Effects of High-Intensity Interval Training and Combined High-Intensity Interval Training Programs on Cancer-Related Fatigue and Cancer Pain: A Systematic Review and Meta-analysis

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APPLIED SCIENCES

ABSTRACT

WANG, L., M. QUAN, D. C. NIEMAN, F. LI, H. SHI, X. BAI, T. XIONG, X. WEI, P. CHEN, and Y. SHI. Effects of High-Intensity Interval Training and Combined High-Intensity Interval Training Programs on Cancer-Related Fatigue and Cancer Pain: A Systematic Review and Meta-analysis. *Med. Sci. Sports Exerc.*, Vol. 55, No. 9, pp. 1620–1631, 2023. **Purpose:** This systematic review and meta-analysis assessed the effectiveness of high-intensity interval training (HIIT) alone and combined HIIT programs compared with usual care on cancer-related fatigue (CRF) and pain related to cancer or cancer-related treatments. **Methods:** Articles published prior to January 2023 were searched in the following digital databases: PubMed, Cochrane Database of Systematic Reviews and Cochrane Controlled Clinical Trials (CENTRAL), Web of Science, Scopus and ScienceDirect. Randomized controlled trials were included that met the following criteria: (i) adult cancer patients and survivors (>18 yr old); (ii) HIIT or combined HIIT programs versus usual care; (iii) assessment of fatigue and pain. Cochrane tool was used for assessing Risk of Bias (RoB) and Review Manager (RevMan 5.2) was used for data analysis. **Results:** Based on limited number (12) of studies included, we found HIIT and combined HIIT interventions have significant effect sizes on reducing both CRF (standardized mean difference, 0.63; 95% confidence interval, 0.42–0.84; $P < 0.001$) and cancer-associated pain (standardized mean difference, 0.44; 95% confidence interval, 0.25–0.63; $P < 0.001$). **Conclusions:** This systematic review and meta-analysis indicate that HIIT and combined HIIT programs can reduce CRF and pain. **Key Words:** EXERCISE, CANCER, HIGH-INTENSITY INTERVAL TRAINING, COMBINED TRAINING PROGRAMS, FATIGUE, PAIN

Cancer-related fatigue (CRF) is caused by cancer or cancer related treatment and is one of the most common side effects of cancer (1–4). Cancer-related fatigue can affect 33% to 37% of cancer patients and survivors and may last a few weeks or months or even years (5). Compared with ordinary fatigue, CRF is more severe, less likely to be neutralized by regular rest, and can affect patients' abilities to finish medical treatment and other pharmaceutical interventions (6,7). Cancer-related fatigue causes disruption in all aspects of quality of life (QoL) and may be a risk factor for reduced survival (8) and high CRF predicted decreased recurrence-free survival and overall survival in breast cancer patients (2).

Cancer-associated pain is a common side-effect related to cancer or cancer treatment in cancer populations. Most individuals will experience moderate to severe pain during the course of their disease and into survivorship (9). In some cases, such as oral cancer, pain is the first sign of cancer, while breast cancer patient will almost certainly not present with breast pain (10). Between 75% and 90% of patients with metastatic or advanced stage cancer will experience significant cancer-induced pain (11). Cancer pain is caused by different processes, such as tumor invasion, compression of nerve plexus, diagnostic or therapeutic surgical procedures (such as biopsies and resection), and tumor treatment (such as chemotherapy and radiation therapy) (9). Cancer pain significantly affects QoL and may be associated with shorter survival in patients with cancer (12,13).

Exercise has been widely used in the rehabilitation of cancer and studies indicate numerous benefits including reductions in CRF and pain for most cancer types during and after cancer

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treatment, and improvements in the therapeutic effect of radiotherapy and chemotherapy (14–23). A meta-analysis concluded that exercise and psychological interventions were even more effective for reducing CRF during and after cancer treatment than available pharmaceutical options (17).

However, according to the exercise prescription recommendations for cancer patients in the second edition (2018) of the American Physical Activity Guidelines (24), the form of exercise generally focuses on aerobic, resistance, and flexibility exercises and their combinations, and the recommended exercise intensity is moderate intensity and greater exercise intensity when the patient's physical condition allows. Accordingly, whether high-intensity interval training, a novel exercise intervention, is suitable for cancer patients, has not yet reached a consensus.

High-intensity interval training (HIIT) is a structured and enhanced interval training involving brief, high-intensity exercise (ranging from 85% to 250% $\dot{V}O_{2max}$ for 6 s to 4 min) separated by brief bouts of low-intensity aerobic rest (ranging from 20% to 40% $\dot{V}O_2$ max for 10 s to 5 min) (25,26). Despite early concerns, HIIT is an effective intervention in improving physical fitness and patient-reported health-related outcomes, and it has been proven to be a safe and feasible treatment for cancer patients (27–29). Including HIIT in a training program implies that greater health-enhancing benefits could be gained in less time, making HIIT a more time-efficient and attractive option.

Although regarded as beneficial, no meta-analysis or systematic review has been conducted on the effectiveness of HIIT and combined HIIT programs in reducing CRF and pain. Recent randomized-controlled trials (RCT) evaluating the effectiveness of HIIT alone or combined HIIT interventions on CRF and cancer pain have reported mixed results. For example, HIIT was linked to reduced CRF in patients with prostate, lung and testicular cancer (30–33) but not breast cancer (34,35), combined HIIT interventions did reduce CRF and pain in breast cancer patients (36–38), but not those with hematologic malignancy (39). Thus, the literature is not clear regarding the effect of HIIT and combined HIIT interventions on CRF and cancer pain.

The main purpose of this meta-analysis was to determine the effect of HIIT and combined HIIT programs on CRF and cancer pain in cancer patients or survivors to improve exercise training guidelines for clinicians. A growing number of RCT have assessed the effects of HIIT or combined HIIT programs on CRF and cancer pain (30–41). A systematic review with meta-analysis would improve scientific understanding in this area and provide a framework for the design of future studies evaluating the effectiveness of physical training interventions in cancer patients and survivors.

METHODS

Protocol. This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (see Supplemental Digital Content 1, PRISMA checklist, http://links.lww.com/MSS/C851) (42). The review protocol is previously registered with the PROSPERO database (CRD42022344923). Ethics committee approval was not sought for the present study because this meta-analysis study was based on data collected from previous clinical trials.

Design. This was designed to be a systematic review and meta-analysis.

Search strategy. We searched the following digital databases: PubMed, Cochrane Database of Systematic Reviews and Cochrane Controlled Clinical Trials (CENTRAL), Web of Science, Scopus and ScienceDirect from inception to January 2023. A search strategy was developed for each of those databases with language restricted to English (see Supplemental Table 1, Supplemental Digital Content 2, Search strategy, http://links.lww.com/MSS/C852). Briefly, articles were searched based on the following MESH terms: "neoplasms," "high-intensity interval training," "aerobic training," "resistance training," "jogging," "walking," "yoga," and "randomized controlled trial."

Inclusion criteria. Articles were included if they: (i) were randomized controlled trials; (ii) included cancer patients and cancer survivors over 18 yr; (iii) used a HIIT or combined HIIT program; (iv) the training program should last for at least 6 wk when resistance training (RT) was conducted; (v) utilized a usual care control group; (vi) evaluated CRF or pain as an outcome.

Exclusion criteria. Articles were excluded if they: (i) were systematic reviews; (ii) included other non-exercise interventions such as relaxation, massage, pharmaceutical treatment or psychological counseling in the experimental group but not in the control group; (iii) were substudies of larger trials; (iv) were not written in English.

Study selection. The titles and abstracts of all originally searched studies were screened by two reviewers (L.W., T.X.) independently. Discrepancies were resolved through discussion. Studies were excluded only if the information in the title and the abstract made it clear that the study was nonrelated to the inclusion criteria. Full texts of articles included in the first step were read independently by two reviewers to assess whether they could be accepted based on the inclusion/exclusion criteria and completeness of the necessary data. Accepted articles were then examined by the third reviewer (Y.S.) to finalize the selection process.

Data extraction. Three reviewers were responsible for data extraction. The following data were assessed and extracted into excel by two reviewers (L.W., X.B.) independently: First author's last name, publication year, the sample size for CRF and pain from each group, mean and SD of each outcome from each group, treatment stage, HIIT or combined HIIT programs, ages of intervention groups, cancer type, during/after treatment, and treatment type. The formulas for the mean and SD prechange to postchange values were as follows: mean change = mean post − mean pre and SD change = SQRT [$(SD^2_{pre} + SD^2_{post}) - (2 \times Corr \times SD_{pre} \times SD_{post})$], where the correlation coefficient (Corr) was set to 0.8 after averaging it for those studies that reported full data based on the Cochrane Collaboration Handbook guidelines (43). We selected total CRF as the outcome of CRF. For pain, we selected "pain" or "bodily pain." When SD was missing in original studies, *P* values, T values, CI, and SE (n%) were used to calculate SD according to the Cochrane handbook (43): SD = SE/SQRT(1/NE + 1/NC); SE = MD/T, whereas T

was obtained from the table of the T distribution corresponded to the *P* value. If T values, CIs and SE were missing, baseline or follow-up SD were used if those SD were presented. Authors of articles were contacted at least three times to obtain missing data. The final data were assessed by the cancer expert Y.S.

Quality assessment. Quality assessment was conducted using the PRISMA recommendations (44). The following items: (i) appropriate generation of random allocation sequence; (ii) concealment of the allocation sequence; (iii) blinding of the assessment and collection outcomes; (iv) proportion of participants lost to follow-up; (v) complete outcome data and (vi) the intention-to-treat principle were assessed by 2 reviewers independently.

Statistical analysis. REVMAN was used for data analysis in this meta-analysis of RCT. Outcome data were classified as continuous variables with effect sizes computed using a 95% confidence interval (95% CI) standardized mean difference (SMD). A positive SMD was defined as a beneficial effect when comparing experimental and usual care groups for outcomes. Standardized mean difference was interpreted as follows: 0.2 represented a small effect size, 0.5 a moderate effect size and 0.8 a large effect size (45). The statistical heterogeneity between studies was assessed using the I^2 statistic: I^2 = 0% to 24% indicated low heterogeneity; I^2 = 25% to 74% indicated moderate heterogeneity; and I^2 = 75% to 100% indicated high heterogeneity (46). The fixed-effects model was used for the forest plot when heterogeneity was low, and the random-effects model was used when heterogeneity was high (46). Subgroup analyses were conducted for the following subgroups: (i) intervention focus (HIIT only or combined HIIT programs); (ii) during/after cancer treatment (according to the method section in a 2018 meta-analysis written by Hilfiker et al. (16). Briefly, studies including patients that were currently on chemotherapy or radiotherapy were defined as "during," whereas those studies including patients currently not on chemotherapy or radiotherapy were defined as "after." For studies including both types of patients were classified according to the majority of patients.); (iii) intervention duration (>12 wk or not, based on a previous meta-analysis) (22); and (iv) intervention frequency (≥3 sessions per week or not). These subgroup analyses depended on whether the number of studies in the target subgroup was sufficient (≥10 studies) to identify factors that could potentially influence the effect of the intervention on listed outcomes with an examination of the heterogeneity between studies (43). A *P* value <0.05 between study variations was defined as a significant statistical difference between subgroups.

Publication bias assessment. The risk of publication bias was assessed through the Egger's regression test (47).

Sensitivity analysis. A sensitivity analysis was performed on CRF and pain to evaluate whether an individual study had an undue influence on the overall result of the meta-analysis. This process involved removing one trial at a time and determining whether statistical conclusions remained the same.

RESULTS

Study selection and characteristics. A total of 13,419 studies were included during the initial selection process with this number reduced to 7262 after removing duplicates and to 59 when article titles and abstracts showed no evidence that they met the inclusion criteria. Full-text assessment resulted in the removal of 47 additional articles. For instance, Demmelmaier et al. (48) conducted an HIIT program, but compared to low-intensity exercise rather than usual care; Edvardsen et al. (49) assessed CRF but could not be calculated because data were not presented as "mean (SD)." Thus, 12 studies met the inclusion criteria and were included for quantitative assessment. In these studies, 5 assessed both CRF and pain (31,32,37,38,41), and 7 assessed CRF only (30,33–36,39,40). Figure 1 shows the selection flowchart that adhered to PRISMA guidelines.

Participants. Table 1 summarizes the characteristics of the studies included in this meta-analysis. The 12 included studies published from December 2012 (33) to November 2022 (41) yielded a sample of 938 participants (EXP = 482, CON = 458; 69.8% female and 30.2% male). The number of participants in each of the 12 studies ranged from 24 to 182. The average age of study participants was 53.9 yr (EXP: 53.4 yr; CON: 54.3 yr). Five studies focused on breast cancer (34–38), two studies reported prostate cancer (30,31), two studies reported mixed cancer (40,41), and 3 studies analyzed lung cancer (33), testicular cancer (32), and hematologic malignancy respectively (39). Nine of the studies assessed cancer patients (30,31,33,34,36–39,41) and 3 studies assessed cancer survivors (32,35,40). As for treatment stage, three studies did not report treatment stage (30,31,39), four studies included patients in stage 4 (32,33,40,41), and the remaining studies reported patients ranged from stage 1 to 3.

Adverse events. Ten of 12 studies (83.3%) reported adverse events. Seven of the 10 studies (70%) reported no adverse events (30,32–35,37,38). Persoon et al. (39) reported eight serious adverse events (SAE), four in each group. One patient in the intervention group strained his calf muscles during a training session, but recovered from this injury within the intervention period. None of these events were considered to be related to study participation. Nine participants withdrew from the 2015 trial by Kampshoff et al. (40), five due to disease recurrence and four because of comorbidities. Reljic et al. (41) reported one knee pain in the intervention group. None of the SAE above were considered to be related to interventions. None of the SAE were thought to be related to the exercise intensity.

Interventions. The intervention groups in 11 of the 12 studies were supervised by trained nurse specialists and physiotherapists, one study performed a nonsupervised home-based intervention (35). Seven studies conducted only HIIT (30–35,41), four conducted combined HIIT and RT programs (36,37,39,40), and one performed combined HIIT plus RT, endurance training and Nordic walking training programs. HIIT comprises 7 to 16 min of training sessions, with RT training protocols including 2 to 3 sets of 6 to 8 exercises with 5 to 25 repetitions. Nordic walking was conducted 2 $h \cdot wk^{-1}$ and endurance training was performed 5 to 10 $min \cdot wk^{-1}$. Intervention durations ranged from 5 wk (30) to 24 wk (38). Training frequency ranged from one to three times per week in all studies.

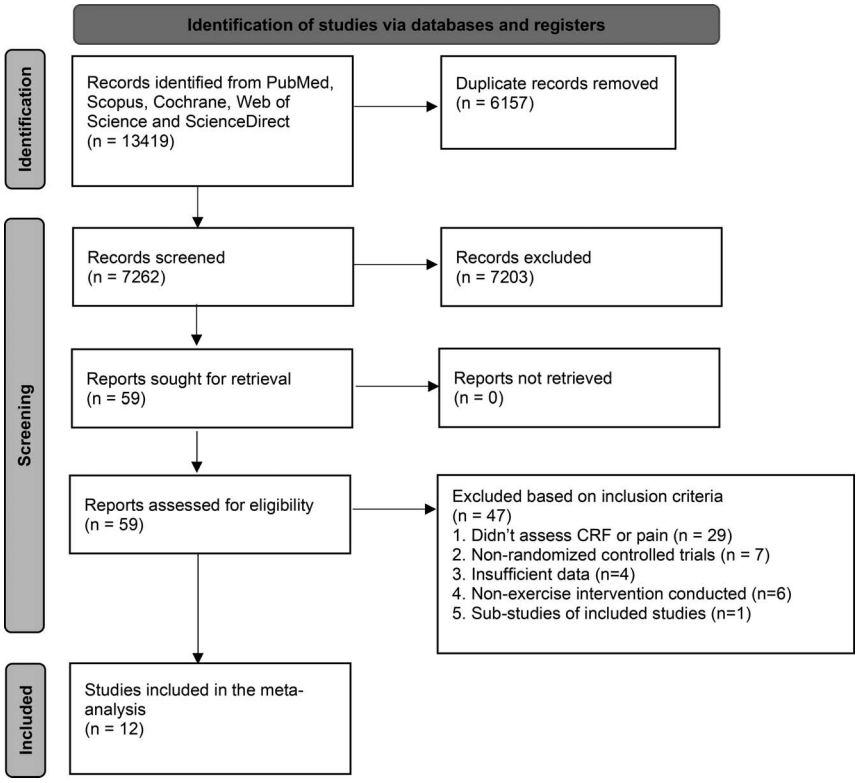

FIGURE 1—Flowchart of the study selection process.

Measurement. Cancer-related fatigue assessment tools varied across the 12 studies. The Piper Fatigue Scale (PFS) was used in two studies (36,37); the Functional Assessment of Chronic Illness Therapy–Fatigue scale was used in three studies (30,32,41); the Cancer Fatigue Scale was used in one study (35); the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was used in two studies (31,33); and the Multidimensional Fatigue Inventory (MFI) scale was used in four studies (34,38–40). Pain was assessed using the EORTC QLQ-C30 scale in four studies (31,37,38,41) and the Short Form 36 Health Survey Questionnaire scale was used in one study (32).

Quality assessment. Quality assessment was included in all of the studies using appropriate generation of random allocation sequence. Ten of the studies used concealment of the allocation sequence (83.3%) (31–33,35–41). Eight of the studies included blinding of the assessment and collection outcomes (66.7%) (33–38,40,41). All of the studies explained the proportion of participants lost to follow-up, all 12 studies reported complete outcome data, and 9 studies incorporated intention-to-treat procedures (75.0%) (30–32,35–40). No study was excluded from the analysis after assessment.

Changes in CRF by intervention. Figure 2 summarizes study data for changes in CRF. The data support significant improvements in CRF (SMD, 0.63; 95% CI, 0.42–0.84; $P < 0.001$) when comparing exercise intervention and control groups. Moderate heterogeneity between studies ($I^2 = 54\%$, $P = 0.01$) was observed

Changes in pain by intervention. Figure 3 summarizes study data for changes in pain. Significant improvements were found in pain when comparing exercise intervention and control groups (SMD, 0.44; 95% CI, 0.25–0.63; $P < 0.001$) (Fig. 3). Low heterogeneity was observed between studies ($I^2 = 12\%$, $P = 0.34$).

Subgroup analysis. Additional statistical analyses were conducted on research design characteristics that may have influenced changes in CRF (Fig. 4). No significant differences were observed between subgroups in these areas: (i) type of exercise intervention focus ($P = 0.96$); (ii) ratio of during-to-after cancer treatment in the study participant pool ($P = 0.62$); (iii) exercise intervention duration ($P = 0.85$); (iv) and exercise intervention frequency ($P = 0.74$). Each subgroup of all areas showed significant benefits of exercise interventions.

Publication bias. The Egger's test was performed on CRF ($P = 0.594$) and pain ($P = 0.802$), and this analysis indicated that no significant publication bias was observed (Fig. 5 and 6).

Sensitivity analysis. The sensitivity analysis showed that the calculated effects were still within the 95% CI of the SMD for change in CRF and pain after removing any one of the studies included. This analysis indicated that the overall result of the meta-analysis was not significantly altered with the removal of individual studies.

DISCUSSION

This meta-analysis of 12 RCT investigated the effects of HIIT and combined HIIT programs on CRF and cancer-associated pain. The results supported that both HIIT and the combination of HIIT and other exercises had a significant effect in alleviating

TABLE 1. Characteristics of included studies.

	Age (yr)		Number (%Female)							Intervention				
Study	EXP	CON	EXP	CON	Cancer Type	During/ After Treatment	Intervention Focus	Treatment Type	Treatment Stage	Duration (wk)	Frequency (/wk)	Volume	Session Length (min)	Intensity
Kang et al (31)	63.9 (7.5)	62.8 (6.9)	26 (0)	26 (0)	Prostate cancer	After	HIIT	Active surveillance	N/A	12	3	HIIT: supervised treadmill walking or jogging, 5–8 × 2 (2) (weeks 1–4); 8 × 2 (2) (week 5 onwards)	28 to 40	85% $\dot{V}O_2$ max (weeks 1–4); 90% $\dot{V}O_2$ max (weeks 5–8); 95% $\dot{V}O_2$ max (week 9 onwards); 40% $\dot{V}O_2$ max (rest)
Persoon (39)	53.5 (N/A)	56.0 (N/A)	50 (41)	47 (33)	Hematologic malignancy	After	HIIT plus RT	Stem cell transplantation	N/A	18	2 (the first 12 wk) to 1 (week 12 onwards)	RT: 6 × 2 × 10 (the first 12 wk)/6 × 2 × 20 (week 13 onwards) HIIT: supervised cycling, 2 × 8	60	For RT: 65%–80% of 1RM (the first 12 wk); 35%–40% of 1RM (the 13th week onwards) for HIIT: blocks of 30s at 65% MSEC were alternated with blocks of 60s at 30% MSEC (the first 8 wk); blocks of 30s at 65% MSEC were alternated with blocks of 30s at 30% MSEC (the 9th week onwards)
Lee et al. (34)	49.1 (7.9)	44.7 (11.2)	15 (100%)	15 (100%)	Breast cancer	During	HIIT	Chemotherapy	1 to 3	8	3	HIIT; supervised cycling, 7 × 1 (2)	30	90% PPO/10% PPO (rest)
Piraux et al. (30)	67.4 (8.9)	71.9 (8.1)	24 (0)	24 (0)	Prostate cancer	During	HIIT	Radiotherapy	N/A	5 to 8	3	HIIT: supervised cycling, 8 × 1 (1)-15 × 1 (1)	26–40	≥85% THR_{max}; ≥60% THR_{max} (rest)
Hwang et al. (33)	61.0 (6.3)	58.5 (8.2)	13 (71.5)	11 (36.4)	Lung cancer	After	HIIT	Targeted therapy	3 to 4	8	3	HIIT: supervised treadmill jogging or cycling, 25	30–40	RPE of 15–17
Kampshoff et al. (40)	54.0 (11.0)	55.0 (11.6)	91 (80)	91 (78)	Mix (6 or more)	After	HIIT plus RT	Chemotherapy	1 to 4	12	2	RT: 6 × 2 × 10 HIIT: supervised cycling, 2 × 8 (the first 4 wk); 8 + 3 × 5 (week 5 onward)	N/A	For RT: 70%–85% of 1RM for HIIT: blocks of 30s at 65% MSEC were alternated with blocks of 60s at 30% MSEC (the first 4 wk); blocks of 30s at 65% MSEC were alternated with blocks of 30s at 30% MSEC (the 5th week onwards, 8 min intervals)
Ochi et al. (35)	48.0 (6)	49.0 (5)	24 (100)	24 (100)	Breast cancer	After	HIIT	Therapies except for hormone therapy	1 to 2	12	3	HIIT: home-based exercise, 8 × 0.33	10	N/A
Mijwel et al. (37)	52.7 (10.3)	52.6 (10.2)	74 (100)	60 (100)	Breast cancer	During	HIIT plus RT	Chemotherapy	1 to 3	16	2	RT: 8 × 2 × 8–12 HIIT: supervised cycling, 3 × 3 (1)	60	For RT: 70%–80% of 1RM for HIIT: RPE 16–18(HIIT)

Koevoets et al. (38)	52.1 (8.6)	52.5 (8.7)	84 (100)	86 (100)	Breast cancer	After	HIIT plus RT, NW, and ET	Chemotherapy	1 to 3	24	N/A	N/A (supervised cycling for HIIT)	N/A	For NW: 40–60% HRR (week 1–4); 60–70% HRR 15–20 min, plus 70–89% HRR 5–10 min (week 5–9); for ET: 60%–75% HRR; for HIIT: N/A; for RT: N/A
Adams et al. (32)	44.0 (11.6)	43.3 (9.9)	35 (0)	28 (0)	Testicular cancer	After	HIIT	Orchidectomy, chemotherapy	1 to 4	12	3	HIIT: supervised uphill treadmill walking or running, 4 × 4 (3)	35	75%–95% $\dot{V}O_2$ max; 5% to 10% below ventilatory threshold (rest)
Hiensch et al. (36)	52.2 (10.1)	52.9 (10.1)	30 (100)	29 (100)	Breast cancer	During	HIIT plus RT	Chemotherapy	1 to 3	16	2	RT: 8 × 2 × 8–12 HIIT: supervised cycling, 3 × 3 (1)	60	For RT: 70%–80% of 1RM for HIIT: RPE 16–18 (HIIT)
Reljic et al. (41)	52.5 (7.5)	58.0 (7.9)	13 (46)	14 (57)	Mix (10 or more)	During	HIIT	N/A	3 to 4	12	2	HIIT: supervised cycling, 5 × 1 (1)	14	80% to 95% HR_{max}

Notes: Age is presented as mean (SD). For resistance training, volume is presented as number of exercise × sets × repetitions; for HIIT, volume is presented as the number of intervals × interval's length in minutes (rest length between intervals in minutes); or presented as total length in minutes if detailed information were missing. For study Koevoets et al., no specific information describing frequency, volume, and session length was found, but we were informed that the program consisted of aerobic and strength training (2 h·wk^{-1}) and Nordic/power walking (2 h·wk^{-1}), and HIIT began at week 10. For cancer stage, stage 1 indicates that cancer is small and has not spread anywhere else; stage 2 shows that the cancer has grown, but has not spread; stage 3 indicates that the cancer is larger and may have spread to the surrounding tissues and/or the lymph nodes (or "glands," part of the immune system); stage 4 indicates that the cancer has spread from where it started to at least one other body organ, also known as "secondary" or "metastatic" cancer.

EXP, experimental group; CON, control group; NW, nordic walking; ET, endurance training; N/A, not available; $\dot{V}O_2$max, maximal oxygen consumption; RM, repetition maximum; MSEC, maximum short exercise capacity; PPO, peak power output; THR, theoretical maximal heart rate; RPE, Borg Rating of Perceived Exertion; HRR, heart rate reserve; HR, heart rate.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Hwang	-5.1	8.38	13	-9.1	12.2	11	4.8%	0.38 [-0.44, 1.19]	2012
Kampshoff	2.8	2.29	91	1.4	2.63	91	12.6%	0.57 [0.27, 0.86]	2015
Persoon	2.7	2.71	50	1.7	2.92	47	10.5%	0.35 [-0.05, 0.75]	2017
Adams	4.2	5.22	35	-1.1	5.49	28	8.2%	0.98 [0.45, 1.51]	2018
Mijwel	-0.07	1.94	74	-1.64	1.83	60	11.4%	0.83 [0.47, 1.18]	2019
Piraux	-1	6.32	24	-5.8	7.29	24	7.4%	0.69 [0.11, 1.28]	2020
Hiensch	0.02	3.46	30	-1.57	2.82	29	8.4%	0.50 [-0.02, 1.01]	2020
Lee	-11.4	8.51	15	-5.3	7.57	15	5.5%	-0.74 [-1.48, 0.01]	2021
Ochi	2.67	6.14	24	-1.25	6.21	24	7.4%	0.62 [0.04, 1.21]	2022
Reljic	7	4.95	12	1	3.41	12	4.1%	1.36 [0.46, 2.27]	2022
Kang	6.2	9.36	26	-3.1	8.55	26	7.4%	1.02 [0.44, 1.60]	2022
Koevoets	3.5	2.82	84	1.1	3.01	86	12.3%	0.82 [0.51, 1.13]	2022
Total (95% CI)			**478**			**453**	**100.0%**	**0.63 [0.42, 0.84]**	

Heterogeneity: Tau² = 0.07; Chi² = 24.13, df = 11 (P = 0.01); I² = 54%
Test for overall effect: Z = 5.86 (P < 0.00001)

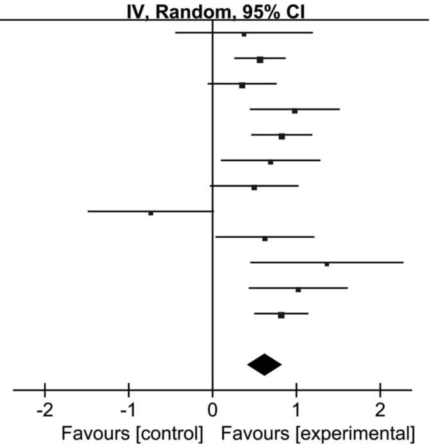

FIGURE 2—Forest plot of SMD and 95% CIs for 12 studies representing changes in CRF in exercise experimental and usual care control groups. A random-effects model was used based on a moderate observed heterogeneity.

CRF and pain in cancer patients and survivors. As described before, CRF causes disruption in QoL and may be a risk factor for reduced survival (8). Besides, in a large longitudinal study of breast cancer patients, CRF predicted decreased recurrence-free survival and overall survival (2). According to a systematic review written by Zylla et al. (12), cancer pain significantly affects QoL and may be associated with shorter survival in patients with cancer. Another systematic review published in the journal of *Medicine & Science in Sports & Exercise*, reported moderate or limited associations between greater amounts of physical activity and decreased all-cause and cancer-specific mortality in individuals with a diagnosis of breast, colorectal, or prostate cancer, with relative risk reductions ranging almost up to 40% to 50% (13). Both CRF and pain contribute to a decrease of QoL and survival rate in cancer populations. Thus, this is an important finding that both HIIT and combined HIIT programs could reduce CRF and pain.

This analysis probed the influence of research designs differences across the 12 studies on changes in CRF. High heterogeneity was found between studies on fatigue. However, no significant effects were found for HIIT alone or combined HIIT programs, the inclusion of cancer survivors during/after cancer treatment, and the duration of exercise training (less or more than 12 wk). Thus, training programs designed to help cancer patients and survivors alleviate CRF can be individualized in accordance with their preferences. A previous meta-analysis of 31 RCT concluded that supervised training programs incorporating aerobic and/or resistance exercise reduced CRF, especially if the program duration was 12 wk or less (22). These investigators reasoned that there may be a ceiling effect in that CRF is reduced within the first month or two of training, with little or no further change experienced after 12 wk. Problems with exercise adherence in the experimental group and the adoption of exercise by the usual care control group were listed as additional factors. High-intensity interval training compared with conventional aerobic exercise (17) is more effective in yielding physiologic changes such as increased mitochondrial oxidative capacity and biogenesis (50,51), and psychosocial improvements such as the improvement of self-efficacy (52). Thus, HIIT exercise sessions can be of shorter duration than conventional exercise training sessions, improving long-term adherence.

A recent review of systematic reviews and meta-analyses suggested that exercise training was effective in reducing CRF across all cancer populations (53). Our focused meta-analysis of HIIT and CRF was not sufficiently powered to determine if the positive results applied to different cancer patient subgroups (Table 1). Additional research is needed to determine whether HIIT programs is effective in all types of cancer.

High-intensity interval training is more than likely efficacious in reducing CRF for both male and female cancer patients

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Adams	3.4	6.71	35	-0.7	5.18	28	13.7%	0.67 [0.15, 1.18]	2018
Mijwel	0.61	15.47	74	-10.63	18.24	60	29.3%	0.67 [0.32, 1.02]	2019
Kang	4.7	10.8	26	2.6	9.58	26	12.1%	0.20 [-0.34, 0.75]	2022
Reljic	11	17.515	12	4	9.8	12	5.4%	0.48 [-0.34, 1.29]	2022
Koevoets	-1	17.16	84	-5.2	15.46	86	39.4%	0.26 [-0.05, 0.56]	2022
Total (95% CI)			**231**			**212**	**100.0%**	**0.44 [0.25, 0.63]**	

Heterogeneity: Chi² = 4.52, df = 4 (P = 0.34); I² = 12%
Test for overall effect: Z = 4.53 (P < 0.00001)

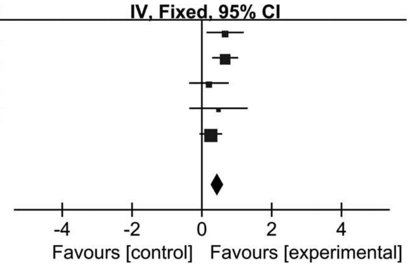

FIGURE 3—Forest plot of SMD and 95% CIs for 5 studies representing changes in pain in exercise experimental and usual care control groups. A fixed-effects model was used based on a low observed heterogeneity.

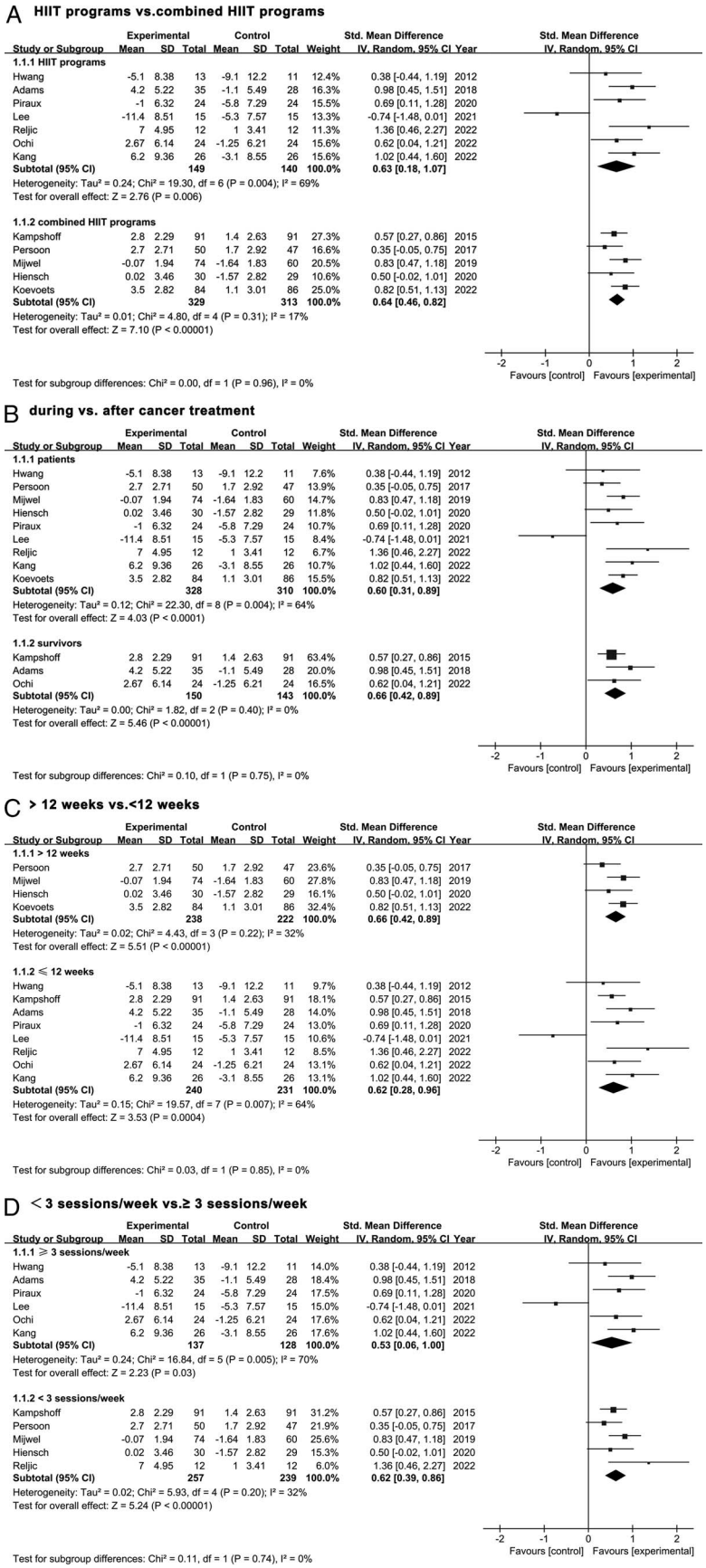

FIGURE 4—Forest plot of SMD and 95% CIs for subgroup analysis on CRF. No significant differences were observed between subgroups for all categories: (A) HIIT programs vs combined HIIT programs; (B) during vs after cancer treatment; (C) >12 wk vs ≤12 wk; (D) <3 times per week vs ≥3 times per week.

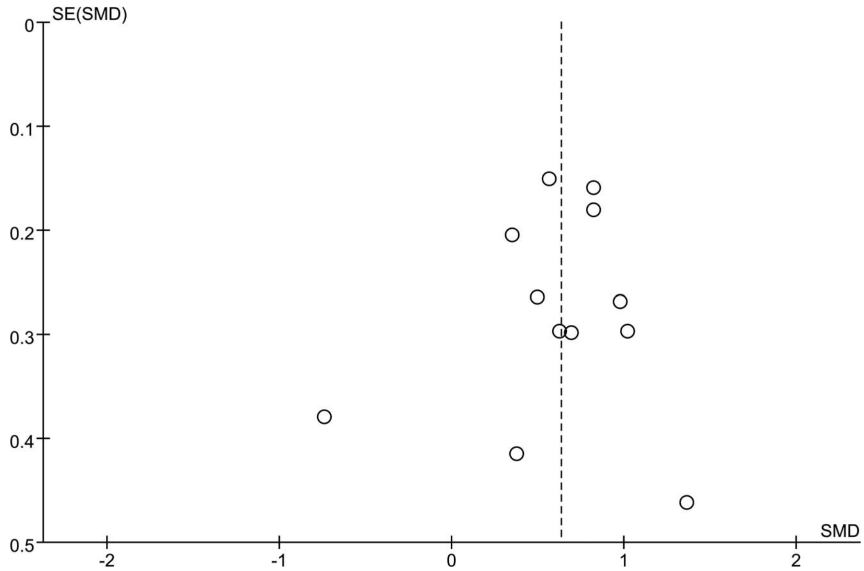

FIGURE 5—Funnel plot of publication bias in CRF. SE, standard error.

and survivors. Four studies in this meta-analysis included both males and females, but a statistical analysis probing the sexual effect of HIIT effects on CRF was not possible (33,39–41). Three of the studies did not provide information on the treatment stage (30,31,39), and the treatment types of the included studies were too many, leading to only one study in each of some subgroups. Thus, effects of those two factors on CRF could not be determined. The interactive effect of clinical treatments on the inverse relationship between HIIT and CRF could also not be probed in this meta-analysis. Future research is warranted to investigate these variables.

The underlying mechanism of the influence of HIIT and combined HIIT exercise on CRF and cancer pain is still unknown. Improvements in peak oxygen consumption and peak power output are significantly correlated with a reduction in CRF (54), HIIT and other exercises that are always combined with HIIT programs, such as resistance training, have significant effects on these functional outcomes (26,55,56). Besides, HIIT leads to the improvement of parasympathetic modulation at rest, and exercise-mediated increases in parasympathetic activity could be an additional mechanism by which exercise training addresses fatigue (54,57). Furthermore, increased IL-6 and IL-6/IL-1ra levels in cancer patients are significantly associated with increased physical fatigue and pain. Both HIIT and progressive RT have been shown to counteract this effect (58,59). There are many other potential exercise-related factors (e.g., psychological changes) that may contribute to the effectiveness of HIIT alone or combined HIIT programs in reducing CRF and cancer pain, and additional research is needed in this area.

The main limitation of this meta-analysis was that the number of studies evaluating the effect of HIIT on CRF in cancer patients was relatively low, and only five of them evaluated

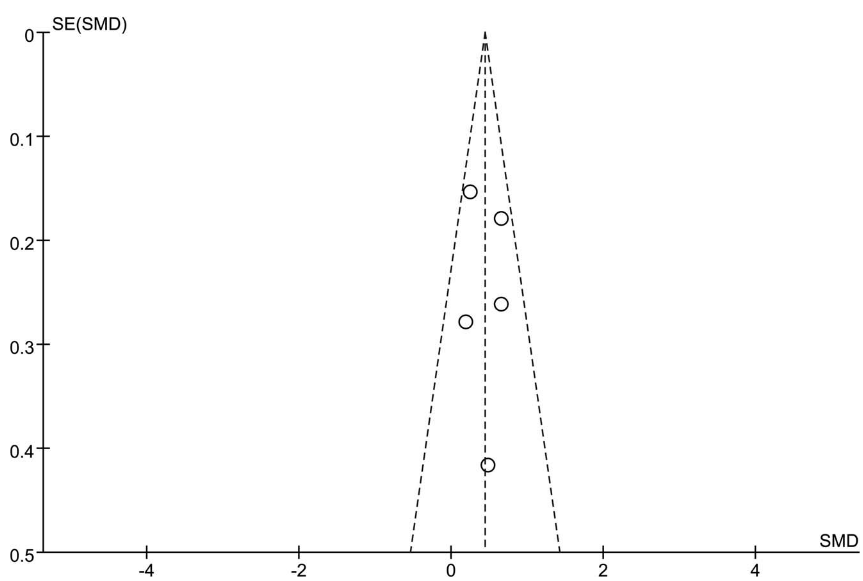

FIGURE 6—Funnel plot of publication bias in pain.

the influence of HIIT on cancer pain. Besides, as described earlier, this meta-analysis lacked sufficient power and data to evaluate sex and clinical treatment effects on HIIT-induced reductions in CRF.

This meta-analysis was novel and had several strengths. Stringent inclusion and exclusion criteria were used for article selection to improve the validity of the meta-analysis. Included studies were RCT that evaluated HIIT, CRF, and cancer pain. Study designs including nonexercise interventions were excluded to make sure the effects of training programs could be isolated. Studies that included pharmaceutical treatments as complementary interventions were excluded because some drugs (e.g., erythropoietin drugs) may have adverse effects on CRF and cancer pain. Furthermore, we excluded studies that conducted RT exercise for <6 wk. It has been suggested that the effect of RT usually occurs after 6 wk of training (60). The data from this meta-analysis support that HIIT and combined HIIT programs are effective in reducing CRF and pain in cancer patients and survivors. This conclusion is consistent with other published reviews and guidelines supporting the vital role of regular exercise for cancer patients and survivors (61–63).

Recent published meta-analysis has proven that HIIT is a safe and feasible intervention in cancer patients and cancer survivors (29,64). There are multiple HIIT and combined HIIT training protocols that can be used for cancer patients and survivors. This analysis and other published guidelines support an exercise training protocol that combines aerobic and resistance training (61–63). Based on included studies, we suggest HIIT sessions with cancer patients should be gradually progressed with an end goal of lasting 20 to 30 min with 1- to 2-min running or cycling intervals performed at an intensity of 85% $\dot{V}O_{2max}$ intermixed with 1- to 2-min active rest periods. RT sessions can consist of 2 sets and 8–12 repetitions of five to eight exercises targeting major muscle groups. We also suggest cooperating stability and flexibility exercises in training programs. Besides, patients and survivors under certain circumstances should following advices from the 2019 *Medicine & Science in Sports & Exercise's* Exercise Guidelines for Cancer Survivors (61). When patients are having issues such as peripheral neuropathy, arthritis/musculoskeletal issues, osteoporosis or lymphedema, they should be introduced with preexercise medical evaluation and modify the recommendations of exercise based on assessments; If patients had lung or abdominal surgery, ostomy, cardiopulmonary disease, ataxia, extreme fatigue, severe nutritional deficiencies, lymphedema exacerbation or bone metastases, the training program should be performed under supervision by trained personnel. and pre-exercise medical evaluation and clearance by physician prior to exercise should be conducted. 1-RM testing for leg strength (e.g., deadlift) should be avoided in patients who have bony metastases in the proximal femur or vertebrae (65). Furthermore, survivor's health history, comorbid chronic diseases and health conditions, and any general exercise contraindications should be investigated before commencing health-related fitness assessments or designing the exercise prescription (66). Care should be taken to individualize the training protocols for each cancer patient or survivor based on symptoms, co-morbidities, physical capabilities, and age (67,68).

CONCLUSIONS

The findings of this systematic review and meta-analysis revealed that cancer patients and survivors engaging in HIIT and combined HIIT training protocols experienced improvements in both CRF and cancer pain. Variance in study designs regarding the ratio of patients-to-survivors among study participants, and the exercise intervention duration and frequency did not confound this finding. The inverse relationship between HIIT and CRF was robust and not significantly altered with the removal of individual studies in this meta-analysis. Thus, despite earlier concerns, HIIT and combined HIIT programs for cancer patients and survivors can be considered an effective and time-efficient training option to reduce CRF and pain.

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Conflict of interest: The authors declare that there is no conflict of interest in the current study. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

Author contributions: Y. S. and P. C. had the idea for the study. X. B., X. W., and T. X. searched and screened the studies and extracted the data. M. Q. and L. W. contributed to statistical analysis. L. W. wrote the first draft of the manuscript. P. C., D. C. N., M. Q., and F. L. revised the manuscript. All authors contributed to the design of the study, contributed to the interpretation and discussion of the data and results, read and agreed on the final version.

REFERENCES

1. Berger AM, Mooney K, Alvarez-Perez A, et al. Cancer-related fatigue, version 2.2015. *J Natl Compr Canc Netw*. 2015;13(8):1012–39.
2. Lawrence DP, Kupelnick B, Miller K, Devine D, Lau J. Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. *J Natl Cancer Inst Monogr*. 2004;32:40–50.
3. Patrick DL, Ferketich SL, Frame PS, et al. National Institutes of Health State-of-the-Science conference statement: symptom management in cancer: pain, depression, and fatigue, July 15-17, 2002. *J Natl Cancer Inst*. 2003;95(15):1110–7.
4. Stark L, Tofthagen C, Visovsky C, McMillan SC. The symptom experience of patients with cancer. *J Hosp Palliat Nurs*. 2012;14(1):61–70.
5. Cella D, Davis K, Breitbart W, Curt G. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. *J Clin Oncol*. 2001;19(14):3385–91.
6. Curt GA, Breitbart W, Cella D, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the fatigue coalition. *Oncologist*. 2000;5(5):353–60.
7. Andrykowski MA, Donovan KA, Laronga C, Jacobsen PB. Prevalence, predictors, and characteristics of off-treatment fatigue in breast cancer survivors. *Cancer*. 2010;116(24):5740–8.
8. Bower JE. Cancer-related fatigue—mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol*. 2014;11(10):597–609.
9. Mantyh PW. Cancer pain and its impact on diagnosis, survival and quality of life. *Nat Rev Neurosci*. 2006;7(10):797–809.

10. Schmidt BL, Hamamoto DT, Simone DA, Wilcox GL. Mechanism of cancer pain. *Mol Interv*. 2010;10(3):164–78.
11. Meuser T, Pietruck C, Radbruch L, Stute P, Lehmann KA, Grond S. Symptoms during cancer pain treatment following WHO-guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology. *Pain*. 2001;93(3):247–57.
12. Zylla D, Steele G, Gupta P. A systematic review of the impact of pain on overall survival in patients with cancer. *Support Care Cancer*. 2017;25(5):1687–98.
13. McTiernan A, Friedenreich CM, Katzmarzyk PT, et al. Physical activity in cancer prevention and survival: a systematic review. *Med Sci Sports Exerc*. 2019;51(6):1252–61.
14. Furmaniak AC, Menig M, Markes MH. Exercise for women receiving adjuvant therapy for breast cancer. *Cochrane Database Syst Rev*. 2016;9(9):CD005001.
15. Daum CW, Cochrane SK, Fitzgerald JD, Johnson L, Buford TW. Exercise interventions for preserving physical function among cancer survivors in middle to late life. *J Frailty Aging*. 2016;5(4):214–24.
16. Hilfiker R, Meichtry A, Eicher M, et al. Exercise and other non-pharmaceutical interventions for cancer-related fatigue in patients during or after cancer treatment: a systematic review incorporating an indirect-comparisons meta-analysis. *Br J Sports Med*. 2018; 52(10):651–8.
17. Mustian KM, Alfano CM, Heckler C, et al. Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. *JAMA Oncol*. 2017;3(7):961–8.
18. Yang M, Liu L, Gan CE, et al. Effects of home-based exercise on exercise capacity, symptoms, and quality of life in patients with lung cancer: a meta-analysis. *Eur J Oncol Nurs*. 2020;49:101836.
19. Shen Q, Yang H. Impact of post-radiotherapy exercise on women with breast cancer: a systematic review and meta-analysis of randomized controlled trials. *J Rehabil Med*. 2020;52(10):jrm00112.
20. Nakano J, Hashizume K, Fukushima T, et al. Effects of aerobic and resistance exercises on physical symptoms in cancer patients: a meta-analysis. *Integr Cancer Ther*. 2018;17(4):1048–58.
21. Mishra SI, Scherer RW, Geigle PM, et al. Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Syst Rev*. 2012;2012(8):CD007566.
22. van Vulpen JK, Sweegers MG, Peeters PHM, et al. Moderators of exercise effects on cancer-related fatigue: a meta-analysis of individual patient data. *Med Sci Sports Exerc*. 2020;52(2):303–14.
23. Cramer H, Lauche R, Klose P, Lange S, Langhorst J, Dobos GJ. Yoga for improving health-related quality of life, mental health and cancer-related symptoms in women diagnosed with breast cancer. *Cochrane Database Syst Rev*. 2017;1(1):CD010802.
24. Piercy KL, Troiano RP, Ballard RM, et al. The physical activity guidelines for Americans. *JAMA*. 2018;320(19):2020–8.
25. Weston KS, Wisløff U, Coombes JS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. *Br J Sports Med*. 2014;48(16):1227–34.
26. Batacan RB Jr, Duncan MJ, Dalbo VJ, Tucker PS, Fenning AS. Effects of high-intensity interval training on cardiometabolic health: a systematic review and meta-analysis of intervention studies. *Br J Sports Med*. 2017;51(6):494–503.
27. Karlsen T, Aamot IL, Haykowsky M, Rognmo Ø. High intensity interval training for maximizing health outcomes. *Prog Cardiovasc Dis*. 2017;60(1):67–77.
28. Lavín-Pérez AM, Collado-Mateo D, Mayo X, et al. Effects of high-intensity training on the quality of life of cancer patients and survivors: a systematic review with meta-analysis. *Sci Rep*. 2021;11(1): 15089.
29. Herranz-Gómez A, Cuenca-Martínez F, Suso-Martí L, et al. Effectiveness of HIIT in patients with cancer or cancer survivors: an umbrella and mapping review with meta-meta-analysis. *Scand J Med Sci Sports*. 2022;32(11):1522–49.
30. Piraux E, Caty G, Renard L, et al. Effects of high-intensity interval training compared with resistance training in prostate cancer patients undergoing radiotherapy: a randomized controlled trial. *Prostate Cancer Prostatic Dis*. 2021;24(1):156–65.
31. Kang DW, Fairey AS, Boulé NG, Field CJ, Wharton SA, Courneya KS. A randomized trial of the effects of exercise on anxiety, fear of cancer progression and quality of life in prostate cancer patients on active surveillance. *J Urol*. 2022;207(4):814–22.
32. Adams SC, DeLorey DS, Davenport MH, Fairey AS, North S, Courneya KS. Effects of high-intensity interval training on fatigue and quality of life in testicular cancer survivors. *Br J Cancer*. 2018;118(10):1313–21.
33. Hwang CL, Yu CJ, Shih JY, Yang PC, Wu YT. Effects of exercise training on exercise capacity in patients with non-small cell lung cancer receiving targeted therapy. *Support Care Cancer*. 2012;20(12):3169–77.
34. Lee K, Norris MK, Wang E, Dieli-Conwright CM. Effect of high-intensity interval training on patient-reported outcomes and physical function in women with breast cancer receiving anthracycline-based chemotherapy. *Support Care Cancer*. 2021;29(11):6863–70.
35. Ochi E, Tsuji K, Narisawa T, et al. Cardiorespiratory fitness in breast cancer survivors: a randomised controlled trial of home-based smartphone supported high intensity interval training. *BMJ Support Palliat Care*. 2022;12(1):33–7.
36. Hiensch AE, Mijwel S, Bargiela D, Wengström Y, May AM, Rundqvist H. Inflammation mediates exercise effects on fatigue in patients with breast cancer. *Med Sci Sports Exerc*. 2021;53(3):496–504.
37. Mijwel S, Backman M, Bolam KA, et al. Adding high-intensity interval training to conventional training modalities: optimizing health-related outcomes during chemotherapy for breast cancer: the OptiTrain randomized controlled trial. *Breast Cancer Res Treat*. 2018;168(1):79–93.
38. Koevoets EW, Schagen SB, de Ruiter MB, et al. Effect of physical exercise on cognitive function after chemotherapy in patients with breast cancer: a randomized controlled trial (PAM study). *Breast Cancer Res*. 2022;24(1):36.
39. Persoon S, ChinAPaw MJM, Buffart LM, et al. Randomized controlled trial on the effects of a supervised high intensity exercise program in patients with a hematologic malignancy treated with autologous stem cell transplantation: results from the EXIST study. *PLoS One*. 2017;12(7):e0181313.
40. Kampshoff CS, Chinapaw MJ, Brug J, et al. Randomized controlled trial of the effects of high intensity and low-to-moderate intensity exercise on physical fitness and fatigue in cancer survivors: results of the resistance and endurance exercise after ChemoTherapy (REACT) study. *BMC Med*. 2015;13:275.
41. Reljic D, Herrmann HJ, Jakobs B, et al. Feasibility, safety, and preliminary efficacy of very low-volume interval training in advanced cancer patients. *Med Sci Sports Exerc*. 2022;54(11):1817–30.
42. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *PLoS Med*. 2021;18(3):e1003583.
43. Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed. John Wiley & Sons Limited; 2019. pp. 109–41.
44. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6(7):e1000100.
45. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale (NJ): Lawrence Erlbaum Associates; 1988. p. 567.
46. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–60.
47. Irwig L, Macaskill P, Berry G, Glasziou P. Bias in meta-analysis detected by a simple, graphical test. Graphical test is itself biased. *BMJ*. 1998;316(7129):470–1.
48. Demmelmaier I, Brooke HL, Henriksson A, et al. Does exercise intensity matter for fatigue during (neo-)adjuvant cancer treatment? The Phys-Can randomized clinical trial. *Scand J Med Sci Sports*. 2021;31(5):1144–59.
49. Edvardsen E, Skjønsberg OH, Holme I, Nordsletten L, Borchsenius F, Anderssen SA. High-intensity training following lung cancer surgery: a randomised controlled trial. *Thorax*. 2015;70(3):244–50.

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50. Daussin FN, Zoll J, Dufour SP, et al. Effect of interval versus continuous training on cardiorespiratory and mitochondrial functions: relationship to aerobic performance improvements in sedentary subjects. *Am J Physiol Regul Integr Comp Physiol*. 2008;295(1): 264–72.
51. Wisløff U, Støylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation*. 2007;115(24): 3086–94.
52. Cormie P, Galvão DA, Spry N, et al. Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. *BJU Int*. 2015;115(2):256–66.
53. Belloni S, Arrigoni C, Caruso R. Effects from physical exercise on reduced cancer-related fatigue: a systematic review of systematic reviews and meta-analysis. *Acta Oncol*. 2021;60(12):1678–87.
54. LaVoy EC, Fagundes CP, Dantzer R. Exercise, inflammation, and fatigue in cancer survivors. *Exerc Immunol Rev*. 2016;22:82–93.
55. Stöggl TL, Björklund G. High intensity interval training leads to greater improvements in acute heart rate recovery and anaerobic power as high volume low intensity training. *Front Physiol*. 2017;8:562.
56. Gomes-Neto M, Durães AR, Conceição LSR, et al. Effect of combined aerobic and resistance training on peak oxygen consumption, muscle strength and health-related quality of life in patients with heart failure with reduced left ventricular ejection fraction: a systematic review and meta-analysis. *Int J Cardiol*. 2019;293:165–75.
57. Abreu RM, Rehder-Santos P, Simões RP, Catai AM. Can high-intensity interval training change cardiac autonomic control? A systematic review. *Braz J Phys Ther*. 2019;23(4):279–89.
58. Schmidt ME, Meynköhn A, Habermann N, et al. Resistance exercise and inflammation in breast cancer patients undergoing adjuvant radiation therapy: mediation analysis from a randomized, controlled intervention trial. *Int J Radiat Oncol Biol Phys*. 2016;94(2):329–37.
59. Irandoust K, Hamzehloo A, Youzbashi L, Taheri M, Ben Saad H. High intensity interval training and L-arginine supplementation decrease interleukin-6 levels in adult trained males. *Tunis Med*. 2022; 100(10):696–705.
60. Souza EO, Ugrinowitsch C, Tricoli V, et al. Early adaptations to six weeks of non-periodized and periodized strength training regimens in recreational males. *J Sports Sci Med*. 2014;13(3):604–9.
61. Campbell KL, Winters-Stone KM, Wiskemann J, et al. Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. *Med Sci Sports Exerc*. 2019; 51(11):2375–90.
62. Segal R, Zwaal C, Green E, Tomasone JR, Loblaw A, Petrella T. Exercise for people with cancer: a clinical practice guideline. *Curr Oncol*. 2017;24(1):40–6.
63. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin*. 2012;62(4):243–74.
64. Palma S, Hasenoehrl T, Jordakieva G, Ramazanova D, Crevenna R. High-intensity interval training in the prehabilitation of cancer patients—a systematic review and meta-analysis. *Support Care Cancer*. 2021;29(4):1781–94.
65. Galvão DA, Taaffe DR, Spry N, et al. Exercise preserves physical function in prostate cancer patients with bone metastases. *Med Sci Sports Exerc*. 2018;50(3):393–9.
66. Ferguson B. ACSM's Guidelines for Exercise Testing and Prescription 9th Ed. 2014. *J Can Chiropr Assoc*. 2014;58(3):328.
67. Stewart B. Advanced cancer and comorbid conditions: prognosis and treatment. *Cancer Control*. 1999;6(2):168–75.
68. Froehner M, Brausi MA, Herr HW, Muto G, Studer UE. Complications following radical cystectomy for bladder cancer in the elderly. *Eur Urol*. 2009;56(3):443–54.