Author’s response to reviews

Title: Association Between Healthy Lifestyle Score and Breast Cancer

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Author’s response to reviews:

Dear Editor,
Thank you very much for your letter informing us of your decision regarding the manuscript entitled “Association Between Healthy Lifestyle Score and Breast Cancer” (NUTJ-D-19-00277). The manuscript has been revised according to the editor’s comments. Responses to the reviewer’s comments have been provided below. Revised texts have been provided in red font. Thank you so much in advance.

Yours Sincerely,

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Reviewer #1:
This manuscript addresses an important issue in the combination of risk factors for breast cancer. I have
a few comments:

INTRODUCTION
1. Line 26-27: It may be more informative to provide a rate here (e.g. per 100,000 women) to provide some context.
2. Lines 30-33: There is actually very limited evidence that diet is related to breast cancer risk. Indeed, the study cited (Michels et al, ref 6), concluded that there was an "apparent lack of association between diet and breast cancer". This section should be rephrased in light of the evidence.
3. Line 37: There have been quite a few studies published on the link between healthy lifestyle index and breast cancer, dating from as far back as 2011 (Sanchez-Zamorano et al, Cancer Epi Biomarkers & Prevention). See also (for example) Arthur et al, 2018, Cancer Causes Control, and Heitz et al, 2018, Breast Cancer Res and Treatment. Thus, a stronger rationale for this study is needed.

METHODS
1- Lines 57-61: Can you provide more information on where the controls were actually selected from? What was the sampling frame?
2- Can you provide a rationale for only including diet, physical activity, and smoking as lifestyle factors? Why were the factors which have been specifically linked to breast cancer (overweight/obesity, alcohol consumption, hormone use, breastfeeding) not included in the index (particularly as you have information on many of these factors)? Neither smoking nor diet have been conclusively linked to breast cancer risk.
   Authors: Thank you for this great point. We added this part in the discussion. Page 19. Lines 325-334
3- The development of the HLS is described twice (lines 113-117) and lines 155-161 - the description differs between the two. For example, the diet score 1 is described as being given to those in the top 40% in line 111 and then the upper two-thirds in line 157; never smoked is score =1 in line 158-159 but ex-smokers are included in this category in line 113. Please clarify.

RESULTS
4- I'm not sure what the analysis comparing dietary intake across HLS categories shows, as diet is actually included in the HLS.
   Authors: Thank you. Although diet has been included in the scoring of lifestyle, one would be interested to know the nutrient intakes of study population across categories of HLS. Because food groups have been used for construction of diet part in the score, not nutrients. Therefore, we think that reporting information on dietary nutrient intakes would help readers to better understand the score.
5- Perhaps this paper should be reframed as describing differences in dietary intake across breast cancer cases and controls. This is perhaps the unique contribution to the literature rather than the HLS, which has some issues as I've noted. It also appears that diet is driving the significant results you find in your HLS models, as neither physical activity (contrary to the literature) or smoking are significant.
   Authors: Thank you. We have compared cases and controls in terms of dietary intakes in Table 2. In the revised version, we discussed the significant contribution of diet to the risk of breast cancer. Lines 298-314. Page 8.

DISCUSSION
6- The introduction states that "we are aware of no study examining the whole lifestyle factors in relation to BC" (line 37, see also my comment 3). However, the discussion then provides many studies which show the association between healthy lifestyle indices and breast cancer. (lines 247-261). Please clarify.
7- Line 276-278. Do you have information about the hormone receptor status of your breast cancer cases? This might help strengthen the argument made here.
Authors: We did not have information on hormone receptor status in the current study. We have added this point to our study limitations. Line 322-324. Page 19.

Minor points:
8- Abbreviations should be defined at first use (e.g. 'HLS' in abstract (line 13) not defined)
Authors: Agreed. Corrected.
9- Table 1 headings show %, however it appears that counts are presented in the table. There is then a footnote that "all values are means + SD unless indicated" - it seems that the only mean presented is age. This table could be more clearly presented.
Authors: Agreed. Corrected.