PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk Factors for Gastric Cancer and Related Serological Levels in Fujian, China: Hospital-based Case-control Study
AUTHORS	YUAN, Ping; Lin, Lan; Zheng, Kuicheng; Wang, Wen; Wu, Sihan; Huang, Liangxiang; Wu, Bingshan; Chen, Tiehui; Li, Xiaoqing; Cai, Lin

VERSION 1 – REVIEW

REVIEWER	XE-Peng FUJIAN MEDICAL UNIVERSITY China
REVIEW RETURNED	15-Mar-2020

GENERAL COMMENTS	This very well designed and written hospital-based case-control study considers the investigation of the relationship between gastric cancer and serum pepsinogen (PG) I, PG II, G-17 levels, the PGI/II ratio, H. pylori infection, as well as the risk factors of gastric cancer, including dietary and lifestyle factors in the Fujian province in China. The study was performed in 180 gastric cancer patients and 180 controls subjects using ELISA kits from BIOHIT, Finland for detection of serum levels of PG I, PG II and G-17 and also ELISA kits for detection of H. pylori antibodies in sera. The authors used also very precise questionnaires for evaluation of dietary habits, lifestyle and mental state. The main finding of the study was that levels of serum PG and G-17 as well as detection of H. pylori antibodies could be useful indicators of gastric cancer location and cancer stage. Remarkable finding was that scalding diet, consumption of pickled vegetables and frequent low mood may be a risk factors for gastric cancer. The authors give a well and clear overview about the study background and raised clearly the aim of the study, which is fulfilled. The authors present detailed description of the patients included in the study and of method used. The statistical analysis was specified and described very carefully. The material studied is large enough and allows to drawn the conclusions. The 7 Tables presented in the paper are accurate, detailed and give a good overview about the studied materials and results. The Results are presented clearly and have been discussed well. This study makes a contribution to studies of better understanding the mechanisms of carcinogenesis and evaluation the possible non-invasive diagnostic markers of gastric cancer patients. However, the following small point needs to be considered: the Fuzhou General Hospital of Nanjing Military Command of the Chinese People's Liberation Army – instead of NO.900 Hospital of the joint support force of the Chinese people's Liberation Army.

REVIEWER	Renato Cannizzaro
	Oncological Gastroenterology Unit, Centro Riferimento Oncologico IRCCS Aviano Italy
REVIEW RETURNED	24-Mar-2020

GENERAL COMMENTS	This is an interesting paper on risk factor in gastric cancer and serological markers. in an area with high incidence of gastric cance. Some points need to be clarified: what is the incidence of depression in same area, the alimentary questonaire can be shown in supplementary, and a comment on chronic atrophic gastritis in the same area is useful as PGi/PGII ratio is related to this disease. A nativ english

REVIEWER	Iktej Singh Jabbal
	Mayo Clinic, Jacksonville, Florida
REVIEW RETURNED	28-May-2020

GENERAL COMMENTS	The relationship between gastric cancer and the mentioned serum markers is already well known and published. With China having a huge incidence of gastric cancer, subjecting the entire population to screening gastroscopy and biopsy is neither feasible nor an easy thing to do. This is where the serum markers come in.
	- It would also have been useful to have an estimate of the combined diagnostic accuracy of all the serum markers on gastric cancer.
	- The need of the hour is to have a large scale study comparing the association between the serum markers and cancer. Going further, this study needs to have a larger sample size to draw conclusions which can be applied to the population at large.
	- It would be useful if the tables included in a publication were self explanatory. It would be helpful to have the abbreviations expanded for each table, which would prevent the readers from going back and forth between the text and the tables.
	- While the text may have accurate values to the last decimal place, rounding off to two decimal places in the tables makes it presentable and easy to read

VERSION 1 – AUTHOR RESPONSE

Responses to Editor Comments
Q1: - The Strengths and Limitations points should be one sentence each.
Re: As suggested, we have revised the strengths and limitations as follow.
Strengths and limitations of study
Fujian Province, high in gastric cancer incidences, is an important research site for exploring the etiologies of gastric cancer.
This study was one of the few studies to use serum indicators as independent variables to analyze the risk factors for gastric cancer.
Strict quality control was conducted in the selection of new cases to ensure comparable results.
However, as a case–control study, recall bias was inevitable and trial studies are required for more accurate results.
Sample size of this study was not large enough, further studies will recruit more subjects.
Q2- Please discuss the limitations of the study in the Discussion section.
Re: As suggested, we have added the discussion of limitations of the study in the Discussion section. They are as follows.

Strengths and limitations
There were some strengths in this study. Firstly, Fujian Province is an area with high incidence of gastric cancer in China. According to the report of Fujian Province, the incidence of gastric cancer collected from tumor registration areas in Fujian Province in 2017 was 31.68/100,000, accounting for 12.47% of all new cancer cases, ranking the third in cancer incidence; gastric cancer mortality rate was 25.90/100,000, accounting for 14.74% of all cancer deaths, also ranking the third in cancer deaths. Therefore, Fujian is an important research site for exploring the causes of gastric cancer. Secondly, strict quality control was conducted in this study in the selection of new cases to make sure the results be comparable. Taking into account the effects of proton pump inhibitors and H receptor antagonists on serum markers, patients who had taken these drugs within a week before recruiting were excluded. With strictly controlling the quality of selected cases, the difficulty in obtaining cases also increased. Thirdly, this study was one of the few studies to use serum indicators as independent variables to explore the risk factors for gastric cancer. However, several limitations should be considered. First, for a case–control study, the causal association between dietary/lifestyle habits and gastric cancer could not be precisely identified. Second, the consumptions of alcohol, tea, and pickled vegetables were self-reported. Subjects often had difficulties in recalling food consumptions and it was also hard to estimate the accurate amount of consumption. Therefore, recall bias and misclassification bias were inevitable. RCT studies shall be conducted for more accurate results. Third, the sample size was relatively small. China has high incidence of gastric cancer and provides favorable conditions for studying it. We plan to expand the sample size in our further researches on gastric cancer.

Responses to Reviewer 1
Q3: However, the following small point needs to be considered: the Fuzhou General Hospital of Nanjing Military Command of the Chinese People's Liberation Army – instead of NO.900 Hospital of the joint support force of the Chinese people's Liberation Army.
Re: Thank you for your suggestion. We did not update the name of the hospital in time. We have changed the name of hospital in all three places.

Responses to Reviewer 2
Q4:This is an interesting paper on risk factor in gastric cancer and serological markers. in an area with high incidence of gastric cance. Some points need to be clarified:
1) what is the incidence of depression in same area.
Re: According to Fang Xiang's report in 2011, in which an epidemiology survey with randomized sampling from 10 counties in Fujian Province was carried out to determine the prevalence and distribution of mental disorders in adults with 15 years of age and older, the prevalence of the non-specific depressive disorder was 2.29% and major depressive disorder was 3.35% in 9986 subjects.
However, in our manuscript, the word "depression" was misused. We were meant to describe someone who often felt troubled in life, which was correlated with the question K4 in the questionnaire: 'How does your life feel? Happy =1, feel troubled, but not much =2, often feel troubled =3'. In fact, this question was only asking the attitudes or feelings of respondents towards life. Therefore, based on the actual survey content on the questionnaire, we revised the expression to better describe the original meaning. We have changed the word "depression" to "often feel troubled" in the manuscript, as well as in table 2.
2) The alimentary questionnaire can be shown in supplementary.
Re: As suggested, we have uploaded the alimentary questionnaire as an attachment.

3) A comment on chronic atrophic gastritis in the same area is useful as PGI/PGII ratio is related to this disease.
Re: As suggested, we added a comment on the PGI/PGII ratio of chronic atrophic

gastritis in the same area in Discussion section. It is as follows:

PG I is primarily secreted by chief cells and mucous neck cells in the fundic glands, whereas PG II is secreted by all gastric glands and the proximal duodenal mucosa[26]. When chronic H. pylori infection with chronic atrophic gastritis (CAG) extends from antrum to corpus of stomach, chief cells are replaced by pyloric glands. Therefore, the concentration of serum PG I will decrease due to damaged secretion ability of gastric mucosa, however the secretion of PG II remains, resulting in a lowered PGI/II ratio, which would reflect the severity of CAG. Patients with premalignant lesions, such as CAG or dysplasia, have considerable higher risks for developing gastric cancer. Our previous study[27] explored the changes of serum PG levels in different gastric cancer states. Results found significant differences in serum PG I , PG II, and PGI/II ratio among the control group, the atrophic gastritis group, and the gastric cancer group (all P<0.001). Serum PG I level and PGI/II ratio were both the lowest in the gastric cancer group and the highest in the control group (all P<0.05).

Q4.4 A native English speaker have to review the paper.
Re: As kindly suggested, we have updated the manuscript thoroughly with a particular focus on the improvement of sentence structure and grammar issues. Zheng Huang, graduated from University of Kentucky in the United States, has proofread this manuscript.

Responses to Reviewer 3
Q5:The relationship between gastric cancer and the mentioned serum markers is already well known and published. With China having a huge incidence of gastric cancer, subjecting the entire population to screening gastroscopy and biopsy is neither feasible nor an easy thing to do. This is where the serum markers come in.
- It would also have been useful to have an estimate of the combined diagnostic accuracy of all the serum markers on gastric cancer.
Re: We couldn't agree with you more. In our study, we found that serum markers were independent risk factors for gastric cancer. In the next stage of our research, we will study the sensitivity and specificity of combined serum markers on early screening for gastric cancer.
- The need of the hour is to have a large scale study comparing the association between the serum markers and cancer. Going further, this study needs to have a larger sample size to draw conclusions which can be applied to the population at large.
Re: Absolutely, we will further expand the sample size to validate our results in the future.
- It would be useful if the tables included in a publication were self explanatory. It would be helpful to have the abbreviations expanded for each table, which would prevent the readers from going back and forth between the text and the tables.
Re: As suggested, we have added notes "PG is pepsinogen, and G-17 is Gastrin-17" Or " PG is pepsinogen" as shown in the notes of each table.
- While the text may have accurate values to the last decimal place, rounding off to two decimal places in the tables makes it presentable and easy to read
Re: As suggested, we have unified the data to two decimal places in all tables for easier reading.

VERSION 2 – REVIEW

REVIEWER	Renato Cannizzaro Centro Riferimento Oncologico IRCCS Aviano Italy
REVIEW RETURNED	27-Jul-2020

GENERAL COMMENTS	We can accept this paper

REVIEWER	Iktej Singh Jabbal Mayo Clinic, Florida, USA
REVIEW RETURNED	03-Aug-2020

GENERAL COMMENTS	Thank you for providing the opportunity to review this interesting work. As mentioned previously, further studies with a larger sample size should be conducted to enable a more robust evidence of association with gastric cancer. This can be a logical next step for this study. The study has otherwise been edited to include all the comments mentioned previously.

REVIEWER	Xiane Peng FUJIAN MEDICAL UNIVERSITY AND CHINA
REVIEW RETURNED	05-Aug-2020

GENERAL COMMENTS	In my view,the study is interesting and has a great applicative value in early screening and prevention for gastric cancer. In this study the authors examined the relationship between gastric cancer and serum PG I, PG II, G-17 levels, the PG I/II ratio, and H. pylori infection. They also investigated the risk factors of gastric cancer, including dietary and lifestyle factors, in the Fujian Province in China. They found that serum PG and G-17 levels, as well as presence of H. pylori antibodies, could be useful indicators of gastric cancer location and cancer stage. Elevation of serum G-17 levels may be indicative of the gastric cancer location, while an increase in the PG II level and a reduction in the PG I/II ratio may imply the clinical stage. They also contend that poor dietary habits, salty food, and anxiety/low mood may be risk factors for gastric cancer, while eating fresh fruit, onion, and garlic, and drinking tea may help protect against this disease. This study is relevant to important clinical issue – gastric cancer. It has a certain positive significance to reduce the incidence of gastric cancer in China.