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Assessment and Physiotherapeutic Interventions in Cancer-Related Fatigue among Breast Cancer Survivors: A Narrative Review

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Abstract
Globally, breast cancer is considered one of the most common types of cancer among women. The National Institute of Health in collaboration with the National Coalition for Cancer Survivorship defines cancer survivors as an individual from the time of cancer diagnosis, through the balance of his or her life. Cancer-related Fatigue (CRF) is described as the distressing side effects of cancer and its treatment associated with physical, mental, and emotional manifestations including generalized weakness, diminished concentration, or attention, decreased motivation or interest to engage in normal activities and emotional lability. There are several validated tools for measuring cancer-related fatigue. The search for the relevant journal was carried out referring through many databases: PubMed, PubMed Central, Cochrane, and PEDro and mainly focuses on the RCTs, clinical trials, and systemic reviews. There are varieties of physical therapy interventions that play a beneficial role in reducing Cancer-related Fatigue followed by improvement in the physical activities, functional status thereby enhancing the lifestyle & quality of life among breast cancer survivors. These interventional programs will only be effective if the patient strictly adheres and follow the pre-designed exercise protocols referring through many guidelines for an effective outcome. The purpose of this research is to identify various effective assessment and physiotherapeutic interventions according to evidence-based studies on cancer-related fatigue among breast cancer survivors.
Keywords: Breast cancer survivors, Cancer-related fatigue, physiotherapy interventions

Abbreviations
ACS: American cancer society.
BCS**:** Breast cancer survivors
BPI: Brief pain inventory.
CPEN: Cancer Patient Educator Resources
CRF: Cancer-related fatigue.
EBCAM: Evidence-Based complementary and alternative Medicine

EBM: Evidence-based medicine.
ECSI: Energy conservation strategies inventory.
EORTC-QLQ-BR23: European organization for research and treatment: Breast-Cancer specific module.
EORTC-QLQ-C30: European organization for research and treatment: Quality of life: C-30 Questionnaire.
FACIT-FATIGUE SCALE: Functional assessment of chronic illness therapy- fatigue Scale
GLOBOCAN_GCO: Global cancer_Global cancer observatory
HADS: Hospital anxiety and depression scale.
HPC: Hindawi Publishing Corporation
HRQOL**:** Health-related quality of life.
MET: Metabolic equivalent task.
MFR**:** Myofascial release.
MNA: Mini nutritional assessment questionnaire.
MOSS-SS: Medical outcome study-sleep scale.
NCCN: National comprehensive cancer network.
NIH: National Institute of health.
NLM: National library medicine
PMC: PubMed Central.
PROMIS FATIGUE SCALE: Patient reported outcome measurement information system fatigue scale.
Qol: Quality of life.

Introduction

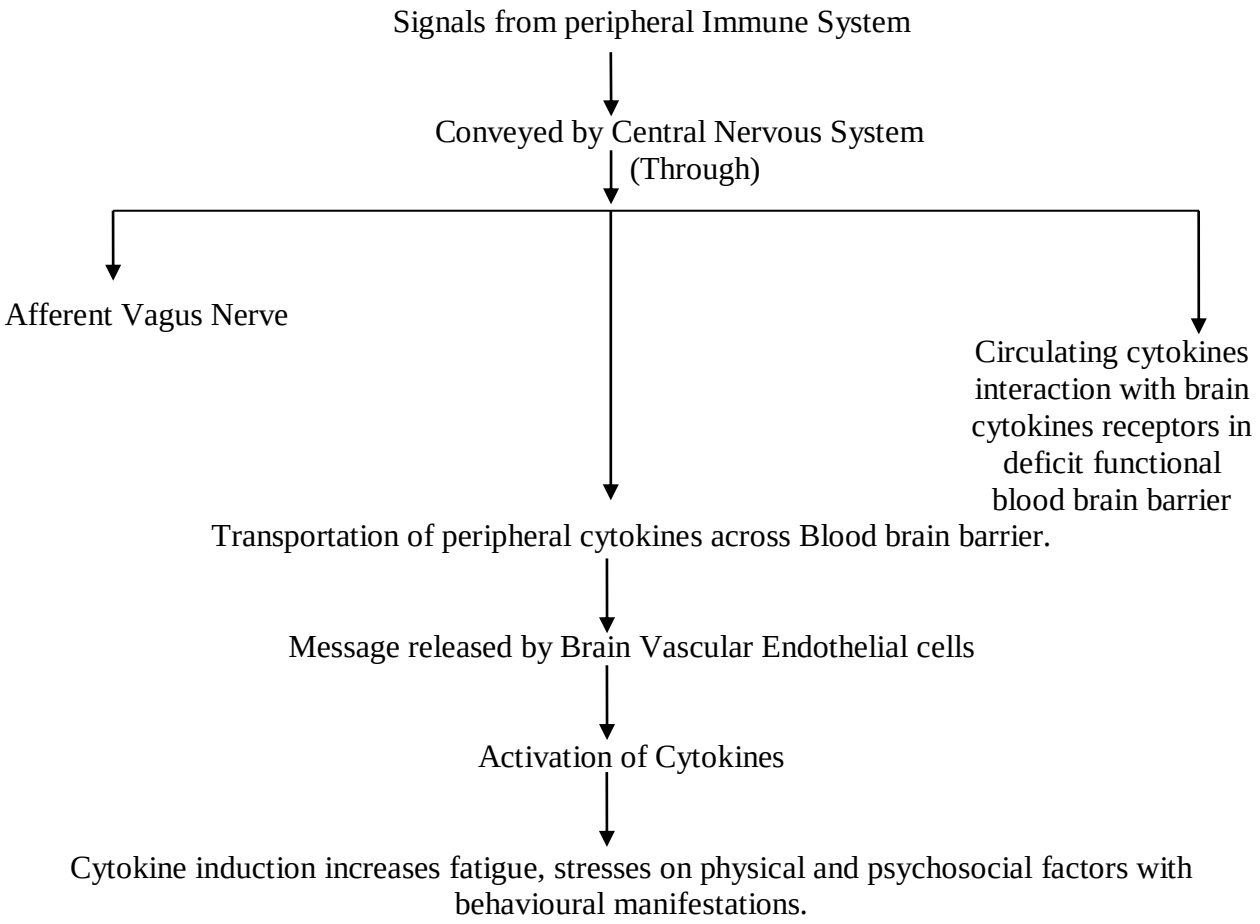
Globally, breast cancer is considered as one of the most common types of cancer among women. [1]
The GLOBOCAN -2018 estimated a cancer burden of 18.1 million with 2, 088, 849 cases of breast cancer, and 9.6 million deaths worldwide for both sexes, and all ages, respectively. The incidence of cancer is 48.4% in Asian countries and 21.0% within the United States of America.[2] The 5-year survival rate of women suffering from breast cancer is 99% with 62% diagnosed within this stage, while 47% diagnosed at early age of 15-39 years as compared to women older than 65 (68%). This difference might be due to delay in screening process.[3] The National Institute of Health in collaboration with the National Coalition for Cancer Survivorship defines cancer survivors as an individual from the time of cancer diagnosis, through the balance of his or her life. [4], [5] The National Comprehensive Cancer Network (NCCN) explained Cancer related fatigue as an upsetting, constant, subjective sense of physical and psychosocial exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning. The patient reports this persistent fatigue with the ongoing treatment, continue during radiation treatment/ chemotherapy, decline somewhat, and continue at a higher than the baseline rate after the treatment. It may also persist for several years in patients with no apparent disease. [6] The incidence rate of CRF during the treatment ranges from 25% to 99% depending on the sample and method of assessment and in most studies 30% to 60% of patients report moderate or severe fatigue symptoms. [7] The factors that contribute to CRF are 1) Physical factors a) Cancer burden b) Treatment side effects (Chemotherapy, radiotherapy, surgery, etc) c) Comorbid medical conditions (Chronic pain, Anemia, etc). [8], [9], [10] 2) Psychosocial factors (Anxiety, depression, coping with chronic illness, sleep disturbances, less food consumption, etc). The non-pharmacological approaches exercise act as an adjunct therapy in reducing burden related to fatigue among breast cancer patients and add support in the oncology Rehabilitation. [14] The

purpose of this research is to identify various effective assessment and physiotherapeutic interventions according to evidence-based studies on cancer-related fatigue among breast cancer survivors.

Mechanism of Cancer Related Fatigue (CRF)

The evidence over past two decades suggested that the pathophysiology of CRF focuses on anemia, cytokine dysregulation (mostly observed with focus on pro-inflammatory cytokines), Hypothalamic-pituitary-adrenal (HPA) axis dysregulation, 5 hydroxy tryptophan (5-HT) neurotransmitter dysregulation, and alterations in adenosine triphosphate, etc. The most observed CRF during cancer treatment targets on the activation of neural immune system by the mechanism of bioactive mediator Peripheral Inflammatory Cytokines [11] as shown in the **[Flow Chart-1]**

[Flowchart 1] Mechanism of CRF [11]



Several studies contributed that physical and psychosocial factors are strongly correlated with fatigue followed by cancer treatment. Andrykowski MA et al (1998) correlates fatigue with sleep disturbance and pain in cancer population. [12] These factors deplete the level of physical functioning in cancer patients and may results to variations in the aerobic and anaerobic pathways. The aerobic pathway reduces the oxygen delivery to the cells with limited ATP synthesis thereby facilitating the anaerobic glycolysis for energy production. This anaerobic glycolysis accumulates the lactic acids as its end product with less ATP generation thereby decreasing the activity of intracellular and interstitial pH leading to additional metabolic stress. The collective burden increases the heart rate, respiratory work, with less effective energy production, and metabolic acidosis. However, these conditions may lead to reduction in physical activities with associated psychosocial factors like anorexia, sleep pattern disturbances, reduced exercise tolerance and stamina, tiredness, and inability to carry out intense physical effort resulting in anxiety and to some extent depression due to sedentary lifestyle of patients over extended period of breast cancer treatment. [13]

Cancer-Related Fatigue Assessment/Screening Scales for Practice and Research

Advancement in cancer assessment/screening increases the number of breast cancer survivors. The assessment of the known treatable factors must be undertaken, among them the physical and psychosocial factors must be initial step in managing fatigue. [15] There are several authenticate tools for measuring Cancer-related fatigue. [16] According to NCCN guideline a self-report scale with grade 0 (no fatigue) to 10 (severe fatigue) assesses various dimensions of CRF including intensity, duration, and interference with functioning. [17] The only drawback of Self- report scale is that the patient barely participates believing that fatigue is untreatable and that the tool is not particularly important and can directly affect the ongoing treatment. [18] There are varieties of other tools for measuring CRF among them; Brief fatigue inventory assesses the psychometric/ psychological properties because of its easy words, translations, and less lengthy procedures that ease the patient to complete it without hindrance. This tool is used for both clinical trials and for screening purposes. [19], [20] **[Table 1]** describes the Screening of various dimensions with more emphasis on physical, & psychological factors associated with CRF that are used in practice settings. These include single-item, multi-item Unidimensional, and Multidimensional assessment tools for measuring CRF as reviewed from various data sources and by Piper and colleagues. [21]

[Table 1] Assessment and Screening of Cancer related fatigue

Tool	Explanation	Reference	Recommendation	Severity
Unidimensional / Single item tool for Screening				
NCCN Intensity scale(s)	0-10 scale (0 = no fatigue, 10 = worst fatigue)	Mock et al (2007) [22]	Recommended for practice and screening fatigue in cancer survivors.	Assesses symptoms of cancer related fatigue severity
Fatigue Intensity Scale (FIS)	0-10 scale (0 = no fatigue, 10 = overwhelming fatigue)	Borneman et al (2007) [23]	Recommended for research selection and practice purpose	Assesses symptoms of cancer related fatigue severity
MD Anderson Symptom Inventory (MDASI)	13-item scale 0-10 scale with 13 symptom items with highest frequency in CRF.	Cleeland CS et al (2000) [24]	Recommended for screening mostly the psychological factors in cancer related fatigue research selection and practice purpose	A self-report scale that assesses severity and its impact on daily functioning during the last 24 hours with internal consistency of α=0.85-0.87.
Functional assessment of cancer therapy: fatigue subscale (FACT-F)	5-point likert scale With 41 symptoms items, found stable with reliability and validity (test-retest r = 0.87) and internally consistent (coefficient alpha range = 0.95-0.96)	Yellen et al (1997) [25]	Recommended for clinical trials and Intervention tool in clinical management and as an outcome measures in health practice self-studies.	Assesses physical and psychological factors in Cancer related fatigue.
Multi item Unidimensional tool for Screening				
Fatigue symptom inventory (FSI)	Likert type 14 item scales in which (14) is not scored; used for qualitative data only. (0= not at all fatigued and 10= as fatigued as I could be)	Jacobsen et al (2007) [26], [27]	Validated with both female and male cancer patients between the age group 18–24.	Assesses severity, Frequency, daily pattern of Cancer related fatigue, & perceived interference with the quality of life.
Brief Fatigue Inventory (BFI)	0-10 scale (0 = no fatigue, 10 = fatigue as bad as one can imagine), 9 item symptoms that provides a global fatigue severity score (1-3, mild; 4-6, moderate; 7-10,	Jean-Pierre et al (2007) [28] Cleeland CS (2016) [29]	Recommended for clinical screening and in National and International Clinical trials.	Assesses the psychometric/ psychological severity of cancer related fatigue (now, usual, worst fatigue during the previous 24 hours that interferes with the

	severe)			daily activity. Its Internal consistency measures are high at 0.8 or more.
Cancer-Related Fatigue Distress Scale (CRFDS)	0-10 scale, 20 symptoms items are measured on a Likert scale, Higher scores indicate greater distress from fatigue symptoms, three additional questions are also asked from the person's current, worst, and usual CRF level.	Holley SK (2000) [30]	Recommended for clinically with good psychometric properties.	Assesses the psychological and other domains of fatigue in cancer patients during the previous week. Its internal consistency reliability was α=0.98 with good construct validity.
Multi-dimensional tool for screening				
Fatigue Assessment Questionnaire (FAQ)	20 items scale. 0-3 scale (0 = not at all, 3 = strongly; (+3) indicates addition of VAS to measure fatigue and distress)	Piper (2004) [31] Beutel et al (2006) [32]	Developed to measure psychometric properties of fatigue in cancer patients.	Assesses the psychometric dimensions (physical, affective, cognitive) of fatigue over past week and month.
Cancer Fatigue Scale (CFS)	15 items scale. 1-5 scale (1 = not at all, 5 = very much) Maximum score is 60 (physical, 1-28; affective, 0-16; cognitive, 0-16)	Piper (2004) [31] Okuyama et al (2000) [33]	Quite simple and complete within two minutes even with patient with advanced cancer. It is primary tested with a cancer patient in Japan.	Assesses the physical and psychometric dimensions of fatigue. Its average test–retest reliability r = 0.69, P < 0.001) with good internal consistency (Cronbach's alpha coefficient for all 15 items = 0.88).
Revised Piper Fatigue Scale (RPFS)	11-point scale including 22 + 5 open-ended items not included in the scoring. 0-10 NRS (i.e., 0= None, 1-3 = Mild, 4-6 Moderate, 7-10 = Severe)	Berger et al (2007) [34] de Jong et al (2006) [35] Piper et al (1998) [36]	1) It is an easy scale and takes only two minutes to complete. 2) It initially measures cancer related fatigue, but now used in other clinical, non-clinical, and healthy groups globally.	Assesses the psychometric dimensions of fatigue in cancer patients (behavioral /severity, affective meaning, sensory, and cognitive/mood) for entire scale. Its reliability is (α =0.97) and subscales well validated in patients with cancer (α = 0.92–0.96).

Multidimensional Fatigue Symptom Inventory	5-point scale of 0-4 with 83 items with (0=not at all. 4=extremely).	Stein KD et al (1998) [37] Stein KD et al (2004) [38]	Recommended for multiple measurement within short time scale.	Assesses cancer related fatigue in terms. general, physical, emotional, and mental manifestations during the past week (α= 0.85-0.96)
Revised Schwartz Cancer Fatigue Scale	6-item scale assesses on 1–5-point Likert scale with 1 "not at all" to 5 "extremely."	Schwartz A et al (1999) [39] Pattanshetty RB et al (2016) [40]	It takes 1-2 min to complete. Scores range from a minimum of 6 to a maximum of 30.	Assesses physical and perceptual dimensions of CRF in the previous 2-3 days. Its reliability is (α = 0.90).

Methodology

The search for the relevant journal was carried out referring through many databases: PubMed, PubMed Central, Cochrane databases, and PEDro. The main emphasis was given on RCTs, clinical trials, and systemic reviews to examine the role of physiotherapeutic interventions in cancer related fatigue among breast cancer survivors.

Result and Discussion

Evidence-Based Physiotherapeutic Interventions

The physiotherapy procedures mostly depend on the underline causes and once the cause is identified then simultaneous improvement is noticeable within the patient's CRF and physical functions by assigning a systematic physical therapy protocol. [41] The CRF is associated with physical, psychosocial, and other domains. [42], [43], [44] Due to this reason a multi-faceted treatment of physical therapy is considered. [45] The growing research on CRF interventions shows a positive response covering the other domains like quality of life, behavioral manifestations other than physical and psychosocial factors. [46]

According to the NCCN guideline, the non-pharmacological treatments are considered effective in treating CRF. [47] The non-pharmacological approach includes 1) Physical exercise, 2) Psychological therapies, 3) Physical modalities, 4) Manual therapies, 5) Acupuncture, 6) Multidisciplinary/interdisciplinary rehabilitation, etc. [48] While Parock et al (2000) experimented on 11 patients with 28 days trial [49] ; Buss et al (2010) on 38 patients with 3 weeks trial [50] reported that a pre-set exercise protocol increases the patient daily physical activity levels with therapies like 1) exercise in bed and sitting position, 2) treadmill walking, 3) cycle ergometer exercises, 4) rhythmic dancing. The evidence suggests that the 12 months of regular exercise on a pre-designed protocol with 5 years follow-up among breast cancer survivors reduces fatigue and improves the quality of life. [51] [**Table-2]** demonstrates some of the evidences on the significant improvement of CRF among BCS by physiotherapeutic Interventions.

[Table 2] Synopsis of studies regarding evidences on physiotherapeutic interventions in Cancer-related Fatigue among Breast Cancer Survivors.

Reference	Publication type	Database	Outcome measurement	Description	Conclusion
Penttinen H et al (2019) [51]	Clinical Trial	PMC	Physical activity by diary, Physical performance by a 2-km walking test, Quality of life by BR-23 questionnaires, fatigue by FACIT-Fatigue scale, Depression by Beck Depression Inventory.	(N=573); RCT shortly after adjuvant treatment into exercise group(n=302) and control group (n=271)with 1-year exercise intervention and 1- year follow-up among BCS	The improvement in physical performance and activity gives a positive change in QoL among Breast Cancer Survivors.
Pyszora A et al (2017) [52]	Clinical trial	PubMed & PMC	Brief Fatigue Inventory, Edmonton Symptom Assessment system, and satisfaction score (SC).	RCT on 60 patient a) Treatment Group (n=30); b) Control Group (N=30) for 3 times a week for 2 weeks.	Physiotherapy program includes 1) Active exercises, 2) Myofascial release, and 3) Proprioceptive Neuromuscular Facilitation reduces fatigue inpatient with CRF and advanced cancer post palliative care.
Kinkead B (2018) [54]	Comparative / RCT	PubMed	Multidimensional Fatigue Inventory, PROMIS Fatigue scale, Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)	RCT on 66 female with stage 0-III post adjuvant therapy, for 6 weeks into Swedish massage therapy (SMT) versus an active control condition (light touch [LT]) and waitlist control (WLC) on persistent CRF	6 weeks of Swedish Massage Therapy reduces fatigue symptoms among BCS.
Suzanna M. Zick (2016) [71]	RCT	PubMed	Pittsburgh Sleep Quality Index (PSQI) and Long-Term Quality of Life Instrument (LTQL) and Brief Fatigue Inventory (BFI) score.	10 weeks randomized, single-blind trial comparing self-administered relaxing acupressure with stimulating acupressure once daily for 6 weeks vs. standard care with a 4-wks follow-up and 5 research visit one at screening, baseline- 3	Acupressure considerably reduces the persistent fatigue compared with usual care, but only relaxing acupressure had significant effects on sleep quality and QoL.

				weeks, 6 weeks, and 10 weeks.	
Irene Cantarero-Villanueva et al (2012) [53]	RCT	Cochrane Review/ EBCAM.	Treatment group Primary tool: Profile of mood states (POMS) questionnaire. Secondary tool: Trunk Curl Static Endurance Test and multiple Sit-to-Stands Test. Control group Minnesota Leisure Time Physical Activity Questionnaire	RCT on 78 BCS between 25- 65 years post adjuvant therapies (First 6 months) into a) experimental/ multimodal (n=39); b) control (n=39) groups with 8 weeks of intervention	The multimodal Gp focused on the core stability exercises and Recovery MFR massage is highly effective for improving physical (muscle strength) and psychological (mood state and fatigue) aspects in BCS after the intervention and 6 months after discharge as compared to the usual treatment group.
Anne Marie Lunde Husebo et al (2014) [58]	RCT	Cochrane review/ HPC	Schwartz Cancer Fatigue Scale- 6, International Physical Activity Questionnaire (IPAQ) Short Form, 6-Minute Walk Test (6-MWT) & an Exercise diary.	RCT on 67 women's post- surgery into exercise group (n=33) 3x/week and 30 minutes brisk walking/day and control group regular physical activity (n=34) at the completion of the chemotherapy ($Post_1$), and 6-month post-chemotherapy ($Post_2$)	The generally recommended exercises 150 min/ week Moderate Vigorous Physical Activity are enough to relieve CRF and restore the physical capacity among patients.
Yuen HK et al (2007) [59]	Clinical Trial	PubMed	Revised-Piper Fatigue Scale, 6MWT	A Pilot study (RCT) between aerobic (AE) & resistance exercises (RE) group and usual care control for 3x/weeks for 12 weeks at home at a light to somewhat hard intensity assessed by Borg Perceived Exertion tool which was analyzed by pre & post-training levels between both groups.	Aerobic exercises are more viable and efficient in improving CRF while RE (Z=2.366, one-tailed P=0.009) improves the functional capacity than the usual care control group.
Cramp F et al (2012) [60]	Systematic review	Cochrane database of Systematic reviews	Meta-analysis for fatigue using a random-effects mode.	Out of 56 studies (4068 participants) with 38 studies compare fatigue between exercise interventions (1461) and	Aerobic exercises are found to be more beneficial with Standard Mean Deviation of (-0.27, 95% CI, -0.37 to

				(1187) control group, participants were studied and analyzed.	0.17) with a moderate heterogeneity of (P = 0.20; I^2 = 20.0%) than the control intervention group in individuals with cancer-related fatigue during and post-cancer therapy
Kessels E et al (2018) [61]	Systematic review and meta-analysis	PMC	Primary outcome by self-report validated questionnaire and secondary outcome by Adherence	Out of 274 trials [11 studies with participants {411 with exercise intervention} {377 with non-exercise intervention}] are selected for analysis for comparison between both groups.	Exercises improve CRF with effect size (Cohen's *d* 0.605, 95% Class Interval 0.235-0.975). The Aerobic exercise are found to be more effective (Δ=1.009, CI 0.222-1.797) than a combination of AE & RE (Δ=0.341, CI 0.129-0.552) with high adherence rate on patient with CRF.
Meneses Echavez et al (2015) [62	A Systematic review and meta-analysis	PubMed	-	9 RCT studies with (n=722participants) were searched for systematic review and meta-analysis from PubMed, CENTRAL, EMBASE, and OVID between January and March 2014 and risk of bias was searched using PeDro scale	Multimodal intervention including aerobic exercise, resistance training, and stretching are more effective with SMD = −0.23; 95% CI: −0.37 to −0.09; *P* = 0.001) than RE (*P* = 0.30) with low risk of bias (6.4 SD +/- 1.0) in controlling CRF for cancer survivors and during treatments.
Meneses-Echavez JF et al (2015) [63]	Systematic review	PubMed	Functional Assessment of Cancer Therapy Fatigue Scale, European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire, Piper Fatigue Scale, Schwartz Cancer Fatigue Scale, and the Multidimensional Fatigue Inventory.	11 studies (n=1350) Participants	Combined AE and RE under supervision show a positive response in fatigue reduction. (SMD=-0.41, 95% CI -0.70 to -0.13); combined AE & stretching (SMD=-0.67, 95% CI -1.17 to -0.17). The joint effect on fatigue was -1.69 (95% CI -2.99 to -0.39 using a random effect model.
Do J et al (2015) [65]	Clinical trial/ RCT	PubMed	(EORTC QLQ-C30), EORTC Breast Cancer-	RCT (n-62) into early exercise group (n-32) 4	Supervised multimodal rehabilitation program

			Specific Quality of Life Questionnaire (EORTC QLQ-BR23), Fatigue Severity Scale	weeks of a multimodal rehabilitation program for 80 min/day, 5 times/week for 4 weeks and delayed exercise group (n=30) completed the same program at the next 4th week among BCS.	improves the physical symptoms, QoL, and fatigue in patients with breast cancers.
Reif K (2013) [68]	Clinical trial/ RCT	PubMed	-	RCT (n=261) into intervention group; receiving a 6-session educational program for 90 min and control group with the usual care.	Findings suggest a significant reduction in CRF (f=76.510, $p<0.001$, $n^2 = 0.248$) with improvement in Qol, anxiety, self-efficacy, physical activity, & fatigue knowledge among the intervention group.
Young Ho Yun (2012) [66]	Comparative study/RCT	PubMed	Primary outcome: (BFI) & (FSS) Secondary outcome: (HRQOL, EORTC QLQ-C30, Hospital Anxiety and Depression Scale, self-report, and short message services).	RCT (n=273) allocated into an intervention group (n=136) and control group (n=137) in an individually tailored 12 weeks intervention program covering 7 areas (NCCN guideline) with various modules and Health navigation program (Self-assessment and graphic reports, health advice and online education, enhanced and short message services, caregiver monitoring and support, and health professional monitoring).	Web-based self-management is considered as an important route for improving fatigue and HRQOL significantly more than the routine care among patient with cancer.

Pyszora A et al (2017) concluded that physiotherapy program that includes 1) active exercise, 2) MFR, and 3) PNF facilitates a considerable reduction of CRF in post palliative care of cancer patients. [52] Similar study was done by Villanueva et al (2012) on 78 patients between the age-group of 25-65 years for a period of 8 weeks. [53] The experimental group receives physical training (core stability exercises) for 4 hours followed by 12 hours of recovery procedures (MFR) 3 times/week for a period of 90 min each. The protocol **[Table-3]** was set for 2 weeks according to ACSM and AHA guidelines and found to be highly effective in improving muscle strength, mood states with the significant improvement seen in fatigue level (0.52) as compared to the previous studies (effect size 0.31, 95% CI 0.22–0.40) post intervention and 6 months after discharge as compared to the control group.

[Table 3] Villanueva-2012 Exercise protocol

Week-I (1-4wks)	Week-II (4-8wks)
Half squad arm, wall pushups, standing hip circumduction, Superman on fit-ball Oblique partial sit-up, etc	Chest press on fit-ball with an elastic band, Seated rows on fit-ball with an elastic band, Isometric abdominal sitting on fit-ball with arm and leg movement, Biceps curl on fit-ball with an elastic band, Biceps curl with an elastic band and leg semi-flexion maintained, Leg curl with fit-ball, etc

The long-term course of cancer treatment is quite frustrating for the patient due to this Kinkead B and colleagues (2018) [54] performed a comparative study on 66 females for 6 wks. The experimental group received Swedish massage therapy and found a significant improvement in fatigue level, psychosocial dimensions, and quality of life. The American college of sports medicine (ACSM) recommended 150 minutes/week moderate to vigorous physical activity (MVPA) for breast cancer patients and survivors. [55] Many available data focus on resisted exercises, balancing exercises, breathing exercises, relaxation, and ergo meter training. [56], [57]

Husebo et al (2014) examine strength training by using a resistance band for arm, legs, and upper body for 3 times/week followed by 30-minutes of aerobic-brisk walking (*light, moderate, vigorous, and very vigorous walking)* and found a positive-relation of these exercises on patients fatigue level. He also suggests that adherence to exercises is the keystone for any exercise-regimen that will reflect its treatment outcome and effectiveness. [58]

Adhering to aerobic exercises provide a better improvement than the combination therapy. Yuen HK (2007) demonstrated that aerobic exercises (AE) improve CRF, while Resisted exercises (RE) assist in improving functional capacity. [59] Cramp F (2012) indicates AE improves the fatigue and various psychosocial domains as compared to resisted exercises or alternative form of exercises. [60] Kessels E (2018) suggested that AE shows a positive effect on patient CRF domains as compared to the combination therapy (AE+RE). [61] Meneses-Echavez (2015) explains that multimodal exercise training i.e., varieties of exercise protocol (AE+ Training Stretching shows a better result as compared to RE individually. [62] Meneses-Echavez JF et al (2015) concluded that combined AE & RE under supervision shows a positive response in fatigue reduction with standard mean deviation (SMD) of 0.41, 95% CI -0.70 to -0.13) as compared to

combined AE & stretching (SMD=-0.67, 95% CI -1.17 to -0.17). [63] Many articles support that patient who receives radiotherapy, experiences less fatigue after engaging with aerobics exercises. [64] Do j et al (2015) combined aerobic and strengthening exercise with a cycle and arm ergometer and a steeper machine with other strengthening exercises including TheraBand**,** and core stability exercises in improving quality of life that decreases stress and anxiety level thereby improving the physical functioning of the patients. [65]

The non-pharmacological approaches are considered well-documented in many relevant data sources. There is a need to enhance patient's exercise motivation by various other modes like web-based self-management, and an educational program.

A study conducted by Young ho and colleague (2012) on 136 CRF patient for a period of 12 weeks by internet-based self-management covering seven-areas including physical and psychosocial domains (According to NCCN guideline) with modules (1) Introduction to CRF, 2) Two-session on energy conservation, 3) Ten session on physical activity, 4) four on nutrition, 5) Seven on sleep hygiene, 6) Seven on pain control, 7) and Eight on distress management and five-areas on Health navigation with modules (Self-assessment and graphic reports, health advice and online education, enhanced and short message services, caregiver monitoring and support, and health professional monitoring). The web based self-management is considered as an effective route for improving CRF and HRQOL more than the routine care among BCS. [66]
According to the Cancer patient education network (CPEN) guideline, patient's educational program assists in depleting the cancer -related deteriorations with improvement in health and health-related quality of life among BCS. [67] Reif K et al (2013) study shows a positive result of a patient's education program on the reduction of CRF ($f=76.510$, $p<0.001$, $n^2 = 0.248$) followed by improvement in Qol and physical activity among Breast Cancer Survivors (BCS). [68]

Schmidt ME (2019) investigated the impact of treatment-related side effects and other factors on 135 Breast cancer survivors who return to work on their quality of life and found that 57% work the same, 22% working time diminished with depressive symptoms appears within 1 year and after 5 years persisting physical fatigue and cognitive problems were the major self-reported reasons among BCS to hinder a return to work. [69] A moderate level of evidence suggesting that Tai chi helps in reducing levels of cortisol and CRF with improvement in limb functions in Breast cancer survivors (BCS). [70]

Conclusion

There are varieties of physical therapy interventions that play a beneficial role in reducing Cancer-related Fatigue followed by improvement in the physical activities, functional status, psychosocial domains; thereby enhancing the quality and lifestyle among breast cancer survivors. The multimodal rehabilitation program including aerobic exercises, combination exercises, (AE+RE+stretching), 150 minutes/week moderate to vigorous physical activity (MVPA), SMT, MFR techniques reduces cancer-related fatigue, smoothen the progress of patient physical activity levels; improves the psychosocial factors anxiety, depression, sleep disturbances, etc and promotes relaxation. The educational program assists patients to maintain or improve health or, in some cases to slow-down the deterioration. Internet-based self-management is considered an important means for reducing fatigue levels and improving HRQOL among patients. A moderate level of evidence suggested Tai-chi exercises also helps in reducing levels of cortisol and fatigue with improvement in limb functions in Breast cancer survivors (BCS).These interventional

programs will only be effective when the patient strictly adhere and follow the pre-designed exercise protocol for a successful outcome. So it is highly recommended that the CRF assessment should be incorporated with the follow-up schedule among breast cancer survivors. Based on the screening, the physiotherapeutic Interventions must be prescribed, so to improve the CRF and Quality of life in Breast Cancer Survivors.

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