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Gastric cancer prevention from the point of helicobacter

To the Editor,

When the first cancer estimates of world were made in 1975, gastric cancer (GC) was the most common neoplasm, making 70% of the total. Although its rate decreased to 6.8% in 2012, it is still the fifth most common malignancy after cancers of the lung, breast, colo-rectum, and prostate and the third leading cause of cancer death in both sexes worldwide (8.8%, 723,000 deaths) (1). Proximal (cardia) and distal (non-cardia) gastric adenocarcinomas have different epidemiological and clinical features. Although there is an increase in proximal GCs, most of the GCs are still distally located, and intestinal-type. *H. pylori* is an established trigger of gastric carcinogenesis; reversibility of precancerous conditions, including intestinal metaplasia (IM), after eradication treatment is a hot topic for research. Therefore, we read with great interest the study by Galiatsatos P et al. (2) on the sensitivity of gastric biopsy for *H. pylori* detection in the presence of IM. The data have once again emphasized the importance of using non-invasive tests and histopathology together in the presence of gastric IM.

Correa (3,4) proposed that gastric cancer does not arise from a normal mucosa but through by a multistep cascade. The active chronic inflammation of gastric mucosa either persists as non-atrophic chronic gastritis without gland loss or advances to multifocal atrophic gastritis. The first significant step in the precancerous cascade, namely, gastric atrophy (GA), is followed by IM, dysplasia, and finally invasive carcinoma. Correa hypothesized that complete IM evolved to incomplete IM and then low-grade dysplasia, which is followed by high-grade dysplasia. Gastric carcinogenesis is a fixed continuous process, and all theoretical definitions are made arbitrarily. In fact, incomplete IM has been considered a "low-grade dysplasia," and similarly, high-grade dysplasia is equivalent to "carcinoma in situ" (5). GA is identified by the loss of gastric glands-either mucus-secreting types of antrum or oxyntic-type of corpus. IM is histologically easy to diagnose and classified as small intestinal (complete)- or colonic (incomplete)-type. Complete IM is characterized by expression of digestive enzymes on the brush border and decreased expression of gastric mucin. While goblet cells, absorptive enterocytes, and paneth cells are present in complete IM, incomplete IM displays only colonic epithelial cells without mucin and a brush border. However, IM is usually a mixed type, carrying both intestinal and colonic features together in the same biopsy sample. Filipe's classification is also used to subtype IM into Type I (complete) and Types II-III (incomplete) according to histochemical detection of different mucins, such as sialomucin and sulfomucin. The extent of atrophy and IM, especially incomplete or Type III metaplasia, implies an increased risk for GC (6). While the term "precancerous conditions" defines GA and IM carrying a high risk for the development of GC, "precancerous lesions" implies gastric histologically defined dysplasia with unequivocal neoplastic epithelium without evidence of tissue invasion (7).

Lauren classification histologically subdivides GC into intestinal type and undifferentiated or diffuse type. The diffuse-type GC usually originates from superficial pangastritis without atrophy in genetically prone young people. Distal GC is related to corpus-dominant gastritis with IM. The IM underlying GC arises from mutations in the gastric glands and spreads throughout the gastric mucosa by crypt fusion. Although this explains the clonal origin of metaplasia and dysplasia, there is also some evidence supporting the role of bone marrow-derived stem cells in gastric carcinogenesis (8,5). Bone marrow cells may replace gastric stem cells lost during the development of atrophy. According to this theory, genetic instability of gastric stem cells or a less well-protected niche in the gastric mucosa may predispose one to mutations in the gastric glands (8,5,9).

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Helicobacter pylori is a gram-negative spiral bacterium that colonizes gastric mucosa. It has coevolved with human beings for more than 50,000 years. Over 50% of the current world's population is infected, usually during childhood, and has persistent infection throughout life. From an evolutionary point of view, *H. pylori* has been neither beneficial nor harmful in comparing the ancient, pre-modern to postmodern stomach. A recent model on the consequences of *H. pylori* infection hypothesizes that the early life benefits, such as reducing infectious diseases, avoiding gastroesophageal reflux disease, controlling allergy, and protecting from metabolic syndrome, have some costs late in life, such as peptic ulcers, anemia, or GC (9). *H. pylori* was classified as a class I carcinogen in 1994 by the World Health Organization (10).

H. pylori fulfills the Correa hypothesis, which was defined several decades before the discovery of *H. pylori*. Acute gastritis is rarely diagnosed based on clinical symptoms, although chronic gastritis develops in almost all persistent infections. *H. pylori* causes chronic inflammation of gastric mucosa, which slowly progresses through the aforementioned premalignant stages to gastric adenocarcinoma. Although 90% of chronic gastritis remains asymptomatic, pre-neoplastic changes and GC develop in 20% and <2% of infected populations, respectively (8). *H. pylori* carries a 6-fold increased risk, mainly intestinal- and distal-type GC.

The gastric manifestation of *H. pylori* infection is highly variable, depending on genetic and immune factors of both bacteria and host, as well as environmental and epigenetic factors. For instance, virulence factors of H. pylori, namely, cagA, vacA, oipA, babA, hopQ, and homA/B, are predictors of gastric atrophy and IM. The cag-positive and vacA s1m1 strain of *H. pylori* is associated with the development of precancerous lesions and GC, while the cag-negative and vacA s2m2 strain leads to non-atrophic gastritis without increased risk of GC. *H. pylori* stimulates both the innate and acquired immune systems. The cellular immune response, but not the innate or humoral immune response, mediates pathogenesis and clearance of the infection in humans. The balance between proinflammatory Th1 cells and immune-tolerant Th2 cells determines the clinical consequence of the infection. A strong Th1 response causes intense gastritis and low bacterial loads, whereas the reverse is observed in predominantly Th2-responsive mice. Gastric atrophy of mice is induced by the Th1 cytokine IFN-γ and augmented by the presence of H. pylori. Although the responses are less polarized in humans than in mice, environmental factors may affect this polarization. The most obvious example of immune polarization against *H. pylori* at a population level is the "Africa phenomenon." It implies low GC prevalence in spite of a high rate of *H. pylori* colonization. It is suggested that co-infestation with parasites leads to a Th2 bias, which avoids gastric atrophy and contributes to the lower GC prevalence in Africa. Contrary to this, the Th1 bias in Japan may be one of the factors leading to a high GC prevalence associated with *H. pylori* (5,9).

Strategies for the prevention of GC need to be developed according to each county's features, such as prevalence of *H. pylori* infection and GC and sources for endoscopy and other laboratory facilities. The potential strategies are **1. Eradication:** *H. pylori* screening and treating positive cases to stop the gastric carcinogenesis cascade; **2. Screening:** serologic or endoscopic screening of GC risk groups to detect precancerous conditions; and **3. Surveillance:** the endoscopic surveillance of patients with precancerous lesions in order to detect and remove dysplastic lesions or early GC just before progression into invasive carcinoma.

1. *H. pylori* eradication treatment

Since *H. pylori* infection is the most consistent risk factor for GC, eradication treatment is a promising strategy to reduce GC, especially in populations with a high prevalence of *H. pylori* infection. The aim is either to restore the inflamed mucosa to its normal healthy state or to prevent further progression of precancerous conditions, namely, GA and IM to precancerous lesions. However, unlike peptic ulcer or maltoma treatment, the effectiveness of eradication in GC prevention has yet to be established. The point of no return in gastric carcinogenesis, as well as other factors contributing to the progression of preneoplastic lesions, has not been determined, either. The other shortcomings of this strategy are the cost of test and treatment, low eradication rates due to high antibiotic resistance, and development of GC despite successful eradication. It is obvious that universal *H. pylori* eradication is not rational and must be targeted to those in whom precancerous lesions can be prevented most.

Endoscopic gastric biopsies usually show presence of both *H. pylori* and precancerous conditions. However, patchy colonization of *H. pylori* on gastric mucosa due to local factors, such as inflammation or acidity, may cause false-negative results. Alternatively, non-invasive tests can be used for the diagnosis of *H. pylori* infection, namely, 13C urea breath test, stool antigen tests with polyclonal or monoclonal antibodies, and immunological tests on saliva or urine. All of these tests have a sensitivity and specificity of over 90%. Low bacterial load causes false-negative results also with non-invasive tests, except for serology. Antibodies against *H. pylori* remain elevated for months, even years, after the disappearance of H. pylori from the stomach. Therefore, validated serological tests should be preferred when gastric H. pylori bacterial load decreases, such as the use of antimicrobial agents or anti-secretory drugs, ulcer bleeding, and presence of extensive IM or MALT lymphoma (7,8). The study of Galiatsatos P et al. (2) published in TJG points to this problem. They retrospectively evaluated 105 cases with IM. Out of 68 cases with *H. pylori*-negative gastric biopsy, 43 had records of urease breath test (UBT), of whom 10 (23.3%) had a positive test. Additionally, about half of the cases with autoimmune gastritis (AIG) (4/9) were *H. pylori*-negative on biopsy but positive with UBT. The authors concluded that gastric IM cases with *H. pylori*-negative gastric biopsy should be considered for UBT,

including cases of AIG. Since histology alone is not reliable for the detection of *H. pylori* in patients with IM, dual testing (i.e., gastric biopsy combined with non-invasive tests) must be preferred in these patients.

Whether GA and IM are reversible following *H. pylori* eradication has been a controversial issue. The meta-analysis done by Wang et al. (11) among 2658 patients showed that *H. pylori* eradication leads to a significant improvement of GA in the corpus while it has no effect on the antral GA or on IM at any location. According to this meta-analysis, IM should be considered a bystander indicating increased GC risk in the surrounding gastric milieu, and GC risk does not decrease after *H. pylori* eradication. Kodama M. et al. (12) followed up in 30 patients after successful eradication in order to evaluate the regression of GA and IM. Five gastric sites were biopsied yearly according to the updated Sydney System for 10 years. Inflammation, activity, and atrophy score at all sites of the stomach were significantly reduced, ranging from 6 months to 6 years after eradication. Nevertheless, IM improved only at the lesser curvature of the corpus. Malfertheiner P. states that *H. pylori* eradication is still of value, even in the presence of GA, but whenever possible, *H. pylori* eradication should be performed before the development of GA and IM (13). Since there is some evidence showing that eradication causes regression of GA but not IM, young people who do not have GA or IM must be the target for H. pylori eradication in order to prevent GC.

Helicobacter pylori eradication heals non-atrophic chronic gastritis. However, it may cause partial regression of GA but not IM. Since eradication treatment may slow the progression to neoplasia, communities with a high prevalence of *H. pylori* infection and GC should be considered as a part of a "screen and treat" policy as an effective strategy for GC prevention (14). The Maastricht IV/ Florence Consensus Report recommends considering H. pylori eradication to prevent GC in first-degree relatives of family members with a diagnosis of GC; patients with gastric neoplasia already treated by endoscopic or subtotal gastric resection; patients with high-risk gastritis, such as severe pangastritis, corpus-predominant gastritis, or severe atrophy; patients with chronic gastric acid inhibition for more than 1 year; patients with strong environmental risk factors for GC (heavy smoking; high exposure to dust, coal, quartz, cement, and/or work in quarries); and *H. pylori*-positive patients with a fear of GC (7).

2. Screening of risk groups for precancerous conditions

Communities with a significant burden of GC can achieve reduction in cancer mortality by screening for precancerous conditions. Although novel biomarkers have been developed for early detection of GC, validated serological tests and endoscopy are the current screening methods for gastric premalignant lesions, particularly for GA. In addition to H. pylori serology, serum pepsinogen I/II ratio, alone or combined with gastrin levels, is used as a non-invasive screening panel with high sensitivity and specificity. Pepsinogen I and II are respectively produced from the fundus and entire stomach. Gastric inflammation increases mainly pepsinogen II, while GA causes more pronounced decreases in pepsinogen I. As a result, the pepsinogen I/II ratio decreases more profoundly as chronic gastritis progresses to GA. A pepsinogen I/II ratio <3.0 provides the best risk assessment for GA and GC; it may be used as a criterion to initiate endoscopic screening for an individual (7). Gastrin is synthesized and secreted from antral G-cells. Serum gastrin levels rise during chronic *H. pylori* gastritis and GA at the corpus, in contrast to antrum-predominant GA (8). A low pepsinogen I/II ratio associated with high gastrin level can be used as a marker of GA.

New imaging techniques, such as magnifying endoscopy, narrow band imaging, and confocal endomicroscopy, have improved the diagnostic efficacy of conventional endoscopy. However, the correlation between endoscopic and histological findings is still not satisfactory, and histology is still the gold standard for the detection of premalignant conditions and lesions. The Sydney system was developed for histological grading of gastritis for both research and clinical purposes. Several features of gastritis, including inflammation, atrophy, and intestinal metaplasia, were separately and semi-quantitatively scored and then graded by using a minimum of 4 gastric biopsies: 2 from the antrum and 2 from the corpus. Furthermore, the severity of gastritis can be histologically staged, similar to clinical cancer staging. The assumption is that chronic *H. pylori* gastritis starts from the antrum and then spreads upward to the corpus in parallel to GA. Therefore, pangastritis and antral GA are theoretically more advanced stages of gastritis in carcinogenesis, and they carry an increased risk of progression to dysplasia and invasive cancer. The joint committee of gastroenterologists and pathologists proposed staging systems first for GA; the Operative Link for Gastritis Assessment (OLGA) and THEN for IM; Operative Link for Gastritis Intestinal Metaplasia (OLGIM) (15,16). Each system stages gastritis from 0 to IV on the combined antrum and corpus scores. GC risk is categorized either as low-risk stages (0-I-II) or high-risk stages (III-IV). Since GC risk progressively increases along the scale, these staging systems not only allow objective data for the research but also provide relevant clinical information (6,7,8).

Marques-Silva L et al. (17) recently published a meta-analysis including 107 studies in the literature. The study revealed that extensive GA and IM might affect 16% and 13% of the world's population, respectively. About half of them harbor these conditions, with extensive involvement of the stomach. The worldwide prevalence of GA is higher in gastric biopsies than serology (33% vs. 24%), in countries with a high versus low incidence of GC (42 vs. 23%), in men than women (32 vs. 28%), and in those aged 40 years or older than younger ones (48 vs. 22%). Additionally, the prevalence of GA is 2.7 times AND 3.8 times higher in patients with endoscopic and serologic diagnosis of *H. pylori* infection, respectively. The higher estimation

of GA was attributed to the sensitivity of serology to detect H. pylori. Although these data show that the worldwide target for screening of precancerous conditions may be as large as one-fourth to one-third of the population, a universal worldwide screening strategy seems to be non-practical at the moment. The main factors determining the strategy for screening precancerous conditions are geographical variation in the incidence of GC, the cost and availability of specific serological tests, an individual's risk justifying invasive investigation by endoscopy, and cultural diversities influencing compliance.

3. Surveillance of patients with precancerous conditions for development of dysplasia or cancer

Surveillance programs aim for secondary prevention of GC and involve endoscopic follow-up of individuals having extensive gastric precancerous conditions for detecting precancerous lesions, namely, dysplasia and early GC. It was reported that the cancer risk of precancerous gastric lesions is comparable to or even higher than the risk of colorectal cancer arising in long-standing inflammatory bowel disease or the risk of esophageal adenocarcinoma developing in Barrett's mucosa (6).

Both OLGA and OLGIM systems categorize stages III and IV as a risk group and recommend restricting surveillance programs to them. The target population with extensive GA and IM may be only 7% in countries with a low to moderate incidence of GC or may reach 16%-27% in high-risk countries (17). Furthermore, clear guidelines are not available for follow-up schedules of surveillance programs. The yearly progression rates to GC are highly variable, ranging from 0% to 2% for GA, from 0% to 10% for IM, and from 0% to 73% for dysplasia (8). According to the recent guidelines of the European Society of Gastrointestinal Endoscopy (ESGE), endoscopic surveillance should be offered to patients who are estimated to have extensive GA and/or IM with 3-year intervals. There is not enough evidence to recommend surveillance for mild to moderate GA or IM restricted to the antrum. Dysplasia as a precancerous lesion definitely needs frequent endoscopic follow-up or treatment. The low-grade dysplasia should be followed up within 1 year after diagnosis if there is no endoscopically defined lesion. The high-grade dysplasia without endoscopic lesion must be immediately reassessed by extensive biopsy sampling of the stomach and then be endoscopically surveyed at 6- to 12-month intervals (6,14). On the other hand, the high incidence of GC in Japan leads to more frequent surveillance recommendations than the ESGE guideline. A yearly follow-up endoscopy is recommended for extensive precancerous conditions rather than every 3 years. Also, moderate to mild GA associated with *H. pylori* is endoscopically re-evaluated every 2 to 3 years in Japan (18).

Areia M, et al. (19) have recently made a systematic review of the cost-effectiveness of GC prevention strategies by using 2395 abstracts and 23 articles in the literature. The evidence showed that population-based serological screening and treatment of *H. pylori*-positive cases are cost-effective. Endoscopy is also cost-effective as a population screening option, depending on the GC incidence and cost of the endoscopy in a particular country. However, the conflicting results do not allow agreement on the endoscopic surveillance of gastric premalignant conditions or lesions. This review once more emphasized the fact that the GC prevention strategy must be individualized according to the needs and available resources of each country.

Gastric cancer is still a major health problem for our county. The age-adjusted incidence and mortality of GC in Turkey are respectively 17.9 and 15.5 per 100,000 for males and 10.9 per and 9.3 per 100,000 for females. Over 10,000 Turkish people had a diagnosis of GC and more than 8000 patients died in 2012 (1). *H. pylori* infection is endemic in Turkey, and 82.5% of the population is infected mainly before the age of 20 (20). Furthermore, due to high antibiotic resistance rates, failure of *H. pylori* eradication is frequent (21,22). Therefore, *H. pylori* is a pivotal factor in determining strategies against GC.

The DISPEN study has prospectively included Turkish patients with dyspepsia in order to evaluate endoscopic findings and the frequency of *H. pylori* infection, GA, and IM in gastric biopsies (unpublished data of the DISPEN study, Turkish Dyspepsia Study Team). After completing a dyspepsia questionnaire, 2534 patients from 43 centers all around Turkey were referred for upper gastrointestinal endoscopy. The gastric biopsies were taken according to the Sydney system and evaluated by one expert pathologist. The mean age was 43, and 64% of patients were women. The endoscopic findings were as follows: 8% normal, 7% duodenal ulcer, 2% gastric ulcer, 12% erosive duodenopathy, 50% hyperemic gastropathy, 12% NSAID-related gastropathy, 1.2% atrophic gastropathy, 11% esophagitis, and 0.2% gastric or esophageal malignancy. The histopathology of gastric biopsies showed 52% *H. pylori* infection, 13% GA, 12% IM, and 0.5% dysplasia.

The DISPEN study pointed out important data for the prevention of GC in Turkey. Currently, *H. pylori* infection is present on gastric biopsies in half of the population. The rate of gastric precancerous conditions is about 10% to 15%, although OLGA and OLGIM did not stage their extensiveness; we can estimate that the screening strategy should target the population over 40 years. We suggest that GC prevention strategies in Turkey should be based on policies, such as "test and treat *H. pylori* before age of 40" and "screen by endoscopy for GA and IM after 40." Surveillance strategies of precancerous lesions in the Turkish population should be developed.

To conclude, we urgently need prospective, multicenter trials covering all parts of Turkey on the effects of *H. pylori* eradication on the progression of the GC cascade. In this way, it will be possible to monitor the eradication rate of HP and implement screening and surveillance strategies for GC prevention in Turkey.

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