

March 10, 2015

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Science Editor, Editorial Office

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Re: Manuscript ID 15996- "Gastric Cancer in Women: A Regional Health-Center Seven Year Retrospective Study."

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 15996.doc).

Title: Gastric Cancer in Women: A Regional Health-Center Seven Year Retrospective Study.

Author: Kunal Suryawala, Demiana Soliman, Monica Mutyala, Shaheen Nageeb, Moheb Boktor, Abhishek Seth, Avinash Aravantagi, Ankur Sheth, James Morris, Paul Jordan, Kenneth Manas, Urska Cvek, Marjan Trutschl, Felix Becker, Jonathan Alexander

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 15996

We appreciate the reviewer's comments and welcome the opportunity to address these queries and concerns in our current manuscript. Based on suggestions in the reviews, we have now addressed all reviewers' comments and editorial requests.

1. The format has been updated
2. All references and typesetting were corrected
3. Additional revisions have been made according to the suggestions of the reviewers

We now re-submit to you a revised version of our study, as well as this cover letter, which answers the reviewers' questions and criticisms, in a point-by-point discussion. The changes made in the revised manuscript are highlighted in **yellow** for clarity.

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

Review 1

Reviewed by **03017750**

The manuscript is well-written and provides interesting results about the ethnic influence on gastric cancer risk in a specific region of the USA. Before its acceptance, some minor corrections should be provided:

In Table 1 legend: Please, specify the meaning of the abbreviations on the table legend.

We thank the reviewer for this editorial comment. We have now included the respective meanings of all used abbreviations in the revised table legend for table 1.

Old: Table 1: 285 patients identified by our study for the period 2005 - 2011, by group

New: Table 1: A total of 285 patients were diagnosed with gastric cancer between 2005 and 2011. Patient numbers are presented per year and grouped by sex and ethnicity. WMs (non-Hispanic white males), WFs (non-Hispanic white females), AAMs (African American males), and AAFs (African American females).

Table 2: Is there any legend for Table 2??

We thank the reviewer for this valuable comment and apologize for mistakenly not providing the appropriate legend for table 2. As suggested, we now included a complete legend for table 2.

Old: Table 2: Clinic visits break down

New: Table 2: A total of 2,763 clinic visits for patients with the primary diagnosis of gastric cancer were identified between 2005 and 2011. The patient numbers are presented per year and grouped by sex and ethnicity. WMs (non-Hispanic white males), WFs (non-Hispanic white females), AAMs (African American males), and AAFs (African American females).

Page 13, Line 5-6: "AAFs represented a large fraction of patients diagnosed with GC below age of 50 (<age of 50)." Is really necessary to write (<age 50)? It seems repetitive for me.

We appreciate this comment by the reviewer and also agree that the chosen form of presentation leads to unnecessary repetitions. Accordingly, we have change the section and deleted the respective (< age 50) sentence.

Old: AAFs represented a large fraction of patients diagnosed with GC below age of 50 (<age of 50).

New: AAFs represented a large fraction of patients diagnosed with GC below age of 50.

Review 2

Reviewed by **02841708**

The authors should revise some problems in this study.

1. In this study, the authors stated their findings differed significantly from U.S. national trends. However, the reason was unclear from this paper. The authors should explain this difference.

We appreciate the reviewer's comment on this important point and we regret not having made this point clearer in the initially submitted manuscript. The main objective of this report was to demonstrate that cumulative studies such as those evaluating national trends may sometimes miss important regional differences in the demographics of disease, in this case gastric cancer. The differences from national trends seen in our study with respect to increased numbers of women being diagnosed with gastric could reflect regional geographic influences on disease penetrance, socio-economic risk factors as well as methods and frequency of surveillance.

2. The entry data is suspicious. Were all the gastric cancer patients in hospital African Americans or non-Hispanic whites? Whether there were other ethnic GC patients in this region? If there had been other ethnic GC patients in this region, what were their epidemiological characteristics?

We appreciate the reviewer's comment on this important point and we regret not having made this point clearer in the initially submitted manuscript. The reviewer is correct that were other than the described 285 African American or non-Hispanic white patients diagnosed with gastric cancer within the study period. Since Hispanics comprise 4.7% and Asians make up 1.7% of the Louisiana population, we did in fact initially evaluate Hispanic and Asian patients in our study population, but found too few cases to sufficiently analyze the obtained data sets in the current study. As we describe in the manuscript (Material and Methods section, page 7, line 22-26) we only identified 3 Hispanic patients who matched the described inclusion criteria for gastric cancer in this study and then excluded them from our study protocol since it was not possible to accurately compare them to the significantly higher patient numbers found for Whites and African Americans.

Since we agree with the reviewer that this is a neglected point of interest, we have now included a clearer explanation in the manuscript.

Old: From the 3 million patients investigated at LSUHSC-S over the seven years study period, only 2.5% were other races than AAs and Ws, which allowed us to only identify 3 Hispanic patients who matched our previously described inclusion criteria for GC (see above). Therefore, we excluded Hispanic patients from our study protocol since it was not possible to accurately compare them to Ws and AAs.

New: From the 3 million patients investigated at LSUHSC-S over the seven years study period, only 2.5% were other races than AAs and Ws, which allowed us to only identify 3 Hispanic patients who matched our previously described inclusion criteria for GC (see above). Therefore, we excluded **all 3** Hispanic patients **diagnosed with gastric cancer** from our study protocol since it was not possible to accurately compare them to Ws and AAs.

3. The 'Discussion' section was too long, and in this section, the authors wrote much that was not related to their results. The authors should rewrite this section.

We really appreciate the reviewers comment and have accordingly changed our Discussion section.

Review 3

Reviewed by **03017762**

The means of this manuscript is unclear. The purpose of this study should be clarified.

We appreciate the critical standpoint of this reviewer and apologize for not better defining the purpose and scientific merit of our study. We feel that our data has merit and represents a valuable scientific contribution since ethnic divisions exist in various nations and create both risks and resistances to medical conditions, a point which may be worthy of consideration outside of the United States. For example, ethnic groupings are not only described in the United States, but also in large nations such as China where at least 55 ethnic groupings have been recognized and regional trends in different diseases have already been described. It is our opinion that the present study has important scientific merit for the World Journal of Gastroenterology and especially for its globally distributed readership. We think particularly because it is the World Journal of Gastroenterology, our article is attractive, since this journal appeals to clinicians and researchers around the world, who might benefit in their daily work from the unique described regional trends in our study. Since we based our research on the population present in North Louisiana, we were able to determine different trends in African Americans and Whites, eliminating the usual problem of an unequal distribution of these ethnic groups within mixed populations. This is a biasing factor, which might lead to underestimated risk stratifications within diverse and unevenly distributed ethnical societies. In line with this, the authors strongly believe that our regional study, demonstrating gastric cancer trends within a nearly equally distributed African American and White population, can lead to more specific risk stratification of even small ethnic groups in global populations.

This being said, we would like to refer to a section in our manuscript (Conclusion section, page 15 to 16, line 24 to 6) in which we critically defined purpose and aim of the current study.

Discussion is too long, unclear, and the same discussions were repeated. This manuscript of assembly is very poor.

We thank the reviewer for these editorial comments. We have now changed the abstract, revised the presented tables including all table legends, shortened the result section and streamlined the discussion part. As seen in the reviewers response to **03017749**, **02841708** and **03017750** we hope that our revised and edited manuscript now please the reviewers critic about the content and assembly of the current manuscript.

Review 4

Reviewed by **03017749**

The morbidity of gastric cancer differs from different region, nation, and ethnicity. This article retrospectively reviewed the morbidity character of Gastric cancer at Louisiana State University Health Sciences Center-Shreveport, and compared it with the U.S. national report. It was concluded that the increase in gastric cancer diagnoses among women at LSUHSC-S is significantly higher than U.S. national averages and local geographic and socioeconomic influences may alter gastric cancer disease course.

My review comment:

- 1. This article mainly focused on the epidemiology study of gastric cancer at a local region, so it seems not necessary to combine the laboratory results of Helicobacter pylori (HP) infection into the article, which make the article more confused, even though the differences could be found.*

We thank the reviewer for this comment and agree that the main focus of our manuscript is concentrated on the epidemiology of gastric cancer at a local region. However, we included the presented data about existing infections with Helicobacter pylori to further guide our discussion about possible changes in the underlying gastric cancer risk factor profile, which might explain observed differences in gastric cancer diagnoses among women. Therefore, we feel that the Helicobacter pylori data represents an important part of our study.

However, we agree with the reviewer that the incorporation of this data might confuse multiple sections within our manuscript. Therefore, we have now shortened and streamlined the mentioned information about Helicobacter pylori diagnosis, and infection rates in our text.

Old: AAFs showed a higher frequency of HP diagnosis accounting for 46.4% of the total HP infection diagnoses. AAFs had significantly more annual HP diagnoses (annual mean of 9.29 ± 1.73) than both AAMs (annual mean of 5.14 ± 1.01 , $p < 0.05$) and WFs (annual mean of 4.57 ± 0.87 , $p < 0.05$) while WMs (annual mean of 1 ± 0.31) had significantly less HP diagnoses than both WFs ($p < 0.05$) and AAMs ($p < 0.05$).

New: Section deleted.

Old: HP infection as a ‘surrogate marker’ for GC risk. In a separate set of studies, we also used a primary diagnosis of HP infection as a ‘surrogate marker’ of additional potential risk of GC at LSUHSC-S from 2005 – 2011 (**Fig. 5**). Strikingly, AAFs had significantly more HP infection primary diagnoses compared to other groups (65 for AAFs, 36 for AAMs, 32 for WFs, and 7 for WMs). At LSUHSC-S, AAFs had more annual HP infection diagnoses (9.29 ± 1) than both AAMs (5.14 ± 1.01 HP infected individuals, $p < 0.05$) and WFs who had a mean of 4.6 ± 0.9 HP infections diagnosed annually ($p < 0.05$). WMs had only 1 ± 0.31 HP infections diagnoses annually which was significantly fewer than AAMs ($p < 0.05$). We also calculated the fraction of each group as a percentage of total HP infection diagnoses. AAs represent $69.6\% \pm 6.1\%$ ($25.1 \pm 3.6\%$ for AAMs and $44.5\% \pm 4.3\%$ for AAFs) of the total HP infection diagnoses. By comparison, Ws made up $30.36\% \pm 6.1\%$ of the HP infection diagnoses with $4.83\% \pm 1.7\%$ for WMs but $25.5\% \pm 5.6\%$ for WFs. Therefore, since HP infection is known to be a risk factor for GC, it is possible that AAFs have some increased risk because of their higher proportion of HP infection diagnoses compared with other groups. It is unclear whether the relatively higher proportion of HP diagnoses in WFs relative to WMs may help to explain the higher apparent increased risk of GC diagnosis in WFs in our study.

New: HP infection as a ‘surrogate marker’ for GC risk. We also used the primary diagnosis of HP infection as a ‘surrogate marker’ of additional risk for GC (**Fig. 5**). Strikingly, AAFs had significantly more HP infection primary diagnoses (65) compared to other groups (36 for AAMs, 32 for WFs, and 7 for WMs). AAFs had more annual HP infection diagnoses (9.29 ± 1) than both AAMs (5.14 ± 1.01 , $p < 0.05$) and WFs (4.6 ± 0.9 , $p < 0.05$). WMs had only 1 ± 0.31 HP infections diagnoses annually, which was significantly fewer compared to AAMs ($p < 0.05$). Therefore, because HP infection is known to be a risk factor for GC, it is possible that AAFs have some increased risk because of their higher proportion of HP infection diagnoses compared with other groups. It is unclear whether the relatively higher proportion of HP diagnoses in WFs relative to WMs may help to explain the higher apparent increased risk of GC diagnosis in WFs in our study.

2. *It is not proper to include the data of other report in the part of results.*

We appreciate the editorial advice from the reviewer about the mentioning of other reports in the Results section of our manuscript. We thank the reviewer for this comment and accordingly have changed the respective sections.

Old: Data were collected on patients as to calculate the annual number of GC cases diagnosed in different population groups at LSUHSC-S. While there was a significant difference in annual numbers of

individuals diagnosed between African American and white ethnicities, unlike national studies, gender did not influence the frequency of diagnosis within racial groups. That is, women within both racial groups were diagnosed at approximately equal proportions as their male counterparts, compared to national trends for incidence of GC, consistent with greater risk for females.

New: Data were collected on patients as to calculate the annual number of GC cases diagnosed in different population groups. During the study period (2005 to 2011), we identified 285 patients who were diagnosed with GC at LSUHSC-S. We found a total of 181 AA (63.5% of the total number of patients, 89 males and 92 females) and 104 W (36.5% of total patients, 54 males and 50 females) patients who were newly diagnosed with GC. While there was a significant difference between AA and W ethnicities in terms of the annual number of individuals diagnosed with GC, gender did not influence the frequency of GC diagnoses within the racial groups. That is, women in both racial groups were diagnosed at approximately equal proportions as their male counterparts.

Old: National trends in GC – Influence of ethnicity and gender. We used the U.S. national trends for GC incidence from 2005-2011 as shown in (Fig. 1B) as a scale for our results, which reflect diagnoses per 100,000 individuals. The national GC incidence (2005 - 2011) was greater among AAMs (mean of 16.3 ± 0.76) than AAFs (8.67 ± 0.34 , $p < 0.001$), WMs (9 ± 0.1 , $p < 0.001$) and WFs (4.05 ± 0.07 , $p < 0.001$). Further, WMs had higher GC incidence than WFs ($p < 0.001$). AAFs also showed a statistically significant higher proportion of GC diagnoses than WFs ($p < 0.001$).

New: We deleted the above mentioned paragraph from the Results section and incorporated the presented data in the discussion section.

3. *Too much abbreviations were used in the abstract, that make the reading more difficult. Some may be eliminated, such as "African Americans (AAs)", which does not appear very often.*

We thank the reviewer for this reasonable comment regarding the reading flow within our abstract. We agree, that the use of multiple abbreviations interrupts the reading flow. Accordingly, we have now changed the abstract as suggested.

4. *Some contents, such as " Our findings differed significantly from U.S. national trends, which found that AAFs and WFs had lower risks for GC than their corresponding male counterparts." should be mentioned in the discussion part, other than in the results.*

We appreciate the reviewers comment and have now moved all respective sentences, which mentioned other then our own results from the result into the discussion section.

5. *Please notice the limitation of word number which the journal requires.*

We thank the reviewer for this important comment. Based on the reviewers suggestion and the required word limitation from the World Journal of Gastroenterology, we have now shortened our discussion from 1729 to 1173 words.

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

Sincerely yours,



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