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Review Article

Effects of physiotherapy in the management of cancer-related pain and fatigue: A systematic review of randomized controlled trials.

Hajra Ameer Shaikh[1], Okasha Anjum[1], Kiran Iqbal[2] & Syeda Wajeeha Raza Zaidi[1]

[1]Department of Physical Therapy and Rehabilitation Sciences, Indus University, Karachi-Pakistan.

[2]Department of Physical Therapy and Rehabilitation Sciences, University of Sialkot, Sialkot-Pakistan.

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Corresponding Author Email: hajraameer90@gmail.com

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Abstract

Background: Cancer is ranked as the 2nd common deadliest disorder worldwide, and the growing incidence demands updating and optimizing the treatment strategies for cancer survivors. However, evidence regarding this area is scarce; therefore, this systematic review aimed to evaluate the effects of Physiotherapy (PT) in managing cancer-related pain and fatigue.

Methodology: Electronic search conducted utilizing Google Scholar, Embase.com, Cochrane CENTRAL via Wiley, Web of Science Core Collection, MEDLINE via Ovid, PEDro, and PubMed. Randomized controlled trials published from 2014 to April 2021 analyzing the effects of PT approaches for cancer-related pain and/or fatigue management in adult cancer patients were included in the review. Sixteen eligible trials were evaluated, of which eight trials addressed Cancer-Related Pain (CRP) while others addressed Cancer-Related Fatigue (CRF). The risks of bias and trials credibility were analyzed via the Cochrane tool to assess bias risk.

Results: Strong evidence favors the effectiveness of various PT approaches mainly, aerobic and resistance exercises for CRF and CRP management. However, endurance exercises, high-intensity interval training, and myofascial release were effective in CRF management. In contrast, Xbox Kinect-based games, stretching, lymphatic drainage, and passive mobilization effectively reduced CRF.

Conclusion: Large body of evidence supports the effectiveness of PT exercises mainly, aerobic and resistance exercises, in cancer-associated pain and fatigue management. Hence exercises prescriptions should be implemented in the treatment plan of cancer patients.

Keywords

Cancer Patients, Cancer-Related Fatigue, Cancer-Related Pain, Exercise, Physiotherapy Management.

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Introduction

Cancer ranks as the 2nd common deadliest disorder around the globe, and its global incidence is suspected to rise to 21 million by 2030[1]. The latest study conducted by McTiernan in 2019 reported that physical activity decreases the risk and improves the survival of several types of cancer[2].

Although traditional treatments for cancer such as hormone therapy, surgery, chemotherapy, and radiotherapy have favorable effects, they also result in various adverse effects mainly, fatigue, pain, anxiety, depression, nausea, and a high risk of developing a tumor[3]. The clinical oncological society of Australia outlined exercise as an integral part of standard treatment to upgrade the overall health and the life expectancy of cancer patients[4].

A growing body of evidence indicates that Physiotherapy (PT) is effective and safe for patients undergoing cancer treatment[5]. PT approaches can reduce the intensity of symptoms associated with cancer. However, the relief is associated with the amount of work done[6]. Recent literature also shows that exercise helps improve anxiety, depression, psychological needs satisfaction, and the quality of life also have a vital role in the recovery of cancer adverse effects[7,8]. A study by So WK et al. found that pain and fatigue often occur together with depression and are referred to as symptom clusters in cancer survivors[9]. It is clear from the evidence that cancer-related pain (CRP) is multidimensional and complex hence highlights the need for innovative multidisciplinary treatment strategies[10].

Fatigue is found to be the common symptom and treatment side effect of cancer[11, 12]. According to National Comprehensive Cancer Network, Cancer-Related Fatigue (CRF) is a persistent and distressing feeling of tiredness associated with cancer or cancer therapy which is not proportional to recent activity[13]. A study shows that CRF cannot be relieved by taking rest or sleep[14]. The latest literature reported rational approaches for the treatment of CRF in which exercise is an integral component[15]. However, a recent evaluation claimed physiotherapists have foundational knowledge and skill in cancer care but, more clinical practices are recommended [16-17].

In the latest version of adult cancer patient recommendations, the optimal treatment strategy for pain management combines pharmacological and non-pharmacological therapies that mainly include exercise and psychotherapy[18]. Similarly, the latest systematic review (SR) also claimed exercise as a measure to reduce CRF[19]. The evidence regarding the incredible effects of PT in oncological rehabilitation is scarce; therefore, this SR aimed to critically analyze the effects of PT in cancer-related-pain and fatigue management and provide a shred of up-to-date evidence.

Methodology

Study Design:

An SR of Randomized Controlled Trials (RCTs) was conducted on several types of cancer patients.

Review Protocol:

The review protocol is according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations[20].

Criteria for Eligibility:

RCTs fulfilling the following criteria was included:

1. The research design must be RCT.
2. Patients diagnosed with any type of cancer, aged ≥18 years.
3. Trials evaluating cancer-associated pain and/or fatigue as an outcome of interest.
4. Trials published from January 2014 to onwards April-2021.
5. The article must be in the English language.

Sources of Information:

Various electronic databases were sought, including Google Scholar, Embase.com, Cochrane CENTRAL via Wiley, Web of Science Core Collection, MEDLINE via Ovid, PEDro, and PubMed.

Search Strategy:

In January 2021, a comprehensive systematic search was carried out using different databases. The key terms used were (''cancer patients'' OR ''cancer survivors'') AND (''pain'' OR ''cancer-

related pain) AND (cancer-related fatigue" OR "fatigue") AND (''exercise'' OR ''physiotherapy'' OR '' oncological rehabilitation'' OR "physical activity") AND (''randomized controlled trial' OR ''RCT'') AND ''custom date range (2014 to 2021)". Titles and/or abstracts were reviewed, and the articles not meeting inclusion criteria were excluded. However, the remaining articles were studied in full to evaluate suitability in consideration with the PRISMA guidelines.

Study Selection:

Initial screening was carried out based on titles, and/or abstracts were also analyzed against the eligibility criteria of the SR. The primary electronic search yielded a total of 300 records, of which 246 trials were excluded based on titles and/or abstracts, duplication, pain and /or fatigue not addressed as the outcome of interest, treatment protocol not defined, and/or not meeting the eligibility criteria. However, 18 studies were recruited to analyze in full, of which 16 relevant RCTs were included in this review, the remaining two articles were excluded based on poor quality and unclear methodology. Out of 16 included trials, eight studies evaluated the effects of PT on CRP, and the remaining eight addressed CRF. The full texts of the trials were found via online search engines and directly contacting authors. The field experts were also contacted to identify any ongoing or missing trials so that no relevant data is missed. All the authors worked together as a team in the screening and review process. The trials selection is outlined in a flow diagram in figure 1.

Extraction of Data:

The information, including trials publication year, location, research design, study population, sample size, treatment applied, duration of follow-up, outcome measures, and main findings, were extracted from the trials and organized via Microsoft Excel.

Risk of Bias:

The assessment of trials' quality was evaluated via the Cochrane tool for assessing the risk of bias[21]. It analyzes biases in seven different manners: random allocation, allocation concealment, blinding of participants, outcome assessment, incomplete outcome data, selective reporting, and other biases. All the authors worked together to analyze trials for the risk of biases.

Results

All 16 trials involved 1,386 cancer patients; the majority of the participants were females with breast cancer. However, lungs, pancreatic, testicular, and other cancer patients were also included.

Effects of physiotherapy in the management of cancer-related pain and fatigue

The sample size of the eight studies related to the effects of PT on CRP was 598, with few trials reported sample size calculation. Most of the RCTs addressed breast cancer patients. However, Visual Analogue Scale (VAS), Numeric Rating Scale (NRS), and Brief Pain Inventory (BPI) were used as outcome measures in most of the trials (Table 1). The follow-up duration of the studies ranges from one to twelve months.

A great variety of PT approaches like passive mobilization, Xbox Kinect-based games, tissue massage, breathing Exs, pilates-based exercises, stretching, Range of Motion (ROM), aerobics, resistance, Manual Lymphatic Drainage (MLD), and teaching Self-administered Complex Decongestive Therapy (saCDT) were found effective in reducing CRP.

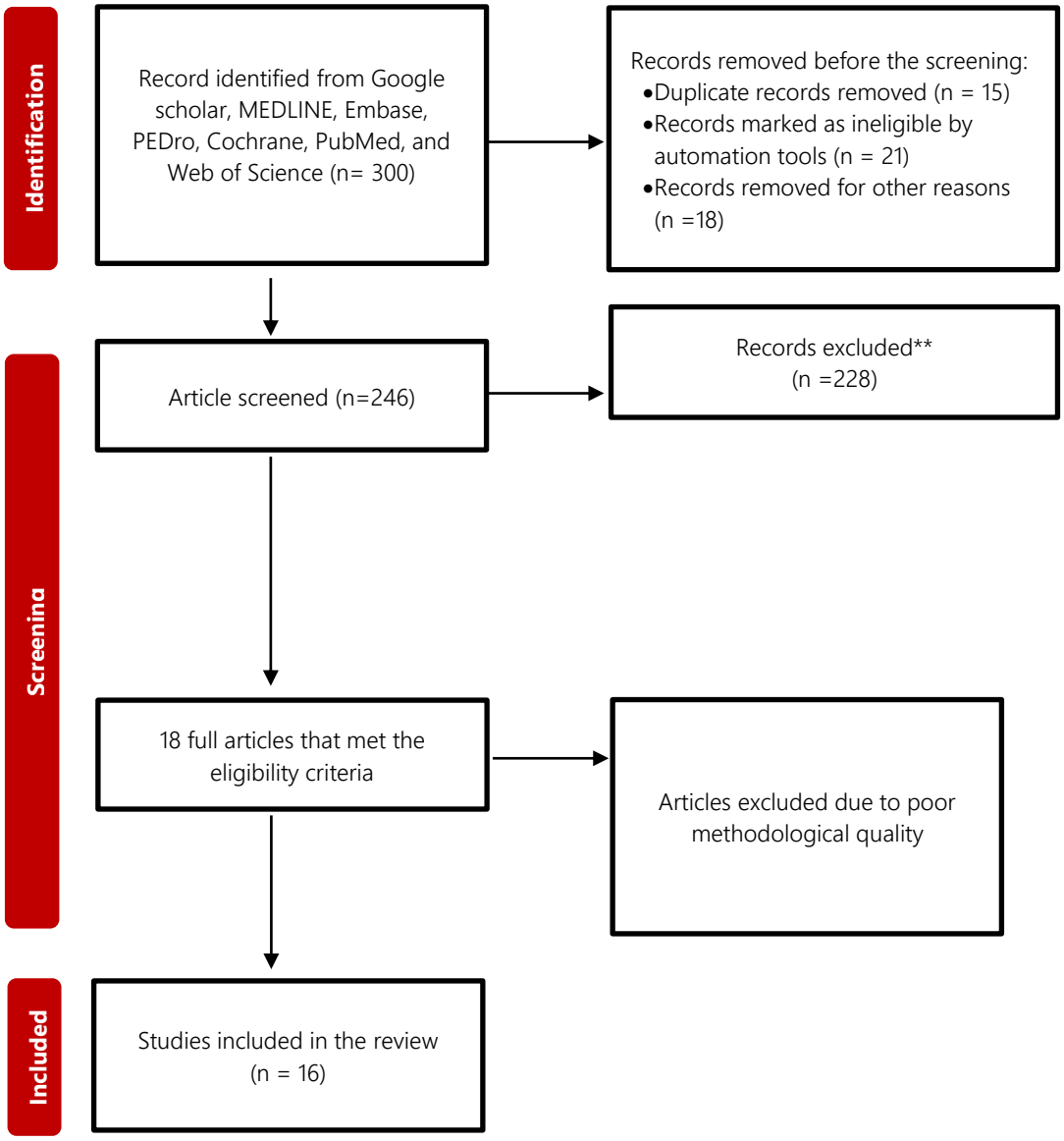

Figure 1: PRISMA 2020 flow diagram

Table 1: RCTs related to the effects of physiotherapy in the management of cancer-related pain.

Authors	Year	Study Population	Sample size	Intervention	Duration of follow-up	Outcome measure	Main finding
Feyzioglu et al.[22]	2020	BCS, females	n=40, (KBRG=20 and SPTG= 20)	KBRG= Received passive mobilization, tissue massage, and VRT via Xbox Kinect-based games that involve upper limb motion (darts, table tennis bowling, beach volleyball, boxing) and Fruit Ninja + warm-up SPTG= Received standard PT (scar tissue massage + passive mobilization) Both the groups under want the treatment for 45 min per session and 02 times a wk.	06 weeks	VAS	Both the groups reported significant changes in CRP ($p< 0.01$). However, no inter-group difference in pain was found ($p>0.05$).
Ligabue et al.[23]	2019	BCRL, females	n =41, (EG=20 and CG =21)	EG= Undergo saCDT, patients were taught self MLD, self-bandage, breathing Exs, muscle reinforcement Exs, mobilization, muscle contracture management + self-management techniques. CG= Usual care (instructions regarding specifically tuned Exs, behavioral + hygienic care)	06 months	NPRS	Teaching saCDT to patients with BCRL is significantly effective in reducing pain.
Jonsson et al.[24]	2019	LCS, both male and females	n =107, (EG=54 and CG =53)	EG= Received standard care+ pre- and post-operative PT (early mobilization, breathing Exs, Exs for thoracic and shoulder ROM) delivered one or two times/day for	03 months	NRS	Pain decreases both preoperatively and 03 months postoperatively, with half of the patients, reported no pain at rest

				10-30 minutes per session) from Monday to Saturday CG= Received standard care for mobility during ADLS not given in-hospital PT treatment.		03 months post-surgery. However, no statistically significant differences were found between the groups (P = .49).
Zengin et al.[25]	2017	BCS, females	n=57, (PEG= 19, CEG=19, HEG=19)	PEG= Pilates-based mat Exs (chest stretch, arms opening, and arm circles, etc.) and Pilates-based theraband Exs. (biceps curl, triceps pull, and rollup, etc.) CEG= Performed breathing Exs, stretching, strengthening, and ROM Exs of shoulder HEG= CEG Exs were given as a home program. All groups performed 45 minutes ex, 03 sessions per wk.	02 months	VAS	The intensity of pain ↓ significantly in all three groups (p < .001) but, pilates and combined Exs were found more effective.
Galiano et al.[26]	2016	BCS, females	n =81, (EG=40 and CG =41)	EG= Internetbased, tailored ex program warm-up + AE+ RE + cool down 90 min session, 3 days/wk. CG= Basic instructions for Ex	06 months	BPI-short form	Tele-rehabilitation via e-CUIDATE system significantly ↓ pain intensity (*P* = .001) and pain interference (*P* = .045) than usual care.
Cho et al.[27]	2016	BCS with AWS, females	n= 48, (PTG=24 and PTMLDG=24)	PTG= Warm-up, 8 stretching Exs, strength exs that include 03 pulley Exs for the upper limb, resistance-band Exs (shoulder abductor, shoulder flexor, and elbow flexor), and cool down, 03 times/wk. PTMLDG= PTG exs +30 mins of MLD daily 5 times/wk	01 months	NRS	Both groups found significant ↓ pain. However, the PTMLD group showed a more significant reduction (P<0.05)

Schmidt et al. [28]	2016	BCS, females	n =103, (EG=54 and CG=49)	EG= Received resistance ex training for 60 minutes, 03 sets of 8 to 12 repetition for 02 times/wk. CG= Relaxation exs for 60 minutes, 2 times/wk.	03 months	EORTC QLQ-C30	No statistically significant difference was found in cytokine concentrations between groups.
Irwin et al.[29]	2015	BCS, females	n=121, (EG=61 and CG=60)	EG= Supervised RE for two times/ wk. + 150 min/week home-based AE (brisk walking and cycling) CG= Usual care + education regarding cancer	12 months	BPI and WOMAC	Supervised RE and AE lead to ↓ pain (P < .001). However, the worst joint pain scores decreased by 29% in EG.

Randomized Controlled Trial (RCT), Breast Cancer Survivors (BCS), Kinect-Based Rehabilitation Group (KBRG), Virtual Reality Therapy (VRT), Standardized Physical Therapy Group (SPTG), Physiotherapy (PT), Visual Analogue Scale (VAS), Breast Cancer-Related Lymphedema (BCRL), Experimental Group (EG), Control Group (CG), Self-administered Complex Decongestive Therapy (saCDT), Numerical Pain Rating Scale (NPRS), Lung Cancer Survivors (LCS), Activities Of Daily Living (ADLS), Numeric Rating Scale (NRS), pilates- based Exercises Group (PEG), Combined Exercise Group (CEG), Home Exercise Group (HEG), Aerobic Exercises (AE), Resistance Exercises (RE), Brief Pain Inventory (BPI), Axillary Web Syndrome (AWS), Physical Therapy Group (PTG), Physical Therapy combined with Manual Lymphatic Drainage Group (PTMLDG), Manual Lymphatic Drainage (MLG), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), Western Ontario and McMaster Universities Osteoarthritis (WOMAC)

The sample size of the eight trials related to the effects of PT on CRF was 788. The study population includes testicular, pancreatic, lungs, breast, and other cancer patients. Most of the trials use the Multidimensional Fatigue Inventory (MFI) as an outcome measure. The follow-up duration of the studies ranges from point five to six months. Several PT techniques like Proprioceptive Neuromuscular Facilitation (PNF), Resistance Training (RT), aerobics, High-intensity Interval Training (HIIT), myofascial release, endurance exercises at high and low-to-moderate intensity were reported to be effective in reducing CRF compared to usual care (Table 2).

Table 2: RCTs related to the effects of physiotherapy in the management of cancer-related fatigue.

Authors	Year	Study Population	Sample size	Intervention	Duration of follow-up	Outcome measure	Main finding
Steindorf et al.[30]	2019	PCS; (males+ females)	n =65, (RTG1= 12 RTG2=31 CG=22)	RTG1= Therapist-supervised ex program facility on weight machines RTG2= Home-based manual ex training facilitated by	06 months	MFI	After 03 months, RT groups showed a significant difference in fatigue as compared to usual care (p<0.05). However, a non-

				weekly phone calls; CG=Usual care RTG1 and RTG2 exercised twice a week for 60 minutes according to the ACSM guidelines.			significant difference was reported after 06 months.
Adams et al.[31]	2018	TCS; males	n =63, (EG=35 & CG = 28)	EG= Performed warm-ups +HIIT (supervised uphill treadmill walking or running +cool-downs, 35 minutes for 3 times/wk. CG= Maintained habitual ex.	03 months	FACT-F	HIIT significantly improved CRF (p=0.003)
Dieli et al.[32]	2018	BCS; females	n =91; (EG=46 & CG= 45)	EG= Performed warm-ups + AE and RE+ cool-down on days 1 and 3 (Total 80 minutes session) and AE on day 2 (Total 30-50 minutes session) CG= Usual care	03 months	BFI	Combine AE and RE indicated great improvement in CRF (p < 0.001).
Pyszora et al.[33]	2017	Mixed, (males+ females)	n =60, (EG=30 and CG=30)	EG= Received PT program that involves active Exs + PNF+ Myofascial release for 30 minutes three times/wk. CG= Usual care	0.5 months	BFI	PT was found as a safe and effective approach for the management of CRF (*P* = 0.03)
Schuler et al.[34]	2017	Mixed, (males+ females)	n =70, (CG= 24, self-directed group=23 and partially supervised group = 23)	Self-directed group= Patients were taught AE+RE at home. Partially supervised group= Patients were taught AE+RE also received twice a wk. ambulatory PT treatment CG = Usual care	03 months	MFI	Results showed that the rate of severe general fatigue was significantly decreased in the partially supervised group as compared to other groups.

Schmidt et al.[35]	2015	BCS, females	n =95, (EG=49 and CG =46)	EG= Received 08 different machines based progressive RE training, 03 sets of 12 repetitions, 60–80%1RM CG= Received supervised relaxation ex program for 02 times/wk.	03 months	FAQ	Finding reported that RE training improves fatigue in cancer patients
Kampshoff et al.[36]	2015	Mixed, (males+ females)	n=277, (HIG= 91, LMIG= 95 and WLC= 91)	HIG= Undergo resistance and endurance Exs at high intensity two sets of 10 repetitions LMIG= Undergo endurance and resistance Exs at low-to-moderate intensity two sets of 10 repetitions. Both interventions were identical and only differed in intensity. WLC = Control	03 months	MFI	HI and LMI Exs significantly reduced physical and general fatigue in comparison with WLC. However, no statistically significant differences between the two interventions were identified.
Husebo et al.[37]	2014	BCS, females	n =67, (EG =33 and CG = 34)	EG= Home-based ex program that includes strengthening Exs (resistance bands for arms and legs) 3 times/ wk. +AE (walking) 30 min/ day during adjuvant CT CG= Encouraged to maintain their regular activity level	06 months	SCFS-6	Findings suggested that generally recommended physical activity levels are enough to relieve CRF as no statistically significant difference was found between groups.

Pancreatic Cancer Survivors (PCS), Resistance Training Group (RTG), Control Group (CG), American College Of Sports Medicine (ACSM), Multidimensional Fatigue Inventory (MFI), Resistance Training (RT), Testicular Cancer Survivors (TCS), Experimental Group (EG), High-Intensity Interval Training (HIIT), Functional Assessment Of Chronic Illness Therapy-Fatigue Scale (FACIT-F), Cancer-Related Fatigue (CRF), Breast Cancer Survivors (BCS), Aerobic Exercises (AE), Resistance Exercises (RE), Brief Fatigue Inventory (BFI), Proprioceptive Neuromuscular Facilitation (PNF), Fatigue Assessment Questionnaire (FAQ), High-Intensity Group (HIG), Low-To-Moderate Intensity Group (LMIG), Wait List Control (WLC), Chemotherapy (CT), Schwartz Cancer Fatigue Scale (SCFS-6)

Risk of bias within trials and quality appraisal

Two reviewers assessed the quality of the trials, and the third independent senior reviewer took the suggestions regarding the disagreements. All the trials showed a low risk of bias in random allocation except Cho et al.[27] reported unclear. In most studies, a high risk of bias regarding participant blinding [22-25, 28-32, 34-36] was found. While in 50% of the trial's outcome assessment, blinding had a high risk of bias [22, 25, 28- 30, 32, 34, 35]. The risk of bias could not be ensured from the method defined for other bias from some studies[27,33,35].

Synthesis of results

All the trials favor the efficacy of various PT approaches mainly, aerobic and resistance exercises, in decreasing cancer-related fatigue and pain. One study suggested that generally prescribed physical activity levels are sufficient to relieve CRF.

Table 3: Cochrane summary of the risk of bias.

Randomized Controlled Trials	Random Allocation	Allocation Concealment	Participants Blinding	Outcome Assessment Blinding	Incomplete Outcome Data	Selective Reporting	Other Bias
Trials related to the effects of PT on CRP							
Feyzioglu et al.[22]	L	L	H	H	L	U	L
Ligabue et al.[23]	L	L	H	L	L	U	L
Jonsson et al.[24]	L	L	H	L	U	H	L
Zengin et al.[25]	L	L	H	H	L	L	L
Galiano et al.[26]	L	U	L	L	L	H	L
Cho et al.[27]	U	U	L	L	L	L	U
Schmidt et al. [28]	L	L	H	H	L	L	L
Irwin et al.[29]	L	U	H	H	H	U	L
Trials related to the effects of PT on CRF							
Steindorf et al.[30]	L	H	H	H	L	H	H
Adams et al.[31]	L	U	H	L	L	L	L
Dieli et al.[32]	L	H	H	H	L	L	L
Pyszora et al.[33]	L	L	U	L	L	L	U
Schuler et al.[34]	L	H	H	H	L	L	L
Schmidt et al.[35]	L	L	H	H	H	L	U

Kampshoff et al.[36]	L	L	H	L	L	L	L
Husebo et al.[37]	L	L	U	U	L	L	L

H-high risk of bias, L-low risk of bias, U-unclear risk of bias, Higgins et al.[21]

Discussion

This SR has enlightened the effects of various PT approaches that reduce pain and fatigue related to cancer by critically analyzing the RCTs conducted over the past 08 years (January 2014 to April 2021). This comprehensive review consists of 16 trials with 1,386 cancer patients; of these trials eight, addresses the effectiveness of PT in reducing CRP and eight on CRF. Most of the population of this review consists of women with breast cancer because among all cancer types. It is one of the most common and important global health issues[38]. However, lung, pancreatic, testicular, and other cancer-type patients were also considered in this review.

The growing incidence of cancer demands a need to update and optimize the treatment approaches for cancer patients. The major challenges faced by health care providers are the management of cancer-associated symptoms. This review suggested various PT approaches like Xbox Kinect-based games, breathing exercises, stretching, ROM, tissue massage, aerobics, and resistance exercises to reduce CRP. However, Michael Bennett et al.[39] shared an interesting finding that Transcutaneous Electrical Nerve Stimulation (TENS) also reduces bone cancer pain.

Some of the findings of this present SR regarding CRF are in line with the previous review conducted in 2016 by Pattanshetty et al. suggested that aerobic exercises, resistance exercises, pilates, acupuncture, and yoga have proven to be effective in cancer survivors[40]. Similarly, one more study by Brown et al.[41] concluded exercise to be effective in improving CRF.

Another important finding of this review is that exercise is safe; however, this study supports the idea to prescribe exercise for cancer patients, and principles of exercise training must be followed along with the consideration of individual's health goals, functional and fitness level[42]. In addition to that, continuous monitoring should be done so that effectiveness of interventions could be assured, also keeping in mind precautions, contraindications, and exercise safety[43].

It is noteworthy that despite the scarcity of evidence regarding this important topic, the present review plays a vital role in reinforcing the incredible effects of PT in oncological rehabilitation. It demonstrates that PT results in clinically significant outcomes in cancer-associated symptoms management and extends patients' survival. Hence exercise prescriptions should be implemented worldwide in the management plan of cancer survivors.

This comprehensive review is the first to our knowledge to critically evaluate the effects of PT. Some of the limitations of this review were that few cancer types were addressed with the most prevalent breast cancer. Furthermore, some trials use a small sample size with a short follow-up duration. In addition, various PT techniques with different doses make it hard to generalize these outcomes to diversified cancer patients. However, despite these limitations, the findings of this review are still clinically significant.

As this particular area of research lies still in its infancy, it is recommended that further high-quality trials addressing which PT intervention, what duration, frequency, and intensity is effective for which specific type of cancer is the need of time.

Conclusion

A large body of evidence favors the effectiveness of various PT approaches mainly, aerobic and resistance exercises, in managing both cancer-associated pain and fatigue. Endurance exercises, high-intensity interval training, and myofascial

release were reported effective in reducing CRF in contrast to Xbox Kinect-based games, stretching, lymphatic drainage, and passive mobilization was found effective in reducing CRP. However, to draw reliable and robust conclusions, high-quality studies are recommended.

Conflicts of Interest

The authors have declared that no competing interests exist.

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