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Effect of Exercise Training on Peak Oxygen Consumption in Patients with Cancer: A Meta-Analysis

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ABSTRACT

Background. **We conducted a meta-analysis to determine the effects of supervised exercise training on peak oxygen consumption (VO_{2peak}) in adults with cancer.**

Methods. **A literature review using Ovid MEDLINE (1950–2010), the Cochrane Central Register of Controlled Trials (1991–2010), AMED (1985–2010), Embase (1988–2010), PubMed (1966–2010), Scopus (1950–2010), and Web of Science (1950–2010) was performed to identify randomized controlled trials examining the effects of supervised exercise training on measurement of VO_{2peak} (via gas exchange analysis) in adults with cancer. Studies were selected using predetermined criteria, and two independent reviewers extracted data. Weighted mean differences (WMDs) were calculated using random effect models.**

Results. **Six studies evaluated VO_{2peak} involving a total of 571 adult cancer patients (exercise, $n = 344$; usual care control, $n = 227$). Pooled data indicated that exercise training was associated with a statistically significant increase in VO_{2peak} (WMD, 2.90 $ml \cdot kg^{-1} \cdot min^{-1}$; 95% confidence interval [CI], 1.16–4.64); however, significant heterogeneity was evident in this estimate (I^2, 87%). Usual care (control) was associated with a significant decline in VO_{2peak} from baseline to postintervention (WMD, -1.02 $ml \cdot kg^{-1} \cdot min^{-1}$; 95% CI, -1.46 to -0.58; I^2, 22%). Sensitivity analyses indicated superior improvements in VO_{2peak} for studies conducted for a shorter duration (<4 months) and following the completion of adjuvant therapy (p-values < .001). Exercise training was not associated with a higher incidence of adverse events, although safety was not rigorously monitored or reported.**

Conclusions. **Supervised exercise training is associated with significant improvements in VO_{2peak} following a diagnosis of early-stage cancer, with minimal adverse events.** ***The Oncologist*** 2011;16:112–120

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Introduction

It is well established that cardiorespiratory fitness as well as change in cardiorespiratory fitness are powerful predictors of mortality in healthy adults as well as those with cardiovascular disease (CVD), even after controlling for traditional CVD risk factors [1–5]. Maximal or peak oxygen consumption (VO_{2peak}) provides the gold standard measurement of cardiorespiratory fitness and is used widely in numerous clinical and research applications [6].

Emerging evidence indicates that VO_{2peak} also may be a parameter of central importance following a diagnosis of cancer. Prior to surgical resection, VO_{2peak} is a strong predictor of perioperative or postoperative complication risk in patients with non-small cell lung cancer (NSCLC) [7–10]. VO_{2peak} is also centrally implicated in the etiology of certain cancer therapy–induced late effects. Specifically, VO_{2peak} is a predictor of anthracycline and trastuzumab-induced left ventricular dysfunction and CVD risk profile (e.g., blood pressure, lipid profile, c-reactive protein) as well as global quality of life (QOL) and fatigue in patients with solid malignancies [11–13]. Finally, there is evidence from one report that VO_{2peak} is also a strong independent predictor of survival in NSCLC patients even after controlling for traditional prognostic factors [14].

Unfortunately, cancer patients have marked reductions in VO_{2peak}. In a series of studies by our group spanning the entire cancer survivorship continuum (i.e., diagnosis to palliation), we observed that VO_{2peak} is consistently ~30% below that of age- and sex-matched *sedentary* individuals without a history of cancer [15, 16]. The precise causes of a poor VO_{2peak} remain to be elucidated but likely reflect normal age-related exercise limitation together with additional direct (injury to the cardiovascular system) and indirect (toxicities secondary to treatment) effects of cytotoxic therapy that, in combination, adversely impact the organ components that govern exercise tolerance [17].

Numerous studies report that structured exercise training is associated with significant improvements in measures of cardiorespiratory fitness and related outcomes across a broad range of oncology settings [18–21]. However, the current evidence base is fraught with important methodological limitations, including nonrandomized designs, small sample sizes, different exercise training modes (aerobic and/or resistance training), and determination of cardiorespiratory fitness using non-VO_{2peak} measures. To clarify this issue, we employed the meta-analysis approach to determine the effect of exercise training on VO_{2peak} in adult cancer patients. A secondary aim was to examine whether the effects of exercise on VO_{2peak} differed as a function of exercise intervention (e.g., type, intensity, duration) or clinical characteristics (e.g., cancer type, treatment status).

Methods

Search Strategy and Inclusion Criteria

A comprehensive literature review was conducted using Ovid MEDLINE (1950–2010), the Cochrane Central Register of Controlled Trials (1991–2010), AMED (1985–2010), Embase (1988–2010), PubMed (1966–2010), Scopus (1950–2010), and Web of Science (1950–2010) with the following Medical Subject Heading terms and text words: oncology, cancer, neoplasms, malignancies, exercise, exercise therapy, and exercise training. Relevant reference lists were also manually searched.

Randomized controlled trials (RCTs) involving adult patients with histologically confirmed cancer that allocated subjects to a supervised exercise training or concurrent nonexercise control group were deemed eligible. Supervised exercise training was defined as interventions consisting of aerobic, resistance, or the combination of aerobic and resistance training as opposed to unsupervised or home-based interventions. Additionally, all eligible studies were required to report a measurement of cardiorespiratory fitness via a cardiopulmonary exercise test (CPET) with gas exchange analysis (to permit assessment of VO_{2peak}). Studies with a participant mean age <18 years, that were not written in English, that were a review article only, and that did not assess the independent effects of exercise training were excluded.

Study Selection, Data Extraction, and Quality Assessment

Two authors (C.L.B. and E.N.P.) independently evaluated study eligibility by reviewing the titles and abstracts of all potential citations according to the inclusion criteria. The same authors independently performed data extraction using standardized data abstraction forms. Disagreements were resolved by consensus in discussion with a third independent author (M.H.). When required, the primary authors were contacted to clarify ambiguous experimental procedures and/or results or provide additional data not provided in the published manuscript. Methodological quality of eligible studies was assessed using the Oxford quality scoring system and Schulz approach to allocation concealment [22]. The risk for bias was assessed with the Cochrane criteria [23].

Data Synthesis and Analysis

For each eligible study, the effect size of exercise training was calculated using the change in VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$) from baseline to postintervention for the exercise and nonexercise control groups. In circumstances when the change from baseline data or corresponding standard deviations were not available, these values were calculated using standard statistical methods assuming a

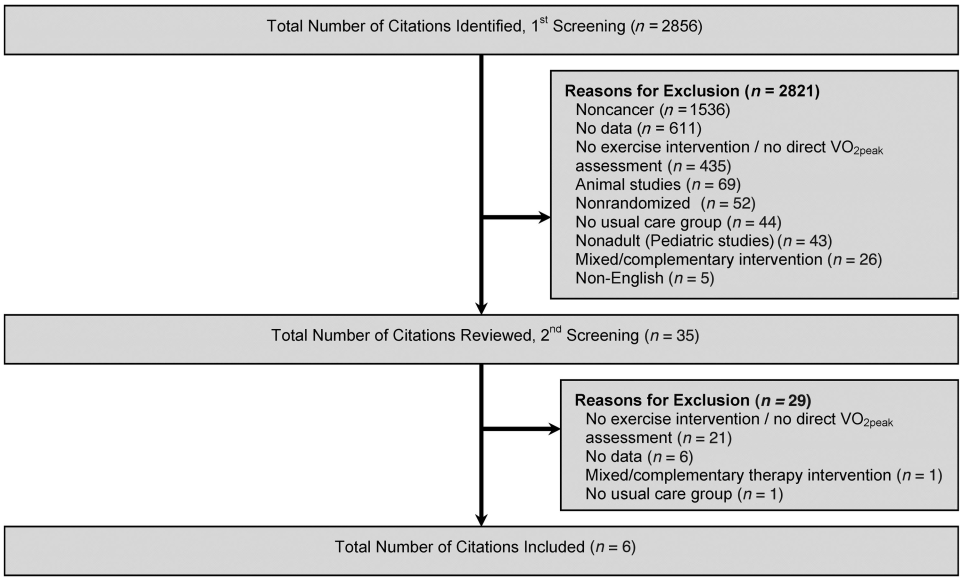

Figure 1. Selection process of eligible studies.

correlation of 0.50 between the baseline and postintervention scores within each subject [24]. Data from all eligible studies were combined as weighted mean differences (WMDs) with 95% confidence intervals (CIs) using the random effects model. Statistical analyses were conducted using Review Manager Software (RevMan 5.0; The Cochrane Collaboration, Oxford, UK). The primary analysis compared the effect of exercise training, regardless of exercise prescription characteristics, with that of the nonexercise control on VO_{2peak}. Sensitivity analyses were performed to investigate whether the effects of exercise on VO_{2peak} differed as a function of exercise intervention or clinical characteristics (e.g., cancer type, treatment status).

Heterogeneity was quantified using the I^2 statistic. I^2 evaluates the percentage of total variation across included studies attributed to heterogeneity as opposed to chance. A value $>50\%$ is considered substantial heterogeneity [25]. The Deeks' χ^2 test was conducted to test for significant heterogeneity reduction in partitioned subgroups [26]. The following subgroup analyses were conducted to investigate possible sources of heterogeneity: (a) intervention length ($\leq$4 months versus $>$4 months), (b) gender/primary cancer diagnosis (all females/breast cancer versus all males/prostate cancer versus mixed), and (c) treatment status (postsurgery and completion of adjuvant therapy versus postsurgery and during adjuvant therapy versus mixed). Publication bias was tested visually using a funnel plot [27] and quantitatively using the Begg adjusted-rank correlation test [28] and Egger regression asymmetry test [29]. Tests were performed using Stata 11.0 (Stata Corporation, College Station, TX).

Results

In total, 2,855 potential citations were identified; after initial review; 35 papers were deemed eligible and underwent full review (Fig. 1). The major reasons for exclusion were: (a) inclusion of participants without a histological diagnosis of cancer, (b) absence of an exercise intervention, and (c) review article. Upon further review, 29 papers were further excluded; reasons for exclusion were: (a) studies did not perform a supervised exercise intervention or did not conduct a direct measure of VO_{2peak}, (b) insufficient data were presented in the paper, (c) exercise training was combined with a concurrent complementary intervention, and (d) no "usual care" control group. Thus, six trials were deemed eligible [20, 21, 30–33] and included in the primary analysis.

Study Characteristics

Study characteristics are provided in Table 1. Three studies performed a two-arm RCT (aerobic training versus control [20, 31] or the combination of aerobic and resistance training versus control [33]) and three conducted a three-arm RCT comparing either different types of exercise (aerobic training versus resistance training) [21, 32] or intensities of aerobic training (low intensity versus moderate intensity) [30]. Three of the six studies were conducted in women with early-stage breast cancer [31–33]; the other studies were conducted among patients with prostate cancer ($n = 1$) [21], non-Hodgkin's lymphoma ($n = 1$) [20], and a combination of colon or breast cancer ($n = 1$) [30]. Three studies were conducted following the completion of definitive adjuvant therapy (i.e., chemotherapy or radiation) [30, 31, 33], two were conducted during defini-

Table 1. Study characteristics

Study	Cancer site	Disease stage	Treatment status[a]	Total (*n*)	Exercise (*n*)	Control (*n*)	Age	Sex (% female)	Prior therapy[b]	Comorbid disease	Concurrent medication
Courneya et al. (2009) [20]	Lymphoma	Early and advanced	On, 44%; Off, 56%	122	60	62	53	41%	RT, 23%; CT, 44%	Arthritis, 31%; hypercholesteremia, 30%; hypertension, 29%	NR
Segal et al. (2009) [21]	Prostate	Early and advanced	On	121	80	41	66	0%	–	NR	NR
Courneya et al. (2007) [32]	Breast	Early	On	242	160	82	49	100%	–	Hypertension, 7%	NR
Herrero et al. (2006) [33]	Breast	Early	Off	16	8	8	50	100%	Sx, 100%; CT, 100%	NR	NR
Courneya et al. (2003) [31]	Breast	Early	Off (46% on ET)	52	24	28	59	100%	Sx, 100%; RT, 71%; CT, 40%	NR	NR
Burnham and Wilcox (2002) [30]	Breast, Colon	Early	Off	18	12	6	54	83%	Sx, 61%; RT, 63%; CT, 88%	NR	NR

[a]On treatment defined as undergoing primary adjuvant therapy (i.e., radiotherapy, chemotherapy); off treatment defined as completion of primary adjuvant therapy.
[b]Only for studies conducted following the completion of primary adjuvant therapy.
Abbreviations: CT, chemotherapy; ET, endocrine therapy, NR, not reported; RT, radiation therapy; Sx, surgery.

tive cytotoxic therapy [21, 32], and one included patients both receiving and following the completion of therapy [20]. No studies reported performing continuous electrocardiogram monitoring during CPET whereas two studies reported monitoring heart rate during exercise training sessions [21, 30]. The methodological quality of trials is presented in Table 2.

Exercise Intervention Characteristics

The exercise intervention characteristics of included studies are provided in Table 3. Intervention lengths were in the range of 8–24 weeks. In all studies, exercise was prescribed 3 times per week, with session durations in the range, on average, of 14–45 minutes. All studies reported prescribing "moderate-to-high intensity" exercise, defined as 40%–80% of peak heart rate, heart rate reserve, or VO_{2peak} obtained from the baseline cardiopulmonary exercise test, whereas one prescribed "low-intensity" training (25%–40% of baseline heart rate reserve). Aerobic training alone was the form of exercise training in three studies [20, 31, 32], two compared aerobic training only with resistance training only [21, 32], and one tested the combination of aerobic and resistance training [33].

Effect of Exercise Training on VO_{2peak}

Six studies examined the effect of exercise training on VO_{2peak}, with 344 participants in the exercise groups and 227 participants in the nonexercise groups. The baseline mean VO_{2peak} was not different between groups in any study ($p > .05$). Pooled data indicated that exercise training was associated with a statistically significant increase in VO_{2peak} (WMD, 2.90 ml·kg^{-1}·min^{-1}; 95% CI, 1.16–4.64); however, significant heterogeneity was evident in this estimate (I^2, 87%) (Fig. 2). Usual care (control) was associated with a significant decline in VO_{2peak} from baseline to postintervention (WMD, −1.02 ml·kg^{-1}·min^{-1}; 95% CI, −1.46 to −0.58; I^2, 22%) There was no evidence of publication bias (Begg adjusted-rank correlation test, $p = .71$; Egger regression asymmetry test, $p = .69$).

Effect of Exercise Training on VO_{2peak} by Exercise Intervention or Clinical Characteristics

Sensitivity analyses were conducted to investigate whether the effects of exercise on VO_{2peak} differed as a function of exercise intervention or clinical characteristics. However, given the small number of eligible studies, it was only feasible to conduct sensitivity analyses based on intervention length (<4 months versus ≥4 months), therapy status (during versus following adjuvant therapy), and exercise modality (aerobic only versus resistance only). Concerning intervention length, for studies conducted for ≥4 months, the overall effect size was 1.21 ml·kg^{-1}·min^{-1} (two studies, 363 patients; WMD, 1.21 ml·kg^{-1}·min^{-1}; 95% CI, 0.50–1.92; I^2, 0%) favoring exercise training. The corresponding pooled effect size for studies <4 months was 4.26 ml·kg^{-1}·min^{-1} (four studies, 208 patients; WMD, 4.26 ml·kg^{-1}·min^{-1}; 95% CI, 2.92–5.60) favoring exercise training, although moderate heterogeneity was evident in this estimate (I^2, 43%). The difference between subgroups was significant (χ^2, 33.49; $p < .001$) favoring studies conducted for <4 months. For therapy status, in studies conducted during adjuvant therapy, the pooled effect size was 1.21 ml·kg^{-1}·min^{-1} (two studies, 363 patients; WMD, 1.21 ml·kg^{-1}·min^{-1}; 95% CI, 0.50–1.92; I^2, 0%) favoring exer-

Table 2. Methodological quality

Study	Description	Reviewers' judgment
Sequence generation		
Burnham and Wilcox (2002) [30]	Matched on VO_{2peak} and randomly assigned to groups	Yes
Courneya et al. (2003) [31]	Stratified by adjuvant therapy and randomly assigned to groups	Yes
Herrero et al. (2006) [33]	Not reported	UN
Courneya et al. (2007) [32]	Stratified by center and chemotherapy and randomly assigned to groups	Yes
Courneya et al. (2009) [20]	Stratified by disease type and treatment and randomly assigned to groups	Yes
Segal et al. (2009) [21]	Stratified by duration of ADT and randomly assigned to groups	Yes
Allocation concealment		
Burnham and Wilcox (2002) [30]	Not reported	UN
Courneya et al. (2003) [31]	Block permutation used to generate allocation sequence within strata	Yes
Herrero et al. (2006) [33]	Allocation concealment unclear	UN
Courneya et al. (2007) [32]	Allocation sequence generated at coordinating center and concealed from project directors	Yes
Courneya et al. (2009) [20]	Generated independently and concealed in opaque envelopes	Yes
Segal et al. (2009) [21]	Central random assignment use (allocation concealment before assignment)	Yes
Blinding		
Burnham and Wilcox (2002)	Not reported	UN
Courneya et al. (2003) [31]	Outcome assessors blinded to group assignment performed testing and determined scores preintervention/postintervention	Yes
Herrero et al. (2006) [33]	Outcome assessors blinded to group assignment measured outcome variables	Yes
Courneya et al. (2007) [32]	Not reported whether outcome assessors were blinded to group assignment	UN
Courneya et al. (2009) [20]	Outcome assessors not always blinded to group assignment	No
Segal et al. (2009) [21]	Not reported whether outcome assessors blinded to group assignment	No
Incomplete (VO_{2peak}) data		
Burnham and Wilcox (2002) [30]	One control subject performed exercise training but was excluded; to maintain matched group status, two subjects matched with excluded control removed from analysis	No
Courneya et al. (2003) [31]	Attrition/reasons for loss to follow-up reported	Yes
Herrero et al. (2006) [33]	All subjects completed pre-exercise/postexercise tests	Yes
Courneya et al. (2007) [32]	Reasons for not completing postintervention assessments uncertain	UN
Courneya et al. (2009) [20]	Attrition/reasons for loss to follow-up reported	Yes
Segal et al. (2009) [21]	Reasons for not completing postintervention exercise test uncertain	UN
Selective outcome reporting		
All studies	Study protocol available and prespecified outcomes reported	Yes
Other sources of bias		
All studies	Appear to be free from other sources of bias	Yes

Yes indicates a low risk for bias; No indicates a high risk for bias.
Abbreviations: ADT, androgen deprivation therapy; UN, unclear risk for bias.

cise training. The corresponding pooled effect size for studies conducted following the completion of therapy was 3.36 $ml \cdot kg^{-1} \cdot min^{-1}$ (three studies, 86 patients; WMD, 3.36 $ml \cdot kg^{-1} \cdot min^{-1}$; 95% CI, 2.20–4.53; I^2, 0%) favoring exercise training. The difference between subgroups was significant (χ^2, 38.62; $p < .001$) favoring studies conducted after therapy completion (Fig. 3). Only two studies directly compared aerobic training with resistance training, with contrasting results. Overall, there was no significant difference in VO_{2peak} as a func-

Table 3. Exercise intervention characteristics

Study	Exercise intervention	Modality	Length	Frequency per wk	Duration range/session	Intensity (range)	Monitoring
Courneya et al. (2009) [20]	Aerobic training	CE	12 wks	3	15–45 minutes	60%−75% VO_{2peak} + x1 INT session in last month at 100% VO_{2peak}	NR
Segal et al. (2009) [21]	Aerobic training versus resistance training	Aerobic training—CE, ET, TM; resistance training—10 UE/LE, 2 sets × 8 reps	24 wks	3	15–45 minutes	Aerobic training, 50%−75% VO_{2peak}; resistance training, 60%−70%, 1 RM	HR during training sessions
Courneya et al. (2007) [32]	Aerobic training versus resistance training	Aerobic training—CE, ET, TM; resistance training—9 UE/LE, 2 sets × 8 reps	17 wks	3	15–45 minutes	Aerobic training, 60%−80% VO_{2peak}; resistance training, 60%−70%, 1 RM	NR
Herrero et al. (2006) [33]	Combined aerobic and resistance training	Aerobic training—CE, ET, TM; resistance training—10 UE/LE, 1–3 sets × 8–15 reps	8 wks	3	20–30 minutes	Aerobic training, 70%−80% HR_{max}; resistance training, 60%−70%, 1 RM	HR and BP during testing
Courneya et al. (2003) [31]	Aerobic training	CE	15 wks	3	15–35 minutes	70%−75% VO_{2peak}	NR
Burnham and Wilcox (2002) [30]	High-intensity aerobic training versus low-intensity aerobic training	CE, SC, TM	10 wks	3	14–32 minutes	High-intensity aerobic training, 40%−60% HRR; low-intensity aerobic training, 25%−40% HRR	HR during training sessions

Abbreviations: BP, blood pressure; CE, cycle ergometry; ET, elliptical trainer; HR, heart rate; HR_{max}, heart rate maximum; HRR, heart rate reserve; INT, interval; LE, lower extremity; NR, not reported; RM, repetition maximum; SC, stair climber; TM, treadmill; UE, upper extremity; x1, one time/wk of interval training.

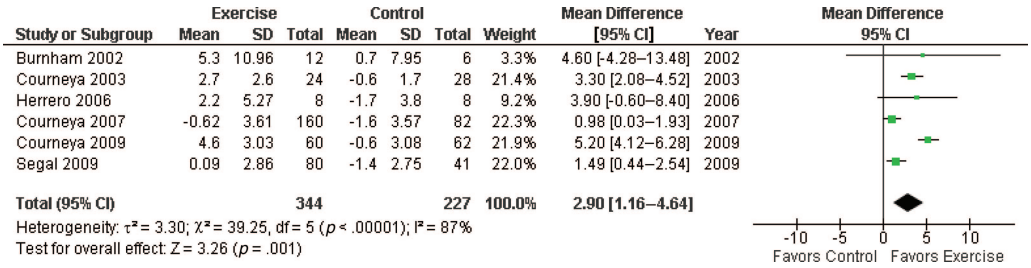

Figure 2. Pooled effects of supervised exercise training, compared with usual care (control), on cardiorespiratory fitness (peak oxygen consumption, VO_{2peak}).

Abbreviations: CI, confidence interval; SD, standard deviation.

tion of exercise modality (WMD, −0.78 ml·kg^{-1}·min^{-1}; 95% CI, −2.45 to 0.88; I^2, 75%).

Adherence, Loss to Follow-Up, and Adverse Events

The mean lost-to-follow-up rate was 8.1% ± 7.2% (range, 0%−20%); there was no evidence for different lost-to-follow-up rates between the exercise and control groups. The mean adherence rate was 88.7% ± 10.1% (range, 70.2%−98.4%); five of six studies reported an adherence rate ≥80% [20, 21, 30, 31, 33]. Finally, all studies reported that adverse events (AEs) were monitored during study conduct. Two AEs were reported during cardiopulmonary exercise testing, nine were reported during exercise training, and two were reported in control participants; a total patient AE rate of 13 per 571 adult patients (2.3%) was found. The most serious AE was a myocardial infarction during aerobic training [21].

Discussion

The principal finding of this meta-analysis was that relatively short-term, structured, moderate-intensity exercise training is associated with significant improvements in the VO_{2peak} in select curative-intent cancer patients both during and following adjuvant therapy. Specifically, the WMD in VO_{2peak} was 2.91 ml·kg^{-1}·min^{-1} from baseline to postintervention, favoring exercise training. The magnitude of change is similar to that reported in a prior meta-analysis that included three studies (two were unpublished dissertations) in women with early breast cancer; McNeely et al. [34] found that VO_{2peak} increased 3.39 ml·kg^{-1}·min^{-1} with exercise training, involving 95 patients in total. The prognostic relevance of this improvement in adult cancer patients is not yet known; however, Myers et al. [1] and Gulati et al. [35] found that the Framingham Risk Score−adjusted mortality risk decreased by 12% and 17% for every 1-MET (3.5 ml·kg^{-1}·min^{-1}) difference in aerobic capacity among

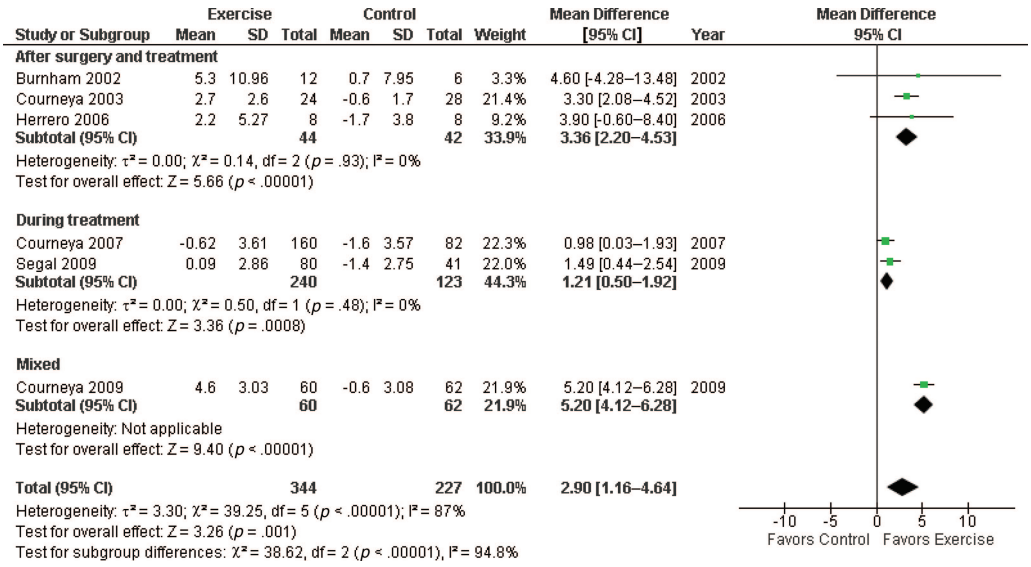

Figure 3. Pooled effects of supervised exercise training, compared with usual care (control), on cardiorespiratory fitness (peak oxygen consumption, VO_{2peak}) by treatment status.

Abbreviations: CI, confidence interval; SD, standard deviation.

asymptomatic men and women, respectively. It is noteworthy that the beneficial effects of exercise training were observed with minimal AEs. In total, 13 AEs were reported across six studies, for a total AE rate of 2.3%. However, the performance (monitoring) of VO_{2peak} assessment did not comply with CPET recommendations for clinical populations [6] or cancer patients [36]. In addition, no study adopted a standardized method for monitoring or reporting nonexercise-related AEs. As such, it is not clear whether the low incidence of AEs reflects the true safety of CPET/exercise training in cancer patients or less than optimal monitoring/reporting of AEs. Cancer is a heterogeneous disease varying considerably in location, pathogenesis, and therapeutic management; thus, the risk for an exercise-related AE is likely highly dependent on these factors. Unfortunately, given the low incidence of AEs, it was not possible to investigate this question. We stress that future studies should strive to comprehensively monitor and report AEs when conducting exercise intervention studies in the oncology setting [36].

A finding of major importance is the significant decline in VO_{2peak} among patients assigned to the usual care control groups. In cross-sectional studies, we found that the VO_{2peak} of cancer patients was consistently ~30% below that of age- and sex-matched *sedentary* but otherwise healthy individuals [13, 15, 16, 37]. The present finding suggests that, without exercise training, VO_{2peak} will remain low or become even further impaired, particularly during adjuvant therapy. The clinical importance of this finding cannot be overstated. First, VO_{2peak} is a strong, independent predictor of mortality in humans with and without CVD [1–5]. Recent work by our group found that, relative to patients with a low VO_{2peak} (<13 $ml \cdot kg^{-1} \cdot min^{-1}$), moderate (13.9–16.9 $ml \cdot kg^{-1} \cdot min^{-1}$) and high (≥17 $ml \cdot kg^{-1} \cdot min^{-1}$) VO_{2peak} levels were associated with a 21%−24% lower all-cause mortality rate in presurgical NSCLC patients. A 1.0 $ml \cdot kg^{-1} \cdot min^{-1}$ decrease in VO_{2peak}, a reduction similar to that observed in patients randomized to the nonexercise control groups, was associated with a 4% greater mortality rate [14]. Second, Paterson et al. [38] demonstrated that a minimum VO_{2peak} of ~15 $ml \cdot kg^{-1} \cdot min^{-1}$ in women and ~18 $ml \cdot kg^{-1} \cdot min^{-1}$ in men aged 85 years was necessary for full and independent living (e.g., garden activities, walking up stairs). Alarmingly, a large proportion of adult cancer patients do not meet this minimum threshold, further highlighting the critical importance of exercise-based rehabilitation following diagnosis. Finally, VO_{2peak} is associated with a broad range of relevant outcomes in cancer patients, including surgical complication risk, certain therapy late effects, global QOL, and fatigue [9, 11–13, 15, 16, 39].

With only six eligible trials, sensitivity analyses were difficult, although significant differences were indicated for two parameters: exercise length and therapy status. Surprisingly, shorter duration exercise interventions (<4 months) were associated with superior VO_{2peak} improvements than in those of longer duration (≥4 months). This finding may be an artifact of when the longer duration studies were conducted as opposed to real differences in intervention length per se. Longer duration studies were, for the most part, conducted during cytotoxic therapy, when smaller improvements in VO_{2peak} are expected. The sensi-

tivity analysis indicating superior VO_{2peak} improvements following rather than during adjuvant therapy supports this notion. Structured exercise interventions in healthy (non-diseased) adult populations typically report an ~15% increase in VO_{2peak} with aerobic-based training following traditional prescription guidelines (3–5 days per week at 50%−75% of baseline VO_{2peak} for 12–15 weeks) [40, 41]. Despite exercise studies in cancer patients employing similar exercise prescriptions, the magnitude of the VO_{2peak} improvement appears lower, suggesting that the use of cytotoxic therapy may attenuate normal cardiovascular and/or skeletal muscle adaptations to exercise training [32, 37]. The reasons for these divergent findings are not known but likely relate to differences in the extent and causes of exercise limitation between healthy adults and those with cancer. In addition to the normal effects of aging, cancer patients are also subject to cytotoxic therapy−induced injury together with profound deconditioning that dramatically depletes the compensatory abilities of the cardiovascular reserve [17]. In addition, these effects are further compounded by treatment-associated weight gain, which also impacts VO_{2peak} [42]. Studies investigating the limitations to exercise, and underlying molecular mechanisms, in cancer patients both during and following therapy are warranted to ensure the optimal efficacy of exercise in the oncology setting.

Caution is warranted when interpreting the present results given the significant heterogeneity evident in the primary and sensitivity analyses. In an effort to minimize heterogeneity, we only selected RCTs that included a measurement of VO_{2peak} via expired gas exchange analysis. Upon closer inspection, the significant heterogeneity is not surprising given the stark between-study differences in cancer diagnosis, cytotoxic therapy, disease stage, and exercise prescription characteristics. There is little doubt that the field of exercise oncology has made significant progress over the past decade; however, findings of our meta-analysis, and prior reviews [34, 43], clearly demonstrate that the current evidence base is emergent, with many fundamental questions (e.g., optimal prescription, timing, and setting of exercise, effects of exercise on tumor biology, and therapeutic efficacy) remaining to be addressed. A major goal of exercise oncology research is to establish evidence-based exercise rehabilitation/physical activity guidelines to maximize the health and longevity of persons following a cancer diagnosis. Clearly, more studies are required to inform such guidelines, but simply increasing the absolute number will not address the current limitations. Instead, in order to advance the field, it is critical that the next generation of studies logically build on and extend current scientific knowledge in homogeneous patient populations/settings applying rigorous RCT methodology. Such an approach will permit definitive conclusions regarding the efficacy of exercise in oncology management. Additionally, as we move into the era of "personalized medicine" in oncology, it will be increasingly important to match the exercise prescription to the clinical/treatment characteristics of a patient subgroup or individual patient. Such a goal is not trivial and will only be achieved by adopting a translational (bed-to-benchside) approach to inform mechanistically driven phase III trials in conjunction with rational correlative science studies to ensure the optimal safety and efficacy of exercise [44].

In conclusion, there is promising evidence that supervised exercise training, compared with usual care (control), is associated with significant improvements in VO_{2peak} following a diagnosis of select early-stage cancer with minimal AEs, although significant heterogeneity is evident. Limited evidence is currently available to suggest that the exercise−VO_{2peak} relationship is different based on exercise intervention or clinical patient characteristics.

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