PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Factors associated with advanced stage at diagnosis of cervical cancer in Addis Ababa, Ethiopia: A population-based study
AUTHORS	Dereje, Nebiyu; Gebremariam, Alem; Addissie, Adamu; Worku, Alemayehu; Assefa, Mathewos; Abraha, Aynalem; Tigeneh, Wondemagegnehu; Kantelhardt, Eva; Jemal, Ahmedin

VERSION 1 – REVIEW

REVIEWER	Emma Allanson The University of Western Australia, Australia
REVIEW RETURNED	17-Jun-2020

GENERAL COMMENTS	This a concise study which highlights some of the challenges contributing to adverse cervical cancer outcomes in low and middle income countries. I have no major comments or significant concerns. In general - change American to English spelling (e.g. gynecologists to gynaecologists) Line 69 change to "detection and removal" or "detecting and removing" as the way it is currently does not have consistency in tense Line 88 - does the 234 new cases represent every single case presenting to these units - as 100% of women consented to being enrolled in the study? This is impressive if this is the case. Line 92 - what is the reference / evidence for these centres representing 99% cases? Line 96 change to "distant" Line 95 - probably worth commenting that these are staged on the old FIGO staging, as I assume they were? Line 173 change do to "did" Line 207 change "will cure" to "will cure one" Line 210 change to "financial hardship is a barrier"

REVIEWER	Prof Peter Gichangi Technical University of Mombasa, Mombasa, Kenya
REVIEW RETURNED	20-Jul-2020

GENERAL COMMENTS	Introduction "However, the findings on stage distribution in Ethiopia and in most parts of Africa are based on hospital-based studies rather than population-based studies and they cannot be generalizable" This is a good justification for the study. However, this statement seems to go against the statement above since the study will use all patients diagnosed …."Therefore, this study was conducted (1) to describe the stage distribution of cervical cancer (2) to identify factors associated with advanced stage of the disease in Addis Ababa, capital city of Ethiopia using all patients

diagnosed from January 2017 through June 2018 among the residents of the city.

Materials and methods
"A multi-center prospective cross-sectional study was conducted among all newly diagnosed patients with cervical cancer among Addis Ababa residents during the 18 months study period from January 1, 2017 to June 30, 2018." It is not clear what is meant by "prospective" cross-sectional…

It is notable that the study recruited participants from cancer treating facilities "The study participants were recruited from seven major public and private health facilities in the city (representing 99% of cervical cancer incident cases among Addis Ababa residents)." Is the reference to 99% meant to mean treatment coverage or incidence of cancer? This needs to be clarified since the two concepts are radically different.

"Distance metastasis (Stage IVb) was determined by reviewing chest x-ray and abdominal ultrasound findings [14]." These are very limited and less informative in picking up distant metastasis. Why were they chosen? Justify.

Results
Stage at diagnosis
"About 5.2% of the patients with cervical cancer had metastasized cancer to lung (2.4%), liver (2.4%) and peritoneum (0.5%) at their diagnosis." Note the limitations of the methods used to make this diagnosis.

Table 3 also has included findings from table 2. Authors should decide which one they want to retain.

Data from participants interview is not presented!

Discussion
"The present study provides data on cervical cancer stage distribution in Addis Ababa along with its predictors based on a prospective, population-based, representative sample and primary data sources."

From the results section, this is the only information provided "More than two-thirds (69.8%) of the patients had tumor size of greater than 4cm. Majority of the cervical cancer cases (91.0%) had a squamous cell carcinoma." Table 1 shows tumor size. Thus, from this, very limited information on cancer distribution at time of diagnosis is provided. This objective is not met.

The assertion that the study was population-based study may not be accurate. First, the population is not defined. In normal circumstances, population would have been interpreted to be human beings living in Addis Ababa. In this case, it seems the population is women with cervical cancer. If this is the case, the population should have been defined.

How did the authors determine the "population" included is representative? The women included were mainly from the treatment facilities! What is the estimated number of cervical cancers cases in Addis Ababa based on national or regional prevalence/incidence? This could inform the authors whether their assertion of whether the included women are representative or not by knowing what proportion they represent of the expected cases in Addis Ababa.

"The strengths of this study are the use of population-based cancer registry and rigorous and multiple data collection methods (patients' interview and medical record review) in a prospective approach to document strong association between late-stage diagnosis and

| | patient and health system factors, including diagnosis delay, in African settings." This statement does not necessarily represent strength. First, there are only two approaches used here – abstraction of clinical data from clinical records and patient interview at the time of diagnosis which are described as "multiple data collection methods". Second, all data was collected at one point in time. What is the prospective component?

The authors have not addressed the limitation of generalisability which was identified in the introduction section.

Are these results generalisable? |
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VERSION 1 – AUTHOR RESPONSE

RESPONSE FOR THE REVIEWER 1 COMMENTS (EMMA ALLANSON)
R1: This a concise study which highlights some of the challenges contributing to adverse cervical cancer outcomes in low and middle income countries. I have no major comments or significant concerns.
Response: We thank the reviewer for the constructive comments.
R1: In general - change American to English spelling (e.g. gynecologists to gynaecologists)
Response: Changed the spelling as recommended by the reviewer.
R1: Line 69 change to "detection and removal" or "detecting and removing" as the way it is currently does not have consistency in tense
Response: Thank you. It is corrected now to "detection and removal"
R1: Line 88 - does the 234 new cases represent every single case presenting to these units - as 100% of women consented to being enrolled in the study? This is impressive if this is the case.
Response: Correct, all the 234 patients presenting to the participating health facilities agreed to participate in the study. Out of these patients, however, three women were not recruited to our study because they went abroad for treatment. We now clarify in the manuscript (page 5, line 94 – 96).
R1: Line 92 - what is the reference / evidence for these centres representing 99% cases?
Response: The reference we used was the Addis Ababa city population-based cancer registry, which actively registers all the incident cancer cases occurring in the city. The registry, however, may not capture all incident cases occurring in the city as some patients visiting local clinics may not be referred to major hospitals or patients may choose not to seek modern medicine. We now recognize this in the Method section (page 5, line 98 - 101) and in the Discussion section as a limitation of the study (page 16, line 237 - 239)
R1: Line 96 change to "distant"
Response: Thank you, it is corrected.
R1: Line 95 - probably worth commenting that these are staged on the old FIGO staging, as I assume they were?
Response: Correct, the 2014 FIGO staging was used to stage cervical cancer patients included in our study. We now add this information on page 5, line 101 - 102.
R1: Line 173 change do to "did"
Response: Thank you, it is changed now.
R1: Line 207 change "will cure" to "will cure one"
Response: Thank you, it is changed now.
R1: Line 210 change to "financial hardship is a barrier"
Response: Thank you, it is changed now.

RESPONSE TO REVIEWER 2 (PROFESSOR PETER GICHANGI)
Thank you again for your comments and suggestions.

R2: Introduction "However, the findings on stage distribution in Ethiopia and in most parts of Africa are based on hospital-based studies rather than population-based studies and they cannot be generalizable" This is a good justification for the study. However, this statement seems to go against the statement above since the study will use all patients diagnosed ...."Therefore, this study was conducted (1) to describe the stage distribution of cervical cancer (2) to identify factors associated with advanced stage of the disease in Addis Ababa, capital city of Ethiopia using all patients diagnosed from January 2017 through June 2018 among the residents of the city.

Response: Apologies, we meant to say "However, previous findings on stage distribution in Ethiopia and in most parts of Africa ...". We now have revised the sentence in the manuscript accordingly. We have included 99% of the incident cervical cancer cases among the residents of Addis Ababa city based on the Addis Ababa Population-based cancer registry.

R2: Materials and methods "A multi-center prospective cross-sectional study was conducted among all newly diagnosed patients with cervical cancer among Addis Ababa residents during the 18 months study period from January 1, 2017 to June 30, 2018." It is not clear what is meant by "prospective" cross-sectional...

Response: Thank you for the comment. The word "prospective" was used to indicate that newly diagnosed patients with cervical cancer were recruited to the study prospectively (over 18 months), rather than retrospectively from review of medical charts. To avoid confusion, however, we now have omitted "prospective".

R2: It is notable that the study recruited participants from cancer treating facilities "The study participants were recruited from seven major public and private health facilities in the city (representing 99% of cervical cancer incident cases among Addis Ababa residents)." Is the reference to 99% meant to mean treatment coverage or incidence of cancer? This needs to be clarified since the two concepts are radically different.

Response: Thanks for the comment. The 99% reference indicates coverage of incident cervical cancer cases recruited into our study based on the total number of cervical cancer cases reported to Addis Ababa population-based cancer registry during the study period. We now clarify this point in the manuscript, page 5, line 98 - 101.

R2: "Distance metastasis (Stage IVb) was determined by reviewing chest x-ray and abdominal ultrasound findings [14]." These are very limited and less informative in picking up distant metastasis. Why were they chosen? Justify.

Response: Chest X-ray and ultrasound are commonly used for assessing distant metastasis of cervical cancer in Ethiopia and other parts of Africa because of lack of modern diagnostic and imaging techniques.

R2: Table 3 also has included findings from table 2. Authors should decide which one they want to retain.

Response: Table 2 presents findings of bivariate analysis and Table 3 presents findings of multivariable analysis. We now present Table 2 as a supplemental material.

R2: Data from participants interview is not presented!

Response: Most of the variables included in Table 1 (socio-demographic characteristics, immediate action after symptom recognition, number of different health facilities visited before diagnostic conformation, source of medical expenses) and date of symptom recognition and date of health facility consultations were from participants' interview.

R2: Discussion "The present study provides data on cervical cancer stage distribution in Addis Ababa along with its predictors based on a prospective, population-based, representative sample and primary data sources." From the results section, this is the only information provided "More than two-thirds (69.8%) of the patients had tumor size of greater than 4cm. Majority of the cervical cancer cases (91.0%) had a squamous cell carcinoma." Table 1 shows tumor size. Thus, from this, very limited information on cancer distribution at time of diagnosis is provided. This objective is not met.

Response: In the Results section, we have provided information on stage distribution (figure 1), proportion of advanced stage with its 95% confidence interval, tumor size, type of tumor, and

information on metastasis. Our intention in the first paragraph of the Discussion section is to provide a summary of the main findings in order to inform the remaining part of the Discussion section.

R2: The assertion that the study was population-based study may not be accurate. First, the population is not defined. In normal circumstances, population would have been interpreted to be human beings living in Addis Ababa. In this case, it seems the population is women with cervical cancer. If this is the case, the population should have been defined.

Response: Thank you for the comment. We say the study was population-based because we included all cervical cancer cases diagnosed in women residing Addis Ababa (a defined population from defined geographical location) during the study period. Women were considered to be residents of Addis Ababa if they live for at least 6 months in the city. We now have included this information in the Methods section (page 5, line 90 - 94).

R2: How did the authors determine the "population" included is representative? The women included were mainly from the treatment facilities! What is the estimated number of cervical cancers cases in Addis Ababa based on national or regional prevalence/incidence? This could inform the authors whether their assertion of whether the included women are representative or not by knowing what proportion they represent of the expected cases in Addis Ababa.

Response: As we stated above, the 231 incident cervical cancer cases recruited from the major hospitals and diagnostic facilities from January 1, 2017 to June 30, 2018 represent about 99% of the cervical incident cases reported to the Addis Ababa population-based cancer registry during the corresponding period. However, the Addis Ababa Population-based Cancer Registry may not capture all cases occurring in the city because some patients seen in local clinics may not have been referred to or refused to go to the major hospitals and diagnostic facilities from which incident cases are collected periodically and because some patients may not seek modern medicine. We now include this information in the Methods and Discussion section.

R2: "The strengths of this study are the use of population-based cancer registry and rigorous and multiple data collection methods (patients' interview and medical record review) in a prospective approach to document strong association between late-stage diagnosis and patient and health system factors, including diagnosis delay, in African settings." This statement does not necessarily represent strength. First, there are only two approaches used here – abstraction of clinical data from clinical records and patient interview at the time of diagnosis which are described as "multiple data collection methods". Second, all data was collected at one point in time. What is the prospective component?

Response: We limited the strength to use of population-based cancer registry and revised the text accordingly. Data were collected over 18 months. We have omitted the word prospective in response to the prior comment.

R2: The authors have not addressed the limitation of generalisability which was identified in the introduction section. Are these results generalisable?

Response: Considering that we have recruited almost all of the incident cervical cancer cases in the city during the study period according to the Addis Ababa population-based cancer registry we think that these results are generalizable. As we mentioned above, however, the study as well as the Addis Ababa cancer registry may not capture all incident cervical cancer cases occurring in the city as some patients might have never visited health facilities or visited local health facilities that do not report cases to the cancer registry or refer to the major health facilities or diagnostic centers. We now add this as a limitation of the study.

We also slightly changed the title of the manuscript for clarity "Factors associated with advanced stage at diagnosis of cervical cancer in Addis Ababa, Ethiopia: A population-based study"