Author's response to reviews

Title: Patient side cost and its predictors for cervical cancer in Ethiopia: A cross sectional hospital based study.

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Author's response to reviews: see over
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Dear Editors,

Thank you for reviewing our manuscript and considering it for publication in BMC Cancer. We would like to also thank the reviewers for reviewing our manuscript. We revised our manuscript based on the comments and feedbacks forwarded from the reviewers and the editor. We hope that the editorial board and reviewers will deem the manuscript scientifically sound and worthy of publication in BMC Cancer.

Please find attached the point-by-point description of our response to each reviewer’s comments. Our response is written in italic and blue/red color.

Kindest regard

Alemayehu Desalegne
Following your editorial Requests:

1. Consent - Please state in the Methods section whether written informed consent for participation in the study was obtained from participants or, where participants are children, a parent or guardian.

   _Comment accepted and appropriate correction done. In our study we include women of the age of 15 and above and children were not included. During our data collection, written informed consent was obtained from all the study participants. A statement addressing the informed consent process is now added at the end of “Study design” section (page 7);_

   “Written informed consent was obtained from each respondent.”

2. Copy Editing - After reading through your manuscript, we feel that the quality of written English needs to be improved before the manuscript can be considered further.

   _The manuscript was sent to professional English language editor who has extensive editorial expertise. We believe that the current version is well edited._

Answers to the reviewers and changes made in the manuscript:

**Reviewer #1**

**Minor Essential Revisions**

1. I think this is an important paper and deserves publication. However, for the reader to gain greater insight into the economic implications for women with cervical cancer, a description of the current Ethiopian health system is necessary. - Is there any government subsidisation? are all expenses out of pocket? What for instance would be expenditure for a woman undergoing surgery for a benign condition by way of comparison.

   _We would like to thank the reviewer for considering our study as interesting. The constructive comments were very helpful in improving our paper. Thank you for reviewing our manuscript._
The reviewer is correct; we do agree that if we include the description of the current Ethiopian health system and health care financing, it will help the reader to understand the current situations in Ethiopia more. But we first decided to leave this out, to make our ‘Background’ section briefer and focused. We suggest that a reader who has special interest can get more description from documents prepared by the Federal Ministry of Health (HSDP IV, NHA) or from reports regularly generated by WHO, UNDP, and World Bank.

For example: (4th NHA 2010)

Currently, the major financers to the Ethiopian health care system were the government, households, and the rest of the world (other sources, like NGO). The private sector is the major manager of health resources, but government also plays a significant role. All private sector actors together managed 44 percent of the national health expenditure (NHE) in 2007/08 (83 percent of which was managed by households), followed by the government, which controlled 42 percent. The rest of the world (NGO, donors, grants and funds) is contributing and managing 14 percent of the total national health expenditure. In fact, the Ethiopian health sector is highly donor dependent, and households are substantially burdened by high spending on health that usually occurs at time of sickness.

Curative care services were still the major functions on which health resources were spent. Curative care services remained as the major target of health expenditures, accounting for 42 percent of NHE (35 percent outpatient and 7 percent inpatient). This share is slightly higher (45 percent) if we include pharmaceutical and medical nondurables, and clinical lab and imaging and other diagnostic services, which are predominantly used for curative care.

2. I also think that the authors need to define the cost of living for Ethiopians, and the difference between rural and urban populations. Providing these contexts will make for a much stronger article.

Because this study is just only cost of illness study on a particular illness (cervical cancer), we don’t want to describe the socio-economic background of Ethiopia and other additional
description regarding cost of living for rural and urban population. As much as possible we tried to be focused on cervical cancer and related topics only.

As information: “Ethiopia has one of the worst health and development indicators in the world even relative to other low-income countries. Poverty, low education levels, inadequate access to clean water, lack of sanitation facilities and poor access to health services have contributed to the high rate of ill-health in the country. It is estimated that 44.2 per cent of the population of Ethiopia lives below the poverty line of under $1.25 per capita per day.” (UNDP 2009)

3. In terms of quoting the current global cancer statistics the authors are advised to consult the latest Globocan data which have been updated.

We had been browsing Globocan and other relevant websites searching for the latest data regarding worldwide distribution of cervical cancer. Unfortunately the latest data available that we found were for the year 2008, that we had used it in this manuscript.
Reviewer #2

Major Compulsory Revisions

1. The introduction is saying cervical cancer is widespread in the world and in Ethiopia. The data is given in almost random form. It needs to be organized better. Firstly absolute numbers of cases, case rates per 100,000 women, deaths per 100,000 women with case fatality rates in percentage terms, breast cancer and lung cancer incidence rates in females should be provided for the world, EURA (region of WHO), developing world, Africa and Ethiopia (where available) – perhaps in tabular form.

*We have addressed the reviewers’ concerns regarding the organization of the introduction in terms of explaining the distribution of cervical cancer by re-organizing the ‘Background’ section based on the comments given (page 4-6). We also change the section heading from Introduction in to “Background”*

2. In the last paragraph of the introduction ad/or in the discussion, mention should be made that this cost analysis can form a partial basis of a full cost-utility analysis of prevention and treatment of cervical cancer in the future in Ethiopia. The paper mention that vaccinations and/or PAP smear screening AND/or HPV DNA testing can be used to reduce morbidity from cervical cancer and subsequent costs in both human lives and money resources.

*We have addressed the reviewer’s concerns regarding the organization of the introduction in terms of explaining the distribution of cervical cancer by adding the following text at the end of ‘Background’ section (page 6). “The results of this study can be used as a basis for a full cost-utility analysis of the prevention and treatment of cervical cancer in the future in Ethiopia.”*

*And the following text in the ‘Conclusions’ section (page 20) “Primary prevention measures, vaccination against HPV and screening, should be initiated and expanded to reduce morbidity from cervical cancer and subsequent costs in both human lives and money resources.”*
3. The valuation of work days should be made on the costs of EMPLOYING the worker, these will not be the same as WAGE costs if the employer pays social security, pensions or employment taxes on behalf of the worker.

*In this cost of illness study, we have done an estimate for the financial burden of cervical cancer by taking into account the patient's perspective. Other costs that were paid or could be paid by employers (social security, pensions or employment taxes) were not included in the perspective of our study. This might be one of the limitations of this study as outlined in the discussion section.*

4. The whole results section should be cut down considerably and basically discuss Tables 2 and 3, without duplicating the data. Some description of what treatment a patient receives during both an outpatient and inpatient visit (eg: I doubt chemotherapy or radiotherapy, but maybe lesion removal or hysterectomy or even extenuration) should be made.

*We have discussed the results from table 2 and table 3 (page 17 &18).*

5. Discussion should include how representative are the costs of the Addis hospital of other hospitals where cancer is treated….an estimate could also be made of the total monetary burden of cervical cancer annually in Ethiopia – also as a [percentage of the total health care budget (for the direct costs)].

*In our study, costs were estimated from patients’ perspective and extrapolation to the national level and/or estimation of the burden to the health care budget will have limited value due to methodological limitation and accurate data were not available on the current prevalence and incidence of cervical cancer for Ethiopia. Moreover, there is no cancer registry system in Ethiopia. So that we didn’t try to extrapolate our result to the national level*

*Regarding the issue of representativeness, as Tikur Anbessa Hospital is the only cancer diagnostic and treatment center, patient of different stage of illness from different socio-economic background, from all over the country came to this Hospital. For this reasons we strongly believe that we had quite representative sample despite we draw our sample from one hospital using consecutive sampling technique.*
Page 6, Study area: “The study was carried out in the Departments of Gynecology/Obstetrics and Oncology/Radiotherapy of Addis Ababa University Tikur Anbessa Specialized Teaching Hospital. Tikur Anbessa Hospital is the only central referral hospital and cancer treatment and diagnostic center in the country that provides services for patients from all over the country...”

6. Table 6 - A discussion should be made as to why outpatient costs rise when there are more employed household members, the person is a farmer, animal dung is used and the person had no companion and lived in Adis.....

We believe that our study could help other researchers in Ethiopia to conduct further analysis regarding the variables identified here as predictors of cost variability and could come up with clear explanation. As we mentioned in the limitation (page 19), there is no previous study which estimates the cost of cervical cancer in sub Saharan Africa. A comparison of our findings with those of other cost of illness studies of cervical cancer in other countries or other disease in Ethiopia would be of limited value because of the difference in the categories of cost, the methods, and the pattern of health services utilization. We appreciate this as one of the limitation of this study.

7. Table 6 - you should also clarify that having stage 2 as the baseline, you found less and more severe cases have a lower length of stay .....explain why??...maybe stage 3 and 4 die quickly....while stage 1 have minor procedures.....what are the stage specific protocols of care???

We have now discussed this in the discussion section as follows:

“"In terms of stages of illness, we found, the cost for stage I was lower compared with stage II and stage III. This finding was similar to findings from other study on cervical cancer (27, 18). The cost for stage IV was less compared with other lower stages. This could be due to the reason that cases at stage one might be recovered with minor procedures while other cases at other stages demand intensive diagnostic and therapeutic procedures as evidenced by the cervical cancer treatment protocol recommended by FIGO (16).”
Minor Essential Points

1. Introduction line 7 delete "to its magnitude"

   Comment accepted. The phrase "to its magnitude" removed.

2. Penultimate paragraph of introduction. You say the etiology is multifactorial, so please name some of the other factors besides HPV.

   In response to the other reviewers comment, the paragraph which describes about the etiology was replaced with review of health economic studies done on cervical cancer.

3. Consider putting a copy of the questionnaire as Appendix I.

   We prepare this manuscript based on data collected using a questionnaire that has some other additional sections. We decided not to put the questionnaire as appendix in order to avoid the ambiguity that may be introduced due to this gross questionnaire.

4. Methods of cost estimation:- please define what you mean by UNPAID work --- is this working on ones own vegetable patch OR household work OR BOTH ??

   We make a revision and we clear out the ambiguity related with a phrase “unpaid”. (See response to reviewer 3, question #5)

5. End of data analysis: - should read sensitivity AND CHECKED for multicollinearity and heteroscedasticity.

   The statistical assumptions and models have been examined for the following assumptions: normality, heteroscedasticity, Multicollinearity, influential observations, and outliers. We add the following statement in the “Data analysis” section, on page 10;

   “Before proceeding to further analysis, the residuals and the data had been examined for the fulfillment of the following statistical assumptions: normality, sensitivity, multicollinearity, and heteroscedasticity.”
6. Predictors for variation:- Model selection should be described….was it forward or backward stepwise etc………………

   We used a forward stepwise selection procedure and we describe on page 10,

   “Multiple linear regressions using a forward stepwise selection procedure was employed…”

7. Data should be given for duration of inpatient stay and stage of cancer

   Duration of inpatient stay in days is given in Table 4, (median (IQR) =16 (41,7)

8. Reference 24 is irrelevant.

   Comment accepted. Reference 24 is removed.

9. Table 2 – it is not clear what "out of TA hospital" means, is this the costs of Ambulatory care?

   In Ethiopia, the only cancer diagnosis and treatment center is located only in the Tikur Anbessa Hospital. We organize our result in two categories, before first arriving/visiting Tikur Anbessa Hospital and at the Tikur Anbessa Hospital. This grouping will help to clearly identify the cost incurred before arriving at the facility where the cancer treatment is provided and to depict a clue regarding the length of delay and associated cost in the diagnosis and treatment of women with cervical cancer. When we say out of the Tikur Anbessa Hospital, it is beyond ambulatory care. It covers all types of care, ranging from nearby health post and traditional practitioner to hospital based health care.

10. Table 3 – What are there TWO headings "at TA hospital"??????

   Comment accepted and the mistake is now corrected. The first sub-heading is “Before first visiting Tikur Anbessa Hospital” and the second is “At Tikur Anbessa hospital”

11. Table 4 – why is duration of stay under INDIRECT COSTS???

   We also agree with the reviewer that duration of inpatient stay in days is not part of indirect cost. We include the row for the duration of stay under sub-heading ‘INDIRECT COSTS’ for
simplification while we organize the report in a table format. We also mention the unit for the duration of stay (in days) to avoid the ambiguity.

12. The investigations category should be referenced and described below the table, similarly for the cost of drugs……

Comment accepted. The following footnotes are added:

*Investigations includes laboratory tests ultrasound, pathological examination, x-ray and any other diagnostic procedures

¥Drugs include all medication prescribed by the physician or any other medication taken in relation with the problems of cervical cancer.
Reviewer #3

Major Compulsory Revisions

1. The question posed by the authors was not well defined relatively to the title and was not the same in the abstract and in the introduction.

   We have addressed the reviewers’ concern by revising the abstract and the introduction to keep the fluency of the ideas from the title through the introduction, the result and discussion. We also slightly modify the title to avoid any ambiguity by adding “Patient side” at the beginning and the new title is as follows; “Patient side cost and its predictors for cervical cancer in Ethiopia: A cross sectional hospital based study.”

2. The introduction could be improved: the paragraph concerning the etiology of cervical cancer should be replaced with an overview of international and national health economic studies on cervical cancer

   Comment accepted and the paragraph concerning the etiology is now replaced with an overview of some other health economic studies (page 5 & 6).

   “With the magnitude outlined above, the economic burden of cervical cancer is considerable and highlights the need for treatment and prevention options for this condition. According to a review research in the United States, annual direct medical costs associated with cervical cancer range from 300 to 400 million USD. With a wide range across studies for estimates of the annual direct medical costs associated with carcinoma in-situ (CIN) which range from 700 million USD to 2.3 billion USD (10). In the United States, although the direct costs of cervical cancer are substantial, only 10% of all expenditures are due to invasive disease; more than two thirds of the total cost being attributable to screening and testing. Annual indirect costs resulting from lost productivity and loss of earnings due to premature death are also significant and are estimated to be higher than the direct costs (11).

   According to a population-based study in Spain, during a four year period (1999-2002), the mean cost of hospitalization due to cervical cancer and carcinoma in situ is 3,098
Euro and 2,192 Euro respectively (12). Another retrospective study done in Tunisia has shown that the direct medical care cost of cervical cancer as ranging from 431 to 4143 Euro (13).”

3. The methodology was not well described: sampling method was not very clear mainly concerning the selection criteria of patients.

To provide more detail information on the methodology and sampling methods, we add a section- “Study population and sampling methods”. We also re-arrange and revise the methods section (see page 6 and 7).

4. The authors did not consider some components of the cost: the title of the manuscript talk about the whole cost of cervical cancer but some components were missing (death related cost, surgical treatment, other indirect costs than productivity losses)

In this cost of illness study, we have assessed the financial burden by taking into account the patient's perspective. Costs here mentioned by the reviewer were not included since it was not included in the perspective of this study. This might be one of the limitations of this study as we have acknowledged in the discussion. In addition we also slightly modify the title (in addition, see response to question #1)

5. Authors should explain and justify the value of some items of cost (unpaid work day, daily gross wage rate)

We addressed the reviewer’s concern by explaining and revising the second paragraph of “Methods of cost estimation” section (page 9).

“Time foregone in seeking care and productive time lost was converted into indirect cost based on the daily wage rate and then multiplied by the number of working days lost. The daily wage rate for monthly paid patients was estimated by dividing their net monthly salary by 30 days. Daily wage rate for daily paid patients were calculated based on the women’s reported daily earnings. The indirect cost for unemployed, students and women who were not able to work due to physical or mental disability were not considered in the calculations (14).”
6. In order to better estimate the magnitude of cervical cancer in the Ethiopian context, authors should add an economic indicator for Purchasing power.

*Based on world bank data, the value of Purchasing Power parity (PPP) conversion factor for Ethiopia for the year 2010 was 0.3 (http://data.worldbank.org/indicator/PA.NUS.PPPC.RF). We gave this information for the readers in the ‘Methods’ section (page 10) so that it will help them to understand and compare our findings to different contexts.*

“The purchasing power parity (PPP) conversion factor for the Ethiopian Birr during the data collection period was 0.3 (15).”

7. Results: in table 6 the coefficient concerning residency should be verified (‘5805.61’ instead of ‘-5805.61’).

*We found negative (-5805.61’) coefficient here in the regression analysis. This could be due to, those mothers coming from out of Addis Ababa paid much higher for food, lodging transportation and other expenditures compared with mothers who were from Addis Ababa*

8. Several limitations of the work were not discussed.

*We agreed that any cost-of-illness analyses should always be viewed in the context of potential limitations. In our revised manuscript we tried to discuss each of the limitations as much as possible.*

“All cost-of-illness study should always be viewed in the context of potential limitations. Some of the costs may be underestimated, some costs may be overestimated and some costs may be totally omitted. This cost of illness study is limited to the patient side cost, even though it would be more comprehensive if it includes other costs to the health system, health care provider, the family and to society at large. Intangible costs (pain, suffering, stigma and discrimination) were not also included due to difficulties in measurement (14). The limitations of self-reported data must also be recognized in interpreting the findings of this study.”
9. It is not reasonable to compare the ratio direct vs. indirect cost of cervical cancer to those of other diseases which have different impacts and needs different treatments… (type II of diabetes, lymphoma)

   We accept the reviewer’s comment. We also agree that comparison of cost data for one disease to another different disease is difficult and could not sound very well (page 19). We have addressed the reviewers’ concern by removing the paragraph in which we had tried to compare the cost of cervical cancer in our study with type II diabetes, lymphoma and lung cancer.

10. The authors contented with relating and with comparing economical results and highlighting « economically » vulnerable profile of the majority of the investigated women without approaching cost determinant factors related to primary and secondary prevention.

   Thank you for an interesting question again. Actually, to the limited extent, we tried to identify main determinant factors for the variability of costs in our descriptive analysis (Table 1) and regression analysis (Table 6). As we mentioned above for question # 8 for the limitation of the study, cost and/or determinant of prevention measure are not included in the scope of our study.

11. The authors should annotate tables in results chapter.

   Comment accepted. All tables are now annotated in the results section.

**Minor Compulsory Revisions**

1. References concerning cancer prevalence in Ethiopia (introduction) should be updated if recent data are available.

   Unfortunately there is no recent study on cervical cancer in Ethiopia. Except very few clinic based studies done long time ago, no studies have been conducted on economic evaluation of cervical cancer in Ethiopia.

2. The authors should recommend primary prevention actions in the conclusion of the abstract.
Comment accepted. A statement explicitly addressing primary prevention is now added and we rephrased the "conclusion" section of the abstract as follows (page 3):

“Primary prevention measures, vaccination against HPV and screening, should be initiated and expanded to reduce morbidity from cervical cancer and subsequent costs in both human lives and money resources. Control of co-morbidity and complication should be emphasized during management of cervical cancer patients. Capacitating regional hospitals and provision of low cost or fee exemption schemes should be arranged and strengthened.”

3. The quality of written English needs some language corrections.

Comment accepted. The manuscript had been sent and edited by a native English speaker who has previous editorial expertise.

4. Table 1 presentation was not appropriate

Comment accepted. Appropriate correction done