2Format for ANSWERING REVIEWERS

January 21th, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6568-review.doc).

Title: Evaluation of routine biopsies in endoscopic screening for oesophagogastric junction (OGJ) cancer

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Name of Journal: *World Journal of Gastroenterology*

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

2 Revision has been made according to the suggestions of the reviewer (NO.00029045 and NO.00038786)

(1) We revised one sentence to avoid confusion: MATERIAL AND METHODS: Study design and Participants: 1st paragraph second sentence:
"Based on previous field studies and population registry data, each county has 10-20 villages. The target population (38-72 years old) accounted for approximately 25% of total residents in each county."

(2) We deleted one sentence to avoid confusion: MATERIAL AND METHODS: Study design and Participants: 2nd paragraph first sentence.

(3) We added two words in one sentence to clarify the process: MATERIAL AND METHODS: Endoscopic examination: 1st paragraph 5th sentence:
"If no mucosal abnormality was detected, 1-2 additional routine biopsies were obtained from the high incidence spot, which is at the right side of OGJ from the axial view, specifically at the most proximal gastric rugae of the lesser curvature."

(4) We add one sentence to declare that we used the same type of endoscope and system throughout the entire study. MATERIAL AND METHODS: Endoscopic examination: 1st paragraph last sentence:
"All endoscopic examinations were performed with the same type of endoscope (Olympus GIF-H260)."

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3 References and typesetting were corrected

4 Other questions from the reviewers that we would like to answer but did not revise the manuscript accordingly.

Reviewer NO.00029045

(1). Regarding to the questions "What about the patients with "positive" finding on normal mucosa? Do these patients underwent follow up? there were evidences of regression of positive finding?"

Findings with clinical implications, specifically high–grade intraepithelial neoplasia (HIN) or worse and were deemed as pathologically "positive" in our study. These patients were offered endoscopic mucosal resection or surgery, depending on the pathological grade. After treatment, different follow-up schemes were provided to these patients according to their pathologic diagnoses. For example, patients with HIN were required to undergo a follow up examination at least once a year. In previous studies by our co-investigators, there was evidence of regression of positive findings among patients who refused to undergo any kind of treatment but only the free follow-up endoscopic examinations. These findings were published in 2005 and 2009(please see reference 18 and 19). The patients with positive findings in our study all underwent different treatment according to their diagnosis. Regression after treatment was common in the follow up of patients with positive findings.

Reviewer NO.00038786

(1). Regarding to the questions" To show distribution of histology (low-grade, high-grade, intramucosal cancer, invasive cancer, etc) is recommended as the biopsy diagnosis in a table even if you diagnosed as only negative or positive. Additionally, final histological diagnosis after treatment is also necessary in a table."

Admittedly the distribution of histology is recommended by the reviewer, this study is a cross-sectional epidemiological study with the aim to determine whether additional routine biopsies at the high incidence spot of OGJ cancer are necessary in national mass screening programs among high-risk populations. Showing the distribution of histology will not be as efficient as dividing the participants into two groups: the ones with positive diagnoses whom follow-ups were provided to after treatment and the ones with negative diagnoses whom only follow-ups were provided to. Moreover, a different paper focusing on the progression and regression of pathological diagnoses in the follow-up after the endoscopic screening is in preparation by our pathology department. Our manuscript, on the other hand, mainly focused on whether the routine biopsies could result in more cases of positive diagnoses when screening for junctional adenocarcinomas.

The reason that we didn't show any final histological diagnosis after treatment is that even though all the patients with positive diagnoses underwent treatment, some of them took a relatively long time to come back for treatment. For example, one patient with positive histology took nearly 8 months to consider whether he wanted to receive our treatment since the endoscopic screening, so we were afraid there might be regression or progression on the original biopsy diagnoses. However, a second paper I mentioned under preparation by our pathology departments will address these questions with the original biopsy diagnoses, the histology diagnoses after treatment and the follow-up biopsy data.

(2). Regarding to the request "Please remake the table 1 to inform of exact numbers of 4 categories, endoscopy normal with pathology positive, endoscopy normal with pathology negative, endoscopy abnormal with pathology positive, and endoscopy abnormal with pathology negative in each county"

The fist reason why we didn't show the exact numbers of 4 categories in each county is that we already mentioned the uneven sampling of villages selected within each county could have resulted in heterogeneity within our study population. However, the purpose of this study was not to compare frequency distributions by counties, and the descriptive analysis of demographic characteristics showed similar mean ages and sex ratios (Table1). And showing the exact numbers of 4 categories would result in 8 more tables which would either not fit in the Table 1 with other important basic information or make it too confusing to read. Besides, the exact numbers of 4 categories in all 8 counties were showed in table 2 which is more illustrative from an epidemiological perspective than redundantly showing the distribution within each county.

(3). Regarding to the suggestion" The readers must want to know the breakdown of 94 cases with normal appearing mucosa with positive biopsy (high-grade, mucosal cancer, invasive cancer). The number of low grade biopsy is also meaningful to show."

As I stated above, this manuscript only focuses on clarifying the existing controversy among doctors regarding the use of routine biopsy of the high incidence spot of the OGJ using population-level data. From an epidemiological perspective, we wanted to decide whether the discovery of the asymmetrical circumferential distribution of lesions at the OGJ or the so-called high incidence spot could be applied in the design of guideline on screening for this cancer among high risk populations. The breakdown of 94 cases with normal appearing mucosa with positive diagnoses or the number of low grade biopsy are of great interests, however, they are not the concern of this manuscript. Several other papers concentrating on different aspects of this study are in preparation. For instance, our pathology department is submitting a manuscript regarding the progression and regression of pathological diagnoses in the follow-up after the endoscopic screening. In that paper, additional information about the breakdown of 94 cases with normal appearing mucosa with positive diagnoses or the number of low grade biopsy would be demonstrated in details.

(4). Regarding to the request" Please describe distribution of abnormal findings on OGJ. Were they mainly located in the right side? Consistency is necessary in both groups in your study subjects."

We already addressed this question in our manuscript. See the last but one paragraph concerning the weaknesses of our study that could merit further discussion. "Second，biopsies obtained from subjects with normal appearing mucosa were all targeted at the high incidence spot of OGJ cancers，whereas biopsies form participants with mucosal abnormality were only taken from visible lesions regardless of the anatomic sites at the OGJ. If all subjects had been biopsied form the high incidence spot of junctional cancers, we would have had more information regarding the prevalence of lesions at this site. Nevertheless, the aim of our study was not to investigate the prevalence of lesions originating from the high incidence spot. Furthermore, it would not have been ethical nor efficient to obtain unnecessary biopsies from participants given the primary goal of our study was to reduce the overall risk involved with endoscopic screening for OGJ cancers."

(5). Regarding to the question" OGJ cancers are closely associated with acid reflux symptoms, esophagitis, Barrett esophagus, H.pylori infection, etc. Did the authors collect these data to find out high-risk group of OGJ cancers?"

We did not find out high-risk group not by collecting risk factors. These eight counties we selected have the highest incidence of UGIC within China according to cancer registry. Due to this fact, we carried out mass screening in the villages we selected within these counties. This study was supported by our national health authorities as a health program conducted in these high-risk counties. All eligible subjects in each village were invited to participate. Every participant who met our inclusion criteria was considered as a high-risk person.

(6). Regarding to the question "Actually, I speculated the authors only targeted on adenocarcinoma in OGJ cancers. However, to confirm this speculation, please describe the fact. In China, squamous cell carcinomas of the esophagus are more predominantly observed. So the reason why the authors focused on adenocarcinoma in OGJ is a little questionable."

We answered this question in our manuscript, please see the Discussion section 5th paragraph. "The eight study sites chosen were formerly known as high risk areas of oesophageal squamous cell carcinoma (OSCC), but recent studies have found out that OGJ cancers and distal gastric carcinomas are increasingly prevalent and the clustering of UGIC were observed in all of these regions[6]. For instance, Cancer registry data from 2009 showed the age-standardized incidence of gastric cancer and oesophageal cancer were 198.55 and 111.99 per 100,000 for men and 69.50 and 53.61 per 100,000 for women respectively in Shexian[23]. Cancers of the OGJ are still classified as gastric cardia cancer (GCC) in the cancer registry and accounted for over fifty percent of new cases of gastric cancer among four high-risk areas of UGIC—namely Cixian, Shexian, Linzhou and Feicheng—from 2006 to 2008[24]. Our results showed 0.802% of the target population had HIN or higher-grade lesions, which is consistent with previous reports regarding high OGJ cancer prevalence among these high-risk areas."

(7). Regarding to the request" Please show the representative cases of endoscopic pictures in normal appearing

mucosa with positive biopsy."

Considering this manuscript mainly focused on the epidemiological content of our study, it would be redundant and inappropriate to include representative cases of endoscopic pictures in this manuscript. However, I would like to send the reviewer some typical pictures of our findings in private. And our endoscopic department has already submitted one paper concentrating on the display of abnormalities on the high incidence spot to a journal.

(8). Regarding to the suggestion "The discussion is too long. Please focus on only relevant topics obtained in this study"

Even though the discussion part is relatively longer than which in most manuscripts, the word count of our manuscript is within the limit. And the reason why we wanted to elaborate more on different aspects of OGJ cancers in China is that only a few papers in English about OGJ cancers in China have been published. Some of the topics and findings in the discussion were obtained from studies we conducted previously and they have only been published in Chinese. With the aim to better communicate with researchers from the world and let them have a look at the research frontier on OGJ cancers in China, we still would like to keep all the content in the discussion section.

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

Sincerely yours,

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