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Review

The Benefit of Exercise in Patients With Cancer Who Are Receiving Chemotherapy: A Systematic Review and Network Meta-Analysis

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Abstract

Objective. This study aimed to determine which therapeutic exercise-based intervention is most effective in improving cardiorespiratory fitness (CRF) in patients with cancer receiving chemotherapy.
Methods. The authors conducted a systematic review with network meta-analysis in MEDLINE (PubMed), Embase, Cumulative Index to Nursing and Allied Health Literature, Scopus, SPORTDiscus, and Web of Science. The authors employed the Physiotherapy Evidence Database and the Revised Cochrane Risk of Bias Tool for Randomized Trials to assess the methodological quality and risk of bias, respectively.
Results. A total of 27 studies were included. Data were pooled using a random-effects model. Adding aerobic training (moderate to high intensity), with or without resistance training, to usual care versus usual care was statistically significant, with a small beneficial effect (aerobic training: standardized mean difference = 0.46; 95% CI = 0.17 to 0.75; aerobic and resistance training: standardized mean difference = 0.26; 95% CI = 0.00 to 0.52) for peak oxygen consumption at the postintervention assessment.
Conclusion. Therapeutic exercise-based interventions to improve short-term CRF in patients with cancer receiving chemotherapy should include moderate- to high-intensity aerobic exercise, with or without resistance training.
Impact. It is important to improve CRF in the oncological population due to its relationship with mortality. The results showed the benefit of exercise to improve cardiorespiratory fitness in the oncology population receiving chemotherapy treatment.

Keywords: Chemotherapy, Exercise Therapy, Oncology

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Introduction

In the last 50 years, the 5-year relative survival rate has improved in patients with cancer from 49% to 68%.[1] It is the result of important improvements in the diagnostic process and treatments, such as chemotherapy.[1–3] However, these treatments are not without negative side effects, such as nausea, vomiting, peripheral neuropathy, cardiovascular diseases, or impairment of cardiorespiratory fitness (CRF).[4–8]

CRF reflects the oxygen transport capacity to the mitochondria and its utilization during exercise.[9] Based on the study by Lakoski et al, the cause of reduced CRF in patients with cancer is multifactorial, with pulmonary, cardiovascular, or peripheral limitations, age, comorbidities, and deconditioning playing important roles.[10] It is related to the function of various systems and provides an objective measure of the overall physical performance.[9,11] CRF is a predictor of cancer mortality and individuals with a high level of CRF have a significant reduction in mortality risk.[11–13] The gold standard for measuring CRF is the maximum oxygen consumption (Vo_2max) measured during an incremental exercise test.[14] We use interchangeably Vo_2max and peak oxygen consumption (Vo_2peak) to facilitate the understanding of our work, we referred to them as Vo_2peak.[14] Howden et al found that Vo_2peak is a suitable measure of cardiovascular function in patients with cancer and a surrogate marker of cancer treatment-induced cardiotoxicity.[15]

Chemotherapy treatment decreased Vo_2peak by 10%, while radiotherapy or endocrine therapy did not change Vo_2peak.[16] Chemotherapy may impact the oxygen cascade and reduce the ability to supply oxygen for adenosine triphosphate resynthesis.[17] It increases mitochondrial oxygen consumption.[18] Additionally, chemotherapy affects myocardial tissue, reducing the ejection fraction of the left ventricle, thereby reducing convective oxygen delivery.[17] It has been highlighted that patients with cancer receiving chemotherapy treatment had a 31% lower Vo_2peak than an age-matched population with no history of cancer.[19] A decrease in Vo_2peak has consequences for the patient's function. A Vo_2peak of $\leq$18.0 mL/kg/min has been considered as functional incapacity to perform basic activities.[20] Vo_2peak is also a measure of cardiotoxicity as well as physical condition. Cardiotoxic cancer treatment reduced Vo_2peak by an average of 7% within 4 months after cancer treatment.[15] This reduction in Vo_2peak has been associated with a 15% to 26% increase in the prevalence of functional disability following cardiotoxic treatment.[15]

The direct toxic effect of chemotherapy on the cardiovascular and respiratory systems appears to be dose dependent. A low level of physical activity during adjuvant treatment could be a mediator of the impairment of CRF.[16,21]

Structured physical exercise appears to be a solution to counteract the CRF impairment due to cancer and chemotherapy.[22,23] Different organizations have written guidelines and recommendations for exercise in patients with cancer.[24] In 2019, Campbell et al collected updated evidence regarding the benefits of exercise in patients with cancer and established exercise prescription guidelines to improve some health-related components such as physical function, anxiety or quality of life, among others.[25] However, to the best of our knowledge, no extensive recommendations have yet been established regarding exercise modality and intensity to improve CRF in patients with cancer receiving chemotherapy. Intensity of interval training has the major influence to generate changes in Vo_2peak in people who are healthy.[26,27] Thus, intensity is a factor to be considered in the improvement of CRF and needs to be studied in depth in patients with cancer receiving treatment. Given the impact of chemotherapy on CRF and the direct impact this variable has on survival, it is necessary not only to show the effectiveness of exercise in improving it but also to establish the optimal form of prescription to achieve the greatest increase in CRF.

Therefore, the aim of this systematic review and network meta-analysis was to synthesize and analyze which type of therapeutic exercise-based intervention, in terms of modality and/or intensity, was most effective in improving CRF in patients with cancer receiving chemotherapy.

Methods

This systematic review and network meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews Incorporating Network Meta-Analysis extension statement.[28] The protocol of this study was registered in the PROSPERO database (CRD42022299513).

Eligibility Criteria

The selection criteria for the systematic review were based on methodological and clinical factors such as population, intervention, comparison, outcomes, and study design criteria.[29]

Population

Patients who were more than 18 years old, had cancer, and were receiving any type of chemotherapy were included (ie, neoadjuvant or adjuvant). Studies in which participants received other treatments, such as surgery or radiotherapy, were included as long as they were receiving chemotherapy. There were no restrictions on gender, type and stage of cancer, or type of chemotherapy.

Intervention and Comparison

All patients in all study groups received the first-choice neoadjuvant or adjuvant chemotherapy. Each study had to include at least 1 arm that included exercise during chemotherapy treatment (ie, aerobic, resistance, or interval exercise). We included studies that had implemented the exercise intervention during the chemotherapy period. Exercise training could have started before, at the same time or after a chemotherapy session.

Outcomes

CRF was assessed through Vo_2peak (Vo_2max or Vo_2peak).[14] Studies were included in which Vo_2peak was either the primary or secondary outcome. Studies were included if they presented data from baseline and after intervention. In order to be included, studies had to present the numerical results derived from the analyses.

Study Design

Randomized controlled trials (RCTs) were included. There was no restriction based on date, publication status, or any specific language.[30]

Search Strategy

We conducted the search for scientific articles from inception to October 15, 2021 in the following databases: MEDLINE

(PubMed), Embase, Cumulative Index to Nursing and Allied Health Literature, Scopus, SPORTDiscus, and Web of Science. The search was updated until April 11, 2023. In addition, we manually checked the reference sections of relevant included studies, checked studies included in reviews related to the topic and contacted authors for further information when necessary. The search strategy employed in each database is shown in Supplementary Material A.1. The search was also adapted and performed in Google Scholar. There were no specific publication date or language restrictions.[30]

Selection Criteria

All identified references were exported to the Rayyan QCRI software, which was employed to remove duplicates and perform the 2-phase screening process.[31] First, we assess the relevance of the studies in relation to the study questions and objectives. This analysis was performed using information from the study title, abstract, and keywords. If there was no consensus or insufficient information, the full text was reviewed. In the second phase of the analysis, the full text of each study was assessed for compliance with the inclusion criteria. The article selection process was conducted by 2 independent researchers (A.H-G. and C.V-R.). Differences between the 2 reviewers were resolved by consensus moderated by a third researcher (L.S-M.).[32]

Data Extraction and Efficacy Measures

Study characteristics and outcome data were extracted by 2 researchers independently (A.H-G. and L.B-G.) using a structured protocol that ensured that the most relevant information was obtained from each study.[33] Exercise interventions were categorized as aerobic exercise, resistance exercise, flexibility exercise (including stretching), high-intensity interval training (HIIT), or moderate-intensity continuous training (MICT). In aerobic and resistance exercise, intensity was categorized as low, moderate, or high according to the reference values indicated by the American College of Sports Medicine's Guidelines for Exercise Testing and Prescription.[34] The term HIIT referred to high-intensity interval exercise. All other exercise modalities and intensities, everything other than HIIT, referred to continuous training.

The different statistical results related to the effect of an exercise training on Vo_2peak were extracted from the postintervention and/or follow-up assessment. All the numeric data were converted to mean and SD. If necessary, CIs and SEs were converted to SDs using the formulas recommended by the Cochrane Handbook for Systematic Reviews of Interventions version 6.2: $SD = \sqrt{(N)} \times [(\text{upper limit} - \text{lower limit})/3.92]$ and $SD = \sqrt{(N)} \times SE$, respectively.[35] The Plot Digitizer software was employed to estimate outcome results when only figures were available (http://plotdigitizer.sourceforge.net).

Methodological Quality and Risk-of-Bias Assessment

We assessed methodological quality using the Physiotherapy Evidence Database.[36] This scale evaluates the internal and external validity of a study through 11 criteria: specified study eligibility criteria; random allocation of individuals; concealed allocation; measure of similarity between groups at baseline; blinding of individuals; blinding of therapists; blinding of assessors; fewer than 15% dropouts; intention-to-treat analysis; between-group statistical comparisons; and point measures and variability data. The criteria were scored as yes (1 point) or no/unknown (0 point). The Physiotherapy Evidence Database score provided an indicator of the methodological quality of each study (9 or 10 = excellent; 6–8 = good; 4 or 5 = fair; 3–0 = poor).[37]

We employed the Revised Cochrane Risk of Bias Tool for Randomized Trials to assess the risk of bias in the selected studies across the following 5 domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported results.[38] Each domain includes signaling questions, answered with yes, probably yes, probably no, no, or no information within domains. These questions lead to a final judgement within domains such as "low risk of bias," "some concerns of risk of bias," or "high risk of bias," which in turn lead to an overall risk of bias for each trial.

Methodological quality and risk of bias were assessed independently by 2 researchers (A.H-G. and L.B-G.), and disagreements were resolved through consensus by a third researcher (F.C-M.). We calculated the linear weighted Cohen κ coefficient[39] using Jamovi software[40] to assess interrater reliability prior to any consensus and estimated the interrater reliability using κ, according to the following values: none: $\kappa = 0.00$ to 0.20; minimal: $\kappa = 0.21$ to 0.39; weak: $\kappa = 0.40$ to 0.59; moderate: $\kappa = 0.60$ to 0.79; strong: $\kappa = 0.80$ to 0.89; and almost perfect: $\kappa = 0.90$ to 1.00.[41]

Overall Strength of the Evidence

The certainty of evidence analysis was based on classifying the results into levels of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation framework. The Grading of Recommendations Assessment, Development, and Evaluation for the certainty of the network estimate was assessed by 2 researchers (A.H-G. and C.V-R.) according to the adaptation from Salanti et al,[42] and it is based on 5 domains: study design, imprecision, indirectness, inconsistency, and publication bias.[43] The evidence was categorized into 4 levels: high, moderate, low, or very low quality of evidence. Supplementary Material A.2 includes the criteria used for each domain.

Data Synthesis and Statistical Analysis

The short-term effect of different exercise modalities on Vo_2peak was analyzed with a frequentist network meta-analysis (C.V-R.) using RStudio software version 1.4.1717, which is based on R software version 4.1.1.[44–46] and different packages.[46–53] R scripts and raw data used for the analysis are available in the Open Science Framework repository (https://osf.io/gzt7y/?view_only=ef1a5517026b4d64b6a2209be9bb2097) and/or by contacting C.V-R. Network meta-analysis allowed to infer an estimation of a comparison's effect size based on direct evidence from observed comparisons in the different primary studies and indirect evidence from the inference of comparisons that have not been actually studied. A network graph was displayed to visualize direct comparisons between exercise modalities.

We used the corrected standardized mean difference (SMD) or Hedges g as an effect measure, along with the corresponding 95% CI.[54] SMDs were interpreted as described by Hopkins et al[55]: >4.0 represented an extremely large

clinical effect, 2.0 to 4.0 represented a very large effect, 1.2 to 2.0 represented a large effect, 0.6 to 1.2 represented a moderate effect, 0.2 to 0.6 represented a small effect, and 0.0 to 0.2 represented a trivial effect. We estimated the degree of heterogeneity and inconsistency among the studies using the Cochran Q statistic test (a P-value of $<.05$ was considered significant) and the inconsistency index (I^2). The Cochran Q test allowed us to assess the presence of between-study heterogeneity and between-design consistency.[56] Despite its common use to assess heterogeneity, the I^2 represented the percentage of variability in the estimate caused by between-study heterogeneity.[57]

Since we pooled different treatments, we could not assume that there was a unique true effect. So, we anticipated between-study heterogeneity and the necessity of a random-effects model to pool effect sizes. To justify the use of a random-effects model, we calculated the difference in total inconsistency of the results between a fixed-effects model and a random-effects model using a full design-by-treatment interaction random-effects model.[58] To hold the assumption of transitivity, studies had to differ only by the treatment applied.[59] If not, indirect evidence was influenced not only by the treatment but also confounders.[42] The statistical manifestation of transitivity was the consistency between comparisons.[59] We performed a net heat plot using a fixed-effects model and a random-effects model to evaluate visually if inconsistency is improved with a random-effects model. Inconsistency was also evaluated with net splitting where network estimates were split into direct and indirect evidence in a forest plot.

The proportion of direct and indirect evidence was printed in an evidence plot. The evidence plot also provided a measure of direct evidence proportion, the minimal parallelism, and mean path length of each estimated comparison.[60] A comparison with a mean path length of >2 indicated indirectness and should be interpreted cautiously.[60] We visually represented the network estimation for each comparison based on direct and indirect evidence in a colored matrix.

Exercise modalities were ranked according to the extent of certainty that 1 technique provide higher improvement than another using P scores (scores of 0–1).[61] The highest P score was indicative of superiority on the other techniques compared. As recommended, we realized a pairwise forest plot in which the "only usual care modality" was used as reference group.[62] We performed a post hoc sensitivity analysis to assess the robustness of our findings (results from patients with breast cancer and results from patients without breast cancer) based on the large amount of breast cancer studies.

Risk of publication bias was assessed with a comparison-adjusted funnel plot and Egger test for funnel plot asymmetry.[42] An asymmetrical distribution in the funnel plot might be indicative of the presence of publication bias.

Results

The study screening strategy is shown in Supplementary Material A.3. Twenty-seven studies were included in the present systematic review and network meta-analysis.[63–89] Supplementary Material B describes the characteristics of the included RCTs (demographic characteristics, interventions, outcomes, and study design).

Characteristics of Included Studies

A total of 2742 participants were included in 27 studies. Some studies referred to the same sample assessed at different time points (ie, after intervention or follow-up).[71,72] This was considered to draw the actual sample of all included studies. The mean age of the included population was 53.4 ± (SD = 11.5) years, and 77.4% were women.

Regarding the type of cancer, 17 studies included participants with breast cancer,[64,68,69,71–73,75,76,81,83,85–91] 1 included participants with colon cancer,[82] 2 included participants with acute leukemia,[65,74] 1 included participants with lung cancer,[80] 1 included participants with pancreas cancer,[84] and 5 included mixed tumor sites.[63,66,70,78,79] Cancer staging was predominantly I to III. The type of chemotherapy was adjuvant in 10 studies,[63,69,71,72,78,81,82,86,91,92] neoadjuvant in 3 studies,[66,73,88] neoadjuvant and adjuvant in 9 studies,[68,70,75,76,83,84,87,89,90] inductive in 1 study,[65] consolidation in 1 study,[74] and myeloablative in 1 study.[79] Two studies did not report the type of chemotherapy.[64,80] Fourteen studies reported a percentage of participants with previous surgery (9.3%–100%, most above 55%),[63,66,69,71,78,80–85,87,89,91] and 9 studies reported participants with radiotherapy (2%–100%, most above 65%).[66,68,70,80–83,87,91]

Regarding the type of intervention, the exercise interventions were aerobic and/or resistance training of low to high intensity. Exercise training was applied following a continuous or interval design. Some studies complemented it with other types of interventions (ie, nutritional, psychological, or physical activity recommendations). Supplementary Material B details the intervention performed in each study. The duration of exercise intervention ranged from 4 to 27 weeks.

Results of the Methodological Quality and Risk of Bias

Of the 27 studies, 17 (63.0%) had good methodological quality,[63,65,66,69–71,73,76,81_83,85–87,89–91], while the remaining 10 studies (37.0%) had fair methodological quality.[64,68,72,74,75,78–80,84,88] Supplementary Material A.4 presents the assessment of methodological quality. Five studies (18.5%) had low risk of bias,[63,66,87,89,90] 12 studies (44.5%) had some concerns of risk of bias,[64,68,69,73,74,76,78,81–83,85,91] and 10 studies (37.0%) had high risk of bias.[65,70–72,75,79,80,84,86,88] Figure 1 summarizes the risk-of-bias assessment. The level of agreement between researchers was strong for the methodological quality assessment ($\kappa = 0.81$) and moderate for the risk-of-bias assessment ($\kappa = 0.79$).

Vo_2peak

Twenty-seven studies were included in the network meta-analysis, for a total of 15 exercise interventions and 42 comparisons (Fig. 2).[63–66,68–76,78–91]

Supplementary Material A.5 shows the distribution of direct comparisons in the included studies. When compared with only usual care, adding aerobic training (moderate to high intensity) to usual care was statistically significant, with a small beneficial effect (SMD = 0.46; 95% CI = 0.17 to 0.75; $P = .002$) on Vo_2peak and a P score of 0.708. Compared to only usual care, adding aerobic and resistance training (moderate to high intensity) to usual care was also statistically significant, with a small-sized beneficial effect (SMD = 0.26; 95% CI = 0.00 to 0.52; $P = .049$) on Vo_2peak and a P score

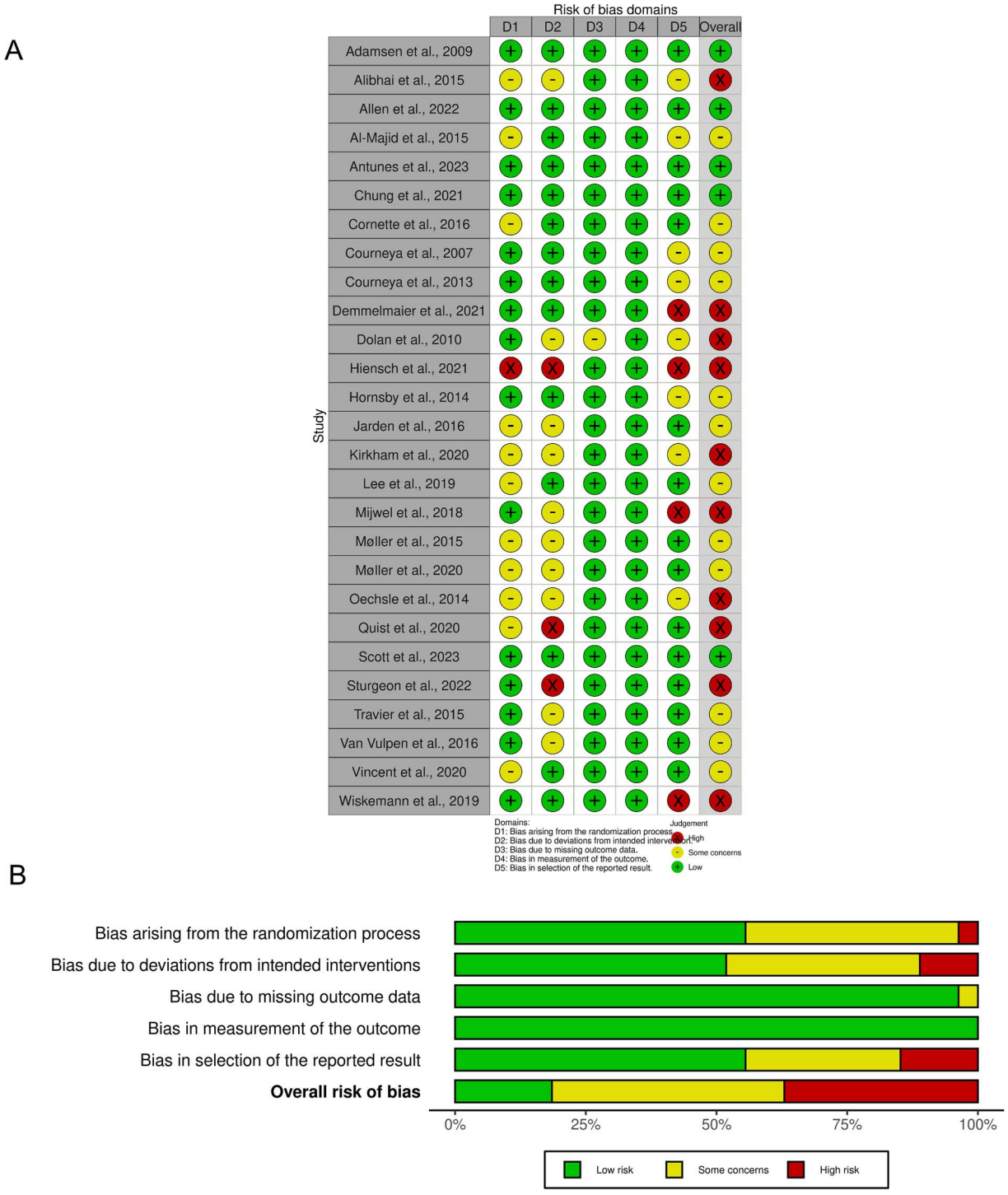

Figure 1. Risk-of-bias assessment for summary of individual studies (A) and aggregate appraisal results (B).

of 0.489 (Figs. 3 and 4; Suppl. Materials A.6 and A.7). The strength of the confidence was low (Suppl. Material A.2). There was a tendency that adding a combination of HIIT and MICT (SMD = 0.43; 95% CI = −0.07 to 0.94; $P = .092$) or aerobic, resistance, and flexibility training at moderate to high intensity (SMD = 0.42; 95% CI = −0.03 to 0.87; $P = .069$) to usual care had a small effect on Vo_2peak when compared to only usual care. When adding aerobic training to usual care, moderate intensity appeared to be less effective than high intensity (SMD = −0.58; 95% CI = −1.16 to 0.00; $P = .051$) (Fig. 3). The Table shows clinical recommendations for exercise application parameters based on the results of this review. The shape of the funnel plot seemed to be symmetrical, and the Egger test for publication bias was not statistically significant ($P = .625$) (Suppl. Material A.8).

The direct and indirect evidence contribution matrix, the direct and indirect comparison information, the net heat plot, and splitting analysis are shown in Supplementary Materials A.9, C, A.10, and A.11, respectively.

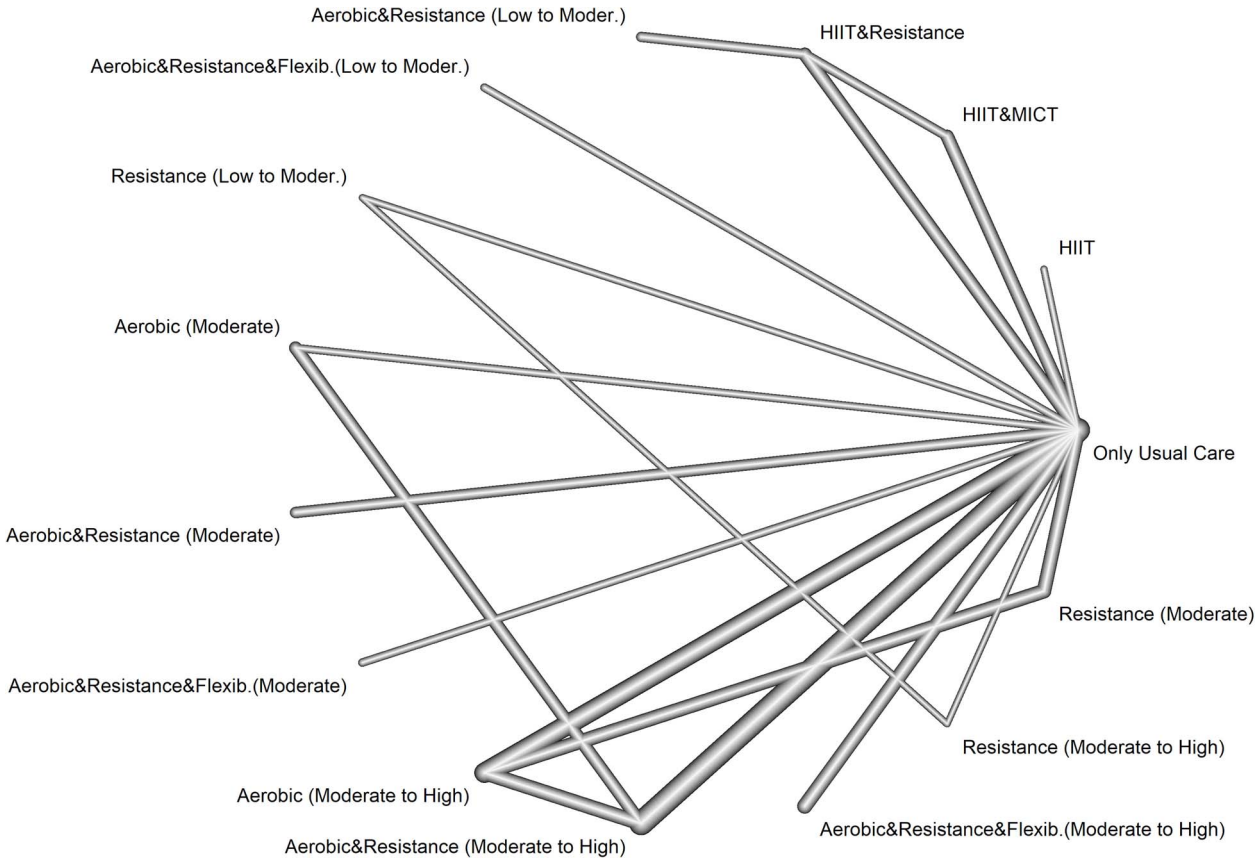

Figure 2. Network graph. The thickness of the connection between the different interventions represents the number of studies in a specific comparison. Flexib = flexibility exercise; HIIT = high-intensity interval training; MICT = moderate-intensity continuous training.

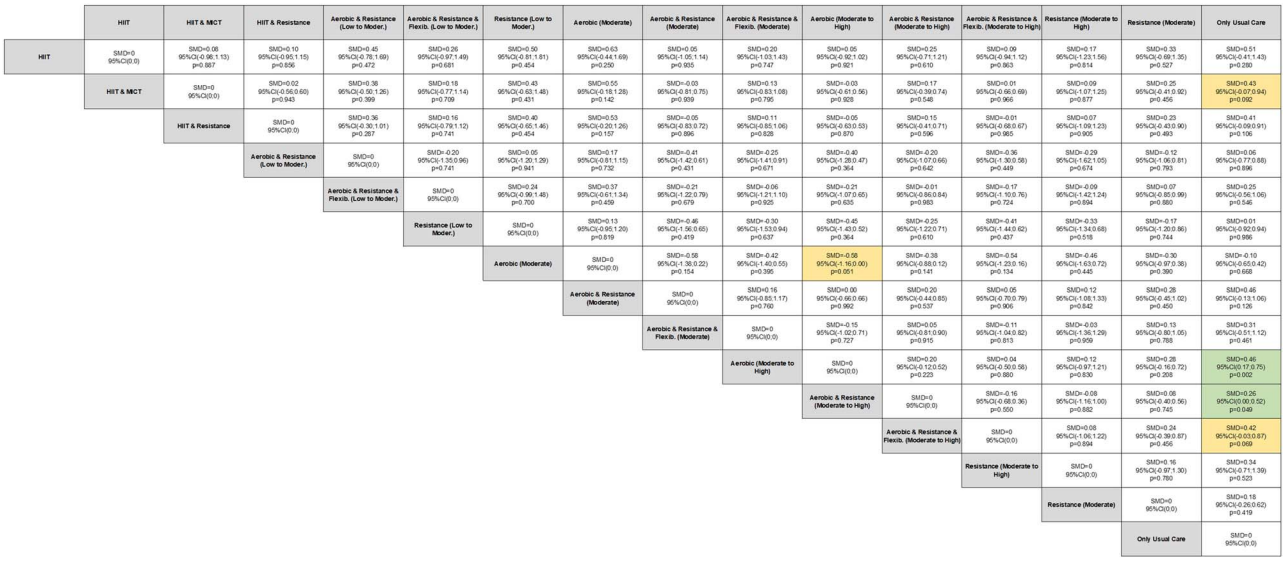

Figure 3. Estimation of the effects from the network meta-analysis. Data are shown as row treatments versus column treatments. Green boxes are statistically significant ($P < .05$). Yellow boxes have a tendency toward being statistically significant ($P < .1$). Flexib = flexibility exercise; HIIT = high-intensity interval training; MICT = moderate-intensity continuous training; SMD = standardized mean difference.

Sensitivity Analysis by Type of Cancer

Eighteen studies were included in the network meta-analysis conducted to assess patients with breast cancer[64,68,69,71–73,75,76,81,83,85–91] and 4 studies were included in the analysis conducted to assess patients without breast cancer[63,66,70,79] (Suppl. Material A.12).

When limited to breast cancer, the results were also statistically significant and showed that the addition of moderate to high intensity exercise appears to be more effective than usual care. When breast cancer studies were removed, adding exercise training to usual care tend to provide benefic effects; however, there was no statistical significance. This

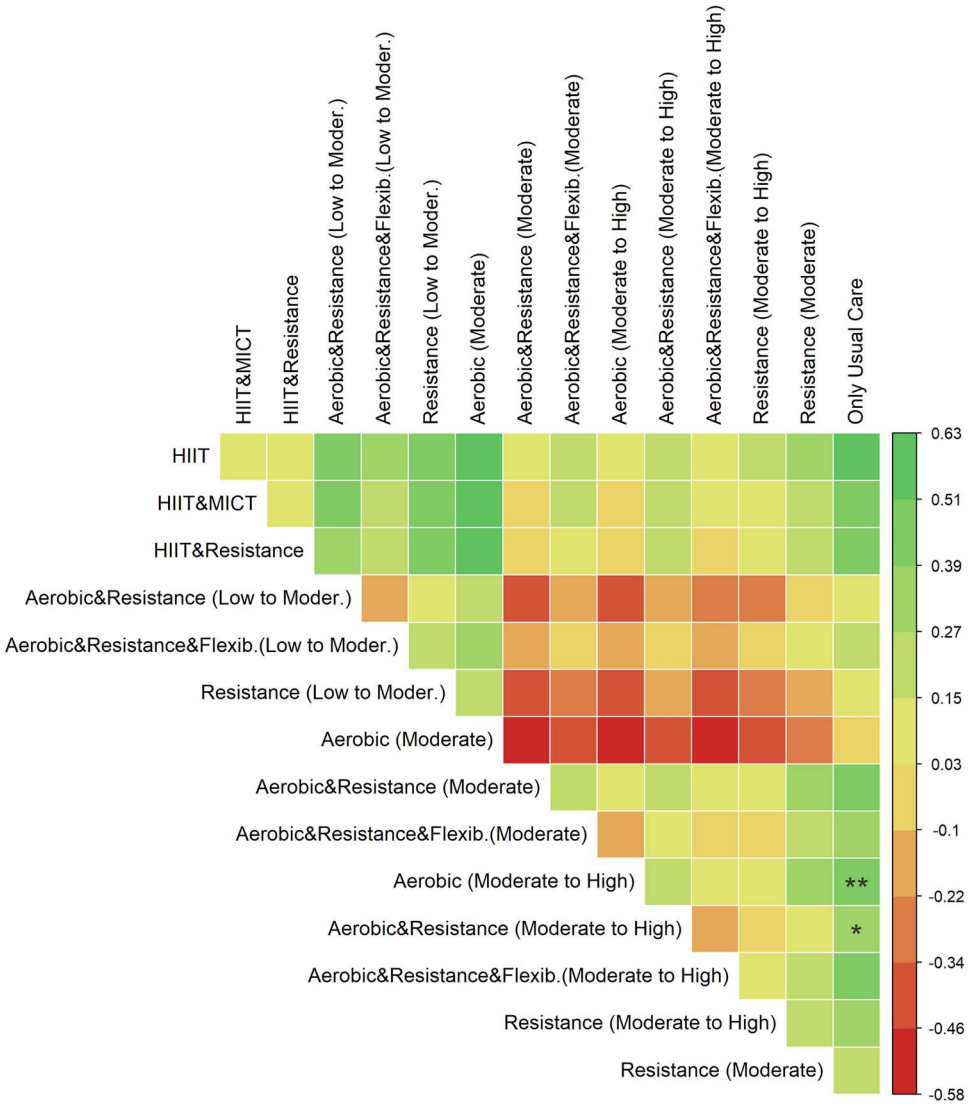

Figure 4. Effect table with all network meta-analysis estimates. The effect size of the comparisons has been represented in a color matrix. The number indicates the pooled effect size based on direct and indirect evidence, and the color ranges from green (Vo_2peak improves) to yellow (no effect) and red (Vo_2peak worsens). *$P < .05$; **$P < .01$. Flexib = flexibility training; HIIT = high-intensity interval training; MICT = moderate-intensity continuous training.

Table. Clinical Recommendations for Exercise Prescription[a]

Type of Exercise	Moderate- to High-Intensity AER Exercise[b]	AER Exercise[c]	RES Exercise[c]
Intervention duration (wk)	9–17		
Frequency (d/wk)	2 or 3	3–5	2 or 3
Session duration (min)	15–45	Vigorous intensity for 75 min/wk or moderate intensity for 150 min/wk or an equivalent combination of the 2	At least 1 set of 8–12 repetitions
Intensity	60%–80% Vo_2max/50%–80% HRmax	Moderate to high intensity (40%–89% Vo_2max/64%–95% HRmax/12–17 RPE)	Start with <30% 1RM and progress

[a]1RM = 1-repetition maximum; AER = aerobic exercise; HRmax = maximum heart rate; RES = resistance training; RPE = rating of perceived exertion; Vo_2max = maximum oxygen consumption. [b]Recommendations based on studies involved in comparisons that showed statistically significant differences. [c]Recommendations adapted to patients with cancer on the basis of the *ACSM's Guidelines for Exercise Testing and Prescription* (10th edition).[34]

analysis highlights that our results may lack of robustness. More studies are needed to confirm the tendencies we found. We want to highlight that exercise modalities are different between breast cancer studies and other type of cancer studies (Suppl. Material A.13).

Analysis of Possible Confounders

The possible influence of exercise parameters on the effectiveness of exercise training added to usual care compared to only usual care was assessed visually (Suppl. Material A.14). In relation to the duration of the intervention, there were

not too many differences in effect sizes between categories. Most studies implemented trainings lasting between 12 and 18 weeks. In relation to the frequency of weekly sessions, most studies performed between 2 and 3 sessions per week, with similar effectiveness. In relation to session duration, the sessions were mostly between 20 and 60 minutes, and these seemed to be the most effective time intervals.

Discussion

The aim of this systematic review and network meta-analysis was to analyze which type of exercise was most effective in increasing CFR in patients with cancer receiving chemotherapy. The results showed that the optimal way to improve CRF in this population in the short term was the use of interventions involving moderate- to high-intensity aerobic exercise. However, the quality of evidence was low and the results are clearly influenced by the large amount of breast cancer studies. We need to be careful in generalizing these results, given that the majority of the study population were women with breast cancer.

We found statistically significant differences when the aerobic exercise, with or without resistance exercise, implemented was of moderate to high intensity. Our results encourage clinicians to implement high-intensity physical training individualizing to what is high intensity for each patient with cancer. Likewise, Ismail et al found that, the higher the exercise intensity, the higher the Vo_2peak improvements in patients with heart failure.[93]

In relation to the modality of exercise in patients with heart failure, it was found that including aerobic exercise, continuous or intermittent, resulted in a 16.5% increase in Vo_2peak, compared to a 9.3% increase with strength training or a 15% increase with combined aerobic exercise and strength training.[94] In patients with type 2 diabetes, aerobic exercise was also found to have greater results than resistance exercise on Vo_2peak.[95] We found statistically significant results in favor of adding aerobic training to usual care. We also found a positive trend when combining aerobic training with resistance training of moderate to high intensity and/or flexibility exercise. Visual pattern of the effect estimates suggests that to improve Vo_2peak in patients with cancer receiving chemotherapy, therapeutic exercise training should involve an aerobic modality and moderate to high intensity. We found that high-intensity aerobic exercise was significantly superior to moderate-intensity aerobic exercise. High-intensity aerobic exercise, compared to low-intensity aerobic exercise, produced a significantly greater increase in Vo_2peak and short-term mitochondrial protein synthesis.[96] Aerobic exercise stimulates the increase of the mitochondrial function through mitochondrial biogenesis and other cellular processes related to mitochondrial functional capacity, among others. However, these complex processes have not yet been studied in depth.[97] We can conclude that there is important benefits to add moderate- to high-intensity training to the chemotherapy treatment of oncological patients. We need further studies that evaluate those interventions that tend to be significant to assess their true effectiveness.

We require more data from the follow-up period to assess whether statistically significant differences would be maintained or dissipate after a period of time following the intervention. Future research should address why the benefits were not sustained in the long term (eg, exercise does not help CRF in the long term, patients stop doing exercise) and what can be done to promote maintenance of the benefits over time. For example, research could evaluate the effectiveness of implementing ongoing exercise programs in patients with cancer after the end of their chemotherapy treatment and cancer survivors.

Patient preference for the type of exercise is a key aspect as it influences expectations of benefit and motivation to perform and maintain exercise.[98] Patients with breast cancer and lower baseline aerobic fitness were found to be more likely to prefer aerobic training.[99] Since patients with cancer typically have low levels of physical activity, it is conceivable that they may tend to choose aerobic exercise, which has been found to be the optimal exercise modality for improving CRF. Enjoyment of exercise was found to be one of the main facilitator of exercise in prostate cancer survivors.[100] Regarding exercise enjoyment, although the optimal exercise to increase CRF seems to be moderate- to high-intensity aerobic exercise based on the findings of this study, it would be essential to tailor and continuously update the exercise parameters to the preferences of each patient, keeping the goal of reaching the optimal parameters (moderate-to-high intensity). Some behavioral interventions may help in achieving this goal (ie, education on the benefits of moderate-to-high intensity).

The methodological design of the network meta-analysis, on the one hand, allowed us to observe which type of interventions is the most effective on CRF. On the other hand, it also provided an overview of the current state of the literature on exercise design in patients with cancer receiving chemotherapy. It appears that moderate to vigorous physical activity before and during chemotherapy may mitigate some side effects, such as CRF or fatigue.[16] The timing of implementation of the exercise intervention in relation to the cancer staging, the chemotherapy treatment, and the physical activity state of the patient should be the future goals of study to optimize the effectiveness of exercise. Repka et al observed no differences in CRF improvement among the types of cancer they assessed (breast, colon, lung, prostate, hematological, gynecological or glandular, and epithelial neoplasm).[101] Although we showed the effect of different exercise modalities on the general patient with cancer receiving chemotherapy, we must take into account the high percentage of female patients with breast cancer in the sample. Although sensitivity analyses by cancer type showed similar tendencies, in the future, we could study those effects specifically according to the pathobiological differences of each type of cancer. Most of the studies compared chemotherapy in combination with an exercise modality versus chemotherapy alone. However, experimental studies comparing different exercise models are scarce. Future research should address these comparisons between different exercise applications with the aim of increasing the evidence for direct comparisons in network meta-analyses and decreasing the imprecision of the results due to the magnitude of indirect estimates. It would also be beneficial to conduct medium- and long-term follow-up evaluations, so that these data can also be statistically analyzed.

Limitations

This systematic review with network meta-analysis had some limitations. First, there was heterogeneity in terms of type and stage of cancer, type of chemotherapy, and/or additional treatments used (ie, surgery and/or radiotherapy). There is an important heterogeneity in exercise training parameters

(training duration, frequency, session duration). All these aspects are confounding factors that must be considered when interpreting the results. Heterogeneity and transitivity affects were considered when assessing the overall strength of the evidence. In addition, 63.0% of the studies were in patients with breast cancer and 77.4% of the sample was women. We have limited ability to generalize these results to each cancer type specifically. Second, most of the evidence is indirect, which could lead to some imprecision in the results and needs to be interpreted with caution. Future studies should use our systemic review to identify which modalities have already been compared and which have not. We need more direct evidence to provide robust results. Third, a practical approach was used to carry out the statistical synthesis categorizing the intervention into general exercise modalities. It is possible that, in multimodal interventions, certain small differences between treatments have not been considered. SMD was used to compare data because the unit of measurement of Vo_2peak was not consistent across articles. Fourth, included studies with a small sample size may lead to small sample bias. Fifth, various direct comparisons were realized by very few studies, there is a need to not overstudy the same exercise modality. Finally, when interpreting our results, it is necessary to consider the level of methodological quality and the presence of concerns related with risk of bias in most of the studies.

Conclusions

The findings of this study showed that adding exercise trainings, aerobic training, interval or continuous, with or without resistance training of moderate to high intensity to chemotherapy is effective to improve CRF in patients with cancer at short term. Clinicians should consider using this type of nonpharmacological intervention in the oncological management.

Author Contributions

Aida Herranz-Gómez (Conceptualization, Methodology, Writing—original draft, Writing—review & editing), Luís Suso Martí (Conceptualization, Writing—review & editing), Clovis Varangot-Reille (Formal analysis, Methodology, Software, Writing—review & editing), Laia Barrachina-Gauchia (Methodology), Jose Casaña (Writing—review & editing), Laura López-Bueno (Writing—review & editing), Joaquín Calatayud (Writing—review & editing), and Ferran Cuenca-Martínez (Conceptualization, Writing—review & editing)

Ethics Approval

This systematic review and network meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews incorporating Network Meta-Analysis (PRISMA-NMA) extension statement.

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Clinical Trial Registration

The protocol of this study was registered in the PROSPERO database (CRD42022299513).

Data Availability

The data (R scripts and raw data) used for the analysis of this study are openly available in Open Science Framework repository at https://osf.io/gzt7y/?view_only=ef1a5517026b4d64b6a2209be9bb2097 and/or by contacting C.V-R.

Disclosures

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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