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Could microbiome analysis be a new diagnostic tool in gastric carcinogenesis for high risk, Helicobacter pylori negative patients?

Turshudzhyan *et al*. Microbiome in gastric tumorigenesis

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Abstract

H.pylori has long been believed to be the major colonizer of the stomach, but recent advances in genetic sequencing has allowed for further differentiation of the gastric microbiome and revealed the true complexity of the gastric microbiome. Sun *et al* conducted one of the few studies specifically evaluating the microbiome in the *H.pylori* negative patient population. They concluded that various stages of gastric carcinogenesis are associated with distinct bacterial taxa that could service both a predictive and diagnostic purpose. While the study has some limitations, the conclusions they make are intriguing and should prompt a larger prospective study to be done that spans multiple geographic regions.

Key Words: Gastric cancer; gastric carcinogenesis; microbiome; dysplasia; intestinal metaplasia

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Core Tip: Gastric tumorigenesis in *H.pylori* negative patients remained a mystery for many years until genetic sequencing allowed for a closer look at the composition of the gastric microbiome. Sun *et al* investigated primary colonizers of the stomach in *H.pylori* negative patients at various stages of gastric tumorigenesis and were able to conclude that there are distinct bacterial taxa associated with these stages. Their study is comprehensive but needs a larger prospective study to further support this hypothesis, particularly in other geographic areas with varying risk profiles.

TO THE EDITOR

We read with great interest the case control study by Sun *et al* [1]. These authors performed a genetic analysis of gastric mucosa from 134 *Helicobacter pylori* (*H.pylori*)

negative patients, which included a variety of gastric pathology: 56 cases of superficial gastritis, 9 cases of atrophic gastritis, 27 cases of intestinal metaplasia, 29 cases of dysplasia, and 13 cases of gastric cancer [1]. Additionally, gastric juice samples from 18 cases of superficial gastritis, intestinal metaplasia, and dysplasia were included and analyzed [1]. Genetic analysis was performed using a 16S rRNA [1]. The goal of the study was to understand whether there is a distinct pattern in the microbiome of various gastric disease types.

The study demonstrated that microbiota of the gastric mucosa varies across different stages of gastric carcinogenesis [1]. Specifically, Sun *et al* found that as the stages of carcinogenesis progress, there is less microbiota variability within gastric mucosa [1]. Of note, their data established that different stages of gastric carcinogenesis had distinguishable microbiota taxa for both gastric mucosa and gastric juice [1]. For example, intestinal metaplasia and dysplasia had predominantly *Ralstonia* and *Rhodococcus* while *Streptococcacaeae* and *Lactobacillaceae* were more prominent in pre-cancerous lesions and gastric cancer [1]. Sun *et al* concluded that their results may facilitate prediction of intestinal metaplasia and dysplasia progression to gastric cancer.

It was long believed that due to the highly acidic environment, *H.pylori* was the predominant colonizer of the stomach. In the recent years, however, genetic sequencing allowed further differentiation of the gastric microbiota [2]. Similar to the study by Sun *et al*, prior studies established that microbial diversity decreased significantly with gastric carcinogenesis [3,4]. There were a few studies, however, that were arguing that the opposite is true. The studies by Castaño-Rodríguez *et al* and Eun *et al* suggested that gastric cancer was associated with increased diversity of microbiome [5,6]. These results were supported by the more recent studies. A recently published study by Dai *et al* analyzed gastric microbiome of 37 patients with gastric cancer using the same 16s rRNA gene sequencing [7]. They concluded that pre-cancerous and cancerous gastric lesions had an increased diversity in microbiome and specifically an abundance of *Lactobacillus*,

Streptococcus, *Bacteroides*, and *Prevotella* [7]. While their conclusions on the increased microbial diversity in gastric cancer argues against conclusions set forth by Sun *et al*, they do agree on the distinguishable bacterial taxa associated with gastric cancer that could be used as a predictive marker of neoplastic conversion in pre-malignant lesions. Perhaps these observational disparities could be attributed to geographic, environmental, and patient population differences or even variability of the microbiome throughout various stages of gastric cancer itself.

Sun *et al* concluded that there are certain bacteria that predispose patients to development of gastric cancer. With this, we wonder, if there are bacteria that would instead be protective against gastric cancer. Goldin and Gorbach were one of the first to establish an association between probiotics and cancer prevention back in 1980 [8]. Since then, multiple studies have attempted to investigate probiotics as a possible adjunct to cancer therapy. Lee *et al* found that *Bacillus polyfermenticus* was able to reduce gastric adenocarcinoma cell proliferation by more than 90% *in vitro* [9]. Similarly, Han *et al* found that *Lactococcus lactis* was able to reduce gastric adenocarcinoma cell proliferation by more than 80% *in vitro* [10]. While both studies were done in vitro, they proposed interesting conclusions that should be further investigated for efficacy in vivo. If proved to be successful and safe in vivo, targeted probiotics could be a new exciting adjunctive therapy for patients with gastric cancer.

The study conducted by Sun *et al* was retrospective. The patients in the study had a known diagnosis of gastric cancer. Subsequently, it is important to consider a theory that the observed bacterial taxa were a result of neoplastic changes rather than bacteria being responsible for cancer development (ie. reactive changes rather than causal association). This theory can be better investigated by a prospective study in which patients at high risk for developing gastric cancer are followed over time and changes in their microbiome are documented along with histopathological or endoscopic findings.

Sun *et al* rightfully excluded patients who were on active antibiotic therapy, however, it is unclear how many of them had significant antibiotic exposure prior to the study. The association between antibiotic use and cancer remains unclear, however, there is literature reporting cases of antibiotic use and subsequent development of malignancy. Petrelli *et al* conducted a systematic review with meta-analysis and concluded that antibiotics were an independent risk factor for cancer development (OR 1.18, 95%CI 1.12-1.24, p< 0.001) [11]. This is the reason we believe a thorough antibiotic use history should be collected on patients in studies investigating microbiome and its effects on cancer development.

Gastric cancer is a prominent malignancy affecting many people worldwide but has a notoriously higher incidence rate in Asia [12]. As a result, many of the studies on this topic originate from Asia. Sun *et al* study, for example, was limited to Peking University Hospitals patient population in China, which may have introduced a geographic confounding variable. This may make their conclusions less applicable to the patients of other geographic areas. The study recruitment period was limited to September 2019 to October 2020. Lastly, gastric juice data was only collected for superficial gastritis, intestinal metaplasia, and dysplasia patients, and not for atrophic gastritis or gastric cancer patients. Despite some of the limitations, the study by Sun *et al* had a comprehensive analysis and proposed very interesting conclusions that should be further replicated in larger studies.

In summary, the authors should be commended for their work. They investigated the microbiome in a large group of patients at different stages of gastric cancer tumorigenesis in an *H.pylori* negative patient population, which is generally understudied. Sun *et al* study set comprehensive exclusion criteria limiting many confounding factors. They have demonstrated a well conducted analysis that showed there are distinct bacterial taxa associated with each of the stages of gastric carcinogenesis that could be of great clinical value and help triage gastric lesions. Going

forward, large prospective randomized controlled trials that encompass multiple geographic areas could help solidify the conclusions set forth by Sun *et al*.

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