

December 18, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6273-revised.doc)

Title: Ecological study of gastric cancer in Brazil: geographic and time trend analysis

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Name of the Journal: World Journal of Gastroenterology

ESPS Manuscript NO.: 6273

The manuscript has been improved according to the suggestions of the reviewers.

1. **Format has been updated**
2. **Revision has been made according to the suggestions of the three reviewers.**

We thank the reviewers for finding the results of our study interesting and for reading in detail our manuscript. We understand that our study is even more consistent after the changes, contributing for the manuscript improvement.

Reviewers' Comments:

Reviewer#1

This manuscript provided limited information of ecological study in gastric cancer.

We have to admit it is difficult to understand this reviewer's point of view. Unfortunately, the reviewer provided very little information on what exactly he/she thinks of our manuscript. We also really wanted to have more information for our analysis and research in general. On the other hand, we are happy to see the results of our investigation. We did our best to build a gigantic database, working in the "real world" with population data reaching millions, of people distributed in thousands of different and heterogeneous municipalities. This is our first effort in order to understand gastric cancer in an ecological study, and we understand we have paved the road to future developments and clarifications.

Reviewer#2

Minor corrections

We thank this reviewer for reading attentively and understanding our manuscript and for giving support to our work.

1) Page 3, Line 13. The authors say: "Spatial distribution of GC showed that rates are higher in the south and southeast." Please revise the "are" to "were".

We apologize for this mistake and it was corrected in accordance to the reviewer's suggestion.

2) Page 3, Line 14. The authors say: "However, while rates in the central-west and south decreased, they increased in the northern regions." Please revise this sentence to make it more clear.

We agree with this reviewer's point of view, and we tried to amend the sentence in order to make it clearer.

3) Page 12, line 13. The authors say: "On the other hand, geographic clustering of GC is still evident in China, and high-risk areas are located in rural areas, especially in the north [32]". Please add the following references at the end of this sentence: Guo P, Huang ZL, Yu P, Li K. Trends in cancer mortality in China: an update. Ann Oncol. 2012 Oct;23(10):2755-62.

We agree with this reviewer's observation, and the reference was included in the manuscript.

4) Table 1 and Table 2 should be revised to be a standard format for publication.

We apologize for this mistake and it was corrected in accordance to the reviewer's suggestion.

Reviewer#3

This data-base based study explores variations in rates of gastric cancer, and consequent deaths, across Brazil over 2005 to 2010.

We thank reviewer #3 for his/her suggestions, which we believe helped us in improving the overall quality of our manuscript.

Comments:

1. There are several errors of English grammar that should be corrected.

We apologize for this, and we managed to revise the entire manuscript for language refinement and corrections.

2. Wouldn't hospital discharge records be more helpful than admission paperwork? (Introduction). Patients may be admitted with symptoms, and be discharged after diagnosis is made with finding of GC. In addition, would the database record patients that were admitted for outpatient procedures (such as endoscopy alone)?

We agree with this comment and we apologize for not being clear enough. Actually, we utilized data regarding the "final" diagnosis, what means exactly hospital discharge records (diagnosis). We corrected the manuscript for precision.

In respect of the second question, we utilized data from all hospital admissions, including procedures (endoscopy) even if hospitalization was for less than 24 hours (day-hospital admissions, for example).

3. Subheadings in sections such as the Results would help the reader.

We included subheadings in the results session as suggested.

4. Page 6 comments on a "tendency for increase" and "clear differences". These phrases should be more explicit - either there was no difference (after statistical analysis) or there was a difference

We apologize for this and we agree with this reviewer's point of view. We rephrased the sentences in order to make them clearer.

5. The first paragraph on page 9 includes a sentence that gives three ranges and then concludes with the word respectively. This same phrase is used later also. It is not clear what this refers to: the authors should make this more clear and precise.

We again agree with this reviewer and we rephrased the sentences.

6. Page 9 refers to the variation according to distance from the sea and urban/rural differences. Are these variations just the same observation? Or are these independent effects?

In fact, these variations are independent in theory. But actually, as we state in the Results session regarding Figure 4, the coast-to-inland gradient in great part overlaps with urban-to-rural areas of the country. We believe that this observation reflects geographic and social-economic features of Brazilian society within the period of time analyzed. In addition, this information may reinforce the notion that the interaction of people with the geographic environments might determine/modulate economic and social development, with influence on demographics and health issues.

7. In the second sentence of the Discussion, the words tends is the wrong tense. However, it should be made clear if this was a distinct difference after statistical analyses. Tended appears vague and unclear.

We did not want to sound too speculative and this is why we decided to keep the descriptive nature of the study. But, we understand this reviewer's point of view, and we followed his/her suggestions.

8. The authors focus on environmental differences to explain variations in locality. Could ethnic (genetic) differences contribute to this? Was ethnicity data available in the database?

This is an interesting question, but unfortunately this data is not available in our database (derived from the municipal registries of the public database/system). Nevertheless, the Brazilian population has the peculiarity of five centuries of ethnic admixtures of Europeans, Africans and native populations.

9. Also is socio-economic data available? Is this another factor (although may not be independent)?

This is another interesting question, and we would be very happy to have such information. However, again, this data is not available in our database. On the other hand, the municipal registries are improving, and we believe that the results from studies like this will probably serve to point out weaknesses and strengths of the current system and pave the road to novel developments in the near future.

10. The Discussion comments about the two types of GC. However, this report does not include any details of the types of GC that were diagnosed in these individuals. Are details of the histology available? If so, this would strengthen the points raised by the authors

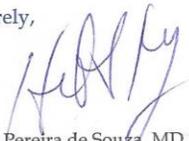
This reviewer is correct. We comment on the types of GC, because the differing pathogenic mechanisms could be associated with discrepancies observed in the spatial/geographic distribution of GC in Brazil. But, unfortunately, through this database we do not have access to histological information.

We thank the reviewers for lending support to our study and for giving us the opportunity to improve the manuscript.

3. References and typesetting were corrected.

Thank you again for publishing our manuscript in the World Journal of Gastroenterology

Yours sincerely,



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