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Helicobacter pylori eradication for gastric cancer prevention

Ting Kin Cheung, Harry H.X. Xia, and Benjamin C.Y. Wong

Department of Medicine, University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong

Gastric cancer is the second most common fatal malignancy in the world. Its incidence is high in East Asia. *Helicobacter pylori* infection is an important factor in the pathogenesis of gastric cancer. Epidemiological studies have established a strong causal relationship between *H. pylori* infection and gastric cancer. *H. pylori* eradication is therefore likely to be one of the most promising approaches to gastric cancer prevention. Animal studies have shown that eradication of *H. pylori* infection, especially at the early stage, is effective in preventing *H. pylori*-related gastric carcinogenesis. However, the available data from human studies show that *H. pylori* eradication does not completely prevent gastric cancer and that it might be useful only in patients without atrophic gastritis or intestinal metaplasia at baseline. Longer follow-up and additional studies are needed to clarify this issue.

Key words: *Helicobacter pylori*, eradication, gastric cancer, intestinal metaplasia, atrophic gastritis

Epidemiology

Gastric cancer is the second most common fatal malignancy in the world, causing more than 750000 deaths annually.[1] About 800000 new cases were diagnosed worldwide in 2000, with 75% in Asia.[2] There are marked geographical variations, with a high incidence in areas of East Asia such as Japan, China, and Korea, the former USSR, tropical South America, the Caribbean, and Southern Europe. On the other hand, areas of South Asia such as India, Pakistan, and Thailand, North America, Australia, and Africa have a much lower incidence.[2,3] There are also considerable variations in the incidence within large countries. For example, the annual age-standardized incidence of gastric cancer in China in 1991 is 19.3/100000 in men and 9.6/100000 in women in Hong Kong, but in Changle, Fujian Province, the incidence is as high as 84.3/100000 in men and 31.7/100000 in women.[4]

Although the incidence of gastric cancer has been decreasing in most countries in the past few decades, the overall survival of patients has remained unchanged. This is probably because curative surgery is not possible in the majority of patients with gastric cancers. Most gastric cancer patients present in the advanced stage of the disease, since early cancers typically have few or no symptoms.

Helicobacter pylori and gastric carcinogenesis

Over the past two decades, epidemiological studies have established a strong causal relationship between *H. pylori* infection and gastric cancer.[5–8] In a study carried out in Linxian, China, Limburg et al.[6] reported that patients with *H. pylori* seropositivity had an 1.87-fold risk of developing gastric cardia cancer, and a 2.04-fold risk for noncardia gastric cancer. Uemura et al.[8] followed 1526 Japanese patients with upper gastrointestinal diseases for 7.8 years, and observed that gastric cancer developed only in *H. pylori*-infected patients, especially those with severe gastric atrophy and intestinal metaplasia (IM). It has also been shown in an animal model that *H. pylori* infection causes gastric cancer in Mongolian gerbils.[9] In addition, there is evidence that familial aggregation of gastric cancer is at least partly due to familial clustering of *H. pylori* infection.[10,11]

The precancerous cascade

The development of gastric cancer has been proposed to start from chronic gastritis to gastric atrophy, IM,

Reprint requests to: B.C.Y. Wong

dysplasia, and finally invasive cancer.[12] It is hypothesized that the initial event in gastric carcinogenesis occurs at the junction of the oxyntic and antral mucosa, and that antral-type mucosa is prone to the development of IM.[13] Therefore, expansion of the antral mucosa toward incisura, corpus, and fundus (pylorocardial extension), or migration of antral mucosa at the gastric body or fundus, may be associated with an increased risk of developing IM. We have previously observed that *H. pylori* infection is associated with the presence of antral-type mucosa at the incisura or body (termed antralization), which, in turn, is strongly associated with gastric atrophy and IM, and with increased cell proliferation and overexpression of Bcl-2.[13,14] Our observations suggest that antralization is an important step (or marker) in the initiation of precancerous lesions. Recently, we reported that aberrant expression of trefoil family factor 2 and mucin 6 may be involved in the process of antralization.[15]

Helicobacter pylori infection plays an initiating role in the pathogenesis of gastric cancer by changing many important factors, including antioxidant agents, reactive oxygen metabolites, and the balance between epithelial cell proliferation and apoptosis. Ascorbic acid is a critical antioxidant, which acts as a scavenger of reactive oxygen species and an inhibitor of *N*-nitrosation, and plays an important role in the prevention of gastric cancer.[16] *Helicobacter pylori* infection is associated with a significant decrease in the concentration of ascorbic acid in gastric juice, which is normalized by the eradication of the infection.[17] Similarly, the gastric level of β-carotene, another antioxidant, is also decreased in *H. pylori* infection.[18] *Helicobacter pylori* can also produce a variety of substances, including ammonia or ammonium-containing chemicals and cytotoxin(s). These products may impair the host defense and render the gastric epithelial cells prone to the activity of direct-acting carcinogens, such as reactive oxygen metabolites, *N*-nitroso-compounds and nitric oxide. Moreover, *H. pylori* infection stimulates neutrophil polymorphs and monocytes to produce excessive reactive oxygen metabolites, which can directly cause extensive DNA damage and mutations.[19–21] More importantly, *H. pylori* infection induces cell apoptosis (a genetically regulated form of programmed cell death), stimulates cell proliferation in the gastric epithelium, and causes alterations or mutations of apoptosis/proliferation-related genes.[12,22–25] Uncontrolled increase in cell proliferation may result in an imbalance between cell apoptosis and proliferation, (i.e., increased cell proliferation without a corresponding increase in apoptosis) and thus increase the risk of gastric cancer development.[24]

Helicobacter pylori eradication and gastric cancer

Currently recommended anti-*H. pylori* infection therapies achieve eradication rates of up to 90%.[26] Several studies have indicated that *H. pylori* screening and eradication is a cost-effective strategy for the prevention of gastric cancer in middle-aged adults, even if the treatment prevents only 20%–30% of *H. pylori*-associated cancers, and that the strategy is particularly beneficial in high-risk populations and in the long term,[27–29] although the feasibility, safety, and appropriate timing of this strategy for cancer prevention in the general population remains to be determined.

Human intervention studies

Precancerous lesions

The initial chemoprevention trials focused mainly on subjects with gastric precancerous lesions such as gastric atrophy, IM, and dysplasia. The end point of the trials was regression (reversal) or progression (including the development of gastric cancer) of these lesions. Conflicting results have been reported on whether these precancerous lesions reverse to normal following successful eradication of *H. pylori* infection[30–54] (Table 1). Well-designed studies (e.g., randomized, double-blinded, and with a placebo control) and/or longer follow-up periods are more likely to reveal regression of the lesions, as it takes time for regression to occur. Sung et al.[41] treated *H. pylori*-positive volunteers with either a 1-week course of omeprazole, amoxicillin, and clarithromycin or placebo. At 1 year after *H. pylori* eradication, acute and chronic gastritis was decreased in both the gastric antrum and corpus and activity of IM was decreased in the antrum. However, there was no regression of IM or gastric atrophy.[41] Four years later, this group of investigators observed not only a remarkable reduction in the severity and activity of chronic gastritis but also marked resolution of IM in the antrum in *H. pylori*-eradicated subjects, whereas continuous *H. pylori* infection led to progressive aggravation of IM and gastric atrophy.[49,51] Correa et al.[42] conducted a randomized, controlled chemoprevention trial in subjects with confirmed gastric atrophy with or without IM. Individuals were assigned to receive anti-*H. pylori* triple therapy and/or dietary supplementation with ascorbic acid or β-carotene, or their corresponding placebos, and then were followed up for an average of 72 months. They found that all three basic interventions resulted in a significant increase in the regression rate of gastric atrophy and IM.[42] Moreover, eradication of *H. pylori* infection produced a marked increase in the regression rate of the precancerous lesions, with a relative risk of 8.7 [95% confidence interval (CI), 2.7–28.2] for gastric atrophy and 5.4 (95% CI, 1.7–17.6) for IM.[42] The same

Table 1. Regression of gastric atrophy and intestinal metaplasia after eradication of *H. pylori* infection

Study (ref. no.)	Country or region	No. of patients	Regression		Follow-up (months)
			Gastric atrophy	Intestinal metaplasia	
Follow-up studies					
Genta et al. 1993 (30)	USA	11	No data	Yes	12
Witteman et al. 1995 (31)	Netherlands	66	No data	No	12
Forbes et al. 1996 (32)	Australia	54	No	No	85
Ciok et al. 1997 (33)	Poland	35	No data	Yes	24
Van der Hulst et al. 1997 (34)	Netherlands	155	No	No	12
Uemura et al. (35)[c]	Japan	132	No data	Yes	36
Tucci et al. 1998 (36)	Italy	20	Yes	No data	36
Satoh et al. 1998 (37)	Japan	20	No	No	12–33
Tepes et al. 1999 (38)	Slovenia	63	Yes	No	24–48
Kyzekova et al. 1999 (39)	Czech	25	No	No	6
Annibale et al. 2000 (40)	Italy	35	No	No	12
Kim et al. 2000 (43)	South Korea	72	No data	Yes	48
Hsu et al. 2000 (44)	Taiwan	63	No	No	12
Ohkusa et al. 2001 (45)	Japan	163	Yes	Yes	12–15
Kokkola et al. 2002 (47)	Finland	22	Yes	Yes	30
Ito et al. 2002 (48)	Japan	22	Yes	Yes	60
Randomized controlled studies					
Sung et al. 2000 (41)[abd]	China	587	No	No	12
Zhou et al. 2003 (49)[abd]	China	552	No	Yes	60
Leung et al. 2004 (51)[abd]	China	435	Yes	Yes	60
Correa et al. 2000 (42)[abe]	Colombia	976	Yes	Yes	72
Ruiz et al. 2001 (46)[abe]	Colombia	132	Yes	No data	72
Mera et al. 2005 (54)[abe]	Columbia	795	Yes	Yes	144
Kamada et al. 2003 (50)	Japan	90	Yes	No	36
Ley et al. 2004 (52)	USA	316	Yes	Yes	12
Kuipers et al. 2004(53)	Netherlands	144	Yes	No	24

[a] Prospective, randomized, case–control studies
[b] Conducted by the same research team
[c] Only patients after endoscopic resection of early gastric cancer included
[d] Only "healthy" volunteers included
[e] Only patients with gastric atrophy and/or intestinal metaplasia included

group recently reported the 12 years of follow-up data, which showed that preneoplastic gastric lesions regressed at a rate equal to the square of the time the patients had been rendered free of *H pylori* infection.[54] Ley et al.[52] reported the results of a 1-year randomized, double-blind, placebo-controlled trial on the effect of *H. pylori* eradication on gastric precancerous lesions in healthy volunteers.[52] They observed that changes in a weighted index score that incorporated the severity of preneoplasia were favorably greater in treated subjects than in placebo subjects, although there was no significant change in the worst biopsy diagnosis from 6 weeks to 1 year between the two groups.[52]

However, there are several impediments to the proper assessment of reversibility, which include failings in histological interpretation, sampling errors, and "spontaneous regression."[55] It seems likely that regeneration of normal oxyntic glands following true glandular atrophy with replacement fibrosis will be at least limited, and restoration of normal differentiation in IM is impossible in the presence of stable mutations in stem cells. In effect, these lesions may have passed a "point of no return."[55]

There are problems using precancerous lesions as surrogate markers in chemoprevention studies. Therefore, the ultimate solution depends on studies that include *H. pylori*-infected individuals, with and without precancerous lesions, and that can demonstrate a reduction in the overall incidence and mortality of gastric cancer.

Gastric cancer

In our prospective, randomized, placebo-controlled, population-based primary prevention study, 1630 healthy *H. pylori* carriers from Changle, Fujian, China, a high-risk region for gastric cancer, were randomized to receive 2 weeks of *H. pylori* eradication triple therapy (omeprazole, amoxicillin and clavulanate potassium, and metronidazole) (n = 817) or placebo (n = 813) in 1994, and followed up for an average of 7.5 years.[56] It was observed that there were 18 new gastric cancer cases during the period of follow-up. Among these new cases, seven were treated with eradication therapy and 11 were

Table 2. Risk factors for development of gastric cancer in subjects receiving anti-*H. pylori* therapy

Variables	Hazard ratio (95% confidence interval)	*P* value
Age per 1-year increment	1.10 (1.05–1.15)	<0.001
Female sex	0.45 (0.16–1.26)	0.13
Daily smoking	6.18 (2.32–16.47)	<0.001
Alcohol use	1.35 (0.48–3.77)	0.57
Dietary intake ≥2 times/week		
Green tea	1.55 (0.58–4.14)	0.38
Preserved vegetables	0.28 (0.04–2.10)	0.22
Salty fish	1.22 (0.49–3.08)	0.67
Fish sauce	1.27 (0.45–3.57)	0.65
Fruit	0.90 (0.21–3.93)	0.89
Fresh vegetables	1.62 (0.64–4.10)	0.31
Anti-*H. pylori* therapy (vs. placebo)	0.63 (0.24–1.62)	0.34
Atrophy, intestinal metaplasia or dysplasia	2.97 (0.94–9.42)	0.06

This table is adapted from reference 56

not ($P = 0.34$) (Table 2). However, among patients without precancerous lesions on presentation, no patient developed gastric cancer during the follow-up after *H. pylori* eradication, whereas six patients in the placebo group developed gastric cancer ($P = 0.02$). Our findings suggest that upper endoscopy and histological assessment of *H. pylori*-positive patients may be indicated in high-risk populations, and that all *H. pylori*-positive patients with no precancerous lesions should consider *H. pylori* eradication for gastric cancer prevention.[56]

A second randomized intervention study showed similar results. In a 12-year follow-up study of 795 *H. pylori* subjects in Columbia, 394 subjects received *H. pylori* eradication treatment and 401 received placebo. During the follow-up, nine cancers were found; four of them developed in the eradication group and five in the placebo group. All of these cancers patients had IM and/or dysplasia at the time of inclusion in the study.[54]

In another study from China, 435 subjects (220 with eradication therapy and 215 with placebo) were followed for 5 years. During the follow-up, four and six patients, respectively, were found to have gastric cancers. All of them, apart from two patients from the placebo group, had IM and/or dysplasia at baseline.

In a study performed in Japan, 1120 subjects with peptic ulcer disease who received eradication therapy were followed. During a mean follow-up period of 3.4 years, eight gastric cancers were found in 944 patients in whom *H. pylori* had been eradicated compared with four cancers in 176 subjects with failed eradication ($P = 0.04$).[57]

Animal models

Nozaki et al.[58] reported that the incidence of gastric cancer was 56.3% in *H. pylori*-infected and *N*-methyl-*N*-nitrosourea (MNU)-treated Mongolian gerbils and 6.3% in animals treated with MNU alone at week 75. Eradication of *H. pylori* infection at early (15 weeks), middle (35 weeks), and late (55 weeks) stages reduced the incidence to 6.7%, 27.3%, and 38.2%, respectively, indicating that eradication of *H. pylori* infection, especially at the early stage, is effective in preventing *H. pylori*-related gastric carcinogenesis.[58]

A recent study using an *Helicobacter felis*-C57BL/6 mouse model showed that all mice with persistent infection developed gastric cancer within 24 months of infection, whereas 30% of the mice that received eradication between 12 and 24 months after initial colonization developed gastric cancer. However, the development of gastric cancer was completely prevented in mice that received eradication within the first 12 months of infection.[59] These findings also suggest that early *H. pylori* eradication could reduce the risk of gastric cancer development.

Future directions

Helicobacter pylori eradication is likely to be one of the most promising approaches in gastric cancer prevention. However, the available data show that *H. pylori* eradication does not completely prevent gastric cancer, and it might be useful only in patients without atrophic gastritis or IM at baseline.[54] Longer follow-up studies are desperately needed to clarify this issue, as the progression from gastritis to preneoplastic conditions to gastric cancer is known to take decades.

Encouraging results have been reported on vaccination against *H. pylori* infection. Studies using animal models have shown that immunization against *H. pylori* not only prevents but also eradicates the infection.[60] Vaccination could be an important strategy in the management of *H. pylori* infection and thus prevention of gastric cancer in humans.

References

1. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997;349: 1269–76.
2. Pisani P, Bray F, Parkin DM. Estimates of the world-wide prevalence of cancer for 25 sites in the adult population. Int J Cancer 2002;97:72–81.
3. Ferlay J, Bray F, Pisani P, Parkin D. Globocan 2000: Cancer incidence, mortality, and prevalence worldwide. Version 1.0. IARC Cancer Base No. 5. Lyon: IARC Press; 2001.
4. Wong BC, Lam SK, Ching CK, Hu WH, Kwok E, Ho J, et al. Differential *Helicobacter pylori* infection rates in two contrasting gastric cancer risk regions of South China. China Gastric Cancer Study Group. J Gastroenterol Hepatol 1999;14:120–5.
5. Eslick GD, Lim LL, Byles JE, Xia HH, Talley NJ. Association of *Helicobacter pylori* infection with gastric carcinoma: a meta-analysis. Am J Gastroenterol 1999;94:2373–9.
6. Limburg P, Qiao Y, Mark S, Wang G, Perez-Perez G, Blaser M, et al. *Helicobacter pylori* seropositivity and subsite-specific gastric cancer risks in Linxian, China. J Natl Cancer Inst 2001;93: 226–33.
7. El-Omar EM, Oien K, Murray LS, El-Nujumi A, Wirz A, Gillen D, et al. Increased prevalence of precancerous changes in relatives of gastric cancer patients: critical role of *H. pylori*. Gastroenterology 2000;118:22–30.
8. 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.
9. Brenner H, Bode G, Boeing H. *Helicobacter pylori* infection among offspring of patients with stomach cancer. Gastroenterology 2000;118:31–5.
10. Watanabe T, Tada M, Nagai H, Sasaki S, Nakao M. *Helicobacter pylori* infection induces gastric cancer in Mongolian gerbils. Gastroenterology 1998;115:642–8.
11. International Agency for Research on Cancer. Schistosomes, liver flukes and *Helicobacter pylori*. In: IARC monographs on the evaluation of carcinogenic risks to humans. IARC Monograph 1994;61:177–241.
12. 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.
13. Xia HH, Kalantar JS, Talley NJ, Wyatt JM, Adams S, Chueng K, et al. Antral-type mucosa in the gastric incisura, body, and fundus (antralization): a link between *Helicobacter pylori* infection and intestinal metaplasia? Am J Gastroenterol 2000;95:114–21.
14. Xia HH, Zhang GS, Talley NJ, Wong BC, Yang Y, Henwood C, et al. Topographic association of gastric epithelial expression of Ki-67, Bax, and Bcl-2 with antralization in the gastric incisura, body, and fundus. Am J Gastroenterol 2002;97:3023–31.
15. Xia HH, Yang Y, Lam SK, Wong WM, Leung SY, Yuen ST, et al. Aberrant epithelial expression of trefoil family factor 2 and mucin 6 in *Helicobacter pylori* infected gastric antrum, incisura, and body and its association with antralisation. J Clin Pathol 2004;57:861–6.
16. Schorah CJ, Sobala GM, Sanderson M, Collis N, Primrose JN. Gastric juice ascorbic acid: effects of disease and implications for gastric carcinogenesis. Am J Clin Nutr 1991;53(1 Suppl): 287S–93S.
17. Banerjee S, Hawksby C, Miller S, Dahill S, Beattie AD, McColl KE. Effect of *Helicobacter pylori* and its eradication on gastric juice ascorbic acid. Gut 1994;35:317–22.
18. Zhang ZW, Patchett SE, Perrett D, Domizio P, Farthing MJ. Gastric alpha-tocopherol and beta-carotene concentrations in association with *Helicobacter pylori* infection. Eur J Gastroenterol Hepatol 2000;12:497–503.
19. Davies GR, Simmonds NJ, Stevens TR, Sheaff MT, Banatvala N, Laurenson IF, et al. *Helicobacter pylori* stimulates antral mucosal reactive oxygen metabolite production in vivo. Gut 1994;35: 179–85.
20. Xia HH, Wong BC. Nitric oxide in *Helicobacter pylori*-induced apoptosis and its significance in gastric carcinogenesis. J Gastroenterol Hepatol 2003;18:1227–30.
21. Xia HH. Association between *Helicobacter pylori* and gastric cancer: current knowledge and future research. World J Gastroenterol 1998;4:93–6.
22. Jones NL, Shannon PT, Cutz E, Yeger H, Sherman PM. Increase in proliferation and apoptosis of gastric epithelial cells early in the natural history of *Helicobacter pylori* infection. Am J Pathol 1997;151:1695–703.
23. Cahill RJ, Xia H, Kilgallen C, Beattie S, Hamilton H, O'Morain C. Effect of eradication of *Helicobacter pylori* infection on gastric epithelial cell proliferation. Dig Dis Sci 1995;40:1627–31.
24. Moss SF, Calam J, Agarwal B, Wang S, Holt PR. Induction of gastric epithelial apoptosis by *Helicobacter pylori*. Gut 1996;38:498–501.
25. Yang Y, Deng CS, Peng JZ, Wong BC, Lam SK, Xia HH. Effect of *Helicobacter pylori* on apoptosis and apoptosis related genes in gastric cancer cells. Mol Pathol 2003;56:19–24.
26. Xia HH, Yu Wong BC, Talley NJ, Lam SK. Alternative and rescue treatment regimens for *Helicobacter pylori* eradication. Expert Opin Pharmacother 2002;3:1301–11.
27. Parsonnet J, Harris RA, Hack HM, Owens DK. Modelling cost-effectiveness of *Helicobacter pylori* screening to prevent gastric cancer: a mandate for clinical trials. Lancet 1996;348:150–4.
28. Fendrick AM, Chernew ME, Hirth RA, Bloom BS, Bandekar RR, Scheiman JM. Clinical and economic effects of population-based *Helicobacter pylori* screening to prevent gastric cancer. Arch Intern Med 1999;159:142–8.
29. Roderick P, Davies R, Raftery J, Crabbe D, Pearce R, Patel P, et al. Cost-effectiveness of population screening for *Helicobacter pylori* in preventing gastric cancer and peptic ulcer disease, using simulation. J Med Screen 2003;10:148–56.
30. Genta RM, Lew GM, Graham DY. Changes in the gastric mucosa following eradication of *Helicobacter pylori*. Mod Pathol 1993;6:281–9.
31. Witteman EM, Mravunac M, Becx MJ, Hopman WP, Verschoor JS, Tytgat GN, et al. Improvement of gastric inflammation and resolution of epithelial damage one year after eradication of *Helicobacter pylori*. J Clin Pathol 1995;48:250–6.
32. Forbes GM, Warren JR, Glaser ME, Cullen DJ, Marshall BJ, Collins BJ. Long-term follow-up of gastric histology after *Helicobacter pylori* eradication. J Gastroenterol Hepatol 1996;11:670–3.
33. Ciok J, Dzieniszewski J, Lucer C. *Helicobacter pylori* eradication and antral intestinal metaplasia—two years follow-up study. J Physiol Pharmacol 1997;48 Suppl 4:115–22.
34. van der Hulst RW, van der Ende A, Dekker FW, Ten Kate FJ, Weel JF, Keller JJ, et al. Effect of *Helicobacter pylori* eradication on gastritis in relation to cagA: a prospective 1-year follow-up study. Gastroenterology 1997;113:25–30.
35. Uemura N, Mukai T, Okamoto S, Yamaguchi S, Mashiba H, Taniyama K, et al. Effect of *Helicobacter pylori* eradication on subsequent development of cancer after endoscopic resection of early gastric cancer. Cancer Epidemiol Biomarkers Prev 1997;6:639–42.
36. Tucci A, Poli L, Tosetti C, Biasco G, Grigioni W, Varoli O, et al. Reversal of fundic atrophy after eradication of *Helicobacter pylori*. Am J Gastroenterol 1998;93:1425–31.
37. Satoh K, Kimura K, Takimoto T, Kihira K. A follow-up study of atrophic gastritis and intestinal metaplasia after eradication of *Helicobacter pylori*. Helicobacter 1998;3:236–40.
38. Tepes B, Kavcic B, Zaletel LK, Gubina M, Ihan A, Poljak M, et al. Two- to four-year histological follow-up of gastric mucosa after *Helicobacter pylori* eradication. J Pathol 1999;188:24–9.
39. Kyzekova J, Mour J. The effect of eradication therapy on histological changes in the gastric mucosa in patients with non-ulcer

dyspepsia and *Helicobacter pylori* infection. Prospective randomized intervention study. Hepatogastroenterology 1999;46: 2048–56.
40. Annibale B, Aprile MR, D'Ambra G, Caruana P, Bordi C, Delle Fave G. Cure of *Helicobacter pylori* infection in atrophic body gastritis patients does not improve mucosal atrophy but reduces hypergastrinemia and its related effects on body ECL-cell hyperplasia. Aliment Pharmacol Ther 2000;14:625–34.
41. Sung JJ, Lin SR, Ching JY, Zhou LY, To KF, Wang RT, et al. Atrophy and intestinal metaplasia one year after cure of *H. pylori* infection: a prospective, randomized study. Gastroenterology 2000;119:7–14.
42. 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.
43. Kim N, Lim SH, Lee KH, Choi SE, Jung HC, Song IS, et al. Long-term effects of *Helicobacter pylori* eradication on intestinal metaplasia in patients with duodenal and benign gastric ulcers. Dig Dis Sci 2000;45:1754–62.
44. Hsu PI, Lai KH, Tseng HH, Lin CK, Lo GH, Cheng JS, et al. Impact of *Helicobacter pylori* eradication on the development of MALT, gland atrophy and intestinal metaplasia of the antrum. Zhonghua Yi Xue Za Zhi (Taipei) 2000;63:279–87.
45. Ohkusa T, Fujiki K, Takashimizu I, Kumagai J, Tanizawa T, Eishi Y, et al. Improvement in atrophic gastritis and intestinal metaplasia in patients in whom *Helicobacter pylori* was eradicated. Ann Intern Med 2001;134:380–6.
46. Ruiz B, Garay J, Correa P, Fontham ET, Bravo JC, Bravo LE, et al. Morphometric evaluation of gastric antral atrophy: improvement after cure of *Helicobacter pylori* infection. Am J Gastroenterol 2001;96:3281–7.
47. Kokkola A, Sipponen P, Rautelin H, Harkonen M, Kosunen TU, Haapiainen R, et al. The effect of *Helicobacter pylori* eradication on the natural course of atrophic gastritis with dysplasia. Aliment Pharmacol Ther 2002;16:515–20.
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. Zhou L, Sung JJ, Lin S, Jin Z, Ding S, Huang X, et al. A five-year follow-up study on the pathological changes of gastric mucosa after *H. pylori* eradication. Chin Med J (Engl) 2003;116:11–4.
50. Kamada T, Haruma K, Hata J, Kusunoki H, Sasaki A, Ito M, et al. The long-term effect of *Helicobacter pylori* eradication therapy on symptoms in dyspeptic patients with fundic atrophic gastritis. Aliment Pharmacol Ther 2003;18:245–52.
51. 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 trial on *Helicobacter pylori* eradication. Gut 2004;53:1244–9.
52. Ley C, Mohar A, Guarner J, Herrera-Goepfert R, Figueroa LS, Halperin D, et al. *Helicobacter pylori* eradication and gastric preneoplastic conditions: a randomized, double-blind, placebo-controlled trial. Cancer Epidemiol Biomarkers Prev 2004;13: 4–10.
53. Kuipers EJ, Nelis GF, Klinkenberg-Knol EC, Snel P, Goldfain D, Kolkman JJ, et al. Cure of *Helicobacter pylori* infection in patients with reflux oesophagitis treated with long term omeprazole reverses gastritis without exacerbation of reflux disease: results of a randomised controlled trial. Gut 2004;53:12–20.
54. 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.
55. Dixon MF. Prospects for intervention in gastric carcinogenesis: reversibility of gastric atrophy and intestinal metaplasia. Gut 2001;49:2–4.
56. Wong BC, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, et al. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA 2004;291:187–94.
57. Take S, Mizuno M, Ishiki K, Nagahara Y, Yoshida T, Yokota K, et al. The effect of eradicating *Helicobacter pylori* on the development of gastric cancer in patients with peptic ulcer disease. Am J Gastroenterol 2005;100:1037–42.
58. Nozaki K, Shimizu N, Ikehara Y, Inoue M, Tsukamoto T, Inada K, et al. Effect of early eradication on *Helicobacter pylori*-related gastric carcinogenesis in Mongolian gerbils. Cancer Sci 2003;94: 235–9.
59. Cai X, Carlson J, Stoicov C, Li H, Wang TC, Houghton J. *Helicobacter felis* eradication restores normal architecture and inhibits gastric cancer progression in C57BL/6 mice. Gastroenterology 2005;128:1937–52.
60. Michetti P, Svennerholm AM. *Helicobacter pylori*—inflammation, immunity and vaccines. Helicobacter 2003;8 Suppl 1:31–5.