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Effects of Aerobic and Resistance Exercises on Physical Symptoms in Cancer Patients: A Meta-analysis

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Abstract

Objective. This study aimed to conduct a meta-analysis to establish the effect of exercise interventions on physical symptoms, including fatigue, nausea/vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, and diarrhea in cancer patients and survivors. *Methods*. We searched articles published before April 2017 using the following databases: Cochrane Library, PubMed/MEDLINE, CINAHL, Scopus, PEDro, Health & Medical Collection, and Psychology Database. Randomized controlled trials (RCTs) of exercise intervention in cancer patients, which evaluated cancer-related physical symptoms using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30, were included. Symptom scale data were extracted for meta-analysis. Subgroup analyses were performed for exercise types (aerobic, resistance, and mixed exercise programs). *Results*. Of the 659 articles, 10 RCTs were included in the meta-analysis, of which the mean PEDro score was 5.43 (SD = 1.28). Fatigue, pain, dyspnea, and insomnia were significantly lower in the intervention group than in the control group at postintervention in cancer patients. However, exercise intervention did not promote or suppress nausea/vomiting, loss of appetite, constipation, and diarrhea in cancer patients. The effect of exercise type on each symptom was not different. *Conclusion.* Exercise intervention was confirmed to improve fatigue, pain, and insomnia and might have reduced dyspnea in cancer patients. However, the benefits of exercise on nausea/vomiting, loss of appetite, constipation, and diarrhea were not shown in any exercise type. Further research is warranted to examine the effects of exercise interventions on physical symptoms in cancer patients.

Keywords

cancer, meta-analysis, exercise, physical symptoms, dyspnea

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Introduction

An estimated 21.6 million new cancer cases are expected worldwide by 2030. This estimate is a stark 53% increase from the latest statistics reported by the World Health Organization in 2012. As screening and treatment continue to progress, the overall number of cancer patients and survivors will increase.[1] Although mortality rates have reduced, many cancer patients still suffer from physical and psychological symptoms. Cancer patients have various physical symptoms. Common symptoms include fatigue, nausea/vomiting, pain, dyspnea, insomnia (sleep disturbance), loss of appetite, constipation, diarrhea, drowsiness, hair loss, sore mouth, and sweating.[2] The 3 types of symptoms are acute, chronic, and late symptoms. Acute symptoms develop before or during treatment but have a short duration. Chronic symptoms may continue for months or years, and late symptoms develop months or years after treatments are

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completed. These 3 types of symptoms at any stage of the cancer trajectory have significant adverse effects on cancer patients.[3] Symptoms also occur as side effects of opioids,[4] chemotherapy,[5] and radiotherapy.[6] All symptoms affect the quality of life (QOL) of cancer patients.

Exercise is widely recognized as an effective nonpharmacological therapy in cancer patients.[7-9] A growing body of evidence supports the idea that increasing physical activity provides important benefits to promote psychological outcomes and physical well-being in cancer patients.[9-12] Exercise has been reported to relieve cancer-related physical symptoms such as fatigue,[8,13-15] pain,[8,16] and insomnia.[8,17,18] However, the effects of exercise on other symptoms, including nausea/vomiting, dyspnea, constipation, diarrhea, and loss of appetite, have not been confirmed by meta-analysis of randomized controlled trials (RCTs). On the other hand, the effects of exercise on physical symptoms might differ by type of exercise.[19] Pain and insomnia have been reported to be relieved by aerobic, but not resistance exercise.[10,16,18] Fatigue is improved by both aerobic and resistance exercises.[13,14,19] Thus, aerobic and resistance exercises should be distinguished when the effects of exercise on cancer-related physical symptoms are examined.

This systematic review aimed to determine the effects of aerobic and resistance exercise interventions on physical symptoms by a meta-analysis of RCTs. These symptoms include not only fatigue, pain, and insomnia, but also nausea/vomiting, dyspnea, loss of appetite, constipation, and diarrhea in cancer patients.

Methods

Protocol and Objective

The systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[20] It was also conducted and reported in accordance with the PRISMA statement[20] (PROSPERO Register code: CRD42018091244). No funding support was received in this study.

Search Methods

We performed a literature search to identify articles published before April 2017 using the following databases: Cochrane Library, the Centre for Reviews and Dissemination, PubMed/MEDLINE, CINAHL, Scopus, PEDro, Health & Medical Collection, and Psychology Database. The search strategy was adapted to each database and based on the following MeSH terms: *cancer, tumor, randomized controlled trial, training, rehabilitation*, and *exercise*. The words *disorder for cancer* were also used for the search (eg, lymphoma, hematopoietic malignancy, carcinosarcoma). In addition, the words *outcome on physical symptoms* were added to the search terms (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 and C15-PAL [EORTC QLQ-C30, QLQ-C15-PAL]). Cancer-related symptoms are frequently examined using the EORTC QLQ-C30.[21] The EORTC QLQ-C30 consists of 30 items, and raw patient responses are transformed to produce scores from 0 to 100 on 5 functional scales, 9 symptom scales, and a scale representing global QOL. Higher functional scale scores indicate better health-related QOL, whereas higher symptom scale/item scores indicate higher level of symptoms. QLQ-C30 symptom scales include fatigue, nausea/vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, and diarrhea. Similarly, QLQ-C15-PAL is a questionnaire developed to assess the QOL of palliative cancer care patients and has the same symptom scale as the QLQ-C30 except diarrhea. Attempts were made to contact authors of trial reports if clarification was necessary. Reference lists of identified eligible articles were cross-referenced and hand searched to identify any additional articles.

We included RCTs that evaluated the effects of exercise intervention by QLQ-C30 in cancer patients and survivors in any setting. Even if the primary outcome was not physical symptoms, studies that reported the QLQ-C30 symptom scale were included. Systematic reviews, editorials, cross-sectional studies, case reports, and case series studies were excluded. The interventions were of sufficient intensity as measured in metabolic equivalent of task, thus excluding stretching exercises, yoga, Pilates, and education. The exercise interventions for shoulder joint in breast cancer patients and pelvic floor muscle training in patients with gynecological cancer were also excluded. Comparisons were with a control group not receiving any (major) exercise intervention or other interventions (eg, cognitive behavioral therapy). Groups with only attention, relaxation, or education were considered as control groups.

Titles and subsequent abstracts of trials were retrieved and screened by 3 independent reviewers (KH, KU, and EM) to identify trials that met the inclusion criteria. A fourth independent reviewer (JN) resolved any discrepancies between the 2 reviewers. Full texts of potentially eligible trials were retrieved and assessed for eligibility by 2 independent reviewers (JN and TF). Articles deemed eligible were included after the full-text screening. To perform the meta-analysis, data details were examined. Studies that did not show numerical data of QLQ-C30 at postintervention were excluded. Final inclusion of eligible RCTs was determined in consensus meetings in which all authors participated.

Quality Assessment

The methodological quality of the studies, including their risk of bias, was assessed using the PEDro Scale, which is based on the Delphi list.[22] The PEDro scale scores the methodological quality of randomized trials out of 10. A PEDro cutoff of 5 points is used widely.[23] The score for each included study was determined by a trained assessor (JN). Additionally,

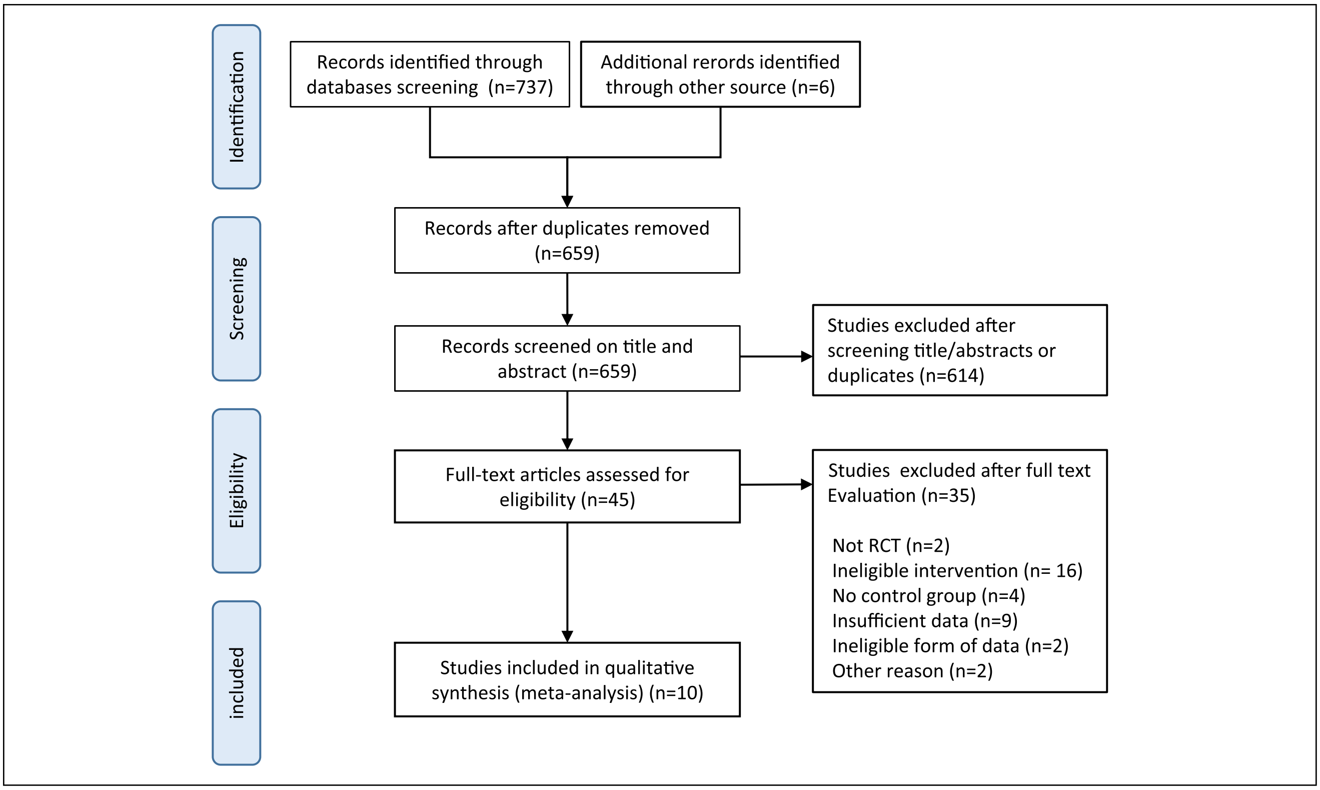


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) study flow diagram of the selection process.
Abbreviation: RCT, randomized controlled trial.

the score, which was shown in the PEDro physiotherapy evidence database, was referred. Final scores were determined in consensus meetings in which all authors participated.

Data Extraction

Data were extracted by one of the authors (JN). When insufficient data were available in the full text, authors were contacted by email for further information. The following data were extracted from each study by 2 investigators: first author's last name, publication year, study location and duration, sample size, type of exercise, and timing of exercise. The following data from the QLQ-C30 physical symptom scales were selected for the meta-analysis: fatigue, nausea/vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, and diarrhea. Means and SDs of postintervention were extracted. It is premised that no significant difference exists between the intervention and control groups at baseline (preintervention).

Data Analysis

All statistical analyses were conducted using Review Manager (RevMan) version 5.1.[24] We calculated standard mean differences (SMDs) with 95% CIs. SMDs were significant if their 95% CIs excluded zero. The random effect model was used as the pooling method to assume heterogeneity between different exercise types. We assessed statistical heterogeneity using the I^2 statistic. We adopted the levels of I^2 suggested by the *Cochrane Handbook for Systematic Reviews of Interventions* (I^2 values of 0%, 25%, 50%, and 75% represented no, low, moderate, and high heterogeneity, respectively).[25] The threshold for interpreting the I^2 value can be misleading. Therefore, we determined the importance of the observed I^2 value by looking at the magnitude and direction of the effect as well as at the strength of evidence for clinical heterogeneity. Subgroup analyses were performed for exercise types (aerobic, resistance, and mixed exercise programs).

Results

Study Selection

The database searches retrieved 743 references, which were reduced to 659 after excluding duplicate articles. The 659 studies were subjected to title and abstract screening, and 614 RCTs were excluded because of irrelevant study design, or issues with population or intervention. A full-text review was performed for 45 RCTs and, consequently, 35 RCTs were excluded. Although 2 articles were appropriate RCTs, they were not included in the meta-analysis because of differences in data form.[26,27] Thus, data extraction was performed on 10 RCTs. Figure 1 shows the outcome of the search process and study selection.

The included studies were conducted in various countries: 4 in Germany,[28-31] 2 in the United States,[32,33] and 1 each in Denmark,[34] South Korea,[35] Australia,[36] and Switzerland.[37] Some of the RCTs were published in more than 1 article.

Study Characteristics

The detailed characteristics of the 10 RCTs are shown in Table 1. All interventions in the RCTs lasted for 16 weeks,[32] 12 weeks,[30,36,37] 8 weeks,[35] 6 weeks,[33,34] 3 weeks,[29] or the duration of hospitalization for cancer treatment.[28,31] The most prevalent cancer type was hematological malignancy,[28,31,33,37] followed by breast cancer.[30,32,35] In 2 RCTs,[29,34] participants with various cancer types were included.

The exercise carried out in the intervention group in RCTs included various exercise programs, which were mainly aerobic, resistance, stretching, and walking exercise. The intervention exercises were difficult to classify strictly. In this study, the intervention exercises in the included RCTs were classified into 3 types: aerobic, resistance, and mixed exercise programs. Aerobic exercise programs were performed in 4 RCTs,[28-30,32] resistance exercise programs in 3 RCTs,[30,33,35] and mixed exercise programs, including both aerobic and resistance exercise programs, in 4 RCTs.[31,34,36,37] In 1 RCT,[30] aerobic and resistance exercise programs were performed in 2 different groups; the data from both groups were extracted and analyzed separately. The timings of the exercise interventions performed were mainly postsurgery, posttransplantation (hematological malignancy), and during chemotherapy. The QLQ-C30 was used as outcome for physical symptoms in all RCTs but not the QLQ-C15-PAL.

Risk of Bias

Given that all included studies were RCTs, the level of evidence from all studies was II according to the National Health and Medical Research Council Hierarchy of Evidence Scale.[38] The assessment of risk of bias showed a mean PEDro score of 5.43 (SD = 1.28; Table 2). Individually, 4 RCTs showed a PEDro score of 4 points,[28] which were slightly lower than the cutoff for high-quality trials.[23,33,35]

Effect of Exercise on Physical Symptoms

A total 10 RCTs were included in a random-effects meta-analysis.[28-37] The efficacy of exercise on physical symptoms in cancer patients was then estimated in a forest plot. The 10 RCTs included in this review consisted of 893 participants: 434 in the exercise groups and 459 in the control group. In 1 RCT,[30] both effects of aerobic and resistance exercise programs were examined. Therefore, 11 intervention groups from 10 RCTs were included in the meta-analysis.

Fatigue. The meta-analysis of 11 intervention groups from 10 RCTs[28-37] showed that fatigue in the intervention group was significantly lower than that in the control group (SMD = −0.30, 95% CI = −0.46 to −0.13, P = .0004; Figure 2A). The statistical heterogeneity was moderate (I^2 = 26%). Subgroup analysis of exercise types demonstrated no significant difference among the 3 subgroups (P = .39; I^2 = 0%). Within only the mixed exercise program subgroup,[31,34,36,37] an improvement effect in favor of the intervention group was found (SMD = −0.41; 95% CI = −0.66 to −0.17; P = .0009; I^2 = 46%).

Nausea/Vomiting. A meta-analysis of 10 intervention groups from 9 RCTs[28-34,36,37] was performed. However, in 1 RCT,[33] the SMD was not calculated because the values of the mean and SD were zero. As a result, no significant difference in nausea/vomiting was found between the intervention and control groups (SMD = −0.09, 95% CI = −0.24 to 0.06, P = .24; Figure 2B). Subgroup analysis of exercise types also demonstrated no significant differences among the 3 subgroups (P = .13; I^2 = 51.6%).

Pain. The meta-analysis of 11 intervention groups from 10 RCTs[28-37] showed that pain in the intervention group was significantly lower than that in the control group (SMD = −0.17, 95% CI = −0.32 to −0.03, P = .02; Figure 2C). The statistical heterogeneity was low (I^2 = 9%). A subgroup analysis of exercise types demonstrated no significant difference among the 3 subgroups (P = .18; I^2 = 41.1%). Within only the mixed exercise program subgroup,[31,34,36,37] an improvement effect in favor of the intervention group was found (SMD = −0.28; 95% CI = −0.47 to −0.09; P = .005; I^2 = 20%).

Dyspnea. The meta-analysis of 11 intervention groups from 10 RCTs[28-37] showed that dyspnea in the intervention group was significantly lower than that in the control group (SMD = −0.22, 95% CI = −0.35 to −0.09, P = .001; Figure 2D). The statistical heterogeneity was low (I^2 = 0%). Subgroup analysis of exercise types demonstrated no significant differences among the 3 subgroups (P = .62; I^2 = 0%). Within only the mixed exercise program subgroup,[31,34,36,37] an improvement effect in favor of the intervention group was found (SMD = −0.27; 95% CI = −0.49 to −0.06; P = .01; I^2 = 33%).

Insomnia. The meta-analysis of 10 intervention groups from 9 RCTs[28-34,36,37] showed that insomnia in the intervention group was significantly lower than that in the control group (SMD = −0.28, 95% CI = −0.41 to −0.15, P < .0001; Figure 2E). The statistical heterogeneity was low (I^2 = 0%). Subgroup analysis of exercise types demonstrated no

Table 1. Characteristics of Studies Included.

Author, Year	Intervention	Participants (Gender, Number, Age)	Cancer Type	Intervention	Duration	Timing	Measure (Outcome)
Adamsen et al,[34] 2009	EX, mixed exercise program vs CON, usual care	Female, 73% EX, 135; 47.2 ± 10.6 years CON, 134; 47.2 ± 10.7 years	Mixed	Resistance exercise: 3 sets of 5-8 repetitions at 70%-100% of 1 RM, 45 minutes Aerobic exercise: 85%-95% of maximum heart rate, 15 minutes 3 times per week	6 Weeks	During chemotherapy	EORTC QLQ-C30, SF-36, physical activity, questionnaire, muscular strength, maximum O_2
Baumann et al,[28] 2011	EX, aerobic exercise program vs CON, usual rehabilitation	Female, 52% EX, 17; 41.4 ± 11.8 years CON, 16; 42.8 ± 14.0 years	Hematological	Aerobic exercise by bicycle ergometer: the intensity was 80% of achieved watt load in the WHO test. 10-20 Minutes of ADL training was also conducted during chemotherapy twice per day	During hospitalization EX: 56.1 days CON: 51.4 days	Posttransplantation	EORTC QLQ-C30, aerobic endurance, maximal strength, lung function
Dimeo et al,[29] 2004	EX, aerobic exercise program vs CON, relaxation control	Female, 26% EX, 34; 55.1 ± 10 years CON, 35; 60.0 ± 9.5 years	Mixed	Biking on a stationary bike; training intensity corresponded to a heart rate of about 80% of the maximal heart rate, 30 minutes daily, 5 days per week	3 Weeks	Postsurgery	EORTC QLQ-C30, ergometer test
Do et al,[35] 2015	EX, resistance exercise program vs CON, usual rehabilitation	Female, 100% EX, 22; 49.7 ± 7.1 years CON, 22; 49.6 ± 10.4 years	Breast	Resistance exercise using elastic tubing. 60% of 1 RM, 3 sets of 10 repetitions, rest for 2 minutes between exercise sets; 5 times per week	8 Weeks	Postsurgery or/and radiotherapy	EORTC QLQ-C30 and BR23, DASH, volume and strength of muscle
Galvao et al,[36] 2010	EX, mixed exercise program vs CON, usual care	Female, 0% EX, 29; 69.5 ± 7.3 years CON, 28; 70.1 ± 7.3 years	Prostate	Resistance exercise: 12 to 6 repetitions, maximum of 2 to 4 sets per exercise Aerobic exercise: 15 to 20 minutes of cardiovascular at 65% to 80% maximum heart rate, twice per week	12 Weeks	During hormonal therapy	EORTC QLQ-C30, DXA, muscle strength, endurance, functional performance, balance, blood samples
Hacker et al,[33] 2011	Resistance exercise program vs Usual care (control)	Female, 26% EX, 9 CON, 10 46.3 ± 16.2 Years (total)	Hematological	Resistance exercise consisted of 11 preselected exercises using elastic resistance bands. The Borg Scale (20-point scale) was used to estimate the intensity of the resistance; 6 times per week	6 Weeks	Posttransplantation	EORTC QLQ-C30, timed stair climb, handgrip strength, 30-s chair-stand test, Fatigue Intensity Scale, quality of life index
Knols et al,[37] 2011	EX, mixed exercise program vs Usual care (control)	Female, 41.2% EX, 64; 46.7 ± 13.7 years CON, 67; 46.6 ± 12.0 years	Hematological	Resistance exercise: dumbbells, squats, barbell rotations, and step-ups Aerobic exercise by bicycle ergometer: 50%-60%, increasing up to 70%-80% of maximum heart rate, 20 minutes, twice per day	12 Weeks	Posttransplantation	EORTC QLQ-C30, muscle strength, walk speed, 6MWT
Ligibel et al,[32] 2016	EX, aerobic exercise program vs CON, wait-list control	Female, 100% EX, 47; 49.3 ± 9.6 years CON, 51; 50.7 ± 9.4 years	Breast	Moderate-intensity aerobic exercise program; the target goal was 150 minutes of moderate-intensity exercise per week	16 Weeks	Presurgery	EORTC QLQ-C30, modified Bruce ramp, treadmill test, physical activity recall interview, FACIT
Schmidt et al,[30] 2015	EX1, aerobic exercise program vs EX2, resistance exercise vs CON, usual care	Female, 100% EX1, 21; 53 ± 12.6 years EX2, 22; 56 ± 10.2 years CON, 26; 54 ± 11.2 years	Breast	EX 1: aerobic exercise by bicycle ergometer: Borg level 11-14, 25-30 minutes EX 2: resistance exercise: 20 repetitions, with 50% of the maximum weight. Any further increase in intensity was based on the Borg scale; twice per week	12 Weeks	Postsurgery and during chemotherapy	EORTC QLQ-C30, QLQ-BR23, MFI, D2-Test; Borg Scale, muscular strength
Wiskemann et al,[31] 2011	EX, mixed exercise program vs CON, attention control	Female, 100% EX, 52; 47.6 (18-70) years CON, 53; 50.0 (20-71) years	Hematological	Aerobic exercise by bicycling and treadmill walking: Borg scale 12-14, 20 to 40 minutes, 3 times per week Resistance exercise using stretch bands resistance. 8-20 repetitions, 2 or 3 sets. Borg scale 14-16, twice per week	During hospitalization EX: 43 (22-120) days CON: 45 (24-92) days	During and after hospitalization	EORTC QLQ-C30, MFI, HADS, POMS, NCCN

Abbreviations: EX, experimental; CON, control; RM, repetition maximum; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; SF, Short Form; WHO, World Health Organization; ADL, activities of daily living; DASH, Disability of Arm, Shoulder and Hand Score; DXA, dual energy X-ray absorptiometry; 6MWT, 6 Minutes Walking Test; FACIT, Functional Assessment of Chronic Illness Therapy; MFI, Multidimensional Fatigue Inventory; D2-Test, evaluation of cognitive function; HADS, Hospital Anxiety and Depression Scale; POMS, Profile of Mood States; NCCN, National Comprehensive Cancer Network.

Table 2. Assessment of Methodological Quality and Risk of Bias With the PEDro Scale.

	Scores[a]											
Author	0	1	2	3	4	5	6	7	8	9	10	Total
Adamsen et al[34]	Yes	1	1	1	0	0	0	1	1	1	1	7
Baumann et al[28]	Yes	1	0	1	0	0	0	0	0	1	1	4
Dimeo et al[29]	Yes	1	1	1	0	0	0	1	0	1	1	6
Do et al[35]	Yes	1	0	1	0	0	0	1	0	1	0	4
Galvao et al[36]	Yes	1	1	1	1	0	0	0	1	1	1	7
Hacker et al[33]	Yes	1	1	0	1	0	0	0	0	0	1	4
Knols et al[37]	Yes	1	1	1	0	0	1	1	1	1	1	8
Ligibel et al[32]	Yes	1	0	1	0	0	1	1	0	1	1	5
Schmidt et al[30]	Yes	1	1	1	0	0	1	0	0	1	1	5
Wiskemann et al[31]	No	1	0	1	0	0	0	0	1	1	1	5

[a]The criteria addressed the following issues: 0, eligibility criteria; 1, random allocation; 2, concealed allocation; 3, groups similar at baseline; 4, participant blinding; 5, therapist blinding; 6, assessor blinding; 7, <15% dropouts; 8, intention-to-treat analysis; 9, between-group difference reported; 10, point estimate and variability reported. Each criterion was given equal weight (ie, 1 point) for a maximum sum score (criteria 1-10) of 10.

significant differences among the 3 subgroups (P = .99; I^2 = 0%). Within only the mixed exercise program subgroup,[31,34,36,37] an improvement effect in favor of the intervention group was found (SMD = −0.28; 95% CI = −0.41 to −0.15; P = .0005; I^2 = 0%).

Loss of Appetite. The meta-analysis of 9 intervention groups from 8 RCTs[28,30-34,36,37] also showed no significant difference in loss of appetite between the intervention and control groups (SMD = −0.08, 95% CI = −0.22 to 0.06, P = .29; Figure 2F). No significant difference was found among the 3 subgroups (P = .50; I^2 = 0%).

Constipation. Nine intervention groups from 8 RCTs[28,30-34,36,37] were included in the meta-analysis. However, the SMD was not calculated in 2 RCTs[28,33] because the values of the mean and SD were zero in the constipation symptom scale. Therefore, the analysis was performed for 7 groups from 6 RCTs.[30-32,34,36,37] No significant difference in constipation was found between the intervention and control groups (SMD = −0.02, 95% CI = −0.16 to 0.12, P = .80, I^2 = 0%; Figure 2G). No significant difference was found among the 3 subgroups (P = .97; I^2 = 0%).

Diarrhea. In 2 RCTs,[30,33] the SMD was not calculated because the values of the mean and SD were zero on the Diarrhea Symptom Scale. Seven intervention groups from 7 RCTs were included in the meta-analysis.[30-32,34,36] No significant difference was noted in diarrhea between the intervention and control groups (SMD = −0.09, 95% CI = −0.33 to 0.14, P = .45, I^2 = 54%; Figure 2H). No significant difference was found among the 3 subgroups (P = .32, I^2 = 12.7%).

Discussion

This systematic review aimed to examine the current body of evidence on the benefits of an exercise intervention for cancer-related physical symptoms. The physical symptoms included fatigue, nausea/vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, and diarrhea, which were evaluated using the EORTC QLQ-C30. The effects of exercise on cancer-related fatigue, pain, and insomnia were examined in some systematic reviews with meta-analysis.[8,39-41] However, to the best of our knowledge, this systematic review with meta-analyses is the first to focus on nausea/vomiting, dyspnea, loss of appetite, constipation, and diarrhea in cancer patients.

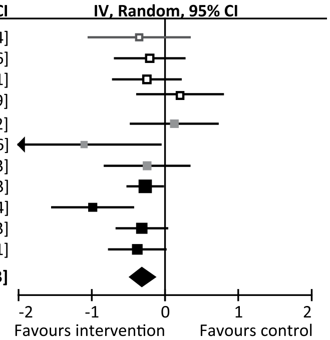
The benefits of exercise on fatigue,[8,15] pain,[8] and insomnia[8,18] in cancer patients were previously confirmed statistically by meta-analysis. In particular, a large number of RCTs and systematic reviews on fatigue exist. Most studies showed the benefit of exercise on fatigue in cancer patients, and the result of our analysis show similar evidence. In contrast, only a few studies investigated the effect of exercise on pain and insomnia. Several meta-analyses showed the benefit of exercise on pain and insomnia[8,18] but had insufficient reliable evidence. Our meta-analysis including 10 RCTs showed the pooled effect of exercise on pain significantly, which establishes the evidence for an effect of exercise on pain and insomnia in cancer patients.

The important result is that exercise intervention leads to mild subjective improvements in dyspnea in cancer patients. Dyspnea is a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity.[42] Dyspnea is also a relatively common and highly debilitating symptom in cancer patients. It often leads to anxiety, depression, and exercise avoidance, thereby worsening deconditioning and reducing health-related QOL.[43] Additionally, cancer treatments are a major cause of dyspnea. Specifically, radiation and chemotherapy can cause pneumonitis, pulmonary fibrosis, pulmonary and cardiac toxicity, anemia, pulmonary emboli, and cachexia in a significant proportion of patients, all of which can initiate or worsen the direct cancer-related sensations of dyspnea.[44] Comorbid disease can be a significant contributor, particularly if cardiac or pulmonary diseases are involved in cancer patients.[45] The main treatment for dyspnea in cancer patients is pharmacotherapy, such as opioids.[46] Exercise may be an effective care for dyspnea in cancer patients. The effect of exercise on dyspnea in cancer patients was examined. Although the benefit of exercise on respiratory function was shown clearly,[47] evidence on the effect of exercise on dyspnea in cancer patients from a meta-analysis was not indicated because of

A Fatigue

Study	Intervention Mean	Intervention SD	Intervention Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Baumann 2011	43.8	22.7	17	52.8	27.1	16	5.0%	-0.35 [-1.04, 0.34]
Dimeo 2004	34	21	34	39	26	35	9.2%	-0.21 [-0.68, 0.26]
Ligibel 2016	29.2	21.4	32	35.5	27.5	43	9.6%	-0.25 [-0.71, 0.21]
Schmidt T 2015A	48	21.8	20	43.5	21.5	26	6.6%	0.20 [-0.38, 0.79]
Do 2015	24	23.4	22	21	23.4	22	6.4%	0.13 [-0.47, 0.72]
Hacker 2011	23.6	13.9	8	46.9	24.1	9	2.4%	-1.11 [-2.15, -0.06]
Schmidt T 2015B	38.6	17.4	21	43.5	21.5	26	6.7%	-0.24 [-0.82, 0.33]
Adamsen 2009	34.6	24.3	135	41	22.7	134	20.7%	-0.27 [-0.51, -0.03]
Galvao 2010	14.8	13.8	29	30.6	17.6	28	7.2%	-0.99 [-1.54, -0.44]
Knols 2011	31.6	22.1	64	38.3	20	67	14.1%	-0.32 [-0.66, 0.03]
Wiskemann 2011	49.7	28.9	52	60.8	29.2	53	12.2%	-0.38 [-0.77, 0.01]
Total (95% CI)			**434**			**459**	**100.0%**	**-0.30 [-0.46, -0.13]**

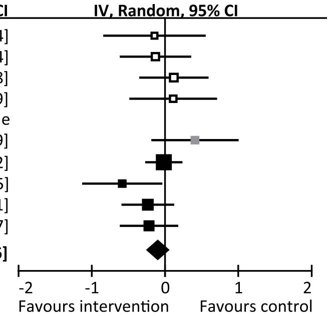
Heterogeneity: Tau² = 0.02; Chi² = 13.57, df = 10 (P = 0.19); I² = 26%
Test for overall effect: Z = 3.55 (P = 0.0004)



B Nausea / vomiting

Study	Intervention Mean	Intervention SD	Intervention Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Baumann 2011	10.8	18.6	17	13.5	17.7	16	4.5%	-0.14 [-0.83, 0.54]
Dimeo 2004	9	20	34	12	25	35	9.1%	-0.13 [-0.60, 0.34]
Ligibel 2016	7.3	11	32	5.4	18.4	43	9.6%	0.12 [-0.34, 0.58]
Schmidt T 2015A	10	17.4	20	8.3	13	26	6.1%	0.11 [-0.47, 0.69]
Hacker 2011	0	0	8	1.9	5.6	9		Not estimable
Schmidt T 2015B	14.3	16.1	21	8.3	13	26	6.2%	0.41 [-0.17, 0.99]
Adamsen 2009	13.4	17.3	135	13.7	18.4	134	28.2%	-0.02 [-0.26, 0.22]
Galvao 2010	0.7	3.3	29	4	7.2	28	7.3%	-0.58 [-1.12, -0.05]
Knols 2011	3.7	9.9	64	6.5	13.4	67	15.9%	-0.24 [-0.58, 0.11]
Wiskemann 2011	13.8	22.3	52	19.2	26.6	53	13.1%	-0.22 [-0.60, 0.17]
Total (95% CI)			**412**			**437**	**100.0%**	**-0.09 [-0.24, 0.06]**

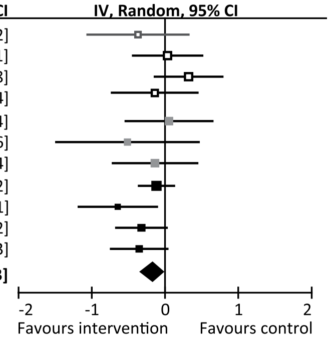
Heterogeneity: Tau² = 0.01; Chi² = 8.94, df = 8 (P = 0.35); I² = 11%
Test for overall effect: Z = 1.17 (P = 0.24)



C Pain

Study	Intervention Mean	Intervention SD	Intervention Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Baumann 2011	22.5	25.6	17	32.3	26.2	16	4.2%	-0.37 [-1.06, 0.32]
Dimeo 2004	30	27	34	29	30	35	8.5%	0.03 [-0.44, 0.51]
Ligibel 2016	25.5	20.3	32	18.9	20.4	43	8.9%	0.32 [-0.14, 0.78]
Schmidt T 2015A	20.8	24.1	20	24.3	25	26	5.8%	-0.14 [-0.72, 0.44]
Do 2015	30.7	28.2	22	29.1	30.4	22	5.7%	0.05 [-0.54, 0.64]
Hacker 2011	18.8	20.8	8	35.2	36.8	9	2.2%	-0.51 [-1.48, 0.46]
Schmidt T 2015B	20.6	28.3	21	24.3	25	26	5.9%	-0.14 [-0.71, 0.44]
Adamsen 2009	14.6	17.1	135	16.8	20.6	134	25.3%	-0.12 [-0.36, 0.12]
Galvao 2010	8	11.9	29	17.3	16.3	28	6.8%	-0.64 [-1.18, -0.11]
Knols 2011	17.8	27.1	64	26.8	28.4	67	14.6%	-0.32 [-0.67, 0.02]
Wiskemann 2011	25	31.8	52	35.8	28.9	53	12.1%	-0.35 [-0.74, 0.03]
Total (95% CI)			**434**			**459**	**100.0%**	**-0.17 [-0.32, -0.03]**

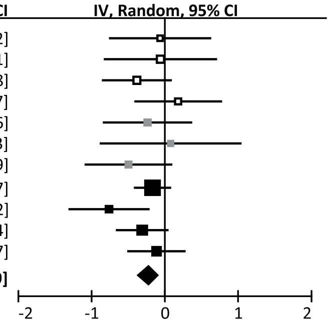
Heterogeneity: Tau² = 0.01; Chi² = 11.30, df = 10 (P = 0.33); I² = 12%
Test for overall effect: Z = 2.31 (P = 0.02)



D Dyspnea

Study	Intervention Mean	Intervention SD	Intervention Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Baumann 2011	27.4	24.3	17	29.2	29.5	16	3.7%	-0.07 [-0.75, 0.62]
Dimeo 2004	30	33	34	32	32	35	7.8%	-0.06 [-0.53, 0.41]
Ligibel 2016	9.3	23.1	32	17.5	19.8	43	8.2%	-0.38 [-0.84, 0.08]
Schmidt T 2015A	31.7	35	20	26.3	24	26	5.1%	0.18 [-0.40, 0.77]
Do 2015	24	27.4	22	30.7	28.2	22	5.0%	-0.24 [-0.83, 0.36]
Hacker 2011	12.5	17.3	8	11.1	16.7	9	1.9%	0.08 [-0.87, 1.03]
Schmidt T 2015B	15	20.1	21	26.3	24	26	5.1%	-0.50 [-1.08, 0.09]
Adamsen 2009	14.3	21.5	135	18.2	24.4	134	30.5%	-0.17 [-0.41, 0.07]
Galvao 2010	6.3	13.6	29	22.6	26.7	28	6.0%	-0.76 [-1.30, -0.22]
Knols 2011	21.8	24.6	64	29.2	23	67	14.7%	-0.31 [-0.65, 0.04]
Wiskemann 2011	30	25.9	52	33.3	31.1	53	11.9%	-0.11 [-0.50, 0.27]
Total (95% CI)			**434**			**459**	**100.0%**	**-0.22 [-0.35, -0.09]**

Heterogeneity: Tau² = 0.00; Chi² = 8.78, df = 10 (P = 0.55); I² = 0%
Test for overall effect: Z = 2.31 (P = 0.02)

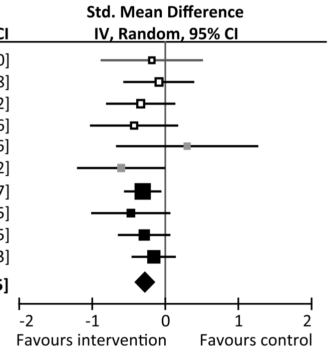


(continued)

E Insomnia

Study	Intervention Mean	Intervention SD	Intervention Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Baumann 2011	35.3	32.2	17	41.7	35.5	16	3.6%	-0.18 [-0.87, 0.50]
Dimeo 2004	31	31	34	34	35	35	7.5%	-0.09 [-0.56, 0.38]
Ligibel 2016	21.8	34.5	32	32.5	28.9	43	7.9%	-0.34 [-0.80, 0.12]
Schmidt T 2015A	35	35	20	50	34.1	26	4.8%	-0.43 [-1.02, 0.16]
Hacker 2011	25	23.6	8	18.5	17.6	9	1.8%	0.30 [-0.66, 1.26]
Schmidt T 2015B	29.8	31.2	21	50	34.1	26	4.8%	-0.60 [-1.19, -0.02]
Adamsen 2009	18.4	23.9	135	26.4	27.5	134	29.0%	-0.31 [-0.55, -0.07]
Galvao 2010	18.7	23.7	29	31.9	31.1	28	6.0%	-0.47 [-1.00, 0.05]
Knols 2011	23	27.4	64	31.5	30.8	67	14.1%	-0.29 [-0.63, 0.05]
Wiskemann 2011	30.8	32.4	52	35.8	31.5	448	20.3%	-0.16 [-0.45, 0.13]
Total (95% CI)			**412**			**832**	**100.0%**	**-0.28 [-0.41, -0.15]**

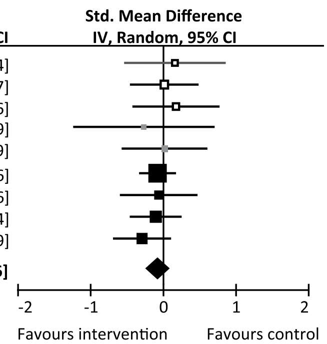
Heterogeneity: Tau² = 0.00; Chi² = 4.83, df = 9 (P = 0.85); I² = 0%
Test for overall effect: Z = 4.17 (P < 0.0001)



F Loss of appetite

Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Baumann 2011	31.4	24.9	17	27.1	27.8	16	4.2%	0.16 [-0.52, 0.84]
Ligibel 2016	10.4	28.5	32	10.1	21.2	43	9.5%	0.01 [-0.45, 0.47]
Schmidt T 2015A	23.3	28.8	20	18.7	24	26	5.8%	0.17 [-0.41, 0.76]
Hacker 2011	12.5	17.3	8	18.5	24.2	9	2.2%	-0.27 [-1.23, 0.69]
Schmidt T 2015B	19.1	29	21	18.7	24	26	6.0%	0.01 [-0.56, 0.59]
Adamsen 2009	12.8	22.3	135	14.6	22.1	134	34.7%	-0.08 [-0.32, 0.16]
Galvao 2010	5.3	15.7	29	6.6	23.5	28	7.4%	-0.06 [-0.58, 0.46]
Knols 2011	8.6	17.2	64	10.7	22.1	67	16.9%	-0.11 [-0.45, 0.24]
Wiskemann 2011	31.7	35.4	52	42.5	37.7	53	13.4%	-0.29 [-0.68, 0.09]
Total (95% CI)			**378**			**402**	**100.0%**	**-0.08 [-0.22, 0.06]**

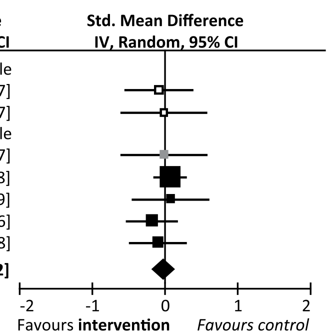
Heterogeneity: Tau² = 0.00; Chi² = 2.80, df = 8 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.07 (P = 0.29)



G Constipation

Study	Intervention Mean	Intervention SD	Intervention Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Baumann 2011	7.8	14.6	17	0	0	16		Not estimable
Ligibel 2016	8.3	21.5	32	10.1	20.6	43	9.3%	-0.08 [-0.54, 0.37]
Schmidt T 2015A	21.6	32.9	20	22.2	36.3	26	5.7%	-0.02 [-0.60, 0.57]
Hacker 2011	4.2	11.8	8	0	0	9		Not estimable
Schmidt T 2015B	21.7	29.2	20	22.2	36.3	26	5.7%	-0.01 [-0.60, 0.57]
Adamsen 2009	20.8	39.4	221	18.4	25.3	134	42.2%	0.07 [-0.15, 0.28]
Galvao 2010	8	19.9	29	6.6	16.6	28	7.2%	0.08 [-0.44, 0.59]
Knols 2011	4.6	17	64	7.7	16.8	67	16.5%	-0.18 [-0.53, 0.16]
Wiskemann 2011	4.2	17.2	52	5.8	14.9	53	13.3%	-0.10 [-0.48, 0.28]
Total (95% CI)			**463**			**402**	**100.0%**	**-0.02 [-0.16, 0.12]**

Heterogeneity: Tau² = 0.00; Chi² = 1.89, df = 6 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.80)



H Diarrhea

Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Baumann 2011	23.5	28.3	17	20.8	26.9	16	8.3%	0.10 [-0.59, 0.78]
Ligibel 2016	17.7	19.4	32	13.9	25.1	43	13.7%	0.16 [-0.29, 0.62]
Schmidt T 2015A	0	0	20	11.11	25.4	26		Not estimable
Hacker 2011	0	0	8	11.1	23.6	9		Not estimable
Schmidt T 2015B	15	27.5	21	11.11	25.4	26	10.5%	0.15 [-0.43, 0.72]
Adamsen 2009	17	26.1	135	13	21.9	134	22.0%	0.17 [-0.07, 0.40]
Galvao 2010	6.6	13.6	29	14.6	23.7	28	11.7%	-0.41 [-0.94, 0.11]
Knols 2011	8.6	18.3	64	18.5	24.6	67	17.6%	-0.45 [-0.80, -0.11]
Wiskemann 2011	10.8	25.5	52	18.3	27.2	53	16.2%	-0.28 [-0.67, 0.10]
Total (95% CI)			**378**			**402**	**100.0%**	**-0.09 [-0.33, 0.14]**

Heterogeneity: Tau² = 0.05; Chi² = 12.92, df = 6 (P = 0.04); I² = 54%
Test for overall effect: Z = 0.76 (P = 0.45)

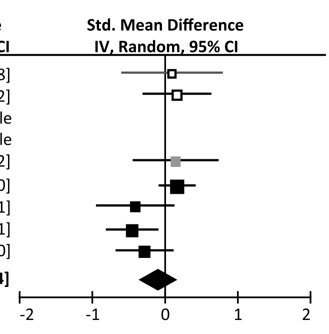


Figure 2. Meta-analysis for the effect estimate of exercise on physical symptoms in cancer patients.
Standardized mean difference (SMD) was calculated for the Random effects model of meta-analysis. IV, inverse of variance; CI, confidence interval. Subgroups were indicated by color in forest plot: aerobic exercise (white), resistance exercise (gray) and mixed exercise program (black). The pooled effects in each subgroups were not shown (see the main text for more details).

insufficient RCTs.[48] Our analysis showed evidence of this effect through a meta-analysis of 10 RCTs. Dyspnea is known to occur frequently in patients with lung cancer, such as non–small-cell lung cancer.[48] However, the number of patients with lung cancer was small in this study; at most 46 out of 780 patients with lung cancer participated in RCTs, which included cancer patients with mixed cancer types.[29,34] Therefore, the influence of cancer type was not strong enough. The results of dyspnea were not different when subgroup analysis by cancer type was performed (data not shown). Although this study has several limitations, the possibility of the effect of exercise on dyspnea in cancer patients was indicated.

Meta-analyses of the effects of exercise on nausea/vomiting, loss of appetite, constipation, and diarrhea in cancer patients have not been performed. Generally, regular exercise and physical activity are speculated to be related to constipation, but only limited evidence is available.[49] According to our meta-analysis, exercise of any type might not be effective on constipation in cancer patients, which might be induced by impact of tumor, opioid as side effect, or physical inactivity.[50,51] This result also supports the negative opinion on the effect of exercise on constipation.[52] With regard to nausea/vomiting and loss of appetite, it could not be concluded whether exercise suppressed or promoted these symptoms. Exercise has been reported to promote nausea/vomiting[53] and could promote loss of appetite[54] in healthy people. In contrast, exercise could also suppress these symptoms in noncancer patients.[55,56] No information is available on the effect of exercise on diarrhea. Our meta-analysis showed that an effect of exercise on these symptoms was not found. It was also considered that exercise at least does not promote these symptoms in cancer patients.

In this study, subgroup analyses were performed for exercise types (aerobic, resistance, and mixed exercise programs). Although a statistically significant difference of effect among exercise types was not detected in all physical symptoms, the pooled effect was different for each subgroup of exercise type. Improvement was observed in fatigue, insomnia, pain, and dyspnea only within the mixed exercise program subgroup. Further RCTs are required to examine the different effects of exercise type on each physical symptom.

This review has several important limitations that should be considered. First, the number of trials was small. The number of RCTs was reduced because the outcome of physical symptom was limited to QLQ-C30 and C15-PAL, which was intended by the authors. In this review and meta-analysis, we found a new possibility of exercise as supportive care to common cancer-related physical symptoms. Detailed meta-analyses with various outcomes and assessment tools should be consequently performed, especially on dyspnea. Second, the number of RCTs that showed the significant effect of exercise on physical symptoms was small, but the result of overall effect (SMD) was significant. Only the RCT by Galvao et al[36] reported a significant effect on all of fatigue, nausea/vomiting, pain, and dyspnea in 28 patients. However, the weight in meta-analysis of the RCT was not very high (7.2% in fatigue; 7.3% in nausea/vomiting; 6.8% in pain; 6.0% in dyspnea), but the risk of bias was low (PEDro score = 7). However, the heterogeneity (I^2) in meta-analysis was low to moderate (26% in fatigue, 11% in nausea/vomiting, 12% in pain, 0% in dyspnea).[25] Additionally, when meta-analysis was performed without RCTs, which had high risk of bias (PEDro score < 5) per the sensitivity analysis, the result of overall effect (SMD) was not changed for all physical symptoms. Therefore, we believe that the results of meta-analyses in this study are acceptable statistically. Third, the cancer type and treatment were not limited in this meta-analysis. Physical symptoms may differ by cancer type. When treatment differs by cancer type, physical symptoms as a side effect of treatments are changed. Fourth, RCTs included in the review had different time frames. Some were performed postsurgery, and others were performed posttransplantation, during chemotherapy, and at other time points. The RCTs that were performed during chemotherapy recorded high values of physical symptoms comparatively.[30,34] Finally, this review included only studies published in the English language as a result of selection; there is low possibility that selection was limited by language.

In conclusion, we confirmed that exercise interventions improve fatigue, pain, and insomnia in cancer patients, as observed in earlier studies.[8,15,18] Additionally, the benefit of exercise on dyspnea in cancer patients was also observed, establishing the novelty of exercise as supportive care. Nausea/vomiting, loss of appetite, constipation, and diarrhea were not promoted or suppressed by any exercise type. Detailed meta-analyses with various outcomes and assessment tools should be performed, and more studies of sufficient quality are warranted.

Declaration of Conflicting Interests

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