

January 28, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2429-review.doc).

Title: 25 Years of Research on the Effects of Exercise Training in Breast Cancer Survivors:
A Systematic Review of the Literature

Author: Claudio Luiz Battaglini, Robert Coleman Mills, Brett Lovell Phillips, Jordan Talmadge Lee, Christina Elizabeth Story, Marcelo Guimaraes Boia Nascimento, Anthony Carl Hackney.

Name of Journal: *World Journal of Clinical Oncology*

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The manuscript has been improved according to the suggestions of reviewers:

1. Reviewer 1.

“Excellent review of the topic. I especially liked the division of the research into time periods. Very good articulation of inclusion and exclusion criteria, with very appropriate focus.”

1. A few concerns include the validity of combining data from multiple studies to generate a combined p-value (in tables). Unless you have the raw data, I do not think you can accurately do this. An alternative method of expressing the results would be discussing the largest trials and their p-values, and changing the tables to a more stream-lined organization (cardiopulmonary function, PRO's, etc. without the types of measures within each category listed) with individual study data (p-values) within each category”.

Answer: Thank you reviewer 1 for the kind words. Our team agrees with reviewer 1 concerns regarding using data from multiple studies to generate a p-value, however, our intent through this review, due to such heterogeneity of sample size, measurements, and exercise prescriptions (major limitations of this fairly young area of research), was to provide readers with a chronological history of the studies conducted so far and at the same time give readers an idea of the potential effects of exercise on the major outcomes evaluated.

To make readers aware of these limitations, cautioning them on interpreting the study results, we mentioned on the manuscript (page 25, lines 21-23) that more data is needed

for a more precise evaluation of the outcomes included in this review and on page 27 (lines 30-36) we outline potential issues associated with the way we analyzed the data; which is exactly what reviewer 1 has pointed out to our team as a concern.

For this type of review, we are confident that the way the data is presented gives readers a very good idea of the history and impact of exercise in breast cancer survivors during the past 25 years, in relation to the types of exercise mode, frequencies of training, and exercise intensities used thus far to promote change in major outcome variables include in this review. Because this area of research that is still in its infancy, it is more appropriate to point out the instruments used to evaluate the outcome variables, thus the construction of our tables had that goal.

We feel confident that this review provides solid information to inform future trials to improve the quality of science and eventually provide more accurate information on the real effects of exercise in breast cancer survivors. As much as we agree with reviewer 1, we truly believe that, taking into account all the limitations of the study in this area thus far, the way the data is presented in this manuscript is appropriate and provides great insight on the current state of knowledge in this area of research. Therefore, respectfully, we do not feel we need to change our tables for this particular project, but for future reviews, with more studies, we will definitely take the reviewer 1 comments into consideration and will most likely abide to the recommendations.

Reviewer 1:

2. “Besides grammatical review/correction, no other changes needed”.

Answer: Our team reviewed the entire manuscript again and corrected all grammatical and editorial issues. Thank you reviewer 1 for alerting us to these issues.

Reviewer 2:

“The arm of this study was to review the effect of exercises for patients with breast cancer in the past 25-years. It is fairly well designed and the statistical analyses appear reasonable. It is worthy of recommending for publication. However, some revisions need to be made before final decision”.

1. “Please avoid using too many long sentences which make readers confused. For example, the sentence “ included in the literature....., and overall quality of life” in page 5, line 6 to 11; sentence “For studies, where there was...were included in the exercise group.” In page 6, line 2 to 5; sentence “3 were home-based interventionsfor two weeks in a supervised setting” in page 11, line 21 to 24.”

Answer:

We agree with the reviewer and we corrected all sentences (Page 5, lines 6-11, page 6, lines 2-5, and page 11, lines 21-24).

2. "The sentence "This may be explained....of all study designs during this period" in page 28, line 4 to 6 and sentence "A few studies... in body composition" in page 28, line 26 to 28 mean unclear, please do more detail explanation."

Answer:

We agree with the reviewer and we clarified both sentences (Page 28, lines 4-6 and 26-28).

3. "The words such as "co-morbidities", "plasticity" is not suitable for key words in this manuscript. The author could make more adequate key words."

Answer:

We agree with reviewer 2 and we revised all key words. We added breast cancer instead of just cancer, we replaced co-morbidities with oncology, replaced plasticity with VO_{2peak} , and even revised the key word adaptation and replaced it with PROs. Thank you reviewer 2 for the great suggestion.

4. "The authors could individually cite your reference in these tables to make reader clear for your summary."

Answer:

Due to the complexity of our tables and the fact that we have cited all of these studies on the text, we would rather not have to include these references to the tables so as to keep not crowd the tables any more than they already are. If the reviewer feels strongly about the need to add these references, we will re-consider adding them to the tables. Our team, however, feels that this is not critical to convey the information already presented in the tables.

5. "The intensity of resistance training (ex: RM) in page 11, line13 did not be mention."

Answer:

Thank you for the important observation. The description of the intensities used in the studies that included resistance training as part of their exercise prescription was included in page 11 (line 14-20).

6. "The detail date about these included studies such as age of patient, cancer stage and co-mobility is lacking".

Answer:

Thank you for the observation. The age detail was added to the text for each time period. Due to the lack of information from many studies on the population studied and other potential co-morbidities, our team was not able to include this information on this review. However, we pointed out at the end of the review (page 31, lines 17-19),

that the information pointed out by the reviewer is extremely important to be included in future studies so the rigor of the science can be improved, allowing for more precise interpretation of studies results.

7. "The abbreviation" Est. Treadmill, mCAFT, 6min and LBM" in table 2 is not defined".

Answer: Our team revised the entire table and deleted all rows with no data, including the rows with LBM. We also added the abbreviation for the mCAFT test per suggestion of reviewer 2.

8. "Sentence" cardiorespiratory function,exercise training ($P < .0001$)" in page 15, line 1 to 2 mean the significant effect after exercise. However the author did not mention which measurement was used."

Answer: The description of the measurement used was added to the text on page 15.

9. "The reference for sentence" An improvement....no significant changes" in page 15, line 2 to 4 should cited."

Answer: References were added the text on page 15, lines 2-4.

10. "Page 15, line 15. Indirectly measured mean which methods?"

Answer: The definition explanation of indirectly measured was added to text.

11. "How many home program or supervised exercise was recruited in period 2000 to 2006?"

Answer: This information was added to page 11 and 12.

12. The result did not show exercise intensity in studies from 2000 to 2006.

Answer: Exercise intensity description was added to the period of 2000-2006 on page 11.

13. The table 2 summary the "strength" but no any description in your result.

Answer: It was added to text (Page 11, lines 9-13) a comment on the results of the strength measures.

14. Some patients received exercise during active treatment and some did not. Could author compare the different effect of exercise in these difference groups? Moreover tell us the benefit or harm.

Answer: The reviewer makes a good point, however, a prior evaluation of the overall changes in the parameters included in this review indicated very little clinical difference between results of studies that evaluated patients undergoing treatment and those off treatment (Page 30, lines 22-25), thus the inclusion of both groups of patients in our analyses.

Therefore, at this time, based on the results of the studies included in this review, we can confidently say that the benefits of exercise training in patients undergoing treatment and those patients who had completed treatment, appears to produce similar results clinically. Furthermore, the evidence from the data included in this review suggests that exercise performed during or post treatment appears to be safe for patients cleared by their physicians to participate in regular exercise. We do not have data to date in any cancer population to be able to confidently state if exercise (the way it is currently administered to cancer patients) is harming these patients. Thus far, it appears that exercise does more good than harm, however more studies are needed to confirm or refute this suppositions.

15. Mild adverse events were reported in studies during 2007 to 2013. Is any event in other period?

Answer: Very little information regarding adverse events was reported prior to 2007. The only other study that presented an adverse event prior to 2007 was a study conducted by Courneya and colleague in 2003. This information was added to the text, page 16, lines 27-28.

16. Page 16, line 28 and page 20. $P=.062$, $P=.022$ and $P=.037$ mean significant?

Answer: On page 16, it is mentioned that the $p=.062$ approached significance for the exercise group 12 min walking test. On page 20, both $p=.022$ and $p=.037$ were explained to readers what they mean.

17. The different definition between treadmill $\dot{V}O_2$ and Est. Treadmill $\dot{V}O_2$ is unclear in the text. Please mention.

Answer: Clarification on the difference between Treadmill $\text{VO}_{2\text{peak}}$ and Est. Treadmill $\text{VO}_{2\text{peak}}$, were included in the text, page 19, Table 3.

18. The abbreviation “BDI, R-Beck” in table 5 is not mentioned.

Answer: These abbreviations were added to table 5.

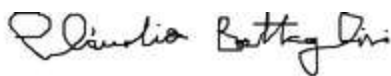
19. Reference should been cited in sentence” This are of study.....development consequences” in page 28, line 30.

Answer: A reference was added to the sentence.

Thank you so much for the opportunity to revise our manuscript for publication on the World Journal of Clinical Oncology. Our team addressed all of the concerns and suggestions made by all reviewers. The reviewers did an excellent job and we do believe that with the modifications made, per reviewers request, the manuscript is stronger and reads better.

Thank you again for publishing our manuscript in the *World Journal of Clinical Oncology*.

Sincerely,



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