

## Responses for reviewers

### Reviewer #1

*The major question in this manuscript is “why the gastric acid and duodenal ulcer did not concern?”. Please re-check this sentence “Adenocarcinoma is predominant in the jejunum in all reports comparing the jejunum and ileum.” In page6, paragraph2.*

#### Response

Thank you for your interesting point. We searched the literature for any relationship between gastric acid and duodenal ulcer and small intestinal cancer, but could not find any good literature pointing out the relationship. Because Vater papillary carcinoma of the duodenum influences the incidence of small intestinal cancer, we exclude the duodenum and compare the jejunum and ileum here. I corrected it as follows.

“When comparing the jejunum and the ileum and excluding the duodenum, adenocarcinoma was more common in the jejunum than in the ileum in all reports.”

### Reviewer #2

*Small intestinal adenocarcinoma is much less common than colorectal adenocarcinoma, and the content of the intestinal tract, which is difficult to absorb, stays in the ileum for a long time: please rewrite the core tip, you are comparing colon and small intestine and then you are saying the content stays in ileum, does not have a flow.*

#### Response

Thank you for your important point. We rewrote the core tip as below.

“When investigating the risk factors for small intestinal adenocarcinoma, an important point to note is that small intestinal adenocarcinoma is often found in the proximal small intestine. Intestinal contents remain in the ileum longer than in the jejunum, so poorly absorbed food is unlikely to be a carcinogenic factor. Animal proteins and lipids, bile concentrations, and aerobic bacteria, which are thought to be

concentrated in the proximal small intestine, may be carcinogens in the small intestine. Since small intestinal adenocarcinoma is much rarer than colorectal adenocarcinoma, it is unlikely that small intestinal villi are involved in carcinogenesis."

*Primary small intestinal malignancies include neuroendocrine tumors, sarcomas, and lymphomas : please include adenocarcinoma.*

Response

We wrote "Primary small intestinal malignancies include neuroendocrine tumors, sarcomas, and lymphomas in addition to adenocarcinomas.", so adenocarcinoma is included.

*Villi and circular folds in the small intestine occupy 98% of the surface area of the intestinal tract: You stated before, small intestine occupies 90% before, now you stated 98%, please explain.*

Response

Thank you for your advice. Since 90% is common knowledge, I changed it to "even reported as 98% and rewritten as below.

"Considering that the small intestinal villi and circular folds have even been reported to occupy 98% of the intestinal surface area<sup>[11]</sup>, the frequency of small intestinal adenocarcinoma per surface area is extremely low compared to that of colorectal adenocarcinoma."

*But no adenocarcinomas appeared at the administration site, which was the jejunum/ileum: what do you mean by intra-vascular, was it given directly to SMA ?, but that goes to duodenum as well and jejunum and ileum ?*

Response

The paper describes it as an intravenous injection. Although tumors occurred in the duodenum in this study, the duodenum was omitted to avoid confusion in our paper because this study was conducted at a time when papilla of Vater carcinoma was not differentiated.

*A mixture of bile and pancreatic juice passes through bile ducts and pancreatic ducts. It is natural to think that the carcinogenic origin in the papilla of Vater is different from that in the small intestinal mucosa. : But the same bile and pancreatic juice comes to small intestine eventually, so how is the exposure different ?*

Response

Thank you for your advice. In the papilla of Vater, the addition of carcinogenicity to the pancreatic and bile ducts was added to the text as follows.

“A mixture of bile and pancreatic juice passes through the papilla of Vater, and the bile and pancreatic ducts themselves have different carcinogenic properties.”

Also, the reason why there are few descriptions of pancreatic juice in the item of “Bile and pancreatic juice” is that there are no reports.

*In addition, reports of small intestinal neuroendocrine tumors are often reported in the jejunum within 1 m from the ileocecal valve: can you please confirm, most common site is TI, within 60cm from ileo-cecal valve.*

Response

Thank you for your advice. Sixty cm seems too strict for this paper, so we chose the paper described 1 m for our paper.

*However, it remains unclear whether immunity can explain why cancer is overwhelmingly less common in the small intestine than in the large intestine because there are few reports on this topic: citations*

Response

This issue is very important. It has been reported that the stem cells of the colonic epithelium are significantly more divided than the stem cells of the small intestinal epithelium. I believe that this division of stem cells is involved in the high incidence of colorectal cancer. However, it is not clear why the stem cells in the large intestine, which do not have villi, divide so often. This problem is not written in this paper because it requires a lot of assumptions.

**Reviewer #3**

*There are still great deal of syntax. Please consider re-revising from a native speaker expert in the filed.*

Response

Thank you for your advice. The English was re-edited by a native speaker specializing in medicine.