Name of journal: *World Journal of Meta-Analysis*

ESPS Manuscript NO: 12910

Columns: Meta-Analysis

**Effect of supervised exercise on aerobic capacity in cancer survivors: Adherence and workload predict variance in effect**

Beaudry R *et al.* Exercise and aerobic capacity in cancer survivors

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**Author contributions:** All authors contributed to the design of the research protocol and interpretation of the data; Beaudry R and Kruger C contributed equally to this work; Beaudry R, Kruger C and McNeely ML contributed to the acquisition of data as described in the methods, preliminary data analyses and wrote the paper; Liang Y performed the meta-regression analyses; Liang Y, Parliament M and Haykowsky M reviewed the paper critically for important intellectual content and approved the version to be published.

**Conflict-of-interest:** The authors declare no conflicts of interest financial or otherwise.

**Data sharing:** Not applicable as a review not basic or clinical research.

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**Received:** July 29, 2014

**Peer-review started:** July 29, 2014

**First decision:** September 16, 2014

**Revised:** December 23, 2014

**Accepted:** December 29, 2014

**Article in press:**

**Published online:**

**Abstract**

**AIM:** To examine the efficacy of supervised aerobic exercise training on aerobic capacity in survivors of cancer.

**METHODS:** We conducted a systematic search identifying randomized controlled trials of supervised aerobic exercise interventions among adult cancer survivors with aerobic capacity (VO2 max/peak) as the primary outcome. We calculated pooled effect sizes and performed multiple regression moderator analysis.

**RESULTS:** We identified 18 studies including 1149 survivors of cancer. Studies included mixed cancer groups (4 studies), breast cancer (10 studies), hematological cancers (2 studies), lung cancer (1 study) and liver cancer (1 study). Survivors of cancer who participated in supervised aerobic exercise training improved aerobic capacity (VO2peak) more than controls (18 comparisons, 1093 participants; standardized mean effect: 0.74; 95%CI: 0.52, 0.96; *P* < 0.001). However, there was significant heterogeneity among the included trials (*I*2: 63%; *P* < 0.001). Sixty-six percent of the between-study heterogeneity was explained by differences in exercise adherence and total exercise workload among studies (R2: 65.8%; *P* < 0.04).

**CONCLUSION:** Supervised aerobic exercise training provides a moderate–to-large beneficial effect on aerobic capacity among survivors of cancer. Aerobic capacity was improved to a greater degree in exercise studies with better participant attendance and higher overall exercise workload.

**Key words:** Exercise; Neoplasms; Physical therapy modalities; Physical fitness; Meta-analysis

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**Core tip:** The optimal exercise prescription for survivors of cancer is unknown and the effect of variations in exercise training parameters on cancer-specific outcomes are poorly understood. Therefore, questions remain over how to best tailor exercise prescriptions to optimize the health outcomes of survivors who are at different time points in their cancer care. We performed a meta-analysis of data from randomized controlled trials examining the effect of supervised aerobic exercise training on aerobic capacity in cancer survivors. We found that aerobic capacity was improved to a greater extent in exercise studies that prescribed a higher exercise workload and had better participant adherence.

Beaudry R, Kruger C, Liang Y, Parliament M, Haykowsky M, McNeely ML. Effect of supervised exercise on aerobic capacity in cancer survivors: Adherence and workload predict variance in effect. *World J Meta-Anal* 2015; In press

**INTRODUCTION**

The burden of cancer continues to increase worldwide due to population growth and aging[[1](#_ENREF_1)].More effective cancer screening and novel treatment therapies have resulted in improved detection, earlier treatment and better disease free and overall survival, with the numbers of cancer survivors growing disproportionately to the number of new cancer cases and deaths[[2](#_ENREF_2)]. Many cancer survivors experience symptoms and side effects related to their cancer or cancer treatment. As many of these effects go undetected and/or untreated, the survivor is placed at increased risk for other health issues such as declining functional status and cardiovascular disease[[3](#_ENREF_3),[4](#_ENREF_4)]. As a result, there is an emerging need for the integration of services and interventions to address the long-term health of survivors[[3](#_ENREF_3)].

Exercise training is gaining recognition as an important intervention to address acute, late and long-term effects of cancer, and is becoming more widely acceptable as confidence in safety is now established. Importantly, evidence is accumulating to support the benefit of exercise to improve the physical functioning and quality of life of survivors. Currently, the optimal exercise prescription is unknown and the effect of variations in exercise training parameters on cancer-specific outcomes are poorly understood[[5](#_ENREF_5)]. Therefore, questions remain over how to best tailor exercise prescriptions to optimize the health outcomes of survivors at different times through the cancer continuum[[5](#_ENREF_5)].

Cardiorespiratory fitness, measured objectively as the highest oxygen consumed during maximal aerobic exercise, provides a means to evaluate associations with disease outcomes. Aerobic capacity is inversely related to the risk of a cardiovascular event and all-cause mortality in healthy individuals and cancer patients[[6-10](#_ENREF_6)]. Aerobic capacity is best increased by habitual aerobic exercise training that is of a moderate-to-vigorous intensity[[11](#_ENREF_11)].

Aerobic capacity (VO2max) is the maximum volume of oxygen that the body can consume during maximal exercise, using at least 60% of the musculature, and while breathing air at sea level[[12](#_ENREF_12)]. This volume is expressed as an absolute rate in litres per minute (L/min) or as a relative rate in millilitres per kilogram of bodyweight per minute (ml/kg/min). VO2peak is the term used most commonly in clinical populations when a true maximal value is not attained[[12](#_ENREF_12)]. For example, the test is described as VO2peak rather than VO2max when the test is carried out on a cycle ergometer (bike) rather than a treadmill, or when the highest value reached on the test is limited by the participant’s symptoms.

A meta-analysis by Jones and colleagues included data from six randomized controlled trials (RCTs) and reported a significant benefit from supervised aerobic exercise training, compared with usual care, on VO2peak [2.90 mL/kg per minute; 95% confidence interval (CI): 1.16, 4.64; *P* = 0.01][[13](#_ENREF_13)]. However, statistical and clinical heterogeneity was found among the exercise trials included in their review, leading them to recommend further research to build on and extend the current knowledge in the field. Since this publication, a number of newer studies have been published. Given this amount of new data, we contend that an updated review is warranted.

The primary purpose of this meta-analysis was to examine the efficacy of supervised aerobic exercise training programs on VO2peak in survivors of cancer. Quality of life was analyzed as a secondary outcome measure. As well we aimed to explore heterogeneity in study findings through subgroup analyses and meta-regression where appropriate.

**MATERIALS AND METHODS**

The review conforms to the requirements of PRISMA reporting standards. The published protocol for the review can be found at: <http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013006215#.U1cOnle9aws>).

***Inclusion criteria***

Studies were considered eligible for inclusion if they were RCTs comparing supervised aerobic exercise training with a placebo, controlled comparison or standard care. For the purposes of the review, exercise was defined as a form of leisure-time physical activity that was performed on a repeated basis over an extended period of time, with the intention of improving fitness, performance or health[[14](#_ENREF_14)]. Studies with an additional treatment arm or combined intervention (*e.g.*, exercise with diet modification) were included only if the effects of exercise could be isolated. A priori, we excluded reports that were available only in abstract form.

Trials were included if they involved adults (17 years and older) diagnosed with cancer who were actively receiving cancer treatment or off treatment. Included studies were required to measure maximal, peak, or estimated maximal oxygen consumption (VO2max/peak) as a study outcome.

***Systematic search***

A search was performed of the databases including OVID MEDLINE (1948 to October 2013), PubMed (1975 to October 2013), SCOPUS (1950 to October 2013), Web of Science (1950 to October 2013), EMBASE (1988 to October 2013), Cochrane Central Registry of Controlled Trials (1991 to October 2013), and LILACS (1982-October 2013). The search strategy was developed and approved by a librarian with extensive database searching knowledge and experience. We searched terms related to cancer (*e.g.*, neoplasms, tumor), exercise (*e.g.*, exercise, exercise therapy/ or motion therapy, aerobic training), publication type (*e.g.*, random allocation, clinical trial), and aerobic capacity (*e.g.*, VO2). The search strategy was modified as necessary for each database. Non-English language publications were eligible for inclusion. To locate unpublished research, we reviewed clinical trial registries and websites housing theses and dissertations. Fourteen experts in the field of cancer and exercise were contacted in order to identify any research that was not published or was pending publication. Table 1 includes an example of the MEDLINE search strategy.

***Coding and reliability***

The titles and abstracts were screened for eligibility by two independent evaluators (C.K. and R.B.), and coded for exclusion or potential inclusion. Potentially eligible manuscripts were obtained and the same evaluators performed a second round of screening to evaluate full eligibility criteria. Any disagreements were resolved by consensus (C.K., R.B., and M.M.). The two evaluators (C.K. and R.B.) then independently abstracted data on study participants, the intervention and control (usual care) protocols, and study outcomes, and assessed for quality. Studies were evaluated using the quality assessment framework for RCTs developed by the Cochrane Collaboration[[15](#_ENREF_15)] to assess risk of bias in the individual studies. Sensitivity analyses were conducted to examine the effect of including studies with high risk of bias.

For the purpose of evaluating exercise prescription variables, exercise intensity was standardized to a single %VO2max value[[16-18](#_ENREF_16)]. For studies that used %VO2max as the intensity prescription the average of the range was used; time spent at different intensities was factored in to create the mean value. High intensity intervals were weighted at 50% of the contributing time. Resistance exercise was not included in intensity ratings. Total exercise workload, or intensity-minutes, was calculated by factoring the exercise intensity by the prescribed exercise volume (program duration, minutes per session and sessions per week).

***Study outcomes and effect size calculation***

Study results were pooled using random effects models. For continuous outcomes, pooled statistics were calculated using mean differences (MD) when data were on a uniform scale and using standardized mean differences (SMD) when data were on different scales. All results were calculated with 95%CI. The SMD was interpreted as 0.2, 0.5 and 0.8 representing small, medium and large effects on outcomes respectively[[19](#_ENREF_19)]. Statistical heterogeneity was assessed using a chi-square test that considered a *P*-value of less than 0.10 to indicate significant heterogeneity. I-squared values, ranging from 0% (homogeneity) to 100% (heterogeneity) were also calculated to quantify variability in study effect and values of 25%, 50% and 75% were used to describe low, moderate and high heterogeneity respectively[[20](#_ENREF_20)]. Subgroup analyses and multiple regression moderator analyses were performed to explore and explain heterogeneity among studies. A priori subgroup analyses included examining the pooled effect estimate by level of supervision of exercise (group or individual), the timing of the intervention (on or off treatment), and cancer type. Meta-regression was performed to explore exercise variables of frequency, time, intensity, duration and adherence on effect estimate.

***Statistical analysis***

A biomedical statistician (Y.L.) provided oversight on the statistical methods, and performed the meta-regression analyses. All data were entered into Review Manager 5.2 and analyzed with SPSS v15 software utilizing meta-regression scripts created by Lipsey and Wilson and Stata/SE (version 13.0)[[21](#_ENREF_21)]. Figures were created using Comprehensive Meta-Analysis (version 3: <http://www.meta-analysis.com/index.php>).

**RESULTS**

***Methodological characteristics***

The search protocol yielded 1269 eligible studies; after removal of duplicates and screening of abstracts, 23 studies remained. Reference tracking and contacting of experts accounted for 4 additional studies. Grey literature and trial register searches yielded no further articles. Full text review of the 27 studies excluded a further 9, leaving 18 studies for qualitative and quantitative synthesis[[22](#_ENREF_22)-39]. One study was not used for the quantitative analyses due to missing data[[32](#_ENREF_32)] and one study was divided into two comparison groups as it involved both on and off treatment subgroups[[27](#_ENREF_27)] (unpublished data provided by author). The remaining 17 studies, generating 18 comparisons, were included in the meta-analyses (Figure 1). Kappa statistics for the inclusion of studies was 0.9 (*P* < 0.001). Following discussion there was 100% agreement in scores between evaluators.

***Risk of bias***

In general there was high or unclear risk of bias for selection (allocation concealment) and detection bias (lack of blinding of outcome assessors) and low risk of bias for attrition (handling of incomplete data) and reporting bias (outcome reporting) among the included studies (Figure 2). Sensitivity analyses were performed after excluding studies with a high or unclear risk of bias for allocation concealment (*n* = 10)[[24](#_ENREF_24),[31-39](#_ENREF_31)] and for use of blinded outcome assessment (*n* = 11)[[24](#_ENREF_24),[26](#_ENREF_26),[27](#_ENREF_27),[31-36](#_ENREF_31),[38](#_ENREF_38),[39](#_ENREF_39)]. The results showed minimal differences in the pooled effect estimates for aerobic capacity based on risk of bias. For allocation concealment, the pooled effect estimate increased by 0.6 (SMD: 0.80; 95%CI: 0.51, 1.25) whilst for blinding of outcome assessment the estimate decreased by 0.4 (SMD: 0.7; 95%CI: 0.35, 1.05). After excluding studies with a high or unclear risk of bias for any factor (*n* = 13), the pooled effect estimate decreased by 0.8 (SMD: 0.66, 95%CI: 0.22, 1.11).

***Cancer survivor characteristics***

The 18 included studies involved 1149 participants of which 576 were randomized to receive an aerobic exercise intervention and the remaining 573 received usual care or no exercise. Participants were on average 53 years of age and 76% were female. Survivors of breast cancer were most commonly studied in both breast cancer specific trials and mixed cancer type trials (14 studies)[[22-26](#_ENREF_22),[28](#_ENREF_28),[29](#_ENREF_29),[33-39](#_ENREF_33)] accounting for 686 participants (60%) of the total participants in the review. Further details on the included studies are provided in Table 2.

***Exercise intervention characteristics***

Ten studies consisted exclusively of aerobic exercise training[[23-27](#_ENREF_23),[29](#_ENREF_29),[30](#_ENREF_30),[33](#_ENREF_33),[34](#_ENREF_34),[38](#_ENREF_38)], six studies included a resistance exercise component with or without flexibility training[[22](#_ENREF_22),[28](#_ENREF_28),[31](#_ENREF_31),[36](#_ENREF_36),[37](#_ENREF_37),[39](#_ENREF_39)], one included physiotherapy exercises and relaxation[[35](#_ENREF_35)], and one included flexibility training plus a dietary intervention[[32](#_ENREF_32)]. Exercise interventions consisted primarily of cycling[[23-31](#_ENREF_23),[34](#_ENREF_34),[39](#_ENREF_39)] or walking/jogging[[23](#_ENREF_23),[24](#_ENREF_24),[32](#_ENREF_32),[35](#_ENREF_35),[37-39](#_ENREF_37)]. Five studies[[22](#_ENREF_22),[23](#_ENREF_23),[28](#_ENREF_28),[35](#_ENREF_35),[38](#_ENREF_38)] offered exercise programs in a class setting (group exercise format) and the remaining 13 studies[[24-27](#_ENREF_24),[29-34](#_ENREF_29),[36](#_ENREF_36),[37](#_ENREF_37),[39](#_ENREF_39)] were individualized exercise programs, although further detail on the level of supervision was not often provided. Eight studies were carried out during active cancer treatment[[22](#_ENREF_22),[26](#_ENREF_26),[29-31](#_ENREF_29),[33](#_ENREF_33),[34](#_ENREF_34),[38](#_ENREF_38)], nine in the post treatment phase[[23-25](#_ENREF_23),[28](#_ENREF_28),[32](#_ENREF_32),[35-37](#_ENREF_35),[39](#_ENREF_39)] and one included participants both on and off treatment[[27](#_ENREF_27)]. The duration of exercise programs ranged from 4-6 wk to 26 wk with individual exercise sessions ranging from 20-90 min including warm up and cool down. Seventeen studies prescribed aerobic exercise that was of moderate intensity with 4 of these studies[[22](#_ENREF_22),[27](#_ENREF_27),[29](#_ENREF_29),[34](#_ENREF_34)] including high intensity intervals. One study combined both low and moderate intensity intervention groups into a single intervention group for their analysis due to the small sample size of the study[[24](#_ENREF_24)]. Further information on the exercise prescription variables is provided in Table 3.

***The effect of supervised aerobic exercise on aerobic capacity***

All eighteen studies reported VO2peak, with 13 studies (14 comparisons) indexing this outcome to body weight (mL/kg per minute)[[23-30](#_ENREF_23),[35-39](#_ENREF_35)], 4 studies measuring absolute (L/min)[[22](#_ENREF_22),[31](#_ENREF_31),[33](#_ENREF_33),[34](#_ENREF_34)], and 1 study measuring percent change in VO2peak(mL/kg per minute)[[32](#_ENREF_32)]. The study measuring percent change in VO2peak was excluded from analysis due to insufficient data on measures of variability.

Pooling of all 18 comparisons showed a moderate-to-large effect estimate (SMD: 0.74; 95%CI: 0.52, 0.96; *P* < 0.001) in favour of supervised aerobic exercise training; however, moderate heterogeneity was found among the included studies (*I*² = 63%; *P* < 0.001) (Figure 3). Pooling of the 13 studies (14 comparisons) reporting VO2peak (mL/kg per minute) showed a statistically significant mean difference in VO2peak of 3.13 mL/kg per minute (95%CI: 2.21, 4.05; *P* < 0.001) in favour of supervised aerobic exercise training; however, again moderate heterogeneity was found among the included studies (*I*² = 58%; *P* < 0.001).

***Subgroup analysis***

Subgroup analyses were performed for level of supervision, treatment timing and cancer type (Table 4). A significantly smaller effect estimate (*P* = 0.003) was found for group/ class-led exercise studies[[22](#_ENREF_22),[23](#_ENREF_23),[35](#_ENREF_35),[38](#_ENREF_38)] (SMD: 0.36; 95%CI: 0.17, 0.56) when compared to studies involving individualized exercise programs[[24-31](#_ENREF_24),[33](#_ENREF_33),[34](#_ENREF_34),[36](#_ENREF_36),[37](#_ENREF_37),[39](#_ENREF_39)] (SMD: 0.87; 95%CI: 0.60, 1.15). Non-significant effects (*P* = 0.11) were observed between on and off treatment studies. Statistically significant differences in pooled effect estimates were observed between cancer types with a significantly larger beneficial effect found among studies including survivors with hematological cancers (*P* < 0.001)[[27](#_ENREF_27),[31](#_ENREF_31)] when compared to other cancer tumor groups (breast cancer, lung cancer and mixed cancer).

***Meta-regression***

Meta regression was performed analyzing the effect estimate with exercise parameters of exercise workload and participant adherence as potential moderators. These two variables, workload and adherence, explained 65.8% (*P* = 0.04) of the between-study variance in effect estimate among the included studies (Figure 4).

***Quality of life***

Nine studies reported data for health-related quality of life as measured by the Functional Assessment of Cancer Therapy –General (FACT-G) scale[[23](#_ENREF_23),[25](#_ENREF_25),[29](#_ENREF_29),[31](#_ENREF_31)], the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire: EORTC –QLQ-C30[[22](#_ENREF_22),[28](#_ENREF_28),[30](#_ENREF_30),[39](#_ENREF_39)] and Medical Outcomes Survey: Short Form: SF36[[38](#_ENREF_38)]. Pooling of all nine studies demonstrated a non-significant effect on quality of life (SMD: 0.3; 95%CI: -0.11, 0.71; *P* = 0.16), with high heterogeneity found among studies (*I2*= 80%; *P* < 0.001). Further details are provided in Table 5.

**DISCUSSION**

This meta-analysis found that supervised aerobic exercise resulted in a moderate-to-large significant benefit on VO2peak in survivors of cancers. The pooled mean difference showed an improvement in VO2peak of 3.13 mL/kg per minute, which is close to one metabolic equivalent (MET) improvement in fitness and similar to the 2.9 mL/kg per minute increase reported by Jones *et al*[[13](#_ENREF_13)] In the general population, each one MET increase in fitness has been found to translate to a 12% decrease in mortality in men[[6](#_ENREF_6)] and a 17% decrease in women[[40](#_ENREF_40)]. In the cancer population, a number of studies have reported an inverse correlation between VO2peak and all-cause mortality, including cardiovascular, lung and breast cancer related deaths[[41-43](#_ENREF_41)].

We did not find an overall significant effect of supervised aerobic exercise interventions on quality of life. Studies in our review used a variety of quality of life measures and when data were pooled significantly high heterogeneity was found. This finding suggests that the differences between study populations and/or differences inherent in the quality of life questionnaires may be factors. Supporting this premise, the pooled data from four studies using the FACT-General scale showed both statistical homogeneity and significant benefit on quality of life.

Our results showed that survivors of cancer participating in individually-based exercise experienced greater improvement in VO2peak than those participating in group or class-led exercise. A reported advantage to group or class-led exercise is the social interaction and group support that may foster improvements in quality of life among survivors. Similar to our findings, a previous meta-analysis comparing group to individual exercise on quality of life in survivors of breast cancer reported that group exercise showed no benefit over individual exercise[[44](#_ENREF_44)]. While the findings of our review appear to support individually based exercise programs for the outcome of aerobic capacity, we found that data were generally lacking on the ratio of the exercise participant to exercise specialist to allow for closer examination of impact of the level of supervision.

In contrast to the meta-analysis by Jones *et al*[[13](#_ENREF_13)] we did not find a significant difference between groups based on the timing of the intervention relative to cancer treatment. Inspection of adherence across studies revealed a bimodal distribution with clusters in the 70-75 and 85-98 percent ranges. This bimodal distribution appeared to reflect on/off treatment status, as better adherence and larger effects were generally seen from exercise intervention studies carried out after completion of cancer treatment. Moreover, the direction of exercise effects compared to usual care may differ in relation to treatment status. For example, Jarden *et al*[[31](#_ENREF_31)] demonstrated that exercise during active cancer treatment prevented a decline in VO2peak when compared to usual care, whereas Kim *et al*[[33](#_ENREF_33)] found that exercise following cancer treatment increasedVO2peak over usual care. More research is required to elucidate the influence of the timing of the exercise intervention through the continuum of cancer treatment and survivorship.

While our overall findings support the benefit of supervised aerobic exercise on VO2peak, the relative benefit varied significantly across studies. As the number of research studies in the area has increased we were able to examine the influence of exercise prescription variables on aerobic capacity. Our analyses showed that VO2peak improved to a larger extent in studies examining survivors of haematological cancers over other cancer groups. However, this finding was based on data from only 2 studies (3 comparisons) and thus, while compelling; further research is needed within this particular cancer subgroup. Of note, significant improvements were found within the subgroups of both breast cancer and mixed cancer groups; however, the effect was smaller.

Better participant adherence and overall exercise workload emerged as important predictors of intervention efficacy. Adherence, in this review, represented attendance to exercise sessions. Data on adherence to intensity and exercise volume were not reported in the majority of trials. Attendance to exercise sessions may reflect the impact of treatment-related side effects, patient motivation, or aspects of the study protocol such as opportunities for making up missed sessions. High adherence to the exercise prescription is critical for ensuring an adequate training stimulus to induce physiological change in cardiorespiratory function. Better reporting of adherence to prescription factors of intensity and duration would allow for more precise examination of the dose response to exercise[[5](#_ENREF_5)].

Previous meta-analyses examining exercise interventions have reported benefit from more intense aerobic exercise interventions for both quality of life and depressive symptoms[[45](#_ENREF_45),[46](#_ENREF_46)]. In the present meta-analysis, however, overall workload rather than intensity alone was found to predict response to exercise. We found that the majority of studies in the review prescribed moderate intensity exercise training, although some included high intensity interval work. Factoring the exercise volume by the prescribed intensity provided a workload metric (*i.e.*, intensity-minutes) for discriminating between trials finding large effects from those with small effects. While some studies prescribing lower exercise volumes showed benefit, a target workload (intensity-minutes) of around 600 intensity-minutes (*e.g.*, 10 wk program of 90 min per week of supervised exercise at 70% VO2peak) appears to represent the threshold workload required to obtain a clinically significant large improvement (effect size > 1.0) in VO2peak. A recent meta-analysis by Carayol *et al*[[47](#_ENREF_47)] examined the effect of exercise on fatigue and quality of life and found a workload in the range of 90-120 min of moderate intensity exercise was more beneficial in improving fatigue and quality of life than higher volumes of exercise. Our findings suggest that improvements in aerobic capacity can be attained at an exercise workload level that, in theory, should not negatively impact fatigue and quality of life.

***Limitations***

The major limitations of this meta-analysis were the assumptions revolving around exercise prescription factors. All intensity values represented average values obtained and were standardized to an estimated %VO2maxvalue. Conversions are imperfect as are average values created from studies using intervals and step protocols. Therefore we acknowledge that there is some associated error in our intensity estimates. As well, no data were provided on actual adherence to intensity among participants in the individual studies to allow more precise estimation of intensity. Thus our crude estimates of targeted intensity functioned merely as a means to determine relative ranking for between study comparisons. Assumptions were also made that resistance exercise provided minimal contributions to VO2peak. A further limitation of our meta-analysis was the small number of included studies, which permitted the analysis of only two moderator variables. Thus, further research is needed particularly in survivors of cancers other than breast cancer.

Studies included in this review were generally of good methodological quality with low risk of bias. However, further attention to study quality is needed, as many studies did not adequately report methods for allocation concealment and use of blinded assessment, limiting our ability to evaluate the impact of risk of bias across studies. Of note, the estimated effect size was lower when excluding studies at high risk of bias; thus, our findings may represent an overestimate of the effect of supervised exercise on aerobic capacity.

A final limitation is that the mechanism(s) responsible for the improvement in VO2peak along the oxygen cascade were not studied in any of the studies included in our review; thus, the favourable finding in VO2peak may be due to improved convective and /or diffusive oxygen transport coupled with improved oxygen utilization by the active muscles[[48](#_ENREF_48)].

Supervised aerobic exercise training was found to have a moderate-to-large beneficial effect on VO2peak. Aerobic capacity increased in a dose response fashion with overall workload, with larger effects found in studies prescribing a higher overall workload of aerobic exercise. Larger benefits were also seen in studies with better participant attendance and among survivors of haematological cancers. There is a need for further randomized controlled trials examining supervised aerobic exercise interventions in understudied but common cancers such as prostate, lung and colorectal cancer.

**COMMENTS**

***Background***

Evidence is accumulating to support the benefit of exercise to improve the physical functioning and quality of life of survivors. Currently, the optimal exercise prescription is unknown and the effect of variations in exercise training parameters on cancer-specific outcomes are poorly understood. Therefore, questions remain over how to best tailor exercise prescriptions to optimize the health outcomes of survivors at different times through the cancer continuum.

***Research frontiers***

A previous meta-analysis included data from six randomized controlled trials (RCTs) and reported a significant benefit from supervised aerobic exercise training, compared with usual care, on VO2peak (2.90 mL/kg per minute; 95%CI: 1.16, 4.64; *P* = 0.01). However, statistical and clinical heterogeneity was found among the exercise trials included in their review, and therefore further research was indicated to build on and extend the current knowledge in the field.

***Innovations and breakthroughs***

Pooling of the 13 studies (14 comparisons) reporting VO2peak (mL/kg per minute) showed a statistically significant mean difference in VO2peak of 3.13 mL/kg per minute (95%CI: 2.21, 4.05; *P* < 0.001) in favour of supervised aerobic exercise training; however, again moderate heterogeneity was found among the included studies (*I*² = 58%; *P* < 0.001). Meta-regression was performed analyzing the effect estimate with exercise parameters of exercise workload and participant adherence as potential moderators. These two variables, workload and adherence, explained 65.8% (*P* = 0.04) of the between-study variance in effect estimate among the included studies.

***Applications***

Supervised aerobic exercise training is an effective intervention to improve aerobic capacity in survivors of cancer. Aerobic capacity increased in a dose response fashion with overall workload, with larger effects found in studies prescribing a higher overall workload of aerobic exercise. Larger benefits were also seen in studies with better participant attendance and among survivors of haematological cancers.

***Terminology***

Aerobic capacity (VO2max) is the maximum volume of oxygen that the body can consume during maximal exercise, using at least 60% of the musculature, and while breathing air at sea level. Aerobic capacity is best increased by habitual aerobic exercise training that is of a moderate-to-vigorous intensity.

***Peer review***

An excellent systematic review.

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**P-Reviewer:** Lim ECW, Tokuhashi Y **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Table 1 Appendix**

1 exp Neoplasms/

2 (cancer\* or neoplasm\* or (tumor\* not tumor necrosis factor) or (tumour\* not tumour necrosis factor) or malignan\* or carcino\* or leukaemi\* or leukemi\* or lymphoma\* or myeloma\* or adenocarcinoma\*).mp.

3 1 or 2

4 exercise therapy/ or motion therapy, continuous passive/ or muscle stretching exercises/ or plyometric exercise/

5 (aerobic\* or exercise or running or treadmill\* or training).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

6 4 or 5

7 3 and 6

8 (VO2 or Aerobic capacity).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

9 7 and 8

10 Limit 9 to clinical trial, all

**Table 2 Description of Included Studies**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
| Ref. | Sample size/ cancer type  | Age (SD/ range)  | Gender (F/M)  | Interventiongroup | Comparisongroup | Key outcomes  | Adverse events |
| On treatment studies/subgroups |
| Adamsen *et al*[[22](#_ENREF_22)], 2009Denmark | *n* = 117Mixed Cancer Groups  | 47.2 (± 6.7) yr  | F: 78M: 39 | Aerobic Training with High-intensity Intervals + Resistance Exercise + Relaxation + Massage  | Usual care: allowed to freely increase physical activity  | Estimated VO2max | Seizure (*n* = 1) |
| Courneya *et al*[[26](#_ENREF_22)], 2007Canada  | *n* = 133 Breast Cancer |  49 yr (26-78) | F: 133 | Aerobic Training | Usual care: continue usual activities  | VO2peakQoL: FACT-Anemia  | Hypotension (*n* = 1)Dizziness (*n* = 1) |
| 1Courneya *et al*[[27](#_ENREF_22)], 2009bCanada  | *n* = 54NHL, HL  | 253.2 yr (18-80) | 2F: 50M: 72 | Aerobic Training with High-intensity Intervals  | Usual Care: continue usual activities  | VO2peak QoL: FACT-B/Ac/An,  | Back (*n* = 1), hip (*n* = 1) and knee (*n* = 1) pain |
| Hornsby *et al*[[29](#_ENREF_22)], 2013United States | *n* = 20Breast Cancer | 51 (± 6) yr | F: 10 | Aerobic Training with High-intensity Intervals  | Control: Continue usual exercise levels | VO2peak FACT-B Adverse Events | Leg pain (*n* = 1) |
| Hwang *et al*[[30](#_ENREF_22)], 2012Taiwan | *n* = 24Lung  | 61 ( ± 6.3) | F: 12M: 12 | Aerobic Training  | Usual Care: general patient education | VO2peak QoL: EORTC | Not reported |
| Jarden *et al*[[31](#_ENREF_22)], 2009Denmark | *n* = 42Mixed Cancer Groups  | 39.1 (12.2) | F: 16M: 26 | Aerobic Training + Resistance Exercise + Flexibility  | Usual Care | Estimated VO2max QoL: EORTC, FACT-An | None |
| Kim *et al*[[33](#_ENREF_22)], 2006United States | *n* = 41Breast Cancer | 51.3 (6.7) yr | F: 41 | Aerobic Training  | Waitlist Control | VO2peak | Not reported |
| MacVicar *et al*[[34](#_ENREF_22)], 1989United States | *n* = 34Breast Cancer | 45.4 (10.2) yr | F: 34 | Aerobic Training with High-intensity Intervals  | Control: Continue normal activities | VO2max L/min  | Not reported |
| Segal *et al*[[38](#_ENREF_22)], 2001Canada | *n* = 66Breast Cancer  | 51 (± 8.7) yr | F: 66 | Aerobic Training  | Control group encouraged to exercise | Estimated VO2maxQoL: SF36 | Not reported |
| Off treatment studies/ comparisons |  |  |  |  |
| Broderick *et al*[[23](#_ENREF_22)], 2013Ireland | *n* = 43Mixed Cancer Groups | 52.3 (8.3) yr | F: 37M: 6 | Aerobic Training | Usual Care | Estimated VO2max QoL: FACT-G, SF36 | Not reported |
| Burnham *et al*[[24](#_ENREF_22)], 2000United States | *n* = 18Mixed Cancer Groups | 54.2 (8.1) yr | F: 15M: 3 | Aerobic Training | Control | VO2peakQoL: LASA | Not reported |
| Courneya *et al*[[25](#_ENREF_22)], 2003Canada | *n* = 50Breast Cancer | 59 (± 6) yr | F: 54  | Aerobic Training | No exercise | VO2peakQoL: FACT-Breast  | Lymphedema (*n* = 3)Gynecological complication (*n* = 1) |
| 1Courneya *et al*[[27](#_ENREF_22)], 2009aCanada | *n =* 68NHL, HL  | 2as per Courneya, 2009b | 2as per Courneya, 2009b | 2as per Courneya, 2009b | 2as per Courneya, 2009b | 2as per Courneya, 2009b | 2as per Courneya, 2009b |
| Herrero *et al*[[28](#_ENREF_22)], 2005 Spain | *n* = 16Breast Cancer | 51 (10) yr | F: 16 | Aerobic plus Resistance Training | No Exercise | VO2peakQoL: EORTC | Not reported |
| Kaibori *et al*[[32](#_ENREF_22)], 2013Japan | *n =* 51Liver Cancer | 68 (9.1) yr | F: 15M: 36 | Aerobic Training + Stretching + Diet Intervention | Diet Intervention | VO2peak | Not reported |
| Mehnert *et al*[[35](#_ENREF_22)], 2011Germany | *n* = 58Breast Cancer | 53 (7.4) yr | F: 58 | Aerobic Training + Physiotherapeutic Exercises + Relaxation | Waitlist Control | VO2max QoL: BIQ | Not reported |
| Naumann, 2011[[36](#_ENREF_36)]Australia | *n* = 21Breast Cancer  | 49 (10) yr | F: 21 | Aerobic Training + Resistance Exercise + Flexibility  | Usual Care | Estimated VO2max QoL: FACT-B | Not reported |
| Rahnama *et al*[[37](#_ENREF_22)], 2010Iran | *n* = 29Breast Cancer  | 58.3 (6.3) yr | F: 29 | Aerobic Training + Resistance Exercise | No exercise | Estimated VO2max | Not reported |
| Thorsen *et al*[[39](#_ENREF_22)], 2005Norway | *n* = 111Mixed Cancer Groups | 39 (8.4) yr | F: 36M: 75 | Aerobic Training + Resistance Exercise | Usual Care | Estimated VO2max QoL: EORTC | Not reported |

1Courneya 2009 publication: Courneya 2009b - subgroup of participants on-treatment; Courneya 2009a - subgroup of participants off-treatment; 2Data as per Courneya 2009b. QoL: Quality of Life; FACT-G: Functional Assessment of Cancer Therapy –General scale; EORTC: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire: SF36: Medical Outcomes Survey Short Form; VO2max: Maximal oxygen consumption; VO2peak: Peak oxygen consumption.

|  |
| --- |
| Table 3 Exercise prescription variables  |
| Ref. | Study duration(wk) | Days/ week | Mins/session(mean)  | Volume | Standardizedintensity(mean) | Workload (intensity minutes) | Adherence(attendance) |
| Adamsen *et al*[[22](#_ENREF_22)]2009 | 6 | 3 | 15 | 270 | 0.83 | 224 | 71%  |
| Broderick *et al*[[23](#_ENREF_22)] 2013 | 8 | 2 | 30 | 480 | 0.57 | 274 | 78% |
| Burnham *et al*[[24](#_ENREF_22)] 2000 | 10 | 3 | 23 | 690 | 0.41 | 281 | 70% |
| Courneya *et al*[[25](#_ENREF_22)] 2003 | 15 | 3 | 25 | 1125 | 0.73 | 816 | 98% |
| Courneya *et al*[[26](#_ENREF_22)] 2007 | 12 | 3 | 30 | 1080 | 0.70 | 756 | 70% |
| Courneya *et al*[[27](#_ENREF_22)] 2009a | 12 | 3 | 30 | 1080 | 0.79 | 858 | 84% |
| Courneya *et al*[[27](#_ENREF_22)] 2009b | 12 | 3 | 30 | 1080 | 0.79 | 858 | 71% |
| Herrero *et al*[[28](#_ENREF_22)] 2006 | 8 | 3 | 25 | 600 | 0.59 | 351 | 91% |
| Hornsby *et al*[[29](#_ENREF_22)] 2013 | 12 | 3 | 23 | 828 | 0.79 | 657 | 82% |
| Hwang *et al*[[30](#_ENREF_22)] 2012 | 8 | 3 | 20 | 480 | 0.6 | 288 | 71% |
| Jarden *et al*[[31](#_ENREF_22)] 2009 | 5 | 5 | 22.5 | 563 | 0.72 | 405 | 80% |
| Kim *et al*[[33](#_ENREF_22)] 2006 | 8 | 3 | 30 | 720 | 0.65 | 468 | 78% |
| MacVicar *et al*[[34](#_ENREF_22)] 1989 | 10 | 3 | NR | - | 0.73 | - | NR |
| Mehnert *et al*[[35](#_ENREF_22)] 2011 | 10 | 2 | 30 | 600 | 0.6 | 360 | NR |
| Naumann *et al*[[36](#_ENREF_22)] 2011 | 8 | 3 | 53 | 1272 | 0.5 | 636 | 84% |
| Rahnama *et al*[[37](#_ENREF_22)] 2010 | 15 | 2 | 35 | 1050 | 0.28 | 289 | NR |
| Segal *et al*[[38](#_ENREF_22)] 2001 | 26 | 3 | NR | - | 0.55 | - | 72% |
| Thorsen *et al*[[39](#_ENREF_22)] 2005 | 14 | 2 | 30 | 840 | 0.62 | 518 | NR  |
|  |  |  |  |  |  |  |  |

|  |
| --- |
| **Table 4 Subgroup analyses** |
| Subgroup Category | Subgroup | No. studies | Mean Difference in mL/kg per minute(95%CI) | *P* value between subgroups | No. studies  | Standardized Mean Difference(95%CI)  | *P* value between subgroups |
| Level of Exercise Supervision | Group Exercise Class | 3 | 1.77 (0.04, 3.51)  | *P* = 0.07 | 4 | 0.36 (0.17, 0.56) | *P* = 0.003 |
| Individual Exercise  | 11 | 3.53 (2.64, 4.43)  | 14 | 0.87 (0.60, 1.15) |
| Treatment Status | On Treatment | 5 | 2.59 (0.7, 4.48) |  *P* = 0.26 | 9 | 0.56 (0.32, 0.81) | *P* = 0.11 |
| Off Treatment | 9 | 3.74 (3.06, 4.42) | 9 | 0.92 (0.56, 1.29) |
| Cancer Tumor Group | Breast | 8 | 2.41 (1.5, 3.31) | *P* = 0.002 | 10 | 0.64 (0.34, 0.88) | *P* = 0.0002 |
| Hematologic | 3 | **5.08 (4.01, 6.16)** | 3 | **1.55 (1.09, 2.02)** |
| Lung | 1 | 2.10 (-1.36, 5.56) | 1 | 0.48 (-0.34, 1.30) |
| Mixed Cancers | 3 | 3.17 (1.34, 5.0) | 4 | 0.41 (0.21, 0.61) |

NR: Not reported.

**Table 2: Exercise Prescription Variables**

**Table 5 Quality of life outcome**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Quality of life measure** | **No. of studies** | **Mean** **difference****(95%CI)** | ***P* value between groups** | **Standardized mean difference****(95%CI)** | ***P* value between groups** |
| All combined | 9 | Not applicable  | ---- | 0.3 (-0.12, 0.70) | *P* = 0.16 |
| EORTC Global  | 4 | 1.45 (0.58, 2.32) |  *P* = 0.001 | 0.13 (-0.06, 0.33) | *P* = 0.17 |
| FACT-G | 4 | 3.25 (-0.41, 6.92) | *P* = 0.08 | 0.47 (0.14, 0.79) | *P* = 0.005  |
| MOS SF36  | 1 | 2.2 (1.34, 3.06) | *P* < 0.001 | 1.22 (0.69, 1.74) | *P* < 0.001 |

EORTC Global: European Organisation for Research and Treatment of Cancer Global Quality of Life Questionnaire; FACT-G: Functional Assessment of Cancer Therapy –General scale; MOS SF36: Medical Outcomes Survey Short Form.

Records identified through database searching
(n = 1823)

* PubMed n = 102
* Medline n = 149
* EMBASE n = 357
* Cochrane n = 16
* Scopus n = 904
* LILACS n = 26
* Web of Science n = 269

## Screening

## Included

## Eligibility

## Identification

Additional records identified through grey literature/ other sources
(n =7)

Records after duplicates removed
(n=1269 )

Records screened by CK and RB
(n=1269 )

Records excluded (n =1242)

* Not specific to cancer (n= 474)
* Not an RCT (n = 166)
* Not aerobic exercise intervention (n = 318)
* Review/Abstract/Commentary (n= 160)
* Other (n = 120)

Full-text articles assessed for eligibility
(n=27)

Full-text articles excluded (n=9)

Studies included in qualitative synthesis
(n=18)

Studies included in quantitative synthesis

(meta-analysis)
(n=17)

**Figure 1 PRISMA flow diagram of study selection process.**

**Figure 2 Risk of bias summary.**

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**Figure 3 VO2 effect size.**

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**Figure 4**

**Figure 4 Meta-regression analysis: Workload, adherence.**