Author's response to reviews

Title: Ovarian cancer survival population differences: A "high resolution study" comparing Philippine residents, and Filipino-Americans and Caucasians living in the US

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The Editors
BMC Cancer
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Dear Editors,

Thank you very much for your kind offer to consider a revised version of our manuscript, "Ovarian cancer survival population differences: A “high resolution study” comparing Philippine residents, and Filipino-Americans and Caucasians living in the US".

We are grateful for the reviewers’ constructive suggestions and have revised the manuscript accordingly (as itemized in an attached document). Please let us know if further changes should be needed.

We have also updated our results, based on refinements done on the computing algorithms. The changes were minor and have not affected the conclusions of the paper.

Again, thank you very much for your review and your interest in this work.

Yours sincerely,

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RESPONSES TO REVIEWER COMMENTS:

Reviewer: Ranjit Manchanda

Reviewer’s report:

Reviewer’s Comments

ABSTRACT

BACKGROUND-
The authors state – “In contrast to most other forms of cancer, surprisingly similar survival rates have been reported for ovarian cancer in developing and developed countries.”

This is a broad statement. The source of this statement in the text (reference 2) only mentions survival rates in some countries. They may wish to change/qualify this to something along the lines “In contrast to most other forms of cancer, data from some developing and developed countries show surprisingly similar survival rates for ovarian cancer.”

Answer: The statement has been revised as suggested by the reviewer (page 2 paragraph 1, lines 1-2).

RESULTS SECTION

The authors may wish to consider providing SE or CI for Relative and absolute survival rates as has been done for hazard ratios.

Answer: We added the SE for the absolute and relative survival rates as suggested (page 2, section 3, lines 2-4)

CONCLUSIONS-
The authors state-“Multivariate analyses disclosed strong survival disadvantages of Philippine residents compared to Filipino-American patients, which most likely reflect differences in access to chemotherapy. Prognosis is no worse among Filipino-Americans than among Caucasians living in the US.”

The authors may wish to consider modifying this statement.

With respect to the first sentence, it is difficult to conclude from the data presented that the differences are due to or most likely due to differences in access to chemotherapy. This may be only one of the contributory factors. Other factors could include type of chemotherapy, level of surgical expertise, treatment in gynaecological cancer centres by multidisciplinary teams, post-surgical residual disease, grade of disease, use of evidence based treatment guidelines, etc.

With respect to the second sentence, the data show that survival is not statistically significantly different between Filipino Americans and Caucasians.
‘Prognosis’ could also include disease free recurrence, quality of life, etc. The authors may wish to consider a more factual statement.

Answer: The statements were modified (page 2, last section).

PAPER

BACKGROUND SECTION

Page 3

In contrast to most other cancers, five-year relative survival rates were surprisingly similar in developed and in developing countries, ranging from 31 to 42% and from 16 to 51% respectively.

The authors may wish to qualify this slightly be suggesting that limited data from some developing and developed countries suggest that .................

Answer: The statement was modified (page 3, paragraph 2, lines 3-5).

The authors may wish to provide actual incidence and mortality rates for ovarian cancer for the 3 populations studied.

Answer: Incidence and mortality rates were added in the background section (page 3, paragraph 1, lines 7-10).

METHODS SECTION

Under SEER 13 – the authors mention exclusion of insitu ovarian cancer cases.

It is not clear to me what this means. Ovarian carcinoma insitu is not a recognised entity. Please clarify.

Answer: The “in situ” ovarian cancer cases referred in the statement are cases which were coded as such, based on the behavior code in ICD-O-3, in both the Philippine and SEER datasets. Although this might not be a recognized entity, there were a few cases coded as such in the databases.

The authors mentioned Hispanics being included among Caucasian population. Please clarify. What proportion of the Caucasian population in the study were of Hispanic ethnicity? Were Hispanics identified excluded? This is not clear and is of relevance as it will create a bias and affects the ethnicity based inferences being drawn. If the Caucasian population includes Hispanics then this has not been brought out in the discussion and should be clearly mentioned.

Answer: Based on the definitions used by SEER, a person with a Hispanic surname/origin may be of any race. Of Caucasian ovarian cancer cases, 10% were identified to be of Hispanic ethnicity. Sensitivity analyses done showed that differences of survival estimates between the Caucasian population with and without Hispanics were less than 1%.
Under Manila and Rizal Cancer Registries-
What is the total sample size from which the 200 sub sample cases were randomly selected?

*Answer:* The total number of ovarian cancer cases in 1993-2002 in the Philippine registries is 2,898. A short statement was added in the text (page 5, last paragraph, first line).

The authors state that complete follow up information was obtained only from 35.8% and some follow-up information from 43.8%. What follow-up information was missing? Were the remaining 20.4% all identified as dead via death certificates? Did the death certificate mention cancer as the cause of death or ovarian cancer as the cause of death?

*Answer:* Follow-up information referred here is survival time. The remaining 20.4% were patients whose only available data pertain to the time of diagnosis, but were not death certificate cases. These were identified through medical records and other registries within the hospitals. The death certificates mentioned cancer as the cause of death. This is now explicitly stated (page 5, last paragraph, lines 5-6).

Data Analysis-
Could the authors elaborate on censoring

*Answer:* A statement on censoring was added (page 6, last paragraph, line 9).

Can the authors clarify which WHO classification is being used e.g. ICD10, C56 (International Classification of Diseases, 10th Revision; Code: C56)

*Answer:* A statement was added in the methods section (page 9, first paragraph, lines 3-6)

Page 7 (last para) Does other types include-Brenner, granulosa cell tumors, germ cell tumors, sex cord stromal cell tumors and NOS? Could the authors elaborate a bit more on the classification and types of tumors.

*Answer:* A statement was added in the methods section (page 9, first paragraph, lines 3-6)

RESULTS and DISCUSSION
One of the extremely interesting findings was that almost half (45% Fillipino and 50% Fillipino Americans) had early stage disease or Stage1&2 disease and that almost half the tumors presented at <50yrs in these population groups. This is in contrast to most data on sporadic ovarian cancer which suggest that it occurs mainly in the post-menopausal age group and predominantly presents at late stages (Stage 3 & 4). Hence it is incorrect to state that more than half the cases were diagnosed in the advanced stages in all three groups. (The number of cancers in Stage 2 alone were also fewer in the Caucasian population but this difference was probably not statistically significant.)

*Answer:* The statement was revised (page 10 paragraph 2 lines 4-6).
This should be hi-lighted more and brought up again in the discussion section and reasons for this postulated or explored. Ovarian cancer is a heterogenous disease and this may reflect differences in heterogeneity and tumor biology in different subpopulations?

Answer: A statement was added in the discussion (page 14 paragraph 2).

With respect to tumor histology it was unclear if the category ‘others’ included ‘NOS’? There is no % for NOS in table-2.

Answer: The “NOS” was not included in the category “others”. There was no proportion given, as the proportions reflect the histology distribution of those with known histology. We added a footnote to Table 1 for clarification.

The difference in both absolute and relative survival (not only relative survival as mentioned in the text) was different between groups 1 and 2 for ages 50-70. (page 9 second para).

Answer: The statement was revised (page 11, first paragraph, last 3 lines)

Why was the survival different in the age groups 50-70 only and not <50 or >70? This does not seem to have been explored in the discussion? An age wise subgroup analysis of histology and stage may provide some indication?

Overall the proportion of epithelial ovarian cancer (EOC) is not very different in the 3 groups. But would looking at the histological distribution in those <50 also show a similar / different picture? The authors may wish to explore this and clarify?

Answer: Regarding the previous two points, additional statements were added in the discussion (page 12, paragraph 2).

Although a significantly higher proportion of Filipino patients compared to the other two population groups received radiotherapy, the clinical significance / inference from this is uncertain. Given the similar proportion of EOC tumors (mainly treated by chemotherapy not radiotherapy) in all the groups, the reason for this is not clear. A sub analysis of histology of RT treated tumors may provide some clue? This could reflect differences in practice and standard of care in the different countries. These issues can be brought up in the discussion section?

Answer: Radiotherapy was added to make use of all available comparable information. In the Cox proportional hazards analysis (Table 4), the addition of radiotherapy in the models had only a small effect in the estimation of relative risk.

The limitations to the study should be emphasised more. Not controlling for grade of disease, chemotherapy access as well as protocols followed, surgical expertise, treatment by gynae-oncologists working in multidisciplinary teams, level of residual disease, evidence based treatment, socioeconomic status, tumor heterogeneity may contribute to the differences observed.

Answer: The limitations section was revised (page 14, last paragraph, lines 2-5; continued to page 15, first paragraph).
RESPONSES TO REVIEWER COMMENTS:

Reviewer: Amy Finch

Reviewer’s report:

Minor essential revisions

1. A brief description of ‘high resolution approach’ would benefit readers not familiar with this term.

Answer: We expanded the description of “high resolution approach” as suggested (page 4).

2. It would be helpful to have a brief explanation of the methods used for the ‘random’ selection of subject from the registries in the Philippines. Is it possible that this selection in anyway influences survival?

Answer: A statement was added (page 5, last paragraph, lines 1-4).

3. The authors state that there was complete 5 year follow-up for 35.8% and some follow-up data for another 43.8%. What data or information is required to qualify as some follow-up data? Further, it would be helpful to know what is considered to be invalid data.

Answer: A statement was added (page 10, first paragraph, lines 5-6).

4. For the 26.2% that were excluded from the Manila and Rizal Cancer Registries, what outcomes would be expected for these excluded patients and how could this affect the findings?

Answer: A statement was added in the discussion (page 15, last paragraph).

5. The authors state that a sub-analysis of chemotherapy was done for the Philippine residents showing that not receiving chemotherapy was related to the risk of death (RR 1.54; 95% CI 1.22-1.94). What percentage of Philippine residents in this study received chemotherapy? Roughly, how does this compare to the expected rate of chemotherapy in US residents? The authors did state that chemotherapy was not available for the populations represented by the SEER data.

Answer: A couple of statements were added in the results and discussion sections (page 10, last paragraph, last sentence; page 12, last paragraph, lines 4-5).

6. Relatively few subjects from all three groups did not receive surgery. As these subjects likely had late stage cancers, they may add little to the survival data as stage is known. Is there any reason Philippine residents would not have surgery aside from late stage at presentation?

Answer: High costs and perceived poor chances of survival are some reasons why Philippine residents might not have availed of any treatment, including surgery. A section in the discussion was revised to highlight this part (page 14, first paragraph, lines 3-5).
Discretionary revisions

1. The description of the amount of 5 year follow-up date available and the exact subject numbers (end of the second paragraph and third paragraph of Manila and Rizal Cancer Registries) was included in the methods section. This could be moved to the beginning of the results section.

Answer: The pertinent sections were moved to the beginning of the results section (page 10, first paragraph).