Author’s response to reviews

Title: Most women diagnosed with cervical cancer by a visual screening program in Tanzania completed treatment: evidence from a retrospective cohort study

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Author’s response to reviews: see over
June 18, 2014

Dr. Martin O'Flaherty
Section Editor
BMC Public Health
BioMed Central
236 Gray's Inn Road
London WC1X 8HB
United Kingdom

Re: MS-1243412312102648
Most women diagnosed with cervical cancer by a visual screening program in Tanzania completed treatment: evidence from a retrospective cohort study

Dear Dr. O'Flaherty:

Thank you for your letter dated May 19, 2014, regarding the above-referenced manuscript. The reviewers’ comments were pertinent and insightful and have helped us to improve our original manuscript submission. We are pleased the reviewers felt the manuscript was interesting and contained valuable information.

The attached pages detail our responses to the points raised by the reviewers. The reviewers’ comments are listed in bold followed by our responses. Edits to the manuscript are shown with tracked changes.

We believe this revised manuscript is much improved over the original and hope this study is now acceptable for publication in BMC Public Health.

We look forward to hearing from you.

Sincerely,

Amr S. Soliman, M.D., Ph.D.
Professor and Chair of Epidemiology
Director, Cancer Epidemiology Education in Special Populations Program
Reviewer 1

1. In Tables 1, 2 and 5, it would aid interpretation if the percentages provided were column percentages rather than row percentages. We thank the reviewer for the comment. We have changed the row percentages to column percentages in Tables 1, 2, and 5.

2. Tables 3, 6 and 7: how were the variables in the final models selected? This is not explained. It is recommended that the authors not use statistical significance exclusively to select variables in the final models. Rather, variables that are considered potential confounders should be included even if they are not statistically significant. We agree that statistical significance should not be used as the sole means of selecting variables for final models. We considered statistical significance, but also related variables (e.g., age and gravidity, education and occupation). We kept place of residence in the final model as it may be a confounder.

3. Table 6: Follow-up time has an OR of 1 with CI of (1-1). Our guess is that the units are days, which is too small a unit to be meaningful. Perhaps use weeks or months as the unit. We thank the reviewer for this suggestion. We have updated Table 6 to reflect an OR based on a unit of one week instead of one day.

Reviewer 2

Major Compulsory Revisions

1. Dar es Salaam is referred to many times in the document. Some explanation for whether this is a village, a city, a region and its relationship to ORCI would be helpful to put the comments in the manuscript into perspective. Is ORCI the only cancer centre in Dar es Salaam or are there other centres? Dar es Salaam is one of thirty administrative regions of Tanzania, and is also the largest city in Tanzania with a population of 4.4 million. ORCI is centrally located within the region and city, very close to the Dar es Salaam city center. ORCI is currently the only specialized cancer treatment center in Tanzania. We have added this explanation in the Methods section.

2. It would be helpful to clearly define "follow-up." Is it the date of the VIA to the date of starting radiation? We have noted in the Methods section that follow-up time was defined as the time between the screening visit date and the first appointment at the treatment clinic.
3. **Tables** - Usually a table has a total per section by column; however, you have chosen to do the total by row. It would be more meaningful to the reader to do it by column and variable.
   We thank the reviewer for the comment. We have changed the row percentages to column percentages in Tables 1, 2, and 5.

4. **Table - age - is this mean or median?**
   All tables use the mean age. We have labeled this at the top of the column.

5. **Is the year of screen the same as the year the cancer was diagnosed?**
   Yes, we assume the cancer is diagnosed at the screening visit, then referred on to the treatment clinic, so the year of diagnosis is the same as the year of screening.

**Minor Essential Revisions**

1. **Pg 5 Methods:** The authors raise the issue of an ORCI screening card. Please define what personal health information is available on the ORCI screening card.
   The ORCI screening card includes information on the screening results (VIA/VILI/colposcopy/biopsy) and follow-up instructions (e.g., referred for treatment, antibiotics prescribed). The most important element was the screening visit number, which allowed linkage back to the screening clinic database which had the same screening results digitized. We have included this clarification in the Methods section of the revised version of the manuscript.

2. **Pg 7** - The first sentence was hard to follow - would suggest restructuring ie., In multivariable models (after adjustment for age and disease stage), education, timing...
   We agree with the reviewer and have restructured it to make it easier to follow.

3. **Pg 8** - Do all women get external beam radiation and only a variable amount of brachytherapy? It was not clear.
   External beam radiation plus brachytherapy was the standard of care when the primary goal of treatment was cure, and external beam radiation alone was the standard of care for palliative cases. However, some curative cases were not given brachytherapy because the equipment was inoperable. We have clarified this in the discussion section.

4. **Pg 8** - Is there a policy reason to explain the findings of the 15% decrease in radiation completion?
   It is possible periodic breakdown of the radiotherapy machines contributed to treatment non-adherence. Changes in health education given to women attending the screening clinic during the study period may also have influenced treatment completion. Further research is needed to explore these hypotheses and better understand the reasons for the decrease in radiation completion.

5. It would be helpful to describe the VIA service ie., do women receive invitation to attend beginning at a certain age; are patients referred from other clinics ie., opportunistic vs population based? How long has VIA screening been going on? Is
it a once in a life time screen or every 5 years etc?
In the first several years of screening clinic operation, the activity was a clinical study, where women were actively recruited from Dar es Salaam for participation and it was not a population-based effort. Later, especially after the end of the study in 2007, women were generally not actively recruited. VIA was not offered prior to November 2002. Only a couple of women in the database had been screened more than once. We have clarified these points in the Methods section.

Discretionary Revisions

1. The manuscript is long and there are 7 tables. Not sure if it is possible to make the manuscript more concise.
   We agree with the reviewer but we realize that it is difficult to cut information due to the complexity of the methods and the need for description and discussion of two major sections of the analysis (follow-up and treatment). However, in the revised version of the manuscript, we have cut some information from the Discussion section, especially the speculative part about the explanations of some findings.

Reviewer 3

Major Compulsory Revisions

1. The description of sources of data and their completeness is difficult to follow.
   What I miss is a clear description of which data sources were used by calendar year, and the completeness of these data. The study covers the period of Nov 2002-Jun 2011. Whether a woman was referred from screening to treatment of invasive disease was defined based on her patient records, diagnostics records, colposcopy records. But biopsy log books were not available before Mar 2005, and patient log books were not available for 2006. 1) Does this mean that before Mar 2005, some patients with invasive cervical cancer may have been not accounted for, and thus those that were accounted for were a selected group? 2) The authors state that “The 2006 patient log book was unavailable, so all 2006 records (n=2,549) were reviewed to identify cervical cancer cases.” From which source were “all 2006 records” retrieved? I would suggest that the whole process of data collection, including sources, numbers and completeness, be included in a revised Figure 1.

Regarding the first point, we do not think some patients with invasive cervical cancer were unaccounted for, because histopathologic results from this time period had already been entered in the screening clinic database. We also found that after March 2005, histopathologic results were rarely inconsistent when the colposcopy results were invasive cancer. It is important to note that we could not rely solely on the histopathologic results to determine cases of cervical cancer, even for the time periods for which a biopsy log book was available, because not all patients with clinically obvious cancer receive a biopsy and not all biopsies are expeditiously processed.

Regarding the second point, all 2006 records were manually retrieved and reviewed in their physical form from the records storage room to identify cervical cancer cases in 2006. Manually reviewing all the records was the best way to identify cases when the log
book was unavailable. We believe this gave us at least an equivalent, if not superior determination of cervical cancer cases for 2006 than what we would have ascertained from the log book, had it been available.

We have updated Figure 1 to reflect these two issues and to make all the data sources and completeness clearer, as recommended by the reviewer.

2. The authors use the term “screening,” however, is that a correct term given that all women with cervical cancer presented with symptoms, sometimes even after prior treatment at a different institution? I would suggest finding a different phrase for this activity because it can be misleading, even though it showed some characteristics typical for screening (e.g. diagnosis at an earlier stage).

We agree with the reviewer this may be misleading and have clarified in the manuscript that women presenting with symptoms of invasive cervical cancer are being diagnosed, rather than screened. However, the program’s primary function is still screening, so we consider these women with symptoms as having attended the screening clinic (rather than calling it a gynecology clinic). It is also possible that some of the 32 women with stage 1 disease who were lost to follow-up were asymptomatic, so they could be accurately described as screened.

Minor Essential Revisions

1. The authors stated that “At ORCI, most women screened by VIA also undergo colposcopy” – please explain why this is the case.

The ORCI screening clinic continues to operate under the protocols used in the original VIA screening study described in the introduction, so most women screened by VIA also undergo colposcopy, as was done in the original study.

2. Could the authors present some indicator of the distribution of the follow-up and treatment duration times?

We thank the reviewer for the comment. We have added a histogram (Figure 3) showing the distribution of follow-up times by place of residence. The treatment duration histogram was not very informative, so instead we have added the mean and standard deviation among those who did and did not complete radiation to the results section to provide further clarification.

Discretionary Revisions

1. If all women in the study presented at “screening” with symptoms, this suggests that no cases of cervical cancer were found in symptomless women. How often do symptomless women have CIN diagnosed?

The screening database did not track symptom status. Therefore, it was not possible to determine how often symptomless women were diagnosed with CIN. Preventive medicine for non-communicable diseases has not been a focus of the Tanzanian health system, so most people perceive hospitals and healthcare facilities only as places to seek medical attention for symptoms of disease. Anecdotally, it is more common recently for asymptomatic women to have CIN detected, perhaps due to policies encouraging VIA
screening of all HIV-positive women.