ANSWERING REVIEWERS

November 19, 2013

Dear Qi Yuan (Editor),

Please find enclosed the edited manuscript in Word format (file name: 6137-topic highlight. doc).

Title: *Helicobacter pylori*-related chronic gastritis as a risk factor for colonic neoplasms.

Author: Izumi Inoue, Jun Kato, Hideyuki Tamai, Mikitaka Iguchi, Takao Maekita, Noriko Yoshimura, Masao Ichinose.

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6137

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

1 Format has been updated

2 Revisions have been made according to the suggestions of the reviewers

Reviewer 1

(1) Statistical analysis on their own published studies is in general poorly described. For example, the statement in Page 4-5 regarding the studies described in Ref 14 and 17 is confusing. It is stated that CAG based on the criteria of PG I ≤70 ng/ml and PG I/II ≤3.0 were not associated with a significantly increased risk of colorectal neoplasm. But adjusted OR of 1.56 and 1.45 are shown in Table 2 for cancer and adenoma, respectively. Does this suggest that P values >0.05?

I think that the reviewer perhaps misinterpreted the data and descriptions in Table 2.

In general, results are considered statistically significant for $P<0.05$ when the 95% CI does not contain the value 1. Both studies with statistically significant results and studies without significant results are listed in Table 2. In addition, Ref 14 is authored by Machida et al.; that is, Ref 14 was not our study but Ref 17 was our own study.

(2) Information in the Tables and description in the text do not closely match to each other. For example, in Page 6, the authors described association of CAG with increased risk of recurrent colorectal neoplasm. This information could not be found in Table 2. But Table 2 information on adenoma was not described in the text.

This comment by the reviewer is a little difficult to understand. I think that the reviewer perhaps misunderstood the results shown in Table 2.

Both Ref 17 and Ref 27 were our own studies. Ref 17 showed the correlation between CAG and colorectal adenoma prevalence (please see second row in Table 2). On the other hand, Ref 27 displayed the correlation between CAG and colorectal neoplasia (adenoma and cancer) recurrence (please see the last row in Table 2).

Reviewer 2

(1) The weak sides or the degree of quality of the current data should be emphasized. Consequently, what the future directions in research may be should be summarized in several sentences more in the conclusion. This can be done by opening a new subtitle before conclusions.

Since our description was incomplete, we have rewritten the material in the Conclusion section in response to the reviewer's comment, as follows (page 14, lines 1-13):

"This review has shown that relatively few studies are available in this field, and the current evidence remains limited. Larger studies with adequate controls for confounders and that compare against normogastrinemic controls with *H. pylori*-free healthy gastric mucosa are necessary to clarify the role of *H. pylori*-related chronic gastritis in carcinogenesis of the colorectum.

In conclusion, based on critical analyses of previous studies, including our own, *H. pylori*-related chronic gastritis may well be associated with an increased risk of colorectal neoplasm. This risk appears to be further enhanced by the progression of atrophy or active inflammation. In areas where *H. pylori* infection is highly prevalent, the stage of *H. pylori*-related chronic gastritis could contribute to the identification of individuals at high risk of colorectal neoplasm. In addition, whether eradication therapy for *H. pylori*-infected subjects reduces the risk of colorectal neoplasm is a problem for future study."

Reviewer 3

(1) Will be careful with abbreviations eg of PG I & CAG in a subtitle etc (please explain) and polish the introduction a bit to set the background of this review in two short, clear paragraphs. The same goes for the rest of the manuscript.

In accordance with the reviewer's comment, detailed information about the PG test and CAG is included in the section "Correlation between *H. pylori*-related chronic atrophic gastritis (CAG) diagnosed on the basis of pepsinogen (PG) test results and risk of colorectal neoplasm", as follows (page 7, lines 2-6):

"The pepsinogen method is a reliable screening method for precancerous lesions of the stomach. In addition, serum PG I and the PG I/II ratio are also valuable markers for gastric acid secretion and the extent of resultant CAG caused by chronic gastritis. The combination of these two serum markers is the one most widely used for the detection of CAG in Japan."

Similarly, a detailed explanation about *H. pylori*-related chronic gastritis is included in the section "Progression of *H. pylori*-related chronic gastritis and risk of colorectal neoplasm", as follows (page 9, lines 10-14):

"Once established in the stomach mucosa, *H. pylori*-related chronic gastritis is generally believed to trigger a series of events involved in stomach carcinogenesis, represented as the gastritis-atrophy-metaplasia-dysplasia-cancer sequence. In addition, gastric atrophy and intestinal metaplasia, an end stage of *H. pylori*-related chronic gastritis, subsequently induce hypochlorhydria that may contribute to colorectal carcinogenesis."

(2) I would certainly expect a stronger, more detailed conclusion.

Following the reviewer's comment and also comment (1) of Reviewer 2, we have rewritten the Conclusion section (page 14, lines 1-13).

3 References and typesetting was corrected

[Reviewer 2 language evaluation: Grade A.

Please refer to attached the file (file name: native check letter), that is recommendation letter by professional English language editing companies.]

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

Sincerely yours,

Izumi Inoue, M.D.

Second Department of Internal Medicine

Wakayama Medical University

811-1 Kimiidera, Wakayama, Wakayama 641-0012, Japan

Tel: +81-734-47-2300; Fax: +81-734-45-3616

E-mail: izumiino@wakayama-med.ac.jp