Author’s response to reviews

Title: Effects of a Parallel Arm Randomized Controlled Weight Loss Pilot Study on Biological and Psychosocial Parameters of Overweight and Obese Breast Cancer Survivors

Authors:

Susan Raatz (susan.raatz@ars.usda.gov)

Andrea Arikawa (andrea.arikawa@unf.edu)

Beth Kaufman (bkaufman@umn.edu)

Mindy Kurzer (mkurzer@umn.edu)

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Effects of a Randomized Controlled Weight Loss Pilot Study on Biological and Psychosocial Parameters of Overweight and Obese Breast Cancer Survivors Susan K Raatz, PhD, MPH, RD; Andrea Y Arikawa, PhD, RD; Beth C Kaufman, PhD; Mindy S Kurzer, PhD Pilot and Feasibility Studies

Dear associate editor,

The authors thank the reviewers for insightful comments into this manuscript. We addressed all reviewers’ comments to the best of our ability. Please find the responses below:

Associate Editor's comments:

The study is well designed and written as a full trial intended to test a hypothesis. However the authors presented the study as a pilot and feasibility study. The authors should therefore provide specific objectives and aims of the pilot and feasibility study, less emphasis on hypothesis testing as the study is not powered to test a hypothesis, next steps (how will this pilot trial inform the
main trial? will there be a main trial?), and follow the CONSORT pilot extension guidelines for reporting this pilot trial.

We agree with the associate editor that this study had originally been written as a full trial. We now revised the language and removed the hypothesis while including primary objective for this pilot study (lines 22 and 23, and 106-108). We also included more information regarding next steps in the conclusion (lines 480-486) and included a CONSORT diagram as suggested by reviewer #1.

Reviewer reports:

Reviewer #1: This is a well-designed study with exceptional selections for rationale and biomarker measures. Well-written.

Well explained rationale of the biomarker selection. In the abstract as well as in the discussion, explain the selection of biomarkers and association with cancer recurrence (maybe in the abstract, simply note "cancer recurrence related" biomarkers?).

As suggested by the reviewer, we included the word recurrence in the abstract (line 24) and also addressed the selection of biomarkers in lines 466-468.

Also note more in the introduction what the association of these factors might be related to weight loss/exercise/diet--- why might one expect these to change?

We included some rationale for the association between these factors and energy balance and the expected change in them in the introduction (lines 87-90).

Intro: needs explanation for the choice of the two interventions, why choose these to compare as intervention/control? Needs more review of the literature. What is the history of programs designed to look at these sorts of intervention, and evidence for effect on weight, both short term and long term, then extend to the added purpose of the pilot study in gaining insight into biomarkers associated with recurrence.

We recognize that not a lot of background was provided regarding weight loss interventions. We included more information, as well as a more detailed rationale for choosing the types of interventions chosen on the last paragraph of the introduction (lines 98-111).
Method.

Very nice touch to choose a 1000-calorie deficit dietary plan based on baseline biometrics/diet of individuals at baseline.

Readers don't "see" that the CR diet is a feeding intervention with prepared meals until methods section! We need to see this earlier (even mention in abstract), as this is a critical factor. And we don't see that not only is there a prescription for exercise, but that they need to show up to DO the exercise 2 x week/4 weeks, while the control only gets counseling. These are interesting and important design features, but need to be addressed earlier in the rationale/intro, relating these choices to past studies and evidence for gaining adherence.

We agree with the reviewer regarding the details of the CR group. We tried to make it more clear what the intervention entailed throughout the text by including the word “feeding” when describing this treatment group. We also included in the abstract and throughout the manuscript the sentence: “1000-calorie deficit feeding and exercise intervention (CR)” to better capture the nature of this treatment.

Why choose 18 weeks for fitness assessment?

An explanation for doing the fitness assessment at 18 weeks was provided in lines 127-129.

Also justify why 1 month past treatment for eligibility---discuss in limitations that some parameters such as inflammation, stress, qol may still be impacted from coming off of treatment so recently and influence the trajectory of recovery (even if in both groups, may be adding noise)

We realized that the criteria for inclusion was not correctly described in the original manuscript. Participants had to have completed all treatments at least 3 months prior to enrollment into the study. We have corrected this mistake (line 144)

Consort flowchart should be included. Blinding information for study staff, participants?

A figure was added to the manuscript with the flowchart and we addressed blinding in lines 130-132. Given the nature of the interventions, neither participants nor study staff were blinded to the treatment allocations. However, laboratory analyses were conducted in blinded samples.
Results/discussion

Needs a separate limitations section to discuss the small sample, imbalance at baseline in BMI, and other factors that didn't get assessed (behavioral, adherence, etc) that might provide more clues to changes.

The limitations section can be found in lines 468-473, where we address the issues with sample size, imbalance of BMI at baseline, lack of assessment of dietary intake which could help with determination of compliance in the WM group and other issues.

Definitely address the lack of diurnal cortisol analysis (a much better predictor of recurrence and/or death)—it is fine to note that the choice for 24 hour urine sample was fine for pilot, but a bigger question would be to look at a full sampling of 2-3 days of diurnal cortisol collection.

Acknowledgement of the best way to assess cortisol was made in lines 434-438.

Finally--- if there is limited adherence (dietary intake or exercise) measures, it is difficult to determine if the results are due to adherence or to the specific type of intervention. (only the CR group kept activity logs, even in the last 6 week follow-up?). This is as much a behavioral study (what works to get women to make these dietary and exercise changes? Do women in CR eat other than what given?) as it is an outcome study. Yes, as a pilot study, it isn't expected that all of these things are measured, but this will be important in the discussion section.

We addressed the fact that we did not include more objective measures of adherence to both interventions, including dietary intake, in the limitations section. Part of the reason was the time commitment involved in filling out all psychosocial surveys and attending periodic study visits. At the same time, we did not feel a great need to assess adherence as we monitored weight loss in the participants and saw that it was occurring.

Make more of the 'pilot' nature of the study and what can be done next (including some of the issues mentioned in above notes). Citations for choices of study design, including the choices around eliminating some of the outliers to re-analyze certain outcomes, would be helpful. (agree with the choices, but it helps to justify your conclusions if you have references that confirm these strategies for analysis in pilot studies). THEN the results need to have a shift in conclusions.

Also make more of the potential of this study to help unpack the links between exercise/nutrition and biomarkers of recurrence. Associating the potential mechanisms related to associations we have seen in the longitudinal data (e.g., more exercise, less recurrence) is a strength of this study,
even as a pilot. It never hurts to say what is needed next…not just "further research" but specifically what might be more rigorously tested.

We included some final thoughts about the direction of a future study and some elements of design to focus on (lines 480-486).

Wonderful potential contribution to the literature.

Reviewer #2: Arikawa and colleagues present findings from a very small randomized controlled weight loss pilot study on biological and psychosocial parameters of overweight and obese breast cancer survivors. The trial is well designed and conducted. The endpoints selected are appropriate and, as the authors suggest, are less commonly incorporated in randomized weight loss trial in cancer survivors. The findings from this small trial are embedded in an overly long discussion regarding the selected study endpoints with 84 citations.

There could be issues raised regarding the fair balance and conclusions regarding several of the presentations made in the introduction and the discussion section. However, as I did not feel that a pilot or feasibility trial entering 21 participants could support such an exhaustive review, I present an alternative. The authors cite a 2014 manuscript which reviewed the then 10 available randomized weight loss intervention trials in women with breast cancer. This issue was update in December 2016 adding 6 additional randomized trials (J Clin Oncology 34(35), December 2016: 4238-4248). This updated citation should be included. That manuscript is one of 11 in a special issue devoted to obesity and cancer in the Journal of Clinical Oncology. Two or 3 of citations will cover the issues raised by the authors and eliminate most of the citation list (the final citation list should optimally be 20 or less). This will free up a couple of references to support why the weight loss strategies were choosen and how the authors view the pros and cons of either approach with respect to potential for incorporation in larger clinical trials with respect to effort and expense.

If this is a pilot or feasibility study (rather than a one of a kind effort), the authors should outline what they anticipate the next step should be.

In summary, the authors should almost entirely eliminate their 84 citation review. They certainly could use those words to present a review of the area in another report but a pilot study of the sample size they present to really support no more than 20 citations.

We have carefully reviewed some of the manuscripts published on the December 2016 issue of the Journal of Clinical Oncology, as suggested by the reviewer. While we were able to replace several references with some of the references suggested by the reviewer, several biomarkers were not addressed in those publications, such as vitamin D, melatonin, cortisol, F2-isoprostanes. We were able to cut 16 references, but added a few more in response to reviewer #1’s
suggestions about including more background information on certain topics. Due to the wide array of biomarkers measured in this pilot study, we felt like we had to justify the measurement of all biomarkers, including background information related to energy balance and breast cancer. This is such a complex issue and it seems impossible to include less references.

We did include more information about our rationale to design the treatments as described (lines 98-111), and we also included more insight into next steps for a larger clinical trial (lines 480-486).