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# Distal-extremity cryotherapy in preventing chemotherapy-induced peripheral neuropathy from paclitaxel administration in people affected by breast cancer: a systematic review.

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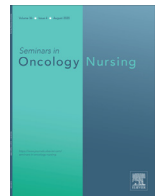
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## Review

## Distal-Extremity Cryotherapy in Preventing Chemotherapy-Induced Peripheral Neuropathy from Paclitaxel Administration in People Affected by Breast Cancer: A Systematic Review

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## ABSTRACT

**Objectives:** To explore the experiences of utilising distal-extremity cryotherapy in reducing chemotherapy-induced peripheral neuropathy during Paclitaxel treatment on physical functioning, clinical and patient-reported outcomes, compared to standard care in people affected by breast cancer.

**Methods:** Four databases and one register were searched on 11 April 2023 to identify all relevant studies meeting the inclusion and exclusion criteria. These were CINAHL (via EBSCOhost), Cochrane Central Register of Controlled Trials, Medline (via EBSCOhost), Scopus, and Web of Science Core Collection, with no limiters placed on any of the searches. Additionally, relevant systematic reviews were scrutinised for potentially relevant studies for screening.

**Results:** Distal-extremity cryotherapy is a safe intervention with minimal risk for serious adverse events. However, insufficient data supports the mainstay clinical use of cryotherapy in reducing chemotherapy-induced peripheral neuropathy from Paclitaxel use within the breast cancer population. Heterogeneity in study design, cryotherapy mode, and measurement tools underscore the need for additional research.

**Conclusion:** Despite limited data on the impact of distal-extremity cryotherapy in preventing chemotherapy-induced peripheral neuropathy, there are valuable implications for nursing practice arising from this review.

**Implications for nursing practice:** Nurses play a vital role in the clinical and experiential journey of people with breast cancer, it is important that they understand the available evidence and act as patient advocates. Assisting patients in understanding current research and encouraging participation in future studies, thereby enhancing our knowledge, and strengthening the available evidence base.

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Breast cancer poses a significant burden worldwide; in 2020, there were 2.3 million new cases diagnosed and 685,000 reported deaths.<sup>1</sup> Many people affected by breast cancer will require chemotherapy as an adjuvant therapy to optimize survival outcomes.<sup>2</sup> Paclitaxel is commonly used as a mainstay treatment but can cause significant toxicities, including chemotherapy-induced peripheral neuropathy (CIPN).<sup>3</sup> CIPN is a common and disabling side effect resulting in altered or lost sensation and significant pain in the hands and feet. Directly influencing mortality outcomes due to treatment delays, dose reductions, and treatment discontinuation.<sup>4,5</sup> The duration and intensity of CIPN symptoms range from temporary changes in physical sensation and function to irreversible nerve damage

accompanied by chronic pain.<sup>6</sup> CIPN negatively impacts self-management of activities of daily living and quality-of-life outcomes during and after treatment in both the short and long term.<sup>7-9</sup>

Approximately 80% of patients report symptoms of CIPN, with estimates that 25% of patients will require dose reduction due to Paclitaxel treatment.<sup>10,11</sup> Neurotoxicity from Paclitaxel can persist long-term, with reportedly 50% of patients recovering from CIPN caused by Paclitaxel within 9 months.<sup>10-12</sup> However, approximately 41% of patients experience long-lasting negative effects of CIPN lasting up to 3 years posttreatment.<sup>10-12</sup> Paclitaxel toxicities typically worsen from cumulative exposure through repeated treatment, infusion duration, drug dose, and prior neuropathy from preexisting medical conditions like diabetes.<sup>13</sup> Currently, no pharmacological cures or preventative care interventions to prevent CIPN are recommended by existing clinical guidelines or oncology specialist resource platforms such as EviQ.<sup>14</sup> Prevention is the safest and most cost-effective method for

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## Layperson Summary

### What we investigated and why

This research aimed to investigate the experiences of using cold/ice therapy on hands and feet (distal-extremity cryotherapy) among people receiving chemotherapy (Paclitaxel treatment for breast cancer) who are affected by nerve damage (known as peripheral neuropathy). We wanted to understand the effects of cold/ice therapy on physical functioning, clinical and patient-reported outcomes when compared to people who received their normal usual care during chemotherapy.

### How we did our research

A systematic review is an authoritative type of research whereby all known existing evidence in relation to cold/ice therapy interventions among people with breast cancer receiving Paclitaxel chemotherapy were analyzed using thorough practices by the researchers. Electronic databases were searched, and research was included based upon set criteria. The research also involved an assessment of the quality of the existing research related to the topic area.

### What we have found

This research has identified that cold/ice therapy is safe among people with breast cancer with little to no serious adverse side effects. However, the research quality conducted to date has problems, which limits the opportunity to understand how effective ice/therapy interventions are in improving peripheral neuropathy toxicity.

### What it means

Currently, there is no evidence-informed available interventions to help patients manage nerve damage toxicities (peripheral neuropathy) during cancer therapy. Future well-designed clinical trials are needed to comprehensively understand the potential benefits of cold/ice therapy given the existing problems with previous research in this area. Patients are encouraged to speak with their healthcare professionals in relation to available clinical trials to test future interventions to alleviate peripheral neuropathy.

heterogeneous clinical groups. Whether cryotherapy efficacy differs across cancer types and chemotherapy regimens is unknown. Focusing on homogeneous clinical groups, such as people affected by breast cancer receiving Paclitaxel, allows for a more precise analysis of cryotherapy's benefits, potentially yielding insights that can inform clinical practice and improve care within this population. Finally, qualitative, and mixed methods studies were not included in the existing previously published systematic review.<sup>4</sup> Incorporating qualitative research will provide valuable insights into participants' experiences with cryotherapy, including their perceptions, challenges, and preferences. Understanding these qualitative aspects within this mixed methods review is essential for optimizing the implementation and utilization of cryotherapy within clinical practice.

To address these knowledge gaps, this systematic review aimed to critically synthesize the impact of distal-extremity cryotherapy in preventing CIPN, specifically for people affected by breast cancer undergoing Paclitaxel treatment. This review also captured information in relation to adherence, acceptability, and feasibility of distal-extremity cryotherapy and qualitative insights into participant's experiences. Important clinical information capturing reduction in treatment delays, dose reduction, and treatment discontinuation comparing the intervention to standard care was also synthesized. This integrative systematic review aimed to address the following clinically focused research question:

- In people affected by breast cancer, what are the experiences of utilizing distal-extremity cryotherapy in reducing CIPN during Paclitaxel treatment on physical functioning, clinical and patient-reported outcomes, compared to standard care?

## Methodology

### Design

An integrative systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,<sup>20</sup> see [Supplementary Table 1](#) for the completed checklist. This systematic review was registered in the PROSPERO International Register of Systematic Reviews (CRD42023425390).

### Literature Search

The PICO (population, intervention, control, and outcomes) framework<sup>21</sup> was used to develop the research question and literature search.<sup>21</sup> Four databases and one register were searched on April 11, 2023, to identify all relevant studies meeting the inclusion and exclusion criteria (see [Supplementary Table 2](#) for the complete search strategy). These were CINAHL (via EBSCOhost), Cochrane Central Register of Controlled Trials, Medline (via EBSCOhost), Scopus, and Web of Science Core Collection, with no limiters placed on any of the searches. Additionally, relevant systematic reviews and reference lists of all included studies were scrutinized for potentially relevant studies. The search architecture was designed by an expert librarian, utilizing the efficient search method for systematic reviews developed at Erasmus Medical Centre.<sup>22</sup> The following search terms were used: (("chemotherapy induced peripheral neuropathy" OR CIPN OR neurotoxic\* OR neuropath\*) AND (cryotherapy OR ice OR cold therapy OR "low temperature procedure\*" OR hypothermia OR "frozen gel\*" OR cryocompression) AND (paclitaxel or taxo\* OR antineoplastic OR chemotherapy) AND ("breast cancer\*" OR "breast neoplasm\*" OR "breast carcinoma\*" OR "breast tumor\*")). Searches were rerun before final analyses for any further relevant studies to be identified and retrieved for inclusion.

managing CIPN.<sup>15</sup> However, emerging evidence suggests a potential benefit to distal-extremity cryotherapy. Cryotherapy induces localized hypothermia to cause vasoconstriction, limiting the distribution of chemotherapy to peripheral nerves by reducing cellular uptake and biochemical activity in the localized areas being therapeutically cooled.<sup>16-19</sup>

A recent systematic review<sup>4</sup> explored the role of distal-extremity cryotherapy in various cancer populations to assess the frequency, severity, and bother of CIPN. This systematic review<sup>4</sup> concluded that distal-extremity cryotherapy is a safe intervention; however, the results are conflicting, and future research was recommended. Several knowledge gaps exist within the current evidence base that informed our systematic review. First, the existing evidence base lacks robust evaluation methodologies to test the feasibility, acceptability, and adherence to distal-extremity cryotherapy. Understanding these factors is crucial for determining the practicality and effectiveness of implementing cryotherapy as a preventive measure for CIPN. Second, cryotherapy efficacy was examined within

### Eligibility Criteria

#### Types of Studies

**Inclusion:** All randomized or quasi-randomized trials conducted in patients affected by breast cancer (irrespective of cancer staging), receiving Paclitaxel chemotherapy regimen comparing distal-extremity cryotherapy intervention(s) to standard care. Appropriate mixed method, qualitative, or quantitative studies were also included. Additionally, relevant systematic reviews were scrutinized for potentially relevant studies.

**Exclusion:** Conference abstracts and non-English language studies.

#### Types of Participants

**Inclusion:** Adult patients (men and women) ( $\geq 18$  years) diagnosed with breast cancer (irrespective of cancer staging) prior to starting active Paclitaxel treatment.

**Exclusion:** Patients  $< 18$  years of age, other cancer types, all other chemotherapy regimens, patients with prior Paclitaxel exposure, and patients with preexisting neuropathy.

#### Types of Interventions

All modes of distal-extremity cryotherapy interventions (crushed ice, frozen gel, and continuous flow hypothermia), durations, and whether applied to hands and feet only, or both were included if they were utilized throughout Paclitaxel chemotherapy regimens. The control was defined as the current standard of care offered within existing clinical pathways.<sup>3</sup>

#### Types of Outcome Measurements

**Primary outcomes:** Identification and grading of CIPN described prior to, during, and post-Paclitaxel chemotherapy regimens.

**Clinical outcomes:** Measured frequency, severity, and bother from CIPN. Treatment delays, dose reduction, and treatment discontinuation. Loss of sensation, loss of manual dexterity of the fingers and hands, and impaired gait.

**Patient-reported outcomes (PROMs):** Surveys measuring health-related quality of life (HRQoL). Data from distress thermometer or equivalent throughout treatment were included.<sup>23</sup> Discomfort/pain and a sense of cold or numbness to distal extremities during and after active cryotherapy were considered secondary outcomes rather than serious adverse events. Qualitative data were also included.

**Health care service use:** Data on the type of health care resources used to assess or treat CIPN-associated side effects were extracted, for example, podiatrist, physiotherapist, and neurologist interventions. The volume and cost of services accessed were also captured.

### Data Collection and Analysis

Following the removal of duplicate articles, two review authors independently performed title and abstract screening of identified articles via Covidence systematic review software. Afterward, the full text of all remaining articles was retrieved and screened by two review authors using a data extraction table, linking together multiple records of the same study. Any disagreements between the two authors were resolved through discussion or consultation with a third review author. The article selection process was described using the PRISMA statement guidelines.<sup>20</sup>

### Assessment of Risk of Bias in Included Studies

The Mixed Method Appraisal Tool (MMAT) allowed for concurrent review of qualitative, quantitative, and mixed methods studies, including non-randomized and randomized controlled trials, to be assessed for methodological quality.<sup>24</sup> Quality scoring enabled evaluation and identification of potential issues related to randomization, allocation concealment, blinding and completeness of outcome data,

selective reporting, and any other possible biases. Any discrepancies between the two review authors were resolved through discussion with a third review author.

### Data Collection Process

Before its use, a data extraction form was developed and piloted. The following data were extracted: authors; publication country; publication date; study design; total number of patients included with attrition and exclusion, with reasons; patient withdrawals from the study; baseline patient characteristics, preexisting peripheral neuropathy or prior chemotherapy use; cryotherapy method; efficacy endpoints; clinical and PROMs; health care service use outside of study; study funding sources; and power calculation. The template for intervention description and replication checklist and guide was piloted and incorporated within, capturing the final tabulated results.<sup>25</sup> One review author extracted study characteristics, and a second review author confirmed that data extractions were accurate. Any disagreements were resolved through discussion or intervention by a third review author.

### Synthesis Methods

In consultation with a health statistician, there was agreement among the review authors that due to high heterogeneity across the included studies, differing endpoints, and the variety of objective and patient-reported measures used in each included study, it was not possible to conduct a meta-analysis. Consequently, this systematic review used the Joanna Briggs Institute methodology for mixed-method systematic reviews to generate a narrative synthesis to explore the experiences of those affected by breast cancer and to determine the physical, clinical and impact on PROMs of distal-extremity cryotherapy in the prevention of CIPN, compared to standard care.<sup>26</sup> A convergent segregated approach was undertaken which involved a separate synthesis of qualitative and quantitative data, generating both qualitative and quantitative evidence, allowing for an integration of the findings during the final stages of the evidence synthesis.<sup>26</sup> The steps involved data reduction (subgroup classification by type of cryotherapy, with results tabulated), data comparison (identifying patterns and themes through clustering and counting and making contrasts and comparisons) and conclusion drawing and verification (synthesis of subgroup analysis to inform a comprehensive understanding of the topic, verified with the primary source of data for accuracy).

## Results

### Study Selection

A total of  $n = 130$  publications were screened, and 10 studies were included in this review, refer to Fig. for PRISMA<sup>20</sup> flowchart. A total of 10 publications were included, see Table 1 (and Supplementary Table 3 for excluded studies).

### Study Designs

Across the 10 studies, 561 participants were included with 500 participants represented in the analysis. The designs included non-randomized trials<sup>17,27,28</sup> (all of which the participants served as their own control), randomized trials<sup>12,15,19,29-31</sup> (two studies were self-controlled), and one retrospective study.<sup>30</sup> The publications were conducted in Belgium,<sup>27</sup> Denmark,<sup>30</sup> Japan,<sup>17,31</sup> Singapore,<sup>19,29</sup> Taiwan,<sup>28</sup> and the United States of America.<sup>12,15,32</sup>

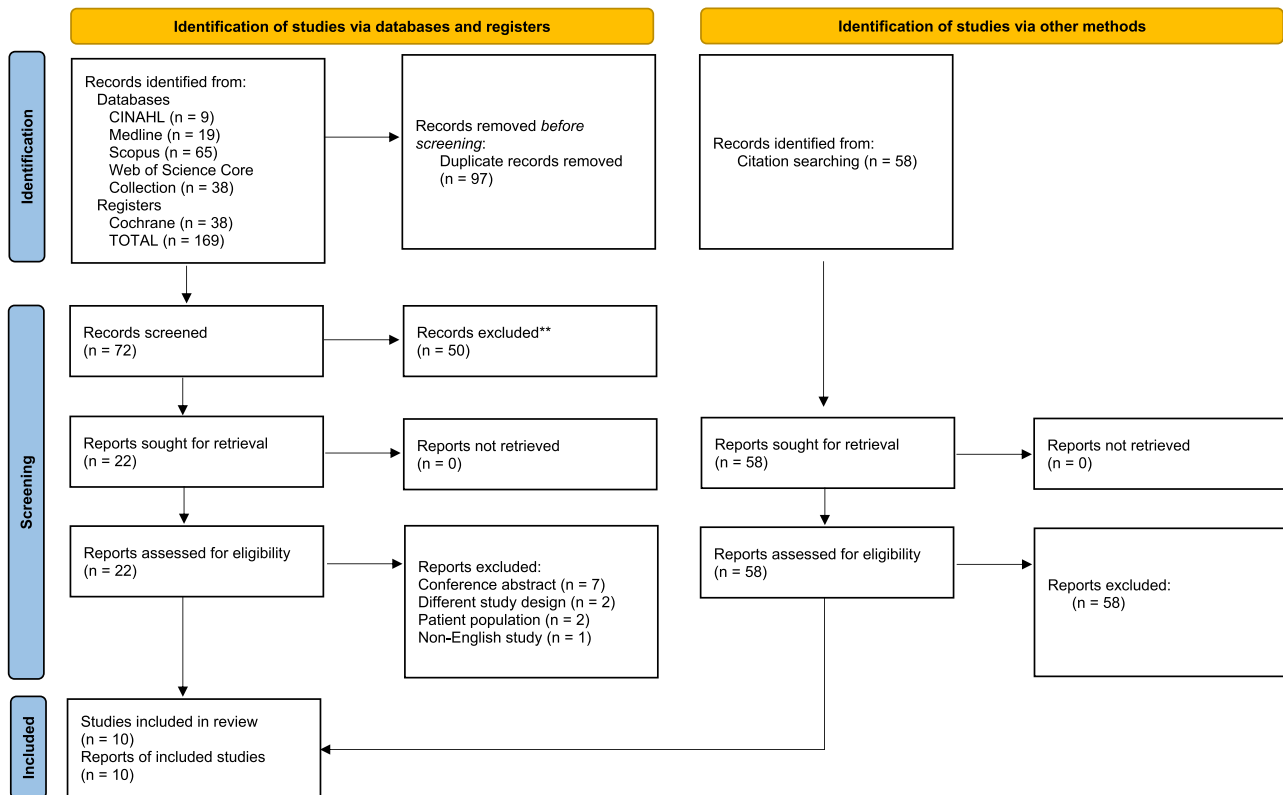


Figure 1. PRISMA flow diagram.

### Quality Appraisal of Studies

Following methodological assessments of the 10 included studies using the MMAT, nine included studies<sup>12,15,17,19,28-32</sup> reported a low risk of bias, with one study<sup>27</sup> reporting inappropriate application of cryotherapy within their design, see Table 2 for quality appraisal. Additionally, it is important to acknowledge that the small sample sizes in these studies<sup>12,15,17,19,27-32</sup> may limit the statistical power and generalizability of the findings.

### Modes of Distal-Extremity Cryotherapy

Three modes of distal-extremity cryotherapy were identified within the included studies, as shown in Table 3 including: crushed ice,<sup>32</sup> frozen gel,<sup>12,15,17,27-31</sup> and continuous flow hypothermia.<sup>19,27</sup> One study<sup>27</sup> compared continuous flow hypothermia to frozen gel cryotherapy.

Crushed ice cryotherapy was investigated in one study.<sup>32</sup> This intervention involved bilaterally applying quart-sized plastic bags filled with two-thirds crushed ice to the palm and dorsum of the hands and gallon-sized plastic bags filled halfway with crushed ice applied to the soles and dorsal side of the feet. The participant's extremities were protected with cotton gloves and cotton socks. Cryotherapy was applied 15 minutes prior, 60 minutes throughout, and 15 minutes posttreatment, with ice changed at the discretion of clinical staff and the participants when melted. No storage temperatures were reported.

Frozen gel cryotherapy was utilized in eight studies,<sup>12,15,17,27-31</sup> with one study<sup>27</sup> comparing frozen gel cryotherapy to continuous flow hypothermia. Four studies investigated one side of the body,<sup>12,17,27,28</sup> and four studies investigated bilateral limbs.<sup>15,29-31</sup> One study applied only gloves,<sup>28</sup> and seven studies<sup>12,15,17,27,29-31</sup> utilized both gloves and socks. Four studies<sup>12,17,27,28</sup> were designed to have the participants serve as their own control and four studies<sup>15,29-31</sup>

with separate intervention and control groups. Participants' hand(s) were covered with glycerine-containing frozen gel glove(s) with wrist straps wrapping around their wrists. The foot/feet were covered with glycerine-containing frozen gel socks with matching straps wrapping around the ankles. The intervention was applied for 90 minutes (15 minutes prior, 60 minutes throughout, and 15 minutes posttreatment), aside from two studies,<sup>12,15</sup> one study<sup>12</sup> applied cryotherapy for a total of 210 minutes, and another study<sup>15</sup> applying cryotherapy for a total of 75 minutes. The equipment was changed every 45 minutes during treatment. Storage temperatures ranged between  $-18$  and  $-30^{\circ}\text{C}$  in gloves and  $-10$  to  $-30^{\circ}\text{C}$  in socks throughout the studies<sup>12,15,27-31</sup>; two studies<sup>17,32</sup> did not report cryotherapy storage temperatures.

Continuous flow hypothermia was investigated in two studies,<sup>19,27</sup> both utilizing one side of the body. In both studies,<sup>19,27</sup> the participant served as their own control. The intervention was applied to targeted limbs by a continuous-flow thermoregulatory device for different durations in each study: 120 minutes<sup>27</sup> (30 minutes prior, 60 minutes throughout, and 30 minutes posttreatment) and 150 minutes<sup>19</sup> (60 minutes prior, 60 minutes throughout, and 30 minutes posttreatment). One study<sup>19</sup> reported a constant temperature of  $22^{\circ}\text{C}$ , and another<sup>27</sup> reported a constant temperature of  $10$  to  $12^{\circ}\text{C}$ .

### Findings Overview

There was a wide variety of outcomes to evaluate physical functioning (PF), clinical, and PROMs, which assessed various cryotherapy interventions to standard care.

### Physical Functioning

#### Crushed Ice Cryotherapy

Not reported.<sup>32</sup>

**Table 1**  
Overview of Included Studies

Author/country	Purpose	Intervention	Sample size	Response rate; attrition/adherence	Study design	Time points	Data collection tools
Coolbrandt et al. <sup>27</sup> Belgium	Compare the incidence of CIPN between frozen-gel cryotherapy and hiloterapy (continuous flow hypothermia).	Continuous flow hypothermia: R) arm + leg frozen-gel cryotherapy: L) hand + foot	<b>Baseline:</b> n = 63 <b>Analysis:</b> n = 62	<b>Response rate:</b> n = 81 met inclusion criteria; n = 63 consented; n = 62 completed study. <b>Frozen-gel:</b> n = 62 <b>Continuous flow:</b> n = 62 <b>Attrition:</b> n = 1 (1) Early treatment discontinuation.	Nonrandomized prospective self-controlled study. Includes participants undergoing weekly Paclitaxel and three weekly docetaxel treatment regimens.	Baseline, wk: 6, 12, 18, and 24 wk after the start of treatment.	<b>Objective data collection:</b> Not reported. <b>Subjective data collection:</b> Patient-reported outcomes version of the Common Toxicity Criteria for Adverse Events (NCI-PRO-CTCAE); Self-reported comfort scale using a 5-point Likert scale.
Griffiths et al. <sup>21</sup> United States of America	Assess the efficacy of cryotherapy to prevent Paclitaxel-induced peripheral neuropathy in women with breast cancer.	Frozen-gel cryotherapy: Gloves and socks. Hand + foot: One-sided (dominant or nondominant).	<b>Baseline:</b> n = 29 <b>Analysis:</b> n = 7	<b>Response rate:</b> n = 180 assessed for eligibility, n = 33 enrolled, n = 29 baseline, n = 7 completed study. <b>Control and Intervention arms:</b> n = 7. <b>Attrition:</b> n = 22 (10) Cold intolerance (6) Declined therapy (4) Lost to follow-up (2) Other.	Randomized controlled trial: Self-controlled case series.	Baseline, wk 2, 5, 9, 12, and 2 wk post final Paclitaxel treatment as follow up.	<b>Objective data collection:</b> Quantitative Sensory Testing (QST). <b>Subjective data collection:</b> Neuropathic Pain Symptom Inventory (NPSI); Brief Pain Inventory (BPI).
Hanai et al. <sup>17</sup> Japan	Determine effects of cryotherapy on objective and subjective symptoms of Paclitaxel-induced neuropathy.	Frozen-gel cryotherapy: Gloves and socks. Hand + foot: One-sided (dominant side).	<b>Baseline:</b> n = 40 <b>Analysis:</b> n = 36	<b>Response rate:</b> n = 44 assessed for eligibility, n = 40 consented, n = 36 completed study. <b>Control and Intervention arms:</b> n = 36 <b>Attrition:</b> n = 4 (1) Pneumonia (1) Hepatopathy (1) Severe fatigue (1) Macular edema.	Prospective self-controlled trial. (Non-randomized controlled).	Not reported	<b>Objective data collection:</b> Tactile disturbance (Semmes-Weinstein monofilament test); Thermosensory disturbance (Thermal stimulator); Vibration perception (Tuning fork); Performance speed (Grooved peg-board test); Electrophysiological signs (Conduction velocity and action potential amplitude). <b>Subjective data collection:</b> Patient-reported assessment (Peripheral neuropathy questionnaire); Cryotherapy tolerability.
Jue et al. <sup>15</sup> United States of America	Compare the frequency and severity of PN and quality of life in patients with breast cancer receiving cold therapy to their hands and feet vs standard of care weekly Paclitaxel treatment regime.	Frozen-gel cryotherapy: Gloves and socks. Hands + feet: Both L) + R).	<b>Baseline:</b> n = 48 <b>Analysis:</b> n = 26	<b>Response rate:</b> n = 48 consented (24 in each arm), n = 26 completed study. <b>Control arm:</b> n = 11 <b>Intervention:</b> n = 15 <b>Attrition:</b> n = 22 <b>Control:</b> (1) Antidepressant use (4) Wanted cryotherapy (6) Gabapentin use (2) Regimen change. <b>Intervention:</b> (2) Cold intolerance (1) Antidepressant use (1) Noncompliance (1) Regimen change (4) Gabapentin use.	Randomized controlled trial.	Data was collected weekly for 12 wk during Paclitaxel treatment; additional QoL follow-up phone call at 16 wk.	<b>Objective data collection:</b> Not reported. <b>Subjective data collection:</b> GEE logistic model: FACT-Taxane, FACT-General, TaxS subscale; National Cancer Institute (2009) Common Terminology Criteria for Adverse Events (CTCAE); Cryotherapy tolerance; Demographic questionnaire

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Table 1 (Continued)

Author/country	Purpose	Intervention	Sample size	Response rate; attrition/adherence	Study design	Time points	Data collection tools
Ng et al. <sup>29</sup> Singapore	Evaluating the efficacy and tolerability of cryotherapy in preventing CIPN in patients with early breast cancer receiving neo/adjuvant weekly Paclitaxel treatment.	Frozen-gel cryotherapy: Gloves and socks. Hands + feet: Both L) + R).	<b>Baseline:</b> n = 38 <b>Analysis:</b> n = 33	<b>Response rate:</b> n = 67 assessed for eligibility, n = 46 consented, n = 38 commenced study. <b>Control:</b> n = 17. <b>Intervention:</b> n = 21. <b>Attrition:</b> n = 7. <b>Control:</b> (1) Discontinued at first visit (4) Discontinued at second visit <b>Intervention:</b> (2) Discontinued at last visit (Still included for analysis).	Randomized controlled trial.	T0: Baseline-PRO and EA. T1: 1-2 wk posttreatment-PRO and EA. T2: 3 mo posttreatment-PRO. T3: 6 mo posttreatment-PRO. T4: 9 mo posttreatment-PRO and EA.	<b>Objective data collection:</b> <u>Electrophysiological assessments (EA):</u> Nerve conduction studies (NCS); Sympathetic skin response (SSR). <b>Subjective data collection:</b> <u>Patient-reported outcomes (PRO):</u> Peripheral neuropathy questionnaire (PNQ) (sensory and motor); European Organization for Research Treatment of Cancer Quality of Life Questionnaire—Chemotherapy-induced Peripheral Neuropathy 20 (EORTC QLQ-CIPN20).
Rosenbaek et al. <sup>30</sup> Denmark	Determine whether cryotherapy with frozen gloves and socks has the potential to reduce dose-limiting events of CIPN among breast cancer patients receiving weekly Paclitaxel.	Frozen-gel cryotherapy: Gloves and socks. Hands + feet: Both L) + R).	<b>Baseline:</b> n = 215 <b>Analysis:</b> n = 215	<b>Response rate:</b> n = 299 assessed for eligibility, n = 119 participants were included from a 2016 cohort that met inclusion criteria, n = 96 participants were included from a 2017 cohort that met inclusion criteria. <b>Control arm:</b> Retrospective study <b>Intervention:</b> Retrospective study <b>Attrition:</b> N/A-Retrospective study.	Retrospective study.	N/A-retrospective study.	<b>Objective data collection:</b> Proportion of patients who completed Paclitaxel at a cumulative dose of 720 mg/m <sup>2</sup> over nine treatment cycles. <b>Subjective data collection:</b> Not applicable.
Ruddy et al. <sup>32</sup> United States of America	Obtain pilot data on cryotherapy efficacy in preventing Paclitaxel-associated neuropathy to inform a more definitive phase III clinical trial.	Crushed ice cryotherapy hands + feet.	<b>Baseline:</b> n = 42 <b>Analysis:</b> n = 39	<b>Response rate:</b> n = 46 met inclusion criteria; n = 42 consented; n = 39 completed study. <b>Control arm:</b> n = 20 <b>Intervention:</b> n = 19 <b>Attrition:</b> n = 3 (3) Nil AUC or QoL analysis.	Prospective randomized controlled trial: Pilot trial.	Wk 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12; for all subjective data collection. Followed by EORTC QLQ-CIPN20 review for mo 1, 2, 3, 4, 5, and 6 following the final 12th wk of Paclitaxel treatment.	<b>Objective data collection:</b> Not reported. <b>Subjective data collection:</b> European Organization for Research Treatment of Cancer Quality of Life Questionnaire—Chemotherapy-induced Peripheral Neuropathy 20 (EORTC QLQ-CIPN20); Common Terminology Criteria for Adverse Events (CTCAE) neuropathy grading; Cryotherapy toleration form; pre- and post-Paclitaxel questionnaire (analgesia use, chronic aches and pain)
Shigematsu et al. <sup>31</sup> Japan	Investigate the efficacy of cryotherapy in preventing peripheral neuropathy and dermatological adverse events in breast cancer patients treated with weekly Paclitaxel.	Frozen-gel cryotherapy: Gloves and socks. Hands + feet: Both L) + R).	<b>Baseline:</b> n = 44 <b>Analysis:</b> n = 44	<b>Response rate:</b> n = 44 participants assessed for eligibility, n = 44 consented, n = 44 completed study. <b>Control arm:</b> n = 22 <b>Intervention:</b> n = 22 <b>Attrition:</b> n = 0.	Randomized phase II study.	Baseline, wk 3, 6, 9, 12.	<b>Objective data collection:</b> Not reported. <b>Subjective data collection:</b> Functional Assessment of Cancer Therapy-Neurotoxicity (FACT-NTX); Common Terminology Criteria for Adverse Events (CTCAE); Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane); Peripheral Neuropathy Questionnaire (PNQ); Cryotherapy compliance.

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Table 1 (Continued)

Author/country	Purpose	Intervention	Sample size	Response rate; attrition/adherence	Study design	Time points	Data collection tools
Sundar et al. <sup>19</sup> Singapore	To determine if continuous flow hypothermia is neuroprotective in breast cancer patients receiving weekly Paclitaxel.	Continuous flow hypothermia (Hilotherapy). Arm and leg: One-sided (side of body randomized).	<b>Baseline:</b> <i>n</i> = 20 <b>Analysis:</b> <i>n</i> = 17 All 20 enrolled patients were included for safety and tolerability analysis.	<b>Response rate:</b> <i>n</i> = 20 patients consented, <i>n</i> = 17 completed study. <b>Control and intervention arms:</b> <i>n</i> = 17 <b>Attrition:</b> <i>n</i> = 3 (1) Infected sarcoma. (2) Did not complete all assessments.	Internally controlled pilot trial-self-controlled. Randomized side of body.	Baseline, and after 1, 3, and 6 mo.	<b>Objective data collection:</b> Nerve conduction studies (NCS) <b>Subjective data collection:</b> Visual analog pain scale (VAS); Subjective tolerance scale; total neuropathy score (TNS)
Yang et al. <sup>28</sup> Taiwan	Determine the efficacy of frozen glove distal-extremity cryotherapy for the prevention of CIPN in hands.	Frozen-gel cryotherapy: Gloves. Hand: One-sided (dominant side).	<b>Baseline:</b> <i>n</i> = 22 <b>Analysis:</b> <i>n</i> = 21.	<b>Response rate:</b> <i>n</i> = 24 met inclusion criteria; <i>n</i> = 22 consented; <i>n</i> = 21 completed study. <b>Control and Intervention arms:</b> <i>n</i> = 21 <b>Attrition:</b> <i>n</i> = 1 (1) Medication change.	Quasi-experimental and prospective self-controlled trial. (Non-randomized controlled).	Wk 1, 4, 8, 12, 16 following the first Paclitaxel treatment.	<b>Objective data collection:</b> Not reported. <b>Subjective data collection:</b> European Organization for Research Treatment of Cancer Quality of Life Questionnaire—Chemotherapy-induced Peripheral Neuropathy 20 (EORTC QLQ-CIPN20); Demography questionnaire.



**Table 2**  
Mixed Method Appraisal Tool (MMAT)-Results of Quality Assessment

Quantitative randomized controlled trials	Item number of checklist						
	S1	S2	2.1	2.2	2.3	2.4	2.5
Griffiths et al.	Y	Y	Y	Y	N	Y	N
Jue et al.	Y	Y	Y	Y	Y	N	Y
Ng et al.	Y	Y	Y	Y	Y	U	N
Rosenbaek et al.	Y	Y	Y	Y	Y	N	U
Shigematsu et al.	Y	Y	Y	Y	Y	U	Y
Sundar et al.	Y	Y	Y	Y	Y	U	Y
S1. Are there clear research questions? S2. Do the collected data allow to address the research questions? 2.1. Is randomization appropriately performed? 2.2. Are the groups comparable at baseline? 2.3. Are there complete outcome data? 2.4. Are outcome assessors blinded to the intervention provided? 2.5. Did the participants adhere to the assigned intervention?							
Quantitative non-randomized	Item number of checklist						
	S1	S2	3.1	3.2	3.3	3.4	3.5
Coolbrandt et al.	Y	Y	Y	Y	Y	N	U
Hanai et al.	Y	Y	Y	Y	Y	N	Y
Yang et al.	Y	Y	Y	Y	Y	N	Y
S1. Are there clear research questions? S2. Do the collected data allow to address the research questions? 3.1. Are the participants representative of the target population? 3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)? 3.3. Are there complete outcome data? 3.4. Are the confounders accounted for in the study design and analysis? 3.5. During the study period, is the intervention administered (or exposure occurred) as intended?							
Mixed methods studies	Item number of checklist						
	S1	S2	5.1	5.2	5.3	5.4	5.5
Ruddy et al.	Y	Y	Y	Y	Y	N	U
S1. Are there clear research questions? S2. Do the collected data allow to address the research questions? 5.1. Is there an adequate rationale for using a mixed-methods design to address the research question? 5.2. Are the different components of the study effectively integrated to answer the research question? 5.3. Are the outputs of the integration of qualitative and quantitative components adequately interpreted? 5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed? 5.5. Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?							

<sup>a</sup>Three levels of assessment quality scores.

Y, yes; U, unclear; N, no.

### Frozen Gel Cryotherapy

Three studies<sup>12,17,29</sup> explored the effects of frozen gel cryotherapy on reducing CIPN. The results were mixed with one<sup>17</sup> of three<sup>12,29</sup> (33%) studies reporting no changes in CIPN symptoms between the study groups. Measurement tools included: performance speed testing,<sup>17</sup> thermosensory disturbances,<sup>17</sup> monofilament testing,<sup>12,17</sup> vibration perception,<sup>12,17</sup> electrophysiological signs,<sup>17,29</sup> and noxious mechanical touch force.<sup>12</sup>

Performance speed<sup>17</sup> was examined using a grooved peg-board test to measure manipulative dexterity and sensory motor speed changes between baseline and completion of the final Paclitaxel treatment (at 12 weeks). A greater delay in performance speed was reported in the control group.<sup>17</sup> The intervention group showed a decrease of -2.5 seconds (SD = 12.0 seconds) in performance time, while the control group exhibited an increase of +8.6 seconds (SD = 25.8 seconds).<sup>17</sup>

Thermosensory disturbances<sup>17</sup> were assessed using a thermal stimulator (3 and 48°C outputs) at baseline and 12 weeks posttreatment. The results indicated that perception of warmth was higher on the intervention side for both the hand 9.9% vs 32.4% (95% CI: 1.25-394.48) and foot 33.4% vs 57.6% (95% CI: 1.25-46.93).<sup>17</sup> However, the perception of coldness was less pronounced on the intervention side for both the hand 2.8% vs 13.9% (95% CI: 0.66-infinite) and foot 12.6% vs 18.8% (95% CI: 0.29-22.11).<sup>17</sup>

Monofilament testing was conducted in two studies.<sup>12,17</sup> One<sup>17</sup> of two<sup>12,17</sup> (50%) studies reported a lower incidence of CIPN symptoms in the intervention group. One study<sup>17</sup> utilized Semmes-Weinstein monofilament testing and reported lower peripheral neuropathy of the hand 27.8% (95% CI: 3.20-828.96) vs 80.6% and foot 25% vs 63.9% (95% CI: 3.32-infinite) of the intervention group, however, the assessment frequency was not reported.<sup>17</sup> In contrast, the second study<sup>12</sup> used innocuous mechanical touch force (g) assessments at baseline, weeks 2, 5, 9, 12, and 2 weeks postfinal Paclitaxel treatment. No difference in CIPN was detected between control and intervention groups hand and foot.<sup>12</sup> Notably, the latter study<sup>12</sup> was canceled after

week 6 of 12 due to high attrition rates, limiting its overall power and generalizability.

Vibration perception was conducted in two studies<sup>12,17</sup> using tuning forks of different frequencies. Both studies<sup>12,17</sup> reported minimal changes in vibration perception between the intervention and control groups. One study<sup>12</sup> used a 64-Hz tuning fork to test for sensitivity to vibratory tuning fork sensation and reported no changes in Rydel-Seiffer test results or CIPN symptoms from using cryotherapy in both hands (SD = 0.05 (0.49)) and foot (SD = 0.48 (1.39)).<sup>12</sup> In comparison, another study<sup>17</sup> found a lower incidence reported in the intervention group's hand 9.7% vs 12.9% (95% CI: 0.03-infinite) and foot 13.8% vs 24.1% (95% CI: 0.41-infinite) utilizing a 128-Hz tuning fork.

Electrophysiological signs were measured in two studies.<sup>17,29</sup> Both<sup>17,29</sup> studies reported no changes in CIPN between the study groups.

Noxious mechanical touch force (g) was performed by one study<sup>12</sup> using Neuropen testing to test for sensitivity to noxious pinprick stimuli. This study<sup>12</sup> found no discernible differences between study groups.

### Continuous Flow Hypothermia

Nerve conduction study<sup>19</sup> was performed to examine trends in Sensory Nerve Action Potential (SNAP) and Compound Motor Action Potential amplitudes over time between the control and intervention groups. There was a consistent decrease in SNAP amplitudes in both the intervention and control limbs over time.<sup>19</sup> The sural nerve in the intervention limb exhibited slightly better preservation of SNAP amplitude when compared to the control limb (-19.9% ± 23.7% vs -25.8% ± 21.8%) at 3 months posttreatment.<sup>19</sup> In contrast, when assessing Compound Motor Action Potential amplitudes for all recorded motor nerves, the intervention limb improved preservation compared to the control limb 3 months posttreatment.<sup>19</sup> Notably, this preservation was more pronounced in the extensor digitorum brevis muscle, especially when stimulating below the fibula head

**Table 3**  
Overview of Distal-Extremity Cryotherapy Interventions

Author/country	Purpose	Intervention	Application	Cryotherapy storage range (°C)
Coolbrandt et al. <sup>27</sup> Belgium	Compare the incidence of CIPN between frozen-gel cryotherapy and hilotherapy (continuous flow hypothermia).	Continuous flow hypothermia: R) arm + leg Frozen-gel cryotherapy: Gloves and socks (study used gloves as both gloves and as socks). L) Hand + foot.	<u>Frozen-gel cryotherapy</u> : Applied for 90 min for Paclitaxel therapy each time. 15 min prior, during (60 min), and 15 min post. Changing gloves and socks every 45 min <u>Continuous flow hypothermia (Hilotherapy)</u> : Applied 30 min prior, during (60 min), and 30 min post.	<u>Frozen-gel cryotherapy</u> : Stored at –18 to –20°C. <u>Continuous flow hypothermia (Hilotherapy)</u> : Constant temperature of 10-12° C.
Griffiths et al. <sup>21</sup> United States of America	Is there a difference in peripheral neuropathy symptoms between control and intervention extremities that can be measured by the Neuropathic Pain Symptom Inventory? Is there a difference in pain between control and intervention extremities that can be measured by the Brief Pain Inventory? Is there a difference in quantitative sensory testing between control and intervention extremities?	Frozen-gel cryotherapy: Gloves and socks. Hand + foot: One-sided (dominant or nondominant). Applied for 210 min for Paclitaxel therapy each time. 15 min prior, during (180 min), and 15 min post. Changing gloves and socks every 45-50 min.	Applied for 210 min for Paclitaxel therapy each time. 15 min prior, during (180 min), and 15 min post. Changing gloves and socks every 45-50 min.	Stored at –25 to –30°C
Hanai et al. <sup>17</sup> Japan	Determine effects of cryotherapy on objective and subjective symptoms of Paclitaxel-induced neuropathy.	Frozen-gel cryotherapy: Gloves and socks. Hand + foot: One-sided (dominant side).	Applied for 90 min for Paclitaxel therapy each time. 15 min prior, during (60 min), and 15 min post. Changing gloves and socks every 45 min.	Not reported.
Jue et al. <sup>15</sup> United States of America	Is the frequency and severity of CIPN different between frozen gloves and socks users and SC? Is there a difference in QoL outcomes for those using frozen gloves and socks opposed to SC?	Frozen-gel cryotherapy: Gloves and socks. Hands + feet: Both L) + R).	Applied for 75 min for Paclitaxel therapy each time. 15 min prior and during (60 min). Changing gloves and socks every 45 min.	Stored at –20 to –24°C.
Ng et al. <sup>29</sup> Singapore	Efficacy of frozen-gel cryotherapy in preventing CIPN for breast cancer patients undergoing Paclitaxel treatment. Describe the tolerance of cryotherapy amongst participants.	Frozen-gel cryotherapy: Gloves and socks. Hands + feet: Both L) + R).	Applied for 90 min for Paclitaxel therapy each time. 15 min prior, during (60 min), and 15 min post. Changing gloves and socks every 30 (+5) min.	Stored at –20°C (Gloves) and –10°C (Socks).
Rosenbaek et al. <sup>30</sup> Denmark	Determine whether cryotherapy with frozen gloves and socks has the potential to reduce dose-limiting events of CIPN among breast cancer patients receiving weekly Paclitaxel.	Frozen-gel cryotherapy: Gloves and socks. Hands + feet: Both L) + R).	Applied for 90 min for Paclitaxel therapy each time. 15 min prior, during (60 min), and 15 min post. Changing gloves and socks every 45 min.	Stored at approx. –20°C for 3 h prior to use.
Ruddy et al. <sup>32</sup> United States of America	Obtain pilot data on cryotherapy efficacy in preventing Paclitaxel-associated neuropathy to inform a more definitive phase III clinical trial.	Crushed ice cryotherapy Hands and feet L) + R).	Patient hands covered with cotton gloves, quart-sized plastic bags 2/3 filled with ice applied on palm and dorsum of hands. Feet covered with cotton socks and similar 1/2 gallon-sized bags filled with crushed ice applied to soles and roof of feet. Applied 15 min before and remained 15 min posttreatment. Ice changed at request of patient.	Not reported.
Shigematsu et al. <sup>31</sup> Japan	Efficacy of frozen-gel gloves and socks for the prevention of CIPN	Frozen-gel cryotherapy: Gloves and socks. Hands + feet: Both L) + R).	Applied for 90 min for Paclitaxel therapy each time. 15 min prior, during (60 min), and 15 min post. Changing gloves and socks every 45 min.	Stored at –20°C.
Sundar et al. <sup>19</sup> Singapore	To determine if continuous flow hypothermia is neuroprotective in breast cancer patients receiving weekly Paclitaxel.	Continuous flow hypothermia (Hilotherapy) Arm and leg: One-sided (side of body randomized).	Applied for a total of 150 min. 60 min prior, during (60 min) and 30 min post.	Constant temperature of 22°C.
Yang et al. <sup>28</sup> Taiwan	Determine the efficacy of frozen glove distal-extremity cryotherapy for the prevention of CIPN in hands.	Frozen-gel cryotherapy: Gloves. Hand: One-sided (Dominant side).	Applied for 90 min for Paclitaxel therapy each time. 15 min prior, during (60 min), and 15 min post. Changing gloves and socks every 45 min.	Stored at –24.3 to –24.7°C

(Intervention:  $-2.1\% \pm 25.3\%$  vs control:  $-18.3\% \pm 30.0\%$ ) and above the fibula head (Intervention:  $-4.3\% \pm 23.9\%$  vs control:  $-18.7\% \pm 32.0\%$ ).<sup>19</sup>

### Clinical Outcomes

#### Crushed Ice Cryotherapy

One crushed ice cryotherapy study<sup>32</sup> reported participant Paclitaxel alterations. However, the data was not rigorously collected.<sup>32</sup> Five of the 39 (13%) participants available for the analysis required a dose reduction.<sup>32</sup> Including two participants within the control group, one required a dose reduction due to CIPN and another due to leukopenia.<sup>32</sup> There were three participants who required dose reduction within the intervention group: one participant due to paraneesthesia and two participants without a provided reason. No recorded reports of Paclitaxel delays or treatment discontinuation were available within the study.<sup>32</sup>

#### Frozen Gel Cryotherapy

Two frozen gel cryotherapy studies<sup>12,30</sup> reported participant Paclitaxel alterations within their reports. In the first study,<sup>12</sup> no standard Paclitaxel dose was reported. However, weekly Paclitaxel mean dose was reported at 185 mg/m<sup>2</sup> (Treatment 1), 184 mg/m<sup>2</sup> (Treatment 5), 183 mg/m<sup>2</sup> (Treatment 9), and 173 mg/m<sup>2</sup> (Final Treatment) for participants with complete data available for the planned 12 weeks prior to the study being canceled after week 6.<sup>12</sup> The second study<sup>30</sup> observed participants retrospectively and discovered that 77% of the 2017 cryotherapy cohort completed the planned cumulative Paclitaxel dose without alteration compared to 64% of the 2016 symptom-based cohort.<sup>30</sup> Neither of these studies reported on Paclitaxel delays or treatment discontinuation.

#### Continuous Flow Hypothermia

One study<sup>27</sup> reported treatment alterations that compared the efficacy of continuous flow hypothermia vs frozen gel cryotherapy. This study primarily included Paclitaxel regimens (67.7%) alongside Docetaxel treatment regimens (32.3%), and the reported treatment modifications were not split between the two different forms of chemotherapy. Four participants stopped treatment early due to CIPN, and five patients required dose reductions due to CIPN symptoms. There were no recorded records of treatment delays within this study.

### Pain Assessments

#### Crushed Ice Cryotherapy

One crushed ice cryotherapy study<sup>32</sup> reported monitoring of participant pain through the Common Terminology Criteria for Adverse Events (CTCAE) and monitoring of prescription and nonprescription analgesia use. The comparison between the intervention and control groups yielded no discernible differences in reported pain scores or participant analgesia usage.

#### Frozen Gel Cryotherapy

Two frozen gel studies<sup>12,29</sup> monitored pain within their study design using different measurement tools and found no discernible differences between treatment groups in Neuropathic Pain Symptom Inventory,<sup>12</sup> Brief Pain, and pain subscale scores.<sup>29</sup>

#### Continuous Flow Hypothermia

Two continuous flow hypothermia studies<sup>19,27</sup> monitored participant pain. Both studies reported reduced pain in utilizing continuous flow hypothermia through the Visual Analog Pain Scale,<sup>19</sup> and the National Cancer Institute CTCAE (NCI-PRO-CTCAE).<sup>27</sup> The Visual Analog Pain Scale,<sup>19</sup> reported nil abnormalities related to pain tolerability throughout the study. Pain scores remained consistently at zero for

all patients across all 12 cycles of Paclitaxel treatment.<sup>19</sup> The NCI-PRO-CTCAE<sup>27</sup> compared monitored pain between continuous flow hypothermia vs frozen gel cryotherapy. The incidence of Grade 3 to 4 pain attributed to continuous flow hypothermia was lower than pain reported by frozen gel cryotherapy participants (11.3% vs 14.5%).<sup>27</sup>

### Cryotherapy Tolerance

#### Crushed Ice Cryotherapy

The crushed ice study<sup>32</sup> measured cryotherapy tolerance using a locally designed Cryotherapy Tolerance Form that was completed at each Paclitaxel administration. This form categorized participant tolerance from "Very well," "Moderately well," "Moderately poorly," to "Very poorly," with a majority of participants (62%) on the final week 12 reporting "Very well" for tolerability.<sup>32</sup> There was no reported patient attrition due to cryotherapy intolerance within the study. Storage and application temperatures were not recorded within the study.<sup>32</sup>

#### Frozen Gel Cryotherapy

Five frozen gel cryotherapy studies<sup>12,15,17,29,31</sup> examined participant cryotherapy tolerability. Direct comparison between these studies proved challenging due to differences in study design, including variations in cryotherapy storage temperatures, application timeframes, whether the intervention was self-controlled, and the use of cryotherapy equipment on different limbs. To maintain a comparison, the self-controlled studies and randomized controlled trials will be grouped together for synthesis. Both self-controlled studies<sup>12,17</sup> used one side of the body (hand and foot) as the intervention and control groups, yielding contrasting results. The first study<sup>12</sup> (randomly selected dominant/nondominant-sided) lacked a specific tolerance framework and reported the highest attrition rates. With 10 (45%) of participants dropping out due to cold intolerance, leading to early termination of the study.<sup>12</sup> The high attrition rate could be attributed to the longer cryotherapy application time (210 minutes<sup>12</sup>) compared to other studies (90<sup>15,29,31</sup> or 75 minutes<sup>17</sup>) and colder storage temperatures (between  $-25$  and  $-30^{\circ}\text{C}$ ).<sup>12</sup> The second self-controlled study<sup>17</sup> (dominant sided) (participants:  $n = 40$  baseline;  $n = 36$  analysis;  $n = 4$  attrition) also lacked a specific tolerance framework. In contrast, reporting no participant attrition from cold intolerance.<sup>17</sup> Cryotherapy storage temperatures were not reported.<sup>17</sup>

All three randomized controlled trial studies<sup>15,29,31</sup> applied cryotherapy to both the hands and feet (left and right) and used separate control and intervention participant groups. The first study<sup>15</sup> reported nurse monitoring every 20 minutes for cold intolerance during cryotherapy application; no reported data from this monitoring was published within their study. There were two episodes of participant attrition due to cold intolerance.<sup>15</sup> Cryotherapy storage temperatures of  $-20$  to  $-24^{\circ}\text{C}$ .<sup>15</sup> Another study<sup>29</sup> recorded patient adherence to cryotherapy to determine causes for device removal. The study reported high device removal rates during each patient cycle for hands and feet.<sup>29</sup> Bathroom breaks (57.8%) and cryotherapy intolerance (36.5%) were the most common reasons for device removal.<sup>29</sup> Overall, 80.9% of participants required temporary interruption of cryotherapy at least once during Paclitaxel administration due to cold intolerance.<sup>29</sup> Reasons for participant attrition were not documented, and cryotherapy storage temperatures were reported as  $-20^{\circ}\text{C}$  (Gloves) and  $-10^{\circ}\text{C}$  (Socks).<sup>29</sup> The final study<sup>31</sup> reported cryotherapy compliance by measuring interruptions to the cryotherapy intervention. Poor compliance to cryotherapy was defined as interrupted cryotherapy or using thermal gloves/socks inside cryotherapy equipment.<sup>31</sup> Good compliance was defined as uninterrupted use for 90 minutes.<sup>31</sup> Seven (32%) participants in the cryotherapy group reported poor compliance and 15 participants (68%) reported good compliance.<sup>31</sup> There were no episodes of attrition from cold intolerance, and cryotherapy equipment was stored at  $-20^{\circ}\text{C}$ .<sup>31</sup>

### Continuous flow hypothermia

Both continuous flow hypothermia studies<sup>19,27</sup> documented cryotherapy tolerance through a subjective tolerance scale,<sup>19</sup> and a 5-point Likert scale (self-reported comfort scale).<sup>27</sup>

The subjective tolerance scale<sup>19</sup> reported no issues in tolerability during the study at baseline and after one, three, and 6-month intervals for all participants available for analysis. Tolerability scores consistently remained at 0 for all participants across 12 weeks of Paclitaxel treatment.<sup>19</sup> Additionally, no attrition directly caused by cryotherapy was detected.<sup>19</sup> Cryotherapy had a constant temperature of 22°C.<sup>19</sup>

A 5-point Likert scale<sup>27</sup> was used as a self-reported comfort scale (0 = very uncomfortable, 4 = very comfortable). Results were consistently higher when comparing limbs applied with continuous flow hypothermia than for limbs applied with frozen gel cryotherapy in the following fields: Contact with glove or cuff (1.492 vs 2.693), cold tolerance (1.206 vs 2.868), impact on mobility (1.544 vs 1.862), and total comfort score (4.207 vs 7.380).<sup>27</sup> There was no participant dropout from cryotherapy intolerance, storage temperatures of -18 to -20°C (frozen gel) and continuous flow hypothermia (constant temperature of 10-12°C).<sup>27</sup>

### Patient-Reported Outcomes

#### Crushed Ice Cryotherapy

The sensory scale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CIPN 20-item scale (EORTC QLQ-CIPN20)<sup>32</sup> and NCI-PRO-CTCAE<sup>32</sup> were used to measure CIPN severity and grading within the crushed ice cryotherapy participant population. No differences were observed between the control and intervention groups.

#### Frozen Gel Cryotherapy

Five frozen gel studies<sup>15,17,28,29,31</sup> included PROMs, with four<sup>15,17,28,31</sup> out of five<sup>15,17,28,29,31</sup> studies favoring the intervention group. There was a range of different PROMs including The CTCAE,<sup>15,31</sup> Patient Neurotoxicity Questionnaire (PNQ),<sup>29,31</sup> Patient Neuropathy Questionnaire,<sup>17</sup> EORTC QLQ-CIPN20,<sup>28,29</sup> Functional Assessment of Cancer Therapy-Neurotoxicity (FACT-NTX),<sup>31</sup> and the FACT-Taxane,<sup>15,31</sup> and one study<sup>15</sup> also incorporated the TaxS Subscale<sup>15</sup> as an additional subscale.

The CTCAE grades sensory and motor CIPN based on participant symptom description reported within two studies.<sup>15,31</sup> Both studies<sup>15,31</sup> reported reduced CTCAE grades in favor of the intervention group. The first study,<sup>15</sup> completed CTCAE evaluation before each Paclitaxel treatment (12 weeks total). Data was merged and analyzed with the neurotoxicity sections of the FACT-Taxane.<sup>15</sup> The results identified the control group was three times more likely to develop CIPN (OR = 3.36, 95% CI [1.3, 8.67]).<sup>15</sup> The second study<sup>31</sup> completed CTCAE evaluation at baseline and completion of weeks 3, 6, 9, and 12 of Paclitaxel treatment. Lower frequency of grade  $\geq 2$  sensory (9% vs 54%) and motor (5% vs 32%) CIPN was reported in the intervention group.<sup>31</sup>

The PNQ measures sensory and motor CIPN, with grades C to E representing moderate-severe CIPN symptoms, and was used in two studies.<sup>29,31</sup> Both studies<sup>29,31</sup> found cryotherapy reduced the prevalence and severity of CIPN on PNQ scores. One study,<sup>29</sup> performed evaluations at baseline (T0), 1 to 2 weeks post final Paclitaxel (T1) (primary endpoint), 3 months post (T2), 6 months post (T3), and 9 months post (T4) treatment.<sup>29</sup> Greatest benefit was observed at T2 in CIPN sensory (14.3% vs 41.2%) and motor (0% vs 29.4%) symptoms in favor of cryotherapy.<sup>29</sup> Additionally, there were no recorded differences between the intervention and control groups for PNQ motor symptoms.<sup>29</sup> The second study<sup>31</sup> evaluated frequency of PNQ Grade D or higher CIPN. Evaluations were performed at baseline and completion of Paclitaxel weeks 3, 6, 9, and 12.<sup>31</sup> Incidence of  $\geq$ Grade D

sensory neuropathy was lower in the intervention group (14% vs 42%).<sup>31</sup> However, no changes were detected in the incidence of  $\geq$  Grade D motor neuropathy between intervention and control groups (14% vs 23%).<sup>31</sup>

The Patient Neuropathy Questionnaire<sup>17</sup> found that CIPN presented more rapidly in the control group than the intervention. Occurrence of severe grades of CIPN was reduced within the intervention side of the body: Hand: 2.8% vs 41.7% and foot: 2.8% vs 36.1%.<sup>17</sup>

The EORTC QLQ-CIPN20 was used within two studies,<sup>28,29</sup> with one<sup>28</sup> of two<sup>28,29</sup> (50%) studies reporting reduced CIPN symptoms within the intervention group. For one study,<sup>29</sup> evaluation was performed at baseline (T0), 1 to 2 weeks post final Paclitaxel (T1) (primary endpoint), 3 months post (T2), 6 months post (T3), and 9 months post (T4).<sup>29</sup> Benefit was only observed at T2 in favor of cryotherapy for CIPN20 sensory ( $\beta = -3.6$ , 95% CI = -10.5 to 3.4) and motor ( $\beta = -7.3$ , 95% CI = -14.6 to 0) symptoms alongside lower autonomic scores ( $\beta = -5.84$ , 95% CI = -11.15 to -0.524).<sup>29</sup> The second study<sup>28</sup> evaluated EORTC QLQ-CIPN20 scores before the first cycle of chemotherapy (T0), and at 4 (T1), 8 (T2), 12 (T3), and 16 weeks post first Paclitaxel (T4). There were lower reported median scores on the CIPN20 across all time points in favor of the intervention group, excluding baseline for motor and sensory symptom scores.<sup>28</sup> In T4 (range 4-16,  $Z = -3.687$ ), CIPN sensory symptoms are significantly reduced in the intervention group (median 5, IQR 4-6,  $\chi^2$  70.52) compared to the control group (median 8, IQR 6-10,  $\chi^2$  110.67).<sup>28</sup> Additionally, CIPN motor symptoms are lessened to a smaller extent at T4 (range 4-16,  $Z = -2.567$ ) in the intervention group (median 4, IQR 4-6.5,  $\chi^2$  29.81) compared to the control group (median 7, IQR 4.5-8,  $\chi^2$  38.45).<sup>28</sup>

FACT-NTX<sup>31</sup> scores were evaluated at baseline and completion of weeks 3, 6, 9, and 12 cycles of Paclitaxel.<sup>31</sup> FACT-NTX scores were lower in the intervention group compared to the control group (41% vs 73%), with an average decrease in subscale score of intervention: 6.1 and control: 11.2.<sup>31</sup>

The FACT-Taxane was used in two studies<sup>15,31</sup> both of which found cryotherapy reduced the prevalence and severity of CIPN. One study<sup>15</sup> collected data weekly for 12 weeks during Paclitaxel treatment and incorporated the TaxS subscale for measuring CIPN. It was reported that participants receiving standard care were three times more likely to develop severe (Grade 3) CIPN compared to the intervention group (OR = 3.64, 95% CI [2.22, 5.97]).<sup>15</sup> The second study<sup>31</sup> collected data at baseline, weeks 3, 6, 9, and 12 (12 weeks total). The results indicated a lower average FACT-Taxane score in the intervention group compared to the control group by 2.0 and 4.6 points, respectively (95% CI, 0.4-4.8).<sup>31</sup>

### Continuous Flow Hypothermia

Two continuous flow hypothermia studies<sup>19,27</sup> reported mixed findings on PROMs. One<sup>27</sup> study reported reduced CIPN prevalence and grading through continuous flow cryotherapy. Each study used different PROMs including the Total Neuropathy Score (TNS)<sup>19</sup> and NCI-PRO-CTCAE.<sup>19,27</sup>

The TNS<sup>19</sup> compared prevalence and grading of CIPN between the intervention and control sides of the body. The TNS reported that 10 of the 20 initial patients (50%) had an increasing TNS during the last two cycles of Paclitaxel, indicating worsened CIPN symptoms over time.<sup>19</sup> No data analysis between intervention and control groups was reported.<sup>19</sup>

The NCI-PRO-CTCAE measured grades of CIPN in two studies,<sup>19,27</sup> with one<sup>27</sup> of two<sup>19,27</sup> (50%) studies reporting lower CIPN grading in favor of the intervention group than in the control. However, one study<sup>27</sup> compared frozen gel cryotherapy and continuous flow hypothermia and did not use a control group in their study design. There was a similar incidence of CIPN between the continuous flow hypothermia and frozen gel cryotherapy (85.5% vs 90.3%), fewer reported

≥Grade 2 (40.3% vs 50.0%) and Grade 3/4 (11.3% vs 17.7%) presentations of CIPN using continuous flow hypothermia compared to frozen gel cryotherapy.<sup>27</sup> Additionally, there was less reported ≥Grade 2 (43.6% vs 61.3%) and Grade 3/4 (22.6% vs 27.4%) sensory and motor side effects from continuous flow hypothermia compared to the frozen gel cryotherapy.<sup>27</sup> These results should be taken with caution, due to the unavailability of frozen gel socks, the researchers resorted to using frozen gel gloves designed for hands to cover the left foot, serving as a substitute frozen gel sock.<sup>27</sup> The second study<sup>19</sup> reported no changes between intervention and control groups in CIPN measurements.

### Quality of Life

**Crushed Ice Cryotherapy**  
Not reported.<sup>32</sup>

### Frozen Gel Cryotherapy

Two frozen gel cryotherapy studies<sup>15,29</sup> evaluated HRQoL and global health status (GHS) during Paclitaxel. Results were mixed, with one<sup>29</sup> of the two<sup>15,29</sup> (50%) studies reporting positive changes in quality of life scores for participants using frozen gel cryotherapy. A Generalized Estimating Equation logistic model that incorporated the FACT-Taxane, FACT-General, and TaxS subscale scorings in one study<sup>15</sup> and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) in the other study.<sup>29</sup>

The Generalized Estimating Equation logistic model<sup>15</sup> reported no overall differences between the intervention and control groups in quality of life scores in physical, social/family, emotional, and functional well-being subscales.<sup>15</sup>

The EORTC QLQ-C30<sup>29</sup> was used to evaluate HRQoL subscales for GHS, PF, role functioning (RF), and pain scores.<sup>29</sup> The intervention group reported higher quality of life scores at 9 months postfinal Paclitaxel treatment in GHS (95% CI = 1.5–19.881), with no differences observed for PF, RF, and pain scores between the groups using linear regression analyses.<sup>29</sup> Additionally, mixed-effects model analyses reported no difference between the intervention and control groups.<sup>29</sup>

**Continuous Flow Hypothermia**  
Not reported.<sup>19,27</sup>

### Healthcare Service Usage

Health service usage was not reported in any of the included studies.<sup>12,15,17,19,27-32</sup>

## Discussion

This systematic review aimed to explore the impact of distal-extremity cryotherapy in people affected by breast cancer receiving Paclitaxel on PF, clinical, and PROMs, compared to standard care. This systematic review represented a total of 500 participants across the 10 studies for analysis. Two studies<sup>17,19</sup> reported promising results of cryotherapy improving PF throughout Paclitaxel chemotherapy, though overall results remained mixed. PROMs demonstrated that most studies<sup>15,17,27,28,31</sup> saw greater improvements in the intervention group, particularly with frozen gel cryotherapy, in reducing the prevalence and severity of CIPN symptoms. Participant tolerance remains the most significant issue in implementing cryotherapy into standard care. However, the safety of cryotherapy was affirmed within the included studies, with no documented cases of serious adverse events or frostbite reported. The only reported adverse events were from discomfort related to numbness, tingling, redness, and irritation of the skin postapplication of cryotherapy.

Cryotherapy was applied using three modes: crushed ice cryotherapy, frozen gel cryotherapy, and continuous flow hypothermia. Frozen gel cryotherapy was the most investigated mode, used in eight studies<sup>12,15,17,27-31</sup> with the greatest variation in application parameters between specific limb coverage, duration (75–210 minutes), and storage temperature (–18 to –30°C) alterations. Methodological disparities across studies made direct comparison challenging, reducing our ability to definitively conclude the safest and most effective application method in reducing the prevalence and severity of CIPN symptoms and promoting participant compliance. This observation highlights the importance for better-designed, larger-scale trials that adhere to consistent cryotherapy application protocols to identify the most advantageous and well-tolerated administration method.

Clinical outcomes from the included studies yielded inconsistent results, with some studies<sup>17,19</sup> indicating modest improvements in CIPN symptoms and nerve conduction parameters and others<sup>12,29</sup> reporting no changes. Additionally, the results risk potential bias and the placebo effect due to the inherent challenge of blinding participants and outcome assessors to an intervention that is physically applied to the participant during treatment. PROMs are also limited by the participants' reporting ability and the outcome assessor's judgment on how reported motor and sensory neuropathic symptoms relate to specific grading levels,<sup>10</sup> as many clinicians underestimate the severity of CIPN symptoms when using patient-reported numerical grading tools.<sup>17</sup> Clinical objective outcomes are far more accurate diagnostic tools within this setting. However, they are more costly, take additional time to implement, and are typically only utilized if the participant is already reporting grade ≥2 CIPN via PROMs.<sup>10,33</sup> Therefore, a combination of objective and PROMs is essential to evaluate efficacy thoroughly within future trial designs to provide a comprehensive understanding of neuropathic preservation through cryotherapy.

Whether cryotherapy improves participant quality of life remains inconclusive. The frozen gel cryotherapy studies yielded mixed results, and the efficacy of crushed ice cryotherapy and continuous flow hypothermia remains inconclusive due to the absence of data. This systematic review highlights the need for further research on cryotherapy's potential impact on the quality of life in CIPN. Additionally, it acknowledges the complexities of assessing quality of life in the context of CIPN, emphasizing the importance of employing comprehensive, longitudinal assessment tools to gain a more nuanced understanding of these phenomena in future studies.

Pain assessment tools lacked heterogeneity, making direct comparisons challenging. Nevertheless, continuous flow hypothermia appears promising in reducing pain and may be better tolerated than frozen gel cryotherapy. Larger sample sizes and standardized pain assessment tools are needed to establish the effectiveness and safety of cryotherapy in managing CIPN in future clinical trial designs.

Frozen gel cryotherapy demonstrated varying degrees of tolerance, with some studies reporting high attrition due to cold intolerance, potentially influenced by differences in cryotherapy application times and storage temperatures. In particular, one frozen gel study<sup>12</sup> ceased early due to high participant attrition from cryotherapy intolerance, this study also reported the longest application times (210 minutes) and coldest storage temperatures (–25 to –30°C).<sup>12</sup> In contrast, the continuous flow hypothermia<sup>19,27</sup> and crushed ice cryotherapy<sup>32</sup> studies reported no participant attrition due to cold intolerance. The choice of cryotherapy mode and its specific parameters can significantly impact participant tolerance.

The included studies did not address the economic impact of CIPN within this population. Higher motor and sensory CIPN grades impose significant financial burdens. An American administrative claims analysis reported that high-grade CIPN costs an extra \$1509 per patient per month in medical fees compared to those without CIPN symptoms.<sup>34</sup> These patients also bear additional expenses for

pain relief, hospitalization, and outpatient services. Another study<sup>35</sup> reported that severe CIPN is associated with higher average total healthcare costs of USD \$17,344 over 12 months. Furthermore, CIPN symptoms are correlated with a decreased capacity to work for 1 year posttreatment.<sup>36</sup> While not exclusive to Paclitaxel-induced CIPN, these studies highlight the increased cost of living experienced in the short to long term by cancer patients with CIPN symptoms. Future studies should include cost analysis incurred by participants for managing CIPN as an additional way to evaluate cryotherapy's efficacy. These limitations underscore the importance of cautious interpretation of results and the necessity for more robust, standardized research in this field.

### Limitations

This systematic review has limitations which should be considered when interpreting its findings. A notable limitation is that most of the included studies had small sample sizes and were statistically underpowered, restricting the generalizability of the findings to a broader population. The inherent heterogeneity in assessment tools and study designs among the included studies posed significant challenges for effectively conducting direct comparisons and generalizability of the data. This diversity makes it challenging to draw overarching conclusions and highlights the need for core outcome sets in future research. The restriction to English language studies may introduce a potential language bias, potentially excluding relevant research conducted in other languages, which could impact the comprehensiveness of the review's findings. There was a lack of reporting on male participants and future studies should strive for more diverse participant populations. There was a notable lack of qualitative evaluation methods in trial designs to provide voice to participants undergoing cryotherapy interventions, and this should be considered in the future.

### Implications for Practice

Despite limitations in study design and high heterogeneity among included studies, this review offers valuable insights for nursing practice. Aiding clinicians in optimizing cryotherapy protocols to enhance patient comfort and tolerance, thereby potentially reducing CIPN symptoms in breast cancer patients undergoing Paclitaxel treatment. As cryotherapy is often used as a patient or nurse-initiated intervention to prevent CIPN, the reported data assists clinicians in choosing cryotherapy devices, implementing appropriate storage temperature ranges, and cryotherapy application guidelines to provide higher comfort and tolerance for breast cancer patients using cryotherapy as higher tolerance was associated with reduced CIPN symptoms, potentially due to longer device application times. Furthermore, this review provides valuable guidance for researchers regarding study design, methodologies, and measurement tools for future trials investigating cryotherapy's efficacy in managing CIPN from Paclitaxel administration in breast cancer. Nurses, being integral to the clinical care and experience of people affected by breast cancer, must comprehend the available evidence and serve as patient advocates. They play a pivotal role in facilitating patient understanding of current research findings and encouraging participation in future studies, contributing to knowledge enhancement and fortifying the existing evidence base.

### Conclusion

This systematic review offers valuable new insights into the potential use of cryotherapy to alleviate CIPN in people affected by breast cancer undergoing Paclitaxel treatment. While there are encouraging findings, particularly in PROMs, the heterogeneity in study design, cryotherapy mode, and measurement tools underscore

the need for additional research. Future investigations should prioritize standardized protocols, larger participant cohorts, and comprehensive data collection methods to strengthen the robustness of the evidence and facilitate more confident recommendations for the clinical use of cryotherapy in the management of CIPN.

### Consent to Participate

Not applicable.

### Consent for Publication

Not applicable.

### Ethics Approval

Not required as systematic review.

### Data availability

supplementary files.

### Declaration of competing interest

The authors declare no potential conflicts of interest.

### CRedit authorship contribution statement

**Kelly Ford:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Maree Duddle:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Murray Turner:** Writing – review & editing, Software, Resources, Methodology, Data curation. **Catherine Paterson:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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### Supplementary materials

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**Supplementary Table 1. PRISMA checklist**

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary table 2



Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Section/topic	#	Checklist item	Reported on page #
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Table 2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6

Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

## **Supplementary File 2: Complete search strategy**

Four databases and one register were searched on 11 April 2023 to identify relevant studies. These were CINAHL (via EBSCOhost), Cochrane Central Register of Controlled Trials, Medline (via EBSCOhost), Scopus and Web of Science Core Collection. No limiters were placed on any of the searches. Searches returned a total of 169 results. Search terms and number of results by database:

### **CINAHL (9)**

((“chemotherapy induced peripheral neuropathy” OR CIPN OR neurotoxic\* OR neuropath\*) AND (cryotherapy OR ice OR cold therapy OR “low temperature procedure\*” OR hypothermia OR “frozen gel\*” OR cryocompression) AND (paclitaxel or taxo\* OR antineoplastic OR chemotherapy) AND (“breast cancer\*” OR “breast neoplasm\*” OR “breast carcinoma\*” OR “breast tumor\*”))

### **Cochrane Central Register of Controlled Trials (38)**

((“chemotherapy induced peripheral neuropathy” OR CIPN OR neurotoxic\* OR neuropath\*) AND (cryotherapy OR ice OR cold therapy OR “low temperature procedure\*” OR hypothermia OR “frozen gel\*” OR cryocompression) AND (paclitaxel or taxo\* OR antineoplastic OR chemotherapy) AND (“breast cancer\*” OR “breast neoplasm\*” OR “breast carcinoma\*” OR “breast tumor\*”))

### **Medline (19)**

((“chemotherapy induced peripheral neuropathy” OR CIPN OR neurotoxic\* OR neuropath\*) AND (cryotherapy OR ice OR cold therapy OR “low temperature procedure\*” OR hypothermia OR “frozen gel\*” OR cryocompression) AND (paclitaxel or taxo\* OR antineoplastic OR chemotherapy) AND (“breast cancer\*” OR “breast neoplasm\*” OR “breast carcinoma\*” OR “breast tumor\*”))

### **Scopus (65)**

TITLE-ABS-KEY ((“chemotherapy induced peripheral neuropathy” OR CIPN OR neurotoxic\* OR neuropath\*) AND (cryotherapy OR ice OR cold therapy OR “low temperature procedure\*” OR hypothermia OR “frozen gel\*” OR cryocompression) AND (paclitaxel or taxo\* OR antineoplastic OR chemotherapy) AND (“breast cancer\*” OR “breast neoplasm\*” OR “breast carcinoma\*” OR “breast tumor\*”)))

### **Web of Science Core Collection (38)**

TOPIC = ((“chemotherapy induced peripheral neuropathy” OR CIPN OR neurotoxic\* OR neuropath\*) AND (cryotherapy OR ice OR cold therapy OR “low temperature procedure\*” OR hypothermia OR “frozen gel\*” OR

cryocompression) AND (paclitaxel or taxo\* OR antineoplastic OR chemotherapy) AND (“breast cancer\*” OR “breast neoplasm\*” OR “breast carcinoma\*” OR “breast tumor\*”))

In addition to the initial searches, a search of citing documents in Scopus and Web of Science Core Collection was completed and yielded a further 58 documents:

**Scopus (11)**

**Web of Science Core Collection (47)**

**Supplementary Table 3:** Excluded studies from full text review

<b>Author &amp; year</b>	<b>Publication title</b>	<b>Reasons for exclusion</b>
Jue <i>et al.</i> (2018)	Cold therapy to prevent chemotherapy-induced peripheral neuropathy in breast cancer patients.	Conference abstract
Accordino <i>et al.</i> (2022)	A randomized adaptive sequential selection trial of cryotherapy, compression therapy, and placebo to prevent taxane induced peripheral neuropathy in patients with breast cancer.	Conference abstract
Ng <i>et al.</i> (2020)	Preventing chemotherapy-induced peripheral neuropathy using cryotherapy in breast cancer patients receiving paclitaxel: a randomized, controlled trial	Conference abstract
Sundar <i>et al.</i> (2014)	Phase I study of safety and tolerance of hypothermia for preventing chemotherapy-induced peripheral neuropathy	Conference abstract
Azab <i>et al.</i> (2021)	The impact of limb hypothermia on the incidence and severity of paclitaxel induced peripheral neuropathy in breast cancer patients	Conference abstract
Shimanuki <i>et al.</i> (2021)	Preventive effects of self-administered cryotherapy on paclitaxel-induced peripheral neuropathy in patients with early-stage breast cancer: a propensity score analysis	Wrong study design
Simsek <i>et al.</i> (2021)	Cold Application and Exercise on Development of Peripheral Neuropathy during Taxane Chemotherapy in Breast Cancer Patients: A Randomized Controlled Trial	Wrong study design
Bandla <i>et al.</i> (2020)	Limb Hypothermia for the Prevention of Chemotherapy-Induced Peripheral Neuropathy - Modality for Optimal Cooling	Wrong patient population
Hanai <i>et al.</i> (2017)	The effects of icing on paclitaxel-induced peripheral neuropathy among breast cancer patients: a self-controlled trial	Conference abstract
Bandla <i>et al.</i> (2020)	Safety and tolerability of cryocompression as a method of enhanced limb hypothermia to reduce taxane-induced peripheral neuropathy	Wrong patient population
Sundar <i>et al.</i> (2016)	The role of limb hypothermia in preventing paclitaxel-induced peripheral neuropathy	Conference abstract

Hanai <i>et al.</i> (2019)	化学療法起因性末梢神経障害対策としての冷却療法：臨床試験結果より [Effects of cryotherapy on chemotherapy-induced peripheral neuropathy: self-controlled clinical trial]	Non-English study
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