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Effectiveness of exercise therapy on chemotherapy-induced peripheral neuropathy in patients with ovarian cancer: A scoping review

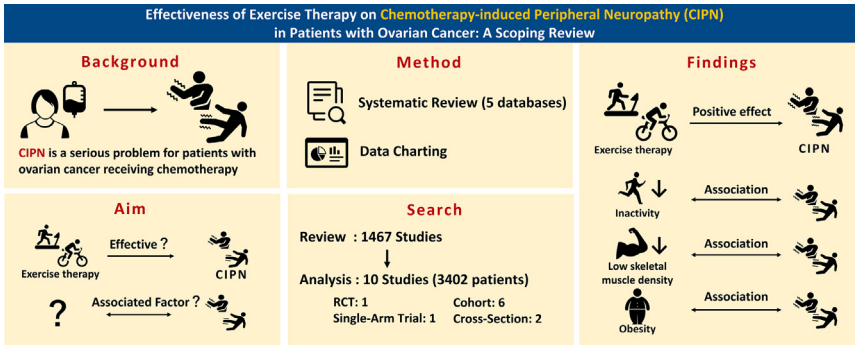
Masanori Konuma [a], Tomohiro Ikeda [a,*], Tomohiro Mitoma [b], Shinsuke Shirakawa [b], Jota Maki [b], Yoshimi Katayama [a], Masanori Hamada [a], Shoji Nagao [b], Toshifumi Ozaki [a]

[a] Department of Rehabilitation Medicine, Okayama University Hospital, 2-5-1 Shikatacho, Kita-ku, Okayama 700-8558, Japan
[b] Department of Obstetrics and Gynecology, Graduate School of Medicine Dentistry and Pharmaceutical Sciences, Okayama University, Okayama 700-8558, Japan

HIGHLIGHTS

- Exercise therapy has potential benefits for patients with ovarian cancer who have chemotherapy-induced peripheral neuropathy (CIPN).
- Daily physical inactivity was associated with a higher incidence of CIPN.
- Low skeletal muscle density was associated with CIPN.
- Physical dysfunction was associated with CIPN.
- Evidence on the effectiveness of exercise for CIPN is still limited and further research is needed.

GRAPHICAL ABSTRACT



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ABSTRACT

Background & aims. Exercise therapy is a potentially beneficial treatment option for chemotherapy-induced peripheral neuropathy (CIPN). However, there is a lack of consensus on the management of CIPN in patients with ovarian cancer. The purpose of this scoping review was to evaluate the evidence on the effectiveness of exercise therapy in patients with ovarian cancer and explore key physical fitness parameters.

Methods. A systematic electronic search was conducted using the MEDLINE, CINAHL, Web of Science, PEDro, and ClinicalTrials.gov databases. Two independent reviewers summarized the features and data from the literature regarding the effectiveness of exercise therapy for CIPN and the association between CIPN and physical fitness parameters.

Results. Ten articles involving 3402 participants were reviewed. The study design included one randomized controlled trial, one single-arm trial, one prospective cohort study, five retrospective cohort studies, and two cross-sectional studies. The mean patient age was >60 years in three studies and 50–60 years in six studies. The mean body mass index was >25.0 kg/m^2 in six studies and not stated in four studies. In six references, patients received platinum and taxane-based chemotherapy. The effectiveness of an exercise therapy program for CIPN was reported in a randomized controlled trial. Two cross-sectional studies highlighted the association between daily physical inactivity and CIPN; two retrospective cohort studies showed an association between low skeletal muscle density and CIPN; one article demonstrated an association between physical dysfunction and CIPN.

* Corresponding author.
E-mail address: pn9375yc@s.okayama-u.ac.jp (T. Ikeda).

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Conclusion. This scoping review indicates that although evidence is lacking, exercise intervention programs for CIPN in patients with ovarian cancer have potential benefits, especially when focused on daily physical activity, skeletal muscle density, and physical function.

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Contents

1. Introduction

Ovarian cancer is one of the most common and lethal gynecological malignancies, accounting for approximately 4 % of global cancer incidence and mortality among women [1,2]. It is detected only in the advanced stages in more than 60 % of individuals, even in high-income countries, and the standard treatment is surgery followed by chemotherapy [3]. Although the survival rates have improved with advances in medical science [4], adverse treatment events remain a challenge for survivors [5].

Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse event in patients with ovarian cancer undergoing chemotherapy and is a risk factor for decreased physical function, reduced quality of life (QOL) [6], and increased falls [7]. Furthermore, unacceptable CIPN may lead to treatment delay, discontinuation, or dose reduction [8] and worsen disease prognosis [9]. CIPN symptoms include sensory, motor, and autonomic dysfunctions, with sensory issues being the more common feature [10]. The prevalence of CIPN among individuals with ovarian cancer undergoing chemotherapy ranges from 30 % to 70 % [11,12]. In addition, CIPN may develop or persist even after treatment. Approximately 51 % of ovarian cancer survivors report CIPN symptoms 2–12 years after diagnosis [13]. However, despite the impact of CIPN on QOL, there is a lack of consensus for evaluating, preventing or treatment CIPN and therefore this is an unmet clinical need.

Recently, several studies [14,15] have reported the effectiveness of exercise in managing CIPN in patients with breast and gastrointestinal cancers, suggesting it as a new strategy for improving or preventing CIPN. Additionally, potential associations between physical fitness parameters and CIPN have been suggested, including the possibility that physical activity may promote the recovery of neurological function [16] and contribute to the prevention of CIPN through improved body composition [17]. However, there is no evidence-based consensus on the management of CIPN in patients with ovarian cancer with specific clinical features such as relatively older, lymphedema, and postoperative nerve palsy. In patients with ovarian cancer, understanding the effects of exercise on CIPN and the clinical mechanisms underlying these effects would aid in developing effective CIPN management strategies. This scoping review aimed to evaluate the evidence on the effectiveness of exercise therapy in patients with ovarian cancer and explore potential associations between physical fitness parameters and CIPN.

2. Materials and methods

We conducted a scoping review to comprehensively map the current knowledge on the effects of exercise therapy on CIPN in patients with ovarian cancer for guiding future research. The Joanna Briggs Institute framework was adopted to conduct scoping reviews [18]. According to this framework, the review process began by defining the objectives and questions, followed by developing the inclusion criteria; describing the planned approach; searching for evidence; selecting relevant studies; extracting, analyzing, presenting data; and summarizing the findings. Reporting adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews [19] (Supplementary Material 1). The protocol for this scoping review was registered within the Open Science Framework prior to the study (https://osf.io/qft48/), in compliance with PRISMA-P guidelines [20].

2.1. Identification of relevant studies

2.1.1. Population

The inclusion criteria were as follows: (1) patients with ovarian cancer undergoing or after chemotherapy, (2) including patients with CIPN, and (3) those aged >18 years. Studies were included if they met all the inclusion criteria (1), (2), and (3). The exclusion criteria were as follows: (1) severe diabetes and other neurological diseases that are difficult to identify based on CIPN; (2) effectiveness of exercise therapy or physical fitness parameters, including daily physical activity, body composition, and physical function were not assessed; (3) not receiving chemotherapy that causes CIPN; and (4) cases who had previously received CIPN-inducing chemotherapy for other malignancies. Studies that met any of the exclusion criteria were excluded.

2.1.2. Concept

The aim of the current scoping review was to investigate the effectiveness of exercise therapy for CIPN in patients with ovarian cancer and the clinical mechanisms underlying these effects. Therefore, patients with ovarian cancer who underwent or were treated with chemotherapy were included. This scoping review included randomized and non-randomized controlled trials, single-arm intervention trials, prospective and retrospective cohort studies, and cross-sectional studies. Systematic reviews, meta-analyses, narrative reviews, case series, case reports, and letters were excluded.

2.1.3. Context

No limitations were imposed on location, race, sex, or language. The study included articles published until June 2024. Both published and unpublished studies were searched.

2.2. Study selection

A systematic electronic search was conducted in the MEDLINE, CINAHL, Web of Science, PEDro, and ClinicalTrials.gov databases and registries. Details of the electronic search strategy for each database and registry are provided in Supplementary Material 2. The search was conducted on June 20, 2024. The searched references were uploaded to Rayyan [21] (Qatar Computing Research Institute, Ar Rayyan, Qatar), and duplicate references were removed. Following a pilot test, titles and abstracts were screened by two independent reviewers (M.K. and T.I.) to assess the inclusion criteria. Potentially relevant studies were retrieved in full-length, and their citation details were imported into Rayyan. The full texts of the selected articles were studies in detail against the inclusion criteria by two independent reviewers (M.K. and T.I.). The reasons for excluding full-text articles that did not meet the inclusion criteria were recorded. Any disagreements between the reviewers (M.K. and T.I.) at each stage of the selection process were resolved through discussion or by an additional reviewer (M. H.).

2.3. Data extraction

Data were exported according to the following guidelines [22]: Two investigators (M.K. and T.I.) developed a data extraction sheet in Microsoft Excel (Microsoft Corporation, WA, USA), which included information about the author(s), year of publication, origin/country of origin, aims/purpose, population, sample size within the source of evidence, assessment methods for CIPN, body composition, daily physical activity, and key findings related to the scoping review question. Two independent reviewers (M.K. and T.I.) exported data into an extraction sheet. The data extraction sheet was not modified or revised when extracting data from the included sources of evidence. Disagreements between the reviewers were resolved through discussion or by inviting an additional reviewer (M.H.). If appropriate, we contacted the authors of the papers to request for missing or additional data.

2.4. Charting, collating, summarizing, and reporting the results

The search results and process for the inclusion and exclusion of studies are shown in the PRISMA 2020 statement, which is an updated guideline for transparently reporting systematic reviews [23]. The characteristics of the included studies and their participants, the effectiveness of exercise therapy, and the relationship between CIPN and physical fitness parameters are presented in the tables and figures.

3. Results

3.1. Study identification

A systematic search of the databases retrieved 1467 results. Duplicates were removed, leaving 433 records. In the primary screening, 443 articles were reviewed based on their title and abstract. In the secondary screening, 49 articles were evaluated for their eligibility based on full text. Ultimately, 10 articles [17,24–32] involving 3402 participants were eligible for inclusion. The process for the systematic search of studies in the databases is shown in Fig. 1.

The flow diagram demonstrates the process of screening and selecting studies.

3.2. Study characteristics

The study characteristics are summarized in Table 1. Four papers [24,29,31,32] were from the United States, two [25,27] were from Canada, and one each from Japan [17], Turkey [30], Brazil [28], and Australia [26]. Study designs included one randomized control trial [24], one single-arm trial [25], one prospective cohort study [30], five retrospective cohort studies [17,28–32], and two cross-sectional studies [26,27]. Two articles [24,25] examined the effectiveness of exercise therapy for CIPN and eight [17,26–32] explored the potential associations between physical fitness parameters and CIPN. Participants were diagnosed with epithelial ovarian cancer in six studies and ovarian cancer in four studies. The mean patient age was >60 years in three studies [17,27,31], 50–60 years in six studies [24–26,28,30,32], and unknown in one study [29]. The mean body mass index (BMI) was >25.0 kg/m^2 in six studies [24,26,27,30–32] and not stated in four studies [17,25,28,29]. The clinical classification was clinical stage III/IV in >50 % of participants in seven studies [17,24,26,28,29,31,32], <50 % of participants in two study [25,30], and not stated in one study [27]. In six references [17,24,26,28,31,32], patients received platinum and taxane-based chemotherapy.

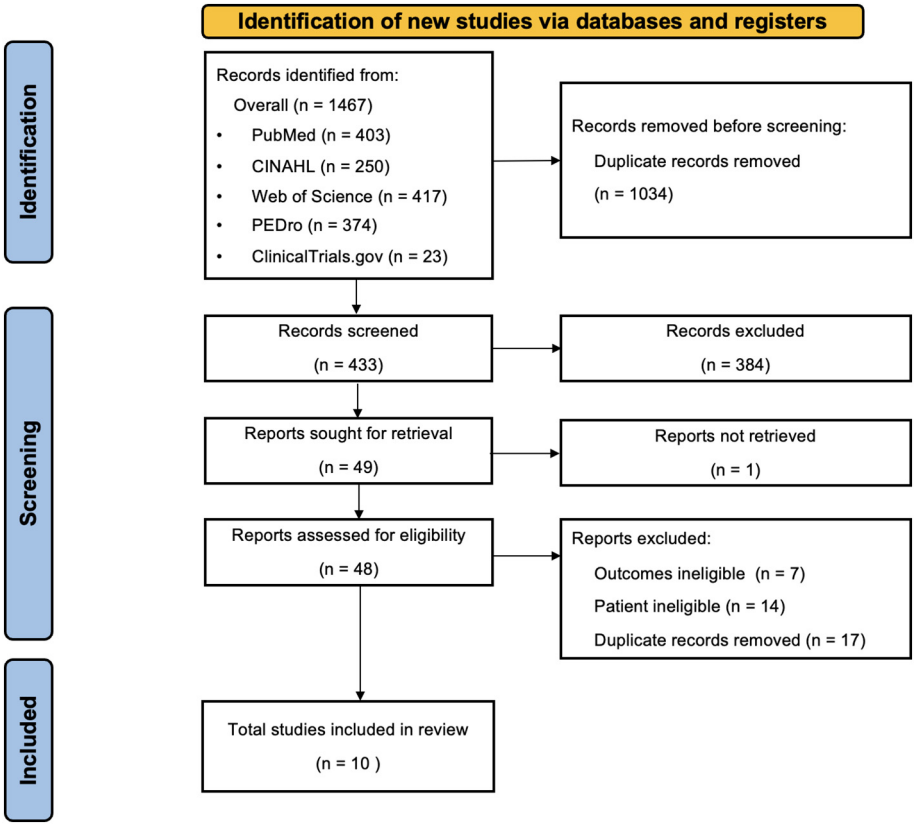

Fig. 1. PRISMA flow diagram of the study selection process.

3.3. Assessment of CIPN and physical fitness parameters

The assessment methods for CIPN and physical fitness parameters, encompassing daily physical activity, body composition, and physical function, are summarized in Table 2. CIPN was assessed using the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity in five studies [24–27,30] and Common Terminology Criteria for Adverse Events classification in four studies [17,28,31,32]. Daily physical activity was assessed based on self-reported symptoms in two studies [26,27]. Body composition indices were investigated in six studies, with four studies [17,28,29,31], assessing skeletal muscle index using computed tomography and two

Table 1
Study characteristics.

Author	Country	Study design	Sample size	Study Population	Survey period
Cao et al. (2023)	USA	Randomized control trial	144	Diagnosis: epithelial ovarian cancer, Age: 57.5 ± 8.3 years, BMI:29.4 ± 7.1 kg/m2, cStage III/IV: 58.2 %, platinum and taxane-based chemotherapy	Post-chemotherapy
Moonsammy et al. (2013)	Canada	Single arm trial	19	Diagnosis: epithelial ovarian cancer, Age: 55.3 years, BMI: NA, cStage III/IV: 32 %, platinum-based chemotherapy	Undergoing or post-chemotherapy
Webber et al. (2019)	Australia	Cross-sectional	1360	Diagnosis: ovarian cancer, Age: 51–60 years, BMI: 27.9 kg/m^2, cStage III/IV: 62.5 %, platinum, and taxane-based chemotherapy	Post-chemotherapy
Stevinson et al. (2009)	Canada	Cross-sectional	359	Diagnosis: ovarian cancer, Age: 60.2 years, BMI: 27.1 kg/m^2, cStage: NA, chemotherapy regimen: NA, chemotherapy regimen: NA	Undergoing or post-chemotherapy
Bruno et al. (2021)	Brazil	Retrospective cohort	239	Diagnosis: epithelial ovarian cancer, Age: 56.3 years, BMI: NA, cStage III/IV: 86.9 %, platinum, and taxane-based chemotherapy	Pre-chemotherapy to chemotherapy phase
Whittum et al. (2023)	USA	Retrospective cohort (Unpublish literature)	174	Diagnosis: epithelial ovarian cancer, Age: NA, BMI: NA, cStage III/IV: 80.4 %, chemotherapy regimen: NA	Pre-chemotherapy to chemotherapy phase
Kızılırmak et al. (2023)	Turkey	Prospective cohort	24	Diagnosis: ovarian cancer, Age: 56 ± 10.1 years, BMI: 26.4 kg/m^2, cStage:II (62.5 %)/III(37.5 %), chemotherapy regimen: NA	Post-chemotherapy
Yoshikawa et al. (2017)	Japan	Retrospective cohort	76	Diagnosis: ovarian cancer, Age: 63 years, BMI: NA、cStage III/IV: 55.2 %, platinum and taxane-based chemotherapy	Pre-chemotherapy to chemotherapy phase
Staley et al. (2020)	USA	Retrospective cohort	201	Diagnosis: epithelial ovarian cancer, Age: 63 years, BMI: 26.9 kg/m2, cStage III/IV: 76.5 %, platinum, and taxane-based chemotherapy	Pre-chemotherapy to chemotherapy phase
Bandera et al. (2015)	USA	Retrospective cohort	806	Diagnosis: epithelial ovarian cancer, Age: 80.6 % over 50 years, BMI: 60.7 % over 25.0 kg/m2, cStage III/IV: 59.8 %, platinum and taxane-based chemotherapy	Pre-chemotherapy to chemotherapy phase

BMI Body mass index.
cStage Clinical Stage.

Table 2
Assessment methods of CIPN and physical fitness parameters.

Author	CIPN	Exercise therapy	Daily physical activity	Body composition	Physical function
Cao et al. (2023)	FACT-GOG/NTX	Moderate-intensity aerobic exercise (150 min per week, 6-month intervention). Participants reported their exercise levels during weekly telephone calls with an exercise trainer.	NA	NA	NA
Moonsammy et al. (2013)	FACT-GOG/NTX	Participants were introduced to the home-based exercise training and provided individualized prescriptions and equipment. Exercise training based on light-moderate aerobic exercise (brisk walking) and 10 resistance training exercises. In parallel, one-hour counselling sessions were held every two weeks by telephone.	NA	NA	NA
Webber et al. (2019)	FACT-GOG/NTX	NA	IPAQ-SF (self-report)	BMI	NA
Stevinson et al. (2009)	FACT-GOG/NTX	NA	Assessment of leisure time exercise behavior (self-report)	NA	NA
Bruno et al. (2021)	CTCEA classification grade ≥ 3	NA	NA	Skeletal muscle mass and density using CT	NA
Whittum et al. (2023)	NA	NA	NA	Skeletal muscle density using CT	NA
Kızılırmak et al. (2023)	FACT-GOG/NTX	NA	NA	NA	6-min walk distance
Yoshikawa et al. (2017)	CTCEA classification grade ≥ 2	NA	NA	Skeletal muscle mass using CT	NA
Staley et al. (2020)	CTCEA classification grade ≥ 1	NA	NA	Skeletal muscle mass using CT	NA
Bandera et al. (2015)	CTCEA classification grade ≥ 3	NA	NA	BMI	NA

All included articles either examined the effectiveness of exercise therapy for CIPN or investigated the association between physical fitness parameters and CIPN to understand its effectiveness.
CIPN Chemotherapy-induced peripheral neuropathy.
FACT-GOG/NTX Functional assessment of cancer therapy/gynecologic oncology group-neurotoxicity.
CTCEA Common terminology criteria for adverse events.
IPAQ-SF International physical activity questionnaire - short form.

[26,32] assessing BMI. Physical function with the 6-min walk test was investigated in only one study [30].

3.4. Effectiveness of exercise therapy on CIPN

There were two studies [24,25] that evaluated the effectiveness of exercise therapy on CIPN. The effectiveness of exercise therapy for CIPN is presented in Fig. 2 and Table 3. The benefits of exercise therapy programs for CIPN have been reported in both randomized controlled [24] and single-arm trials [25]. A randomized clinical trial [24] demonstrated that a 6-month aerobic exercise therapy significantly improved self-reported CIPN symptoms. Furthermore, in a subgroup analysis, compliance with moderate aerobic exercise for 150 min/week was inversely correlated with CIPN. A single-arm trial [25] reported that CIPN did not worsen during chemotherapy in patients with ovarian cancer. However, no improvement in CIPN was observed after treatment.

3.5. Potential associations between CIPN and physical fitness parameters

The relationship between CIPN and physical fitness parameters, including daily physical activity, body composition, and physical function, is presented in Fig. 2 and Table 3. Two cross-sectional studies [26,27] have reported inverse associations between daily physical inactivity and CIPN. Stevinson et al. [27] reported that the American College of Sports Medicine (ACSM) physical activity guidelines [33], namely 150 min/week of moderate physical activity, is extremely low at 28 % for patients with ovarian cancer. Furthermore, CIPN was inversely correlated with compliance with this guideline. Two studies identified low skeletal muscle density before chemotherapy as a risk factor for CIPN [28,29]. Only one study reported an association between physical function, with 6-min walk test, and CIPN [30]. One study [17] reported skeletal muscle loss before chemotherapy as a risk factor for CIPN, whereas two studies [28,31] found that it was not a risk factor. Bandera et al. [32] reported that BMI before chemotherapy is not a risk factor for CIPN, whereas Webber et al. [26] found that overweight and obesity correlate with CIPN.

4. Discussion

4.1. Summary of main results

This scoping review, encompassing data from 10 articles involving 3402 participants, summarizes the effectiveness of exercise therapy in patients with ovarian cancer and the association between physical fitness parameters and CIPN. Only one randomized clinical trial demonstrated the effectiveness of exercise therapy programs for CIPN in patients with ovarian cancer [24]. Moreover, this review demonstrated daily physical inactivity, skeletal muscle density, and physical dysfunction (6-min walk distance) as physical fitness parameters associated with CIPN. Meanwhile, associations of CIPN with skeletal muscle loss and overweight have also been reported, but the results are inconsistent.

4.2. Interpretation of results

4.2.1. Effectiveness of exercise therapy programs

A randomized clinical trial reported on the effectiveness of exercise therapy programs for CIPN in patients with ovarian cancer [24]. It demonstrated that a 6-month aerobic exercise therapy significantly improved self-reported CIPN symptoms and thus may be a strategy for preventing CIPN. Furthermore, given the results of the subgroup analysis, it may be essential to adhere to 150 min/week of moderate-intensity aerobic exercise. This means compliance with the guidelines proposed by the ACSM [33]. A single-arm trial reported that CIPN did not worsen

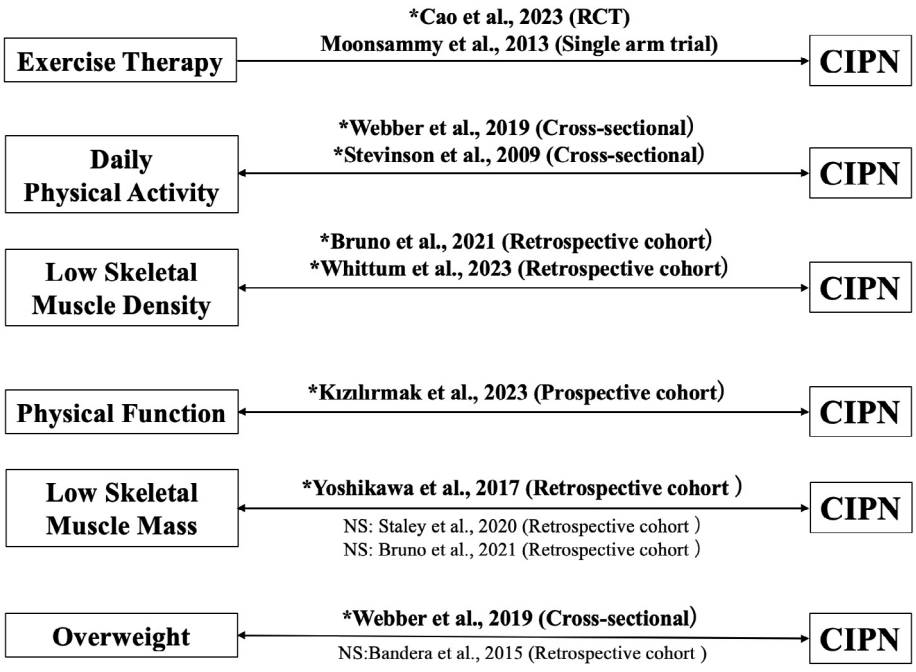

Fig. 2. Association between chemotherapy-induced peripheral neuropathy and physical fitness parameters in patients with ovarian cancer.
CIPN: chemotherapy-induced peripheral neuropathy.
RCT: randomized control trial.
*: Significant associations between CIPN and physical fitness parameters.
NS: No significant associations between CIPN and physical fitness parameters.

during chemotherapy in patients with ovarian cancer though no improvement was observed after chemotherapy. A similar trend was observed in other previous studies [14,15]. Hence, exercise therapy appears to be a potentially effective intervention for CIPN in patients with ovarian cancer, similar to that in patients with breast and gastrointestinal cancers [14,15]. Beyond its impact on CIPN, exercise therapy also improves physical fitness [34], QOL [35], fatigue [36], and depression [37] in patients with ovarian cancer, highlighting its broader clinical value.

4.2.2. Potential association between CIPN and daily physical activity

Two cross-sectional studies [26,27] demonstrated an association between daily physical inactivity and CIPN. The potential of daily physical activity to directly enhance neurological function recovery [16] and suppress neuropathic pain [38] has been suggested as a clinical mechanism explaining its impact. Indirectly, daily physical activity may alleviate CIPN by enhancing body composition and physical function, as highlighted in this review. Daily physical activity is a non-pharmacologically modifiable factor and should be incorporated into exercise therapy programs. Given the low compliance rate with the ACSM guidelines in the cross-sectional study [27] and their inverse correlation of compliance with CIPN, the CIPN management program may need to focus on compliance with the ACSM guidelines. Nonetheless, further studies are required to elucidate these mechanisms.

4.2.3. Potential association between CIPN and body composition

Two studies [28,29] reported that low skeletal muscle density before chemotherapy is a risk factor for CIPN. Several studies [39–42] have also reported that low skeletal muscle density is associated with adverse chemotherapy outcomes. Our results align with those of previous studies including patients with other types of cancer. Interestingly, decreased skeletal muscle mass was identified a risk factor for CIPN in one study [17] but not in the other two [28,31]. One study [26] reported being overweight is a risk factor for CIPN, whereas other study [32] did not. These inconsistent findings underscore the need for further

Table 3
Main findings regarding the impact of exercise therapy on CIPN and its potential associations.

Author	Main Findings
Cao et al. (2023)	Six-month aerobic exercise therapy significantly improved self-reports of CIPN.
Moonsammy et al. (2013)	There was no worsening of CIPN in patients with ovarian cancer during chemotherapy. However, there was no improvement in CIPN observed after treatment.
Webber et al. (2019)	CIPN associated with underactivity and overweight/obesity, respectively
Stevinson et al. (2009)	ACSM physical activity guideline compliance and CIPN were inversely correlated.
Bruno et al. (2021)	Adverse events including CIPN correlated with low skeletal muscle density and subcutaneous fat, but not with low skeletal muscle mass.
Whittum et al. (2023)	Low skeletal muscle density before chemotherapy is a risk factor for CIPN.
Kızılırmak et al. (2023)	Significant correlation between 6-min walking distance and FACT-GOG/NTX score.
Yoshikawa et al. (2017)	Skeletal muscle loss before chemotherapy was a risk factor for CIPN
Staley et al. (2020)	Skeletal muscle loss before chemotherapy was not a risk factor for CIPN
Bandera et al. (2015)	BMI before chemotherapy is not a risk factor for CIPN.

CIPN Chemotherapy-induced peripheral neuropathy.
ACSM American College of Sports Medicine.
FACT-GOG/NTX Functional assessment of cancer therapy/gynecologic oncology group – neurotoxicity.

investigation. Body composition can be improved with exercise therapy [34], and combined nutritional therapy is expected to enhance its effects [43]. Thus, developing programs focusing on body composition, particularly skeletal muscle density, should be considered as a part of CIPN management.

4.2.4. Potential association between CIPN and physical function

Only one study has reported an association between physical dyfunction, with the 6-min walk test and CIPN. Physical function has been reported to be associated with treatment tolerability [44]. This finding is similar to those of studies including patients with gynecological cancer [45] and supports the findings of this review. Exercise therapy has been reported to improve treatment tolerability in other types of cancer [46] and may be beneficial in reducing the incidence of CIPN in patients with ovarian cancer.

4.3. Implications of the present review

Patients with ovarian cancer often experience mobility difficulties due to CIPN, further exacerbated by lymphedema and motor paralysis from pelvic surgery and chemotherapy [47,48] and their relatively older age compared to breast cancer patients [49,50]. These issues emphasize the unmet need for management strategies that address mobility limitations and improve QOL in this population.

This scoping review is the first to explore the effectiveness of exercise therapy for CIPN in patients with ovarian cancer and to identify critical physical fitness parameters, providing essential insights into the management of CIPN. Although clinical trials specific to ovarian cancer are limited to two, the present findings align with research in other cancer types [14,15], supporting exercise therapy as a promising non-pharmacologic intervention for CIPN. Moreover, this review identified potential associations between CIPN and factors such as daily physical inactivity, skeletal muscle density, and physical dysfunction. These factors could serve as a target for interventions given the relationship that has been hypothesized based on the data. Therefore, these findings highlight the importance of future research to establish a CIPN management program focused on preventing or improving these fitness parameters.

4.4. Limitations

This study has several limitations. First, the evidence on the effectiveness of exercise therapy for CIPN was inadequate, because only one randomized controlled trial was included. Second, this review failed to completely achieve our purpose of exploring key factors from a physical fitness perspective due to the lack of evidence and data in the identified studies. Third, no study objectively assessed CIPN or daily physical activity. Fourth, the impact of other risk factors (e.g., depression) on CIPN could not be considered. Finally, the stage of the treatment journey was not consistently reported across studies. Key details, such as the number of therapy lines received by participants, timing since treatment completion, and variability in treatment regimens, were often lacking. These factors are critical in understanding the development and persistence of CIPN and may influence the effectiveness of exercise interventions. Future research should address these gaps to provide a more comprehensive understanding of CIPN and refine exercise therapy strategies accordingly.

5. Conclusions

This scoping review summarizes the current evidence on the effectiveness of exercise therapy in patients with ovarian cancer, exploring key factors from a physical fitness perspective. Our findings indicates that although evidence is lacking, exercise intervention programs for CIPN in patients with ovarian cancer have potential benefits, especially when focused on daily physical activity, skeletal muscle density, and physical function. Future efforts should be directed toward developing and validating more effective programs through clinical trials.

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Data statement

We will be able to provide data as needed.

CRediT authorship contribution statement

Masanori Konuma: Methodology, Conceptualization. **Tomohiro Ikeda:** Visualization, Software, Methodology, Conceptualization, Writing – original draft. **Tomohiro Mitoma:** Resources, Investigation, Formal analysis. **Shinsuke Shirakawa:** Project administration, Investigation, Formal analysis, Conceptualization, Writing – original draft. **Jota Maki:** Validation, Supervision, Writing – review & editing. **Yoshimi Katayama:** Visualization, Software, Methodology, Investigation, Formal analysis. **Masanori Hamada:** Validation, Software, Project administration, Formal analysis, Conceptualization, Writing – original draft. **Shoji Nagao:** Validation, Supervision, Writing – review & editing. **Toshifumi Ozaki:** Supervision, Project administration, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2024.12.007.

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