Dear Reviewers and Editors,

We thank you for reading the whole manuscript with so much interest as well as providing these illuminating comments and encouragement that enlighten us. We really appreciate it. Based on reviewers' comments and suggestions, we have made substantive amendment in the entire manuscript to improve its quality. The changed contents are highlighted in the revised manuscript file. Here are the point-by-point responses:

Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade A (Priority publishing)
Conclusion: Major revision
Specific Comments to Authors: In this case-control study, Pan et al reported an inverse relation between Helicobacter pylori Infection and the risk of esophageal precancerous lesions in drinkers. They also found a consumption of peanut might decrease the risk of H. pylori infection in a rural adult Chinese population. It is an interesting study. I have some comments and questions:

1. In this study, serum immunoglobulin G (IgG) antibodies by an ELISA assay (KingMed Diagnostics Group Co., Ltd. Guangzhou, China) were used for H. pylori infection screening. According to the result (Table 1), the mean ages of case group (with esophageal precancer lesion, EPL) and control group were 62.85 and 63.01 y/o. But the positive rates of H pylori infection were 23.5% and 29.0% in each group. The prevalence of H pylori infection in people aged more than 60 y/o was about (or more than) 50% in the previous studies. Hence, the positive rate of H pylori infection in this study was far less than the previous studies. Is the lower positive rate of H pylori infection due to selection bias after matching? Authors may draw a figure about study flow chart and explain how the case group and control group were found. Please give the information of the H. pylori infection rates by age classification in the study area (such as Huai'an District, Huai'an City, Jiangsu province). Moreover, please give the sensitivity and specificity of the ELISA test used for H. pylori infection screen in this study.

Response: The prevalence of H pylori infection in the previous studies was much higher than ours, which also confused us. The H. pylori infection rates by age classification in the study area Huai'an is unavailable, but there is a previous study published in 2000 which reported H. pylori infection rate in a Huai'an population (The Relationship between Helicobacter pylori Infection and Gastric Cancer in High and Low Incidence Areas for Upper Digestive Tract Cancers in Jiangsu Province (written in Chinese)). In this study, Huai'an was selected as a high incidence area for upper digestive tract cancers and Pizhou was selected as a low incidence area. They used ELISA and latex agglutinate test for H. pylori infection detection, and found that the prevalence of Hp infection among gastric cancer group/upper digestive tract cancers group in low incidence area of Pizhou (66.67%/63.46%) was significantly

higher than that in high incidence area of Huai'an (38.64%/39.33%). However, in high incidence area of Huai'an, the prevalence of Hp infection in non-cancer controls and the healthy family members of the cancer cases were higher than cases as well (46.81% and 47.83%). Therefore, both this previous study and our study found that the prevalence of Hp infection in Huai'an may be much lower than that in other areas, and the prevalence in upper digestive tract cancers or EPL cases can be lower than that in non-cancer population in this region. 20 years has passed, the improved living conditions may result in a decrease in the prevalence of Hp infection. But the low prevalence of Hp infection in Huai'an is very interesting, which can be further studied in the future. We also further discuss this phenomenon in the discussion (page 12, line 258-272, and page 13, line 283-284).

We draw a flowchart of study population and sample collection (Figure 1), and mention it in materials and methods in page 7, line 155-156 now.

Sensitivity of the ELISA test was 97.9 % with 95% CI: 88.9 % to 99.9% and specificity was 100% with 95% CI: 86.8 % to 100 %. We add this information in materials and methods in page 8, line 166-167 now.

2. According to the reference cited in this study (reference 21), the esophageal precancer lesions were detected by endoscopic finding using Lugol iodine solution spray. One of the hypotheses in this study is patients with H. pylori infection would develop atrophic gastritis and decrease the gastric acid production. Decreased gastric acid results into less reflux into the esophagus. EPL in the lower third of esophagus may be more associated with H. pylori infection. Are there any records or analyses about the localization (upper third, middle third, lower third in the esophagus) of EPL lesions and H. pylori infection?

Response: It is a very good suggestion. Based on the paper (Can patients determine the level of their dysphagia? World J Gastroenterol. 2017;23(6):1038-43), we add the definition of upper, mid and lower thoracic esophagus in materials and methods in page 7, line 150-155, and analyze the localization of EPL and Hp infection by Fisher exact test (page 8, line 173-174). The results are added in page 9, line 195-199 and Table 2. EPL in the lower thoracic esophagus has the lowest positive rate of Hp infection, which may support the hypotheses to some extent, but the difference was not statistically significant. We add this in the discussion as well (page 10, line 227-229).

3. Could authors describe more detail about the alcohol drinking volume evaluation? Questionnaire or lifetime alcohol drinking table? Because many kinds of wines (west, east, Chinese local wines) are available in China, the "current drinking status (alcohol units consumed/day)" may be difficult to be estimated. Did author use AUDIT or CAGE to evaluate the possibility of alcoholism in this study?

Response: Based on the questionnaire, details of alcohol use were collected, including the calculated alcohol units consumed per day (1 unit is 8g or 10ml of pure alcohol), duration of drinking habit (years), age at starting drinking, and types of alcoholic beverages regularly consumed (e.g. beer, wine and liquor). Cumulative consumption of alcohol (unit-years) was also calculated.

In the questionnaire, subjects need to provide the data of the amount of beer/wine/liquor/any other alcoholic drinks consumed per day, thus we can approximately estimate the alcohol units consumed per day by selecting the commonest alcohol level for these alcoholic beverages. But we didn't evaluate the possibility of alcoholism. Now we describe more detail about the alcohol drinking volume evaluation in materials and methods in page 7, line 160-162.

4. Because water contamination with H. pylori may be an important route for this bacterial infection, the sources of drinking water, such as tap water, deep well water or shallow wells, surface water, may be included in the analysis as a confounding and adjusted factor.

Response: Thanks for this suggestion! We used logistic regression model and found that there was no significant association between H. pylori infection and source of drinking water in this study (as shown in the following table). In addition, the number of "shallow wells and surface water" was too small. We also tried to analyze the data using the source of drinking water as a confounder, but the results were not influenced significantly. Therefore, we did not adjust this factor.

Table. Association between *H. pylori* infection and source of drinking water

Category	*H. pylori* (+) n = 105	*H. pylori* (−) n = 295	Adjusted OR (95% CI)[*]	*p* value
Source of drinking water				
Tap water	69	163	1.00 (reference)	
Deep well water	34	128	0.67 (0.41-1.11)	0.118
Shallow wells and surface water	2	4	1.105 (0.17-7.04)	0.916

[*] Unconditional logistic regression model, adjusted for gender, age, BMI, education level, annual income, number of cigarettes per day and alcohol units consumed per day.

5. In one study by Kuepper-Nybelen J (AP&T, 2005), a regular but moderate consumption of alcohol (consuming 25-50 g alcohol/day) from various sources may facilitate elimination of H. pylori infection. In the current study, H. pylori infection may decrease the risk of EPL in drinkers in a rural adult Chinese population. Is there a possibility of drinkers without H. pylori infection having more alcohol consumption? Hence, the decreased risk of EPL in drinkers with H. pylori infection may be related to a less alcohol drinking. In the same condition, people may drink wine and take

peanut at the same time in China. People who eat peanut may have drink more wine and get more risks of EPL.

Response: Thanks for the thought-provoking comment! Based on this hypothesis, we further analyze the association between H. pylori infection and alcohol units consumed/day (as shown in the following supplementary table 1 and 2). The results shows that there may be a nonsignificant decreasing trend of H. pylori infection rate when alcohol consumption is increasing. Therefore, this result may support the previous study that alcohol intake facilitates elimination of H. pylori infection to some extent, and there is a possibility of drinkers without H. pylori infection could have more alcohol consumption. However, because the result is not statistically significant, and there was no significant association between alcohol consumption and EPL risk in Huai'an in both this study and the study of reference 21, it is hard to address whether the reduced EPL risk in drinkers with H. pylori infection was associated with a less alcohol drinking. Now we add the two following tables in the supplementary material file and further discuss this in the results (page 9, line 203-204) and discussion (page 11, line 234-244), and cite the study by Kuepper-Nybelen J (AP&T, 2005).

In addition, we further analyze the association between peanut consumption and alcohol drinking. The results are added in Supplementary Table 3 and page 9-10, line 208-210), there may be a positive association between them ($P_{trend} < 0.05$). Therefore, the inverse association between peanut consumption and the risk of H. pylori infection may be mediated by alcohol drinking. We also discuss this in the discussion (page 11, line 251-255), and modify the conclusion of the abstract.

Supplementary Table 1. Association between *H. pylori* infection and drinking status

Category	*H. pylori* (+) n = 105	*H. pylori* (−) n = 295	Adjusted OR (95% CI)[*]	*p* value
Current drinking status (alcohol units consumed/day, 1 unit is 8 g or 10 mL of pure alcohol)				
Non-drinker	80	218	1.00 (reference)	
<4	6	14	1.18 (0.43-3.29)	0.750
4-	12	37	0.99 (0.46-2.14)	0.977
8-	7	26	0.76 (0.29-2.00)	0.576

[*] Unconditional logistic regression model, adjusted for gender, age, BMI, education level, annual income and number of cigarettes per day.

Supplementary Table 2. *H. pylori* infection and drinking amount in drinkers

Alcohol units consumed/day	*H. pylori* infection			*P*[*]
	Negative	Positive	Positive rate	
<4	14	6	30..0%	
4-	37	12	24.5%	0.771
8-	26	7	21.2%	

[*] χ^2 test, $\chi^2 = 0.520$.

Supplementary Table 3. Association between consumption of peanut and alcohol drinking

Category	Drinkers n = 102	Non-drinkers n = 298	Adjusted OR (95% CI)[*]	p value
Consumption of peanut				
No	4	13	1.00 (reference)	
< once/week	80	258	0.57 (0.15-2.18)	0.415
once/week - < 3 times/week	14	23	1.63 (0.35-7.65)	0.536
≥3 times/week	4	4	2.05 (0.24-17.67)	0.515
P_{trend}				0.044

[*] Unconditional logistic regression model, adjusted for gender, age, BMI, education level, annual income and number of cigarettes per day.

6. Minor correction: table 1, BMI, underweight (<24.0), may correct into (<18.5)
Response: "Underweight (<18.5)" has been corrected in Table 1 now.

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: The article entitled " Inverse Relations between Helicobacter pylori (H.pylori) Infection and Risk of Esophageal Precancerous Lesions in Drinkers and Peanut Consumption: A Case-Control Study in a Rural Adult Chinese Population " by the Da Pan et al. is devoted to the role of H. pylori in the risk of Esophageal Precancerous Lesions. The design of the study is well organized. The title, abstract and keywords correspond to the text of the article. The materials and methods section provides links with a detailed description of the methods. The authors examined a large group of patients. The selection and exclusion criteria were clearly defined and used. Methods of statistical processing of the data obtained were used. Using enzyme immunoassay to detect H.pylori, the authors obtained a low incidence of this bacterium in the examined groups. The authors found that H.pylori infection is associated with a reduced risk of Esophageal Precancerous Lesions in drinkers among the adult rural population of China, and peanut consumption leads to a reduced risk of H.pylori infection. It has also been shown that the risk of developing Esophageal Precancerous Lesions increases in malicious (more than 20 cigarettes per day) smokers. Based on this, it is necessary to conduct a multifactorial analysis of the relationship of these indicators for the development of Esophageal Precancerous Lesions. The authors appropriately cite the latest and relevant references. The data obtained by the authors are important for understanding the role of Helicobacter pylori for humans. Currently, there is more data indicating the positive role of this bacterium for humans. The review published in the WJG presents data that this bacterium probably is a commensal, or symbionote (Helicobacter pylori: Commensal,

symbiont or pathogen? World J Gastroenterol 2021; 27(7): 545-560.DOI: https://dx.doi.org/10.3748/wjg.v27.i7.545). The data presented by the authors confirm the postulate made in the review. Minor remarks: - in the abstract and in the materials and methods, it is necessary to represent the age of patients as (X ±SD years), and not as (±2 years) - in table 1, "Underweight (<24.0)" should be written "Underweight (<18.5)" - throughout the text of H. pylori, it is required to write in italics

Response: Thank you so much for your detailed comments. For the multifactorial analysis, we used multivariate logistic regression model to analyze the relationship of the indictors for the EPL risk with adjustment for confounders, and subgroup analysis was also conducted in Table 2.

The recommended paper (Helicobacter pylori: Commensal, symbiont or pathogen?) is a good review of the data of Helicobacter pylori. We found that the content of the review is important, thus we add some sentences (page 10-11, line 230-234) in the discussion based on this review and cite this reference.

We add "200 EPL cases aged 62.85 ± 6.03 and 200 healthy controls aged 63.01 ± 6.08" in the abstract (page 4, line 77-78) and in the materials and methods (page 7, line 157-158). "Underweight (<18.5)" has been corrected in Table 1 now. The text of H. pylori is written in italics in this paper.

(1) Science editor:

The manuscript is of potential interest; however, several issues need to be addressed. First, the sample size is small (200 cases and 200 controls), and so the findings should be framed as preliminary evidence since no firm conclusions can be made based on these numbers. Authors are invited to expand on the potential mechanism(s) by which peanut consumption decreases risk of H. pylori infection. Could this be due to confounding? The manuscript will benefit from addition English language editing. Please addressed the other concerns raised by the reviewers.
Language Quality: Grade C (A great deal of language polishing)
Scientific Quality: Grade C (Good)

Response: Thank you for your comments. We add this limitation of the sample size in page 12, line 276-278. Based on the comments and suggestions provided by Reviewer 1, we further discuss the potential mechanism by which peanut consumption decreases risk of H. pylori infection in page 11, line 251-255, and add a new supplementary Table 3. Although the inverse association between peanut consumption and the risk of H. pylori infection may be mediated by alcohol drinking, alcohol consumption has been adjusted as a confounder in the logistic regression model. Therefore, further studies are required to evaluate the association between peanut consumption and H. pylori infection. In addition, a native speaker, Mr Rob

Unwin, who is from the UK, just improved the language of the paper. We thank him for the proof reading in the acknowledgments.

(2) Company editor-in-chief:

I recommend the manuscript to be published in the World Journal of Gastrointestinal Oncology. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Response: Thank you for your suggestions. We have made substantive amendment in the entire manuscript to improve its quality based on reviewers' comments and suggestions. The changed contents are highlighted in the revised manuscript file. We also try the tool RCA and believe that this tool will be very useful in our following studies.