Peer Review File
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Reviewer A

Comment 1:
Abstract:
1. Please in the Background section use present time grammar (i.e. we report).
2. Please to the first sentence of the Results section, add that this is "Globally in 2019, [...]" for clarification.
3. "Males had higher [...], and both increased with age." This is grammatically incorrect, as "Males" is the subject, and is now incorrectly referred to later by "both". Please consider starting the sentence with "Higher [...] rates were observed in males compared to females, and both [...]", so that "both" refers to the correct terms.

Reply 1:
1. We have modified our text as advised. (see Page 5, line 66-68)
2. We have modified our text as advised. (see Page 5, line 74)
3. We have modified our text as advised. (see Page 6, line 84-86)

Comment 2:
Main text:
4. In the Results "Global Level" section, the sentence "During the same period, the number of new cases of increased by [...]" misses the term "esophageal cancer" in it. Alternatively, the second word "of" could be deleted.

5. In the conclusion at the end, the authors state that "incidence, deaths, DALY rates have declined, which may be related to the improved treatment in recent years." However, this is not accurate, because incidence rates are actually likely unrelated to treatment changes. Rather, issues discussed above in the Discussion section should be added to this specific sentence as potential explanations, including decreases in smoking and alcohol consumption.

Reply 2:
4. We have modified our text as advised. (see Page 12, line 205-206)
5. We have modified our text as advised. (see Page 27, line 426-428)

Comment 3:

Figures and Tables:
- Largely OK. However, in Figure 5 it is unclear what the difference is between the box plots and the lines. Which of those belong to which y-axis (left or right)? The legend only distinguishes male and female, but not boxplots versus line plots.

Reply 3:
To account for this, an explanatory note has been added to the legend to clarify this point.

Changes in the text: We have modified our text as advised. (see Page 43-44, Figure 5)

Reviewer B:

Comment 1:
The following sentence is copied from the Introduction of your submitted manuscript:

" Understanding cancer burden patterns will allow us to assess the effectiveness of current prevention strategies and provide a more scientific foundation for optimizing early prevention and cancer management..."

Could you please explain, how and to which extend this statement applies to your data or the other way around!

Reply 1:
Esophageal cancer is an important contributor to the global cancer burden. With the global ageing in population and expansion in population size, a further increase in the burden of esophageal cancer could be expected, especially for adenocarcinoma, which is positively associated with an increasing prevalence of obesity, metabolic syndrome, and socioeconomic development. Over the last three decades, the incidence rate of esophageal adenocarcinoma has risen rapidly, surpassing that of squamous cell carcinoma in several western countries, and more recently, in some eastern countries

Therefore, more resources should also be committed to the formulation of evidence-based prevention strategies for both squamous cell carcinoma and adenocarcinoma. For instance, both smoking cessation and control of alcohol consumption are recommended to reduce the risk of squamous cell carcinoma, especially for populations in western countries. For adenocarcinoma, it is critical to slow down the growing rates of obesity and metabolic syndrome, as many of them are also important risk factors for other common chronic diseases like cardiovascular diseases and other cancers.

To cope with the low survival rate of esophageal cancer, early detection through screening and cancer management are of great importance, particularly for the high-risk populations. Currently, population-based targeted screening endoscopy is feasible in improving survival and is cost-effective for high-risk groups of both squamous cell carcinoma and adenocarcinoma. Additionally, the premalignant lesions of esophageal cancer can now be treated with more advanced technology which is much less invasive than open surgery.

Comment 2:

Another of your sentences:
"Meanwhile, we observed substantial variations of morbidity and mortality in different regions and populations, demonstrating the importance of a more specific hotspot delineation to identify high-risk groups."

You are right, and this needs to be done. It is not the global burden of disease data providing " ... a more scientific foundation for optimizing early prevention and cancer management..." It´s data that reflect the local circumstances and risk/genetic factors.

Please, avoid suggestions that overestimate data from the GBD database.

Reply 2:
We are very sorry for our inaccurate expression in the manuscript and we have revised from "Understanding cancer burden patterns will allow us to assess the effectiveness of current prevention strategies and provide a more scientific foundation for optimizing early prevention and cancer management." to "Understanding cancer burden patterns may provide further insights into the specific etiology and management of esophageal cancer."

Changes in the text: We have modified our text as advised. (see Page 8, line 128-129)

Reviewer C

Comment 1:
PAGE 11, lines 272-273
It is good to compare the results of the GLOBOCAN project with the results of this study. To avoid confusion and to help readers' understanding, which case is appropriate to use the result of GLOBOCAN, further explanation is needed in the discussion session.

Reply 1:
GLOBOCAN provides national estimates, including incidence, mortality, and prevalence, by cancer site and sex in 185 countries/territories for 36 cancer types. However, GLOBOCAN does not provide estimates over time for all locations, correlations with risk factors, or estimates for disability-adjusted life-years (DALYs).

GBD project estimates incidence, mortality, years of life lost, years of life lived with disability, and DALYs by age and sex for 87 risk factors and risk factor combinations for 204 countries and territories annually. In the present study, incidence, mortality, and DALYs per 100,000 population in 2019 estimates worldwide were presented by sex and age. The percentage changes in all- age and age- standardized rates from 1990 to 2019 were shown to reflect the trends of cancer burden worldwide.

Our findings are generally consistent with the Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) project, although our estimates were slightly lower than theirs. These discrepancies are due to incomplete data in both datasets and differences in modelling. Specifically, since GBD weights data based on the level of data completeness, it might give more weight to data from high-income countries, which have more complete data and lower esophageal cancer incidence rates. In other words, data from low-income regions may be more appropriate using the GLOBOCAN results.

Changes in the text: We have modified our text as advised. (see Page 19, line 320-322)

Reviewer D

Comment 1:
Line 73-74: What other deaths (EC or cancer in general) and DALYs is this statement compared to? And what is reference period?

Reply 1:
In this statement, we described the number of deaths and DALYs attributable to EC in 2019 and comparison between 1990 and 2019, without comparing to other deaths (EC or cancer in general) or DALYs. So it would be greatly appreciated if you could explain it in more detail.

Comment 2:
Line 125-126: Please what were the data sources for the risk factors and DALYs, etc.?

Reply 2:
Risk factors and DALYs came from the same sources as morbidity and mortality. Detailed information about the data sources used for each location in this study can be found on the GBD 2019 Data Input Sources Tool website.

Risk factor quantification was based on the GBD 2019 comparative risk assessment. Details on the modelling approach for each risk factor are available in "*The global burden of cancer attributable to risk factors, 2010-19: a systematic analysis for the Global Burden of Disease Study 2019*".

DALYs were calculated by summing years lived with disability (YLDs) and years of life lost (YLLs). YLDs were estimated by classifying 10-year cancer prevalence into four sequelae and multiplying the prevalence by corresponding disability weights: diagnosis and treatment, remission, disseminated and metastatic, and terminal phase. A time duration of 5 months was used to define the diagnosis and primary therapy phase, 4.6 months used to define the metastatic phase, and 1 month used to define the terminal phase. The remaining time was assigned to the controlled phase. The YLLs were estimated by multiplying the estimated number of deaths by age with a standard life expectancy at that age. Details of estimation methods and data sources have been published in previous study entitled "*Cancer Incidence, Mortality, Years of Life Lost, Years Lived with Disability, and Disability-Adjusted Life Years for 29 Cancer Groups From 2010 to 2019: A Systematic Analysis for the Global Burden of Disease Study 2019*".

Changes in the text: We have modified our text as advised. (see Page 11, line 178-179 & 181)

Comment 3:
Line 163: This is a repetition of the beginning of this sentence.

Reply 3:
We have modified our text as advised. (see Page 12, line 197-198)

Comment 4:
Line 168-169: What was the rate in 1990 and 2019 resulting 0.2% decrease in 2019?

Reply 4:
The global age-standardized incidence rates were 8.1 (95% UI: 6.4-8.8) and 6.5 (95% UI: 5.7-7.2) in 1990 and 2019, respectively.

Comment 5:
Line 174: Results in line 168 to 174 has not been linked to any results table. Please point these figures to a table.

Reply 5:
Considering the reviewer's suggestion, we have linked results in line 168-174 to Table 1.

Changes in the text: We have modified our text as advised. (see Page 12, line 209)

Comment 6 & 7:
Line 234-235: Please can you indicate what the expected pattern is? This would make the results more understandable with just a reference to Figures 4B, S1-S2.
Line 237: Please state the exact level that is expected.

Reply 6 & 7:
The expected pattern represented the average relationship between SDIs and age-standardized rates for esophageal cancer based on values from all countries from 1990 to 2019.

Changes in the text: We have modified our text as advised. (see Page 16, line 272-274)

Comment 8:
Line 239: Delete one of the fullstop (.)

Reply 8:
We have modified our text as advised. (see Page 17, line 281)

Comment 9:
Line 272-276: The excess of 69,000 new cases and 46,000 deaths are quite substantial. Can the authors test for any significance in their estimates compared to the of the GLOBOCAN.

Reply 9:
The age-standardized annual incidence and death rates reported in GBD and GLOBOCAN cannot be compared as different standard populations have been used. These discrepancies are due to incomplete data in both datasets and differences in modelling. For example, weighting the data by the level of their completeness in GBD might give more weight to data from high-income countries, where data are more complete and esophageal cancer incidence rates are low.

Comment 10:
Line 331-333: How does SDI and socioeconomic status compare? Can the authors throw more light on this comparison? For instance, national and individual or household levels?

Reply 10:
The inverse association between age-standardized DALY rates and SDI may be attributed to several correlated and interconnected variables. Specifically, low SDI is a proxy for lower intake of certain nutrients and exposure to certain environmental risk factors associated with esophageal cancer. Previous studies have identified that, in Malawi, the country with the highest incidence of esophageal cancer, Fe, Mg, Zn, and Se intake were generally lower, which might be related to the local low pH soils. Moreover, low SDI was associated with unimproved water sources, poor oral health, consumption of hot beverages, air pollution, and exposure to biomass smoke, which were proven to be well-established risk factors for esophageal squamous cell carcinoma. Also, the lack of effective diagnostic tools in low-income countries may give rise to the high incidence rate of esophageal cancer. These findings may help us understand the substantial decline in the incidence of esophageal squamous cell carcinoma, which may be related to the improved socioeconomic status worldwide.

Changes in the text: We have modified our text as advised. (see Page 23, line 389-397)

Comment 11:
Line 346-350: Please can the authors mention the model used to reduce this bias and how their choice of model compares to other models?

Reply 11:
We have mentioned the above-mentioned model in *Methods* section, which was recommended by GBD 2019 Diseases and Injuries Collaborators. Detailed information is listed below.

Some locations had high-quality incidence and mortality cancer registry data, whereas data were sparse in other locations. Therefore, incidence and mortality estimates were obtained with a combination of available data and modelling. We first calculated the mortality-to-incidence ratios (MIRs) in regions where incidence and mortality data were available in the same year. For other regions, a linear-step mixed-effects model with logit link functions was utilized to estimate MIRs, using the Healthcare Access and Quality (HAQ) Index, age, and sex as covariates. The estimates generated by this model were smoothed over time and space and further adjusted by spatiotemporal Gaussian process regression. The estimated mortality data for each region were calculated by multiplying the incidence data by the MIRs. The observed and estimated mortality data from MIRs were then fed into the Cause of Death Ensemble model (CODEm) to generate final mortality estimates. CODEm developed different personalized models with the highest predictive validity by integrating all available data and covariates to obtain the best fit.

Reviewer E

Comment 1:
As stated in the introduction, esophageal cancer can be divided in 2 histological subtypes i.e adenocarcinoma and squamous cell carcinoma. However, the difference in these 2 subtypes was not reported in the data (i.e. the epidemiology trends are not subdivided by histological subtype).

More data on the difference between these 2 subtypes in terms of incidence rates and mortality would be interesting. This would also improve the discussion section of the article where the authors report on the incidence rate and risk factors for squamous cell carcinoma versus adenocarcinoma.

Reply 1:
The two main histological subtypes of esophageal cancer, esophageal squamous cell carcinoma and esophageal adenocarcinoma, have distinct risk factors, incidence trends, and geographical distributions, but data for these two subtypes are not currently captured independently in GBD. Hence, we suggest collection of data by histological subtype, where possible. In this paper, by linking the GBD estimates to subtype distribution of esophageal cancer to certain region or area, we were able to find a partial solution to this limitation. More data are warranted on the difference between these two subtypes in terms of incidence rates and mortality.

Comment 2:
In the results section, the authors do not report on the patient inclusion process. Are certain patients excluded? A flowchart demonstrating the patient inclusion process could be beneficial.

Reply 2:
This study did not involve the inclusion and exclusion of patients. Data sources from GBD 2019 included vital registration (22020 site-years), vital registration-samples (825 site-years), verbal autopsy (514 site-years), and cancer registry (5288 site-years). Specifically, Cancer Incidence in Five Continents (CI5) volumes I–XI contains data on cancer incidence from cancer registries of high quality in a substantial proportion of the countries/regions around the world. Data on the population size, numbers of new cancer cases, crude incidence rate, adjusted incidence rates, and standard errors reported by age, gender, cancer type, country, region, and calendar year were available in CI5.

Reviewer F

Comment 1:
As the authors have observed an overall decline since 1990, however, there seemed to have been an increase in incidence and mortality in the last two years, this warrants a more detailed analysis looking at several time periods, for example 10 or 5 year periods, if this data is available. If not the differences between 2017 and 19 should be emphasised.

Reply 1:
Thank you for your kind comments and useful suggestions for strengthening our study. We have noticed that there seemed to have been an increase in incidence and mortality in the last two years. As we know, many factors, including lifestyle changes, exposure to risk factors, and expanding coverage of tumor detection and reporting, have contributed to the temporal trends of EC incidence. More importantly, since the marked alterations in risk factors over the last decades, EC incidence might be subsequently changed in the near future. The changes in the past two years are not sufficient to indicate the trend of future incidence of EC. Further knowledge of the future trends of EC incidence is therefore critical for understanding and planning in regard to this disease burden and permits the modification of the national health system to respond to future challenges.

Previous studies have described EC incidence, but these studies were retrospective in nature and consequently lacked insight into the future EC burden. Additionally, the number of cancer cases or deaths is the total number of people within a population who have either been diagnosed with or die from cancer, and this is greatly influenced by the size and age composition of the population. This information is critical to understanding and planning for the disease burden. To address this limitation, a Bayesian age-period-cohort modeling study is underway to project both the future number of EC cancer cases and incidence through 2039. Our predictions are of importance for the re-allocation of limited medical resources and to update the prevention strategies for EC.

Comment 2:
The authors commented in the limitations section in the Discussion that there was no or little data on the two main subtypes, OAC and OSCC, available. However, in lines 279-283 the authors briefly discuss that there was a decrease in incidence rate in regions with OSCC as major subtype and increase in regions with OAC as major subtypes. It would be very interesting to see the countries / regions presented ordered

or clustered by major subtype so it can be seen in tables and figures that there are differences between areas with different prominent subtypes.

Reply 2:

The two main histological subtypes of esophageal cancer, esophageal squamous cell carcinoma and esophageal adenocarcinoma, have distinct risk factors, incidence trends, and geographical distributions, but data for these two subtypes are not currently captured independently in GBD. Hence, we suggest collection of data by histological subtype, where possible. In this paper, by linking the GBD estimates to subtype distribution of esophageal cancer to certain region or area, we were able to find a partial solution to this limitation. More data are warranted on the difference between these two subtypes in terms of incidence rates and mortality.