The Effects of Exercise on Symptoms of Chemotherapy-Induced Peripheral Neuropathy in Cancer Survivors: A Systematic Review and Meta-Analysis

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PROBLEM IDENTIFICATION: Chemotherapy-induced peripheral neuropathy (CIPN) can cause treatment delays or discontinuation. Exercise can improve CIPN, but the effects have been inconsistent.

LITERATURE SEARCH: 12 databases and 5 websites were searched from database inception to December 22, 2023, for primary studies that were reported in English and examined the effects of exercise on CIPN in cancer survivors.

DATA EVALUATION: 20 studies (N = 1,308 total participants) were identified and reviewed.

SYNTHESIS: Using a random-effects model, exercise slightly improved symptoms of CIPN (Hedges's g = 0.28, Hartung-Knapp adjusted 95% confidence interval [0.12, 0.45], p = 0.002). The 95% prediction interval showed that the true effect size of future studies would likely range from –0.1 to 0.66. Frequency of performing exercise moderated the effect size, further improving symptoms.

IMPLICATIONS FOR NURSING: Nurses can encourage cancer survivors to engage in exercise, such as resistance training, aerobic exercise, balance training, and/or yoga. Nurses can refer cancer survivors to trained exercise specialists or provide information about finding a community exercise program for patients with cancer.

KEYWORDS chemotherapy-induced peripheral neuropathy; cancer survivors; exercise

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Chemotherapy-induced peripheral neuropathy (CIPN) is defined as a set of symptoms caused by damage to the peripheral nerves from chemotherapy or other drugs that are used to treat cancer (American Cancer Society, 2024). CIPN manifests with a variety of symptoms and is characterized more by sensory symptoms than by motor function symptoms. Sensory symptoms include allodynia, cold-induced neuropathy, loss of heat sensitivity, paresthesia, dysesthesia, numbness, tingling, and neuropathic pain (Han & Smith, 2013; Zajączkowska et al., 2019). These CIPN symptoms can become severe and cause treatment delays, dose reduction, or treatment discontinuation, which affect treatment outcomes.

CIPN is commonly found in patients who received neurotoxic chemotherapy agents, including taxanes, platinum compounds, vinca alkaloids, and bortezomib (Loprinzi et al., 2020; Zajączkowska et al., 2019). These neurotoxic agents have various mechanisms that cause CIPN, but the main target of neurotoxic drugs is the neurons (Carozzi et al., 2015; Zajączkowska et al., 2019). Platinum compounds usually damage the dorsal root ganglion, leading to apoptosis in the sensory neuron and altering mitochondrial function, resulting in pathologic function in neuronal and glial cells with membrane excitability (Carozzi et al., 2015; Zajączkowska et al., 2019). Taxanes interrupt microtubule function, impair axonal transport, alter the activity of ion channels, and result in hyperexcitability of peripheral neurons (Zajączkowska et al., 2019). Vinca alkaloids bind β-tubulin, leading to severe alteration in axonal microtubules, swollen axons, and damaged nerve fibers (Carozzi et al., 2015). Neurotoxic agents also alter cellular levels.

The incidence of CIPN depends on several risk factors, including the class of chemotherapy agents, dose per cycle, infusion duration, cumulative dose, comorbidities, and genetic susceptibility (Argyriou et al., 2014). The incidence varies from 11% to 87% in taxanes and from 49% to 100% in platinum compounds, and the incidence is about 60% in vinca alkaloids (Argyriou et al., 2014; Zajączkowska et al., 2019). The prevalence of CIPN varies from 19% to more than 85% of patients receiving any kind of neurotoxic agents (Zajączkowska et al., 2019). Platinum compounds, particularly oxaliplatin, are the most neurotoxic, causing the highest prevalence of CIPN in about 70% of patients (Burgess et al., 2021). CIPN can occur after chemotherapy initiation and persist for months or years after discontinuing treatment. About 31%–44% of patients treated with docetaxel or paclitaxel reported CIPN symptoms after six years (Burgess et al., 2021). Therefore, long-term CIPN symptoms interfere with the health of cancer survivors.

No medication has been approved by the U.S. Food and Drug Administration to treat or prevent CIPN symptoms (Loprinzi et al., 2020). However, the American Society of Clinical Oncology guidelines suggest that clinicians may prescribe duloxetine orally for cancer survivors with painful CIPN who have completed chemotherapy treatments, but the benefit is limited (Loprinzi et al., 2020). Of note, this guideline does not specify the dose of duloxetine for these individuals (Loprinzi et al., 2020). Duloxetine is approved by the U.S. Food and Drug Administration to treat chronic musculoskeletal pain, diabetic neuropathy pain, major depressive disorder, and generalized anxiety disorder (Eli Lilly and Company, 2010).

Several experimental studies revealed that exercise improved CIPN symptoms, such as abnormal sensitivity to touch and peripheral neuropathy pain (Chen et al., 2020; McCrary et al., 2019; Wu et al., 2022). Exercise, a subtype of physical activity, aims to improve or maintain physical fitness through planned, structured, and repetitive body movements (Caspersen et al., 1985). However, the effects of exercise on CIPN symptoms have been inconsistent across primary studies. The American Society of Clinical Oncology guidelines also state that there is insufficient evidence to recommend exercise to prevent or treat CIPN (Loprinzi et al., 2020). Although preliminary evidence suggests a potential benefit from exercise on CIPN symptoms, a comprehensive meta-analysis is needed to synthesize all relevant studies on the effect of exercise on CIPN to support clinical practice and guide future research.

To the authors' knowledge, six meta-analyses, with few primary studies, have examined the effects of exercise on CIPN symptoms, but the findings were controversial. Five of these studies showed that an exercise intervention significantly improved CIPN symptoms; however, the findings were based on only two to five studies (Brownson-Smith et al., 2023; Crichton et al., 2022; de Arenas-Arroyo et al., 2023; Lin et al., 2021; Streckmann et al., 2022). In contrast, another study reported that exercise effects were insignificant in improving neuropathy symptoms in cancer survivors, but only four primary studies were included (Guo et al., 2023). With the current meta-analysis, the authors aimed to evaluate the effects of exercise on CIPN symptoms in cancer survivors. In addition, the moderating effects of source characteristics, participant features, methods (including quality indicators), and intervention components were examined.

Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist guidelines were used as an outline in reporting this study (Liberati et al., 2009). This study did not require institutional review board approval because human subject data were not used.

Literature Search and Selection Criteria

A comprehensive search was conducted in the following 12 electronic databases from their inception dates to December 22, 2023: CINAHL® Plus, PubMed®, Scopus®, Ovid/MEDLINE®, Cochrane Central Register of Controlled Trials, PsycINFO®, ProQuest, Web of Science, ScienceDirect, SPORTDiscus, EBSCOhost, and ClinicalKey. A search was also performed on five websites: https://clinicaltrials.gov, www.asco.org, www.nccn.org, https://scholar.google.com, and www.ons.org. The search was limited to English-language reports. The first author (U.K.) screened possible studies by looking at relevant titles and abstracts. The first (U.K.) and second (S.H.) authors then independently screened studies for eligibility based on the inclusion criteria. The reference lists of the potential studies, review articles, and the previously conducted meta-analyses were also screened. Studies published in peer-reviewed journals and unpublished studies (e.g., dissertations) were both searched to reduce publication bias.

An experienced nursing reference librarian was consulted to conduct a systematic search. Broad search terms were used for all databases, including

cancer survivors OR *cancer patient* OR *cancer** AND *chemotherapy-induced peripheral neuropathy* OR *chemotherapy-induced neurotoxicity* OR *taxane-induced peripheral neuropathy* OR *CIPN* OR *peripheral neuropathy* AND *exercise* OR *physical activity* OR *resistance training* OR *muscle stretching exercise* OR *aerobic exercise* OR *exercise movement techniques* OR *balance exercise* OR *exercise tolerance*. These search terms were used to search all databases. To enhance the comprehensiveness of the search, CINAHL Subject Headings and PubMed Medical Subject Headings were exploded.

Inclusion criteria for primary studies were as follows: (a) examined any exercise intervention and had a comparison group with at least five participants per group, (b) included participants who were aged 18 years or older with any type of cancer who were receiving or had received chemotherapy, (c) measured CIPN symptoms quantitatively, and (d) reported in English. Quasiexperimental studies and randomized trials were included, with comparison groups that differed only by exercise intervention.

Exclusion criteria for studies were as follows: (a) examined exercise for other types of neuropathies (e.g., diabetic neuropathy), (b) qualitative studies, (c) review articles (e.g., systematic review or meta-analysis), or (d) reported insufficient data for calculating the effect size after emailing the primary study's corresponding author twice.

Data Coding

All eligible studies were reviewed, and a codebook was developed with clear coding descriptions for items in the following five categories: source, methods, intervention features, participant characteristics, and outcome data to calculate the effect size. The codebook was circulated to the research team for feedback, and it was then refined based on the research team's suggestions. The codebook was pilot tested with five studies before the formal coding implementation to ensure that coding rules were clear and understandable.

Source characteristics were coded to include the exercise intervention, target population, age eligibility (aged 18 years or older), minimum sample size of at least five people per group, and availability of comparison groups ("yes"/"no" for all). Publication year, funding, and countries where the studies were conducted were also coded. Methods were coded to include the setting from which participants were recruited and study quality indicators, including study design (i.e., randomized or quasiexperimental), type of comparison group (i.e., control or attention-control group), sampling strategy (i.e., random or convenience), group assignment (i.e., randomized or nonrandomized), concealed allocation ("yes"/"no"), data collectors blinded ("yes"/"no"), analysis methods (i.e., intention-to-treat, as-treated, or per-protocol analyses), exercise fidelity measured ("yes"/"no"), a priori power analysis estimation ("yes"/"no"), and whether demographic characteristics were compared at baseline and if they were equivalent ("yes"/"no").

Intervention features were coded, including counters or self-monitoring, telephone call follow-ups, and incentives. Length in days and weeks across the intervention as originally planned; the total planned number of structured intervention sessions; and session duration in minutes, including supervised and unsupervised exercise, minutes to perform exercise per week, number of days to perform exercise per week (frequency), prescribed level of exercise intensity ("yes"/"no"), supervision of exercise (e.g., supervised, unsupervised, mixed), exercise format (e.g., individual, group/family), mode of exercise (e.g., live, virtual, telephone), exercise types (e.g., aerobic, resistance, stretching, balance, yoga), and timing of exercise intervention with treatment (e.g., before, during, or after chemotherapy), were coded.

Participant information was coded to include sample sizes at assignment and at data analysis, dropout numbers, attrition rates, number of male and female participants and their race (e.g., White, American African, Asian), cancer sites, and chemotherapy agents. The means and SDs of participants' ages were recorded. For the CIPN symptom outcome, means, SDs, and sample sizes at baseline and at analysis were recorded. If researchers did not report mean and SD, other statistical values that may be used to calculate the effect size were coded. In the case of missing statistics needed for computing the effect size or unclear information, the first author (U.K.) sent an email requesting the missing data or asking for clarification about unclear information to the primary study's corresponding author. If a response was not received after two emails, the study was excluded.

Because the study aimed to understand the long-term effects of exercise, data were recorded from the last time point. The effect direction of the exercise was determined by comparing post-test CIPN scores of the exercise groups with the comparison groups. Because researchers used different measures reflecting different directions, studies were coded so that improved CIPN symptoms were reflected as a positive direction. Some primary researchers included two treatment groups and one control group. In this

case, the control sample was halved to provide a comparison group for both exercise groups while not counting any control participants twice (Borenstein et al., 2021).

Two trained coders, who had taken a comprehensive meta-analysis course, coded the data independently to ensure consistency and accuracy. All data were compared across coders. If there were any discrepancies, the third author (J.K.S.) resolved the disagreement. The two coders independently entered their data into REDCap, version 12.5.4. The datasets were then exported to IBM SPSS Statistics, version 27.0, and compared for errors. The coders corrected their errors and compared again until all errors were corrected.

Quality Assessment and Data Analysis

Study quality was assessed by coding the method characteristics as suggested by Conn and Rantz (2003). Quality indicators consisted of group assignment method, group equivalence, concealed allocation, data collector blinded, a priori power estimation, intervention fidelity examined, attrition, and intention-to-treat analysis. Study quality indicators were examined as moderators.

The study characteristics were described using IBM SPSS Statistics, version 27.0. Comprehensive Meta-Analysis Software, version 4.0, was used for the meta-analysis. A random-effects model was used because the primary studies were heterogeneous in terms of a variety of cancer sites and variations of exercise intervention components. In a random-effects model, each primary study is weighted by the inverse of its variance, which is the sum of the within- plus between-studies variances (Borenstein et al., 2021). A standardized mean difference (Cohen's d) was calculated for each study using the independent post-test groups with 95% confidence intervals (CIs). Because Cohen's d has a slight overestimation bias, Hedges's g was used to adjust for this overestimation (Borenstein et al., 2021; Cooper et al., 2019). Standardized mean differences were used because researchers measured CIPN symptoms using a variety of scales with different metrics; standardization allows comparisons across metrics (Cooper et al., 2019). In addition, because some research teams used multiple measures for symptoms, Comprehensive Meta-Analysis Software, version 4.0, was used to compute a combined effect for those studies.

The Knapp-Hartung adjustment was employed because of the small number of studies. This adjustment does not adjust the effect size point estimates but modifies the standard error of the mean and uses the T distribution when computing 95% CIs (Borenstein et al., 2021). Therefore, it yields wider 95% CIs, which is more accurate compared to the conventional method of using the Z distribution for this computation (Borenstein et al., 2021).

An outlier effect size was identified by inspecting the forest plot, which displayed the effect sizes of the individual primary studies. The effect of the outlier was examined using a sensitivity analysis to enhance the consistency of the results (Borenstein et al., 2021). Heterogeneity was further investigated by computing the Q statistic, or weighted sum of squares, which reflects the total dispersion. A significant Q statistic likely reflects varying true effects across studies (Borenstein et al., 2021). However, with a nonsignificant Q statistic, it cannot be concluded that the true effect sizes do not vary across studies. This latter case might be because of the low power from a small number of studies (Borenstein et al., 2021). In addition, the 95% prediction interval was computed, which reflects the distribution of true effect sizes across studies (Borenstein et al., 2021).

CIPN symptoms are typically worse while receiving chemotherapy and gradually improve after treatment cessation for most patients (Burgess et al., 2021). Therefore, spontaneous recovery was examined by comparing pre- and post-test scores across exercise and control groups separately. Improvement across the control groups would likely suggest a spontaneous recovery across the control groups. Because pre- and post-test scores are likely correlated (Conn et al., 2009), these single-group analyses were conducted under two different assumptions: correlated ($r = 0.8$) and uncorrelated ($r = 0.0$) (Conn et al., 2009).

To address heterogeneity, moderator analyses were conducted to illustrate how the effect size varied as a function of source, methods, intervention, and participant characteristics. For subgroup analysis, a meta-analytic analog of analysis of variance was used for categorical moderator analyses when there were at least four comparisons per group for each categorical moderator to produce meaningful findings (Fu et al., 2010). Meta-regression analysis was used for continuous moderators when there were at least 10 comparisons to enhance the meaningfulness of the analysis (Borenstein et al., 2021).

Risk of Publication Bias

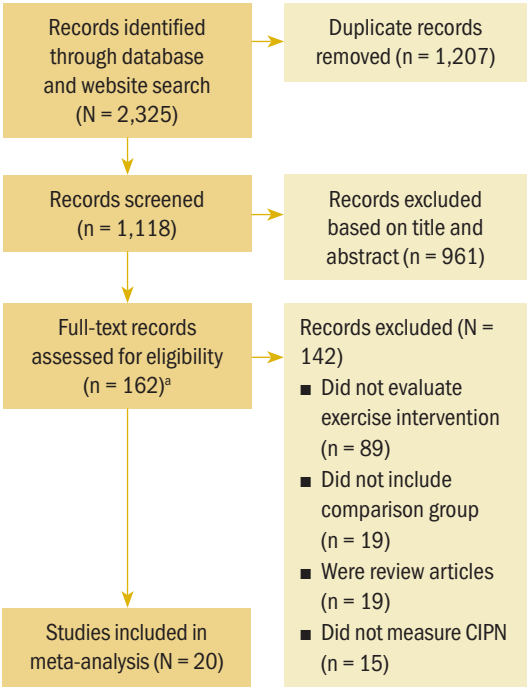
A funnel plot was generated to display the relationship between effect sizes on the horizontal and standard errors on vertical axes (Borenstein et al.,

2021). Asymmetrical plots suggest publication bias (Cooper et al., 2019). Begg and Mazumdar's rank correlation test was computed to examine the presence of funnel plot asymmetry. This test computes a rank correlation between the deviations of individual effects from the mean and their variances using a normalized version of Kendall's tau (Cooper et al., 2019). Egger's linear regression was also used to test the relationship between the observed treatment effects and their standard errors (Lin et al., 2018). A significant result implies publication bias or funnel plot asymmetry (Cooper et al., 2019; Lin et al., 2018).

Results

The initial search of the 12 electronic databases and 5 websites yielded 1,118 studies after removing duplicates. Because their titles and abstracts were not relevant to the topic, 961 studies were excluded. An additional five studies were identified from reference lists, resulting in 162 eligible studies. Of these, 142 studies were excluded because they did not evaluate an exercise intervention (n = 89), did not include a comparison group (n = 19), were review articles (n = 19), or did not measure CIPN symptoms (n = 15). A total of 20 studies met the inclusion criteria for this meta-analysis (see Figure 1).

FIGURE 1. PRISMA Flow Diagram



[a] Includes 5 records identified from a hand search
CIPN—chemotherapy-induced peripheral neuropathy; PRISMA—Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Study Characteristics

The included studies were published between 2012 and 2023 and included 18 published journal articles (Bahar-Ozdemir et al., 2020; Bao et al., 2020; Bland et al., 2019; Cao et al., 2023; Clark et al., 2012; Dhawan et al., 2020; Gui et al., 2021; Hammond et al., 2020; Henke et al., 2014; Ikio et al., 2022; Kleckner et al., 2018; Knoerl et al., 2022; Müller et al., 2021; Saraboon & Siriphorn, 2021; Şimşek & Demir, 2021; Streckmann et al., 2019; Visovsky et al., 2014; Zimmer et al., 2018), 1 dissertation (Kanzawa-Lee, 2020), and 1 conference paper (Kleckner et al., 2019). Of the 20 studies, 8 were conducted in the United States, 4 in Germany, 2 each in Canada and Turkey, and 1 each in India, Japan, China, and Thailand. Across all studies, participants were recruited from healthcare centers. Most studies (n = 16) used control groups, which received usual care, as comparison groups (Bahar-Ozdemir et al., 2020; Bao et al., 2020; Bland et al., 2019; Dhawan et al., 2020; Gui et al., 2021; Hammond et al., 2020; Henke et al., 2014; Ikio et al., 2022; Kleckner et al., 2018, 2019; Knoerl et al., 2022; Müller et al., 2021; Saraboon & Siriphorn, 2021; Şimşek & Demir, 2021; Streckmann et al., 2019; Zimmer et al., 2018). The remaining studies (n = 4) used comparison groups that received health education as an attention control (Cao et al., 2023; Clark et al., 2012; Kanzawa-Lee, 2020; Visovsky et al., 2014).

Exercise Characteristics

A summary of exercise characteristics is presented in Table 1. The exercise intervention was heterogeneous across the 20 studies. Three studies used yoga as an intervention (Bao et al., 2020; Clark et al., 2012; Knoerl et al., 2022). Ten studies used combined exercise for their exercise intervention (Bahar-Ozdemir et al., 2020; Bland et al., 2019; Dhawan et al., 2020; Gui et al., 2021; Henke et al., 2014; Kleckner et al., 2018, 2019; Şimşek & Demir, 2021; Visovsky et al., 2014; Zimmer et al., 2018). For example, one study combined aerobic exercise with stretching exercises (Gui et al., 2021), whereas four studies combined aerobic exercise with resistance training (Henke et al., 2014; Kleckner et al., 2018, 2019; Visovsky et al., 2014). Three studies combined resistance and balance training (Bahar-Ozdemir et al., 2020; Dhawan et al., 2020; Şimşek & Demir, 2021), and two studies combined aerobic

TABLE 1. Summary of Exercise Characteristics of Included Studies (N = 20)

Study (Country)	Design, Participant Ages, Cancer Site, and CIPN Measure	Exercise Type	Duration, Frequency, and Intensity
Bahar-Ozdemir et al., 2020 (Turkey)	■ Design: quasiexperimental (N = 70) ■ Age (years) □ Exercise group: $\bar{X}$ = 52 (SD = 10) □ Control group: $\bar{X}$ = 53.6 (SD = 11.9) ■ Cancer sites: colorectal, gastric, lung, ovarian, breast, cervical, pancreatic, head and neck ■ CIPN measure: PainDETECT questionnaire	■ Home-based exercise program □ RT (e.g., muscle strengthening, hip and knee, ankle pumping, toe walking) □ Balance exercise (e.g., side walking, tandem walking, walking backward, crossover walking, balancing on 1 leg)	■ Program duration: 10 weeks ■ Session duration: N/A ■ Frequency: 5 days per week ■ Intensity: 2 sets and 10 repetitions of lower-limb RT
Bao et al., 2020 (United States)	■ Design: RCT (N = 41) ■ Cancer sites: breast, ovarian, uterine ■ CIPN measure: NRS	■ Yoga (e.g., breath work, posture, flexibility, strength, balance)	■ Program duration: 8 weeks ■ Session duration: 60 minutes ■ Frequency: in-person group classes twice per week; home practice 5 times per week when group classes were not held ■ Intensity: N/A
Bland et al., 2019 (Canada)	■ Design: RCT (N = 27) ■ Age (years) □ Total: $\bar{X}$ = 50.2 (SD = 10.2) □ Exercise group: $\bar{X}$ = 51 (SD = 8.1) □ Delayed exercise group: $\bar{X}$ = 49.5 (SD = 11) ■ Cancer site: breast ■ CIPN measures: EORTC QLQ-CIPN20, clinical sensory testing (2 non-automated quantitative sensory tests: vibration sensation and temporal summation of pain or pinprick)	■ Supervised multimodal exercise □ Aerobic training (e.g., treadmill, cycle ergometer, elliptical trainer) □ RT (e.g., using machines, free weights, or resistance bands to target the upper and lower limb and abdominal strength) □ Balance exercise (e.g., 2 single-leg standing on a stable surface and unstable surface); 6–8 repetitions (20–30 seconds per exercise)	■ Program duration: began 1 week before the first chemotherapy cycle and ended 2–3 weeks after the last cycle ■ Session duration: 40 minutes the week after chemotherapy, 25–35 minutes on nonchemotherapy weeks, and 15–30 minutes after week 3 ■ Frequency: 3 days per week for multimodal exercise and 2 days per week for home-based exercise ■ Intensity: lower intensity (50%–55% HRR) the week after chemotherapy, increasing to 75% HRR by week 8; for RT, start at 1 set of 10 repetitions at 50% of the estimated 1RM, progressing to 2 sets of 10–12 repetitions at 65% 1RM, and reduce to 1 set per exercise for 1 week after chemotherapy.
Cao et al., 2023 (United States)	■ Design: secondary RCT (N = 134) ■ Age (years): $\bar{X}$ = 50.2 (SD = 10.2) ■ Cancer site: ovarian ■ CIPN measure: FACT/GOG-NTX 11-item neurotoxicity subscale	■ Home-based aerobic exercise □ Brisk walking	■ Program duration: 6 months ■ Session duration: 150 minutes per week ■ Frequency: N/A ■ Intensity: moderate intensity
Clark et al., 2012 (United States)	■ Design: RCT (N = 36) ■ Age (years): $\bar{X}$ = 59 (SD = 8.6) ■ Cancer sites: ovarian, colon, breast, brain, Hodgkin lymphoma, NHL, appendiceal, peritoneal ■ CIPN measure: FACT/GOG-NTX 11-item neurotoxicity subscale	■ Yoga □ Breathing and body scan to relax the body; gentle stretching □ Maintaining a supine position on the floor or sitting □ Relaxed breathing and systematic muscle relaxation	■ Program duration: 6 weeks ■ Session duration: 60 minutes ■ Frequency: once per week ■ Intensity: N/A

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TABLE 1. Summary of Exercise Characteristics of Included Studies (N = 20) *(Continued)*

Study (Country)	Design, Participant Ages, Cancer Site, and CIPN Measure	Exercise Type	Duration, Frequency, and Intensity
Dhawan et al., 2020 (India)	■ Design: RCT (N = 45) ■ Age (years) □ Exercise group: $\bar{X}$ = 50.5 (SD = 7.9) □ Control group: $\bar{X}$ = 52.5 (SD = 6.6) ■ Cancer sites: ovarian, cervical, lung, head and neck ■ CIPN measures: LANSS, CIPN Assessment Tool	■ Home-based muscle strengthening and balancing exercises □ Lying-down position (e.g., ankle motion, hip abduction, leg raise) □ Sitting position (e.g., digit abduction and adduction, wrist motion, elbow flexion/extension, knee flexion/extension, toe tapping) □ Standing position (e.g., 1-legged stand, toe stand, hip extension, tandem forward walking)	■ Program duration: 10 weeks ■ Session duration: 30 minutes ■ Frequency: daily ■ Intensity: N/A
Gui et al., 2021 (China)	■ Design: quasiexperimental (N = 79) ■ Age (years) □ Exercise group: $\bar{X}$ = 50 (SD = 8) □ Control group: $\bar{X}$ = 52 (SD = 7) ■ Cancer sites: colorectal, gastric, liver, pancreatic ■ CIPN measures: FACT/GOG-NTX 11-item neurotoxicity scale, BPI	■ Comprehensive gymnastics (3 times) □ Lying down, moving hands/fingers and feet/toes 10 times; standing, slowly raising arms, stretching out, and drawing back fingers 10 times; slowly letting arms fall, placing hands on hips, and heeling 10 times ■ Quick walking training	■ Program duration: 2 weeks ■ Session duration: N/A ■ Frequency: daily (morning and evening) ■ Intensity: walking 1–3 km
Hammond et al., 2020 (Canada)	■ Design: RCT (N = 48) ■ Age (years): N/A ■ Cancer site: breast ■ CIPN measures: NRS, S-LANSS, vibration analysis testing, pressure algometry	■ Nerve gliding home-based exercise and education program (e.g., stretching and range-of-motion exercise of the neck and upper limb, axillary webbing exercise)	■ Program duration: during and after chemotherapy until symptoms subside ■ Session duration: 5–10 minutes ■ Frequency: daily home-based program ■ Intensity: Exercise 3 times.
Henke et al., 2014 (Germany)	■ Design: RCT (N = 29) ■ Age (years): N/A ■ Cancer site: lung ■ CIPN measure: EORTC QLQ Lung Cancer–13 peripheral neuropathy subscale	■ Strength training (e.g., bridging exercise, abdominal exercise, biceps curl, triceps extension using an elastic band of medium resistance (4.6 lb resistance at 100% elongation) ■ Endurance training (e.g., walking in the hallway, stair walking)	■ Program duration: began the first day of chemotherapy and ended after completing third cycle of chemotherapy ■ Session duration: N/A ■ Frequency: 5 days per week for endurance training and every other day of the week for strength training ■ Intensity: moderate intensity endurance training (maintain 55%–70% of HRR); repeat each strength training exercise as many times as possible.
Ikio et al., 2022 (Japan)	■ Design: RCT (N = 39) ■ Age (years): N/A ■ Cancer sites: hematologic, GI ■ CIPN measures: Michigan Hand Outcomes Questionnaire, Visual Analog Scale, FACT/GOG-NTX 11-item neurotoxicity scale	■ Unsupervised exercise included: □ Muscle strength exercise (e.g., grip and pinching movement performed at 40%–60% of the maximum muscle strength using a hand and finger exerciser) □ Manual dexterity training (e.g., origami, paper training) □ Sensory function training (e.g., material identification, tactile perception practice)	■ Program duration: began during the first chemotherapy cycle and ended after 2 chemotherapy cycles ■ Session duration: 30 minutes ■ Frequency: 3 days (or more) per week ■ Intensity: The load for manual dexterity was adjusted until participants felt it was “a little difficult” to “difficult.”

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TABLE 1. Summary of Exercise Characteristics of Included Studies (N = 20) *(Continued)*

Study (Country)	Design, Participant Ages, Cancer Site, and CIPN Measure	Exercise Type	Duration, Frequency, and Intensity
Kanzawa-Lee, 2020 (United States)	■ Design: RCT (N = 60) ■ Age (years) □ Exercise group: $\bar{X}$ = 56.8 (SD = 11.7) □ Control group: $\bar{X}$ = 59 (SD = 9.6) ■ Cancer sites: colon, rectum, colorectal, pancreatic, esophageal ■ CIPN measure: EORTC QLQ-CIPN20	■ Home-based aerobic walking intervention	■ Program duration: 8 weeks ■ Session duration: 10–60 minutes ■ Frequency: 3–5 days per week ■ Intensity: moderate intensity
Kleckner et al., 2018 (United States)	■ Design: secondary analysis of RCT (N = 355) ■ Age (years) □ Exercise group: $\bar{X}$ = 55.6 (SD = 11.8) □ Control group: $\bar{X}$ = 55.9 (SD = 9.7) ■ CIPN measure: patient-reported CIPN symptoms (e.g., numbness and tingling, hotness/coldness in hands and feet)	■ Home-based unsupervised exercise □ Walking aerobic exercise □ RT: 10 band exercises (squat, side bend, leg extension, leg curl, chest press, row, calf raise, overhead press, biceps curl, triceps extension); 4 band exercises (front raise, lateral raise, internal rotation, external rotation)	■ Program duration: 6 weeks ■ Session duration: N/A ■ Frequency: daily ■ Intensity: low to moderate intensity for aerobic exercise (60%–85% of HRR); maximum of 4 sets of 15 repetitions of low to moderate intensity RT
Kleckner et al., 2019 (United States)	■ Design: pilot RCT (N = 19) ■ Age (years): $\bar{X}$ = 65 (SD = 11) ■ Cancer sites: breast, GI, myeloma, genitourinary ■ CIPN measure: EORTC QLQ-CIPN20 sensory scale	■ Home-based walking and RT	■ Program duration: 12 weeks ■ Session duration: N/A ■ Frequency: N/A ■ Intensity: low to moderate intensity
Knoerl et al., 2022 (United States)	■ Desgin: RCT (N = 44) ■ Age (years): N/A ■ Cancer sites: breast, GI, gynecologic ■ CIPN measure: NRS, EORTC QLQ-CIPN20 sensory and motor subscales	■ Yoga (e.g., breathing exercise, upper and lower extremity stretching, structured postures and movements)	■ Program duration: 8 weeks ■ Session duration: 45 minutes ■ Frequency: N/A ■ Intensity: N/A
Müller et al., 2021 (Germany) (RT)	■ Design: RCT (N = 170) ■ Age (years) □ Exercise group: $\bar{X}$ = 53.4 (SD = 11.7) □ Control group: $\bar{X}$ = 54.5 (SD = 11.9) ■ Cancer sites: breast, prostate, pancreatic, colorectal, stomach, esophageal, cervical, bladder, lung, tongue ■ CIPN measures: TNSr, clinical exam, NCS, CMAP, SNAP, EORTC QLQ-CIPN15	■ Supervised RT: leg press, knee extension and flexion, rowing, lateral pull down, shoulder internal and external rotation, butterfly, butterfly reverse ■ Home-based RT: core stability exercises, including supine position, prone position, quadruped position, and plank position	■ Program duration: about 20 weeks ■ Session duration: 45 minutes (machine based), 15 minutes (home based) ■ Frequency: 2 times per week (machine based), once per week (home based) ■ Intensity: 1RM strength was conducted at each machine (training weights based on guideline of 70%–80% 1RM).
Müller et al., 2021 (Germany) (SMT)	■ Design: RCT (N = 170) ■ Age (years) □ Exercise group: $\bar{X}$ = 51.7 (SD = 10.8) □ Control group: $\bar{X}$ = 54.5 (SD = 11.9) ■ Cancer sites: breast, prostate, pancreatic, colorectal, stomach, esophageal, cervical, bladder, lung, tongue ■ CIPN measures: TNSr, clinical exam, NCS, CMAP, SNAP, EORTC QLQ-CIPN15	■ SMT, including bipedal narrow stance, dynamic exercise, single leg stance, and tandem stance	■ Program duration: about 20 weeks ■ Session duration: 35 minutes ■ Frequency: 3 times per week ■ Intensity: progress based on individually perceived difficulty

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TABLE 1. Summary of Exercise Characteristics of Included Studies (N = 20) *(Continued)*

Study (Country)	Design, Participant Ages, Cancer Site, and CIPN Measure	Exercise Type	Duration, Frequency, and Intensity
Saraboon & Siriphorn, 2021 (Thailand)	■ Design: RCT (N = 30) ■ Age (years) □ Exercise group: $\bar{X}$ = 45 (SD = 3.9) □ Control group: $\bar{X}$ = 45.5 (SD = 4.6) ■ Cancer sites: ovarian, cervical ■ CIPN measure: Michigan Diabetic Neuropathy Score	■ Balance exercise on a foam pad including the following 10 standing exercises: double leg standing, single leg standing, neck flexion/extension, free leg swinging, heel and toe rising, neck and trunk rotation, touching the floor, walking in place, sideways walking, and forward walking	■ Program duration: 6 weeks ■ Session duration: 60 minutes ■ Frequency: twice per week ■ Intensity: dependent on participants' physical capacity
Şimşek & Demir, 2021 (Turkey)	■ Design: RCT (N = 90) ■ Age (years): N/A ■ Cancer site: breast ■ CIPN measure: CIPN Assessment Tool	■ Home-based exercise: strengthening and stretching (e.g., foot dorsiflexion, plantar flexion, gastrocnemius stretching, hamstring stretching, quadriceps exercises, biceps, hand flexion/extension) and balance exercises (e.g., hip flexion/extension, hip abduction, knee flexion)	■ Program duration: 12 weeks ■ Session duration: 15–30 minutes ■ Frequency: 5 times per week ■ Intensity: 10 repetitions performed in weeks 1–3; 60 repetitions performed in weeks 4–6; 30 repetitions performed in weeks 7–9
Streckmann et al., 2019 (Germany) (SMT)	■ Design: pilot RCT (N = 40) ■ Age (years) □ Exercise group: $\bar{X}$ = 56 □ Control group: $\bar{X}$ = 59 ■ Cancer sites: NHL, lung, breast, ovarian, colorectal, pancreatic ■ CIPN measure: FACT/GOG-NTX 11-item neurotoxicity scale	■ SMT: 4 exercises per session, performing progressively difficult balance exercises on unstable surfaces	■ Program duration: 6 weeks ■ Session duration: 12 minutes on average ■ Frequency: twice per week ■ Intensity: 3 times; 20 seconds per each exercise
Streckmann et al., 2019 (Germany) (VT)	■ Design: pilot RCT (N = 40) ■ Age (years) □ Exercise group: $\bar{X}$ = 56 □ Control group: $\bar{X}$ = 59 ■ Cancer sites: NHL, lung, breast, ovarian, colorectal, pancreatic ■ CIPN measure: FACT/GOG-NTX 11-item neurotoxicity scale	■ VT performed on a slide-alternating vibration platform; participants stood on the platform while wearing tight-fitting antislip socks or gymnastic shoes with thin soles on their forefoot.	■ Program duration: 6 weeks ■ Session duration: 4 progressing sets lasting for 30 seconds to 1 minute (about 4 minutes per session) ■ Frequency: twice per week ■ Intensity: 18–35 Hz and amplitude of 2–4 mm
Visovsky et al., 2014 (United States)	■ Design: pilot RCT (N = 19) ■ Age (years): $\bar{X}$ = 48.8 ■ Cancer site: breast ■ CIPN measure: FACT-Taxane	■ Home-based exercise program: aerobic (e.g., walking, progressive interval training) and strength training exercises (e.g., bicep curls, triceps extension, front and lateral raises, shoulder press, calf raises, lunges, supine leg curls, supine leg extensions)	■ Program duration: 12 weeks ■ Session duration: not specified for weeks 1–3; 30 minutes for weeks 4–16 ■ Frequency: 5–7 days weekly (aerobic training) and 3 times weekly (strength training) ■ Intensity: light to moderate aerobic exercise; for strength training, 1–2 sets of each exercise with 8 repetitions 1–2 times per week at weeks 1–3, 2–3 sets and 8–12 repetitions of each exercise per session at weeks 4–16

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TABLE 1. Summary of Exercise Characteristics of Included Studies (N = 20) *(Continued)*

Study (Country)	Design, Participant Ages, Cancer Site, and CIPN Measure	Exercise Type	Duration, Frequency, and Intensity
Zimmer et al., 2018 (Germany)	■ Design: RCT (N = 30) ■ Age (years) □ Exercise group: $\bar{X}$ = 68.5 □ Control group: $\bar{X}$ = 70 ■ Cancer sites: colorectal, rectosigmoid junction ■ CIPN measure: FACT/GOG-NTX 11-item neurotoxicity scale	■ Multimodal exercise: balance training (e.g., balance pads, balancing on lines), coordination practice (e.g., cherry pit pillow), endurance training (e.g., cross-trainer, bicycle ergometer, walking), RT (e.g., circuit training, including bench press, lateral pull down, leg press, seated row, abdominal exercise), and cooldown (e.g., relaxing, stretching, breathing, mobilization exercises)	■ Program duration: 8 weeks ■ Session duration: 60 minutes ■ Frequency: twice per week ■ Intensity: 10 minutes of endurance training (Borg Rating of Perceived Exertion Scale level of 12–13 = 60%–70% of maximum heart rate); 20 minutes of RT 2 times with 8–12 repetitions (weight = 60%–80% of hypothetical 1RM, Borg Core-Ratio 10 Scale level of 6)

BPI—Brief Pain Inventory; CIPN—chemotherapy-induced peripheral neuropathy; CMAP—compound muscle action potential amplitude of peroneal nerve; EORTC QLQ—European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire; exam—examination; FACT/GOG-NTX—Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity; FACT-Taxane—Functional Assessment of Cancer Therapy–Taxane; GI—gastrointestinal; HRR—heart rate reserve; LANSS—Leeds Assessment of Neuropathic Symptoms and Signs; N/A—not available; NCS—nerve conduction studies; NHL—non-Hodgkin lymphoma; NRS—numeric rating scale; 1RM—1 repetition maximum; RCT—randomized controlled trial; RT—resistance training; S-LANSS—Leeds Assessment for Neuropathic Symptoms and Signs–self-report version; SMT—sensorimotor training; SNAP—sensory nerve action potential amplitude of sural nerve; TNSr—Total Neuropathy Score–reduced; VT—vibration training

exercise with resistance and balance training (Bland et al., 2019; Zimmer et al., 2018). Seven studies used a single exercise modality for their interventions (Cao et al., 2023; Hammond et al., 2020; Ikio et al., 2022; Kanzawa-Lee, 2020; Müller et al., 2021; Saraboon & Siriphorn, 2021; Streckmann et al., 2019). When considering the exercise modality, resistance training (n = 11) was commonly used as an intervention component. Aerobic exercise (n = 9) and balance training (n = 9) were the second most frequently used as exercise components.

Across the 20 studies, 9 used supervised exercise (Bahar-Ozdemir et al., 2020; Cao et al., 2023; Gui et al., 2021; Henke et al., 2014; Knoerl et al., 2022; Saraboon & Siriphorn, 2021; Şimşek & Demir, 2021; Streckmann et al., 2019; Zimmer et al., 2018), and 7 used unsupervised exercises (Dhawan et al., 2020; Hammond et al., 2020; Ikio et al., 2022; Kanzawa-Lee, 2020; Kleckner et al., 2018, 2019; Visovsky et al., 2014). In one study with two treatment groups (Müller et al., 2021), unsupervised sensorimotor training was provided for one group, and supervised and unsupervised resistance training was provided for the other group. The three remaining studies used supervised and unsupervised exercises (Bao et al., 2020; Bland et al., 2019; Clark et al., 2012). In nearly all studies (n = 19), exercises were delivered to participants on an individual basis. Only one study delivered exercise in a group setting (Clark et al., 2012). In almost half of the studies (n = 9), counters or self-monitoring such as tracking sheets were used as methods to enhance intervention adherence (Bland et al., 2019; Cao et al., 2023; Clark et al., 2012; Dhawan et al., 2020; Ikio et al., 2022; Kanzawa-Lee, 2020; Kleckner et al., 2018; Knoerl et al., 2022; Visovsky et al., 2014). Six studies used telephone follow-up calls to monitor adverse events related to exercise and encourage adherence (Bahar-Ozdemir et al., 2020; Cao et al., 2023; Dhawan et al., 2020; Hammond et al., 2020; Knoerl et al., 2022; Müller et al., 2021). In only five studies, intervention fidelity was assessed (Ikio et al., 2022; Kanzawa-Lee, 2020; Saraboon & Siriphorn, 2021; Şimşek & Demir, 2021; Visovsky et al., 2014). Sixteen studies prescribed exercise intensity in their protocol (Bahar-Ozdemir et al., 2020; Bland et al., 2019; Cao et al., 2023; Gui et al., 2021; Hammond et al., 2020; Henke et al., 2014; Ikio et al., 2022; Kanzawa-Lee, 2020; Kleckner et al., 2018, 2019; Müller et al., 2021; Saraboon & Siriphorn, 2021; Şimşek & Demir, 2021; Streckmann et al., 2019; Visovsky et al., 2014; Zimmer et al., 2018). For example, three studies maintained participants' heart rates between 50% and 85% of heart rate reserve (low to moderate intensity) for aerobic training (Bland et al., 2019; Henke et al., 2014; Kleckner et al., 2018). Three studies used the Borg Rating Scale of Perceived Exertion to measure exercise intensity levels to maintain a low to moderate intensity for participants (Kanzawa-Lee, 2020; Kleckner et al., 2018; Zimmer et al., 2018).

Most studies (n = 17) measured CIPN symptoms using only patient-reported outcomes, such as the PainDETECT questionnaire (Bahar-Ozdemir et al., 2020; Bao et al., 2020; Bland et al., 2019; Cao et al., 2023; Dhawan et al., 2020; Gui et al., 2021; Henke et al., 2014; Ikio et al., 2022; Kanzawa-Lee, 2020; Kleckner et al., 2018, 2019; Knoerl et al., 2022; Saraboon & Siriphorn, 2021; Şimşek & Demir, 2021; Streckmann et al., 2019; Visovsky et al., 2014; Zimmer et al., 2018). Three studies used patient-reported outcomes and objective quantitative assessments of the function of the peripheral nervous system, including quantitative sensory testing, such as vibration sensation and pinprick, pressure/pain thresholds, reflexes, and deep sensitivity; and nerve conduction studies, such as compound muscle action potential amplitude of peroneal nerve and sensory nerve action potential amplitude of sural nerve (Bland et al., 2019; Hammond et al., 2020; Müller et al., 2021).

Study Quality

Nearly all the studies (n = 18) were randomized controlled trials (Bao et al., 2020; Bland et al., 2019; Cao et al., 2023; Clark et al., 2012; Dhawan et al., 2020; Hammond et al., 2020; Henke et al., 2014; Ikio et al., 2022; Kanzawa-Lee, 2020; Kleckner et al., 2018, 2019; Knoerl et al., 2022; Müller et al., 2021; Saraboon & Siriphorn, 2021; Şimşek & Demir, 2021; Streckmann

TABLE 2. Primary Study Quality Indicators (N = 20)

Study	Design	RA	CA	Blinded	A Priori Power	IF	ITT	Group Equal	Attrition (People)
Bahar-Ozdemir et al., 2020	Quasi	N	N	N	Y	N	N	N	10
Bao et al., 2020	RCT	Y	Y	N	Y	N	Y	Y	5
Bland et al., 2019	RCT	Y	Y	N	Y	N	N	Y	4
Cao et al., 2023	RCT	Y	N	N	Y	N	N	Y	15
Clark et al., 2012	RCT	Y	Y	N	N	N	Y	Y	4
Dhawan et al., 2020	RCT	Y	Y	N	Y	N	Y	Y	4
Gui et al., 2021	Quasi	N	N	N	N	N	N	N	0
Hammond et al., 2020	RCT	Y	N	Y	Y	N	Y	Y	12
Henke et al., 2014	RCT	Y	Y	N	Y	N	N	Y	17
Ikio et al., 2022	RCT	Y	Y	Y	Y	Y	Y	Y	13
Kanzawa-Lee, 2020	RCT	Y	N	N	Y	Y	Y	Y	N
Kleckner et al., 2018	RCT	Y	Y	N	N	N	Y	Y	65
Kleckner et al., 2019	RCT	Y	N	N	N	N	Y	Y	0
Knoerl et al., 2022	RCT	Y	Y	N	Y	N	Y	Y	8
Müller et al., 2021	RCT	Y	Y	Y	Y	N	Y	Y	14
Saraboon & Siriphorn, 2021	RCT	Y	Y	Y	Y	Y	Y	Y	4
Şimşek & Demir, 2021	RCT	Y	Y	N	Y	Y	Y	Y	0
Streckmann et al., 2019	RCT	Y	Y	Y	Y	N	Y	Y	1
Visovsky et al., 2014	RCT	Y	Y	N	N	Y	Y	Y	0
Zimmer et al., 2018	RCT	Y	Y	N	Y	N	Y	Y	6

CA—concealed allocation; IF—intervention fidelity; ITT—intention-to-treat analysis; N—quality indicator not reported or unable to be determined; quasi—quasiexperimental; RA—randomized assignment; RCT—randomized controlled trial; Y—quality indicator reported

TABLE 3. Characteristics of Primary Studies Included in the Meta-Analysis (N = 20)

Characteristic	n[a]	k	Min	Q1	M	Q3	Max	$\bar{X}$	SD
Mean age (years)									
Total sample	9	10	48.8	52.5	56.7	59.7	65	56.2	5
Control group	12	14	45.5	52.4	54.5	59	70	55.4	5.7
Exercise group	12	14	45.1	50.9	54.5	56.9	68.5	54.5	5.5
Sample size at analysis									
Total sample	20	22	14	25	36.5	64.8	355	59.5	72.4
Control group	20	22	5	10.8	17	29	185	28.1	37.5
Exercise group	20	22	7	11.5	20	35.3	170	31.4	35.6
Attrition (%)									
Total sample	20	22	–	3.8	13.3	20	37	13.3	10.1
Control group	19	21	–	1.4	10	19.7	48	12.6	12.8
Exercise group	19	21	–	–	13.6	21.1	29	13.6	10.1
Gender (%)									
Female	17	19	30	43.3	80.2	93.1	100	72.7	24.2
Male	15	17	–	–	5.7	46.9	70	22.1	26.6
Race (%)									
African American	3	3	3.3	3.3	11.1	–	19.5	11.3	8.1
Asian	3	3	4.4	4.4	12.2	–	25.8	14.1	10.8
White	6	6	56.1	57.6	72.1	87	88.2	72.2	14.1
Cancer type (%)									
Breast	10	12	12.9	40	71.2	92.3	100	65.6	28.8
Digestive system	9	11	–	14.6	26.7	95	100	42.1	38.6
Respiratory system	6	8	–	0.3	4.6	13.5	63	12.4	21.2
Head and neck	3	4	1.1	1.2	1.3	5.4	6.7	2.6	2.7
Hematologic malignancy	3	4	3	4.6	13.3	44.3	52.4	20.7	22.2
Female genital	8	10	–	2.8	15.7	83.3	100	35.6	40.2
Male genital	1	2	1.1	1.1	3	–	4.9	3	2.7
Urinary system	1	2	–	–	0.6	–	1.2	0.6	0.9
Treatment (%)									
Platinum compounds	11	13	2.4	11.2	28.6	63.2	100	44.2	32.5
Taxanes	11	13	11.9	37.8	51.9	86.2	100	58.3	30.1
Vinca alkaloids	4	6	–	1.1	8.9	23.1	52.4	14.6	19.3
Multiple chemotherapy agents	8	9	14.3	25.2	46.7	88.9	100	53.1	32.9
Intervention									
Number of days across intervention	18	20	14	42	56	84	183	70.9	44.8
Number of days to perform exercise per week	18	20	1	2	4	7	7	4.3	2.2
Number of weeks across intervention	18	20	2	6	8	12	26	10.1	6.4
Number of total exercise intervention sessions	17	19	6	12	32	60	108	37.9	28.4
Number of weekly structured exercises	17	19	1	2	3	7	9	4.1	2.4
Minutes to perform exercise per session	17	19	4	20	30	60	150	41.2	34.5
Minutes to perform exercise per week	16	18	8	56	105	165	420	128.2	98.4
Days after intervention outcome was measured	20	22	–	–	–	114	183	47.7	78
Total study quality indicator scores	20	22	–	4	5	6	7	4.6	1.7

[a] Number of sample studies
k—number of comparisons with data on characteristic; M—median; max—maximum; min—minimum; Q1—first quartile; Q3—third quartile

et al., 2019; Visovsky et al., 2014; Zimmer et al., 2018). In five studies, data collectors were blinded (Hammond et al., 2020; Ikio et al., 2022; Müller et al., 2021; Saraboon & Siriphorn, 2021; Streckmann et al., 2019). Most of the studies used intention-to-treat analysis (n = 15) (Bao et al., 2020; Clark et al., 2012; Dhawan et al., 2020; Hammond et al., 2020; Ikio et al., 2022; Kanzawa-Lee, 2020; Kleckner et al., 2018, 2019; Knoerl et al., 2022; Müller et al., 2021; Saraboon & Siriphorn, 2021; Şimşek & Demir, 2021; Streckmann et al., 2019; Visovsky et al., 2014; Zimmer et al., 2018). Additional information about study quality indicators is presented in Table 2.

Characteristics of Primary Studies

Two studies consisted of two treatment groups (Müller et al., 2021; Streckmann et al., 2019). Therefore, the 20 reviewed studies provided 22 comparisons. Descriptive characteristics are presented in Table 3. The total number of participants in the analysis was 1,308, which consisted of 691 participants in exercise groups and 617 participants in comparison groups. Most studies (n = 15) included only participants with solid tumors (Bahar-Ozdemir et al., 2020; Bao et al., 2020; Bland et al., 2019; Cao et al., 2023; Dhawan et al., 2020; Gui et al., 2021; Hammond et al., 2020; Henke et al., 2014; Kanzawa-Lee, 2020; Knoerl et al., 2022; Müller et al., 2021; Saraboon & Siriphorn, 2021; Şimşek & Demir, 2021; Visovsky et al., 2014; Zimmer et al., 2018), whereas three studies included participants with various cancers (solid tumor and hematologic) (Ikio et al., 2022; Kleckner et al., 2018; Streckmann et al., 2019). Two studies did not report cancer types (Clark et al., 2012; Kleckner et al., 2019).

Effect of Exercise on CIPN Symptoms

Supplemental Figure 1 online illustrates the forest plot of the effect sizes of the 22 comparisons and the summary effects. Solid squares display the weighted effect of the primary studies. The size of each square varies based on the study's precision. Study precision includes variance, standard error, and 95% CI, and is heavily influenced by sample size. Studies with good precision are assigned more weight than studies with poor precision. The width of the horizontal line through each square represents the 95% CIs for each study. Narrower lines reflect a greater precision. The diamond delineates the summary effect of 0.47. The width of the diamond represents the 95% CIs of the summary effect size. The single line at the bottom represents the 95% prediction interval, which reflects the range of true effects of similar studies that may be conducted in the future (Borenstein et al., 2021).

The forest plot showed one outlier (Şimşek & Demir, 2021), with an effect size of 6.68 (95% CI [5.3, 8.06], p < 0.001). The sensitivity analysis showed the summary effect dropped from 0.47 to 0.28 (Hartung-Knapp–adjusted 95% CI [0.12, 0.45], p = 0.002) after removing the outlier (see Supplemental Figure 2 online). Therefore, the effect of exercise was significant even after removing the outlier. To put the effect sizes in context, 21 comparisons (n = 19 studies) resulted in improved CIPN symptoms; only 3 studies showed significant improvement (Dhawan et al., 2020; Gui et al., 2021; Kleckner et al., 2018). Finally, the single-group pre- and post-test comparisons showed no improvement for either correlated or uncorrelated analyses for exercise and control groups. Of note, the control group effect sizes were negative, indicating worsening, albeit nonsignificant, CIPN scores (see Table 4).

Results of Moderator Analyses

Although the Q statistic was not significant (Q = 27.13, degrees of freedom = 20, p = 0.13), indicating a trivial amount of observed dispersion (Borenstein et al., 2021), conducting moderator analyses may generate future hypotheses. No categorical moderators that influenced effect size were found (see Table 5). The meta-regression analysis revealed that the weekly

TABLE 4. Random-Effects Analysis of Exercise Intervention on Chemotherapy-Induced Peripheral Neuropathy Symptoms

Comparison	n[a]	k	ES	SE	95% CI	t	p(t)
Exercise group pre- versus post-test scores (r = 0.0)	16	18	−0.01	0.16	[−0.34, 0.33]	−0.03	0.98
Exercise group pre- versus post-test scores (r = 0.8)	16	18	0.07	0.12	[−0.2, 0.33]	0.53	0.6
Comparison group pre- versus post-test scores (r = 0.0)	16	18	−0.16	0.17	[−0.52, 0.2]	−0.93	0.36
Comparison group pre- versus post-test score (r = 0.8)	16	18	−0.19	0.26	[−0.73, 0.35]	−0.75	0.46

[a] Number of sample studies
CI—confidence interval; ES—effect size (Hedges's g); k—number of comparisons; r—correlation between pre- and post-test scores; SE—standard error
Note. All analyses reflect the Hartung-Knapp–adjusted 95% CI.

exercise frequency was significantly associated with effect size (see Table 6).

Publication Bias

The funnel plot of standard errors against effect sizes appeared somewhat symmetrical (see Supplemental Figure 3 online). The Begg and Mazumdar rank correlation test (Kendall's tau = 0.18, p = 0.13, one-tailed) and Egger's regression test were not significant (intercept = 0.5, 95% CI [–0.73, 1.72], p = 0.41, two-tailed). These findings suggested that publication bias was unlikely.

TABLE 5. Effects of Exercise on Chemotherapy-Induced Peripheral Neuropathy Symptoms Across Categorical Moderators

Moderator	n[a]	k	ES	SE	Variance	95% CI	Z	p(Z)	F_{bet}	p(F_{bet})
Concealed allocation									0.19	0.67
Yes	13	15	0.27	0.11	0.01	[0.06, 0.48]	2.49	0.01		
No	6	6	0.32	0.11	0.01	[0.11, 0.52]	3.04	0.002		
Data collectors blinded									–	0.96
No	14	14	0.28	0.1	0.01	[0.09, 0.48]	2.86	0.004		
Yes	5	7	0.25	0.14	0.01	[0.02, 0.48]	2.13	0.03		
Intention-to-treat analysis									0.39	0.54
Yes	14	16	0.26	0.1	0.01	[0.06, 0.45]	2.61	0.01		
No	5	5	0.34	0.11	0.01	[0.12, 0.56]	3.02	0.003		
Intervention fidelity									0.32	0.58
No	15	17	0.27	0.09	0.01	[0.1, 0.44]	3.1	0.002		
Yes	4	4	0.39	0.19	0.04	[0.03, 0.76]	2.09	0.04		
A priori power estimation									0.01	0.9
Yes	14	16	0.28	0.1	0.01	[0.1, 0.47]	2.97	0.003		
No	5	5	0.3	0.13	0.02	[0.05, 0.54]	2.33	0.02		
Exercise intensity									0.03	0.86
Yes	15	17	0.26	0.06	0.004	[0.14, 0.38]	4.18	< 0.001		
No	4	4	0.24	0.36	0.13	[–0.46, 0.94]	0.68	0.5		
Supervised exercise									1	0.39
Supervised	8	9	0.32	0.13	0.02	[0.06, 0.58]	2.43	0.02		
Unsupervised	8	8	0.36	0.12	0.01	[0.12, 0.59]	2.97	0.003		
Mixed	4	4	0.05	0.16	0.03	[–0.26, 0.36]	0.29	0.77		
Exercise protocol									1.42	0.27
Combined exercise	9	9	0.41	0.14	0.02	[0.14, 0.68]	3	0.003		
Single exercise	7	9	0.21	0.09	0.01	[0.03, 0.4]	2.28	0.02		
Yoga	3	3	–0.03	0.22	0.05	[–0.46, 0.4]	–0.13	0.9		
Self-monitoring									0.09	0.76
No	10	12	0.3	0.1	0.01	[0.11, 0.5]	2.99	0.003		
Yes	9	9	0.26	0.12	0.02	[0.02, 0.5]	2.15	0.03		
Follow-up telephone call									0.07	0.79
No	13	14	0.3	0.09	0.01	[0.12, 0.47]	3.35	0.001		
Yes	6	7	0.27	0.14	0.02	[0.001, 0.54]	1.97	0.049		

[a] Number of sample studies
CI—confidence interval; ES—effect size; k—number of comparisons; SE—standard error
Note. Outlier was removed before conducting the subgroup analysis.

Discussion

The purpose of this meta-analysis was to examine the effects of exercise on CIPN symptoms in cancer survivors. Overall, exercise showed mild improvement in CIPN symptoms. Similar to most of the previous meta-analyses (Brownson-Smith et al., 2023; Crichton et al., 2022; de Arenas-Arroyo et al., 2023; Lin et al., 2021; Streckmann et al., 2022), this analysis found that exercise significantly improved CIPN symptoms. However, the findings were not aligned with those of Guo et al. (2023), who found that exercise did not improve CIPN symptoms based on four studies (effect size = 0.02).

The magnitude of the mean effect sizes in the current study was close to that of the studies by de Arenas-Arroyo et al. (2023) (effect size = –0.27, n = 5 studies, k = 6 comparisons) and Streckmann et al. (2022) (effect size = 0.43, n = 5 studies, k = 6 comparisons), but less than that of the studies by Crichton et al. (2022) (effect size = –0.89, n = 2 studies), Brownson-Smith et al. (2023) (effect size = –0.71, n = 4 studies) and Lin et al. (2021) (effect size = 0.53, n = 5 studies). The difference in the mean effect size between the current study and the previous meta-analyses might be because more primary studies were included. The current study's findings are likely more reflective of the prior research.

A subgroup analysis was conducted to explore relationships between the effect sizes and potential sources of heterogeneity, which aimed to generate hypotheses for future studies. No significant difference was found across subgroups. This might be because the power was too low to detect a difference. Future researchers can further explore potential sources of heterogeneity. In the meta-regression analysis, weekly exercise frequency significantly moderated the effect of exercise on CIPN symptoms. That is, for every one day per week increase in the frequency of exercise, CIPN scores improved by about 0.09. It is likely that this effect size is too small to be clinically significant. Future studies can examine the effects of various weekly exercise frequencies.

The synthesis of exercise characteristics showed that most studies used combined exercise for their

TABLE 6. Effects of Exercise on CIPN Symptoms Across Continuous Moderators

Moderator	n[a]	k	Slope	SE	T^2	T	F_{model}	$p_{(Fmodel)}$
Participant characteristic								
Age (years) (mean)	9	10	0.01	0.02	–	–	0.15	0.71
Female gender (%)	16	18	0.001	0.004	0.03	0.17	0.12	0.74
Male gender (%)	15	16	–0.001	0.004	0.03	0.18	0.12	0.73
Solid tumor cancer type (%)	17	19	–0.005	0.005	0.03	0.17	0.77	0.39
Treated with taxanes (%)	10	12	0.001	0.004	–	–	0.05	0.82
Treated with platinum compounds (%)	11	13	0.002	0.003	0.01	0.12	0.78	0.4
Method characteristic								
Total attrition rate (%)	19	21	–0.01	0.01	0.02	0.16	1.88	0.19
Total study quality indicator score	19	21	–0.02	0.04	0.03	0.11	0.29	0.6
Number of days measuring CIPN	18	20	–0.002	0.001	0.03	0.17	1.77	0.2
Intervention characteristic								
Number of days across intervention	17	19	–0.002	0.002	0.03	0.18	1.22	0.28
Number of weeks across intervention	17	19	–0.01	0.01	0.03	0.18	1.22	0.28
Number of total exercise intervention sessions	16	18	0.003	0.004	0.04	0.2	0.54	0.47
Number of weekly exercise intervention sessions	16	18	0.06	0.03	0.03	0.16	3.85	0.07
Minutes to perform exercise per session	16	18	–0.003	0.002	0.05	0.23	2	0.18
Frequency of exercise (days per week)	17	19	0.08	0.04	0.03	0.16	4.82	0.04
Duration of exercise (minutes per week)	15	17	0.0004	0.001	0.07	0.26	0.09	0.76

[a] Number of sample studies
CIPN—chemotherapy-induced peripheral neuropathy; k—number of comparisons; SE—standard error; slope—meta-regression coefficient; T—SD of true effect of the regression line; T^2—variance of true effect of the regression line
Note. Outlier was removed before conducting the meta-regression analysis.

interventions as opposed to a single exercise or yoga. Although a subgroup analysis revealed no difference between the three interventions (combined, single, and yoga), combined exercise (effect size = 0.41) and single exercise (effect size = 0.21) interventions were likely to improve CIPN symptoms, but yoga (effect size = –0.03) was not. The synthesis also revealed that resistance training was commonly used in the exercise protocols. It often was combined with balance and/or aerobic training. However, a subgroup analysis could not be conducted to detect the difference in each type of exercise because too few studies examined just one type. Therefore, only a well-rounded exercise routine, such as resistance training, aerobic exercise, balance training, stretching exercise, or yoga, can be recommended. Future studies can examine the effects of specific types of exercise on CIPN symptoms.

Of note, the single-group analyses showed no improvement in CIPN scores between pre- and post-test. However, the control groups' symptoms were found to have worsened. The worsening of the control groups' symptoms and the slight, but nonsignificant, improvement of the exercise groups' symptoms resulted in significant overall effect sizes when the two groups were compared at post-test.

Strengths and Limitations

This study was an updated comprehensive systematic review and meta-analysis of the effects of exercise on CIPN symptoms in cancer survivors. The inclusion of quasiexperimental studies was a major strength of this study. One limitation of this study was that it included only studies written in English; therefore, some relevant studies published in other languages may have been missed. Another limitation was the moderator analyses. Because of the small sample sizes of the included studies, confidence in drawing a conclusion about these analyses was limited; however, future studies can use the moderator variables highlighted in this study to generate additional research questions.

Implications for Nursing and Research

Nurses can educate and encourage cancer survivors to engage in exercise, including resistance training (e.g., using machine training, free weights, or resistance bands), aerobic exercise (e.g., treadmills, brisk walking), balance training (e.g., bipedal stance, single/double leg standing, tandem stance), or yoga. Nurses can play a significant role in referring cancer survivors to exercise specialists familiar with people with cancer to address a range of physical abilities and challenges. Future studies can determine what types and amounts of exercise are most effective in improving CIPN symptoms.

KNOWLEDGE TRANSLATION

- Exercise should be considered as nonpharmacologic treatment for relieving symptoms of chemotherapy-induced peripheral neuropathy in cancer survivors.
- To implement exercise for cancer survivors, healthcare providers should consider the exercise type, session minutes, frequency, and intensity.
- Exercise programs can be targeted to cancer survivors with chemotherapy-induced peripheral neuropathy through consultation with interprofessional teams.

Conclusion

CIPN symptom management is a challenge for nurses and other healthcare providers. In the studies reviewed, exercise improved CIPN symptoms; however, because of the small sample of studies and heterogeneity, the findings should be generalized cautiously to patients with CIPN symptoms. Additional primary research is needed in this area. Nursing leaders can consider using the moderator findings of this review to guide the development of exercise protocols in healthcare settings for cancer survivors.

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QUESTION GUIDE FOR A JOURNAL CLUB

Journal clubs can help to increase and translate findings to clinical practice, education, administration, and research. Use the following questions to start discussion at your next journal club meeting. Then, take time to recap the discussion and make plans to proceed with suggested strategies.

1. Discuss the literature about the relationship between exercise and chemotherapy-induced peripheral neuropathy (CIPN).
2. What are some of the current limitations regarding the effects of exercise on CIPN in the published research?
3. Describe scenarios for discussing exercise with cancer survivors with CIPN.

Visit https://bit.ly/1vUqbVj for details on creating and participating in a journal club. Contact pubONF@ons.org for assistance or feedback. Photocopying of the article for discussion purposes is permitted.