Reviewer #1

1. _My objections relate to the use of too vague phrases and very few references._

   Response

   Thank you for your advice. Added citations to increase contents are shown in the paper. However, ambiguous statements can be unavoidable, as the origin is not elucidated.

2. _Lack of logic in the first sentence of the Abstract: "Helicobacter pylori (H. pylori) infection causes dysbiosis in the intestinal flora, such as small intestinal bacterial overgrowth…" -> dysbiosis is a state of a lower amount of microbes, while SIBO as the name indicated is an overgrowth, thus maybe "changes" may be better_

   Response

   That is a good point. I revised it as follows.

   "_Helicobacter pylori (H. pylori)_ infection changes the intestinal flora, such as small intestinal bacterial overgrowth,"

3. _[Abstract] - "subjects carrying H. pylori vacuolar-forming toxin (VacA) antibody" -> should be "vacuolating cytotoxin A (VacA)"_

   Response

   Thank you for pointing out my careless mistake. I corrected it to vacuolating cytotoxin A.

4. _[Introduction] - "In this study, we will examine and discuss the effects of H. pylori infection on the small and large intestines." -> in this study only one author is present, thus "we" is may not the best_

   Response

   I appreciate your advice. I changed We to I.

5. _[Effects of Helicobacter pylori components] - "… confirmed by a stool test" -> confirmed by a stool antigen test in the routine diagnosis [Effects of Helicobacter pylori_

components] - Again should be "vacuolating cytotoxin A (VacA)"

Response

Thank you for your comment. I changed it in the same way as above.

6. *[Effects of Helicobacter pylori components] - the expression "DNA synthesis" is very unfortunate, because it does not introduce anything; there should be information about the expression of some genes, etc., the information about the increase in DNA synthesis is completely irrelevant*

Response

I understand what you mean. However, the research on DNA synthesis is carried out using the labeling index, therefore it is unknown what kind of gene was amplified. Information on this has been added to the text.

"Studies have reported that the bacterial component of *H. pylori* promotes DNA synthesis in a small intestinal cell line (IEC-6), as evaluated by the labeling index[14]."

7. *[Effects of Helicobacter pylori components] - A similar situation exists with the expression "bacterial component"; is it as general as possible. Is it some kind of toxin, enzyme, membrane proteins or maybe a peptidoglycan? The Author should be very precise in the description of information form the literature*

Response

Thank you for your great advice. At the moment, VacA is the main report, followed by CagA. VacA is currently the hot topic for colorectal tumors. We have increased the number of references and improved the content as follows.

"Butt J et al. recently observed an increased risk of developing colorectal cancer in individuals carrying serum antibodies against VacA of *H. pylori*[16]. Rassow J et al. reported in a review that VacA forms chloride (Cl^-) channels that enter the cell and mitochondrial membranes, and VacA causes loss of mitochondrial membrane potential, mitochondrial fragmentation, formation of reactive oxygen species, autophagy, cell death and gastric cancer[17]. Since Cl^- channel abnormalities are involved in cystic fibrosis, which is known to be associated with colorectal cancer, this VacA-induced Cl^- channel

abnormality may be involved in colorectal cancer[18]. Because Butt J et al. did not directly examine the bacterial cell components of the intestinal tract but examined serum antibodies, the effect of bacterial components could not be determined. However, blood antibodies are unlikely to be carcinogenic. Therefore, bacterial cell components have a high probability of being involved."

8. *[Changes in the intestinal flora] - "H. pylori is often infected ..." -> H. pylori is often infecting (people may be infected, not bacteria)*

   Response

   Thank you for pointing out the incorrect English. I changed it to "*H. pylori* often infect the stomach at an early age"

9. *[Changes in the intestinal flora] - "H. pylori increases Bifidobacterium" -> H. pylori increases an amount of Bifidobacterium*

   Response

   Thank you for pointing out my English mistaken. I corrected the point that were pointed out.

10. *Table 1: expression "bacterial component", "gastrointestinal hormone", "host immune response" or "immunological effects" are to broad, each time they must be named very precisely*

    Response

    I deeply understand what you pointed out, and I feel dissatisfied at the same time. Most reports are about phenomena, but do not test that investigate the cause. Therefore, this table may be ambiguous. I added the followings about this point.

    "Unfortunately, the wording in Table is ambiguous because it is not known exactly how *H. pylori* is involved in the disease."

__Re-reviewer:__

I would like to thank the Author of the manuscript for adhering to my comments. Although

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they may seem critical, the Author improved the manuscript, which contributed to the improvement of its quality (in this context, I am particularly thinking of increasing the amount of literature references and clarifying the necessary details). At the moment, the article is ready for publication.

Response

Thanks for your comments.

Reviewer #2

1. *Authors said that "Gastrin levels are reported to be high in patients with colorectal cancer[24]. On the other hand, recent reports have shown that gastrin is not associated with colon tumors[25]" Authors need to analysis the difference of the two research, the former research study the progastrin, amidated gastrin, and glycine extended gastrin level, found that plasma levels of progastrin, but not amidated gastrin or glycine extended gastrin, are significantly elevated in patients with colorectal cancer; the latter study the total gastrin level and found that hypergastrinemia did not increase the risk for any colonic neoplasms.*

Response

Thank you for your advice. Regarding gastrin, the text has been modified and improved as follows.

"Moreover, intestinal tract hormones, especially gastrin, are assumed to cause overgrowth in the large intestinal mucosa and to be closely related to large intestinal tumor development [29, 30]. And, the level of progastrin, but not gastrin, is reported to be high in patients with colorectal cancer[31]. In colorectal cancer, the gastrin receptor is overexpressed, and gastrin-binding capacity is increased 10-fold over that in normal colonic epithelium[32]. It has also been reported that the expression of gastrin and its receptor promotes the progression from colorectal adenoma to cancer[33]. In mice, gastrin treatment enhanced colon cancer cell growth and invasion and decreased oxidative stress and apoptosis[34]. Additionally, G-protein coupled receptor 56, which is expressed in colonic stem and cancer cells, is upregulated in transgenic mice overexpressing human progastrin[35]. Thus, although it is experimentally likely that gastrin and/or progastrin is involved in colon tumors, a recent patient study has found that gastrin was not associated with colon tumors[36]. At this time, I believe that gastrin and VacA are suitable candidates

to explain the development of colorectal tumors due to *H. pylori* infection."

2. Authors may need to discuss more about the mechanism of HP may causes colon tumor.

Response

I appreciate your advice. Regarding the mechanism of *H. pylori* may causes colon tumor, in addition to the gastrin mentioned above, the following sentences were added to improve it.

In Effects of Helicobacter pylori components

"Butt J et al. recently observed an increased risk of developing colorectal cancer in individuals carrying serum antibodies against VacA of *H. pylori*[16]. Rassow J et al. reported in a review that VacA forms chloride (Cl⁻) channels that enter the cell and mitochondrial membranes, and VacA causes loss of mitochondrial membrane potential, mitochondrial fragmentation, formation of reactive oxygen species, autophagy, cell death and gastric cancer[17]. Since Cl⁻ channel abnormalities are involved in cystic fibrosis, which is known to be associated with colorectal cancer, this VacA-induced Cl⁻ channel abnormality may be involved in colorectal cancer[18]. Because Butt J et al. did not directly examine the bacterial cell components of the intestinal tract but examined serum antibodies, the effect of bacterial components could not be determined. However, blood antibodies are unlikely to be carcinogenic. Therefore, bacterial cell components have a high probability of being involved."

In Changes in the intestinal flora

"It has been pointed out that dysbiosis may be associated with colorectal carcinogenesis[26], and research on this front is progressing. *H. pylori* causes dysbiosis, including SIBO, which may be the cause of colorectal cancer. It is hoped that further research will determine whether *H. pylori*-induced dysbiosis is associated with colorectal cancer."