Author's response to reviews

Title: Does comorbidity explain the ethnic inequalities in cervical cancer survival in New Zealand? A retrospective cohort study

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Author's response to reviews: see over
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Dr Christina Chap
Executive Editor
BioMed Central

Re: MS: 1119583359408355 “Does comorbidity explain the ethnic inequalities in cervical cancer survival in New Zealand? A retrospective cohort study” Naomi Brewer, Barry Borman, Diana Sarfati, Mona Jeffreys, Steven T Fleming, Soo Cheng and Neil Pearce

Dear Dr Chap,

Thank you for considering our manuscript for publication in BMC Cancer and for sending us the comments from the three reviewers.

We here respond to these comments.

Reviewer 1: Mette Nørgaard

Reviewer 1 raises four major compulsory revisions and two minor essential revisions.

Major compulsory revisions:

1. “The authors present five different ways of measuring comorbidity”
   We agree that we have presented very detailed findings for the various measures of comorbidity, perhaps more than was needed to answer the main question that the paper is addressing (i.e. whether comorbidity explains the ethnic inequalities in cervical cancer survival in New Zealand). We did this because, to our knowledge, this is the first time that such detailed analyses of comorbidity have been conducted in New Zealand. However, we agree that this may not be necessary in the context of the current paper. Furthermore, to try to decide whether one measure was superior to the others would be difficult, if not impossible, in the current paper, because the various measures all give similar results (in terms of their effects as confounders of the ethnic differences in survival), and there are not sufficient numbers to attempt to distinguish between them. In addition, such analyses would require a separate paper, with different aims to the current one. As suggested by Reviewer 1, we have therefore noted in the manuscript that the one-year and five-year look-back periods gave similar findings, and that the Charlson and Elixhauser methods gave similar findings, and that we have therefore only presented the findings using the Elixhauser method, and some of the individual comorbid conditions on which this method is based. We have amended the tables to reflect these changes but without using “track changes” as the tables would have become very difficult to read. We would like, if
possible, to include the full set of analyses as a set of web-based tables, or to note that they are available, upon request, from the authors.

2. “...Patients with cervical cancer and comorbidity will...have a higher mortality of causes other than cancer...”
   We have added a sentence to the first paragraph of the discussion to address the issue of more deaths from other causes being expected in women that have a comorbidity as well as cervical cancer.

3. “In the study population 555 women were excluded because of lacking FIGO stage...excluding them is a loss of usable information”
   We agree that it would have been preferable to not have to exclude these women; however, our previous analyses\(^1,2\) have shown that it is necessary to adjust for stage (since it is an important confounder), and the reality is that the Cancer Registry does not have stage data for these women. As Reviewer 2 notes, excluding these women is unlikely to be problematic because we are making a comparison within the group of women who do have stage data, and “there appears to be minimal potential for bias”. On the other hand, trying to include them (e.g. by using methods to impute the missing data) would involve major assumptions and is likely to introduce significant bias, while achieving at best a modest increase in the study precision because of the larger numbers involved. We have therefore, instead, conducted a basic sensitivity analysis (as suggested by Reviewer 1 and Reviewer 2) by conducting three sets of analyses: (i) the analyses included in the paper in which we have adjusted for stage and excluded the women with missing stage data; (ii) analyses including the women with and without missing stage data, in which we have adjusted for stage with a dummy variable representing the women with missing stage data; and, (iii) analyses including the women with and without missing stage data, but not adjusting for stage. The three sets of analyses yielded the same patterns. For example, the “crude” hazard ratios (HRs) for Māori women were 1.56 (as shown in Table 4), 1.82, and 2.11, respectively for the three sets of analyses (these differences are not surprising since the third analysis is not adjusted for stage and the second analysis is only partially adjusted for stage, whereas the first analysis (excluding women with missing stage) is fully adjusted for stage, and is therefore likely to be the most valid). Adjusting for comorbidity using the Elixhauser method changed these estimates to 1.55, 1.80, and 2.06, respectively, and adjusting for the 12 individual comorbid conditions changed them to 1.44, 1.74, and 2.00. Thus, the patterns are the same in all three analyses, but we have used the first method (excluding women with missing stage), because it is necessary to adjust for stage, and this is the only approach that enables us to do this validly. We have, however, noted in the text that we tried all three methods and they yielded similar patterns.

4. “A rule of thumb is that there has to be at least 10 cases per confounder variable.”
We have removed Table 3 from the paper. However, as noted above, we would like, if possible, to include the full set of analyses (including this table) as a set of web-based tables, or to note that they are available, upon request, from the authors.

Minor essential revisions:
1. “A description of how time of follow-up is measured is lacking.”
   We have added a description of how time of follow-up was measured to the penultimate paragraph of the Methods section (page 7).

2. “In table 3 the reference group is not clear...”
   As noted above, we have now removed Table 3 from the paper. However, since, as stated previously, we would like to include the full set of analyses (including this table) as a set of web-based tables, we have added a footnote to the table making it clear that the comparison groups are those women that do not have that individual comorbidity.

Reviewer 2: John Condon

Reviewer 2 is generally positive about the paper but raises one minor essential revision and three discretionary revisions.

Minor essential revisions:

1. “One of the main potential weaknesses of the study is the large proportion of women excluded from [the] analysis because of missing data.”
   We have responded to this issue above in point 3 of the ‘Major compulsory revisions’ requested by Reviewer 1. After undertaking the basic sensitivity analyses, the patterns are the same in all three analyses, but we have used the first method (excluding women with missing stage), because it is necessary to adjust for stage, and this is the only approach that enables us to do this validly. We have, however, noted in the text that we tried all three methods and they yielded similar patterns.

Reviewer 2 also notes the discrepancy between the text (Results, para 2) which states that 555 women had missing FIGO stage data, and Table 1 which states that 621 women had missing stage data. As the reviewer suggests, there is some overlap between the women with missing stage data, those that were registered only on the date of death, those who could not be assigned a socioeconomic position (NZDep2001), and those who were registered after 30 June 2005 (and therefore had a potential follow-up time of less than six months). We have amended the text to clarify this.

Discretionary revisions:

1. “Results para 1...”
This sentence has now been removed since we are no longer discussing the Charlson Comorbidity Index or five-year look-back period findings.

2. “Results para 4...”
We have left the list of thirteen individual conditions and their HRs in this paragraph because Table 3 has now been removed.

3. “The ‘Conclusions’ paragraph repeats points made in the previous paragraph...and could be deleted”
It is our understanding that it is BMC Cancer style to include a ‘Conclusions’ paragraph. We have therefore not deleted it as suggested by the reviewer but have amended the previous paragraph to remove the repetition.

**Reviewer 3: Lois Ramondetta**

Reviewer 3 is also generally positive about the paper but raises four minor essential revisions.

Minor essential revisions:

1. “The authors should...provide numbers re incidence and mortality for Cx Ca in New Zealand”
Incidence and mortality rates for cervical cancer for Māori, Pacific and ‘Other’ women are already provided in the first paragraph of the Background. Reliable estimates for Asian women in New Zealand are not available.

2. “[R]e write the paragraph number two on page 6...”
We have rewritten the paragraph to make it more clear.

3. “[E]xpand on mortality from other causes referenced in the first sentence of the discussion.”
As noted above for Reviewer 1, we have added a sentence to the first paragraph of the discussion to address the issue of more deaths from other causes being expected in women that have a comorbidity as well as cervical cancer.

We thank the reviewers for their useful comments, and we hope that the revised manuscript is now acceptable for publication.

Thank you once again for considering this manuscript.

Yours sincerely,
Naomi Brewer

**References**