

## Peer Review File

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### Review Comments

This article addresses the highly pertinent topic of cancer-related cognitive impairment and its existing treatments, underscoring its significance in current research. While the paper holds promise, it falls short in certain areas that are crucial for meeting the scientific and academic standards expected in this field. The paper appears as a potential Narrative Review; however, it lacks an explicit methodology. Although it is not intended to be a systematic review, briefly outlining the search strategy used to gather the reviewed literature would substantiate its scholarly foundation. Additionally, the paper requires either a detailed discussion or expanded conclusions to fully encapsulate the implications of the findings. Below, I provide a list of considerations for the authors, ranging from simple comments and suggestions to more substantial concerns that need addressing.

*We reformatted the article to a narrative review and included the section of 2. Method as Table 1.*

1) Consider eliminating subheading 1.1 "Background" as it appears redundant. The content under this subheading fits seamlessly into Section 1, "Introduction," serving as an effective preamble to the article.

*We removed the subheading of 1.1 "Background."*

2) The statement "cancer is no longer viewed as an incurable disease" seems overly broad. It's important to note that the information from lines 69 to 76 primarily pertains to breast cancer. I suggest moderating the tone of this assertion or specifying which types of cancer are no longer considered deadly. The statement could be directly linked to breast cancer to ensure clarity and accuracy in the context provided.

*We removed the statement and then shifted the focus to the fact that long-term symptom management is receiving increasing attention (Lines 85-89)*

3) Line 69: Why has the survival rate improved? Is it solely due to early detection (as stated in line 60), or have advancements in interventions and treatments also played a significant role? It's worth noting that line 202 mentions for the first time that the improved survival rate is attributed to advances in cancer treatments. This raises the question: Are these statements contradictory, or is the improvement due to a combination of both factors? Clarification is needed to ensure the coherence and accuracy of the claims made in the article.

*In revising the introduction, we removed Line 69. A revised statement is provided on Line 275-276 and includes that the survival rate is attributed to both advances in detection and cancer treatments. We also provided appropriate references.*

4) Line 73: I see no need for the abbreviation "CI" as it no longer appears in the text.

*We have removed CI and replaced it with CRCI, which has been defined.*

5) Line 75: "QoL" should be written without parentheses.

*We have revised this as suggested.*

6) Line 81: It seems that the word “cognitive” is missing before “function”.

*In the revision, this sentence was edited.*

7) Generally, in many cases, cognitive deficits align with subjective complaints, yet upon conducting neuropsychological evaluations, no significant deviations from the norm are observed. This raises the question: Are we truly dealing with Cognitive Impairment? Are the tests and evaluations employed sensitive enough for this type of deterioration? Is "chemo fog" genuinely a significant cognitive decline, or should we consider categorizing it as a milder form of impairment? I recommend that the authors address this aspect and discuss the discrepancy between subjective and objective deterioration. This issue is later touched upon in section 2.2.4 and requires further clarification.

*We defined the term CRCI used in this review and explained its manifestations (See section 1.1).*

*We included paragraphs that explain the discrepancy between subjective and objective measures (Lines 126-136).*

8) The authors frequently mention that cognitive impairment is associated with cancer and its treatment; however, they do not thoroughly discuss this implication. Logically, for a tumor to impact cognitive function, it must be located within the central nervous system; otherwise, there is no objective basis for such an effect. Regarding interventions, most studies focus on the role of chemotherapy, hormonal treatments—primarily aromatase inhibitors and Selective Estrogen Receptor Modulators (SERMs), for its toxicity. Additionally, radiotherapy could also have implications if its application is near the central nervous system. It is essential that the authors more effectively address this aspect to clarify the direct and indirect effects of cancer treatments on cognitive functions.

*We stated that CRCI in non-CNS cancer survivors could occur before the initiation of cancer treatments and also explained the potential mechanisms that underlie this relationship. In addition, we described the potential mechanisms that explain the effects of cancer treatments (radiation, hormones, and chemotherapy) on CRCI (See section 1. Introduction)*

9) Consider rephrasing "Although there is still much we don't understand" to a more scholarly tone such as, "Despite ongoing research, substantial gaps in our understanding persist."

*We revised it as suggested.*

10) It appears that Heading 2 is missing.

*Throughout the manuscript, we revised and re-arranged subheadings to be pertinent to the focus of this review.*

11) Linked with point 8: The authors seem to attribute all reported cognitive impairments to chemotherapy. However, it raises the question: Are cognitive impairments found exclusively post-chemotherapy? Do patients who have not undergone chemotherapy, or those before initiating chemotherapy, also report cognitive deterioration? Regarding the introduction, it is essential to either broaden the information to include the general cognitive

profile of cancer and all related interventions or to specifically focus on breast cancer patients who have undergone chemotherapy, as the current narrative suggests. It is unclear from the outset, as the authors initially appear to address cancer and cognitive impairment in general, yet the literature predominantly centers on breast cancer and CRCI post-chemotherapy. The authors need to justify this specific focus on CRCI related to chemotherapy, such as its being the primary medical treatment and its association with the most evident cognitive alterations. Likewise, the manuscript's title should better address the specific focus on Cancer-Related Cognitive Impairment (CRCI) to accurately reflect the content and scope of the study.

*As mentioned in the response on #9, we explained that not only chemotherapy, but also other types of cancer treatments can induce CRCI in non-CNS cancer survivors (Lines 105-116)*

*We also explain in the overview of findings that the review includes non-CNS cancer survivors but the extent literature is still primarily in breast cancer survivors. We also added a section on future research needs which includes a call for CRCI research in other cancer populations.*

12) Line 185: It appears that there is a missing detail in the phrase "18 months after to work." This could be clarified to "18 months after treatment to return to work" or similar, depending on the intended meaning.

*We revised it to "18 months after treatment"*

13) Section 2.2.4, titled "Need for the Identification and Treatment of CRCI," does not seem appropriately placed under "Impact of CRCI on QoL." It would be more suitable as a new, standalone section given its distinct focus and importance.

*We make it a standalone section.*

14) Line 227: There is an unnecessary black space in "patient , and."

*We have removed this spacing.*

15) Line 239-240: Here, the authors refer to non-CNS tumors for the first time. It raises the question: Does the previously reported literature on CRCI also include non-CNS tumors? Although it seems to be the case, discussing this earlier in the manuscript would have provided clearer context and continuity.

*We clarified in the introduction that this review will focus on CRCI in non-CNS cancer survivors, although many studies have been conducted on breast cancer survivors (Lines 93-95)*

16) Are the level 5 and 6 headings the same? The main heading "Non-pharmacological Interventions" and its subheading appear to use the same formatting. I suggest employing a different style for the subheadings to enhance the document's structure and improve visual differentiation.

*We have adjusted the headers throughout the manuscript, in part to match the journal requirements.*

17) Line 288: What were the characteristics of the control group? Was it a passive control group (e.g., a waiting list), or an active control group? If it was the latter, what parallel activities did the control group undertake?

*We have added this detail to the manuscript. This was a wait list control group who received emails regarding general health topics (healthy eating, stress reduction, and general brain health).*

18) Line 324: Recent studies have focused on multidomain CCT, rather than targeting a specific cognitive domain. This approach is not limited to cancer but extends to other pathologies and the healthy population. The outcomes, particularly the transfer effects, seems to surpass those of traditional single-domain focused interventions. Could the authors incorporate this broader application and its benefits?

*We have added material regarding how cognitive training may be focused on one or more cognitive domains and their added benefits.*

*And we also added relevant citation including:*

*Sung CM, Lee TY, Chu H, Liu D, Lin HC, Pien LC, Jen HJ, Lai YJ, Kang XL, Chou KR. Efficacy of multi-domain cognitive function training on cognitive function, working memory, attention, and coordination in older adults with mild cognitive impairment and mild dementia: A one-year prospective randomized controlled trial. J Glob Health. 2023 Jun 30;13:04069. doi: 10.7189/jogh.13.04069. PMID: 37387548; PMCID: PMC10312047.*

19) An extensive list of various non-pharmacological interventions is provided. The authors highlight the benefits observed in some of these interventions. However, they do not discuss the shortcomings or studies that report no effects, nor do they explore possible explanations for these discrepancies.

*We have added in the overarching section that we are reporting on non-pharmacological interventions that have shown the most promise in relationship to improving CRCI. We also acknowledge for each intervention the limitations of the evidence and the need for more research to determine efficacy (Lines 350-360)*

20) Overall, the authors mention the cognitive benefits of the interventions, but overlook transfer effects to other domains such as fatigue, daily functioning, social interaction, or quality of life. Given the significance the authors place on quality of life (QoL), I suggest that the review include a discussion on the benefits of the interventions in these areas as well.

*We have added this to the overview of the deficiencies of the studies to date. In addition, we have added additional paragraphs related to CRCI Interventions and other co-related symptoms which encompasses the impact of these promising interventions on correlated symptoms and overall quality of life.*

21) Generally, it has been noted that pharmacological interventions vary significantly in dosage and application. I suggest that the authors also address these variations in non-pharmacological interventions. One of the main limitations, in addition to the small sample size mentioned, is the lack of consensus on application protocols as well as the absence of an active control group (i.e., sham intervention).

*We have added this to the manuscript in the overview in the section and in the discussion of each intervention.*

22) In the summary, the authors discuss the negative effects of CRCI on "everyday functioning, work ability and productivity, and overall quality of life." However, the results of the review—covering both pharmacological and non-pharmacological interventions—focus primarily on the cognitive domain. Does improvement in cognitive function also imply improvements in these other areas? I believe the authors should include references to studies that report improvements not only in cognitive functioning but also in areas such as everyday functioning.

23) The authors provide, albeit briefly, some practical implications and future research directions, such as addressing CRCI in the workforce. However, the manuscript lacks a substantive discussion section. This part of the article needs elaboration:

What conclusions have the authors drawn from this review? What guidelines or recommendations can they offer to the broader scientific community? Which types of interventions and designs have shown the largest effect sizes in the results?

Additionally, the applicability of the findings to other types of cancer should be clarified. The authors should initially focus their study on CRCI in non-CNS tumors, specifically in breast cancer survivors, and consider CRCI that occurs after chemotherapy. This focus would help in tailoring interventions more effectively and could provide a clearer framework for applying the findings across different contexts.

I would like to know the authors' opinion on the optimal timing for interventions: Should we wait until subjective complaints arise, or until there is clinically significant deterioration, or perhaps consider interventions as a preventive measure even before starting cancer treatment? This approach could significantly influence the management and outcomes of CRCI

*We appreciate these comments and have added more in-depth material to the summary regarding interventions that not only may improve CRCI as well as other correlated symptoms and QoL. We gave examples of CT interventions impacting these other correlated symptoms as well as identified how CRCI is part of the psychoneurological symptom cluster and how interventions designed to address multiple symptoms have advantages. While we don't identify exercise/PA as superior to other interventions as full scale effectiveness studies have not been completed in cancer survivors; we do extoll its impact on an array of correlated symptoms, its overall benefit, and the initiatives to implement this in standard oncology practice. (Lines 437-466). We also added appropriate references to support these statements.*

*In addition, we added a Future Directions for Research and Practice Section in which we identify just some aspects of the changing climate and needs for cancer survivors as related to CRCI (Lines 468-507)*