Reviewer’s report

Title: Coronary Heart Disease and Mortality Following a Breast Cancer Diagnosis

Version: 1 Date: 14 Apr 2020

Reviewer: Na-Jin Park

Reviewer's report:

The revision is much improved and reads well.

Here are some areas that need clarification.

1. Radiotherapy is listed as potentially cardiotoxic therapies of interest in the background as well as goal statement. Authors defined receipt of breast cancer treatment by chemotherapy, left-sided radiation, hormone therapy, and Herceptin in the Methods and then went on 8 categories of medications. However, Table 2 shows medications, but no data on (left-sided) radiation. The majority of breast cancer patients are likely to receive radiotherapy across all stages. If this is a result of missing data, it is critical to clarify. I also wonder if this missing has led to very small number of patients received any cancer treatment. Please clarify this in Table 2 or text.

2. Missing data from the EHR is a limitation as addressed. I assume that CVH metrics presented in Table 2 would be based on some missing data. You may include one more column for sample size for each or including missing category. However, my recommendation is to revise Table 2 showing distributions by outcomes, both CHD and death, instead of characteristics of whole study population.

3. Are 3 age groups based on age at breast cancer diagnosis? Or age at baseline consistent with time at collecting CVH variables (within 5 years prior to diagnosis)?

4. Table 2 shows that diabetes appears to be a major comorbidity in this study population. Older age and black race are associated with poor baseline health (e.g., diabetes and hypertension) as well as with higher CHD and death as you reported. Older age is associated with less aggressive treatment with early stage disease, and black women are likely to receive more aggressive treatment (i.e., chemotherapy) with advanced disease. Because of such strong evidence, there may be confounding effect bigger than we think. Also, small % of treatment puzzles me in that perspective. I recommend create a new table showing distributions (frequency and percentage) of CVH (0, 1, 2) and cancer treatment (yes, no) by each age group and race.

5. Although similar synergistic interactions of CVH and treatment on CHD and death are main focus in Fig 2, I also notice that independent effect of treatment is bigger on death but not on CHD. This may be due to all-cause death that included death from breast
cancer. Black patients are more susceptible to death from breast cancer. Again, this is a good point for further discussion.

6. If you provide sample sizes in Table 1 as mentioned above, Fig. 1 can be presented by %, not in count. Current presentation took me some time to figure out. Also, present age by order (20-40, 40-60, &gt; 60) in Fig. 1, as presented elsewhere in the manuscript.

7. Authors choose to show the performance results for death prediction in Table 3 as supplementary. Due to some confounding potentials addressed above, I am interested in CHD prediction not death, which is also potentially more relevant to preventive interventions in clinical settings. Please present data of CHD prediction results in text instead of current death information. Supplementary table may include both results or one (I prefer CHD in that case). Also follow instruction for supplementary materials.

8. In statistical analysis, lines 19-28 are lengthy and unclear.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

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