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ORIGINAL REPORT

Efficacy of Exercise Therapy on Cardiorespiratory Fitness in Patients With Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

Purpose

To evaluate the effects of exercise therapy on cardiorespiratory fitness (CRF) in randomized controlled trials (RCTs) among patients with adult-onset cancer. Secondary objectives were to evaluate treatment effect modifiers, safety, and fidelity.

Methods

A systematic search of PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Library was conducted to identify RCTs that compared exercise therapy to a nonexercise control group. The primary end point was change in CRF as evaluated by peak oxygen consumption (VO_{2peak}; in mL $O_2 \times kg^{-1} \times min^{-1}$) from baseline to post-intervention. Subgroup analyses evaluated whether treatment effects differed as a function of exercise prescription (ie, modality, schedule, length, supervision), study characteristics (ie, intervention timing, primary cancer site), and publication year. Safety was defined as report of any adverse event (AE); fidelity was evaluated by rates of attendance, adherence, and loss to follow-up.

Results

Forty-eight unique RCTs that represented 3,632 patients (mean standard deviation age, 55 ± 7.5 years; 68% women); 1,990 (55%) and 1,642 (45%) allocated to exercise therapy and control/usual care groups, respectively, were evaluated. Exercise therapy was associated with a significant increase in CRF (+2.80 mL $O_2 \times kg^{-1} \times min^{-1}$) compared with no change (+0.02 mL $O_2 \times kg^{-1} \times min^{-1}$) in the control group (weighted mean differences, +2.13 mL $O_2 \times kg^{-1} \times min^{-1}$; 95% CI, 1.58 to 2.67; I^2, 20.6; $P < .001$). No statistical significant differences were observed on the basis of any treatment effect modifiers. Thirty trials (63%) monitored AEs; a total of 44 AEs were reported. The mean standard deviation loss to follow-up, attendance, and adherence rates were 11% ± 13%, 84% ± 12%, and 88% ± 32%, respectively.

Conclusion

Exercise therapy is an effective adjunctive therapy to improve CRF in patients with cancer. Our findings support the recommendation of exercise therapy for patients with adult-onset cancer.

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INTRODUCTION

The direct adverse consequences of locoregional and systemic anticancer therapies together with effects secondary to treatment (eg, deconditioning, aging) culminate in significant and marked impairments in cardiorespiratory fitness (CRF).[1-3] CRF, as measured by peak oxygen consumption (VO_{2peak}), is an integrative assessment of global cardiovascular function,[4] declines between 5% and 26% during exposure to various systemic combinational regimens across numerous cancer populations,[1,5,6] and may not recover after treatment cessation.[1,7,8] Despite good performance status, up to 80% of patients with cancer have significant and marked impairments in VO_{2peak}.[1,9-11] Moreover, emerging evidence indicates that poor VO_{2peak} is associated with a higher prevalence of acute and chronic treatment-related toxicities (eg, cardiovascular disease risk factors),[2,8,12-14] higher symptom burden (eg, poor health-related quality of life, fatigue),[15-17] and increased risk of death as a result of any cause as well as cancer-specific mortality after a cancer diagnosis.[1,18,19] Hence, strategies to prevent and/or recover poor VO_{2peak} in the large and rapidly growing population of cancer survivors[20] are of major clinical importance.

ASSOCIATED CONTENT

Data Supplement
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Exercise therapy is a central component of comprehensive rehabilitation demonstrated to improve VO_{2peak} and hard clinical end points, including reductions in cardiovascular mortality, hospital admissions, and improvements in quality of life in numerous clinical conditions.[21,22] To our knowledge, only one prior meta-analysis has been specifically designed to examine the efficacy of exercise therapy on VO_{2peak} in patients with cancer.[23] However, this analysis, included fewer than six randomized clinical trials (RCTs), which represented a small number of patients ($n < 600$) and which did not incorporate findings from the relatively large number of contemporary studies. Thus, the effect of exercise therapy on VO_{2peak} after a cancer diagnosis is unclear.

Accordingly, we conducted a meta-analysis and systematic review to update and extend prior work and to evaluate the effects of exercise therapy on VO_{2peak} in patients with adult-onset cancer. Secondary aims were to examine whether the effects differed as a function of treatment response modifiers and to evaluate safety and treatment fidelity.

METHODS

Data Searches and Sources

A systematic search was conducted by a research informationist (K.M.) by using the Cochrane Central Register of Controlled Trials (Wiley), Embase (Elsevier), PubMed (National Library of Medicine), and Cumulative Index to Nursing and Allied Health Literature (EBSCO) from inception to October 2016 (Fig 1). The search strategy consisted of four components developed with a combination of relevant keywords and controlled vocabulary that included exercise training intervention, cardiovascular reserve capacity, cancer, and RCT (Data Supplement). An updated search was conducted on February 15, 2018, to identify recently published RCTs. This analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses–statement,[24] with registration at the international prospective register of systematic reviews (PROSPERO identifier: CRD42016050220).

Study Eligibility Criteria

RCTs that involved adult patients (age ≥ 18 years) with histologically confirmed adult-onset cancer and allocation to an exercise therapy or nonexercise control group with evaluation of CRF were eligible. Exercise therapy was operationalized and categorized as (1) aerobic (endurance) exercise therapy: chronic (≥ 3 weeks) repeated sessions (≥ 15 minutes per session)[25]; (2) resistance therapy: chronic (≥ 3 weeks) repeated sessions of voluntary muscle contractions against a resistance greater than that normally encountered in activities of daily living (≥ 15 minutes per session)[25]; and (3) combined aerobic and resistance therapy: as operationalized in the prior examples. The treatment schedule was classified as (1) standard prescription (ie, uniform exercise dosing across the intervention period after an initial lead-in period)[26] or (2) nonlinear prescription (ie, nonuniform, alternating exercise doses across the intervention period after an initial lead in).[26]

Study Selection and Data Extraction

Two authors (J.M.S. and E.S.) independently evaluated study eligibility by reviewing the titles and abstracts of all potential citations according to the inclusion criteria, performed data extraction by using standardized data abstraction forms (extracted variables in the Data Supplement), and evaluated risk of bias by using the Cochrane risk-of-bias tool.[27] Data were only extracted from the primary RCT article (and online supplement, or referenced protocol summary on a clinical trial database, if available). Disagreements were resolved by consensus in discussion with a third independent author (G.J.K.).

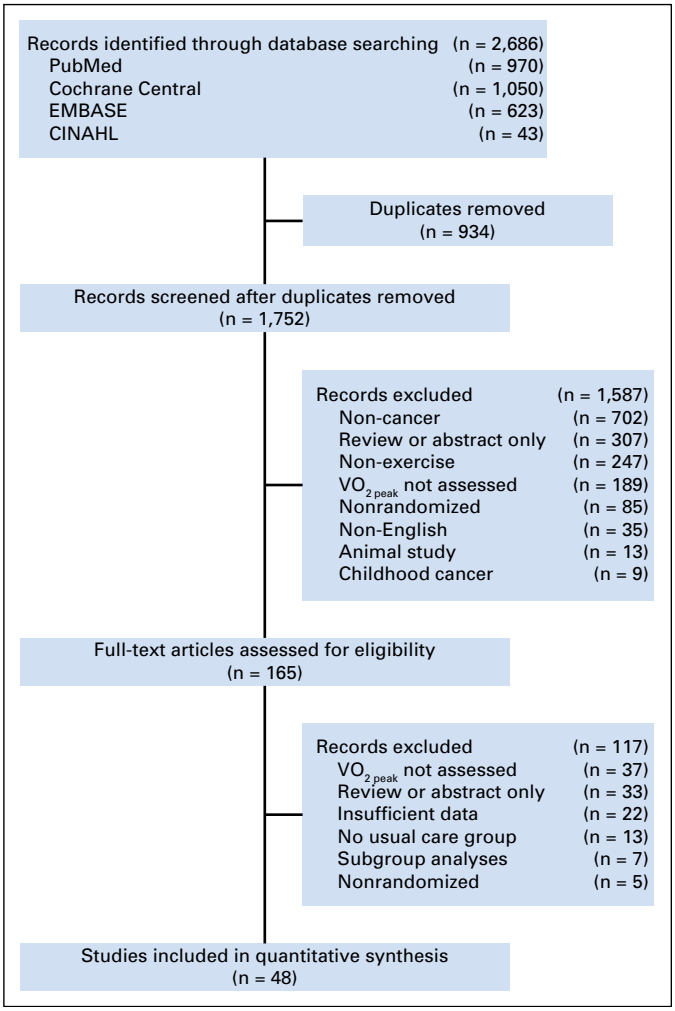

Fig 1. Study selection process. CINAHL, Cumulative Index to Nursing and Allied Health Literature; VO_{2peak}, peak oxygen consumption.

End Points

The primary end point was direct (ie, gas exchange analysis)[4] or estimated (ie, predicted on the basis of submaximal or maximal physiologic parameters) measurement of VO_{2peak} in mL $O_2 \times kg^{-1} \times min^{-1}$. Treatment fidelity was evaluated by assessing rates of attendance (ie, ratio of total attended to planned treatments), adherence (ie, ratio of planned sessions successfully completed at the planned duration and intensity to sessions attended),[26] and loss to follow-up (LTF; ie, ratio of patients who did not complete postintervention VO_{2peak} assessment to number randomly assigned). Safety was defined as report of any serious or nonserious adverse events (AEs) of any grade.[28] Full definitions of VO_{2peak} assessment, exercise therapy, treatment schedule and prescription components, treatment fidelity, and safety are provided in the Data Supplement.

Data Synthesis and Analysis

For each eligible article, the effect size was calculated by using the mean and standard deviation (SD) of change in VO_{2peak} from baseline to postintervention for the exercise and control groups. When only the mean and SD were reported, the SD of the change was calculated by the square root of $(SD^2_{baseline} + SD^2_{postintervention})$. This approach assumes a correlation of zero between the baseline and postintervention measures.[29] Mean levels and SDs of VO_{2peak} before and after exercise intervention from individual RCTs were used to calculate the sum of the differences in the individual studies and were weighted by the individual variances for each study to

derive weighted mean differences (WMDs) with 95% CIs by using both fixed effects and random effects.[30] The weight given to each study was determined by the precision of its estimate of effect and equals the inverse of the variance.[30] The primary analysis estimated the overall difference in change of VO_{2peak}, regardless of prescription and schedule characteristics or treatment fidelity. Five studies compared two different exercise therapy interventions versus a single control group; in these circumstances, the exercise therapy groups were combined as per standard guidelines.[29] Subgroup analyses investigated whether efficacy differed as a function of the following: (1) exercise prescription characteristics: modality (aerobic only *v* combined), schedule (standard *v* nonlinear), length (median split, $<$ 12 weeks *v* $\geq$ 13 weeks), and supervision (supervised *v* nonsupervised and the combination of supervision and nonsupervision); (2) study characteristics: intervention timing (during therapy *v* presurgery *v* after primary adjuvant therapy), primary cancer site (breast *v* other); and (3) publication year (median split, $<$ 2014 *v* $\geq$ 2015). The means and SD of the change in CRF were combined across case groups, which accounted for differences in sample size. The technical error (TE) in VO_{2peak} was used to evaluate whether there was a minimal detectable change above the measurement error. The TE is a conservative measure of assessor error and day-to-day variation and is calculated by taking the square root of the sum of squared differences of repeated measures divided by the total number of paired samples multiplied by two.[31] On the basis of prior work,[32] we considered a VO_{2peak} change of 1.28 mL $O_2 \times kg^{-1} \times min^{-1}$ or more representative of the minimal detectable change (1 $\times$ the TE of VO_{2peak}).[31]

The percentage of variability across the pooled estimates attributable to heterogeneity beyond chance was estimated with the I^2 statistic (ie, low [0% to 25%], moderate [26% to 75%], and high [76% to 100%] severity of between-study heterogeneity) and by the leave-one-out approach, as appropriate.[33] Statistical heterogeneity across the trials was evaluated with the Kendall τ correlation and the Cochran *Q* statistic to test the null hypothesis that there were no differences in effect size across studies.[29] The potential for publication bias was evaluated visually by constructing a funnel plot to display the precision of the estimate of the effect size (the reciprocal of its standard error) against the estimate of the effect size (odds ratio, on a logarithmic scale)[34] as well as formally by the Rosenthal fail-safe number.[35] All statistical analyses were conducted in R software, version 3.3.1, including the metafor package.[36] A *P* value $<$ .05 was considered statistically significant.

RESULTS

The updated search yielded 467 records. A total of 2,686 potential records were identified, and 934 duplicates were removed using the EndNote citation management software program (Clarivate Analytics, Philadelphia, PA). A total of 1,752 records remained for title and/or abstract screening. After review, 165 articles were deemed eligible and underwent full review (Fig 1). A total of 48 articles, which represented 48 independent RCTs,[37-84] were included in the primary analysis.

Risk of Bias and Publication Bias Assessment

Adequate sequence generation and allocation concealment was reported in 40 (83%) of 48 articles and 36 (75%) of 48 articles, respectively. Twenty-three (48%) of 48 articles reported blinding of testing personnel to treatment allocation. Finally, 30 (63%) of 48 articles and 42 (88%) of 48 articles were free of attrition bias and selective outcome reporting, respectively (Data Supplement). The Cochran *Q* test for heterogeneity was 49.5 ($P > .05$), and the Kendall τ correlation was 0.65 (95% CI, -0.55 to 1.84). The funnel plot suggested minimal publication bias (Data Supplement), and the Rosenthal fail-safe number indicated that 1,391 null studies would be required to reduce significance to .05.

Study and Patient Characteristics

Of the 48 trials, 23 (48%) were published between 2001 and 2014, and the remainder were published in 2015, or later. The 48 trials included a total of 3,632 patients; 1,990 patients (55%) and 1,642 patients (45%) were allocated to exercise therapy and control groups, respectively (Table 1). The mean SD patient age was 55 $\pm$ 7.5 years, and 68% of patients were women. Exercise history and CRF values lower than age-matched sedentary normative values were eligibility criteria in 11 studies (23%) and one study (2%), respectively. The mean SD sample size was 75 $\pm$ 67. VO_{2peak} data from a total of 3,394 patients were reported—exercise (n = 1,873) and control (n = 1,521). Twenty-one (44%) of 48 studies were conducted in breast cancer. A total of 27 studies (56%) were conducted after the completion of primary adjuvant therapy. A detailed summary of individual study characteristics is provided in the Data Supplement.

CRF Assessment and Exercise Prescription Characteristics

VO_{2peak} was directly measured in 30 trials (63%) and was estimated in 18 trials (38%) (Data Supplement). In trials that used direct VO_{2peak} measurement, two (7%), 17 (57%), and eight (27%) reported equipment calibration, test protocol, or acceptable CRF test criteria, respectively. In those that estimated VO_{2peak}, seven (39%) of 18 reported the method to predict VO_{2peak}. ECG rhythm monitoring was conducted in 14 (29%) of 48 studies. In the 48 trials, 27 (56%) tested aerobic (endurance) therapy, whereas 18 trials (38%) tested combination therapy. The majority of trials (43; 90%) adopted a standard prescription scheduling approach; 31 trials (65%) used a supervised location; and 27 trials (56%) had an intervention length $\leq$ 12 weeks (Data Supplement). Exercise intensity was monitored by ratings of perceived exertion and heart rate in seven studies (15%) and 19 studies (40%), respectively; the method of intensity monitoring was not reported in 19 articles (40%).

Effects on CRF

VO_{2peak} increased by +2.80 mL $O_2 \times kg^{-1} \times min^{-1}$ with exercise therapy compared with +0.02 mL $O_2 \times kg^{-1} \times min^{-1}$ in the control group, which resulted in a between-group WMD of +2.13 mL $O_2 \times kg^{-1} \times min^{-1}$ (95% CI, 1.58 to 2.67 mL $O_2 \times kg^{-1} \times min^{-1}$; I^2, 20.6; $P < .001$; Fig 2), which favored exercise therapy. The WMD effect size (ES) did not substantially change upon removal of any single study (mean ES, 2.13; minimum ES, 1.95; maximum ES, 2.23). Subgroup analyses found no significant differences on the basis of any treatment modifier (Table 2). Change in VO_{2peak} was greater than the TE of measurement (1.28 mL $O_2 \times kg^{-1} \times min^{-1}$) for exercise therapy prescriptions that followed a nonlinear schedule compared with standard scheduling (+1.38 mL $O_2 \times kg^{-1} \times min^{-1}$; 95% CI, -0.93 to 3.69 mL $O_2 \times kg^{-1} \times min^{-1}$; $P = .242$).

Safety and Fidelity

AEs, attendance, adherence, and LTF rates were reported in 30 (63%), 32 (67%), seven (15%), and 45 (94%) of 48 articles, respectively. Overall, a total of 44 AEs was reported, and the AEs consisted predominantly of nonserious events, such as dizziness, chest pain, and muscle-related pain. Serious AEs were myocardial infarction and hip fracture (Data Supplement). Overall, the mean

SD LTF rate was 11% ± 13%; there were no differences between exercise and control groups ($P = .964$). The mean SD attendance and adherence rates were 84% ± 12% and 88% ± 32%, respectively.

DISCUSSION

Findings of this meta-analysis demonstrate that exercise therapy is an efficacious adjunctive strategy to improve VO_{2peak} in patients with adult-onset cancer. Such findings may be of clinical importance, because impaired VO_{2peak} appears to be a ubiquitous phenotype both during[1] and years after treatment cessation,[9,10] and it correlates with heightened symptom burden[15] and poorer clinical outcomes.[1,18,19] Collectively, these findings support the recommendation of exercise therapy to prevent and/or mitigate cancer treatment–associated reductions in VO_{2peak} or to recover impaired VO_{2peak} in the post-treatment setting.[85,86]

Table 1. Trials Included in the Meta-Analysis (N = 48)

Variable	No. of Trials (%)
Publication year	
2000-2014	23 (48)
2015-2018	25 (52)
Region of origin	
Americas	19 (48)
United States	10
Canada	8
Brazil	1
Europe	22 (46)
Netherlands	5
United Kingdom	4
Denmark	3
Italy	2
Norway	2
Spain	2
France	1
Germany	1
Ireland	1
Asia	4 (8)
Iran	2
Korea	1
Taiwan	1
Australia	3 (6)
Sample size	
≤ 50	24 (50)
51-100	13 (27)
≥ 101	11 (23)
No. of participants	3,632 (100.0)
Group allocation	
Exercise	1,990 (55)
Control	1,642 (45)
Mean age, years (SD)	55 (7.5)
Female sex	2,336 (68)
Cancer site	
Breast	21 (44)
Prostate	6 (13)
Mixed	6 (13)
Lung	4 (8)
Other	4 (8)
Hematologic	3 (6)
Colorectal	2 (4)
GI	2 (4)
Setting	
Presurgery	5 (10)
During treatment	14 (29)
During and after primary adjuvant therapy	2 (4)
After primary adjuvant therapy, years	27 (56)
< 1	9 (19)
1 to 5	9 (19)
> 5	3 (6)
Time not reported	6 (13)

Abbreviation: SD, standard deviation.

The magnitude of exercise-induced VO_{2peak} improvements observed in this meta-analysis is slightly lower than that in comparable prior reports.[23,87] For example, McNeely et al[87] reported that exercise therapy increased VO_{2peak} by a WMD of +3.39 mL $O_2 \times kg^{-1} \times min^{-1}$ compared with control in three trials among patients with early-stage breast cancer, whereas Jones et al[23] found a WMD improvement of +2.90 mL $O_2 \times kg^{-1} \times min^{-1}$compared with control in six studies (four in breast cancer studies) that involved 571 patients. The precise reasons for the discrepant findings are not clear but likely relate to differences in study cohorts, such as inclusion of a broader range of malignancies, larger sample sizes (and therefore greater heterogeneity in exercise response), investigation of different exercise prescriptions, and a higher proportion of trials conducted during therapy in contemporary versus earlier work. Nevertheless, the observed VO_{2peak} improvement observed in this study may be clinically meaningful. At least three independent cohorts indicate that direct measurement of VO_{2peak} (measured after diagnosis) is a strong, significant predictor of all-cause[1,88] and cause-specific mortality,[89] even after adjustment for important clinical covariates, in patients with metastatic breast cancer and non–small-cell lung cancer. Moreover, Laukkanen et al[90] found that a 1.0 mL $O_2 \times kg^{-1} \times min^{-1}$increase in VO_{2peak} during 11 years was associated with an adjusted 9% reduction in all-cause mortality in asymptomatic men after approximately13 years of follow-up. Overall, our findings support the national exercise cancer guidelines that endorse "avoidance of inactivity"[85] but do not necessarily support recommendations to follow the American College of Sports Medicine physical activity guidelines[25] because most trials examined the efficacy of an exercise dose of approximately 100 to 135 minutes per week (three times weekly for 30 to 45 minutes per session). Elucidation of the appropriate dose, timing, and length of exercise therapy as well as whether improvements in CRF correspond with hard clinical end points are major research priorities in this field.

The primary analysis estimated the overall benefit of exercise therapy without consideration of potential response modifiers; subgroup analyses may provide insight into characteristics that modify the exercise-to-VO_{2peak} response relationship. Our finding that exercise therapy prescriptions that observe a nonlinear dosing schedule were superior to standard scheduling (on the basis of a between-subgroup difference greater than the TE of measurement) is consistent with the only other prior report that directly compared these approaches in patients with chronic obstructive pulmonary disease.[91] Collectively, these findings create the provocative notion that approaches that individualize therapy intensity on the basis of specific physiologic thresholds together with continual progression of exercise dose (in conjunction with appropriate rest/recovery, also known as periodization) may optimize VO_{2peak} improvements. Nevertheless, such a notion is speculative at present, given the small number of trials that have investigated this prescription approach in cancer and other clinical populations. The findings of an ongoing trial to test the efficacy of traditional

versus nonlinear aerobic therapy scheduling in post-treatment patients with early-stage breast cancer[92] (with results expected in late 2018) will address this important question directly.

It is worth noting that the current approach—identification of treatment-response modifiers via subgroup analyses—may be inherently limited because of the inability to consider variability in individual response to exercise therapy.[31,93,94] For instance, the mean change in VO_{2peak} after 24 weeks of aerobic therapy among patients with prostate cancer was 9% for the overall cohort but ranged from −18% to +32% when individual patient-level data were considered.[95] Other studies have reported similar findings.[31,93,94] Elucidation of the heterogeneity in VO_{2peak} response to exercise therapy will be critical to inform a precision medicine approach[96]—one that encompasses personalized risk stratification to guide targeted exercise prescriptions.[97] Rigorous testing and implementation of such an approach pose significant challenges to

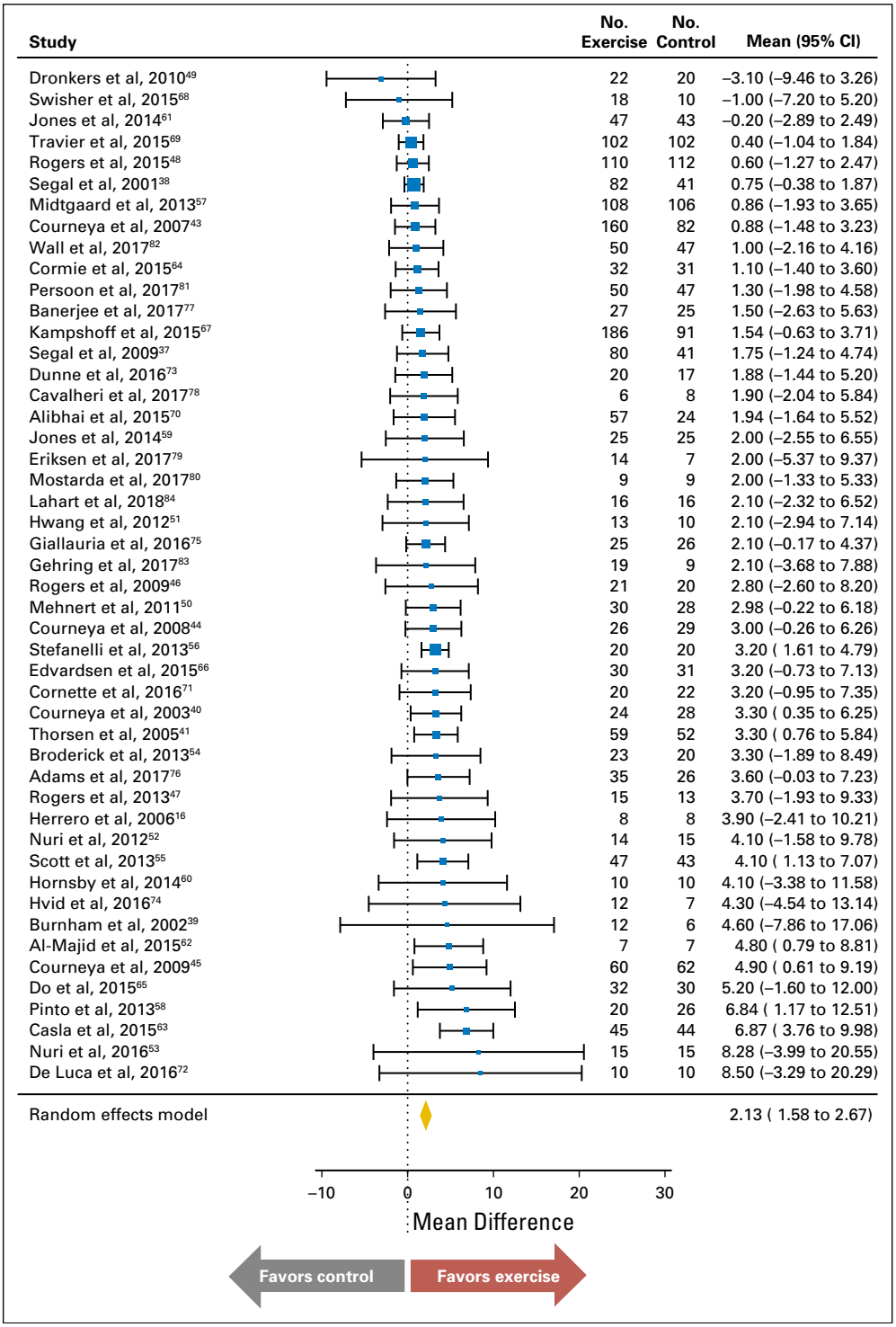

Fig 2. Pooled effects of exercise training compared with non-exercise control on cardiorespiratory fitness (peak oxygen consumption, VO_{2peak}).

Table 2. Treatment Effect Modifiers

Treatment Modifier	No. of Studies	No. of Patients by Arm		WMD			
				Between Ex and Control Arms*		Between Modifier Subgroups†	
		Ex	Control	Mean (95% CI), direction	*P*	Mean (95% CI), direction	*P*
Setting							
Therapy							.130
Presurgery	5	103	89	+2.36 (0.86 to 3.86), Ex	< .001	−1.08 (−2.16 to 0.00), during *v* after	
During	14	505	475	+1.37 (0.58 to 2.16), Ex	< .001	−0.99 (−2.50 to 0.55), during *v* presurgery	
After	27	910	864	+2.45 (1.71 to 3.19), Ex	< .001		
Population						+0.10 (−1.15 to 1.35), other	.874
Breast	21	681	676	+2.19 (1.37 to 3.00), Ex	< .001		
Other	20	1,192	845	+2.29 (1.34 to 3.24), Ex	< .001		
Prescription							
Schedule						+1.38 (1.37 to 1.54), nonlinear	.304
Standard	43	1,475	1,388	+2.15 (1.48 to 2.83), Ex	< .001		
Nonlinear	5	133	133	+3.43 (1.09 to 5.77), Ex	.003		
Modality						+0.14 (−1.37 to 1.09), combined	.824
Aerobic	27	860	820	+2.31 (1.54 to 3.09), Ex	< .001		
Combined	18	748	701	+2.17 (1.22 to 3.13), Ex	< .001		
Length, weeks						+1.00 (−2.02 to 0.03), ≤ 12 weeks	.057
≤ 12	27	778	721	+2.60 (1.84 to 3.59), Ex	< .001		
> 13	21	830	800	+1.60 (0.81 to 2.59), Ex	< .001		
Supervision						−0.74 (−1.99 to 0.52), non/combined	.250
Supervised	31	1,052	960	+2.36 (1.74 to 2.98), Ex	< .001		
Non/combined	14	569	531	+3.29 (1.53 to 5.06), Ex	< .001		
Publication year						+0.27 (1.37 to 1.54), 2001-2014	.620
2001-2014	23	756	748	+2.27 (1.49 to 3.06), Ex	< .001		
2015-2018	25	852	773	+2.00 (1.23 to 2.77), Ex	< .001		

Abbreviations: Ex, exercise; WMD, weighted mean difference.
*Represents the WMD between exercise and control within treatment modifier subgroup (eg, exercise *v* control during therapy).
†Represents the WMD between modifier subgroups (eg, aerobic *v* combined).

the field but could hold tremendous promise to optimize the safety and efficacy of exercise therapy in clinical settings.[97]

Finally, results of this study demonstrate that exercise therapy is a safe and feasible intervention strategy for patients with cancer both during and after primary anticancer treatment. However, this conclusion must be interpreted with caution because of the low number of studies that monitored AEs as well as the lack of standardization in those that monitored AEs. Similarly, the fidelity of exercise therapy appears high, as demonstrated by low LTF rates (< 15%) and high attendance rates (approximately 80%). These end points, however, provide limited insight into the actual feasibility/tolerability of exercise therapy. In oncology drug trials, tolerability/feasibility is first evaluated in phase I studies that use end points such as treatment discontinuation, interruption, and dose modification. Such metrics have not been applied to exercise trials but may provide critical information beyond traditional measures.[59,98] Inadequate monitoring and reporting of safety and treatment fidelity not only diminish study rigor and quality but also could lead to erroneous conclusions about the harm-to-benefit ratio of exercise therapy in a given indication. The design, conduct, and reporting of exercise-oncology trials should adhere to established guidelines, such as CONSORT for nonpharmacological trials,[28] as well as relevant extensions, such as CONSORT-Harms and the Template for Intervention Description and Replication (TIDier).[99] Such efforts will improve the reproducibility and interpretation of exercise-oncology trials that, in turn, will allow for evidence-based exercise guidelines and optimal translation of exercise into clinical practice.

A limitation of this study is the inclusion of patient cohorts who are predominantly middle-aged women with early-stage breast cancer; thus, generalizability of our findings to other cancer populations require caution. Other limitations include relatively small sample sizes, short-term intervention period, and no long-term follow-up data to evaluate clinical events.

In summary, exercise therapy is an effective adjunctive therapy to improve VO_{2peak} in patients with cancer. Our findings support the recommendation of exercise therapy to augment, mitigate decline, and/or recover impaired VO_{2peak} in patients with cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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