing–review and editing. **Robert U. Newton:** Conception and design and writing–review and editing. **Dennis R. Taaffe:** Conception and design and writing–review and editing. **Lorna Mansell:** Acquisition of data and analysis and/or interpretation of data. **Brianna Fleay:** Acquisition of data and analysis and/or interpretation of data. **Christobel Saunders:** Conception and design and writing–review and editing. **Caitlin Fox-Harding:** Conception and design and writing–review and editing. **Favil Singh:** Conception and design, acquisition of data, analysis and/or interpretation of data, and writing–review and editing. All authors approved the final version of the article.

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CONFLICT OF INTEREST STATEMENT

Pedro Lopez reports fees for professional activities from the University of Western Australia. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data used in the present study such as data extraction templates, forms, and analysis will be made available on reasonable request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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