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7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

Title: Association of Helicobacter pylori infection with colorectal polyps and malignancy in China.

Reviewer's code: 03260089

Position: Peer Reviewer

SPECIFIC COMMENTS TO AUTHORS

- Abstract, first sentence "Gastric Helicobacter pylori (H. pylori) are related to" Are there other types of H. pylori (non-gastric)? Why "are"? - Write the number of included patients in the abstract - Introduction, "Therefore, early screening and detection of precancerous lesions can prevent the occurrence and development of CRC." Cite, for example, Senore C et al. Management of Pt1 tumours removed by endoscopy during colorectal cancer screening: Outcome and treatment quality indicators. Eur J Surg Oncol. 2018 Dec;44(12):1873-1879. - "H. pylori ... and it is involved in tumorigenesis of extragastric target organs" Specify one or two examples - Did you include patients with Lynch syndrome? - You had an adenoma detection rate of about 60%, it is very high, try to explain the reason - Correct table 1 caption - Why p value in table 1 are all 0? The same is true for table 2 - Compare in a table, with the p value, the clinical characteristics of the group (for example age of group with polyps and group without polyps)

Reply:

Dear reviewer,

Thanks very much for your review, we have corrected the expression mistakes in the article. We didn't include patients with Lynch syndrome. We mean that the H. pylori positive rate in the adenomatous polyp group was 59.95%, instead of the adenoma detection rate of about 60%. Best



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wishes.



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PEER-REVIEW REPORT

Title: Association of Helicobacter pylori infection with colorectal polyps and malignancy in China.

Reviewer's code: 02462321

SPECIFIC COMMENTS TO AUTHORS

Association of Hp infection with CR polyps and malignancy in China By Man Wang et al The AA analyzed retrospectively 6,358 pts (out of 11,552) by means of colonoscopy, gastroscopy and 14C-UBT: 3872 CR polyps, 304 CRC, 2362 no colonic abnormalities. They found that 1)Pts with Hp infection and multiple polyps have an increased risk of CRC, compared with that of pts with solitary polyps. 2)Pts with adenomatous polyps have a higher incidence of Hp infection than those with non-adenomatous polyps. 3)Pts with Hp-associated atrophic gastritis or I.M. are at high risk of CRC They conclude that gastric Hp infection and Hp-associated AG or IM elevate the risk of polyps and CRC by 2.19 and 3.05 times respectively. Necessity of earlier and frequent colonoscopies is consequently stressed. Major comments: 1) As the Hp infection rate in China is more than 50% and pts with polyps in this study are more than pts without polyps (3872 vs 2362), the association found by the AA may be only the result of a simple coincidental co-existence of two highly incident conditions in this population. 2) Moreover, multiple polyps pts have per se an increased risk of CRC compared with pts with solitary polyps. The AA must pinpoint these possibilities in the discussion session. 3)Language needs minor polishing: In discussion session, -3rd sentence, the last word "population" is redundant (to be removed) -The sentence "The mechanism from Hp infection..." to be corrected> "The mechanism of Hp infection..." -In Table 1 the word "association" is repeated -In Table 1 and 2 the p-value column shows only "0" (at least in



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my PC): should be completed.

Reply:

Dear reviewer,

*Thank you very much for your review. We don't think this is a coincidence. The weighted mean prevalence of *H. pylori* infection across all years was 55 % for the Chinese datasets, and it was 35 % for the US datasets[1]. One study showed that current gastric *H. pylori* infection is associated with an increased risk of colorectal polyps in African Americans. They concluded patients with *H. pylori* induced gastritis may benefit from early screening colonoscopy as a preventative measure for colorectal cancer[2]. *H. pylori* infection rates are higher in the Chinese population, and we think our conclusions are meaningful. What's more, we have corrected the errors in the form as required. Best wishes.*

1.Nagy P, Johansson S, Molloy-Bland M. Systematic review of time trends in the prevalence of Helicobacter pylori infection in China and the USA. Gut Pathog.2016 Mar 15;8:8.doi: 10.1186/s13099-016-0091-7]

2.Brim H, Zahaf M, Laiyemo AO, Nouraie M, Pérez-Pérez GI, Smoot DT, Lee E,Razjouyan H, Ashktorab H. Gastric Helicobacter pylori infection associates with an increased risk of colorectal polyps in African Americans. BMC Cancer. 2014 Apr 28;14:296. doi: 10.1186/1471-2407-14-296.



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Title: Association of Helicobacter pylori infection with colorectal polyps and malignancy in China.

Reviewer's code: 02840182

SPECIFIC COMMENTS TO AUTHORS

The authors investigated relationship between H. pylori and CRC/colorectal polyps. They evaluated presence of H. pylori between groups in their retrospective study. The study has some advantages and limitations as well. The manuscript is well written. Groups have large number of patients. Although presence of H. pylori is more frequent in patients with colorectal polyp and CRC is still frequent in H. pylori negative groups. So a direct association could not establish between H. pylori and these pathological conditions. Other factors that have not been investigated are likely to affect developing these pathological conditions. And some corrections are required. 1. However, the polyp size and locations were not associated with H. pylori ($P=0.26$; $P=0.08$).... Please indicate p values separately according to the locations. 2. There is a writing error in table I 3. P values can not be 0. Please indicate two digits after the comma in tables and use same format in other sections. 4. Early colonoscopy screening and surveillance would may be necessary to reduce the risk of colonic polyps and CRC in patients with H. pylori infection. Further investigation would is required...

Reply:

Dear reviewer,

Thank you very much for your responsibe and careful reviewing. Except for age and gender, BMI, drinking and smoking and the genetic susceptibility, some undetermined factors have not been further analyzed in this study. This is a flaw in this study and has been listed in the discussion. However, sample sizes we have included is large, Our research still has certain



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reference significance for preventing gastrointestinal cancer. What's more, we have corrected the errors in the article as required. Best wishes.

Title: Association of Helicobacter pylori infection with colorectal polyps and malignancy in China.

Reviewer's code: 02954663

SPECIFIC COMMENTS TO AUTHORS

The manuscript is a well-written study of the interrelation between H pylori and CRC/colorectal polyps. Several same studies have been performed with discordant results, probably, this interrelationship is population-dependent and under influence of environmental and genetic factors. The number of cases is impressively great and the results are convincing. My concerns are: - why have you not used the Kudo or Paris classifications to determine which type of adenomas are associated with H. pylori? please comment on this - what about the flat adenomas: between 6000 cases, You most have had flat adenomas? - H. pylori is acquired in childhood, polyps occur later in life: please comment on the possibility of polyp prevention by proper eradication therapy; - where the pathologists examining gastric and colon samples experts in their field? -

Reply:

Dear reviewer,

Thank you very much for your careful and detailed review. In our department, NBI has been used in recent years. Not all patients were observed the glandular morphology of colon mucosa. Kudo classification is not popular, but we are learning it now. In the past, our department used Yamada classification to classify colorectal polyps. In recent years, we began to use Paris classification to classify colorectal polyps.



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Because of some cases were classified by Yamada classification, some were Paris classification, so it is difficult for us to investigate the correlation between Paris classification and H. pylori. We will do further research on this in the future. A total of 1588 patients with adenomatous polyps, most of them are flat adenomas. Hu et al[1] found that after successful eradication of H. pylori, the colorectal adenoma ratio might decrease. Relevant information has been added in our study. Pathologists are the deputy director or chief physician of the pathology department of our hospital. All the pathologists are good at analyzing both gastric and colon samples. Best wishes.

[1] Hu KC, Wu MS, Chu CH, Wang HY, Lin SC, Liu CC, Su TH, Liao WC, Chen CL, Liu CJ, Shih SC.

Decreased Colorectal Adenoma Risk After Helicobacter pylori Eradication: A Retrospective Cohort Study.

Clin Infect Dis. 2019 May 30;68(12):2105-2113 [PMID: 30566695 DOI: 10.1093/cid/ciy591]



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Title: Association of Helicobacter pylori infection with colorectal polyps and malignancy in China.

Reviewer's code: 02520359

SPECIFIC COMMENTS TO AUTHORS

Well written retrospective study examining the possible association of Helicobacter pylori infection with colorectal polyps and malignancy in Chinese patients. This study has several limitations stated in the manuscript, however this study has enrolled large number of patients to strengthen the results. The authors have to explain their main indications to perform gastroscopy and colonoscopy at the same time and to summarize them in a table, and to discuss more any confounding factors. The authors they don't give any information regarding the duration of H. pylori infection, the role of drinking and smoking and the genetic susceptibility.

Reply:

Dear reviewer,

Thank you very much for your review, we have revised it as required and added the confounding factors of drinking, smoking and the genetic susceptibility. In the study we mentioned that histopathological examination and ¹⁴C-urea breath test can only diagnose the current infection of H. pylori. We did not consider the possible effect of the duration of H. pylori infection on colorectal polyps and CRC. This is our limitation. Best wishes.