Which exercise prescriptions optimize VO_{2max} during cancer treatment? – A systematic review and meta-analysis

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ABSTRACT

The aims of the present systematic review and meta-analysis were to investigate the effect of exercise on maximal oxygen uptake ($\dot{V}O_2$max) and to investigate whether exercise frequency, intensity, duration and volume are associated with changes in $\dot{V}O_2$max among adult patients with cancer undergoing treatment. Medline and Embase through OvidSP were searched to identify randomized controlled trials. Two reviewers extracted data and assessed the risk of bias. The overall effect size and differences in effects for different intensities and frequencies were calculated on change scores and post intervention $\dot{V}O_2$max data, and the meta-regression of exercise duration and volumes were analyzed using the Comprehensive Meta-Analysis software. Fourteen randomized controlled trials were included in the systematic review, comprising 1332 patients with various cancer types receiving (neo-)adjuvant chemo-, radio- and/or hormone therapy. Exercise induced beneficial changes in $\dot{V}O_2$max compared to usual care (effect size = 0.46, 95% Confidence Interval = 0.23–0.69). Longer session duration (p =

0.020), and weekly duration ($p = 0.010$), larger weekly volume ($p < 0.001$), and shorter intervention duration ($p = 0.005$) were significantly associated with more beneficial changes in $\dot{V}O_2max$. No differences in effects between subgroups with respect to frequency and intensity were found. In conclusion, exercise has beneficial effects on $\dot{V}O_2max$ in patients with cancer undergoing (neo-)adjuvant treatment. As interventions with larger exercise volumes and longer session durations resulted in larger beneficial changes in $\dot{V}O_2max$, exercise frequency, intensity and duration should be considered carefully for sufficient exercise volume to induce changes in $\dot{V}O_2max$ for this patient group.

Key words: aerobic exercise training, cardiorespiratory fitness, FITT-factors, meta-synthesis, RCT

Introduction

Increasing numbers of people are living with the short- and long-term adverse effects of cancer and cancer treatment (1). The American College of Sports Medicine and the American Cancer Society recommend physical exercise as an intervention strategy to help patients with cancer to manage symptoms, improve physical capacity, and improve quality of life during and after treatment (2, 3). Prospective observational studies have shown that physically active cancer survivors have a lower risk of cancer recurrence and improved survival than inactive cancer survivors (2).

Cardiorespiratory fitness, assessed by measurement of the maximal oxygen uptake ($\dot{V}O_2max$), is the most important predictor of all-cause mortality in both healthy individuals and patients with cardiovascular disease (4, 5). Additionally, a low $\dot{V}O_2max$ is associated with increased cardiovascular mortality in patients with breast cancer (6, 7). Compared with healthy individuals, substantially lower $\dot{V}O_2max$ values have been observed in patients with various types of cancer (8) as well as in patients with breast cancer (6, 9-11) and prostate cancer (12) before, during, and after cancer treatment.

Sufficient $\dot{V}O_2max$ in patients is related to higher physical activity level (13) and daily functioning and fewer toxic effects of radiotherapy, chemotherapy, and androgen deprivation therapy on the cardiovascular system, respiratory system, and skeletal muscles (14-20). Frequency, intensity, and duration determine the total exercise volume. To improve $\dot{V}O_2max$, the training principle of overload must be present by increasing frequency, intensity, or exercise duration above the initial physical exercise levels (21). Regular aerobic exercise training (AET) following this principle of overload may improve $\dot{V}O_2max$ by peripheral adaptations within the muscles and increased cardiac output (22).

The number of exercise trials aiming to improve $\dot{V}O_2max$ in patients with cancer has increased during the last few decades. Two meta-analysis in 2011 and 2018 concluded that AET is associated with significant and clinically relevant beneficial changes in $\dot{V}O_2max$ among patients both when undergoing cancer treatment and when finished (23, 24). However, these meta-analyses did not investigate the role of exercise frequency, intensity, type and time (FITT factors) on the change in $\dot{V}O_2max$, nor did they exclusively include studies investigating the effect of exercise during cancer treatment.

Two recent randomized controlled trials (RCTs) (25, 26) investigated the effects of different exercise programs and weekly exercise volumes on $\dot{V}O_2max$ among patients with breast cancer undergoing cancer treatment. Van Waart et al. (26) found less decline in cardiorespiratory fitness during chemotherapy in patients randomized to a supervised moderate- to high-intensity combined resistance and aerobic exercise program compared with patients participating in a home-based low- to moderate -intensity, aerobic exercise program and patients randomized to a usual care control group. Courneya et al. (25) compared the effects of different exercise types and volumes on $\dot{V}O_2$max in patients with breast cancer and found the effect of higher aerobic exercise volume to be superior.

In the healthy population, there is evidence that AET involving moderate to high intensity exercise for at least 40 to 60 minutes per session, three times per week is effective in improving $\dot{V}O_2$max (27). Time efficiency can be enhanced by increasing the exercise intensity and shortening the duration (28). No consensus has yet been reached regarding the optimal exercise prescriptions in terms of FITT factors of exercise to improve $\dot{V}O_2$max in patients undergoing treatment for cancer.

The present systematic review and meta-analysis of RCTs was performed to determine the effect of AET on $\dot{V}O_2$max and elucidate how the FITT factors may influence training-induced changes in $\dot{V}O_2$max among patients with cancer receiving adjuvant or neoadjuvant treatment.

Methods

Search strategies

An electronic database search of Medline and Embase was performed through OvidSP. To identify relevant papers, the search was based on predefined terms regarding population, intervention, comparison, and outcome (PICO terms) using both MeSH terms and free text: Population (P): patients with cancer who are undergoing (neo-)adjuvant cancer treatment; Intervention (I): supervised and unsupervised physical exercise interventions involving an aerobic component; Comparison (C): patients receiving standard of care or who were on a waiting list or on attention control; and Outcome (O): cardiorespiratory fitness. The literature search was conducted in April 2016 and updated in January 2019. Reviews and references of relevant papers were searched for additional studies.

Search string:

1. exp neoplasms/
2. (cancer or neoplasm* or tumor*).ti,ab.
3. 1 or 2
4. exp exercise/ or exercise*.ti,ab.
5. exertion*.ti,ab.
6. training.ti,ab.
7. running.ti,ab.
8. (physical adj1 activ*).ti,ab.
9. (workout or work out).ti,ab.
10. 4 or 5 or 6 or 7 or 8 or 9
11. exercise test/
12. ((o2 or oxygen) adj (uptake or consumption*)).ti,ab.
13. vo2max.ti,ab,hw.
14. fitness/
15. fitness.ti,ab.
16. aerobic capacity/
17. aerobic capacit*.ti,ab.
18. physical endurance/
19. physical fitness/
20. fitness.ti,ab,hw
21. exp oxygen consumption/
22. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 3 and 10 and 22
24. clinical trial/ or controlled study/ or randomized controlled trial/
25. (intervention* or rct or trial or trials or randomized).ti,ab,hw.
26. 24 or 25
27. 23 and 26

Inclusion criteria

The present meta-analysis included RCTs of adult (>18-year old) patients with cancer that evaluated the effects of an exercise intervention with an AET component during treatment compared with a usual care control group. Studies in patients with all cancer types during (neo-)adjuvant treatments (radiotherapy, chemotherapy, radio chemotherapy, or hormone therapy) with curative intent were included. Additionally, studies were included when the cardiorespiratory fitness test was conducted at baseline and at the end of the exercise intervention, directly through measurements of maximal oxygen uptake or indirectly by estimating $\dot{V}O_2max$ from a maximal exercise test. We excluded studies in which patients participated in an exercise intervention before or after surgery and did not receive any concurrent adjuvant cancer treatment, studies evaluating combined lifestyle interventions, for example interventions focusing on exercise and diet or other medical/dietary supplements, studies investigating patients both during and after treatment, and studies that examined cardiorespiratory fitness with a submaximal exercise test.
If relevant information regarding FITT factors and $\dot{V}O_2max$ in both patients randomized to the exercise group and the control group could not be derived from the published paper or via correspondence with the author, the study was included in the systematic review but not in the meta-analysis.

Study selection and data extraction

One reviewer (A.C.H.B.) removed duplicates and screened titles and abstracts for eligibility. Full-text assessments were done by two reviewers (A.C.H.B. and M.G.S.).

After assessing eligible studies for the meta-analysis, two additional reviewers (L.M.B. and S.B.) also reviewed and accepted the decisions involving inclusion of studies. Details regarding study inclusion are provided in the CONSORT statement (Figure 1).

Reviewers A.C.H.B. and M.G.S. independently extracted information regarding the study population: country, cancer site, disease stage, medical treatment, number of patients at baseline and at follow-up, age, and sex. Both reviewers also independently extracted the characteristics of the exercise interventions, methods of $\dot{V}O_2max$ testing, and post-intervention $\dot{V}O_2max$ scores or changes from baseline (in L/min, mL/min, mL/min/kg, or metabolic equivalents of task [METs]). If not reported, the outcomes of patients randomized to the exercise and control groups were derived via correspondence with the author.

The classification of prescribed exercise intensity was based on the American College of Sports Medicine guidelines (29). The input for classification was information on the *prescribed* intensity. If the prescribed exercise intervention in a study had an intensity range that overlapped two intensity levels (i.e., low and moderate), the study was referred to by these two intensities (i.e., low–moderate intensity). Consequently, five categories were defined: low, low–moderate, moderate, moderate–high, and high intensity. Exercise intensity was indicated by the value of METs; we used a value of 1.5 METs to indicate low intensity, 3.0 METs to indicate low–moderate intensity, 4.5 METs to indicate moderate intensity, 6.0 METs to indicate moderate–high intensity, and 7.5 METs to indicate high intensity exercise (30). We calculated the weekly exercise volume as follows: exercise intensity (MET value) × duration × frequency.

Risk-of-bias assessment

Risk-of-bias assessment was performed by two independent reviewers (A.C.H.B. and M.G.S., L.M.B., or S.B.) using TESTEX, a validated 15-item scale specific for assessing risk of bias in exercise training studies (31). Each study was rated according to 5 items on study quality and 10 items on reporting, with a maximum score of 15 points. The quality assessments of the reviewers were compared, and disagreements were resolved by discussion among all four raters.

Statistical analysis

To adjust for differences in $\dot{V}O_2max$ at baseline, we used independent group differences to calculate effect sizes. There were three different formats used when calculating effect sizes, depending on the information available in the paper. By one procedure post intervention means, confidence intervals (CI's) and sample sizes of both intervention and control group were used to calculate effect sizes. Second, if differences between groups were reported, the mean difference, sample size of both intervention and control group, independent groups p-value and number of tails were used to calculate effect sizes. Last, if only raw differences were reported, the mean difference with the upper and lower limit, sample size of both intervention and control group and CI were used to calculate effect sizes. Hedges' g was calculated to adjust for small sample sizes (32). A study was considered an outlier and excluded from further analyses if the 95% CI of the calculated effect size did not overlap with the 95% CI of the overall effect size. Cohen's convention was used to interpret the effect sizes: an effect size of 0.2 was considered small, 0.5 was considered moderate, and 0.8 was considered large (33). Because the samples and interventions were expected to be heterogeneous, the effect sizes were pooled with a random-effects model, taking differences in the effects between the studies into consideration. The I^2 statistic was reported as an indicator of heterogeneity, with an I^2 of 25% representing low heterogeneity, 50% representing moderate heterogeneity, and 75% representing high heterogeneity (34). Subgroup analyses were conducted to study the differences in effects between studies with several exercise- and intervention-related characteristics: 1; frequency of training sessions per week categorized into 2-3 times/week, 3 times/week and ≥4 times/week, 2; intensity categorized using MET values, 3; delivery mode dichotomized into supervised when a supervised exercise component was included and unsupervised when there were no instructor present. Additionally, we performed a meta-regression analysis to study the association of $\dot{V}O_2max$ with the 4; session duration, 5; weekly exercise duration, 6; weekly exercise volume, 7; intervention duration referring to the duration of the intervention period in weeks, and 8; intervention volume calculated as the total exercise volume × intervention duration. When reporting and analyzing session durations from combination trials (AET+RET), the total exercise session duration was reported and used in the analyses. Due to the observed variety in exercise prescriptions regarding type of exercise (i.e. cycling, running, walking, football-activities and interval vs continuous exercise etc.), there were too few studies to investigate this particular FITT factor. In the following text, *FITT* will refer to frequency, intensity and time (duration).

In the meta-regression, Z-values and p-values were presented to provide information about the regression coefficient and significance of the relationship between the variable and the effect size.

To study the possible interference of including resistance exercise, we also conducted sensitivity analyses in which combination trials (RET+AET) (35-38) were excluded. All analyses were conducted using Comprehensive Meta-Analysis software, version 2.2.064 (National Institutes of Health, Bethesda, MD, USA).

Publication bias was investigated by inspecting the funnel plot, and Duval and Tweedie's procedure (39). This procedure imputed missing studies to achieve symmetry around the center of the funnel plot. The effect was then recalculated based on this procedure. Publication bias was suggested by the presence of significant dispersion between the true effect size and the calculated effect size as seen by Egger's test. An alpha level of $p \leq 0.05$ was set as the criterion for statistical significance.

Results

Study characteristics

In total, 2038 unique records were identified from the database search, and 124 full texts were assessed for eligibility. In accordance with our preset criteria, 14 RCTs were included in the systematic review (Fig. 1). Five studies did not present sufficient data to calculate effect sizes, but we obtained data from four studies (36-38, 40) through author correspondence. For one study, we were unable to obtain data to calculate effect sizes (41), resulting in a total of 13 studies included in the meta-analysis. One study (38) presented results for female and male patients separately and was therefore included separately in the present study, resulting in a sample size of 14 comparisons in the meta-analysis.

Study population characteristics

The 14 studies in the systematic review (35-38, 40-49) encompassed 1332 patients (range, 14–269 patients per study), with 751 in the intervention group and 581 in the control group (Table 1). Various cancer types and (neo-)adjuvant treatments were represented in the studies: seven studies included patients with breast cancer receiving chemotherapy (37, 41-43, 45), radiotherapy (40), or both (46); three studies included patients with prostate cancer receiving radiotherapy (47, 48) or androgen deprivation therapy (49); three studies included patients receiving chemotherapy for colon cancer (38), acute myeloid leukemia (36), or mixed cancer types (35), respectively; and one study included a mixed cancer population (44) receiving a variety of treatments (radiation and/or chemotherapy). The patients' mean age varied from 45 to 69 years, and 70% of the participants were women.

Exercise intervention characteristics

Eleven of the included RCTs were two-armed studies comparing aerobic exercise (40, 42, 44-47, 49) or combined aerobic and resistance exercise (35-38) with a control group (Table 2). Three RCTs were three-armed studies comparing aerobic exercise and resistance exercise separately with a control group (41, 43, 48). In two studies exercise sessions were unsupervised (40, 44), and in 12 studies exercise sessions were supervised by an exercise instructor. The median frequency of exercise was 3 days/week (range: 2–5 days/week); seven studies prescribed "high" intensity exercise (35, 41, 43, 45-48), five "moderate–high" (36-38, 42, 49), and two "low–moderate" (40, 44) intensity exercise. The median duration of exercise sessions was 35 min (range, 27–90 min). One study did not present the time exercised during each session (41) and the median duration of the interventions was 11.5 weeks (range, 5–24 weeks). The median weekly exercise duration was 120 min (range, 80–270 min), and the median weekly exercise volume was 720 MET min/week (range: 390–2025 MET min/week).

Methods of cardiorespiratory fitness testing

The $\dot{V}O_2max$ was measured directly in 11 studies: while running or walking on a treadmill in seven studies (40-44, 46, 48) and while bicycling on a cycle ergometer in four studies (37, 38, 45, 49) (Table 2). Two studies included a maximal treadmill test with the modified Bruce protocol to estimate $\dot{V}O_2max$ (36) or to calculate METs (47). One study estimated $\dot{V}O_2max$ indirectly using a stepwise work capacity test on a stationary exercise cycle (35). Of the studies included in the meta-analysis, the type of exercise modality performed during the exercise sessions matched the modality of the cardiorespiratory fitness test (i.e., cycling and running) (35, 36, 40, 42-48). In one study, the participants conducted their cardiorespiratory fitness test on a cycle ergometer and performed football exercises during the exercise sessions (49). In two other studies, a cycle ergometer was used in the test but the type of AET performed during exercise sessions was not reported (37, 38).

Risk-of-bias assessment

The median TESTEX score was 11.5 (range, 3–14) (Table 3). Three studies (37, 38, 45) reported blinding of the outcome assessors. Six studies (36, 40, 43, 44, 46, 48) monitored physical activity in the control group. Seven studies (35, 37, 38, 43-45, 48) used an intention-to-treat analysis. Four studies (42, 43, 45, 48) provided a clear plan for progression of the prescribed exercise by increasing frequency, session duration, and intensity throughout the intervention period, aiming to adjust the relative total exercise volume for the participants. In one study, both frequency and session duration were adjusted during the intervention (49). In one study (36), exercise intensity was adjusted based on self-reported perceived exertion. In two studies (37, 38), a combination of self-reported perceived exertion and heart rate (HR) monitoring was used to identify training progression. In one of these studies, the maximum HR was reassessed by a submaximal cardiopulmonary exercise test every 4 weeks (37), and in the other study, the reassessment method was not reported (38). Two studies reported adjustment of intensity based on HR measurements but lacked information on how these adjustments were made (46, 47). Four studies (35, 40, 41, 44) did not report any form of intensity monitoring or adjustments of frequency, intensity, and/or session duration throughout the exercise intervention period.

Adherence

In three studies, intensity and duration were included in the assessment of adherence to the intervention (36, 45, 46). In another three studies, adherence was mentioned but the authors did not include any descriptions on how they assessed adherence and to what part of the intervention they measured adherence (40, 43, 48). Two other studies reported adherence to frequency and duration, but not to intensity (37, 44), while three studies only reported the attendance rate (35, 42, 49). In one study, self-reported adherence to all of the FITT factors was registered at the end of the intervention (38), and in two studies the authors did not report any attendance or adherence to the prescribed exercise intervention (41, 47).

Meta-analysis and overall effects

After excluding one outlier (42), a significant moderate positive effect was found on $\dot{V}O_2max$ (effect size = 0.46, 95% CI = 0.23–0.69) (Table 4 and Fig. 2). Heterogeneity was indicated to be high ($I^2 = 64$, $p = 0.001$).

Analysis of FITT factors

We found no significant differences between studies with different exercise frequencies ($p = 0.140$) and intensities ($p = 0.090$) with respect to improvements in $\dot{V}O_2max$ (Table 4).

Improvements in $\dot{V}O_2$max were significantly larger for studies with larger session durations (z-value, 2.30; p = 0.020), longer weekly exercise durations (z-value, 2.53; p = 0.010), and larger weekly exercise volumes (z-value, 3.57; p < 0.001). The intervention volume was also significantly associated with the intervention effects on $\dot{V}O_2$max (z-value, 1.96; p = 0.049). Studies with shorter intervention durations showed significantly larger improvements in $\dot{V}O_2$max than studies with longer intervention durations (z-value, −2.80; p = 0.005). The results of the sensitivity analysis including studies evaluating AET only were in line with the primary analyses for exercise frequency (p = 0.740), intensity (p = 0.740) and the intervention volume (z-value, 2.14; p = 0.030). In contrast to the main analyses, the sensitivity analyses showed no significant differences in effects on $\dot{V}O_2$max across session duration (z-value, 0.61; p = 0.540), weekly exercise duration (z-value, 1.60; p = 0.110) or intervention duration (z-value, -0.44; p = 0.660).

Assessment of publication bias

There was a symmetric distribution when investigating the funnel plot. The trim-and-fill procedure suggested that three studies were missing, resulting in an adjusted effect size of 0.38 (0.12–0.60). Egger's test was not statistically significant (p = 0.197), suggesting no publication bias.

Discussion

This systematic review and meta-analysis of 13 studies showed that exercise interventions with an aerobic component during (neo-)adjuvant cancer treatment resulted in positive changes in $\dot{V}O_2$max compared with standard care control. We found a larger beneficial effect of increased session duration, weekly exercise duration, and weekly exercise volume on $\dot{V}O_2$max.

The observed significant moderate beneficial effect on $\dot{V}O_2$max among patients with cancer who followed an exercise intervention during (neo-)adjuvant treatment compared with the control group corresponds to results reported in two previous meta-analyses (23, 24). However, in contrast to these previous meta-analyses, we exclusively focused on studies that included patients undergoing (neo-)adjuvant treatment and performed maximal assessments of cardiorespiratory fitness. The choice of only including maximal exercise tests exclusively was based on the knowledge that the use of submaximal exercise tests to predict $\dot{V}O_2$max often over- or underestimate $\dot{V}O_2$max (50). Overestimation of $\dot{V}O_2$max among patients with cancer undergoing treatment may result from chemotherapy-induced autonomic dysfunction causing higher heart rate at rest and at submaximal exercise levels (50). The observed moderate beneficial changes in $\dot{V}O_2$max are clinically relevant because $\dot{V}O_2$max is an important predictor of all-cause mortality (4, 5). Our results, combined with previous findings of impaired $\dot{V}O_2$max among patients with cancer (6, 8-12, 51) emphasize the clinical importance of increasing or maintaining $\dot{V}O_2$max in this phase of the cancer trajectory.

In contrast to healthy populations in which AET aims to *improve* cardiorespiratory fitness, only small improvements, maintenance or a less steep decline of $\dot{V}O_2$max is expected in patients undergoing chemotherapy (23). This is confirmed in previous randomized controlled trials (25, 26, 43, 46, 52). Previous studies in patients with prostate cancer treated with ADT, have also presented small improvements or maintenance in $\dot{V}O_2$max (48, 49).

To our knowledge, the present meta-analysis is the first to study the effect of frequency, intensity, session duration, weekly duration and weekly volume on $\dot{V}O_2$max only in a population of patients with cancer undergoing (neo-)adjuvant treatment. Our finding that longer session durations are associated with improvements in $\dot{V}O_2$max is supported by a meta-analysis of Huang et al. (53), who found a dose–response relationship between an increasing session duration and $\dot{V}O_2$max in healthy older people performing exercise. Prescribing exercise sessions of long enough duration may thus be important to have beneficial effects on $\dot{V}O_2$max in patients with cancer. Notably, Huang et al. (53) found a ceiling effect; the $\dot{V}O_2$max gain did not increase further after approximately 45 minutes. Due to the relatively small number of studies and the large variation in intervention characteristics, it is difficult to derive whether a ceiling effect exists among patients with cancer. The most optimal session duration needs to be confirmed in future studies.

Our observation that longer weekly exercise durations and larger weekly exercise volumes were more beneficial than shorter durations corresponds to previous findings by Courneya et al. (25), who investigated patients exercising during chemotherapy for breast cancer. The authors found that an increased weekly exercise duration of 150 min AET at 70% to 75% of $\dot{V}O_2$peak resulted in more beneficial changes in $\dot{V}O_2$max than AET with a weekly duration of 75 min at the same intensity. This was also observed in a meta-analysis of exercise trials in healthy young adults on the combined effect of session duration and intensity on $\dot{V}O_2$max (54). Although the exercise duration and volume seem important to increase or maintain $\dot{V}O_2$max, we cannot determine the specific recommended exercise duration or volume from the present study.

The finding of smaller beneficial changes in $\dot{V}O_2$max in interventions with longer durations may result from lower adherence in longer exercise interventions (55). We cannot investigate this issue based on the information given in the included studies in the present systematic review. As Nilsen et al (56) advocates, more novel methods for reporting exercise volume and adherence throughout the entire exercise intervention are needed.

No differences in $\dot{V}O_2$max were found between subgroups with respect to exercise frequency and intensity. This finding was unexpected and in contrast to previous studies of healthy populations in which strong associations between exercise frequency and intensity were reported. Huang et al. (53) found a dose–response relationship of cardiorespiratory fitness when studying the effect of different exercise intensities in older adults (67.45 ± 5.25 years of age). An intensity ceiling was found around 70% to 73% of HR reserve, and higher intensities did not induce further enhancements in $\dot{V}O_2$max (53). Huang et al. (53) also found that a frequency of 3 to 4 days/week was the most effective in changing $\dot{V}O_2$max among this population.

Of note, small sample sizes may have also affected the results in our meta-analysis; 6 of the studies included intervention groups comprising only 7 to 29 patients (38, 40, 42, 45, 47, 49). Consequently, there were large CIs and overlaps in CIs within the different frequency and intensity groups.

Results from published exercise interventions investigating the effect of exercise intensity among patients undergoing treatment for cancer have shown that higher intensities tend to be more efficient for improving or maintaining $\dot{V}O_2$max. Van Waart et al. (26) found that moderate- to high-intensity exercise had larger effects on $\dot{V}O_2$max than low- to moderate-intensity exercise. Importantly, whether these findings are caused by the prescribed intensity levels or by other differences related to the exercise programs (e.g. exercise type or supervision) remains unclear. Larger improvements in $\dot{V}O_2$max after high intensity compared to low-moderate intensity exercise were also found in the RCT by Kampshoff et al. (57), who studied the effects of exercising after the completion of (neo-)adjuvant treatment. The findings in these particular exercise interventions are supported in the present study by the – although not statistically significant – larger effects on $\dot{V}O_2$max in studies with higher intensity. More importantly, the findings of the present meta-analysis points to the direction that total exercise volume seems to be more important than exercise intensity alone, although this must be confirmed in future studies.

The fact that all FITT factors will interchangeably influence the effect on $\dot{V}O_2$max makes it challenging to disentangle whether it is one specific variable or a combination of variables that results in larger improvements in $\dot{V}O_2$max within a limited number of studies. Consistent with findings in a previous review of patients with cancer (58), the studies included in the present meta-analysis used a variety of exercise programs, prescribing different frequencies, levels of intensity, session and intervention durations and types of exercise. Given the lack of consensus regarding optimal and specific exercise prescriptions for patients with cancer undergoing treatment (59) and generally in the exercise oncology literature (21), this diversity in the content of exercise interventions is not surprising. This large heterogeneity in combinations of FITT factors makes it challenging to separately compare individual factors and may be a second explanation for why we did not find differences in effects on $\dot{V}O_2$max between different exercise frequencies and intensities.

In a healthy population, both moderate and high intensity exercise are effective to improve $\dot{V}O_2$max (27, 54). However, in a meta-analysis of exercise trials among healthy young adults no enhanced effect of high intensity compared to moderate intensity was observed on $\dot{V}O_2$max, but as in our study there was rather a dose-response relationship between exercise volume and $\dot{V}O_2$max (54). However, in a meta-analysis on studies including healthy elderly people (53) and in patients with coronary heart disease (60), results suggested a beneficial effect of an increasing exercise intensity on $\dot{V}O_2$max (53).

It should, however, be noted that our findings on exercise intensity are based on the prescribed and not the actual performed exercise intensity. Additionally, prescribed intensities were often based on heart rate. Prescribing optimal exercise intensity for patients undergoing cancer treatment is challenging with heart-rate-based intensity protocols (61, 62), because chemotherapy and/or radiation may impact the cardiac, pulmonary and vascular system, hemoglobin concentration, and oxidative capacity (63), which further alters HR_{rest} and reduces HR reserve.

Strengths and limitations

The strengths of the present study are the systematic searches of two large databases, our specific focus on patients during (neo-)adjuvant cancer treatment only, the exclusive inclusion of interventions with aerobic components, and the systematic investigation into the role of FITT factors. In addition, we included only studies with direct and indirect assessments of $\dot{V}O_2$max, resulting in a high internal validity. Although we accepted different exercise modes when performing the $\dot{V}O_2$max tests, most of the RCTs (35, 36, 40, 42-48) conducted the same exercise mode during the test and during the intervention, assuming that this aspect is not a limitation. Another strength of the present study is that we performed a quality assessment of the included RCTs and found that most of them reported their prescribed frequency, intensity, time, and type of exercise (35-38, 40, 42, 43, 45-49). However, some important limitations should be noted. First, the heterogeneity among studies was high, possibly due to the diversity of sample sizes, cancer types and treatments, characteristics of exercise programs, and methods and exercise modes included during the $\dot{V}O_2$max test. Second, the number of studies included in the present meta-analysis to investigate differences in intervention characteristics, FITT factors, and associations with changes in $\dot{V}O_2$max was rather small. Third, it was not possible to adjust for $\dot{V}O_2$max scores at baseline in all studies. Studies without adjustment could have a risk of regression to the mean (42, 45); thus, patients with lower baseline $\dot{V}O_2$max values have a greater potential to enhance their $\dot{V}O_2$max than patients with higher baseline values (64). Fourth, with respect to the FITT factor time, the time spent in both AET and RET was included when reporting and analyzing the session duration from the four combination trials (35-38) (Table 2). Fifth, the impact of different types of exercise and modalities was not assessed in our study. Finally, 70% of the included participants are women, most of them with breast cancer, which hampers the generalization of the results to patients with other types of cancer. However, this gender distribution reflects the current body of research in the field of exercise oncology (65, 66).

Conclusion and perspectives

The present systematic review and meta-analysis supports earlier findings that exercise interventions with an aerobic component have beneficial effects on $\dot{V}O_2$max in patients undergoing (neo-)adjuvant treatment for cancer compared to control (23, 24). This finding highlights the importance of exercise during (neo-)adjuvant treatment to prevent reductions in $\dot{V}O_2$max from the time of diagnosis and during (neo-)adjuvant treatment. By also studying the effect of frequency, intensity and duration on $\dot{V}O_2$max in a more detailed matter, the present study supplies the field with a more specific understanding of how different exercise prescriptions could have various impact on this important clinical outcome.

We observed larger beneficial changes in $\dot{V}O_2$max among exercise interventions with longer session durations, weekly exercise durations, and larger weekly exercise volumes. With respect to frequency and intensity, no differences between subgroups were found, but as weekly exercise duration and volume are a function of frequency, intensity and session duration, the *combination* of these variables seems important. Due to the mentioned limitations with prescribed intensities and adherence, cautions need to be taken when interpreting our results regarding how different exercise prescriptions may influence $\dot{V}O_2$max. We cannot omit intensity being an important exercise factor, and more studies are needed. Though, based on our findings, exercise duration and volume seem most important to maintain or increase $\dot{V}O_2$max. Exercise frequency, intensity and duration should therefore be considered carefully for sufficient exercise volume to induce beneficial changes in $\dot{V}O_2$max when prescribing exercise for patients with cancer. To better individualize exercise prescriptions, there is a need for well-designed structured exercise intervention trials investigating how aerobic exercise performed at different frequencies, intensities, and/or durations affect $\dot{V}O_2$max in different groups of patients with cancer. Future studies should also report adherence to the different FITT factors as part of the planning of exercise interventions for cancer patients undergoing (neo-)adjuvant treatment.

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