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Editorial

EDITORIAL

A New Gastric Cancer Among Us

Martin J. Blaser, Yu Chen

Affiliations of authors: Department of Medicine (MJB, YC), Department of Microbiology (MJB), NYU Perlmutter Cancer Center (MJB, YC), and Department of Population Health (YC), New York University School of Medicine, New York, NY

Correspondence to: Martin J. Blaser, MD, New York University School of Medicine, 550 First Ave, Bellevue CD689, New York, NY 10016 (e-mail: martin.blaser@nyumc.org).

In 1900, gastric cancer was the leading cause of cancer death in the United States and in many countries (1). This cancer, nearly all of which is attributable to decades-long gastric colonization by *Helicobacter pylori* (2), has been declining with the progressive disappearance of these bacteria (3). This has been very good news, indeed a triumph (1), and the trends began long before *H. pylori* was discovered in 1983, with cohorts born in the late 19th century (1).

Then, a new cancer arose—adenocarcinoma of the esophagus (EAC). In some individuals, this cancer occurred on the other side of the Gastro-Esophageal Junction (GEJ) involving the gastric cardia, but most such cancers are considered anatomical variants of EAC (4); tumors on either side of the GEJ can be considered as the GEJ cancers. The trend to increasing numbers of the GEJ cancers was first observed in the United States around 1970 (5), representing cohorts born after the turn of the 20th century, and increasing rapidly, across many developed countries (6–9). In non-Hispanic whites in the United States, the incidence of GEJ cancers now is higher than the traditional noncardia gastric cancers (10). Much evidence shows a strong inverse relationship of *H. pylori* with GEJ cancers, and their precursor lesions—Barrett's esophagus and gastroesophageal reflux disease (GERD) (11–13). Thus, the accumulating evidence indicates that *H. pylori* contributes to causing distal gastric cancers and to protecting from GEJ cancers; the fall of the former and the rise of the latter are consistent with the disappearance of *H. pylori* in developed countries (3,14).

In this issue of the Journal, Anderson and colleagues report a new pattern in gastric cancer epidemiology (15) as a continuation of their pioneering work published in 2010 (16); the current study is large, well conducted, and presents robust results. This pattern appears to identify a new form of noncardia stomach cancer. We say "new" because of several salient features.

First, there is a strongly age-specific effect. The estimated annual percentage change (EAPC) in age-standardized rates (ASR) of noncardia gastric cancers is negative overall, as now expected from the continued *H. pylori* decline. Across all sites, noncardia cancers are decreasing at an EAPC of –2.6% in those older than age 50 years, continuing the "triumph" (1). However, in the population of those younger than age 50 years, the incidence of these cancers is rising, at 1.3% annually. This large net difference confirms prior studies (16).

Second, there is a particular tissue distribution. The largest incidence increase (4.6% annually) involves cancers originating in the gastric corpus; this site specificity confirms prior work (17). Although the trends center on the corpus, adjacent gastric areas also are affected, with annual 1.6% increases in fundus cancers. Older persons also show this site-specific trend. In those older than age 50 years, gastric cancer is decreasing approximately 3% to 4% annually at most noncardia sites, but little in the corpus and fundus.

Third, there is a strong sex effect. In the population younger than age 50 years, the rise of noncardia gastric cancers is more pronounced in women (2.6%) than in men (0.2%); this is mostly attributable to corpus cancer increases (6.0% annually in women vs 3.0% in men). Gastric cancer has always been more common in men (1,18), but these data in women predict an unprecedented reversal.

In total, this age period–cohort analysis suggests a new type of cancer: centered in the gastric corpus, especially in women younger than age 50 years, mostly in non-Hispanic whites and in areas with less poverty, and increasing rapidly in incidence, yet affecting older age groups, adjacent sites, and men to a lesser extent. With this group's prior work (16,17), we can see a new epidemic, centered in post–World War II birth cohorts. We call these the "CYF" (corpus-dominant, young age–dominant, female-dominant) gastric cancers. Further analyses should examine continuing trends as to whether CYF risk factors differ from other noncardia cancers and whether CYF cancers are rising elsewhere. Large increases in corpus atrophic gastritis rates in Swedes younger than age 44 years suggests similarity (19). Just as EAC began in highly industrialized countries, and now is spreading widely, CYF cancers may follow a similar pattern.

Importantly, what is causing this new disease? Most obvious may be changing gastric microecology (3). *H. pylori*, the ancient dominant gastric microbiota constituent, has been progressively disappearing, beginning in industrialized countries, with the rest of the world following. Without *H. pylori*, other gastric microbiota differ (20). In one hypothesis, the microbes filling the *H. pylori*–vacant niche are especially injurious to the gastric

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mucosa either directly or via altered gastric physiology. Parallel events may have happened before, fueling the rise in GERD, Barretts, and EAC, and clearly associated with *H. pylori* loss (21). Because CYF differs, the microbiota or physiologic changes likely vary from those promoting EAC.

We speculate that gastric microecology has progressively changed in successive birth cohorts. Initial changes, beginning in the 19th century, led to declines in both *H. pylori* and noncardia gastric cancer. Second, in cohorts beginning in the early 20th century, the changes fueled the rise of the GEJ adenocarcinomas. Stage III, occurring chiefly in the post–World War II birth cohorts, is fueling the CYF cancer increases. This timing parallels the antibiotic era, possibly reflecting dysbioses caused by substantial exposures. Combined studies of antibiotic exposure, microbiota, and cancer subtypes and premalignant states together will allow hypothesis testing.

Pathogenesis of the CYF cancers also could involve autoimmunity, either primary or secondary to microbiota change. Autoimmune diseases are more prevalent in women and have been linked to gastric cancer (22). Obesity also may be playing a role, as the Swedish report suggests (19), as could hormonal changes, but smoking, acid-blocking agents, and salt intake appear insufficient to explain the CYF specificities.

The rapid increases in younger women are especially alarming, as they have largely been protected from gastric cancer until after menopause (18). In persons younger than age 50 years, the increases in incidences of the GEJ adenocarcinomas are now greater in women than in men. With changing menarche and contraception trends, reproductive factors should be examined to explain the differing sex patterns. We speculate, but true understanding of the roots of the oncogenesis is critically needed. Advanced gastric cancer is usually incurable, with five-year survival rates ranging from 5% to 15% (23), and gastric cancer in younger adults has a disproportionate impact on total number of years of life lost. We are in debt to Anderson and colleagues for their keen observations (15–17), which sound a warning about a growing menace.

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