Reviewer's report

Title: Physical activity before and after breast cancer diagnosis and survival - The Norwegian Women and Cancer cohort study

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Reviewer: Elizabeth Poole

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In this study of breast cancer survivors participating in the NOWAC cohort, the authors evaluated both pre- and post-diagnosis physical activity levels in relation to overall and breast cancer-specific survival. Importantly, because they had information on both pre- and post-diagnosis physical activity, they could evaluate the impact of changing physical activity on survival. As this is only the third study to evaluate the impact of change in activity, this could be an important contribution to the literature. However, there are some key methodologic questions that must be addressed, including categorization of change (both of physical activity and BMI), appropriate time scales, and potential confounding by BMI.

Major compulsory revisions

1. Background, 2nd paragraph/Discussion, 7th paragraph: The authors state that only one study has examined changed in activity from pre- to post-diagnosis. This is untrue. There is a publication in the HEAL study from 2008 (Irwin et al, JCO, 2008) that examined change in pre- to post-diagnosis activity. The authors cite this as reference 15 in their discussion of both pre- and post-diagnosis physical activity.

2. Methods, 1st paragraph: The authors provide only a brief description of the NOWAC study; from this description it is unclear that the NOWAC study is a prospective cohort study of cancer incidence that is now taking advantage of the fact that they have information on post-diagnosis physical activity among women with breast cancer and can, therefore, evaluate both pre- and post-diagnosis activity in relation to breast cancer survival. Please provide additional information about the NOWAC study so that it is clear to readers what the original study design was. This is particularly important for the information on pre-diagnosis activity, since it was prospectively collected and not recalled by breast cancer patients.

3. Methods, 9th paragraph: The authors state that they categorized their 10 level PA variable into two categories (inactive, levels 1-4 and active, levels 5-10). However, this is misleading, as the results for both pre- and post-diagnosis activity (Figures 2 and 3) show all 10 levels. These cutoffs only apply to the change analysis – the authors should make that clear in their description of the analysis. Further, given the availability of 10 levels, the authors should have used finer cutpoints for the change analysis, as it would also allow for finer analysis of change (i.e., does the effect of post-diagnosis activity depend on where women
started). This would be a key contribution to the literature on post-diagnosis physical activity and the likely impact of intervention.

4. Methods, 9th paragraph: The authors state that they reduced their change in physical activity variable to 2 levels (reduced/maintained inactive and increased/maintained activity). However, by doing this, the authors have reduced their change analysis into the exact same analysis as the post-diagnosis physical activity analysis (i.e., all the women who reported low post-diagnosis physical activity are in the reduced/maintained inactive group and all the women who reported high post-diagnosis physical activity are in the increased/maintained active group). Using finer categories would alleviate this problem as well.

5. Methods, 9th paragraph: The authors adjusted their post-diagnosis activity analyses (and presumably the change analyses) for the time between diagnosis and physical activity assessment (#1 year vs. > 1 year). However, this is not the best analysis. Because women are essentially immortal until they report their post-diagnosis physical activity (i.e., women had to have survived long enough to complete a post-diagnosis questionnaire), this could cause bias in the analysis. The better approach is to enter women into the analysis on the date they completed the questionnaire rather than their date of diagnosis. While it is unlikely that this introduced much bias in this case (because breast cancer survival is high), the authors conduct the analysis using left truncation, with date of questionnaire completion as the beginning of follow-up, rather than date of diagnosis.

6. Methods, 9th paragraph: The authors should evaluate the impact of adjusting for BMI, as BMI is one of the most consistently associated risk factors for mortality.

7. Results (in general): I wonder if the results for pre- and post-diagnosis activity would be more stable if the authors combined two categories (i.e., 1 and 2, 3 and 4, 5 and 6 and so on). This would preserve the variability that the authors had available to them, while improving the stability of the estimates.

8. Figures 1 and 2: It would be extremely helpful to have information on the number of cases and events.

9. Results, 4th paragraph/Figure 5: The authors state that stratification by BMI revealed similar trends among normal vs. overweight women. However, in figure 5, it looks like the trend towards better survival with higher activity is only apparent among normal weight women. For women with a BMI #25, the highest levels of physical activity seem to have no benefit or even some indication of increased risk of dying. (The same is true for breast-cancer specific mortality in additional file 1.)

10. Results, 5th paragraph: The authors should describe how categories of post-diagnosis BMI change were defined. Also, the results for women who maintained their post-diagnosis BMI are very similar to those whose post-diagnosis BMI increased. Therefore, I wouldn’t interpret the results based only on the statistical significance.

11. Discussion, 3rd paragraph: The authors note only 3 studies of “total” post-diagnosis activity and breast cancer prognosis; however, the authors only
note 2 citations (the studies in HEAL and LACE, which DO measure total activity). Then they note one additional study of recreational activity and all-cause mortality. However, there are many more, many of which were cited by the authors in other sections of the manuscript, including in the same paragraph. It is unclear what the authors mean by “total” activity, as the Nurses’ Health Study only captured recreational physical activity and not activity during work or commuting (although some questionnaires included household activities). Please clarify this paragraph – why are the studies in the WHI and the Long Island Breast Cancer study not included in the total number of studies that have evaluated this question?

12. Discussion, 8th paragraph: The authors should add more discussion of the fact that increasing physical activity was not associated with survival improvements among women who lost weight after diagnosis. Is this simply that women who lose weight, in general, are likely sicker than women who don’t? Is the increased physical activity likely to be causing the weight loss? Are these women who are going from overweight to normal/underweight? Women who were normal/underweight losing even more weight? Are these just small numbers? This finding seems like a mixed message and it deserves some attention.

Minor essential revisions

13. Methods, 2nd paragraph: The authors should note how cause of death was identified.

14. Methods, 3rd paragraph: The authors should tell the reader how much time elapsed between completion of the enrollment questionnaire and breast cancer diagnosis. (The authors provided detailed information about this for the interval between diagnosis and post-diagnosis physical activity, but it is entirely possible that physical activity was measured a long time before diagnosis and didn’t reflect activity at the time of diagnosis, thereby lessening the ability to detect an association between pre-diagnosis activity and survival.)

15. Discussion, 3rd paragraph: The authors cite reference 15 as an analysis of Nurses’ Health Study data. This is incorrect; reference 15 is an analysis of the HEAL cohort. The Nurses’ Health Study analysis of post-diagnosis physical activity doesn’t appear in the manuscript. (Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. JAMA. 2005;293(20):2479-2486.)

Discretionary revisions

16. Background, 2nd paragraph: The authors define 10 MET-hrs per week as “walking 2 miles in 30 minutes at a rate of 1 mile every 15 minutes 5 days a week”. They could remove “at a rate of 1 mile every 15 minutes” as this is clear from “2 miles in 30 minutes”.

17. Methods, 2nd paragraph: the authors state that case identification was “equal to” ICD10 codes. It would be better to state that identification was “based on” ICD10 codes.

18. Results, 1st paragraph: The authors could remove “at time of” in the phrase
“mean age at time of death was…”

19. Results, 2nd paragraph: The authors state that “Of the 980 women who reported a pre-diagnostic PA level of active, 79.6% were categorized as maintained active…” This would be more clearly worded as “980 women were categorized as active prior to diagnosis (i.e., activity level of 5 or higher); 79.6% maintained their activity level post-diagnosis.” However, I strongly reiterate my comment from above that finer categories of activity would add greatly to this paper.

20. Results, 2nd paragraph: The authors state that “[t]he increase in BMI observed in this study was similar to the increase in BMI during follow-up in the NOWAC study…” The authors should clarify that they are referring to changes in BMI in the full NOWAC cohort.

21. Discussion, 4th paragraph: This paragraph seems to be a discussion of change in levels rather than a discussion of post-diagnosis levels; the authors should consider moving it to the section on change in activity.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.