Determinants Of Exercise Adherence Among Breast Cancer Patients Undergoing Chemotherapy: A Systematic Review

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ABSTRACT

Purpose: To systematically explore the determinants of exercise adherence and maintenance in patients undergoing chemotherapy using a socio-ecological approach.

Method: Literature identified in PubMed, Science Direct, SCOPUS, and Cochrane Reviews was searched from January 2010 to the end date restricted to the end of March 2022. We included full-text articles that: 1) were conducted among adult cancer patients undergoing chemotherapy; 2) quantitatively assessed factors associated with the intervention, adherence, and maintenance, and 3) were published in English. The methodological quality of the selected literature was examined using the PEDRO score. Methodological quality ranged from 4 to 8 as rated on the PEDRO scale with a median score of 7 of 10, confirming "high" methodological quality. All literature were rated as high qualitative literature with a score of >4 of which 9 scored high scores.

Results: Nine articles were included and focused on determinants of exercise adherence and evaluated 20 potential determinants: 29 demographic and clinical, 27 psychological, 10 physical, 4 social factors, and 1 environmental factor. We found there is a positive correlation between adherence and many factors which includes location/ centre, VO2 Peak, Disease stage, depression, endocrine symptoms, few exercise limitations, shorter chemotherapy protocols, body-mass index, and high baseline endurance time from the multivariant analysis.

Conclusion: The most prominent determinants of adherence to exercise interventions were location of the rehabilitation centre, VO2 Peak, Disease stage, depression, endocrine symptoms, few exercise limitations, shorter chemotherapy protocols, body mass index, high baseline endurance time from multivariant analysis. To increase the number of cancer patients who will benefit, these results shin developing and implementing implementation of future exercise interventions.

Keywords: Physical activity, Exercise, Intervention adherence, Determinants, Neoplasms, Behaviour, Systematic review, Breast cancer

INTRODUCTION

Cancer is a large group of diseases that start in almost any organ or tissue of the body when abnormal cells grow uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body and/or spread to other organs[1] In particular, the breast cancer imposes a huge burden on individual, family, society and government, and associated with high mortality and morbidity. An estimated 2.3 million females were diagnosed with breast cancer in 2020, accounting for approximately 24.5% of all cancer cases worldwide [2] and in India it is 13.5%[3] . The global prevalence of breast cancer is 11.6%, whereas it is 27% in India for the year 2018. Worldwide mortality is 13%, in India it is 11.7%[4]. In the recent years of medical advancement, subjects with breast cancer are being treated through chemotherapy, radiation therapy, hormonal therapy, and surgery. Chemotherapy is associated with side effects like cancer-related

fatigue, muscle atrophy, toxicities and reduced cardiorespiratory fitness[5].A decline in physical function is also seen. Performing exercises regularly will decrease symptoms and also improve physical function[6]. Recover back to pre-diagnosis level is a problem for many of the patients.

During chemotherapy 50% of the patients are not adhering to the exercises[7] .According to literature exercise adherence is unclear during chemotherapy[8.]This may be due to treatment related side effects like neuropathic pain (33%), changed body image, fatigue, weight gain[7]. Patient education, motivational strategies, and doctor-patient relationship improves exercise adherence. Poor adherence causes poor control of conditions, reduces effects of therapy, increase cardiovascular events all these lead to relapses, hospitalizes, complications or even death.[9]

Exercise adherence, defined as the extent to which the participants followed the exercise prescription according to the intervention protocol[10] Exercise adherence during and after cancer treatment is a challenging issue. Clinical and cost effectiveness of exercise programs could be enhanced by improving adherence to such programs. This requires better understanding of the factors associated with adherence. From the literature it is evident that adherence range from 54% to 78%. To improve adherence, it is essential to know the relevant and modifiable factors. Literature suggested that determinants of adherence to exercise during cancer treatment may differ from determinants after completion of primary cancer treatment. Different time periods have different determinants but the little is known. Therefore, the aim of this systematic review was to find the determinants of exercise adherence in cancer patients undergoing chemotherapy.

METHODS

Search Strategy
The online databases, PubMed, ScienceDirect, SCOPUS, and Cochrane Reviews were searched from January 2010 to March 2022. Four primary keywords were taken into consideration for the literature search which includes exercise adherence, breast cancer, chemotherapy, and determinants. Further, the synonyms or MeSH terms for the keywords were identified. Four search terms pertaining to exercise (Exercise OR physical activity OR physiotherapy OR physical therapy), four terms for cancer (Cancer OR Carcinoma OR Tumour OR Tumours), three terms for determinants (determinants OR risk factors OR predictors), three terms for adherence

(adherence OR regular OR compliance) were identified combined using Bloom's taxonomy. In addition, the references from previously published literature were searched.
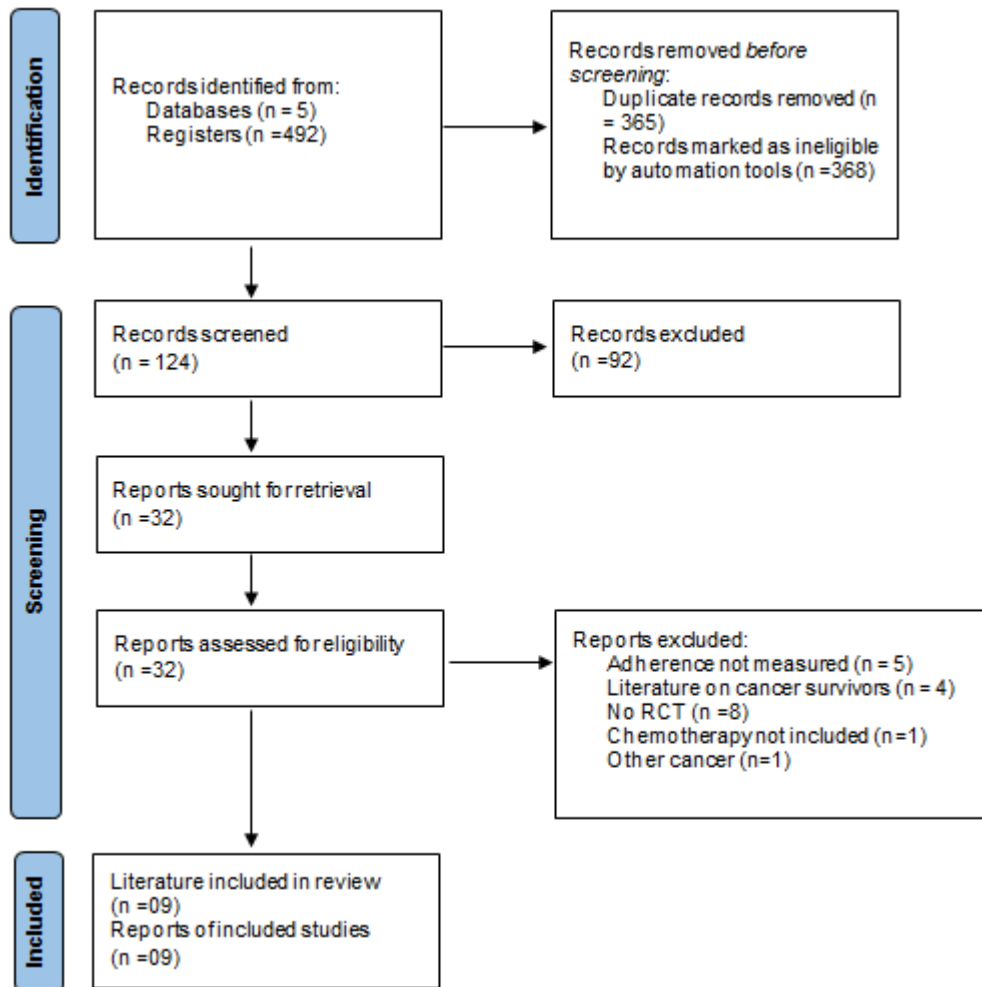
Study Selection
Literature of any design was considered for inclusion; if they were published in English, women having breast cancer of age above 18 years undergone chemotherapy, that reported exercises adherence determinants of exercise adherence, categorical or continuous variables. Literature with a diagnosis of breast cancer underwent surgery, radiotherapy, cognitive impairment at baseline, and published non-English articles were excluded. Data from literature that had exercise adherence in breast cancer patients who had undergone chemotherapy were extracted. Data extraction involved retrieval of authors, study design, population characteristics, adherence measurement, interventions and reasons for non-adherence and statistical methods. Reviewers evaluated the abstracts and full-text and conflicts were resolved accordingly.

Selection Process and Data Extraction
Screening of all four databases was performed in two phases. First titles and abstracts of identified articles were screened to excluded articles based on inclusion and exclusion criteria. In case of disagreement full-text article was screened for eligibility. When necessary, it was discussed with the second author and resolved by discussion.

Data Extraction
Data is extracted using PRISMA guidelines using (1) first author's last name, year of publication, country, and trial name; (2) design; (3) population (number of participants, gender, age, cancer type(s), stage, and treatment modalities); (4) exercise intervention (extent, duration, type, frequency, treatment phase, intensity, adherence facilitation, and control group program); (5) outcome (outcome measures of adherence and measurement instruments); (6) results (adherence rate, univariable and multivariable analysis, and variance in exercise intervention adherence explained by analysed factors (R or area under the curve. Reviewers conducted the search and data were extracted, and the methodological quality of included papers was evaluated using Physiotherapy Evidence Database (PEDro) scale. Articles were given a score of one for each item, those with a score > 4 were graded as high-quality studies and those scored <4 were graded as low methodological quality.

Figure 1: PRISMA flow diagram to identify eligible studies

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Identification
┌─────────────────────────────┐      ┌─────────────────────────────┐
│ Records identified from:    │      │ Records removed before      │
│   Databases (n = 5)         │ ───► │ screening:                  │
│   Registers (n =492)        │      │   Duplicate records removed │
│                             │      │   (n = 365)                 │
│                             │      │   Records marked as         │
│                             │      │   ineligible by automation  │
│                             │      │   tools (n =368)            │
└─────────────────────────────┘      └─────────────────────────────┘

Screening
┌─────────────────────────────┐      ┌─────────────────────────────┐
│ Records screened            │ ───► │ Records excluded            │
│ (n = 124)                   │      │ (n =92)                     │
└─────────────────────────────┘      └─────────────────────────────┘

┌─────────────────────────────┐
│ Reports sought for retrieval│
│ (n =32)                     │
└─────────────────────────────┘

┌─────────────────────────────┐      ┌─────────────────────────────┐
│ Reports assessed for        │ ───► │ Reports excluded:           │
│ eligibility (n =32)         │      │   Adherence not measured    │
│                             │      │   (n = 5)                   │
│                             │      │   Literature on cancer      │
│                             │      │   survivors (n = 4)         │
│                             │      │   No RCT (n =8)             │
│                             │      │   Chemotherapy not included │
│                             │      │   (n =1)                    │
│                             │      │   Other cancer (n=1)        │
└─────────────────────────────┘      └─────────────────────────────┘

Included
┌─────────────────────────────┐
│ Literature included in      │
│ review (n =09)              │
│ Reports of included studies │
│ (n =09)                     │
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RESULTS

Selection of Studies

The primary search strategy identified 489 potentially relevant papers, of which 124 remained after discarding duplicates (Figure No 1). After screening based on title and abstract, 32 papers were potentially eligible for inclusion. 09 of these papers met predefined eligibility criteria.

Characteristics of Included Studies

1985 breast chemotherapy cancer patients were included. Of these 1196 were assigned to exercise intervention. All literature used RCT design and were conducted in the United States, Netherlands, Sweden, and Canada. Eligibility criteria were heterogeneous among studies, with differences in cancer type(s), cancer treatment phase, exercise interventions, and patient characteristics. A full description of the different study characteristics is depicted in Table 1.

In five studies, the exercise intervention was performed at a rehabilitation centre (centre-based)

[11–15], in two studies, the intervention was performed at the patient's home (home-based)[16,17] in two articles interventions were both supervised and home- based. [10,18] Duration of exercise interventions ranged from 5 weeks to 24 months. Various physical exercise modalities were used in the selected studies: aerobic (brisk walking, cycling, treadmill, or swimming), strength (resistance, stretching, and postural exercises).

Methodological Quality Assessment and Qualitative Analysis

Nine literature were scored using PEDro score (Table 2). Methodological quality ranged from 4 to 8 as rated on the PEDro scale with a median score of 7 of 10, confirming "high" methodological quality. All literature were rated as high qualitative literature with a score of > 4.

Measurement Instruments and Outcome Measures of Adherence

Exercise adherence, defined as the extent to which the participants followed the exercise prescription

according to the intervention protocol, was assessed based on the FITT principles and dropout rates.[10] Adherence was measured using pedometer, Paffenbarger Physical Activity Questionnaire PPAQ[17], self-report and attendance records[18], daily exercise log[6] number of supervised exercise sessions attended divided by the number of supervised exercise sessions prescribed.[19]

Univariable and Multivariable Analyses of Selected Literature

Many determinants were investigated which were socio-demographic, physical, physiological and behavioural factors. Highly significant ($p \leq 0.01$) and significant ($p < 0.05$) or borderline significant ($p < 0.10$) associations between exercise intervention adherence and various factors were identified in univariate or bivariate analysis. Thereafter, these factors were included in a multivariate analysis to finally derive predictors of adherence to exercise intervention. One study did not describe a univariable or bivariable.[12]

Adherence rates ranged from 62% to 87%. Data and level of significance of exercise adherence of univariate and multivariate analyses are summarized in Table2. All factors gathered in

multivariate analysis in each study were summarized and weighted as determinants of exercise adherence.

Determinants Based on Univariant and Multivariant Analysis (Table 3)

In this study, we adopted an ecological model to categorize determinants of exercise adherence in cancer patients.

1. Demographic and Clinical: Marital status, disease stage, Education, smoking, chemotherapy cycles, treatment-related mood disturbance, hours spent sleeping or reclining at baseline, higher baseline endurance time, positive attitude towards exercise during chemotherapy

2. Psychological: Depression, feeling sick, fatigued, vacation and Quality of life (QOL)

3. Physical: VO2 Peak, muscular strength, fewer endocrine symptoms, body-mass index, baseline physical fitness, pre-treatment fatigue level

4. Social: Fewer exercise limitations

5. Environmental factors: Location of fitness center

Table 3: Determinants of exercise adherence

	Determinant	Univariant analysis	Multivariant analysis
Demographic	Marital status	Shang et al.2012, van Waart et al.2020	
	Disease stage (Advanced disease)	Courneya et al.2008; Swenson et al.2010, van Waart et al. 2020	Courneya 2008; Courneya and McKenzie, 2014
	Education (Better education)	Courneya et al.2008	
	Smoking	Courneya et al.2008	
Clinical	Six or more cycles of chemotherapy	Courneya et al.2008, kirkham et al. 2018, Swenson et al.2010, Nyrop et al. 2018	Courneya and McKenzie.2014
	Treatment-related mood disturbance	Shang et al.2012	
	Hours spent sleeping or reclining at baseline	Swenson et al.2010	
	Higher baseline endurance time	van Waart 2020	Nyrop et al. 2018; van Waart et al.2020
	Positive attitude towards exercise during chemotherapy	van Waart et al.2020	
Psychological	Depression	Courneya et al.2008	Courneya et al.2008
	Feeling sick, and fatigued	Courneya et al. 2008, Shang et al.2012, Swenson et al. 2010	
	Higher baseline quality of life (QoL)	Bland 2018	

Physical	VO2 Peak	Courneya 2008	
	Muscular strength	Courneya 2008	
	Fewer endocrine symptoms		Courneya and McKenzie 2014
	Body mass index		Courneya and McKenzie, 2014
	Baseline physical fitness (Shang 2012)	Nyrop 2018 Shang 2012	
	Pretreatment fatigue level,	Shang 2012	
Social	Fewer exercise limitations		Courneya and McKenzie, 2014
Environmental	Location/center	Courneya 2008	Courneya 2008 Courneya and McKenzie,2014

DISCUSSION

This study provides a comprehensive overview of determinants of exercise adherence in breast cancer patients during chemotherapy. Nine Literature included in this review reported exercise adherence.[12,6,18,13,17,14,10,15,11] There is a positive correlation between adherence and many factors which includes location/centre, VO2 Peak, disease stage, depression, endocrine symptoms, exercise limitations, shorter chemotherapy protocols, body mass index, high baseline endurance time from multivariate analysis. The location of treatment centres has a significant effect on exercise adherence which is essential for the well-being of elderly patients, and is thus a critically important component of care.[21] Courneya et al (2008,2014) in his two studies mentioned that the location of the rehabilitation centre contributes highly in predicting adherence to centre-based exercise interventions during chemotherapy in breast cancer patients.[11,19] A longer distance to travel for cancer care is known to be associated with less frequent use of recommended services and could be a burden to cancer patients. Travel time is considered to be a direct cost of cancer care that mainly imposes a financial burden on the patients and their families.[22]

In a study by Mahadevan, on COPD patients non-adherence to exercise training is seen due to travel distance i.e.,>30 minutes.[23] For a study on colorectal cancer who are undergoing chemotherapy and cancer-related fatigue, patients did not give consent to participate in a study because of travel distance.[24,25] Two studies identified a positive correction between exercise adherence and VO2peak i.e., the high VO2 peak showed high adherence.[11,20] In a study by Dalle 2011, low physical fitness was reported as a barrier for not participating in exercise as they were weak and got tired and breathless.[26]

Disease/treatment-related barriers accounted for over 50% of all missed exercise sessions and the majority of breast cancer patients reported multiple exercise barriers during chemotherapy[12]. Many side effects of chemotherapy may influence the amount of exercise completed during chemotherapy.[15] Chemotherapy was inversely associated with the willingness to participate. There is one study that found no relation between cancer treatment and adherence to high-intensity and low-to-moderate-intensity exercises, other study found chemotherapy and its side effects were associated with low adherence to physical exercise programs. One explanation for these contradictory results may be that chemotherapy is a generic term that includes different drugs and various possible side effects. There were no differences in willingness to participate based on other medical variables, and this is consistent with previous work on this topic[27]

Previous literature [18,28]mentioned that endurance and pre-chemotherapy physical activity have more exercise adherence. A study done on Lymphoma patients regarding predictors of exercise adherence, showed that there is poor exercise adherence in inactive patients at baseline.[29] Being diagnosed with BC as well as the treatment received has a strong impact on the lives of these women, including in their self-image, sexual health, psychological attitudes, and psychiatric disorders such as anxiety or depression, even in the BC survivors.[30] After chemotherapy women tend to have a lack of motivation immediately after a period of post-treatment depression, resulting in reduced levels of Physical activity (PA). A positive belief in PA regarding outcomes efficacy kept the women

motivated to adhere to their program.[31] Body mass index is identified as a predictor of adherence in breast cancer patients undergoing chemotherapy as the rehabilitation was slow and that they still experience—fatigue even after completing treatment was perceived as surprising, even though they slowly began to feel stronger and stronger during the PA period. As physical fitness got better and feelings of fatigue decreased, motivation increased to engage in PA. Improved mental attitude, decreased stress, increased sense of control, and increased confidence was also experienced. The feeling of being unattractive with hair loss and skin problems caused by chemotherapy was compensated by gaining muscle mass and reducing total body fat.[31]

CONCLUSION

The most prominent determinants of adherence to exercise interventions were the location of the rehabilitation centre, VO2 Peak, disease stage, depression, endocrine symptoms, few exercise limitations, shorter chemotherapy protocols, body mass index, and high baseline endurance time from multivariate analysis. To increase the number of cancer patients who will benefit, these results should be considered in developing and implementing future exercise interventions for the management of breast cancer.

Table 1: Summary of findings

S No	Author and Title	Study Design	Methodology	Adherence	Determinants of Exercise Adherence
1	Courneya 2008 Barriers to Supervised Exercise Training in a Randomized Controlled Trial of Breast Cancer Patients Receiving Chemotherapy	A prospective, three-armed, randomized controlled trial	n=242 Aerobic and resisted exercise groups which are supervised	Adherence to the supervised exercise program during chemotherapy was 72.0 and 68.2% in the AET and RET groups, respectively (p=0.411).	Determinants: 1. feeling sick 2. fatigue 3. loss of interest 4. vacation 5. nausea/vomiting 6. work issues and pain accounted for over 50% of all missed exercise sessions
2	Courneya, 2008, Canada, START trial Moderators of the effects of exercise training in breast cancer patients receiving chemotherapy	Three-armed RCT	<u>Population (n)</u> T: n=242, C: n=82, RET: n=82, AET: n=78 <u>Gender (%)</u> Women 100% <u>Age</u> T: 49.2, C: 49.0, RET: 49.5, AET: 49.0 <u>Cancer type</u> BC <u>Stage</u> I to IIIA <u>Treatment</u> Adjuvant CT	Adherence rate 70.2%	Univariable analysis ↑Location/center (r=0.30; p<0.001) ** Multivariable analysis ↑Location/center (β=0.28; p =0.001) **
3	Courneya, 2014, Canada, CARE trial Subgroup effects in a randomised trial of different types and doses of exercise during breast cancer chemotherapy	Three-armed RCT	<u>Population (n)</u> T: n=301, STAN: n=96, HIGH: n=101, COMBINATION n=104 <u>Gender</u> (%) - Women 100% <u>Age</u> T: 50.0, STAN: 49.2, HIGH: 50.1, combination: 50.5 <u>Cancer type</u> BC <u>Stage</u> I to IIIa <u>Treatment</u> Initiating adjuvant Chemotherapy	Adherence rate 73%	Univariable analysis ↑Location/center (r=0.42; p<0.001) ** Multivariable analysis ↑Location/centre (β=0.41; p<0.001) **

4	Shang 2012 Who Will Drop Out and Who Will Drop in Exercise Adherence in a Randomized Clinical Trial Among Patients Receiving Active Cancer Treatment	Two arm RCT	Population (n) T: n= 126, I: n=68, C: n=58 Gender (%) Women, T: 38.9%, I: 39.7%, C: 37.9% Age T: 60.2, I: 59.8, C: 60.6 Cancer type BC, CRC, PC, others Stage 0 to III Treatment RT, CT, COT, BT	Adherence rate I: 67,7%, C: 87.9%	Multivariate analysis (HPRA) ↑Physical fitness (β=0.51; p<0.01) **, ↑exercise history (β=0.01; p<0.01) **
5	Van Maart Hanna 2020 Adherence to and satisfaction with low-intensity physical activity and supervised moderate-high intensity exercise during chemotherapy for breast cancer	RCT	Onco-move protocol: Home-based low intensity 30 min/day, 5 days/week, at an intensity level 12 to 14 on the Borg Scale of perceived exertion On-track –protocols supervised high intensity, combined resistance and aerobic exercise program twice weekly resistance exercises of six large muscle groups with two series of eight repetitions at 80% of one-repetition maximum, followed by 30 min of aerobic exercises with an intensity of 50% to 80% of the maximal workload estimated by the steep ramp test	On track- 62% Onco-move-59%	Higher baseline physical fitness was associated with higher adherence to home-based components. Higher disease stage and having a partner were associated with adherence to OnTrack supervised sessions.

	Bland Kelcey 2018 Predictors of attendance to an oncologist-referred exercise program for women with breast cancer	RCT	N=68 Supervised aerobic and resistance exercise was prescribed 3 times/ week during treatment, then 1or2 times /week for 20 additional weeks.		Univariate predictors of attendance included marital status, income, primary caregiver, pre-treatment employment status, chemotherapy dose disruption, total number of chemotherapy dose disruptions, and baseline physical and mental component using (RAND-36), and self-reported moderate-to-vigorous physical activity (MET hours/week). In multivariant analysis - Higher baseline quality of life (QoL) predicted higher attendance during chemotherapy ($\beta = 0.51\%$, 95 CI: 0.09, 0.93)
7	Swenson 2010 Physical activity in women receiving chemotherapy for breast cancer: adherence to a walking intervention	Longitudinal observation study-RCT	36 patients	Participants randomized to physical activity were advised to walk 10,000 steps per day and received initial physical therapy consultation and ongoing motivational interviewing. Multilevel modeling was used to identify variables that predict adherence.	Baseline inactivity predicted adherence. Adherence to the walking program was compromised during chemotherapy but improved after chemotherapy completion.

| 8 | Kirkham 2018

Exercise Prescription and Adherence for Breast Cancer | RCT | 68 women
Supervised 1-hour protocol- aerobic, resisted, moderate intensity exercises 3 times/week.
Adherence to exercise frequency (i.e., attendance), intensity, time/duration, and barriers to adherence were tracked and compared during chemotherapy versus radiation, and during treatment (chemotherapy plus radiation, if received) versus after treatment. | | Attendance decreased with cumulative chemotherapy dose and was lower during chemotherapy than radiation and after treatment than during treatment (p < 0.01).
Adherence to exercise intensity was higher during chemotherapy than radiation (p = 0.06) and was higher during than after treatment (p= 0.01).
Overall adherence to the resistance prescription was poor, but was higher during chemotherapy than radiation (p < 0.01) |
| 9 | Mazzoni 2020

Exercise Adherence and Effect of Self-Regulatory Behavior Change Techniques in Patients Undergoing Curative Cancer Treatment: Secondary Analysis from the Phys-Can Randomized Controlled Trial | Multicentre RCT | FITT principle and dropouts on adherence
BCT on exercise adherence

Two groups 1. High intensity- with BCT, without BCT 2. LMI –with BCT without BCT | Exercise adherence rate ≥50% for each FITT-principle and dropout rates at ~30% | Self-regulatory BCTs did not show improvement in exercise adherence. The main reason for the decrease in adherence is disease and treatment-related symptoms, and medical appointments. |

AET=aerobic exercise training; T= Total, I=Intervention; C=Control; CT=chemotherapy; PA=physical activity; RET =resistance exercise training; RT= radiation therapy; TTM= Transtheoretical Model; BCT= Behaviour change techniques; FITT= Frequency, Intensity, Time and Type, LMI= Low to moderate intensity exercise; ** = significant

Table 2: Pedro Score- Quality Assessment Tool

Item	Courneya 2008	Shang 2012	Van Maart 2020	Bland Kelley 2018	Swenson 2010	Kirkham 2018	Mazzoni 2020	Courneya 2014	Courneya 2008
Inclusive and Exclusive Criteria	1	1	1	1	1	1	1	1	1
Randomization	1	1	1	1	1	1	1	1	1
Concealed allocation	1	0	1	1	0	0	1	1	1
Group similarity at baseline	1	1	1	1	1	1	1	1	1
Blinding of patients	0	0	1	1	1	0	1	0	1
Blinding of therapists	0	0	0	0	1	0	1	0	1
Blinding of assessors	0	0	0	0	1	0	1	0	1
Obtained measures of >85%of >1 outcome	1	1	1	0	1	1	1	1	1
Intention to treat analysis	1	1	1	1	0	1	1	1	1
Between-group statistical comparisons	1	1	1	0	0	0	1	1	1
Point measure variability data	1	1	1	1	1	1	1	1	1
Total	**7/10**	**6/10**	**8/10**	**7/10**	**7/10**	**5/10**	**10/10**	**7/10**	**10/10**

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