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# **Review Article**





# The Impact of Exercise on Fatigue among Patients Undergoing Adjuvant Radiation Therapy: A Systematic Review and Meta-analysis

Kurvatteppa Halemani<sup>1\*®</sup>, Alwin Issac<sup>2®</sup>, Prabhakar Mishra<sup>3®</sup>, Edlin Mathias<sup>4®</sup>

<sup>1</sup>College of Nursing, Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS), Lucknow, Uttar Pradesh, India <sup>2</sup>College of Nursing, All India Institute of Medical Sciences (AIIMS), Bhubaneswar, Odisha, India

<sup>3</sup>Department of Biostatistics and Health Informatics, Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS), Lucknow, Uttar Pradesh, India

<sup>4</sup>Manipal College of Nursing, Manipal, MAHE, Manipal, Karnataka, India

# Article Info

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\*Corresponding Author: Kurvatteppa Halemani, Email: kurru.hali@gmail.com

#### Abstract

**Introduction:** Cancer is a leading cause of death among all age groups. Globally, cancer patients undergo one or more treatment modules, which often bring about fatigue, depression, anxiety, and muscle weakness. Therefore, this systemic review and meta-analysis aims to investigate randomized control trials (RCTs) on this subject.

**Method:** We conducted a systemic search of studies published in PubMed, MEDLINE, CINAHL, ClinicalKey, Cochrane Library, and Google scholar, in English language between 2005-2020. Two authors independently appraised the selected RCTs for evaluating the effectiveness of physical exercise on fatigue among patients undergoing adjuvant radiation therapy (RT). This systemic review and meta-analysis was conducted based on the Cochrane risk bias assessment tool, using RevMan 5.3 software.

**Results:** A total of 1440 participants from 12 trials were involved in the systemic review, 6 trials comprised 718 participants picked for meta-analysis. Physical exercise was found an effective intervention for reducing general fatigue and physical fatigue and some other variables (e.g. anxiety, depression, pain, quality of life, and sleep pattern) among patients undergoing adjuvant radiotherapy in the treatment group as compared to the control group.

**Conclusion:** Physical exercise is an effective intervention on multidimensional fatigue among patients undergoing adjuvant RT. The studies are registered with PROSPERO and available in online.

## Introduction

Cancer is a terminal illness which has the potential for swift origination of unusual cells that develop beyond their usual edge, and which then occupy adjacent parts and organs of the body.<sup>1,2</sup> Globally, cancer is the sixth leading causal agent of death and in the year 2020, cancer was accountable for an approximate ten million death. In 2020, the worldwide cancer load is estimated to have ascended to 19.3 million novel cases and lung cancer accounts as the most common type and causative factor for cancer demise. Globally, one among 5 men and one among 6 women acquire cancer during their lifespan, and one among 8 men and one among 11 women perish to this terminal illness.<sup>3</sup>

Though novel treatments have revolutionized cancer management, the type of management that a person incurs would devolve on the type and phase of cancer. Radiation therapy (RT) uses beams of intense energy to kill cancer cells by hampering their deoxyribonucleic acid. Cancer cells whose deoxyribonucleic acid is damaged beyond mending, halt division or die.<sup>4</sup> As like other cancer treatments, RT causes side effects that vary with the type and location of cancer, dose of RT, and individual's general health. Side-effects arise from the damage to healthy cells and tissues near the treatment area. Innovational and precise advancements in RT have reduced the treatments side-effects as compared to earlier times.<sup>5</sup> Commonly reported side-effects among those undergoing RT include fatigue, sore skin, alopecia, anorexia, diarrhea, and fertility issues.<sup>6,7</sup>

Patients undergoing RT are usually affected by the scar formation in the joints, which reduces their range of motion and flexibility.<sup>8,9</sup> Physical inactivity following and during cancer treatment could lead to muscle atrophy, osteoporosis, diabetes mellitus, and heightened risk for cardiovascular diseases.<sup>10,11</sup> Exercise is an effective therapeutic intervention that has the potential to counteract the side-effects of cancer treatment, and has received due attention in the rehabilitation of oncologic patients.<sup>12,13</sup> The present day emphasis is on non-pharmacologic

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and complimentary therapies viz. aerobic exercises, meditation, and yoga improves the physical health and psychological wellbeing.<sup>14,15</sup> Exercise provides numerous beneficial outcomes viz. improved quality of life (QoL), enhanced aerobic capacity, immunologic parameters, and physical strength, and various studies have reported the role of physical exercise in cancer prevention.<sup>16,17</sup>

Fatigue is one among the most common, initial, and long-standing side-effect patients undergo during RT.<sup>18,19</sup> Almost all the patients would experience fatigue during the course of their treatment and approximately one-third will have persistent fatigue for year's post-treatment.<sup>20,21</sup> RT induced fatigue is a clinical subtype of cancer treatment related fatigue.<sup>22,23</sup> RT induced fatigue is a subjective sense of weariness prevailing over time, that interfere with the day-to-day activities of patient, deteriorates the QoL of patient and their family members, and is not alleviated by decent rest or nap.<sup>24,25</sup> Although the proposed underlying pathology of RT related fatigue is due to mitochondrial dysfunction, RT induced fatigue is underrated and undertreated side-effect.<sup>26,27</sup>

Cancer survivors are vulnerable to many of the barriers and challenges to exercise viz. embarrassment to exercise with other people, physical limitations, and being too busy with day-to-day works.28,29 Nurses and other healthcare providers are in a unique position to introduce and reinforce physical activity interventions. Counseling on physical activity recommendations could drastically reduce the adverse events following cancer treatment.<sup>30,31</sup> However, there is no clear evidence on the most effective exercise for cancer survivors. Till date, this would be the primary systematic review and meta-analysis on the impact of physical exercise on fatigue in patients receiving RT. Results of the review would furnish novel perception on the efficacy of physical exercise on fatigue among those undergoing RT. Aim of this study intended to evaluate the evidence concerning the efficacy of physical exercise on fatigue, among patients diagnosed with cancer undergoing adjuvant RT.

#### **Materials and Methods**

The systematic review and meta-analysis was registered in PROSPERO (International database of prospectively registered systematic reviews in health and social care) with the register number CRD42021227224. The quantitative systematic review and meta-analysis was adopted to assess the efficacy of physical exercise on fatigue, among patients undergoing adjuvant RT. This review was carried out based on Cochrane collaboration guidelines and reported using Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.<sup>32</sup>

Search scheme was evolved using the search or keywords connected to PICO (population or patient, intervention, comparator or control, and outcome). Dual authors separately searched databases viz. PubMed, MEDLINE, CINAHL (Cumulative Index to Nursing and Allied Health Literature), ClinicalKey, Cochrane Library, and Google Scholar for studies published in between 2005-2020. Authors searched for RCTs that employed physical exercise as an intervention among patients undergoing adjuvant RT. MeSH (Medicals Subject Heading) terms and free keywords that were used during online search were: radiation therapy, cancer treatment, physical exercise, aerobic exercise, regular exercise, resistance exercise, muscle stretching, fatigue, tiredness, and exhaustion. The references of relevant trials and systematic reviews that matched review criteria were manually searched. After screening the titles and abstracts, twinned records and trials were removed. Left over full text articles were screened as per the inclusion criteria. The participants were patients diagnosed with cancer receiving adjuvant RT, who had a random allocation to either a treatment group which received physical exercise as intervention, or a control group where received usual care. The studies were selected based on the study characteristics and eligibility criteria namely, RCTs published in English language from 2005-2020, studies conducted after ethical committee clearance, exercise as the intervention among the interventional group, and fatigue as the primary outcome assessed.

Search scheme retrieved 1440 studies from various databases, and 5 studies from printed materials. During initial screen 164 twinned articles were discarded. 1260 articles were removed after screening titles and abstract, as they didn't meet the criteria of the review using predetermined inclusion and exclusion criteria. After screening the full text of the remaining articles, 9 studies were discarded as they did not match PICO statement of the systematic review and meta-analysis. Finally, 12 trials were selected for quantitative and narrative synthesis, and 6 trials were included for meta-analysis<sup>33-38</sup> (Figure 1).

The participants in the experimental group received physical exercise interventions, whereas control group

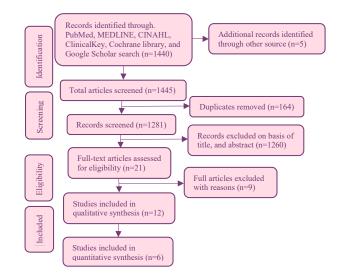


Figure 1. Preferred reporting items systemic review and meta-analysis (PRISMA) flowchart.

received usual routine care or usual treatment of the hospital. Fatigue was the primary outcome of our systemic review and meta-analysis. However, authors also evaluated secondary outcomes viz. anxiety, depression, pain, quality of life, and sleep pattern. Two authors independently extracted the data from the included trials and any dissimilarity between the first two authors was resolved in discussion with a third reviewer. The data extraction process was carried out based on the data extraction form: author name, country, year of publication, sample size, type of cancer, type of treatment, instrument, primary outcome, and secondary outcomes. Methodological quality of trials was assessed by Cochrane's collaboration's "risk of bias tool." The tool contains six items: 1: sequence generation, 2: allocation of concealment, 3: blinding of participants and personnel, 4:blinding of outcome assessment, 5:completeness of reported data, and 6:selective reporting.<sup>39,40</sup> After appraising, studies were categorized into low risk, high risk and unclear risk of bias (Figure 2).

The quality of included trials were appraised by Cochrane risk of bias assessment tool.<sup>40</sup> The tool comprised six quality items, of which majority of studies met all criteria except performance bias. Due to nature of intervention and outcome measures (instruments used for data collection), most of the studies reported 'high risk bias' on blinding of participants and personnel (performance bias) (Figure 2).

The RCTs involved in this review used multidimensional fatigue scales and questionnaires: Multidimensional Fatigue Inventory (MFI),<sup>37,41</sup> Brief Fatigue Inventory (BFI),<sup>42,43</sup> Fatigue Assessment Questionnaire (FAQ),<sup>33,38</sup>

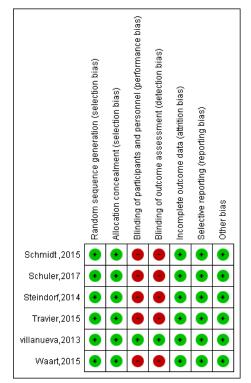


Figure 2. Summary of risk of bias assessment.

Functional Assessment of Cancer Therapy Fatigue (FACT-F),<sup>44,45</sup> Piper Fatigue Scale (PFS),<sup>36</sup> and Fatigue Symptom Inventory (FSI).<sup>46</sup> The multidimensional fatigue questionnaires measured general fatigue, physical fatigue; all multidimensional questionnaires scores were directly in proposition to fatigue (high scores indicate increased fatigue). The post-intervention outcome was measured in two stages (3 and 6-months post physical exercise interventions). A few studies reported six-month post intervention outcomes: general fatigue,<sup>34,35,38</sup> mental fatigue,<sup>34,37</sup> affective fatigue,<sup>36</sup> and cognitive fatigue.<sup>36</sup>

Fatigue was the primary outcome assessed in our systemic review and meta-analysis. Scores of fatigue was compared between patients in the intervention and control group. Intervention group received physical exercise, whereas control group given as usual care; except in two studies participants received relaxation technique.33,38 Meta-analysis was done after pooling the results of RCTs. Effects of physical exercise was evaluated by using a random-effects model to compute weighted mean differences, and standardized mean differences between intervention and control group. The standardized mean difference was calculated after adjusting standard deviation. Heterogeneity between the studies was ruled out by using I<sup>2</sup> test. Heterogeneity considered based on I<sup>2</sup> value namely < 25%, 25-75%, and > 75% as low, moderate, and high heterogeneity respectively. Similarly, chi-square test was used for subgroup analysis. RevMan software version 5.3 used for computing and analysis of pooled data. In-order to provide quality of evidence, Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach and guidelines was adopted.<sup>47</sup> The outcome measures are presented in Table 1 and Figures 3 & 4.

## Results

The systematic review and meta-analysis involved 1440 participants from 12 experimental studies, of which 721 participants were in the intervention group and 719 subjects in the control group. The overall sample size ranged from 45 to 222, the mean (SD) of all participants ranged from 45 (8) to 66.3 (7). Majority of the participants were diagnosed with breast cancer, except in three trials, wherein participants were diagnosed with other malignancies.<sup>34,43,44</sup> As part of cancer treatment, majority of the participants were exposed to RT followed by chemotherapy or vice-versa. Fatigue was the primary outcome of all included trials, and fatigue was measured by multi-dimensional fatigue questionnaires and fatigue scales. Physical exercise comprises the aerobic exercise, resistance exercise, and aquatic exercise.<sup>36</sup> Notably, first intervention was given during RT or chemotherapy. Total duration of the intervention ranged from 3-26 weeks. Physical exercise session ranged from 15-60 minutes

## Table 1. Characteristic of studies in the review

Author, Country (year)	Type and mode of	<b>C 1 1</b>		Intervention	Duration of	0.1	
	exercise	Sample size	Duration of Session of intervention exercise/week			follow up fatigue outcome	Outcome measure
Segal et al, <sup>44</sup> Canada (2009)	Resistance and aerobic exercise program under supervision	$T^a = 81$ $I^b = 40$ $C^c = 41$	Started during RT to 24 weeks (24 weeks)	15-45 minutes per week	UC	Immediate after completion of intervention and 24 weeks	Decreased general fatigue (P=0.01)
Carayol et al,41 France (2019)	Resistance exercise program (APAD) under supervision	T=143 I=72 C=71	Started during RT or CT to 26 weeks (26 weeks)	150 minutes per week	UC	Immediate after completion of intervention, 6-month and 1-intraval	Decreased general fatigue (ES = $0.28$ ), anxiety, (ES = $-0.24$ ) & depression, (ES = $-38$ ) (Negative ES in favor to exercise)
Steindorf et al, <sup>38</sup> Germany (2014)	Resistance exercise program under supervision	T=155 I=77 C=78	Started during first day of RT to 12 weeks (12 weeks)	60 minutes/2 times	Relaxation exercise	13 weeks (post intervention)	Decreased general fatigue ( $P$ =0.044), pain ( $P$ =0.040) & improve Qol ( $P$ =0.035)
Travier et al, <sup>35</sup> Netherlands (2015)	Resistance and aerobic exercise program under supervision	T=182 I=93 C=89	Started after 6 weeks of diagnosis to 18 weeks (18 weeks)	60 minutes/2 times	UC	18 weeks (after intervention)	Decreased general fatigue (ES = -0.23) physical fatigue (ES = -0.30) (Negative ES in favor to exercise)
Courneya et al, <sup>45</sup> Canada (2007)	Resistance and aerobic exercise program under supervision	T=160 I=78 C=82	Intervention 1 <sup>st</sup> or 2 <sup>nd</sup> week of cancer treatment to 18 weeks (18 weeks)	15-45 minutes per 2-3 times weeks	UC	Immediate post intervention and 6 months follow the intervention.	QoL, fatigue, depression, and anxiety favored the exercise groups
Rogers et al, <sup>46</sup> USA (2017)	Better exercise adherence after treatment for cancer under supervision	T=222 I=110 C=112	The first intervention started after completion of primary cancer treatment to 12 weeks (12 weeks)	30-60 minutes per week	UC	Immediate after completion of intervention and 3 months follow the intervention.	Decreased mental fatigue ( $P$ =0.02), fatigue interference ( $P$ =0.01), depression ( $P$ =0.01), and anxiety ( $P$ =0.01)
Schuler et al, <sup>34</sup> Germany (2017)	Resistance exercise like walking, bicycling, or running under supervision	T=47 I=24 C=23	Started during or after completed or within 3 months of treatment to 12 weeks (12 weeks)	20-30 minutes/2 times	UC	12 weeks (after intervention)	Decreased general fatigue ( $P = 0.00$ ), physical fatigue ( $P = 0.00$ ), mental fatigue ( $P = 0.01$ ), and reduce activities, motivation & anxiety ( $P = 0.01$ )
Cantarero- Villanueva et al, <sup>36</sup> Spain (2013)	Aquatic exercise; warm up, aerobic and cool down exercise	T=61 I=32 C=29	The first intervention started after 18 weeks of cancer treatment. (8 weeks.)	60 minutes/3 times	UC	Immediate after completion of intervention and 6 months.	Decreased total fatigue $(P=0.02)$ , affective fatigue cognitive fatigue, and sensory fatigue $(P < 0.01)$
Schmidt et al, <sup>33</sup> Germany (2015)	Resistance exercise program under supervision	T=95 I=49 C=46	The first intervention started 1 <sup>st</sup> or 2 <sup>nd</sup> cancer treatment, to 12 weeks (12 weeks)	60 minutes/2 times	Relaxation exercise program	Post intervention at 13 weeks	Exercise reduced physical fatigue and stabilized QoL during chemotherapy
van Waart et al <sup>37</sup> Netherlands (2015)	Resistance exercise program under supervision	T=153 I=76 C=77	The first intervention started during first CT cycle continued until 3 weeks after the last cycle(3weeks)	50 min minutes/2 times	UC	Post intervention at 13 weeks (approximately 6 months from 1 <sup>st</sup> intervention)	Reduce general fatigue $(P=0.04)$ Physical fatigue $(P=0.01)$ , reduce activity $(P=0.04)$ , reduce motivation $(P=0.04)$
Chen al, <sup>42</sup> China (2013)	Qigong (Chines exercise) program under supervision	T=96 I=49 C=47	The first intervention started during RT cycle continued until 5-6 weeks(5-6 weeks)	40 minutes per week	UC	Immediate post intervention, 4 weeks, 12 weeks & end of RT	Reduced fatigue ( $P < 0.05$ ), depression ( $P < 0.01$ ), improve QoL ( $P < 0.05$ )
McQuade et al, <sup>43</sup> USA (2017)	Qigong (Chine' exercise) tai program under supervision	T=45 I=21 C=24	The first intervention started during RT cycle continued until 5-6 weeks	40 minutes per week	UC	Immediate post intervention, 4 weeks, 12 weeks & end of RT	Increased sleep duration $(P < 0.03)$ , and reduce fatigue $(P < 0.00)$ with QoL

Abbreviations: RT, Radiation therapy; APAD, adapted physical activity and diet counseling; ES, Effect size; QoL: Quality of life. <sup>a</sup> Total; <sup>b</sup> Intervention group; <sup>c</sup> Control group.

	Exercise		Usual care				Std. Mean Difference	Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1.1.1 General fatigue									
villanueva,2013	3.7	1.7	32	5.7	1.6	32	3.7%	-1.20 [-1.73, -0.66]	_ <b>—</b>
Waart,2015	11.8	3.6	76	13.1	3.9	76	5.7%	-0.34 [-0.67, -0.02]	
Travier,2015	9.1	3.7	102	10.1	4.3	102	6.3%	-0.25 [-0.52, 0.03]	
Steindorf,2014	5.4	2.3	77	5.9	2.2	77	5.8%	-0.22 [-0.54, 0.10]	
Schuler,2017	9.4	4.9	23	9.9	3.5	23	3.4%	-0.12 [-0.69, 0.46]	<u> </u>
Schmidt,2015		20.6	49		19.2	49	4.9%	-0.01 [-0.41, 0.38]	
Subtotal (95% CI)	00.1	20.0	359	00.1	10.2	359	29.8%		•
Heterogeneity: Tau <sup>2</sup> =	0.0610	hi <b>≊</b> – 1		- 6 (P -	- 0.02				•
Test for overall effect:			•	- 0 ()	0.02	,,, = 0,			
1.1.2 Physical fatigue	)								
Waart,2015	9	4	76	11.7	4.2	76	5.7%	-0.66 [-0.98, -0.33]	
Travier,2015	8.6	4.4	102	9.9	4.3	102	6.2%	-0.30 [-0.57, -0.02]	
Steindorf,2014	5	2.8	77	5.7	2.7	77	5.8%	-0.25 [-0.57, 0.06]	
Schuler,2017	9.3	5	23	10.1	4	23	3.4%	• • •	
Schmidt 2015	39.9	25	49		24.5	49	4.9%		_ <b>_</b>
Subtotal (95% CI)			327			327	26.0%		•
Heterogeneity: Tau² = Test for overall effect: .				= 4 (P =	0.15);	l² = 40'	%		
1.1.3 Mental fatigue				_					
Schuler,2017	6.5	2.6	23	8	4.1	23	3.3%	-0.43 [-1.01, 0.16]	
Waart,2015	10.1	3.5	76	10.5	4	76	5.8%		
Travier,2015 Subtotal (95% CI)	9.8	4.8	102 201	9.8	4	102 <b>201</b>	6.3% <b>15.4%</b>		•
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: .				= 2 (P =	0.42);	l² = 0%			
1.1.4 Affective fatigue	,								
villanueva,2013	3.8	2.3	32	6.8	2	32	3.6%	-1.38 [-1.92, -0.83]	<u> </u>
Steindorf,2014	5.3	2.6	77	5.8	2.7	77	5.8%	-0.19 [-0.50, 0.13]	-+
Schmidt ,2015		23.5	49		21.9	49	4.9%	-0.10 [-0.50, 0.29]	
Subtotal (95% CI)	20.0	23.3	158	23.2	21.9	158	4.9%	• • •	
Heterogeneity: Tau <sup>2</sup> =	0.2010	hiZ – 4		- 2/0	- 0.00			-0.02 [-1.10, 0.10]	
Test for overall effect: .				- 2 (P'	- 0.00	04), 1° =	0/70		
1.1.5 cognitive fatigue	e								
villanueva,2013	3.7	1.8	32	5.6	2.2	32	3.8%	-0.93 [-1.45, -0.42]	<u> </u>
Schmidt 2015		25.3	49		25.1	49	4.9%		-+
Steindorf,2014	4.9	3.2	77	4.9	3	77	5.8%	0.00 [-0.32, 0.32]	_ <b>_</b>
Subtotal (95% CI)			158		Ŭ	158	14.5%		
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: .			19, df=	= 2 (P =	0.01);				
Total (95% CI)			1203			1203	100.0%	-0.30 [-0.44, -0.17]	•
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: . Test for subgroup diffe	Z = 4.34	↓ (P < 0	).0001)						-2 -1 0 1 2 Exercise Usual care

Figure 3. Meta-analysis on effectiveness of physical exercise for fatigue dimensions in threemonths.

for 1-3 times per week. Post intervention outcome was measured between three and six months.

We involved six trials, comprising 718 participants for meta-analysis to evaluate the efficacy of physical exercise. This included 359 participants in the intervention group, and remaining 359 participants were in the control group.<sup>33-38</sup> Although fatigue was primary outcome, it was further sub classified into general fatigue, physical fatigue, mental fatigue, affective fatigue, and cognitive fatigue. We used forest plots with summary for evaluating the effectiveness of physical exercise on fatigue among cancer patients. The effect of physical exercise was measured in three months and six months of post-intervention (Figure 3 and 4).

The summary of the forest plot after three months of intervention showed that physical exercise was significant

and effective intervention for reducing general fatigue

(SMD: -0.33; 95% CI: -0.58, -0.07; P = 0.01;  $I^2 = 63\%$ ) and physical fatigue (SMD: -0.31; 95% CI: -0.51, -0.10; P = 0.00;  $I^2 = 40\%$ ) (Figure 5).

Other fatigue dimensions such as mental fatigue (SMD: -0.09; 95% CI: -0.28, 0.11; P=0.38;  $I^2=00\%$ ), affective fatigue (SMD: -0.52; 95% CI: -1.19, -0.15; P=0.13;  $I^2=87\%$ ) and cognitive fatigue (SMD: -0.34; 95% CI: -0.84, -0.16; P=0.19;  $I^2=78\%$ ) are effective towards the exercise but clinically wasn't found significant. The total heterogeneity of multidimensions fatigue was (SMD: -0.34; 95% CI: -0.84, 0.16; P=0.00;  $I^2=63\%$ ). However, subgroup analysis of multidimension fatigue was not statistically significant ( $\chi^2=3.97$ , df=4, P=0.41) (Figure 3).

Similarly, six months post-intervention assessment data showed that physical exercise as an effective intervention

		ercis	-	Usual care			Std. Mean Difference	Std. Mean Difference	
Study or Subgroup		SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.1.1 General fatigue		~		E 17	4.0		7.00	0.7014.07 0.071	
villanueva,2013 Waart,2015	4	2 3.5	32 76	5.47 10	1.8	32 76	7.0% 11.7%	-0.76 [-1.27, -0.25] -0.29 [-0.61, 0.03]	
rvaan,2015 Travier,2015		3.5 4.5	102	10.1	4.6 4.3	102	13.1%	-0.29 [-0.81, 0.03] -0.20 [-0.48, 0.07]	
Schuler,2017		4.9	23	9.9	4.5	23	5.9%	-0.12 [-0.69, 0.46]	
Subtotal (95% CI)	3.4	4.3	233	9.9	3.0	233	37.7%	-0.31 [-0.53, -0.09]	•
Heterogeneity: Tau <sup>2</sup> =	0.01: C	hi² =	4.05. d	f = 3 (P =	= 0.26				-
Test for overall effect:									
1.1.2 Physical fatigue	e								
Steindorf,2014	8.2	4.1	76	9	4.7	76	11.7%	-0.18 [-0.50, 0.14]	
Schuler,2017	9.3	5	23	10.1	4	23	5.9%	-0.17 [-0.75, 0.41]	-+-
Travier,2015	9.4	5	102	9.9	4.3	102	13.1%	-0.11 [-0.38, 0.17]	-
Subtotal (95% CI)			201			201	30.7%	-0.14 [-0.34, 0.05]	•
Heterogeneity: Tau² =	•			f= 2 (P =	= 0.94	); I² = 0	)%		
Test for overall effect:	Z=1.42	2 (P =	0.15)						
1.1.3 Mental fatigue									
Schuler,2017		2.6	23	8	4.1	23	5.8%	-0.43 [-1.01, 0.16]	
Naart,2015	10.1	3	76	9.7	4.2	76	11.7%	0.11 [-0.21, 0.43]	±
Subtotal (95% CI)			99	=		99	17.5%	-0.10 [-0.62, 0.41]	-
Heterogeneity: Tau² = Test for overall effect:				r=1 (P=	= 0.11	);	10%		
1.1.4 Affective fatigu	e								
villanueva,2013	4.4	2.4	32	6.47	2.2	32	6.9%	-0.89 [-1.40, -0.37]	
Subtotal (95% CI)			32			32	6.9%	-0.89 [-1.40, -0.37]	◆
Heterogeneity: Not ap	•								
Fest for overall effect:	Z = 3.38	3 (P =	0.0007	7)					
1.1.5 Cognitive fatigu	е								
villanueva,2013	3.69	1.9	32	5.09	2.3	32	7.1%	-0.66 [-1.16, -0.15]	
Subtotal (95% CI)			32			32	7.1%	-0.66 [-1.16, -0.15]	◆
Heterogeneity: Not ap	•								
Test for overall effect:	Z = 2.55	5 (P =	0.01)						
Total (95% CI)			597			597	100.0%	-0.29 [-0.45, -0.12]	•
Heterogeneity: Tau <sup>2</sup> =					P = 0	.04); I²:	= 48%		
Fest for overall effect:				r .					Exercise Usual care
est for subaroup diff	erences	s: Chi	<sup>z</sup> = 9.92	2. df = 4	(P = 0	1.04), I <sup>z</sup>	= 59.7%		

Figure 4. Meta-analysis on effectiveness of physical exercise for fatigue dimensions in six months.

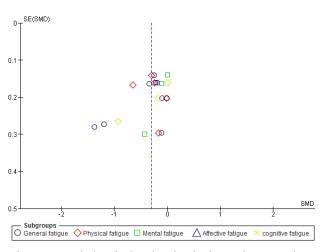


Figure 5. Funnel plot of selected studies for fatigue dimensions three months of postintervention Standard Mean Difference (SMD).

for reducing general fatigue (SMD: -0.31; 95% CI: -0.53, -0.09; P=0.00; I<sup>2</sup>=26%), affective fatigue (SMD: -0.89; 95% CI: -1.40, -0.37; P=0.00) and cognitive fatigue (SMD: -0.66; 95% CI: -1.6, -0.15; P=0.01) (Figure 6).

Although dimensions of physical fatigue (SMD: -0.14; 95% CI: -0.34, -0.05; P = 0.15,  $I^2 = 0\%$ ) and mental fatigue

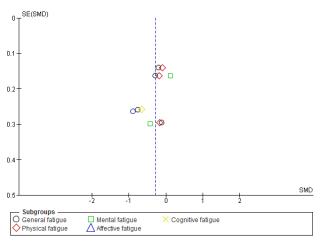


Figure 6. Funnel plot of selected studies for fatigue dimensions six months of post-intervention Standard Mean Difference (SMD).

(SMD: -0.10; 95% CI: -0.62, 0.41; P=0.70,  $I^2=60\%$ ) are reduced post-intervention fatigue scores, but it was not proved statistically significant. The total heterogeneity of multidimensions fatigue was (SMD: -0.29; 95% CI: -0.45, -0.12; P=0.00,  $I^2=48\%$ ). Even though, subgroup analysis multidimension fatigue was statistically significant

# $(\chi^2 = 9.92, df = 4, P = 0.04)$ (Figure 4).

Findings of our meta-analysis reveals that performing exercise from the initial day of chemotherapy up to 3 months of chemotherapeutic intervention, is found to be statistically significant in reducing the general fatigue and physical fatigue among cancer patients. Similarly, exercise is an effective intervention on mental fatigue, affective fatigue, and cognitive fatigue; but there was no statistical significance. With the findings of our study, we assume that are numerous factors contributing to cancer related fatigue during radiotherapy or adjuvant radiotherapy among cancer patients. Similarly, individual differences may influence fatigue scores with exercise. Performing exercise from the initial day of chemotherapy up to 6 months of chemotherapeutic intervention, has a statistical significance on fatigue dimensions namely general fatigue, affective fatigue, and cognitive fatigue. Although physical fatigue and mental fatigue were sensitive to physical exercise, it was not statistically significant. Individual fatigue dimensions to physical exercise rely on exercise and patient treatment. Therefore, in order to enhance the overall well-being of patients during adjuvant treatment, it is important to make a distinction between type of exercise, treatment, and fatigue dimensions accordingly.

Begg's and Egger's test was used to find any publication bias. We have not found any publication bias [P > 0.53,  $\beta 1 = 0.33$ , SE of  $\beta 1 = 0.63$ ] i.e., when P value is more than 0.05 implicates low publication bias.

## Discussion

The result of this systematic review and meta-analysis revealed physical exercise as an effective intervention in general and physical fatigue, among cancer patients undergoing adjuvant radiotherapy. Fatigue is one among the major issue reported by the cancer patients, especially those patients who are seeking adjuvant RT. Radiation beams may harm the normal cells, due to which the majority of patients exhibit the various level of physical and mental symptoms. However, early screening, proper treatment, and rehabilitation may alleviate these symptoms. Many studies have reported physical exercise as an effective intervention for RT-related fatigue. For instance, physical exercise with appropriate supervision would have beneficial effects on fatigue in patients undergoing RT.<sup>39,48</sup>

Our meta-analysis included RCTs which were registered in clinical trials registry [(EK 280092012)<sup>34</sup> (NCT01468766)<sup>49</sup> (NCT01106820)<sup>33</sup> (NTR2159)<sup>37</sup> (NTR2138)<sup>35</sup>]. Although one of the study did not report their clinical trial registry number, in their manuscript they have mentioned about the clinical trial registration.<sup>36</sup> All the included studies had used physical exercise as the intervention and its effect on fatigue was the primary outcome assessed (Table 1, Figures 3 & 4).

Findings in our systematic review and meta-analysis differ from the previous meta-analysis on the effect of

physical exercise on fatigue among patients undergoing adjuvant RT. Since patient's complains of fatigue and the level of fatigue varies as cancer treatment progresses, we evaluated the efficacy of exercise on fatigue and variations in fatigue dimensions at three months and six months intervals.

When pooled data for analysis, we investigated more details of each studies for effectiveness of physical exercise on fatigue dimensions. Our review findings are derived from recent published studies in high indexed journals, and most of the included studies were conducted in developed countries. Therefore, our study result is more sensitive and yielding the highest evidence in the hierarchy. Previous studies have recommended that relaxation techniques namely yoga, and other pharmacological interventions as an effective intervention for cancer-related fatigue.<sup>50-52</sup> Our review findings favor physical exercise as probably the most sensitive intervention for reducing cancer-related fatigue.

For instance, there is seldom of evidence on specific physical exercise to reduce cancer-related fatigue. Therefore, timing and duration of exercise should be fixed based on the patient severity and type of treatment. Other than for fatigue, the physical exercise is effective in managing insomnia, depression, anxiety, pain, and in improving the quality of life.<sup>43,45</sup>

On comparing existing evidences on effectiveness of physical exercise among cancer patients, findings of our systematic review and meta-analysis emphasizes the necessity of involving physical exercise in clinical practice to lessen multidimensional fatigue among cancer patients undergoing RT. Nevertheless, physical exercise alone may not alleviate cancer-related fatigue. Therefore, additional studies are warranted to determine the effect of physical interventions on specific cancer treatment, type of cancer and that could improve the health status of cancer patients. However, at present many breast cancer specialists widely recommend aerobic exercise for breast cancer patients who are undergoing RT, which helps to strengthen shoulder muscle and maintain a good range of movements. Additionally, further RCTs may be conducted to explore the effectiveness of exercise on treatment related multidimensional fatigue among cancer patients.

## Conclusion

Findings of our meta-analysis concluded that physical exercise was significant for reducing general fatigue, physical fatigue, mental fatigue, affective fatigue, and cognitive fatigue. Physical exercise was also found to reduce the anxiety, depression, pain, and enhanced the sleep and quality of life, of patients undergoing adjuvant RT. There is limited sound RCTs published in the English language to assess the effectiveness of specific physical exercise among patient undergoing RT; therefore, it is challenging to conclude the effectiveness of a particular physical exercise in reducing fatigue dimensions among

# **Research Highlights**

# What is the current knowledge?

There are RCTs that have ascertained the efficacy of exercise on cancer-related fatigue, however, there are no meta-analysis done on the efficacy of exercise on fatigue dimensions.

# What is new here?

This systematic review and meta-analysis of RCTs generate a strong evidence for physical exercise as the most sensitive intervention in reducing cancer-related fatigue.

patients undergoing adjuvant RT. Therefore, vigorous RCTs are needed in the future for sound evidence on the effectiveness of physical exercise on fatigue among patients undergoing adjuvant RT.

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#### **Authors' Contributions**

KH: Conceptualization; KH, AI, PM, EM: Data curation; KH, PM, EM: Visualization; KH, AI: Writing-original draft; KH, AI, EM: Writing- review & editing. All authors have read and agreed on the final version of the manuscript.

#### **Ethical Issues**

This project being a systematic review and meta-analysis, did not require an ethical approval as no direct information or intervention were performed on humans.

#### **Conflict of Interest**

The authors declare no conflict of interest in this study.

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