Author’s response to reviews

Title: Obesity and breast cancer outcomes in chemotherapy patients in New Zealand – a population-based cohort study

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Author’s response to reviews:

BCAN-D-17-00920

Obesity and breast cancer outcomes in chemotherapy patients in New Zealand - a population-based cohort study.

General. The paper has been substantially revised, and expanded in accordance with the reviewers’ comments. Several references have been added. The track changes file is therefore complex. New clean files have been submitted.

Editor Comments:

In addition to the comments below, when revising your manuscript please include section headings in the methods to highlight the different sections. Please also include the descriptions of the sub-group and sensitivity analyses in the statistical analyses section of the methods and describe only the results of these analyses in the results.

Changes made in methods section.
Reviewer reports:

Joanne Kotsopoulos (Reviewer 1): BCAN-D-17-00920 Obesity and breast cancer outcomes in chemotherapy patients in New Zealand - a population-based cohort study.

The current study is a well-powered and robust analysis of obesity and breast cancer outcomes, as well as overall outcomes, among breast cancer patients from New Zealand. The authors describe the methodology quite well, along with the statistical analysis; however, the discussion lacks from critical interpretation of prior studies as well as of their findings.

Some specific comments are as follows:

1. Introduction: although referencing a meta-analysis is a simple way to summarize prior findings, there needs to be more focus on key findings from the larger/well-designed studies and the existing literature surrounding why obesity might impact prognosis.

   The introduction has been expanded to include these issues (and discussion also).

2. Results: the tables and figures are well displayed; however, the paper refers to single factor HR's while the tables refer to Crude HR's. This should be consistent, and the Crude HR should be replaced with age-adjusted HRs.

   Tables and texts changed to ‘unadjusted’

3. Results, Figure 2: did the frequencies differ by ethnicity? If yes, can you please provide p values?

   Yes: now given in Table and text; cross reference added

4. Results, Figure 3: the authors should show the risk estimates and p-values and provide more description on what is being displayed in this figure.

   Added, with cross reference to related Table

   Also, some more discussion and interpretation of these estimates is needed in the text; particularly given the impact of low BMI on favorable outcomes. This should not be ignored.

   Added in results and in discussion
5. Results, Tables/Figures: a little more information in the legends are needed to ensure these are stand-alone documents. For example, what are the adjusted HRs adjusted for?

Details added to each

6. Results: where are the results for the subgroup analyses? I especially think the analyses stratified by ethnicity are important to show and discuss. What about the pre- vs post-menopausal analyses? Given the literature showing menopausal status as an effect modifier, why was this not discussed further?

New table 4 added, with related text.

7. Discussion: The authors discuss prior findings; however, they do not critically discuss key findings from the larger, more impactful studies. It would be helpful to the reader to understand the landscape of the current evidence regarding obesity and breast cancer outcomes. Also, there is no mention of mechanisms mediating such associations.

Added in discussion, and also in introduction.

Sarah Nechuta (Reviewer 2): BMC Cancer Review

Obesity has been extensively studied in association with breast cancer recurrence and survival. However, gaps in knowledge remain including understanding changes in adiposity over time, mechanisms underlying the role of obesity in breast cancer outcomes and metastasis, and the associations in understudied racial/ethnic groups. This study addresses one of these limitations as stated by the authors as "the first assessment of obesity and breast cancer outcomes...New Zealand patients treated with chemotherapy". Overall, the study methodology is sound. The findings are that obesity is not associated with breast cancer recurrence or survival outcomes in this population.

It is important the authors make clear that this is based on one measure of BMI and the timing of measurement in relation to diagnosis.
Details added and discussed.

Further, as findings are null, inclusion of a formal evaluation of statistical power based on number of events for at least one of the primary outcomes is needed.

We disagree, as we feel that the presentation of a post-hoc power calculation is inappropriate: see, for example, [1-3]. We discuss the power limitations of the study, using the confidence limits of the results.

Finally, some limitations in the methods and scientific writing need to be addressed as detailed below.

Abstract,

1. In Background, last paragraph, replace "series" with cohort 2. Methods section is unclear. "followed for life?" replace with last follow-up data and provide median follow-up time for the cohort.

Done

3. It is unclear that the primary analysis was conducted among 1049 women (and the rational for this) based on how the methods section in the abstract is written.

Revised slightly, but it seems clear

4. Provide timing of BMI assessment in relation to diagnosis, specifically mean and range.

Timing given. Mean and range not given as precise time of recording not recorded; comment added in discussion

5. Results, need a "and" in between "type of surgery" and "receptor status" when describing the subgroup analyses

Done
6. Conclusion, include the timing of BMI to help with interpretation, such as obesity at time of treatment initiation or at least postdiagnosis.

Done

Background

1. The last sentence of the first paragraph of the introduction is unclear. Chemotherapy patients are mentioned, but then the reduced response is described in relation to aromatase inhibitors, which are not a type of chemotherapy.

Modified

3. Replace "series" with cohort to be more clear in the first sentence of the second paragraph

Done

4. "So had virtually complete data on BMI"….why does restricting to women who received chemotherapy result in complete data on BMI, this is unclear.

Removed ‘so’; comment added in discussion.

Methods

1. First sentence of the methods resident should be "residents"

Minor point, but we disagree: ‘resident in the region’ is an adjectival phrase.

2. Information on some of the data used in the analysis is missing. All variables mentioned in Table 1 should be described in the methods with the data source. Specifically, information on measurement is lacking for menopausal status, facility, cancer treatment (chemotherapy, hormonal therapy, radiotherapy, surgery), and outcomes including recurrence, metastasis, and mortality. Is any information available on the validity of recurrence/metastasis outcomes? In
addition, information is needed on how data were collected on anthropometric measurements and on timing of measures in relation to diagnosis of breast cancer.

Details added in methods, and in discussion

3. Was the proportional hazards assumption evaluated?

Yes; added in methods, results, and discussion.

Results

1. The first paragraph has missing parentheses and could use some editing.

Done

2. In page two of the results, the sentence "Despite this, the proportion of obese patients tended to increase with more advanced stage...." Is repetitive with the sentence below this that states "Obesity tended to be greater in women with advanced disease..)."

Revised

3. In the paragraph under the heading "Outcomes in relation to BMI…” The whole follow-up period is described as "12 years" but earlier in the abstract 14 years is mentioned.

Corrected: 14 is correct
Tables

1. BMI units need to be mentioned at least in the title of each table. For example, Table 1 has no units.

2. Table 2 and 3 both need footnotes describing adjustment factors.

3. Table 2, add the word therapy after "hormonal" in the title. Table 3, provide a footnote providing the n in each subgroup (a and b), that is excluded from the table.

All suggested additions done.

Elisabetta Rapiti (Reviewer 3): This is an interesting article investigating different outcomes in a population of New Zealand breast cancer patients according to BMI, focusing in particular on the effect of obesity among women who were treated with chemotherapy.

Contrarily to the great majority of published literature on this topic, the results of the study show no association between obesity and breast cancer mortality, overall mortality, recurrences or metastases.

The main problem is relative to the categorization of the BMI and the choice of the reference category. The authors categorize BMI in 5 categories with the first category including patients with BMI <21 and the reference category being the patients with BMI 21-24. According to the WHO international classification of BMI the so-called "normal" or "lean" category is "18.50-24.99", and is the category chosen as reference from most studies, while patients <18.50 are considered underweight. The choice of the authors to include in the first category a number of patients with "normal" BMI is likely due to the very low number of true underweight patients in the study sample (<18.5 n=8). Given that the focus of the paper is on obesity patients, I think the authors should not include these 8 women in the analysis and should compare the other categories to the category of patients with 18.5-24.99 including also the remaining 73 patients of normal weight.
We considered this carefully prior to the analysis, and we disagree. The WHO grouping is used mainly in relating obesity to the occurrence of disease and to mortality effects at the population level. The literature on outcome in breast cancer patients shows a non-linear pattern with, in the main meta-analysis, minimum risk at around BMI 20-21 [4]. So we wanted to assess risks in a group of minimum BMI, and also to assess how risk changed in groups with higher BMI, so using a reference group with low, but not minimum, BMI was appropriate. Many studies of breast cancer prognosis have used this approach.

Detailed comments.

Methods:

The authors should give more details on the Waikato clinical breast cancer register and on the cancer registry ascertainment of vital status and cause of death. In particular they should indicate if there were patients lost to follow-up.

Details added in methods. All patients are censored at the date of last follow-up, or at death.

For the estrogen and progesterone receptor status it would be useful to know at which level they were considered positive.

Added, in methods

The authors state they adjusted the Cox models for "all the baseline characteristics except Her-2". Could they be more explicit and list the variables included in the models (is primary treatment also included and if yes how?).

Done

Why did they choose to include all the variables? Only few variables differ according to BMI. Are all the baseline characteristics associated to the outcomes? The choice to include in the model all the variables may result in an overadjustment and problems of collinearity between (ex. age and menopausal status).
We included all these variables as they have all been shown to be associated with breast cancer outcomes in our extensive studies using these data sources, and they are all considered clinically relevant. The results appeared stable, and results with reduced models gave very similar results.

Results:

The percentages of obese women in the text, second paragraph, are 69%, 55% and 30% while in Table 1 they are 69%, 57% and 33%.

In the next page in line 7 you say "Obesity was marked more common in patients treated in the private health care sector than in the public sector." While in table 1 is shown the opposite.

In table 1 the column of "% obese" seems not correct for most of the variables.

Also the percentages in the rows "Total breast conserving surgery", "Total mastectomy", "Total with RT" and "Total without RT" are not correct.

Table 1 has been revised, and it and the text are now consistent.

In Table 2 and 3 the authors should add a footnote to specify the variables included in the adjusted models.

Done
References


