Effect of exercise on cancer-related fatigue: A systematic review

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ABSTRACT

Cancer is the second leading cause of death in the world and cancer-related fatigue (CRF) is the most common disease in cancer patients that received radiotherapy, chemotherapy, hormone therapy and biotherapy. Many studies recommended physical activity and exercise to improve fatigue. This systematic review aims to provide a qualitative synthesis of Randomized Clinical Trials (RCTs) evaluating the effects of Aerobic, Resistance, Endurance and combined exercises on CRF versus control or different exercise group in cancer adult patients and survivors that did not receive palliative care. This systematic review is written and presented according to PRISMA protocols. Articles in the English language were collected using the PubMed and WoS databases from 2001 January 1st to 2019 September 1st. Only RCTs lasted 5 weeks or more were analysed of which CRF outcomes were examined. A total of 15 RCTs met our inclusion criteria. Different outcomes in CRF self-reports were found between Aerobic, Resistance, Endurance and Combined exercises. Findings suggest that exercise improves CRF, especially with aerobic or combined programs. The outcomes of trials could help exercise professionals to properly plan the sessions by dosing the volume and intensity. Nevertheless, more studies are needed to better understand the benefits of physical exercise on cancer patients.

Keywords: Aerobic; Resistance; Endurance; Combined exercise; Physical activity; Cancer.

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INTRODUCTION

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death. It is the second leading cause of death in the world and its incidence is growing, with 21.7 million new yearly cases predicted worldwide by 2030 (Torre et al., 2015). Five states with the highest incidence are Denmark (338/100,000), France (325/100,000), Australia (323/100,000), the USA (318/100,000) and South Korea (308/100,000) (Kessels et al., 2018). For example, the American Cancer Society (2019) estimated 1,762,450 of new cases for cancer in USA and about 371,000 in Italy during 2019 (AIOM, 2019). Cancer is caused by internal factors, such as inherited genetic mutations, hormones, and immune conditions and external factors, such as tobacco, infectious organisms, and an unhealthy diet; in 2012, USA registered about 5% of all cancers were caused by inactivity (Parkin et al., 2011). Furthermore, Cancer was estimated to have resulted in 208.3 million disability-adjusted-life-years in 2015 (Bernsten et al., 2017). One of these is cancer-related fatigue (CRF) (Akechi et al., 1999).

CRF is defined by the National Comprehensive Cancer Network (NCCN, 2003) as "*a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning*"; 70–100% of patients being treated for cancer are affected by CRF, which can be more distressing and disruptive to daily activities than the pain associated with the disease (Curt et al., 2000). It is a common disease in patients who received radiotherapy, chemotherapy, hormone therapy and biotherapy (Jacobsen et al., 1999; Robinson & Posner, 1992; Sitzia & Huggins, 1998; Stone et al., 2000). CRF was added to "*International Classification of Disease*" (Cella et al., 2001) and guidelines for its management were made (NCCN, 2003). Its effects may be incurred during treatments and they persist for many months or years (Bower et al., 2000; Broeckel et al., 1998). The effects of CRF also have deleterious influences on patients' and survivors' physical, mental, and emotional well-being (Cataldi, Latino, Greco, & Fischetti, 2019; Hofman et al., 2007). Several factors have been identified in research as contributing to fatigue, but it is still unclear what is most influent (Ryan et al., 2007). Physiological and psychosocial factors play a part in the specific mechanisms involved in the development of CRF (Ahlberg et al., 2003; Fischetti et al., 2019); an import contribute was made by muscular metabolism (Brown et al., 2005; Forsyth et al., 1999; Isaksson et al., 2002; Lane et al., 1998; Lee et al., 2003; McCully et al., 1996). For assessment and management of CRF, different scales and questionnaire were made (Cleeland et al., 1999; Mendoza et al., 1999; Piper, 1997; Piper et al., 1989; Piper et al., 1998; Schwartz, 1998; Schwart & Meek, 1999; Smets et al., 1995; Sutherland et al., 1999).

The NCCN's (2015) clinical practice guidelines recommend physical activity and exercise to improve fatigue, undergoing and/or after treatments. A recent meta-analysis showed that both exercise and psychological treatments have small effect sizes in CRF, whereas medication has no effects, with most effects of exercise during cancer therapy (Mustian et al., 2017). Despite the evidence of training's benefits, cancer survivors or patients report a significant decline in exercise after diagnosis, with less than 50% engaging in a beneficial exercises program (Humpel & Iverson, 2007; Midtgaard et al., 2009). A Cochrane systematic review and meta-analysis by Cramp and Byron-Daniel (2012) examined the effects of exercises on CRF in patients who received palliative or non-palliative treatments. Another review of Kessels et al. (2018) exceeded this problem establishing the effects of exercises on CRF in a population not suffering from specific end-life-distress, but they used only MET to quantify the intensity of exercises. Also, we included RCT 3-armed.

This study aims to provide a systematic review of RCTs evaluating the effects of Aerobic, Resistance, Endurance and combined exercises on CRF versus control or different exercise group, confronted from baseline to one or more follow-ups, in cancer patients and survivors who were adult (18 years old or more) and who did not receive palliative care. Different self-report used for fatigue outcomes and exercise intensity was registered by common methods as percentage of HR_{max} (Cinke & Thomas, 1981) or HR_r (Cheng et al., 2002), RPE (Borg, 1970), METs (Mendes et al., 2018), 1RM (Delorme & Watkins, 1948) and VO_{2peak} (Noonan & Dean, 2000).

METHODS

Search strategy and information processing

The systematic review is written and presented according to PRISMA protocols (Liberati et al., 2009). PubMed (a search engine for free access to the MEDLINE database of citations and abstracts of biomedical research articles) and Web of Science (online scientific information service, provided by Thomson Reuters, integrated in ISI Web of Knowledge, WOK, containing original articles based on clinical trials) databases were used to obtain all the data used in this study. The keywords used were: ("*cancer patients*" OR "*cancer survivors*") AND ("*fatigue*" OR "*cancer-related fatigue*") AND "*exercise*" AND "*randomized controlled trial*" AND "*free full text*" AND "*custom date range*" ("*2001 January 1st to 2019 September 1st*"). The search string was ("*cancer patients*" [All Fields] OR "*cancer survivors*" [All Fields]) AND ("*fatigue*" [All Fields] OR "*cancer-related fatigue*" [All Fields]) AND "*exercise*". There was a custom date range published from 2001 January 1st to 2019 September 1st.

Eligibility criteria

Table 1. PICOST eligibility criteria.

Parameter	Inclusion criteria	Exclusion criteria
Patients	Adults (≥ 18 years) living with or beyond cancer diagnosis not receiving palliative care, undergoing or post therapy and/or treatment	Patients < 18 years Patients receiving palliative care Patients without cancer Patients with unrecoverable metastatic disease
Intervention	Physical activity with AE, RE, EN and/or combined exercises	Yoga, Dance, Qigong, Powerlifting, Tai chi, Pilates, Mindfulness, Chess, Physiotherapy, Music therapy, CBT, EMS, Isometric training, Psychoeducation, Diet and Dietary supplements
Comparator	Non-exercise control group; RE, AE or EN exercise group	Non-exercise control group receiving additional care, such as diet, CBT, physiotherapy, etc.
Outcome	Perceived of Fatigue measured by self-report questionnaire	No fatigue result
Study design	RCTs with length of follow up of 5 weeks or more	Non-RCTs RCTs lasted 4 weeks or less No English language
Timing	From 2001 January 1st to 2019 September 1st	Before 2001 and after 2019 September 1st

Abbreviations: AE, Aerobic; RE, Resistance; EN, Endurance; CBT, Cognitive Behavioural Therapy; EMS, Electric Muscular Stimulation; RCTs, Randomized Controlled Trials.

A summary of the inclusion and exclusion criteria for this review is shown in PICOST (Miller, 2001) Table 1. Each of the identified articles was independently analysed by three researchers. Patients were adults (≥18 years) living with, or beyond, any cancer diagnosis, undergoing or after some therapy and/or treatment; they didn't receive palliative care but active treatment as surgery, radiotherapy (included ADT), chemotherapy and/or hormone therapy. Metastatic diseases were included if it was not unrecoverable. We included RCTs in which were Aerobic, Resistance, Endurance and/or combined exercise. We examined only RCT in which were CRF outcomes. Only Randomized Controlled Trials were analysed, which were published from 2001 January 1st to 2019 September 1st. We considered acceptable RCT which lasted 5 weeks or more and had one or multiple follow-ups for inclusion. We considerable acceptable all intensity of exercise if it was correctly reported. We excluded Yoga, Qigong, Tai chi, Powerlifting, Pilates and Dance exercises because they need a specialist trainer and some of them request a good motor activity experience. Every study had at least one control group, who didn't exercise, and could compare two or more group if it was a 3-armed trial. Outcomes had to underline changes in fatigue and were expressed in quantitative measures by a validated self-report questionnaire. Only English language was acceptable for inclusion study.

Data collection process and analysis

Two independent reviewers extracted data available in the full free texts. All variables for which data were sought are: a) Fatigue severity, measured by self-report questionnaire validated to assess and manage CRF in patients or survivors and expressed in *p*-value; b) Number of patients of interventions or control groups, sample mean age, gender of patients; c) Type of cancer and treatment; d) Type of exercise, its intensity and its frequency; e) Length of study analysis; f) Intervention in groups.

The principal summary measures were expressed as standardizes difference in means (Cohen's *d*) of CRF and *p*-value to quantify the idea of statistical significance of evidence. It is assumed that an effect size $d \geq 0.80$ represents a large effect, $0.50 \leq d < 0.80$ medium and $d < 0.50$ small (Cohen, 1988). *P*-value is generally considered an $\alpha = .05$ as a threshold value under which data has a statistical significance (Wasserstein & Lazar., 2016).

Additional analyses

We analysed 4 different interventions:

1. Aerobic exercises as walking, jogging, swimming, biking and running. For stay in aerobic training, level of intensity was between 40-65% HR_{max}, 50-75% HR_r, or 35-50% VO_{2peak}.
2. Resistance exercises as muscular contraction on machine or with resistance band. The intensity wasn't over 85% 1RM.
3. Endurance exercises that trained cardiovascular and respiratory system with high intensity (> 80% HR_r or 75%< VO_{2peak} < 95%)
4. Combined two or more of precedent interventions.

RESULTS

Study selection

The search strategy found 1880 RCTs, of which 827 were free full texts. After checking for duplicates, remained 651 RCTs. From these, 47 trials were included for independent screening. 32 trials were excluded and only 15 respected the inclusion criteria (reported in Table 1) and were included in the systematic review. The PRISMA flow diagram (Moher et al., 2009) reported in Figure 1 reports an overview of "*study selection*".

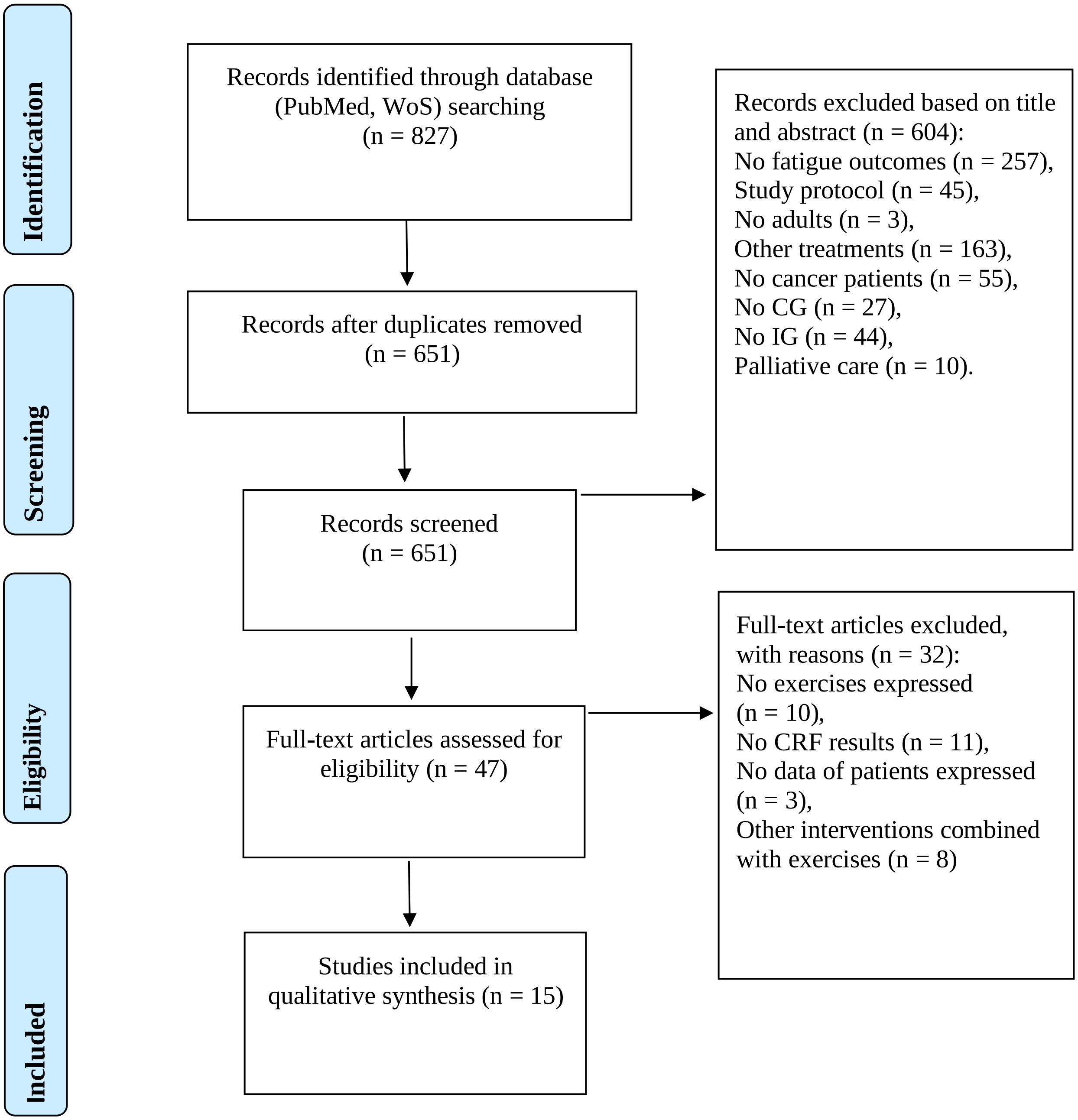


Figure 1. Flowchart on the literature search of exercise effects on cancer-related fatigue.

Study characteristics

All 15 trials were RCTs (Adams et al., 2018; Cormie et al., 2015; Dieli-Conwright et al., 2018; Galiano-Castillo et al., 2016; Hojan et al., 2016; Hwang et al., 2008; Kampshoff et al., 2015; Monga et al., 2007; Paulo et al., 2019; Penttinen et al., 2019; Pinto et al., 2005; Schmidt et al., 2015; Segal et al., 2009; Shobeiri et al., 2016; Steindorf et al., 2014). Table 2 reviews all patient details. In total, 1664 patients were included in the trials, of whom 376 were men and 1288 were women. 905 patients were randomized in an intervention group (IG1+IG2) and 749 were randomized in a control group of which 36 received a basic recommendation for exercise (Galiano-Castillo et al., 2016) and 142 followed relaxation treatment (Paulo et al., 2019; Schmidt et al., 2015; Steindorf et al., 2014). The weighted average age was 54.91. In 9 RCTs patients reported breast cancer (Dieli-Conwright et al., 2018; Galiano-Castillo et al., 2016; Hwang et al., 2008; Paulo et al., 2019; Penttinen et al., 2019; Pinto et al., 2005; Schmidt et al., 2015; Shobeiri et al., 2016; Steindorf et al., 2014), in 4 reported prostate cancer (Cormie et al., 2015; Hojan et al., 2016; Monga et al., 2007; Segal et al., 2009), in 1 reported testicular cancer (Adams et al., 2018), in 1 multiple cancer (Kampshoff et al., 2015). In 8 trials patients were still undergoing different therapies (Cormie et al., 2015; Hojan et al., 2016; Hwang et al., 2008; Monga et al., 2007; Paulo et al., 2019; Schmidt et al., 2015; Segal et al., 2009; Steindorf et al., 2014), in 3 trials patients completed therapies (Kampshoff et al., 2015; Penttinen et al., 2019; Shobeiri et al., 2016) and in 4 trials patients were analysed after therapies (Adams et al., 2018; Dieli-Conwright et al., 2018; Galiano-Castillo et al., 2016; Pinto et al., 2005). Exercise interventions lasted from 5 weeks (Mendes et al., 2018) to 5 years (Penttinen et al., 2019), of which 11 trials did follow-up at baseline and after treatment (Adams et al., 2018; Cormie et al., 2015; Dieli-Conwright et al., 2018; Galiano-Castillo et al., 2016; Hojan et al., 2016; Hwang et al., 2008; Kampshoff et al., 2015; Pinto et al., 2005; Shobeiri et al., 2016; Schmidt et al., 2015), 3 RCTs did 3 different follow-up (baseline, T1 and T2) (Paulo et al., 2019; Segal et al., 2009; Steindorf et al., 2014) and other one trial did 6 follow-ups (Penttinen et al., 2019).

Table 2. Patients details.

Study	Patients	IG1	IG2	CG	Age (yrs.)	Gender
Paulo et al. (2019)	36	18	0	18	65	female
Shobeiri et al. (2016)	53	27	0	26	43	female
Galiano-Castillo et al. (2016)	72	36	0	36	48	female
Schmidt et al. (2015)	95	49	0	46	53	female
Adams et al. (2018)	63	35	0	28	44	male
Penttinen et al. (2019)	444	235	0	209	53	female
Dieli-Conwright et al. (2018)	91	46	0	45	53	female
Steindorf et al. (2014)	155	77	0	78	56	female
Kampshoff et al. (2015)	277	91	95	91	54	f = 223; m = 54
Hojan et al. (2016)	54	27	0	27	68.5	male
Monga et al. (2007)	21	11	0	10	69	male
Segal et al. (2009)	121	40	40	41	66	male
Hwang et al. (2008)	37	17	0	20	46	female
Cormie et al. (2015)	63	32	0	31	68.5	male
Pinto et al. (2005)	82	39	0	43	53	female
ALL	1664	780	135	749	54.91*	f = 1288; m = 376

**Weighted average of age; IG, intervention group; CG, control group; m, male; f, female.*

Results of individuals studies

The results are summarized in Table 3. Thirteen RCTs found improvements in CRF (Adams et al., 2018; Cormie et al., 2015; Dieli-Conwright et al., 2018; Galiano-Castillo et al., 2016; Hojan et al., 2016; Hwang et al., 2008; Kampshoff et al., 2015; Monga et al., 2007; Paulo et al., 2019; Pinto et al., 2005; Segal et al., 2009; Shobeiri et al., 2016; Steindorf et al., 2014), one trial found improvements only in patients who were not affected of depression (Schmidt et al., 2015) and other one trial found improvements in patients who changed intensity of exercise or physical performance (Penttinen et al., 2019). Four types of exercise intervention were used: Aerobic (Monga et al., 2007; Pinto et al., 2005; Segal et al., 2009; Shobeiri et al., 2016); Resistance (Schmidt et al., 2015; Segal et al., 2009; Steindorf et al., 2014); Endurance (i.e., High Intensity Interval Training) (Adams et al., 2018), Combined (Cormie et al., 2015; Dieli-Conwright et al., 2018; Galiano-Castillo et al., 2016; Hojan et al., 2016; Kampshoff et al., 2015; Mendes et al., 2018; Paulo et al., 2019; Penttinen et al., 2019). One of these trials (Segal et al., 2009) found improvements in CRF with aerobic

Table 3. Studies that investigated the effects of exercise on cancer-related fatigue.

Article	-n IG1 -n IG2 -n CG -Age (sm) -Sex	-Cancer -Treatment	-Outcome instrument -P-Value	-Exercise -Intensity -Frequency	-Time follow-up -All Outcomes compared	Activity IG	Control Group
RCT (2x3) Paulo et al. (2019)	-n = 18 -n = ∅ -n = 18 -65 years -female	-Breast (100%) -Undergoing aromatase inhibition therapy	-EORTCQLQ-30 -p < .001 (IG vs. CG)	-AE+RE -60-85% HR_{max} (AE) -Max rep (RE) -3 d/w	-9 Months -Improved: CRF, Nausea, Dyspnoea, Sleep disturbance, Physical fitness, etc.	Warm-up + 40' RE exercises on machine + 30' AE exercise + cool-down	45' of Stretch and relaxation exercise, 2 d/w
RCT (2x2) Shobeiri et al. (2016)	-n = 27 -n = ∅ -n = 26 -43 years -female	-Breast (100%) -Completed surgery and RT o CT	-EORTCQLQ-30 -p < .001 (IG vs. CG)	-AE -50-75% HR_r -2 d/w	-10 Weeks -Improved: CRF, Nausea, Pain, Dyspnoea, Insomnia, physical and mental fitness and QoL	Warm-up (5-10' of stretching and moderate walking) + 15' of AE exercise + 5' of cool down	Usual Care and sedentary lifestyle
RCT (2X2) Galiano-Castillo et al. (2016)	-n = 36 -n = ∅ -n = 36 -48 years -female	-Breast (100%) -After RT and/or CT	-PFS -p < .05 (IG vs CG)	-AE+RE -ACSM guidelines -3 d/w	-6 Months -Improved: CRF, Health status, Physical and Cognitive fitness	90' of training with warm-up + AE and RE exercises + cool down	Basic recommendation for exercises
RCT (2x2) Schmidt et al. (2015)	-n = 49 -n = ∅ -n = 46 -53 years -female	-Breast (100%) -Undergoing adjuvant CT	-FAQ -p < .098 (patients with high lv of depression) -p < .038 (patients without depression)	-RE -60-80% 1RM -2 d/w	-12 Weeks -Improved: CRF, social and role f.	8 machines based progressive RE training (3 sets x 12 repetition); no AE exercises	Relaxation accord to Jacobsen (Jacobsen & al., 1999)
RCT (2X2) Adams et al. (2018)	-n = 35 -n = ∅ -n = 28 -44 years -male	-Testicular (100%) -After RT, CT or others	-FACT-F -p = .003	-High Intensity Interval-Training -75-95% VO_{2max} -3 d/w	-3 Months -Improved: CRF, Mental component and vitality	Warm-up 5' + HIIT 25' (4 sets x 4', 3' of active recovery in 3 intervals) + cool down	Maintained baseline exercise lv
RCT * Penttinen et al. (2019)	-n = 235 -n = ∅ -n = 209 -53 years -female	-Breast (100%) -Completed CT and RT or started ET	-FACIT-F -p = .065 (in patients without increment of MET-h/w)	-AE + RE + EN -RPE 14-16 -Incremented MET-h/w or changed physical performance	-5 Years -Improved: CRF, Physical and Role fitness	1 day with 60' of AE exercises and circuit training 2 days (at least) of EN exercise	Maintained baseline exercises lv

			-p = .002 (in patients with increment of MET-h/w) -p = .003 (patients who changed p. performance)	-3 or more d/w			
RCT (2x2) Dieli-Conwright et al. (2018)	-n = 46 -n = ∅ -n = 45 -63 years -female	-Breast (100%) -After CT e RT	-BFI -p < .001 (IG vs CG)	-AE + RE -65-80% HR_{max} -60-80% 1RM (weight increased by 10-15%) -3 d/w	-12 Weeks -Improved: CRF, Physical fitness, QoL	Day 1 and 3: 5' warm-up + 70' RE and AE exercises + 5' cool down Day 2: 30-50' of AE exercises	Usual care
RCT (2x3) Steindorf et al. (2014)	-n = 77 -n = ∅ -n = 78 -56 years -female	-Breast (100%) -Undergoing adjuvant RT	-FAQ -p = .044	-RE -60-80% 1RM -2 d/w	-12 Weeks - Improved: CRF, Pain	60' with 8 different machine-based RE exercise (3 sets of 8-12 reps)	Relaxation without RE and AE exercises
RCT (2x2) Hojan et al. (2016)	-n = 27 -n = ∅ -n = 27 -68.5 years -male	-Prostate (100%) -Undergoing RT	-FACT-F -p < .001	-AE + RE -65-70% HR_r -70-75% 1RM -5 d/w	-3-5 Months -Improved: CRF, Physical fitness and Well-being	5' warm-up + 30' AE exercise + 15 RE exercise + 5' cool down	Activity of daily living without physical exercises
RCT (3X2) Kampshoff et al. (2015)	-n = 91 (HI) -n = 95 (LMI) -n = 91(WLC) -54 years -male (20%) -female (80%)	-Breast (65%), -Colon (17.7%), -Ovarian (4.3%), -Lymphoma (9.4%), -Cervix (1.7%) -Testis (1.9%) -Completed CT	-MFI -p<.05 (HI vs WLC) -p < .05 (LMI vs WLC)	-RE + EN -HI 70-85% 1RM and ≥ 80% HR_r -LMI 40-55% 1RM and 40-55% HR_r	-12 Weeks -Improved CRF (HI and LMI) and Physical f. (HI and LMI)	6 RE exercises for LMI and HI (2 sets of 10 rep) 2x8' at different workload for LMI and HI	Wait list control
RCT (2x2) Monga et al. (2007)	-n = 11 -n = ∅ -n = 10 -69 years -male	-Prostate (100%) -Undergoing RT	-PFS -p < .001	-AE -Maintained target HR -2 or more d/w	-8 Weeks -Improved: CRF, Physical performance and Well-being	10' warm-up + 30' AE (walking) + 5-10' cool down	Usual care without exercises

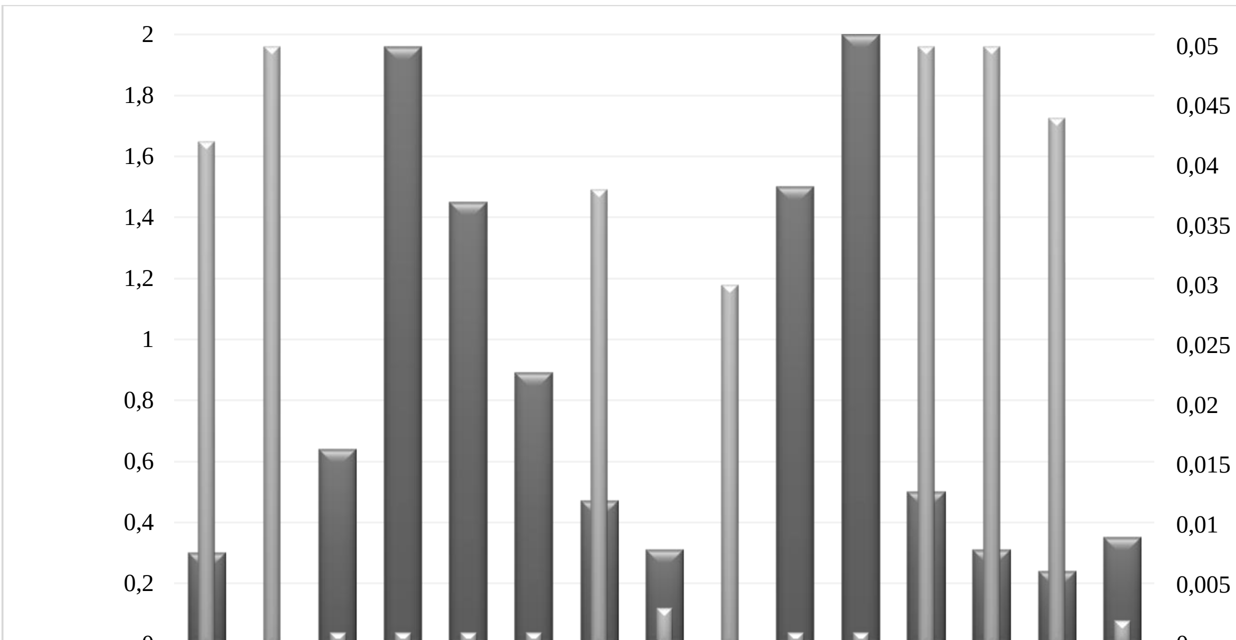
RCT (3x3) Segal et al. (2009)	-n = 40 (RE) -n = 40 (AE) -n = 41 (CG) -66 years -male	-Prostate (100%) -Undergoing RT	-FACT-F -p < .004 (AE vs CG at first follow-up) -p < .002 (RE vs CG at last follow-up)	-RE or AE -60-70% 1RM -50-75% VO_{2max} -3 d/w	-12-24 Weeks -Improved: CRF (AE vs CG at week 12; RE vs CG at week 24), etc.	5' warm-up + 10 different exercises (2 sets of 8-12 rep) + 15-45' of AE exercises (cycle ergometer, treadmill or elliptical + 5' cool down	Usual care
RCT (2x2) Hwang et al. (2008)	-n = 17 -n = ∅ -n = 20 -46 years -female	-Breast (100%) -Undergoing RT	-BFI -p < .05	-AE+RE -50-70% HR_{max} -3 d/w	-5 Weeks -Improved CRF, QoL, Pain, ROM	10' warm-up + 30' of AE and RE exercises	Usual care
RCT (2x2) Cormie et al. (2014)	-n = 32 -n = ∅ -n = 31 -68.5 years -male	-Prostate (100%) -Undergoing ADT	-FACIT-F -p = .042	-AE+RE -70-85% HR_{max} -60-85% 1RM -2 d/w	-3 Months -Improved CRF, Mental health, Sexual and Physical fitness, Body composition	Warm-up + 20-30' of AE exercises + 8 RE exercises (1-4 sets of 6-12 rep) + cool down. Total of 60'.	Usual care
RCT (2x2) Pinto et al. (2005)	-n = 39 -n = ∅ -n = 43 -53 years -female	-Breast (100%) -After RT, CT and/or HT	-LASA -p = .001	-AE -55-65% HR_{max} -2 to 5 d/w	-12 Weeks -Improved: CRF and Physical activity	10-30' of AE exercises	Maintained lv of daily activity

**RCT including 3 study-arm and 6 follow-ups. Abbreviations: AE, Aerobic; RE, Resistance; CRF, Cancer Related Fatigue; RT, Radiotherapy; CT, Chemotherapy; HT, Hormone Therapy; ADT, Androgen Deprivation Therapy; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT-F, Functional Assessment of Chronic Illness Therapy- Fatigue Scale; BFI, Brief Fatigue Inventory; PFS, Piper Fatigue Scale; MFI, Multidimensional Fatigue Inventory; FAQ, Fatigue Assessment Questionnaire; LASA, Linear Analogue Self-Assessment; IG, Intervention Group; CG, Control Group; Sm, Simple mean; HI, High Intensity; LMI, Low-To-Moderate Intensity; WLC, Wait List Control; HIIT, High Intensity Interval Training; ACSM, American College of Sport Medicine.*

exercise at first follow-up and with resistance exercise at last follow-up. Intensity of the exercise varied from low (Galiano-Castillo et al., 2016; Hwang et al., 2008; Pinto et al., 2005; Shobeiri et al., 2016) to moderate (Cormie et al., 2015; Dieli-Conwright et al., 2018; Hojan et al., 2016; Monga et al., 2007; Segal et al., 2009; Paulo et al., 2019; Schmidt et al., 2015; Steindorf et al., 2014) to high (Adams et al., 2018) or changed during treatment (Kampshoff et al., 2015; Penttinen et al., 2019). The most important outcomes were shown in two Aerobic treatment trials (Monga et al., 2007; Shobeiri et al., 2016) and two Combined treatment trials (Dieli-Conwright et al., 2018; Paulo et al., 2019).

Outcomes of RCTs

The outcomes of trials are represented in Figure 2. Two RCTs didn't report Cohen's *d* (Hwang et al., 2008; Penttinen et al., 2019). The two three-armed studies (Kampshoff et al., 2015; Penttinen & al., 2019) showed different *p*-value for every experimental group confronted to control group. The most important effect size was found in four trials (Dieli-Conwright et al., 2018; Monga et al., 2007; Paulo et al., 2019; Shobeiri et al., 2016).



	Cormie et al., 2014	Hwang et al., 2008	Pinto et al., 2005	Paulo et al., 2019	Shobeiri et al., 2016	Galiano-Castillo et al., 2016	Schmidt et al., 2015	Adams et al., 2018	Penttinen et al., 2019*	Monga et al., 2007	Dieli-Conwright. et al., 2018	Hojan et al., 2016	Kampshoff et al., 2015**	Steinforf et al., 2014	Segal et al., 2009***
Cohen's d	0,3	0	0,64	1,96	1,45	0,89	0,47	0,31	0	1,5	2	0,5	0,31	0,24	0,35
P-value	0,042	0,05	0,001	0,001	0,001	0,001	0,038	0,003	0,03	0,001	0,001	0,05	0,05	0,044	0,002

*Where Cohen's d results 0 we haven't found value in trial. *In this trial there were 2 different p-value: .03 for group who changed performance and .02 in group who incremented MET. **In this trial there were 2 different p-value and effect size: Low to Moderate Intensity reported p < .05 and d = 0.31; High Intensity reported p < .05 and d = 0.35. ***In this trial there where 2 different p-value and effect size: Resistance Training reported p = .002 and d = 0.35; Aerobic Training reported p = .080 and d = 0.24. Groups were analysed at 24 weeks follow-up versus Usual Care group.*

Figure 2. Effect size and p-value of trials.

DISCUSSION

Summary of evidence

This study aims to investigate the effect of exercise on CRF, how exercise was used during the last decade and which is the best exercise program in the cancer patient. The results reported in Table 3 and Figure 2 recommend that aerobic exercise improves CRF better than other treatments, but it also provides good outcomes combined with resistance training. To get the best results, the better way is doing exercises at least two days/week, for eight or more weeks. The studies in which are reported best improvements followed a low to moderate intensity of exercises, showing the same effects in men and women. Thus, according to NCCN (2015) and the American College of Sports Medicine (2018), physical activity makes better the quality of life in cancer patients and improves psychological and physiological fitness.

Implication

The positive effects found after an exercise treatment underline the importance of daily activities in the patient's life during cancer disease. The preventive intervention allows us to increase the wellbeing of cancer patients improving fatigue sensation and helping patients undergoing therapy to continue their activity of life. Furthermore, exercise programs can increase muscle strength, physical fitness, physical and psychological function, body composition and can positively impact biomarkers associated with cancer progression (Stout et al., 2017). Changes on CRF are associated with other factors as pain, insomnia, depression, anxiety, mood disturbance and physiological distress factors (Ahlberg et al., 2003). In a study of Fiuza-Luces et al. (2013), exercise training was considered as a "*poly-pills*" for its multiple effects (Stefani et al., 2016) and Van Waart et al. (2015) showed the beneficial outcomes observed in patients with cancer.

Limitations

The main limitations of this systematic review are:

- A small number of trials used to find exercise effects on CRF;
- A small number of cancer types. The most of patients had breast or prostate cancer;
- Some trials didn't report effect size;
- Researchers measured fatigue with different self-report scale and for different length; this can't afford us to advise a better way to select a design of research;
- Patients were undergoing different therapy (chemotherapy, radiotherapy, etc.) or they concluded it and we can't choose the best exercise treatment for every care;
- In some trial patients did exercises without the supervision of a specialist during the session; this is a limitation to quantify accurate data;
- Some trials reported several outcomes in follow-ups which were done at a different moment.

CONCLUSIONS

Based on this systematic review and the findings of the investigated studies shown in Table 3, we conclude that exercise improves CRF, especially with aerobic and combined programs. This systematic review can help the exercise professional to plan exercise sessions correctly and we recommend increasing quality and quantity of exercise in cancer patients by monitoring every parameter during sessions. Nevertheless, more studies are needed to value the effects of physical exercise training on cancer patients and CRF should be assessed as a primary outcome.

AUTHOR CONTRIBUTIONS

SC, GG, MM and FF developed the research concept and study design. SC, GG, and MM performed the literature review and data collection. SC, GG and MM wrote the manuscript. GG and FF reviewed the manuscript. All authors contributed intellectually to the manuscript, and all authors have read the manuscript and approved the submission.

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