Author’s response to reviews

Title: Gastric Helicobacter pylori Infection Associates with an Increased Risk of Colorectal Polyps

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Author’s response to reviews: see over
Dear Dr. Solera,

Enclosed is our revised manuscript entitled “Gastric Helicobacter pylori Infection Associates with an increased Risk of Colorectal Polyps” for your consideration for publication in BMC Cancer. We would like to thank you for the opportunity to resubmit our manuscript that has greatly benefited from the reviewers’ comments. Attached to this submission is an answer to the reviewers’ raised concerns. We report the results of an original research, not published or under consideration elsewhere. This is the first report of an increased H. pylori associated risk of colon polyps formation in a unique population with high risk of colon cancer. Our epidemiological and serological analysis showed that current gastric H. pylori infection is associated with an increased risk of colorectal polyps in African Americans. Patients with gastric H. pylori may benefit from early screening colonoscopy as a preventative measure for colorectal cancer.

The reviewer’s comments:

Reviewer 1: Asahi Hishida

1) As the association of HP infection with CRC risk is not yet established and thus may be unfamiliar to most of the general readers, this reviewer recommends the authors to make their introduction a bit more like a systematic review style (a bit more precise review of this association would be appreciated).

Response: The introduction section has been revised to address the reviewer’s comment and new publications have been added including two recent review papers on the subject:


2) As many of the readers may not be familiar with the “baseline alarm features” (page 9), and this notion is considered important in the context of CRC early detection/prevention, I recommend the authors to describe/explain it briefly in the corresponding section.

Response: The “baseline alarm features” term was used like ‘high risk features’ in this paper. We did remove this term and are using only “high risk features that we define below under point#6 and in the text of the paper.

3) How was the Cag A positive rate in the study population, and how was it compared with the general African-American population? Are the Cag A’s of H. pylori residing in Af-Am patients’ stomachs Western type Cag A’s or Eastern type ones? Related to this, what is supposed to be the clinical implications of HP Ab- & Cag Ab+ subjects in Table 4?

Response: The Cag-A was not determined in the epidemiological study group (n=1256). In this group, only immunohistochemistry was performed using an anti-HP antibody. The Cag-A was determined serologically only in the prospectively collected samples (n=163, Table 4). We did not perform DNA sequencing to determine which Cag-A type our patients were infected with.

4) Is the sample size of the present study population large enough to draw a reliable conclusion, including those of the subgroup analyses (H. pylori status, etc.)?

Response: As for the epidemiological study, the sample size have generated statistically significant outcomes that are reliable. The serological section of our paper, while performed on a smaller sample size, generated data in the same direction as the epidemiological study pointing to an association of gastric H. pylori infection with increased colon polyp risk.

5) While the study population is limited to Af-Am in the present study, some readers may also be curious about this association in other races/ethnicities. Please discuss if possible.

Response: We have included new and recent publications in other populations in this version both in the Introduction and discussion sections (See point#2 above). Also, we have discussed and compared our findings to Indian, Finnish and other populations in the discussion.

6) The “baseline high risk” in Table 2 may need some additional explanation, maybe in the footnotes or in other appropriate sections. Please consider describing it.

Response: The following criteria have been added to define high risk factors for colon polyps or adenomas; “lower GI blood loss, abdominal mass and/or family/personal history of colorectal polyps or cancer”.

Reviewer 2: Lucia Braga
Discretionary Revisions
1-The title,
The present study was conducted in well defined population,
the title should be Gastric Helicobacter pylori Infection Associates with an Increased Risk of Colorectal Polyps in African American
Response: The suggested change in title was incorporated.

2-The abstract,
The conclusion of the abstract needs be reviewed The H.pylori serological results
did not show statistically significant association with an increased risk of colorectal polyps in the sample population evaluated.

**Response:** The statement referring to serological results have been edited to address the reviewer’s comment. The non-statistical significance of the serological data is cited in the results section in the abstract while the conclusion section refers to “This study showed that current gastric H. pylori infection is associated with an increased risk of colorectal polyps in African Americans.” Instead of the previous statement: “Epidemiological and serological analysis showed………..”

3-Methods
In the present Study Helicobacter was demonstrated by immunohistochemistry staining. It is necessary to add the reference of the anti- Helicobacter immunohistochemical stain used.

**Response:** The following statement has been added to Methods section; “A Novocastra Liquid mouse monoclonal ant-\textit{H. pylori} antibody was used (NCL-L-HPylori, Clone#ULC3R, Leica Biosystems)”.

4-Results
Table 2 shows that chronic active gastritis were associated with adenoma unadjusted OR (95% CI): 1.3 (1.0-1.8); \( P=0.04 \) It would be important to evaluate whether this variable remains significantly associated with adenoma in multivariate analyze.

**Response:** We thank the reviewer for his comment. We have performed a multivariate analysis (See Table 3), where we clearly show that chronic active gastritis alone does not remain significant.

Based on the results showed in Table 1, 367 patients had chronic active gastritis, of those 305 were H.pylori positive and 62 were H.pylori negative. It will be interesting to analyze specifically the association of H.pylori-positive chronic active gastritis with colonic lesions.

**Response:** This was checked in a separate analysis and reported in Table 2. Due to co-linearity we were not able to enter both “HP” and “HP positive chronic active gastritis” together in multivariate models, so we tried them in two separate multivariate analyses.

5- References
The references are relevant to the article, however it should be updated since recently it has been published several papers including a meta-analysis study.

**Response:** The paper has been revised in light of new publications that have been added to the references’ section (See response to point#2 by the first reviewer).

Thank you for your time and consideration.

Sincerely,

Hassan Ashktorab, Ph.D.