

Peer Review File

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Round 1

Reviewer A

This paper is a systematic review and meta-analysis evaluating the effects of treatments for pain and numbness in cancer survivors. The topic is of clinical interest to many oncologists and other physicians as with advancing anti-cancer therapies, the number of cancer survivors will be ever increasing and it is not uncommon for them to experience pain and numbness along their survivorship path, which heavily affects their quality of life. However, it seems that the evidence available in the literature so far is of sparse quantity and low quality.

Listed below are some comments and questions.

Comment 1:

1. Regarding the literature search, it was mentioned that three electronic archives of publications were searched, including PubMed, CINAHL and PsycINFO. How was this search strategy ensured to have achieved an adequate coverage? Would more of the other databases like Embase, Web of Science and Google Scholar be considered as well?

Reply 1: According to your recommendation, we have conducted a systematic search using MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Web of Science, in addition to PubMed, PsycINFO, and CINAHL. We did not search using Google Scholar because it is not a common academic database.

Changes in the text: Page 3, line 123

Comment 2:

2. Apart from the search databases, were there other ways implemented to make the search more comprehensive and representative of the entire available literature? For example, was there any review of the cited papers in the retrieved articles and of the references of these articles to look for further eligible articles? Were there personal communications with the researchers or experts on the subject to identify unpublished articles or to obtain data not included in the original publications?

Reply 2: Thank you for your comment. We performed an additional search of cited papers and references for further eligible articles. We did not try to identify unpublished articles. Ellison et al.'s (1997) study had missing data, and we contacted the corresponding author via e-mail but were unable to obtain the missing data.

Changes in the text: Page 5, line 192

Comment 3:

3. Would more keywords be considered for the literature search? For instance, “therapy”, “drug”, “medication” and “strategy” in addition to “treatment” or “management”.

Reply 3: We have modified keywords for search as ["cancer survivors" AND (pain OR numbness OR tingling) AND (treatment OR management OR therapy OR strategy OR drug OR medication)].

Changes in the text: Page 3, line 122

Comment 4:

4. Was the quality evaluation of the studies carried out by more than one person independently using pre-established criteria? How was the degree of agreement and what were the reasons of discrepancies?

Reply 4: Two authors independently evaluated the quality of evidence using GRADE guidelines. Quality of evidence was assessed in five treatments for pain (non-opioid pharmacotherapy, acupuncture, education/CBT, physical exercise, and alternative medicine) and four treatments for numbness (non-opioid pharmacotherapy, acupuncture, education/CBT, and physical exercise). The degree of agreement was 67%, and the reasons for discrepancies were mainly related to inconsistency and imprecision.

Changes in the text: Page 5, line 205

Comment 5:

5. "Seven RCTs were excluded due to inapplicable data for the pooled estimate". Given the small number of available studies, especially in some of the subgroup analyses, would more details be given regarding the specific reasons of excluding those 7 RCTs? Were there attempts to try to obtain further relevant raw data from the original authors?

Reply 5: In the revised manuscript, the missing mean and SD values were estimated from the median and interquartile range using Wan's method (Wan et al. BMC Med Res Methodol 2014;14:135). The SD values in Ellison 1997 were missing, and we contacted the corresponding author via e-mail, but we could not obtain the missing data. Subsequently, missing SDs were imputed from other studies (Cochrane handbook for systematic reviews of interventions, version 6.3, 2022). With the above attempts, the number of excluded papers was reduced to zero in the new analysis. We have added details of the exclusion according to your suggestion.

Changes in the text: Page 5, line 175

Comment 6:

6. The subjects of the studies were recruited from various healthcare settings in quite a number of different countries, also over a wide range of age from 18-87 years. However, there were 17 out of the 28 studies which included breast cancer survivors only. How would the authors comment on the generalisability of the results in this regard?

Reply 6: Thank you for your comment. As you pointed out, biases in the type of cancer, age, and race of participants are serious limitations with regard to the generalizability of our results. We have added this concern in the Limitations section. Changes in the text: Page 14, line 566

Comment 7:

7. What proportion of the patients recruited in the studies was having active cancer or receiving ongoing anti-cancer therapies? As it was mentioned that the cause of pain or numbness was poorly documented in the original studies, would it be possible that some of the patients were actually having cancer-related pain or numbness, which responded to concurrent anti-cancer therapies?

Reply 7: Thank you for your comment. The proportion of patients having active cancer or receiving ongoing anti-cancer therapies is not clear. Some studies clearly described that patients with recurrent and advanced disease were excluded, but others did not. We have added this concern in the Limitation section. Changes in the text: Page 14, line 563

The cause of numbness was chemotherapy-induced peripheral neuropathy (CIPN) in all the included studies. In the revised manuscript, we reexamined the causes of pain in the included studies. As a result, 10 studies investigated aromatase inhibitor-associated arthralgia in breast cancer survivors; eight investigated persistent post-mastectomy pain in the neck, shoulder, and upper limb; four investigated CIPN; one investigated dyspareunia; one investigated shoulder pain in postsurgical head and neck cancer survivors; and one investigated postsurgical neuropathic pain. We have modified the description of the cause of pain accordingly.

Changes in the text: Page 7, line 278

Comment 8:

8. As the treatment strategies and assessment schedules were very heterogeneous among the included studies, it is difficult to draw conclusions as to whether a certain type of intervention is efficacious. This might also be considered as one of the limitations of this systematic review.

Reply 8: Thank you for your feedback. As you pointed out, these points are major limitations. We have added this concern in the Limitations section.

Changes in the text: Page 14, line 562

Reviewer B

Comment 1:

Wonderful review. Well written and summarizes the evidence for interventions for pain and numbness in cancer survivors.

Only recommendation, starting in paragraph 331, would use non-judgmental language. Replace opioid misuse with non-medical opioid use. Also, opioid addiction with opioid or substance use disorder.

Otherwise, a nice summary examining an under-researched area.

Reply 1: Thank you for your appreciation. We have modified the phrases according to your suggestion.

Changes in the text: Page 11, lines 452-461

Reviewer C

Comment 1:

This article is exciting because it tries to answer an important question the efficacy of pain treatments on cancer survivors but it suffers from significant shortcomings.

First for a study on cancer survivors, it is essential to define accurately this notion which seems particularly unclear in your text : “Studies involving terminally ill cancer patients and those in which most participants were receiving active cancer treatment were excluded.” When you include studies with active treatments it’s seems impossible to conclude!

Reply 1: As per your comment, it is preferable to exclude patients receiving active cancer treatment and with the progressive disease to improve the quality of the study. However, since there are only a few studies with definitive eligibility, we have set a certain range for the inclusion criteria. We have clarified the inclusion criteria and added this concern in the Limitations section.

Changes in the text: Page 4, line 135; Page 14, line 563

Comment 2:

Moreover, the term survivor is not clearly defined

Reply 2: According to your suggestion, we have modified the definition of cancer survivors. In the revised manuscript, cancer survivors were defined as those who had completed active cancer treatment, including surgery, chemotherapy, and radiation therapy; whose conditions were stable; and who had no evidence of recurrent or progressive disease. Breast cancer survivors receiving hormone therapies were

included if they had no recurrent or progressive disease. If it was not clear whether they met the inclusion criteria, studies including more than 50% of patients with stage III or IV cancer, receiving active cancer treatment, or with terminal diseases were excluded.

Changes in the text: Page 4, line 135

Comment 3:

The other insufficiency is the conception of “Numbness” which is clearly a symptom of neuropathic pain. It seems difficult to assess neuropathic pain on a single symptom and an evaluation of numbness alone appears to be not pertinent. So, you have probably ruled out relevant studies.

Reply 3: As per your feedback, we might have ruled out relevant studies. In the revised manuscript, we have added the keyword “tingling” in the search terms, which would reduce, though not completely, the exclusion of relevant studies.

Changes in the text: Page 3, line 125

Comment 4:

Introduction

L 70 : your references on cancer pain incidence are a bit old and I suggest you use more recent one like that of M van Beuken : (van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, et al. Update on prevalence of pain in patients with cancer: Systematic review. and meta-analysis JPSM).

Reply 4: We appreciate your suggestion. We have modified the Introduction section based on recent reviews.

Changes in the text: Page 2, line 82

Comment 5:

Methods

Despite the definition of survivors as well as the notion of Numbness need improvements

The analysis methodology is correct.

The bias assessment is well done, and the tables are easy to read and explicit

Reply 5: Thank you for appreciating our analysis methodology and bias assessment. According to your suggestion, we have modified the definition of cancer survivors. As you pointed out, the notion of numbness was complicated, but simplification was needed to conduct a meta-analysis. Thus, we used “numbness” and “tingling” as search terms.

Changes in the text: Page 3, line 125; Page 4, line 135

Comment 6:

Results

I understand why you do not found results for pharmaceutical treatments. Probably because you do not define neuropathic pain and a high rate of pain in cancer survivor is neuropathic.

Reply 6: As you pointed out, some studies investigated the efficacy of gabapentinoids or duloxetine on pain and numbness in cancer patients; however, these studies were not included in the present meta-analysis because the subjects were either undergoing active cancer treatment or had advanced disease and were not eligible for the present meta-analysis. We have added a note on this topic in the Discussion section.

Changes in the text: Page 12, lines 472

Comment 7:

Discussion

If you do not find evidence on pharmacological treatment efficacy it's probably due to your definition

Reply 7: As you pointed out, the difference between the search terms “cancer patients” and “cancer survivors” may have caused the difference in the search results. Although there were RCTs that examined the efficacy of pharmacotherapy in cancer patients, there were a few RCTs for cancer survivors. We have added a note on this topic in the Discussion section.

Changes in the text: Page 12, line 472

Reviewer D

The study examines the efficacy of different treatments for pain and numbness in cancer survivors, and finds in meta analyses that acupuncture, education/cognitive behavioral therapy, physical exercise, and alternative medicine could reduce pain with effect sizes ranging from low to moderate/high. Non-opioid pharmacological therapy did not demonstrate a significant effect on pain. The efficacy of treatments to reduce numbness was only examined in three small RCT's and results were non-significant.

My comments to the manuscript are as follows.

Introduction:

Comment 1:

This section conveys nicely the size of the problem, but the rationale for doing this study could be more explicitly explained.

Reply 1: According to your suggestion, we have added a description of the problems of numbness to explain the rationale for doing this meta-analysis.

Changes in the text: Page 2, lines 82–90

Methods:

101 Data sources and search methods

Comment 2:

Is the search string available?

Reply 2: According to the other reviewer’s suggestion, we have changed the search string from [“cancer survivors” AND (pain OR numbness) AND (treatment OR management)] to [“cancer survivors” AND (pain OR numbness OR tingling) AND (treatment OR management OR therapy OR strategy OR drug OR medication)].

Changes in the text: Page 3, line 122

Comment 3:

The literature search is rather outdated, being nearly 2 years old. A refreshed literature search would be appropriate.

Reply 3: According to your suggestion, we have performed a new search until April 30, 2022.

Changes in the text: Page 4, line 127

Comment 4:

108 Types of studies

It might be helpful to further define patients in “active cancer treatment”. So adjuvant chemotherapy and radiotherapy in the study period is OK?

Reply 4: According to your suggestion, we have modified the definition of cancer survivors. Cancer survivors were defined as those who had completed active cancer treatment, including surgery, chemotherapy, and radiation therapy; whose conditions were stable; and who had no evidence of recurrent or progressive disease. Breast cancer survivors receiving hormone therapies were included if they had no recurrent or progressive disease. If it was not clear whether they met the inclusion criteria, studies including more than 50% of patients with stage III or IV cancer, receiving active cancer treatment, or with terminal diseases were excluded.

Changes in the text: Page 4, line 135

Comment 5:

119 Types of treatments

A further definition of the various treatment categories would be helpful.

Reply 5: In the revised manuscript, subgroup analyses were conducted for each treatment. For example, we performed subgroup analysis for physical exercise focusing on exercise type, exercise frequency, and duration.

Although alternative medicine includes a wide variety of therapies, the number of individual studies was small, and it did not seem appropriate to create further subdivided treatment categories.

Changes in the text: Page 5, line 189

Comment 6:

125 Types of outcome measures

I'm lacking information about the follow-up time and if more time-points are reported, which one is preferred?

Reply 6: We apologize for not clarifying the follow-up time. In the revised manuscript, we have presented the duration and follow-up time of each intervention in Table 1. The follow-up time was set after the completion of the intervention. If the outcome was not measured upon the completion of the intervention, the follow-up time was set at the time of the first measurement of the outcome after its completion.

Changes in the text: Page 4, line 159

Comment 7:

Self-reported pain only (or is f.x. pressure-pain threshold measurements eligible)?

Reply 7: Although some studies measured the pressure-pain threshold, we used only pain and numbness scores from validated self-reported questionnaires.

Comment 8:

131 Selection of studies and assessment of search results

Was any software used for this process, i.e. covidence?

Reply 8: We did not use any software, including covidence.

Comment 9:

Line 173-4: "115 were excluded after reading the full text due to irrelevant

population, unexpected outcome,...”. Is “unexpected” the correct word? Maybe “irrelevant” or “inapplicable” would be more appropriate?

Reply 9: Thank you for your suggestion. Reviewer E also pointed out the same issue, and the text was revised accordingly.

Changes in the text: Page 6, line 215

Comment 10:

Line 174: “...seven RCTs were excluded due to inapplicable data for the pooled estimate...” – It looks as if you did not keep these studies in your review, but I would expect you to keep the studies in your review but not use them in meta analysis due to inapplicability of data/estimates. Please make sure this is clarified.

Reply 10: In the revised manuscript, missing mean and SD values were estimated from the median and interquartile range using Wan’s method (Wan et al. BMC Med Res Methodol 2014;14:135) and missing SD was imputed from other studies (Cochrane handbook for systematic reviews of interventions, version 6.3, 2022). With the above-mentioned attempts, the number of excluded studies was reduced to zero. We have modified the text to clarify the details of exclusion according to your suggestion.

Changes in the text: Page 5, line 175

Comment 11:

189 Treatments

It would be preferable with more information about the different treatments in the studies, i.e. different forms of physical exercise, intensities, types of alternative medicine, duration of treatments etc.

Reply 11: According to your suggestion, we have added the details of each treatment in the Results section. Furthermore, subgroup analysis was conducted for each similar cluster within each treatment. For example, we performed a subgroup analysis for physical exercise focusing on exercise type, exercise frequency, and duration.

Changes in the text: Pages 7-11

Comment 12:

196 Outcome measures

Follow up time is lacking information throughout this manuscript, including here.

Reply 12: Thank you for your comment. As also previously mentioned, we have added information about follow-up time. In the revised manuscript, we present the duration and follow-up time of each intervention in Table 1. The follow-up time was

set after the completion of the intervention. If the outcome was not measured upon the completion of the intervention, the follow-up time was set at the time of the first measurement of the outcome after its completion.

Changes in the text: Page 4, lines 159

Comment 13:

229 Meta-analysis for all types of treatments

Is it valuable to pool effects of all treatments together? How do we then know what to offer the patients? I would recommend not presenting these results as they are of little value to the reader or to clinicians in general. And is it even arguable to perform this analysis?

Reply 13: According to your suggestion, we have removed the results of the meta-analysis for all types of treatments for pain and numbness. Instead, in the revised manuscript, subgroup analyses were conducted for each treatment.

Changes in the text: Page 5, line 189

Comment 14:

Line 252; “Heterogeneity between studies was low, but not significant ($I^2=0\%$; $P=0.81$).” Should it be AND not significant?

Reply 14: We have modified the texts according to your suggestion.

Comment 15:

279 analysis for physical exercise

For these results to be useful for clinicians it would require much more in-depth information about the exercise interventions, modalities, intensities, duration, load, and follow-up time.

Reply 15: According to your suggestion, we performed a subgroup analysis for physical exercise based on exercise type, exercise frequency, and duration.

Changes in the text: Page 9, line 352

Comment 16:

291 Subgroup analysis for alternative medicine

What are the types of alternative medicine and what is the follow-up time?

Reply 16: According to your suggestion, we have added the details of each treatment in alternative medicine. Follow-up times are presented in Table 1.

Changes in the text: Page 10, line 392; Table 1

Comment 17:

372: “limitations including the small number of participants (N=61), biased population of breast cancer survivors only”. What is meant by “biased” here?

Reply 17: Thank you for your comment. We intended to say that the studies included only breast cancer survivors, which may cause bias. In the revised manuscript, the content was changed, and the description was removed.

Comment 18:

398 Limitations

- The lack of a registered protocol may be viewed as a limitation.

Reply 18: We have added this as a limitation according to your suggestion.
Changes in the text: Page 14, line 557

Comment 19:

410 CONCLUSION

What would be clinical implications from your research? Can you elaborate?

Reply 19: Our analysis revealed that physical exercise had a large effect on pain with moderate quality of evidence. In the revised manuscript, we elaborated on the implication of our research.

Changes in the text: Page 14, line 573

Reviewer E

This systematic review and meta-analysis provides an important overview of the effect of different treatments on pain and numbness after cancer. However, adjustments should be made.

Large concerns:

Comment 1:

The authors did not register the protocol of their review in advance.

Reply 1: Thank you for your comment. We have added a limitation regarding the lack of a registered protocol.

Changes in the text: Page 14, line 557

Comment 2:

The search is outdated: the last search was performed in June 2020.

Reply 2: We have performed a new search until April 2022.

Changes in the text: Page 4, line 127

Comment 3:

The extracted data from the RCTs should be adjusted in the meta-analysis because, according to the Cochrane review, it is not allowed to combine mean post-intervention values and mean changes values in SMD meta-analysis.

Source: [https://handbook-5-](https://handbook-5-1.cochrane.org/chapter_9/9_4_5_2_meta_analysis_of_change_scores.htm)

[1.cochrane.org/chapter_9/9_4_5_2_meta_analysis_of_change_scores.htm](https://handbook-5-1.cochrane.org/chapter_9/9_4_5_2_meta_analysis_of_change_scores.htm)

The author should choose to extract the mean post-intervention values or the mean change values.

Reply 3: Thank you for pointing out our serious mistake. In the new analysis, we used post-intervention mean and SD values to obtain SMD. We modified the description of “data extraction and synthesis” in the Methods section. The new analysis changed the results of education/CBT from positive to negative.

Changes in the text: Page 5, line 175

Small concerns:

Comment 4:

Overall, well written, but some grammar mistakes and wrong wording choices throughout the text.

Line 174: Wrong word usage: unexpected --> not sought for.

Line 325: Wrong word usage: although --> and

Reply 4: We have modified the word usage according to your suggestion.

Changes in the text: Page 6, line 215

Comment 5:

In academic writing, first-person pronouns should be avoided. Reformulate sentences with “we”.

Line 34: We conducted a systematic search in PubMed, CINAHL, and PsycINFO

Line 114: We included cancer survivors aged ≥ 18 years irrespective of tumor type, tumor stage, or type of anticancer treatment received.

Line 156: We prepared a funnel plot to evaluate the publication bias and visually examined it for signs of asymmetry.

Line 160: We only used data that could be extracted from published articles.

Line 340: We found no evidence for or against opioid use as a treatment for pain and numbness in cancer survivors.

Reply 5: Thank you for your valuable feedback. We have modified these texts according to your suggestion.

Abstract:

Comment 6:

The text in the abstract should stand by itself without having to read the full-text version of the article. Therefore, it is advised to add the effect sizes of all the outcomes in the abstract.

Reply 6: Thank you for your comment. We have added the effect sizes of all the outcomes in the abstract according to your suggestion.

Changes in the text: Page 2, lines 48–61

Comment 7:

In the results the authors report that the quality of the evidence ranged from “very low to low” however in the abstract, the authors report “very low to moderate”. Correct to “very low to low” please.

Reply 7: We appreciate your pointing out our error. In the new analysis, the quality of evidence was rated moderate in physical exercise on pain, low in acupuncture on pain, and very low in other treatments on pain and numbness. We have thus modified the texts accordingly.

Changes in the text: Page 2, line 63

Introduction:

Adequately written.

Method:

Comment 8:

The authors perform subgroup analyses. However, it is not clear if the authors’ goal is to reduce the high heterogeneity or to test the robustness? Please add some information in the method about the additional analyses. Currently, it is not described

in the method.

- Normally, subgroup analysis can only be performed when described in the protocol (but there is no protocol).
- Sensitivity analysis could be performed afterwards, but it is to test the robustness of the effect, not to reduce the high heterogeneity.

According to my understanding, the authors perform sensitivity analysis and not subgroup analysis. Please, if I am correct, adjust this in the text.

Reply 8: According to your suggestion and that of other reviewers, we performed a re-analysis. In the revised manuscript, we performed a subgroup analysis for each of the treatments. The lack of a registered protocol is a major limitation that has been added to the Limitations section.

Changes in the text: Page 5, line 189; page14, line 557

Comment 9:

Add some additional explanation to the ROB assessment method, such as categories, scorings.

Reply 9: According to your suggestion, we have added the explanation of the risk of bias categories and assessment method.

Changes in the text: Page5, lines 196

Results :

Comment 10:

Provide examples for the included non-opioid pharmacological therapy: line 191

Reply 10: According to your suggestion, we have provided examples of included treatments for non-opioid pharmacological therapy.

Changes in the text: Page 6, lines 233

Comment 11:

Reformulate this sentence from “but” to “and”.: Line 252, 265 and 298

“Heterogeneity between studies was low, but not significant ($I^2=0\%$; $P=0.81$).”

because when I^2 is homogenous there is no difference between both studies and for this reason P is not significant.

Reply 11: Thank you for your comment. We have modified the texts according to your suggestion.

Comment 12:

Concerning Figure 1 - the flow chart of the study selection.

Some corrections:

“Irrelevant population” --> “wrong population”,

“Not expected outcome” --> “wrong outcome”,

“Irrelevant study design” --> “wrong study design”

Reply 12: Thank you for your comment. We have modified Figure 1 and the text according to your suggestion.

Changes in the text: Page 6, line 215; Figure 1

Comment 13:

Concerning Table 1 – Characteristics of the included studies.

Small correction: Frensham 2018 “increase in bodily pain” might be confusing use “improvements in bodily pain”.

Reply 13: Thank you for your suggestion. However, the source “Frensham 2018” was excluded in the new analysis due to the wrong population.

Discussion: Adequately written.

Conclusion: Adequately written.

Reviewer F

The purpose of this study was to identify current treatment options for pain and numbness in cancer survivors and to evaluate their effects. The results indicated that there is low to moderate evidence for the efficacy of treatments for pain or numbness in cancer survivors. Overall, I thought the manuscript was well written but I had severe concerns about the search strategy and why the authors were focusing on pain and numbness only. I hope the authors find my comments to be helpful.

Introduction

Comment 1:

The authors focus the introduction on pain only, while the focus of the study is pain and numbness. Thus, I think more information is needed in the introduction as to why the authors are focusing on pain and numbness for the meta-analysis. It seems like the authors should only focus on pain or broaden the search to neuropathic pain (e.g., numbness, tingling, and pain).

Reply 1: According to your suggestion, we have revised the Introduction section and added the description of numbness. Furthermore, we added “tingling” in the new search terms for studies in the revised manuscript.

Changes in the text: Page 3, lines 85; Page 3, line 125

Results

Comment 2:

A PRISMA flow diagram would be preferred to the flow diagram currently presented.

Reply 2: Thank you for your comment. We have modified Figure 1 according to your suggestion.

Comment 3:

As a researcher who focuses on chemotherapy-induced peripheral neuropathy, the authors are missing many trials that focused on treatments for neuropathy in cancer survivors. Thus, this leads me to believe that the search strategy was suboptimal. Table 2 of the linked article lists many randomized controlled trials testing treatments for established CIPN. <https://ascopubs.org/doi/10.1200/JCO.20.01399>

Reply 3: The target population for our meta-analysis included cancer survivors after completion of active cancer treatment, while most studies focusing on CIPN included patients receiving active cancer treatment. Therefore, these studies were not included in our meta-analysis. We have clarified the definition of cancer survivors and added an explanation for why many studies investigating CIPN were not included.

Changes in the text: Pages 4, line 135; Pages 13, line 538

Round 2

Reviewer A

Thank you for your effort in making the changes to the manuscript. This version has much improvement compared with the last.

Reviewer B

The authors have addressed my concerns and the concerns of the other reviewers. the systematic review provides useful information.

Reviewer C

All comments have been correctly addressed.

This work was hard to manage as clinical situations are very heterogeneous.

Great job.

Reviewer E

Thank you for following the advised adjustment and for resending the manuscript entitled: Efficacy of treatments for pain and numbness in cancer survivors: a systematic review and meta-analysis. However, I still have some concerns. Additionally, I advise that the whole paper be spell-checked by a native English-speaking person.

Small concerns:

Comment 1: Wrong wording choices throughout the text.

Abstract – method: individuals/people/patients should be put first: cancer patients --> ‘individuals/people with cancer’ or ‘patient diagnosed with cancer’

> Thank you for your comment. We have modified the text according to your suggestion.
Changes in the text: Page 3, line 5; Page 5, line 10

Comment 2:

Introduction: “While pain in cancer survivors remains poorly studied and understood, it is mostly considered to be a consequence of cancer treatments including surgery, chemotherapy, and radiation therapy (4).” --> In my opinion ‘Aromatase inhibitors’ should be added to this listing.

> Thank you for your comment. We have added hormone therapy in cancer treatments according to your suggestion. The word "hormone therapy" was chosen instead of "aromatase inhibitors" to be consistent with other sentences.

Changes in the text: Page 6, line 4

Comment 3:

“Non-opioid pharmacotherapy, including duloxetine, is recommended for the treatment of CIPN in patients receiving active cancer treatment, but its efficacy on persistent numbness in cancer survivors is unclear (6)”--> I think we would also like to know the efficacy of Duloxetine on pain?

> Thank you for your comment. We have revised the text from “efficacy on persistent numbness” to “efficacy on persistent pain and numbness”.

Changes in the text: Page 6, line 19

Comment 4:

Method: “Two review authors independently screened the retrieved abstracts and excluded the clearly irrelevant articles.” --> please remove ‘clearly’.

> We have modified the text according to your suggestion.

Changes in the text: Page 10, line 8

Comment 5:

Results: “reported the results of electroacupuncture and auricular acupuncture separately, thus the results of the two groups were combined into a single intervention

group using the method in the Cochrane handbook for systematic reviews of interventions (17).” --> this information should be reported in the method section, not the result section.

> Thank you for your comment. We have modified the methods section according to your suggestion.

Changes in the text: Page 11, line 7

Comment 6:

“Shergill, Y., Rice, D. B., Khoo, E. L., Jarvis, V., Zhang, T., Taljaard, M., ... & Poulin, P. A. (2022). Mindfulness-based stress reduction in breast cancer survivors with chronic neuropathic pain: a randomized controlled trial. *Pain Research and Management*, 2022.”

I think this RCT about mindfulness in cancer survivors with neuropathic pain, is an interesting RCT to add to your SR. This RCT has been published in April 2022.

> Thank you for your suggestion. We have added this study to our meta-analysis. By this revision, the number of included studies and included cancer survivor were changed, and the result of the meta-analysis of education/CBT was changed.

Changes in the text: Page 19, line 7