Helicobacter Pylori and Gastric Precancerous Lesions: An update

Helikobakter Pilori ve Midenin Prekanseröz Lezyonları: Bir Güncelleme

Ibrahim Koral Onal[1], Mevlut Kurt[2], Nasser Alizadeh[1], Fatih Saygili[3], Mehmet Ibis[1], Ramazan Yildiz[4]

[1] Department of Gastroenterology, Gazi University Medical School, Ankara, Turkey
[2] Department of Gastroenterology, Abant Izzet Baysal University Medical School, Bolu, Turkey
[3] Department of Gastroenterology, Turkiye Yuksek Ihtisas Education and Research Hospital, Ankara, Turkey
[4] Department of Medical Oncology, Gazi University Medical School, Ankara, Turkey

ABSTRACT

Gastric cancer (GC) develops through a multistep process known as the gastritis-atrophy-metaplasia-dysplasia-cancer sequence associated with alterations in the expression of host oncogenes and tumor suppressor genes after several decades. *Helicobacter pylori* (*H. pylori*) infection is the most consistent risk factor for GC, and its elimination is, therefore, the most promising strategy to reduce the incidence of this malignant disorder. However, the results of the relevant studies are controversial as to whether the *H. Pylori* eradication effectively induces the regression of gastric preneoplastic lesions. The inconsistencies are likely due to the heterogeneity in studies with respect to the number of biopsy samples taken, the method of histologic classification of findings, sample size, and the duration of the follow-up. Additionally some probable or well-defined factors other than *H. Pylori* may influence the progression of gastric preneoplastic lesions. Lastly, the real existence of a "point of no return" may partially explain the controversial findings. Here, we present an index case, and review data about the role of *H. pylori* during gastric carcinogenesis, and subsequently discuss information available from recent studies to evaluate the benefit of the *H. pylori* eradication for the regression of gastric precancerous lesions.

Key Words: Atrophic gastritis, gastric cancer, *Helicobacter Pylori,* metaplasia, prevention, precancerous conditions

Received: 03.19.2015 **Accepted:** 05.22.2015

ÖZET

Mide kanseri birkaç dekad boyunca konak onkogenleri ve tümör supresör genlerde meydana gelen değişikliklerle ilişkili olarak gastrit-metaplazi-displazi-kanser sıralaması olarak bilinen birçok-basamaklı-süreç içerisinde gelişir. *Helikobakter Pilori* (*H. pilori*) enfeksiyonu mide kanseri ile ilişkisi en net olan risk faktörü olup eliminasyonu bu malign hastalığın insidansını düşürmek açısından en çok umut vaad eden stratejidir. Buna rağmen *H. Pilori* eradikasyonunun gastrik preneoplastik lezyonların regresyonunu indüklemesi üzerine yapılan çalışmaların sonuçları tartışmalıdır. Tartışmalar genellikle çalışmalarda alınan biyopsi sayısı, bulguların histolojik klasifikasyon metodu, örneklem sayısı ve takip süresi gibi parametrelerdeki heterojeniteden kaynaklanmaktadır. Ek olarak *H. Pilori* dışında bazı muhtemel veya iyi tanımlanmış faktörler gastrik prekanseröz lezyonların progresyonunu etkileyebilir. Son olarak, "dönüşü olmayan bir nokta" nın gerçekten var olması tartışmalı bulguları kısmen izah edebilir. Burada bir indeks vaka sunmakta, *H. Pilori'nin* gastrik karsinogenezdeki rolüne dair bilgileri gözden geçirmekte ve ardından *H. Pilori* eradikasyonunun gastrik prekanseröz lezyonların regresyonu açısından faydasını değerlendirmek üzere güncel çalışmalardan elde edilen bilgileri takdim etmekteyiz.

Anahtar Sözcükler: Atrofik gastrit, gastrik kanser, *Helikobakter pilori,* metaplazi, önleme, prekanseröz durumlar

Geliş Tarihi: 19.03.2015 **Kabul Tarihi:** 22.05.2015

INTRODUCTION

Association between *H. pylori* and gastritis was recognized since 1970s, but in 1982 H.*pylori* was cultured as a gastric bacterium, and now, it is a known cause of gastritis, many of gastric and duodenal ulcers, gastric cancer (GC) and mucosa associated lymphoid disease (1-11). Worldwide, gastric cancer is one of the most common cancers, and *H. pylori* infection seems to be a necessary, although not sufficient, cause of GC (12-16). Many studies have provided data that the eradication of *H. pylori* could reduce the occurence of peptic ulcer and GC (1,3-11). But there is still controversy about whether eradication of *H. pylori* enhances the regression of gastric precancerous lesions and virtually eliminates the risk of GC. Here, we present an index case, and review the data about the role of *H. pylori* during gastric carcinogenesis, and subsequently discuss theinformation available from recent studies to evaluate the benefit of the *H. pylori* eradication for the regression of gastric precancerous lesions.

CASE REPORT

A 49-year-old, male patient was admitted to our clinics with the complaint of epigastric pain. He reported a previous history of *H. Pylori* infection but he could not remember whether he had an eradication therapy. Upper gastrointestinal endoscopy (UGE) was performed to see a flat lesion measuring 1,5 cm in diameter in the gastric antrum. Endoscopic biopsy sample of the lesion was consistent with a low-grade dysplasia whereas there were *H. Pylori* gastritis and intestinal metaplasia in the gastric corpus and neighbouring antrum. The flat lesion was removed by an endoscopical mucosal resection, and a low grade dysplasia with negative reection margins was detected on a pathological examination. Bismuth containing quadruple therapy was administered to treat *H. Pylori*, and an urea breath test one month after the therapy confirmed the clearance of microorganisms. A follow-up UGE after 6 months revealed a new flat lesion measuring 1,5 cm diameter in the corpus.

Address for Correspondence / Yazışma Adresi: Ibrahim Koral Onal, MD, Department of Gastroenterology, Gazi University Medical School, Besevler, 06560, Ankara, Turkey. E-mail: koralonal@yahoo.com
©Telif Hakkı 2015 Gazi Üniversitesi Tıp Fakültesi - Makale metnine http://medicaljournal.gazi.edu.tr/ web adresinden ulaşılabilir.
©Copyright 2015 by Gazi University Medical Faculty - Available on-line at web site http://medicaljournal.gazi.edu.tr/
doi:http://dx.doi.org/10.12996/gmj.2015.38

The biopsy was consistent with adenocarcinoma, and the patient underwent a total gastrectomy and lymph node dissection. Pathological examination revealed an early gastric cancer and negative lymph nodes. The patient is still free of recurrence one year after the surgical therapy.

Our case was a good example of *H. pylori* associated gastric preneoplastic and neoplastic conditions showing that *H. pylori* gastritis, intestinal metaplasia, dysplasia and early gastric cancer could be diagnosed in the same patient. And the reason why the *H. pylori* eradication was not successful to prevent the development of gastric cancer in this patient is addressed in the following sections.

H. Pylori and Gastric Carcinogenesis

GC is categorized as intestinal- or diffuse-type according to the presence or absence of glandular growth pattern. It has been hypothesized that GC develops through a multistep process known as the gastritis-atrophy-metaplasia-dysplasia-cancer sequence that is associated with alterations in the expression of host oncogenes and tumor suppressor genes after several decades (17-19). *H. pylori* is the most common factor in the development of GC via this sequence, but its role is not completely known (20). *H. pylori* is a gram-negative, spiral-shaped pathogen that colonizes the stomach of about half of the world's population (21). The bacterium produces urease, which hydrolyze urea to ammonia to neutralize the gastric acidity. The cytotoxin-associated gene A (CagA) protein and vacuolating cytotoxin (VacA) protein are the other virulence factors. *H. pylori* can be defined as cagA-positive and cagA-negative strains according to the presence or the absence of cagA gene.

H. pylori-associated chronic active inflammation is usually considered to induce a host immune response, and the cellular damage in the affected gastric mucosa resulting from oxidative stress, which may initiate a series of intracellular molecular and numerous subsequent genetic and epigenetic events (22,23). CagA-positive *H. pylori* infection induces a more severe gastric mucosal inflammation and atrophic gastritis that result in the development of intestinal-type gastric adenocarcinoma following this sequence (17). Infection of CagA-positive *H. pylori* is also associated with gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Several studies have showed the possibility that highly active inflammation induced by *H. pylori* is intensely involved in the development of cancer, mainly of diffuse-type with advanced malignant potential, without passing through this sequence (18,20,22). The highly active inflammation in *H. pylori*-infected chronic atrophic gastritis-negative subjects as indicated by the low serum pepsinogen I/II ratio ≤3.0 together with high *H. pylori* antibody titer >500U/ml, carries a high risk of diffuse-type gastric cancer (24).

Why are CagA-positive *H. pylori* strains more detrimental to the gastric mucosa with respect to the development of GC (25)? Virulent *H.pylori* strains have the cag pathogenicity island (cag PAI), a 40-kb DNA segment which encodes CagA. The cagA-encoded CagA protein is delivered into bacterium-attached gastric epithelial cells through the bacterial type IV secretion system. In the host cells, CagA localizes to the inner leaflet of the plasma membrane, where it undergoes tyrosine phosphorylation by Src or c-Abl kinases (19). Tyrosine-phosphorylated CagA then acquires the ability to disturb SHP-2 phosphatase, deregulation of which is involved in a variety of human malignancies. The tyrosine phosphorylation location of CagA is characterized by the existence of an EPIYA motif (26). Four different EPIYA segments, EPIYA-A, -B, -C and –D have been identified in the EPIYA-repeat region according to the sequences flanking the EPIYA motifs (27,28). East Asian CagA, which encloses the EPIYA-D segment, shows stronger SHP-2 binding than does Western CagA, which encloses the EPIYA-C segment (27,29). Hummingbird phenotype of gastric epithelial cells is induced by CagA (19). This phenotype is eliminated by inhibition of CagA tyrosine phosphorylation, interruption of the CagA–SHP-2 complex or knockdown of SHP-2 expression by siRNA (26,30,31). Deregulation of SHP-2 by CagA is a major concern in the setting of cell transformation because mutations in PTPN11 gene that encodes SHP-2, have been found in various human malignancies (32,33). A polymorphism of PTPN11 gene has been proposed as a risk factor for gastric atrophy and gastric cancer among Japanese patients with H. pylori infection (34).

CagA also binds to and inhibits partitioning-defective-1b (PAR1b)/microtubule affinityregulating kinase-2 (MARK2) polarity-regulating kinase to disrupt tight junctions and epithelial apical-basolateral polarity (35-37). The antral mucosa is protected by Gastrokine 1 (GKN1), which supports healing by facilitating restitution and proliferation after damage (38). GKN1 is downregulated in gastric epithelial cells infected by *H. pylori*, and its expression is lost in gastric cancer and precancerous lesions, such as intestinal metaplasia (39,40). GKN1 gene copy number and expression in gastric cells and mucosal tissues of humans are decreased by CagA-positive *H. pylori*. GKN1 binds to the CagA protein, and inhibits CagA/SHP-2 complex formation. It is suggested that GKN-1 may inhibit the CagA-induced cell growth, colony formation, antiapoptotic activity, cell proliferation, cell migration, cell invasion, epithelial mesenchymal transition (EMT), reactive oxygen species production, and genetic alteration. GKN1 can also predict the CagA expression and the risk of GC. These GKN1 activities can collectively contribute to suppress the carcinogenic effects of CagA (41). It is suggested that GKN1 might be a target to inhibit clinical outcomes of CagA.

H. pylori causes epigenetic dysregulation to promote gastric carcinogenesis, but the roles and functions of microRNAs (miRNAs) in this multi-stage cascade are not fully explored (42). MiR-490-3p was downregulated in gastritis, intestinal metaplasia and adenocarcinoma during *H. pylori* and MNU-induced gastric carcinogenesis, and its epigenetic silencing stimulated gastric tumorigenesis by upregulating SMARCD1, a SWI/SNF chromatin remodelling complex subunit involved in cancer progress. High expression of SMARCD1 was associated with poor survival independent of the tumor staging (42).

In addition, CagA was involved in the activation of β-catenin and NF-κB signaling pathway, which promotes proliferation and inflammation (41). Furthermore, the activation of the NF-κB signaling induces potent pro-inflammatory cytokines, such as interleukin (IL)-1β, -6, -8, -10 and TNF-α (41,43). These cytokines were associated with inflammation, cell proliferation, antiapoptosis in numerous cancer cells. A mutation in the E-cadherin gene may cause inherited and sporadic gastric cancer of the diffuse type (44,45). The interaction between CagA and E-cadherin leads to the inhibition of the complex with beta-catenin, initiating cytoplasmic and nuclear accumulation of beta-catenin. Numerous genes including cdx1 are transactivated by CagA-deregulated beta-catenin. Cdx1 manages genes involved in intestinal differentiation, this observation is a clue that CagA-deregulated b-catenin is involved in the progress of intestinal metaplasia, a precancerous transdifferentiation of gastric mucosa to an intestinal phenotype (19).

The effectiveness of treating H.Pylori in promoting regression of gastric preneoplastic lesions

It was already mentioned that *H. pylori* infection is the most consistent risk factor for gastric cancer and its elimination is, therefore, the most promising strategy to reduce the incidence of gastric cancer (8). Based on the strong association between *H. Pylori* and gastric cancer and Correa hypothesis (46), one would expect this bacterium to accelerate the development and/or progression of gastric preneoplastic lesions and antibiotic eradication treatment would be considered as a unique opportunity as a chemo-preventive strategy against the gastric cancer. However the results of the relevant studies are controversial as to whether the *H. Pylori* eradication effectively induces the regression of gastric preneoplastic lesions (47-49). A variety of reasons may explain this contradiction: First, the studies are heterogenous with respect to the number of biopsy samples taken, the method of histologic classification of findings, sample size, and the duration of the follow-up. Second, there are some probable or well defined factors other than *H. Pylori,* which may influence the progression of gastric preneoplastic lesions such as the high intake of salt and salt-preserved foods (50), smoking (51), alcohol (52), dietary fiber intake (53), low socioeconomic status (54), the family history of gastric cancer (55) and obesity (56). And lastly, the real existence of a "point of no return" may partially explain the controversial findings. The term 'point of no return' has been defined as the point in a sequence of events when it is no longer possible to reverse the course or stop the process. Actually it should be considered that gastric lesions like intestinal metaplasia actually may be a biomarker associated with an increased risk for, rather than the precursor of, gastric cancer (57,58).

H.Pylori Eradication and Atropiıc Gastritis

The data of various published studies were pooled in two meta-analyses in an effort to answer the critical question of whether atrophic gastritis (AG) of the stomach is reversible after the *H. pylori* eradication (49.59). In the first meta-analysis (2007), the pooled odds ratio with 95% confidence interval (CI) was 0,554 (0.372–0.825) with a test for overall effect Z = –2.91 and $p = 0.004$ for antrum AG whereas it was 0.209 (0.081–0.538), Z = –3.24, $p < 0.001$ for corpus AG (57). These results indicated that *H. pylori* eradication has beneficial long-term effects on AG (59). In the second meta-analysis (2011), the inverse variance weighted mean differences (WMD) and 95% CIs for gastric mucosal histological scores were estimated to compare the histological scores before and after *H. Pylori* eradication (49). For antral AG, the pooled WMD with 95% CI was 0.12 (0.00–0.23) and p = 0.06, whereas it was 0.32 (0.09–0.54) and p = 0.006 for corpus AG. These oucomes showed a significant improvement in AG in the corpus after the *H. pylori* eradication was observed (49).

In a recent randomised, placebo controlled trial designed to evaluate the effect of a selective cyclooxygenase-2 inhibitor alone and combined with *H. pylori* eradication on the evolution of precancerous gastric lesions, more than half of the participants (56.5%) with severe AG at baseline persisted in this state or reverted to a lesser lesion (60). A randomized double-blind study in the first-degree relatives of gastric cancer patients showed that a regression was observed in 61,8% of the patients for antral AG and in 35,6% of the patients for corporal AG following the *H. pylori* eradication (P<0.0001 as compared with non-eradicated group) (61). All these results are generally in good agreement with those obtained from Correa's studies, which showed that an effective anti-*H. pylori* treatment may interfere with the precancerous process, by increasing the rate of regression of AG (62). This regression of atrophy was further confirmed after a 12-year-follow-up (63). As a conclusion, a multidisciplinary pannel agreed that the *H. pylori* eradication may lead to a partial regression of AG although it is unclear whether the effects of the treatment vary with the location and the extent of atrophy (64).

H.Pylori Eradication and Intestinal Metaplasia

Correa et al. showed that anti-*H. pylori* treatment resulted in a reduced risk of progression in gastric preneoplastic lesions (17% vs 23% in placebo group) at the end of a 6-year follow-up (62). Later extension of this study showed a significant regression in the histopathology score as a function of the square of the *H. pylori* negative time (63). Additionally, 20% (70/182) of subjects with IM at baseline who were *H. pylori* negative at 12 years had no atrophy or IM at that point, as compard with 5% (9/183) among those who were *H. pylori* positive (63). But these results were not confirmed by two meta-analyses, which revealed that no improvement was shown for IM following the *H. Pylori* eradication (49,59). A recent study did not find statistically significant beneficial effects on the progression of advanced gastric lesions after the *H. Pylori* eradication, and only about one third of participants with IM at baseline persisted in this state or reverted to a lesser lesion (60). Massarrat et al. reported that the regression of IM occurred in the antrum of corpus of the treated subjects over four-and-a-half years but progression of IM in the antrum was more frequent in non-*H. Pylori* eradicated patients (18,8% vs 5,9% $p < 0.05$) (61). This finding was consistent with the results of another study which showed that the persistent *H. Pylori* infection was an independent risk factor associated with the IM progression (OR 2.13 (95% CI 1.41–3.24)) (65). As a conclusion, it has been generally agreed that the *H. Pylori* eradication does not appear to reverse IM but it may slow its progression to neoplasia, and therefore, is recommended (65).

H.Pylori Eradication and Dysplasia

Although the end of the Correa process, gastric cancer, is reached in only about 5% of patients with advanced AG/IM, Correa's sequence is still widely preferred to define the progression or the regression of gastric precancerous lesions (66). Accordingly, the regression of dysplasia following the *H. Pylori* eradication would not be expected because such an effect could not be observed in the earlier steps of IM (60,61,64). In fact, the results of the relevant studies confirmed this expectation that dysplastic lesions are not affected by eradication. At the end of a 12-year-follow-up period following the *H. Pylori* eradication, Mera et al. found no significant changes in dysplasia (63). Among the nine new gastric cancer cases during this period, five were in the *H. Pylori* treatment group with four dysplasia and one IM at baseline (63). In another long-term-follow-up study, *H. pylori* treatment did not significantly reduce the combined prevalence of dysplasia or gastric cancer (47). Among subjects who had dysplasia in 1994, six (4,2%) progressed to gastric cancer with the active *H. pylori* treatment, and 10 (6,6%) progressed to gastric cancer with placebo in 2003 in this study (47). A recent study showed that the *H. pylori* eradication or celecoxib treatment may enhance the regression of advanced gastric lesions but no statistically significant effects were observed in any histopathology categories including dysplasia by treatment arm (60). Longer follow up studies with adequate sample sizes may answer the question of the effect of *H. pylori* clearance on dysplasia.

H.Pylori Eradication for the Prevention of Metachronous Neoplastic Lesions

It is still not clear whether the *H. pylori* eradication can reduce the incidence of metachronous cancer after endoscopic resection in patients with gastric dysplasia or cancer. In a multi-centre, open-label, randomised controlled trial, 544 patients with an early gastric cancer, were randomly assigned to receive an *H pylori* eradication regimen (n=272) or to be in the control group (n=272) (67).

At the 3-year follow-up, a metachronous gastric carcinoma was detected in 9 patients in the eradication group and 24 in the control group. In the modified intention-to-treat population, adjusting for the loss to follow-up, the hazard ratio for metachronous gastric carcinoma was 0.339 (95% CI 0.157-0.729; p = 0.003) (67). The authors conclued that the *H. Pylori* eradication after endoscopic resection of early gastric cancer could prevent the development of metachronous gastric carcinoma (67). But a recent prospective, randomised contolled trial did not confirm the findings from this dataset. In this study, 10 out of 444 patients in the eradication group and 17 out of 457 patients in the control group developed metachronous gastric carcinoma during a median follow-up period of 3 years, and the difference was not significant (p=0.15) (68). In a retrospective study, it was shown that metachronous gastric cancer developed in 13 patients (14,3%) in the *H. Pylori* persistent group, and in 15 patients (8,5%) in the eradicated group (p = 0.262) during an overall follow-up period ranging from 1.1 to 11.1 years (median 3.0 years) (69). A multivariate logistic regression analysis indicated that the baseline severe mucosal atrophy and a follow-up of more than 5 years were independent risk factors for the development of metachronous gastric cancer (69). As a conclusion, further research into the role of H pylori eradication after endoscopic resection in patients with gastric tumors is warranted.

CONCLUSION

H. pylori-associated chronic active inflammation may initiate numerous genetic and epigenetic events which may result in gastric cancer, and CagA gene is critical for the activation of oncogenic pathways. The *H. pylori* eradication may lead to a partial regression of AG, but it does not seem to reverse IM or dysplasia. However, the *H. pylori* eradication may slow the progression of gastric preneoplastic lesions to neoplasia, and therefore, is recommended.

Conflict of Interest

No conflict of interest was declared by the authors.

REFERENCES

1. Ernst PB, Peura DA, Crowe SE. The Translation of Helicobacter pylori Basic Research to Patient Care. Gastroenterology 2006; 130: 188-206.
2. Kivi M, Johansson AL, Reilly M, Tindberg Y. Helicobacter pylori status in family members as risk factors for infection in children. Epidemiol Infect 2005; 133: 645-52.
3. Epplein M, Nomura AM, Hankin JH, Blaser MJ, Perez-Perez G, Stemmermann GN, et al. Association of Helicobacter pylori infection and diet on the risk of gastric cancer: a case–control study in Hawaii. Cancer Causes Control 2008; 19: 869-77.
4. Rugge M, Capelle LG, Cappellesso R, Nitti D, Kuipers EJ. Precancerous lesions in the stomach: From biology to clinical patient management. Best Pract Res Clin Gastroenterol 2013; 27: 205-23.
5. Bin L, Meng L. Helicobacter pylori eradication for preventing gastric cancer. World J Gastroenterol 2014; 20: 5660-5.
6. Pan KF, Formichella L, Zhang L, Zhang Y, Ma JL, Li ZX, et al. Helicobacter pylori antibody responses and evolution of precancerous gastric lesions in a Chinese population. Int J Cancer 2014; 134: 2118-25.
7. Faribourz MG, Farahnaz J, Yaghoub R, Tolou H. Screening of Precancerous Gastric Lesions by Serum Pepsinogen, Gastrin-17, Anti-Helicobacter Pylori and Anti- Caga Antibodies in Dyspeptic Patients over 50 years Old in Guilan Province, North of Iran. APJCP 2014; 15: 7635-8.
8. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, et al. Management of Helicobacter pylori infection—the Maastricht IV/ Florence Consensus Report. Gut 2012; 61: 646-64.
9. Moayyedi P, Soo S, Deeks J, Delaney B, Harris A, Innes M, Oakes R, et al. Eradication of Helicobacter pylori for non-ulcer dyspepsia. Cochrane Database Syst Rev 2003; 2: CD002096.
10. Bytzer P, Dahlerup JF, Eriksen JR, Jarbøl DE, Rosenstock S, Wildt S; Danish Society for Gastroenterology. Diagnosis and treatment of Helicobacter pylori infection. Dan Med Bull 2011; 58: C4271.
11. Chey WD, Wong BC; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of Helicobacter pylori infection. Am J Gastroenterol 2007; 102: 180825.
12. Wroblewski LE, Peek RM Jr, Wilson KT. Helicobacter pylori and gastric cancer: factors that modulate disease risk. Clin Microbiol Rev 2010; 23: 713-39.
13. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. Helicobacter pylori infection and the development of gastric cancer. N Engl J Med 2001; 345: 784-9.
14. Kikuchi S. Epidemiology of Helicobacter pylori and gastric cancer. Gastric Cancer 2002; 5: 6-15.
15. Sepulveda AR, Graham DY. Role of Helicobacter pylori in gastric carcinogenesis. Gastroenterol Clin North Am 2002; 31: 517-35.
16. Brenner H, Arndt V, Stegmaier C, Ziegler H, Rothenbacher D. Is Helicobacter pylori infection a necessary condition for noncardia gastric cancer? Am J Epidemiol 2004; 159: 252-8.
17. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process-First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res 1992; 52: 6735-40.
18. Correa P, Houghton J. Carcinogenesis of Helicobacter pylori. Gastroenterology. 2007; 133: 659-72.
19. Hatakeyama M. Helicobacter pylori and gastric carcinogenesis. J Gastroenterol 2009; 44: 239-48.
20. Yoshida T, Kato J, Inoue I, Yoshimura N, Deguchi H, Mukoubayashi C, et al. Cancer development based on chronic active gastritis and resulting gastric atrophy as assessed by serum levels of pepsinogen and Helicobacter pylori antibody titer. Int J Cancer 2014; 134: 1445-7.
21. Cover TL, Blaser MJ. Helicobacter pylori in health and disease. Gastroenterology 2009; 136: 1863-73.

22. Nardone G, Rocco A, Malfertheiner P. Review article: helicobacter pylori and molecular events in precancerous gastric lesions. Aliment Pharmacol Ther 2004; 20: 261-70.
23. Correa P. Does Helicobacter pylori cause gastric cancer via oxidative stress? Biol Chem 2006; 387: 361-4.
24. Watanabe M, Kato J, Inoue I, Yoshimura N, Yoshida T, Mukoubayashi C, et al. Development of gastric cancer in nonatrophic stomach with highly active inflammation identified by serum levels of pepsinogen and Helicobacter pylori antibody together with endoscopic rugal hyperplastic gastritis. Int J Cancer 2012; 131: 2632-42.
25. Huang JQ, Zheng GF, Sumanac K, Irvine EJ, Hunt RH. Meta-analysis of the relationship between cagA seropositivity and gastric cancer. Gastroenterology 2003; 125: 1636-44.
26. Higashi H, Tsutsumi R, Muto S, Sugiyama T, Azuma T, Asaka M, et al. SHP-2 tyrosine phosphatase as an intracellular target of Helicobacter pylori CagA protein. Science 2002; 295: 683-6.
27. Higashi H, Tsutsumi R, Fujita A, Yamazaki S, Asaka M, Azuma T, et al. Biological activity of the Helicobacter pylori virulence factor CagA is determined by variation in the tyrosine phosphorylation sites. Proc Natl Acad Sci USA 2002; 99: 14428–33.
28. Higashi H, Yokoyama K, Fujii Y, Ren S, Yuasa H, Saadat I, et al. EPIYA motif is a membrane-targeting signal of Helicobacter pylori virulence factor CagA in mammalian cells. J Biol Chem 2005; 280: 23130-7.
29. Naito M, Yamazaki T, Tsutsumi R, Higashi H, Onoe K, Yamazaki S, et al. Influence of EPIYA-repeat polymorphism on the phosphorylation-dependent biological activity of Helicobacter pylori CagA. Gastroenterology 2006; 130: 1181-90.
30. Higashi H, Nakaya A, Tsutsumi R, Yokoyama K, Fujii Y, Ishikawa S, et al. Helicobacter pylori CagA induces Ras-independent morphogenetic response through SHP-2 recruitment and activation. J Biol Chem 2004; 279: 17205–16.
31. Higuchi M, Tsutsumi R, Higashi H, Hatakeyama M. Conditional gene silencing utilizing the lac repressor reveals a role of SHP-2 in cagA-positive Helicobacter pylori pathogenicity. Cancer Sci 2004; 95: 442-7.
32. Tartaglia M, Niemeyer CM, Fragale A, Song X, Buechner J, Jung A, et al. Somatic mutations in PTPN11 in juvenile myelomonocytic leukemia, myelodysplastic syndromes and acute myeloid leukemia. Nat Genet 2003; 34: 148-50.
33. Bentires-Alj M, Paez JG, David FS, Keilhack H, Halmos B, Naoki K, et al. Activating mutations of the noonan syndrome-associated SHP2/PTPN11 gene in human solid tumors and adult acute myelogenous leukemia. Cancer Res 2004; 64: 8816-20.
34. Goto Y, Ando T, Yamamoto K, Tamakoshi A, El-Omar E, Goto H, et al. Association between serum pepsinogens and polymorphismof PTPN11 encoding SHP-2 among Helicobacter pylori seropositive Japanese. Int J Cancer 2006; 118: 203-8.
35. Amieva MR, Vogelmann R, Covacci A, Tompkins LS, Nelson WJ, Falkow S. Disruption of the epithelial apical-junctional complex by Helicobacter pylori CagA. Science 2003; 300: 1430-4.
36. Saadat I, Higashi H, Obuse C, Umeda M, Murata-Kamiya N, Saito Y, et al. Helicobacter pylori CagA targets PAR1/MARK kinase to disrupt epithelial cell polarity. Nature 2007; 447: 330-3.
37. Zeaiter Z, Cohen D, Musch A, Bagnoli F, Covacci A, Stein M. Analysis of detergent-resistant membranes of Helicobacter pylori infected gastric adenocarcinoma cells reveals a role for MARK2/Par1b in CagA-mediated disruption of cellular polarity. Cell Microbiol 2008; 10: 781-94.
38. Toback FG, Walsh-Reitz MM, Musch MW, Chang EB, Del Valle J, Ren H, et al. Peptide fragments of AMP-18, a novel secreted gastric antrum mucosal protein, are mitogenic and motogenic. Am J Physiol Gastrointest Liver Physiol 2003; 285: 344-53.
39. Nardone G, Rippa E, Martin G, Rocco A, Siciliano RA, Fiengo A, et al. Gastrokine 1 expression in patients with and without Helicobacter pylori infection. Dig Liver Dis 2007; 39: 122-9.
40. Shiozaki K, Nakamori S, Tsujie M, Okami J, Yamamoto H, Nagano H, et al. Human stomach-specific gene, CA11, is down-regulated in gastric cancer. Int J Oncol 2001; 19: 701-7.
41. Yoon JH, Seo HS, Choi SS, Chae HS, Choi WS, Kim O, et al. Gastrokine 1 inhibits the carcinogenic potentials of Helicobacter pylori CagA. Carcinogenesis. 2014; 35: 2619-29.
42. Shen J, Xiao Z, Wu WK, Wang MH, To KF, Chen Y, et al. Epigenetic silencing of miR-490-3p reactivates the chromatin remodeler SMARCD1 to promote Helicobacter pylori-induced gastric carcinogenesis. Cancer Res 2014 in press.
43. Brandt S, Kwok T, Hartig R, Konig W, Backert S. NF-kappaB activation and potentiation of proinflammatory responses by the Helicobacter pylori CagA protein. Proc Natl Acad Sci USA 2005; 102: 9300-5.
44. Guilford PJ, Hopkins JB, Grady WM, Markowitz SD, Willis J, Lynch H, et al. E-cadherin germline mutations define an inherited cancer syndrome dominated by diffuse gastric cancer. Hum Mutat 1999; 14: 249-55.
45. Becker KF, Atkinson MJ, Reich U, Becker I, Nekarda H, Siewert JR, et al. E-cadherin gene mutations provide clues to diffuse type gastric carcinomas. Cancer Res 1994; 54: 3845-52.
46. Correa P. Helicobacter pylori and gastric carcinogenesis. Am J Surg Pathol 1995; 19: 37-43.
47. You WC, Brown LM, Zhang L, Li JY, Jin ML, Chang YS, et al. Randomized double-blind factorial trial of three treatments to reduce the prevalence of precancerous gastric lesions. J Natl Cancer Inst 2006; 98: 974-83.
48. Ito M, Haruma K, Kamada T, Mihara M, Kim S, Kitadai Y, et al. Helicobacter pylori eradication therapy improves atrophic gastritis and intestinal metaplasia: a 5-year prospective study of patients with atrophic gastritis. Aliment Pharmacol Ther 2002; 16: 1449-56.
49. Wang J, Xu L, Shi R, Huang X, Li SW, Huang Z, et al. Gastric atrophy and intestinal metaplasia before and after Helicobacter pylori eradication: a meta-analysis. Digestion 2011; 83: 253-60.
50. Fock KM, Talley N, Moayyedi P, Hunt R, Azuma T, Sugano K, et al; Asia-Pacific Gastric Cancer Consensus Conference. Asia-Pacific consensus guidelines on gastric cancer prevention. J Gastroenterol Hepatol 2008; 23: 351-65.
51. Ladeiras-Lopes R, Pereira AK, Nogueira A, Pinheiro-Torres T, Pinto I,Santos-Pereira R, et al. Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. Cancer Causes Control 2008; 19: 689-701.
52. Tramacere I, Negri E, Pelucchi C, Bagnardi V, Rota M, Scotti L, et al. A meta-analysis on alcohol drinking and gastric cancer risk. Ann Oncol 2012; 23: 28-36.
53. Zhang Z, Xu G, Ma M, Yang J, Liu X. Dietary fiber intake reduces risk for gastric cancer: a meta-analysis. Gastroenterology 2013; 145: 113-20.
54. Shin CM, Kim N, Yang HJ, Cho SI, Lee HS, Kim JS, et al. Stomach cancer risk in gastric cancer relatives: interaction between Helicobacter pylori infection and family history of gastric cancer for the risk of stomach cancer. J Clin Gastroenterol 2010; 44: 34-9.
55. Brenner H, Arndt V, Stürmer T, Stegmaier C, Ziegler H, Dhom G. Individual and joint contribution of family history and Helicobacter pylori infection to the risk of gastric carcinoma. Cancer 2000; 88: 274-9.
56. Chen Y, Liu L, Wang X, Wang J, Yan Z, Cheng J, et al. Body mass index and risk of gastric cancer: a meta-analysis of a population with more than ten million from 24 prospective studies. Cancer Epidemiol Biomarkers Prev 2013; 22: 1395-408.
57. Mesquita P, Raquel A, Nuno L, Reis CA, Silva LF, Serpa J, et al. Metaplasia-a transdifferentiation process that facilitates cancer development: the model of gastric intestinal metaplasia. Crit Rev Oncog 2006; 12: 3-26.
58. Meining A, Morgner A, Miehlke S, Bayerdörffer E, Stolte M. Atrophy-metaplasia-dysplasia-carcinoma sequence in the stomach: a reality or merely an hypothesis? Best Pract Res Clin Gastroenterol 2001; 15: 983-98.
59. Rokkas T, Pistiolas D, Sechopoulos P, Robotis I, Margantinis G. The long-term impact of Helicobacter pylori eradication on gastric histology: a systematic review and meta-analysis. Helicobacter 2007; 12: 32-8.
60. Wong BC, Zhang L, Ma JL, Pan KF, Li JY, Shen L, et al. Effects of selective COX-2 inhibitor and Helicobacter pylori eradication on precancerous gastric lesions. Gut 2012; 61: 812-8.
61. Massarrat S, Haj-Sheykholeslami A, Mohamadkhani A, Zendehdel N, Rakhshani N, Stolte M, et al. Precancerous conditions after H. pylori eradication: a randomized double blind study in first degree relatives of gastric cancer patients. Arch Iran Med 2012; 15 :664-9.
62. Correa P, Fontham ET, Bravo JC, Bravo LE, Ruiz B, Zarama G, et al. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter pylori therapy. J Natl Cancer Inst 2000; 92: 1881-8.
63. Mera R, Fontham ET, Bravo LE, Bravo JC, Piazuelo MB, Camargo MC, et al. Long term follow up of patients treated for Helicobacter pylori infection. Gut 2005; 54: 1536-40.
64. Dinis-Ribeiro M, Areia M, de Vries AC, Marcos-Pinto R, Monteiro-Soares M, O'Connor A, et al; European Society of Gastrointestinal Endoscopy; European Helicobacter Study Group; European Society of Pathology; Sociedade Portuguesa de Endoscopia Digestiva. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). Endoscopy 2012; 44: 74-94.
65. Leung WK, Lin SR, Ching JY, To KF, Ng EK, Chan FK, et al. Factors predicting progression of gastric intestinal metaplasia: results of a randomised coverbentiresamievatrial on Helicobacter pylori eradication. Gut 2004; 53: 1244-9.
66. Varis K, Sipponen P, Laxén F, Samloff IM, Huttunen JK, Taylor PR, et al. Implications of serum pepsinogen I in early endoscopic diagnosis of gastric cancer and dysplasia. Helsinki Gastritis Study Group. Scand J Gastroenterol 2000; 35: 950-6.
67. Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, et al; Japan Gast Study Group. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. Lancet 2008; 372: 392-7.
68. Choi J, Kim SG, Yoon H, Im JP, Kim JS, Kim WH, et al. Eradication of Helicobacter pylori after endoscopic resection of gastric tumors does not reduce incidence of metachronous gastric carcinoma. Clin Gastroenterol Hepatol 2014; 12: 793-800.
69. Maehata Y, Nakamura S, Fujisawa K, Esaki M, Moriyama T, Asano K, et al. Long-term effect of Helicobacter pylori eradication on the development of metachronous gastric cancer after endoscopic resection of early gastric cancer. Gastrointest Endosc 2012; 75: 39-46.