Author's response to reviews

Title: The Association of Alcohol Consumption with Mammographic Density in a Multiethnic Urban Population

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Version: 5 Date: 31 January 2015

Author's response to reviews: see over
To the Editors of BMC Cancer,

We appreciate the opportunity to submit our revised manuscript “The Association of Alcohol Consumption with Mammographic Density in a Multiethnic Urban Population” to BMC Cancer. We appreciate the thoughtful comments and suggestions that were made by the reviewers and we have made substantial revisions in response to these comments. Below, we have highlighted the major compulsory revisions and the minor and discretionary revisions suggested by the reviewers in the manuscript. The original reviewers’ comments are numbered and our responses are listed below. As a reminder, the original line numbers previously mentioned by reviewers have shifted due to manuscript edits.

Manuscript # 2703507081411279

REVIEWER 1

Major Compulsory Revisions

1. Methods, lines 77-79: Were data on hormone therapy use or menopausal status collected? As noted above, menopausal status and HT use are important determinants of mammographic density. Menopausal status and HT use should be adjusted for in all analyses, or this should be acknowledged as a limitation if data were not available.
   a. In addition to lines 135-136, we have inserted additional text that acknowledges in Methods (line 84-85) that we have collected data on “reproductive history (including menopausal status and hormonal contraceptive use).”
   b. We have also restructured analyses to include confounders that altered the association between alcohol intake and any mammographic density measure by more than 10% in the age-adjusted model; therefore, all models now include hormone contraceptive use and menopausal status amongst other confounders (see Table 2). This was also addressed in the Abstract.

2. Results, line 158: Further commentary on the woman with 70 servings/week of liquor would be useful. Did the investigators judge this report to be accurate? Were results similar to those reported in the manuscript when this observation was excluded from analyses?
   a. We have included a statement that we expect the report of 70 servings/week of alcohol to be accurate. As our primary exposure construct was categorical, this value does not alter the estimates. When our construct is modeled continuously (g/week), this value does not change overall estimates. Please see the end of the 3rd paragraph of Results.

3. Results, lines 176 and 183: Why was an additive interaction tested? Typically, a multiplicative interaction is assessed in a regression model. Further details on the approach to testing for interaction are needed in the Methods section.
   a. When examining cross-product terms in a linear regression model one is assessing additive interactions. We included detail on how we tested for interaction in the statistical analysis section of Methods.

4. Table 2: It seems counterintuitive that alcohol could be significantly associated with percent density, but not associated with either dense area or non-dense area, from which percent density is calculated. This could be due to the fact that each density measure is adjusted for a different set of covariates. Revising these results to adjust for a common set of covariates would be useful.
   a. We have restructured analyses to include confounders that altered the association between alcohol intake and any mammographic density measure by more than 10% in the age-adjusted model; therefore, all models include the same adjustments (see statistical analysis section in Methods).
b. We have also expanded the Discussion to hypothesize why different associations were found in different measures of mammographic density. Please see the beginning of the 4th paragraph in Discussion.

5. Discussion, lines 239-241: As currently written, perhaps in error, this sentence contradicts itself and also is not consistent with the findings reported. The study found no significant effect modification by race/ethnicity, though did find a suggestion that perhaps the effect was strongest in Whites. The small sample size limits the ability to test for interaction, and this should be noted as a limitation.
   a. We provide greater clarity to this point and address this limitation. Please see 1st and 3rd paragraph as well as the discussion on limitations in Discussion.

Minor Essential Revisions

6. Abstract: The abstract does not discuss the race/ethnic stratified results at all, though this was clearly a primary goal of the analysis and truly represents the unique contribution of this manuscript beyond existing literature.
   a. We have addressed this in the Abstract.

7. Background, paragraph 2: The authors nicely discuss the literature on alcohol and density and differences in alcohol consumption by race/ethnicity, but they fail to take this a step further and discuss how this could result in the association between alcohol and density varying by race/ethnicity (and why this would be important to know).
   a. We have expanded the introduction to address this concern in the 3rd paragraph of the Background section.

8. Methods, lines 69-70: Were any women diagnosed with breast cancer from the mammogram used in the study? If so, were these participants included in the analyses?
   a. We excluded 5 women who had a previous diagnosis of breast cancer (please see population in Methods) and no women were diagnosed with breast cancer from the mammogram used in the study.

9. Methods, line 78: Was BMI self-reported by participants or measured as part of the clinical interview?
   a. Participant BMI was calculated from self-reported weight and height recorded in patient’s chart. This information has been added to Methods.

10. Methods, lines 108: Please clarify if mammograms were captured on film and then digitized or if digitally acquired images were used.
    a. We collected film mammograms and then digitized them and returned the films. This information has been added to Methods.

11. Results, lines 178-183: Were the results in the analyses of dense breast area similar to those observed for percent density?
    a. In the data presented for the BMI stratified analyses in Results (6th paragraph), we have added results for dense area and non-dense area.

12. Discussion: A more thorough discussion of alcohol’s effects on estrogen is needed.
    a. We have expanded the discussion to include alcohol’s effect on estrogen in lines 272-275.

13. Conclusion: The ability to look at racial/ethnic groups that are understudied is what truly makes this manuscript unique, and these results should also be included in the final conclusion.
    b. We have expanded our conclusion in the Discussion section to emphasize the importance of the role of race/ethnicity.

Discretionary Revisions
14. Abstract: It would be helpful to provide more detail on the study design and how density was assessed.
   a. We have included detail on study design and density measures in the Abstract.

15. Background, lines 53-55: The comment on breast density legislation does not seem relevant here, and is a
distraction from an otherwise nicely written introduction.
   b. Statements on the Breast Density Inform Law were removed from the Introduction.

16. Figure 1 and Table 1 are largely redundant. Perhaps rows could be added to Table 1 indicating the
distribution of <=7 servings/week and >7 servings/week.
   a. We agree and have removed Figure 1 and added servings/week to Table 1.

Reviewer 2

Major Compulsory Revisions
1) Categorization of alcohol consumption – In the method section, what the definition of a weekly serving is, is not given.
   a) We have added more detail for the definition of servings within the alcohol intake assessment section in
      Methods (lines 101-107).

2) Categorization of alcohol consumption – Investigators could use the continuous measure of alcohol
   consumption and examine a linear trend in the association....The mean grams of ethanol/week is given for
different subgroups, but it’s not used as an exposure variable in the linear regression models.
   a) We appreciate the comment and as a secondary analysis, we now examine the linear association by
      modeling mammographic density and alcohol intake as a continuous variable. This information is
      added throughout the Methods, Results, and Discussion sections.

3) Categorization of alcohol consumption – Very few women (n=14) reported consuming the highest alcohol
   serving category. This...is inappropriate to use when examining the association in multiple subgroups due
to low power to detect differences.
   a) We understanding the limitations presented by the reviewer and we have also included analyses from
      an alternative definition of alcohol consumption (i.e. a continuous measure of alcohol consumption) in
      the text.

4) Categorization of different ethnic groups - is there a difference between Hispanic Caribbean and Hispanic
   Non-Caribbean, could the two groups be combined to form a Hispanic group?
   a) Hispanic Caribbean women are from Spanish-speaking Hispanic Caribbean countries and Hispanic
      Non-Caribbean are not from Spanish-speaking Hispanic Caribbean countries. This difference may
      indicate cultural differences in alcohol intake behavior and mammographic density. We therefore
      decided not to combine the two groups.
   b) The two groups were also distinct in our outcome measure of percent density. Hispanic Caribbean
      women had significantly lower percent density than Hispanic non-Caribbean women; therefore, we
      chose not to combine these groups (please see Results section, paragraph 2)

5) I think it would be important to investigate differences in drinking patterns amongst Natives and Non-
natives. The study categorized women who were born in the Caribbean or had at least one parent born in
the Caribbean as ‘Caribbean’ but then described all Caribbean women as Caribbean-born – how many
were not born in the US. Nativity would influence alcohol intake but also other risk factors which influence
mammographic density, such as reproductive factors, thus should be further examined here.
   a) We agree with the reviewer, and in addition to our original text detailing differences in drinking patterns
      amongst Natives and US born women (please see 3rd paragraph of Results), we also now indicate the
      percentage of women born outside the US (please see the first line of the 2nd paragraph in Results).
   b) We included nativity, as well as reproductive factors (See reviewer 1, response to comment 1), as
      potential confounders to the association between mammographic density and alcohol.
c) Lastly, we acknowledged as a limitation the inability to examine the associations between alcohol intake and mammographic density stratified by nativity given the small number of women that consume high amounts of alcohol (>7 servings/week) and are born outside the US (n=2).

6) The outlier (African Caribbean women who reports drinking 70 servings of liquor/week) should be removed and analysis repeated as it is skewing the results.
   a) See Reviewer 1, response to comment 2.

7) I wonder if using a change in estimate approach here, where there are three measures of the same outcome and different covariates are included in the three models, is appropriate as it is difficult for the reader to interpret.
   a) See Reviewer 1, response to comment 4.

8) It is not clear if a forward or backward step-wise approach was used. Was there a large effect in the fully adjusted model?
   a) We detailed our analysis, with additional information on adjustments for confounders within the statistical analysis section of Methods. Table 2 allows the readers to compare effect sizes from age-adjusted models and the fully adjusted models.

9) Table 1 should reflect the aims of the paper and thus I think it should be stratified by exposure (ever/never drinkers).
   a) We respect Reviewer’s comment; however, a major aim of our paper is that few studies have examined the association in racial/ethnic minority populations. Reviewer 1 has raised the point that our Aim is an important contribution and requires more emphasis. Therefore, as raised by Reviewer 1, we have further emphasized this aim in the Abstract and the Discussion (please see Reviewer 1, response to comments 6 and 13). Therefore, we have chosen to leave the table as is.

10) Information on other confounding factors such as nativity, contraception, history of breast cancer, reproductive factors also needs to be included - was data complete for all confounding factors?
    a) We have re-worded the first two paragraphs of the Results section to include this information. We have also acknowledged the missing data for confounders in the statistical analysis section of Methods where “Less than 3% of data on confounders was missing.” Women with a history of breast cancer were not eligible to participate in the study as detailed in population under Methods.

11) Fully adjusted model for the BMI analysis is not presented – was there strong evidence of an association in the stratified analysis after accounting for other confounding factors?
    a) We present age and BMI adjusted models to mitigate over-adjustment in our stratified analyses (discussed in the first paragraph of the discussion). In addition, we emphasize that fully adjusted models were essentially the same in the 6th paragraph of the Results section.

12) I don’t think this study, using the alcohol measures currently presented, is suitable to assess effect modification by ethnicity in the association between alcohol and mammographic density. The message in the paper is not consistent, for example in the results section (line 172/173) you state that no association was observed in African American women, in contrast to your comment in the discussion (line 251) where a positive association between alcohol intake and percent density in African American women is described. In Figure 2 there is little evidence of an association in African American women. Why are Hispanic Caribbean women included in the analysis when no participants report drinking >7 servings/week?
    a) We acknowledge that our message was unclear and therefore we have edited the discussion to have greater clarity and consistency (please see Reviewer 1, response to comment 5). As few studies have examined the association in racial/ethnic minority population; we feel it important to include all racial/ethnic groups with large enough sample sizes to provide preliminary evidence.
    b) Regarding Hispanic women, though they are light drinkers, light drinking (≤7 drinks/week) is associated with increased breast cancer risk and therefore, may also be associated with increased mammographic density.
c) As raised by Reviewer 1, we have emphasized the limitation of testing for interaction by race/ethnicity (Reviewer 1, response to comment 5).

13) In the discussion a new analysis is introduced (line 265-268) – this should be in the methods and results section.
   a) This is not a new analysis. The results were from the reference de Vogli et al. To eliminate confusion, we have removed some of the detail of this study’s findings.

14) The discussion does not address why different associations were found in different measures of mammographic density (percent versus absolute dense area) and how this relates to BMI and other studies.
   a) We have expanded the Discussion to hypothesize why different associations were found in different measures of mammographic density, including an expansion of our discussion regarding BMI. Please see the beginning of the 4th paragraph in Discussion and the last section within our discussion on limitations.

Minor Essential Revisions
15. N to be included in Table 2 and Figure 2 and 3.
   a. We have included N to all tables and figures

Warm Regards,

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