Chapter 12
Prevention of Gastric Cancer by *Helicobacter pylori* Eradication: Current Evidence and Future Prospects

Jyh-Ming Liou, Jaw-Town Lin, and Ming-Shiang Wu

Abstract Ecological studies showed higher cumulative incidence of gastric cancer in countries with higher prevalence of *H. pylori* infection. Meta-analysis of case–control studies nested within prospective cohort showed that *H. pylori* infection was associated with a 5.9-fold increased risk of non-cardia gastric cancer using blood samples collected more than 10 years. *H. pylori* was associated with increased risk of both diffuse type and intestinal type gastric cancer. Cag-A seropositivity was associated with higher risk of gastric cancer. Prospective cohort studies showed that gastric cancer developed in 1–3 % of *H. pylori* infected subjects. Gastric cancer was successfully induced in Mongolian gerbils and INS-GAS transgenic mice after inoculation of *H. pylori*. The incidence of gastric dysplasia and gastric cancer could be reduced in mice treated with eradication therapy. Recent meta-analysis of randomized control trials showed a significant reduction in the risk of gastric cancer in *H. pylori* infected subjects who received *H. pylori* eradication therapy. Based on these evidences, it is well agreed that *H. pylori* is a causal risk factor of gastric cancer. However, large well-designed randomized trials are highly anticipated to assess the effectiveness of the screen and treat strategy as well as the changes in the antibiotic resistance and risks in the development of gastroesophageal reflux disease, obesity, and allergic diseases after *H. pylori* eradication.

J.-M. Liou
Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

J.-T. Lin
Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

School of Medicine, Fu Jen Catholic University, New Taipei, Taiwan

M.-S. Wu (✉)
Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

Departments of Internal Medicine and Primary Care Medicine, National Taiwan University Hospital, National Taiwan University, College of Medicine, No. 7, Chung-Shan S. Road, Taipei, Taiwan
e-mail: mingshiang@ntu.edu.tw

H. Suzuki et al. (eds.), *Helicobacter pylori*, DOI 10.1007/978-4-431-55705-0_12

Keywords *Helicobacter pylori* • Gastric cancer • Prevention • Eradication • Trial

12.1 Introduction

Gastric cancer remains the third most common cause of cancer related mortality worldwide [1]. After the discovery of *Helicobacter pylori (H. pylori)* in 1982, [2] many researchers have investigated the association of this bacterium with the gastric cancer, including adenocarcinoma and lymphoma [3–5]. In this chapter, we will summarize the landmark studies and trials in humans and in animals that provide important evidence to the causal association of *H. pylori* and gastric cancer. Whether gastric cancer can be prevented through screening and eradication of *H. pylori* will also be discussed. We will start with the ecological association of prevalence of *H. pylori* and incidence of gastric cancer in different countries. Then we will show the results from observational studies in human (case–control studies, nested case–control studies, and cohort studies). We will next present the results from interventional trials in human and in animal models. Finally, we will discuss the effectiveness, regimen to be used, the recurrence rate, and potential harms of the mass screening and eradication strategy to prevent gastric cancer in the community.

12.2 Ecological Association of Prevalence of *Helicobacter pylori* and Incidence of Gastric Cancer in Different Countries

The EUROGAST study group conducted a multicenter ecological study in 13 European countries to investigate the association between *H. pylori* infection and gastric cancer [6]. Random selection of 200 population-based subjects aged 25–34 and 55–64 years (50 males and 50 females from each age group) was done in each country [6]. They found significant associations between the cumulative incidence and mortality rates of gastric cancer with prevalence of *H. pylori* using the linear regression analysis [6]. They further estimated a sixfold increased risk of gastric cancer among populations with 100 % *H. pylori* infection compared to those without *H. pylori* infection [6].

The Asian population accounted for 72.9 % (527,074/723,027) of gastric cancer related mortality according to the GLOBOCAN 2012 database [1]. About 700,000 Asian people develops gastric cancer annually [1]. The age standardized incidence rate (ASR) of gastric cancer in Asia is shown in Fig. 12.1. The ASR of gastric cancer is higher than 20 per 100,000 in China, Japan, Korea, and Mongolia, and is lower than 10 per 100,000 in Hong Kong, India, Indonesia, Malaysia, Pakistan, Philippines, Singapore, and Thailand [1]. Generally, the ASR of gastric cancer correlates with the prevalence of *H. pylori* in Asia (Fig. 12.1). However, the ASR of gastric cancer is low in India, Pakistan, and Philippines despite the high prevalence

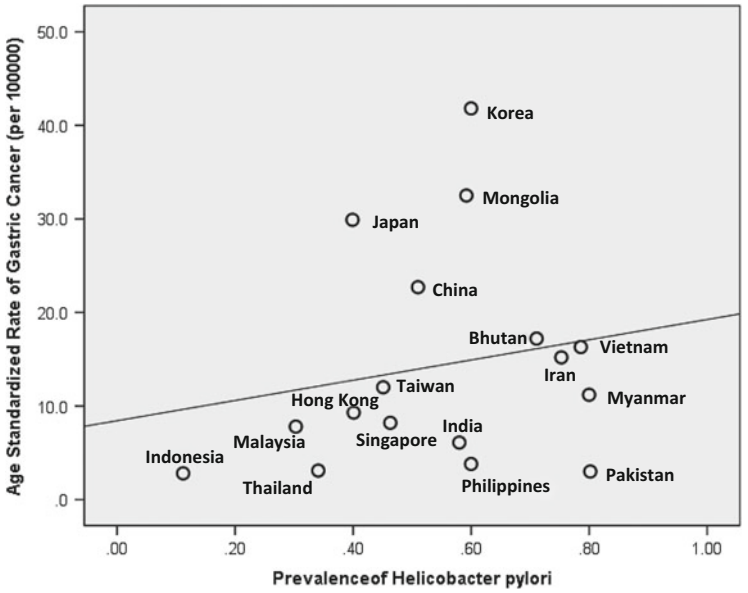

Fig. 12.1 Ecological association of prevalence of *Helicobacter pylori* and incidence of gastric cancer incidence in Asia-Pacific region [7, 8] (Note. Data were retrieved from the World Health Organization Internal Association of Cancer Registries (http://globocan.iarc.fr/Pages/age-specific_table_sel.aspx), the Taiwan Cancer Registry (http://cph.ntu.edu.tw/main.php?Page¼A5B2))

of *H. pylori* infection [7, 8]. Differences in dietary habits and genetic predisposing factors might account for this so called Asian Enigma, although underdiagnosis of gastric cancer and other competing causes of mortality might also contribute to the discrepancies [7, 8].

12.3 Association of *H. pylori* and Gastric Cancer in Observational Studies

12.3.1 Retrospective Case Control Studies

After the discovery of *H. pylori*, many retrospective case control studies have been conducted to assess its association with gastric cancer [9, 10]. The seroprevalence of *H. pylori* was significantly higher among the 112 incidence gastric cancer patients compared with the 103 matched controls (odds ratio 2.6, 95 % CI 1.4–5.0) [9]. However, conflicting results have been reported. Although some studies showed positive association of *H. pylori* and gastric cancer, others failed to confirm the association. One of the reasons for the contradictory results was the loss of *H. pylori* infection in the atrophic stomach at the time of gastric cancer diagnosis. Therefore, these studies tended to underestimate the risk of gastric

cancer. Meta-analysis of case control studies showed that *H. pylori* was associated with 1.81-fold increased risk of gastric cancer [10]. Subsequent studies further showed the association of CagA seropositivity and gastric cancer [11].

12.3.2 Nested Case Control Studies

Conducting case control studies nested within prospective cohorts which used the blood samples collected before the development of gastric cancer may overcome the above mentioned limitation of the retrospective case control studies. In a Japanese American male cohort in Hawaii enrolled from 1967 to 1970, 109 of the 5908 men developed gastric cancer by 1989 [5]. The seroprevalence of *H. pylori* was 94 % in the gastric cancer patients, compared to the 76 % in the matched controls (odds ratio 6.0, 95 % CI 2.1–17.3) [12]. In another cohort of 128,992 persons followed since mid-1960, the seroprevalence was 84 % among the 186 patients with gastric cancer, compared to the 61 % in the 186 matched controls (odd ratio 3.6, 95 % CI 1.8–7.3) [13]. Based on the results from nested case control studies, *H. pylori* was classified as a class I human carcinogen by the International Agency for Research on Cancer in 1994.

Subsequent meta-analysis of 12 nested case control studies including 1228 gastric cancer cases showed that the association with *H. pylori* was restricted to non-cardia gastric cancers (odds ratio 3.0), but not the cardia gastric cancer. It was associated with increased risk of intestinal type and the diffuse type gastric cancer at non-carida portions [14]. They further showed a stronger association (OR 5.9) when the blood samples used for serology testing was collected more than 10 years before the diagnosis of gastric cancer [14]. Several nested case–control studies have been reported after that meta-analysis. Therefore, we performed an updated meta-analysis and the results were shown in Table 12.1 and Fig. 12.2 [13–28]. Taken together with the assumption that the prevalence of *H. pylori* infection were 35 % and 80 % in developed and in developing countries, respectively, it was estimated that about 65–80 % of gastric cancer could be attributed to *H. pylori* infection [14].

12.3.3 Cohort Studies

Hansson et al. estimated the risk of gastric cancer in 57,936 patients with gastric ulcer and duodenal ulcer in a large hospital-based retrospective cohort registered between 1965 and 1983 in the Swedish Inpatient Register [29]. Gastric cancer developed in 782 of the 29,287 patients with gastric ulcer (standardized incidence ratio 4.3; 95 % CI 4.0–4.6) after an average follow-up of 8.3 years [29]. In contrast, gastric cancer developed only in 136 of the 24,456 patients with duodenal ulcer (standardized incidence ratio 0.9, 95 % CI 0.7–1.1) after an average follow-up of 10.1 years [29]. The standardized incidence ratio (SIR) for gastric cancer among

Table 12.1 Association of *Helicobacter pylori* and gastric cancer in nested case control studies

Study	Country	Cohort enrolled year	Cohort size	Median Follow-up (years)	Mean age of GC at diagnosis	Male % among cases	No of HP (+) cases	Number of GC cases	No of HP (+) controls	Number of controls
Forman 1991 and Wald 1997 [15, 16]	UK	1975–1982	21,500	8.7	54 (39–69)	100 %	38	56	72	174
Parsonnet 1991 [13]	USA	1964–1969	128,992	15	68 (44–90)	69 %	94	111	67	111
Nomura 1991 [12]	USA	1967–1970	5908	13.8	72 (56–85)	100 %	103	109	93	109
Lin 1995 [17]	Taiwan	1984–1986	9775	2	63 (43–80)	100 %	20	29	129	146
Aromaa 1996 [18]	Finland	1968–1972	39,268	9.5	62 (32–85)	62 %	73	84	121	146
Webb 1996 [19, 20]	China	1986–1989	18,244	4.8	63 (49–76)	100 %	168	188	451	548
Siman 1997 [21]	Sweden	1972–1992	32,906	5.1	56 (38–70)	93 %	46	56	110	224
Watanabe 1997 [22]	Japan	1987	2858	3.6	69 (46–86)	58 %	41	45	170	225
Hansen 1999 [23]	Norway	1972–1986	101,601	12	56 (34–68)	75 %	166	208	619	983
Limburg 2001 [24]	China	1985	29,584	3.6	61 (36–75)	62 %	113	181	99	192
Shin 2005 [25]	Korea	1993–1994	10,699	2.6	63	66 %	72	86	278	344
Kamangar 2006 [26]	Finland	1985–1988	29,133	5.8	59 (50–70)	100 %	195	234	176	234
Sasazuki 2006 [27]	Japan	1990 and 1993	123,576	n/r	57 (40–69)	67 %	478	511	383	511
Palli 2007 [28]	Europe	1992–1998	360,000	6.1	n/r	55 %	195	233	625	910

GC gastric cancer, *HP Helicobacter pylori*, *n/r* not reported

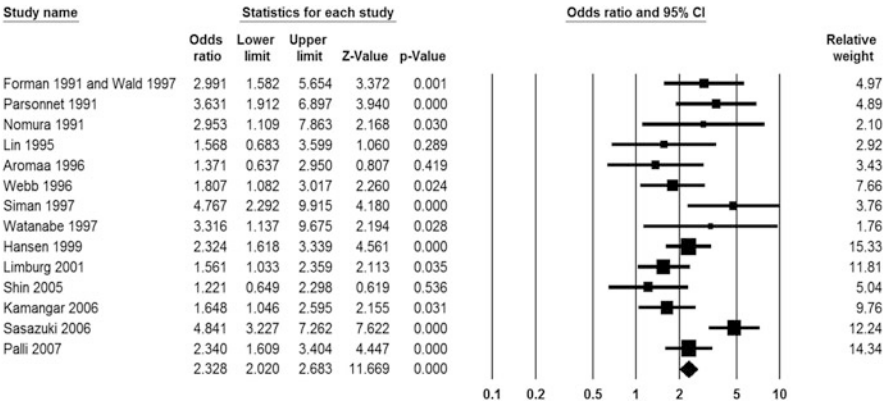

Fig. 12.2 Updated meta-analysis of nested case–control studies on the *H. pylori* infection and the gastric cancer risk [13–28]

patients with gastric ulcer and duodenal ulcer were 1.8 (95 % CI 1.6–2.0) and 0.6 (95 % CI 0.4–0.7), respectively [29]. This study indicated that compared to the general population, patients with gastric ulcer have increased risk of gastric cancer, whereas those with duodenal ulcer have reduced risk of gastric cancer.

Uemura et al. prospectively enrolled 1246 *H. pylori* infected and 280 non-infected Japanese patients who had peptic ulcer disease, gastric hyperplasia, or non-ulcer dyspepsia between 1990 and 1993 [30]. The *H. pylori* status was determined by histology, rapid urease test, and serology testing in all subjects. The mean ages at baseline were 52.3 and 52.7 years among *H. pylori* positive and negative patients, respectively. After a mean follow-up of 7.8 years, gastric cancer developed in 2.9 % (36/1246) among *H. pylori* positive patients. Interestingly, none (0/280) of the *H. pylori* negative subjects developed gastric cancer during the follow-up periods [30]. Gastric cancer developed in 4.7 % (21/445) of patients with non-ulcer dyspepsia, in 3.4 % (10/297) of patients with gastric ulcers, and in 2.2 % (5/229) of patients with gastric hyperplastic polyps [30]. However, none of the patients with duodenal ulcer (0/275) developed gastric cancer during follow-up periods [30]. In another prospective cohort study, Hsu et al. followed 618 *H. pylori* infected and 607 *H. pylori* negative patients with non-ulcer dyspepsia, gastric ulcer, and duodenal ulcer between 1990 and 1998 [31]. After a mean follow-up of 6.3 years, gastric cancer developed in 1.1 % (7/618) and 0 % (0/607) among *H. pylori* infected and negative patients, respectively [31]. They further showed that the presence of intestinal metaplasia at baseline was an independent risk factor of subsequent gastric cancer.

12.4 Animal Models

12.4.1 H. pylori *Induced Gastric Cancer in Animal Models*

Watanabe et al. inoculated *H. pylori* orally in 55 five-week-old male Mongolian gerbils. Another 30 gerbils were selected as controls. *H. pylori* were constantly detected in all of the inoculated gerbils throughout the study period [32]. Severe active chronic gastritis, ulcer, and intestinal metaplasia were observed in substantial number of gerbils examined since 26 weeks after inoculation of *H. pylori* [32]. Gastric adenocarcinoma was detected in 37 % (10/27) of gerbils 62 weeks after inoculation of *H. pylori* [32]. Wang et al. inoculated *H. felis* in insulin-gastrin (INS-GAS) transgenic mice. Gastric cancer developed in 75 % (6/8) of the INS-GAS mice that were greater than 20 months old [33]. Lee et al. further showed that inoculation of *H. pylori* may induce severe dysplasia and gastric cancer in INS-GAS transgenic mice 28 weeks after inoculation [34]. These studies provide important evidence that gastric cancer could be induced in animals after long-term *Helicobacter* infection.

12.4.2 Eradication Trials in Animal Models

It is also important to evaluate whether the elimination of *H. pylori* from infected animals could reduce the risk of gastric cancer. Lee et al. treated *H. pylori* infected transgenic INS-GAS mice with triple therapy containing omeprazole, clarithromycin, and metronidazole at 8, 12, or 22 weeks after inoculation of *H. pylori* infection [34]. They found that the severity of gastric dysplasia was significantly reduced in the mice treated with triple therapy compared to control mice [34]. More interestingly, they observed that gastric intraepithelia dysplasia was completely prevented in mice treated with 7-day triple therapy as early as 8 weeks after inoculation of *H. pylori* [34]. Romero-Gallo et al. conducted a similar study in Mongolian gerbils [35]. Thirty five gerbils were inoculated with *H. pylori* strain 7.13, a prototype strain which can induce gastric cancer [35]. These gerbils were treated with 14-day triple therapy containing lansoprazole, amoxicillin, and clarithromycin at 4 ($n = 20$) or 8 weeks ($n = 15$) after inoculation of *H. pylori*. Another 23 *H. pylori* inoculated gerbils not treated with antibiotics served as control groups. They found that gastric dysplasia or cancer developed in >60 % of the gerbils with persistent *H. pylori* infection, compared to none in the eradicated group [35]. These studies provided evidence that early eradication of *H. pylori* in animals may prevent the development of gastric dysplasia or cancer [34–36].

12.5 Eradication Trials in Human

12.5.1 Effect of H. pylori *Eradication on the Regression of Gastric Precancerous Lesions*

12.5.1.1 Cohort Studies

Several cohort studies confirmed that eradication of *H. pylori* may reduce the acute and chronic inflammation of gastric mucosa [37, 38]. However, whether the gastric precancerous lesions can be regressed after *H. pylori* eradication remains controversial [37, 38]. Ohkusa et al. showed that glandular atrophy in the corpus and intestinal metaplasia in the antrum improved 12–15 months after successful *H. pylori* eradication [37]. In a community mass eradication program, Lee et al. also showed that the incidence rate of gastric atrophy reduced from 8.2/100-person-years to 3.5/100-person-years after *H. pylori* eradication [38]. However, Lee et al. showed that the incidence rate of gastric intestinal metaplasia was not reduced after *H. pylori* eradication [38]. More well designed studies, preferably randomized trials with sufficient follow-up period and adequate biopsy number are needed to assess whether the gastric intestinal metaplasia could be regressed after *H. pylori* eradication.

12.5.1.2 Randomized Trials

In a factorial randomized trial in Columbia, 852 subjects with gastric precancerous lesions were randomized to receive *H. pylori* eradication therapy, ascorbic acid supplement, or β-carotene supplement ($2^3 = 8$ groups) [39]. The primary outcome was the risk of progression of gastric precancerous lesions. They found that patients treated with *H. pylori* eradication therapy were more likely (relative risk 8.7, 95 % CI 2.7–28.2) to have regression of the gastric precancerous lesions [39]. Sung et al. also showed that acute and chronic inflammations were significantly reduced after *H. pylori* eradication compared to the untreated group 1-year later [40]. However, neither gastric atrophy nor intestinal metaplasia showed significant improvement in the treated group [40]. You et al. showed that the risk of severe atrophic gastritis, intestinal metaplasia, dysplasia, and gastric cancer were significantly reduced (OR 0.60, 95 % 0.47–0.75) in the group treated with *H. pylori* eradication, compared to the untreated group [41]. Wong et al. showed that the precancerous lesions were more likely to be regressed in the group treated with *H. pylori* eradication (OR 1.8, 95 % CI 1.2–22. 8), compared to the placebo group [42]. These collectively indicated that eradication therapy provide beneficial effect on the regression of precancerous lesions compared to the untreated group.

12.5.2 Effect of H. pylori *Eradication in the Prevention of Gastric Cancer*

12.5.2.1 Cohort Studies

In a nationwide cohort study using the Taiwan National Health Insurance Database (NHID), Wu et al. included 80,255 patients who were hospitalized between 1997 and 2004 with a primary diagnosis of peptic ulcer disease and received *H. pylori* eradication therapy [43]. These patients were classified as "early eradication" (within 1 year) and "late eradication" (after 1 year). They found that "late eradication" was associated with increased risk of gastric cancer compared to the general population (standardized incidence ratio, SIRs 1.36, 95 % CI 1.24–1.49), whereas the SIR of the "early eradication" population was similar to that of the general population (SIR 1.05, 95 % CI 0.96–1.14) [43]. They further showed that early eradication was an independent protective factor for gastric cancer (hazards ratio 0.77).

12.5.2.2 Randomized Trials

Eight randomized trials that compare the *H. pylori* eradication and placebo on the primary prevention of gastric cancer and its precursor lesions have been reported [39–42, 44–51]. However, none of the included subjects developed gastric cancer during the follow-up periods in two of these trials [50, 51]. A randomized trial assessed the effect of *H. pylori* eradication compared to no treatment in the secondary prevention of metachronous gastric cancer in patients who received endoscopic resection for early gastric cancer [52]. The demographic characteristics of these trials were summarized in Table 12.2 [39–42, 44–49, 52]. It is noteworthy that the primary outcome was the incidence of gastric cancer in only one of these trials. Wong et al. showed insignificant reduction in the risk of gastric cancer at the end of study [42]. New cases of gastric cancer developed in 7 and 11 subjects who received *H. pylori* eradication and placebo, respectively (Hazard risk 0.63, 95 % CI 0.24–1.62) [42]. In the subgroup analysis in subjects who did not have gastric precancerous lesions at baseline, none of the subjects in the treated group developed gastric cancer compared to 6 subjects in the placebo group ($p = 0.02$) [42]. The result indicated that eradication therapy should be given as early as possible in the primary prevention of gastric cancer. Other trials used the gastric precancerous lesion as the primary outcome. In a 15-year follow-up report, Ma et al. showed that a total of 34 and 52 subjects in the treated and untreated groups developed gastric cancer, respectively [48]. In a recent meta-analysis, Ford et al. demonstrated a significant reduction in the gastric cancer incidence in healthy *H. pylori* infected subjects who received *H. pylori* eradication compared to the untreated group [53].

Table 12.2 Randomized trials comparing the efficacy of *H. pylori* eradication on the prevention of gastric cancer and its precursor lesions

Study	Country	Settings	Subjects	Mean age (years)	Gender Male %	% with precancerous lesions at baseline	Primary outcome	Follow-up periods (years)
Correa et al. [39]	Columbia	community	Healthy subjects	51.1 (26–69)	46.1 %	100 %	Gastric precancerous lesions	6.0
Leung and Zhou et al. [40, 44, 45]	China	community	Healthy subjects	52 (35–75)	47.8 %	33.7 %	Gastric precancerous lesions	10
Wong et al. [42]	China	community	Healthy subjects	42.2 (35–65)	54 %	37.7 %	Gastric cancer incidence	7.5
Saito et al. [46]	Japan	community	Healthy subjects	n/r (20–59)	n/r	n/r	Gastric precancerous lesions	>4
You et al. [41]	China	community	Healthy subjects	46.8 (35–64)	50 %	64 %	Gastric precancerous lesions	14.7
Wong et al. [47]	China	community	Healthy subjects	53 (35–64)	46.4 %	100 %	Gastric precancerous lesions	5
Fukase et al. [52]	Japan	Hospital	Post ESD/EMR EGC patients	68.5 (20–79)	76.5 %	n/r	Metachronous gastric cancer incidence	3

ESD endoscopic submucosal dissection, *EMR* endoscopic mucosal resection, *EGC* early gastric cancer, *n/r* not reported

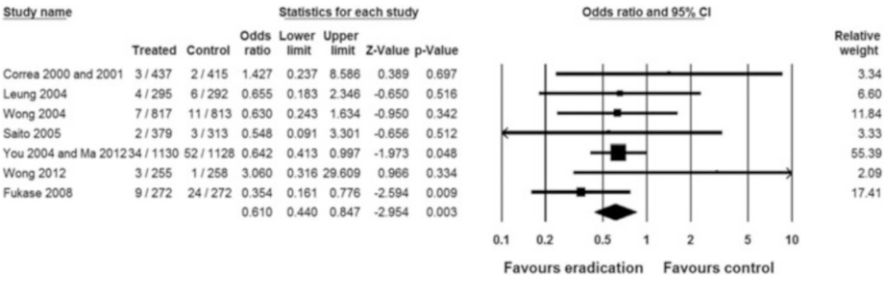

Fig. 12.3 Updated meta-analysis of randomized interventional trials of gastric cancer prevention by *H. pylori* eradication [39–42, 44–49, 52]

In an open-label randomized trial, Fukase et al. assessed whether eradication of *H. pylori* may reduce the risk of subsequent metachronous gastric cancer in patients who receive endoscopic resection compared to untreated control group [52]. They showed that 7 of the 272 patients in the eradication group developed gastric cancer after a 3-year followed-up, compared to 24 of the 272 patients in the control group (Odds ratio 0.35, 95 % CI 0.16–0.78) [52]. An updated meta-analysis which included the result of this trial was shown in Fig. 12.3 [39–42, 44–49, 52]. The results provide evidence that eradication of *H. pylori* in asymptomatic infected subjects or those with early gastric cancer may reduce the risk of gastric cancer.

12.5.2.3 Ongoing Randomized Trials

There are four ongoing large randomized trials being conducted in China, Korea, and Latvia aiming to compare the efficacy of *H. pylori* eradication versus placebo or non-antibiotic treatment in the primary prevention of gastric cancer (Table 12.3). Another placebo controlled randomized trial in UK aimed to assess the efficacy of *H. pylori* eradication in the primary prevention of peptic ulcer bleeding in chronic aspirin users. All of these trials used the triple therapy or the bismuth quadruple therapy for *H. pylori* eradication. Another randomized trial from Taiwan compare the screening and eradication strategy for *H. pylori* versus no screening in the reduction of gastric cancer risk. It is expected that the results from these trials will provide more information on the primary prevention of gastric cancer through *H. pylori* eradication.

Table 12.3 Ongoing trials comparing the efficacy of *H. pylori* eradication on the risk of gastric cancer

Clinical trial registration number	Country	Subjects	Age (years)	Design	Experiment group	Control group	Estimated sample size	Primary outcome
NCT02047994	Latvia	Healthy *H. pylori* infected subjects	40–64	Open label	Triple therapy	No treatment	30,000	Gastric cancer mortality
NCT02112214	Korea	Healthy *H. pylori* infected subjects	40–60	Double blind	10-day Bismuth quadruple therapy	Placebo	11,000	Gastric cancer incidence
NCT01678027	Korea	Sibling or offspring of patients with gastric adenocarcinoma	40–65	Double blind	7-day triple therapy	Placebo	1810	Gastric cancer incidence
ChiCTR-TRC-10000979	China	Healthy residents in Linqu County	25–54	Double blind	10-day bismuth quadruple therapy	10-day bismuth + omeprazole + placebo	184,786	Gastric cancer incidence
NCT01506986	UK	*H. pylori* infected aspirin user	≥60	Double blind	7-day triple therapy	Placebo	33,000	Peptic ulcer bleeding
NCT01741363	Taiwan	Healthy subjects	50–75	Open label	*H. pylori* screening and FIT	FIT alone	40,000	Gastric cancer incidence

FIT fecal immunochemical test

12.6 Screening and Eradication of *H. pylori* for the Primary Prevention of Gastric Cancer in the Community

12.6.1 Three Different Study Designs of Trials Addressing on Different Issues

There are several important issues to be addressed regarding the primary prevention of gastric cancer (Fig. 12.4). The first issue is whether the risk of gastric cancer can be remarkably reduced in *H. pylori* infected subjects after *H. pylori* eradication therapy. Several randomized controlled trials have shown a reduction in the risk of gastric precancerous lesion and gastric cancer in *H. pylori* infected subject after eradication of *H. pylori* (Table 12.2). The second issue is whether the strategy of screening and eradication of *H. pylori* is feasible to reduce the risk of gastric cancer. However, none of the previous randomized trials addressed on this issue. The third issue is whether the incidence of gastric cancer in a population can be reduced after the implementation of mass screening and eradication for *H. pylori*. Randomized control trial is lacking on this issue. Yet, a prospective cohort study in Matsu Island in Taiwan has been reported [38].

12.6.2 Population-Based Mass Screening and Eradication Programs

Lee et al. conducted a mass screening and eradication program in the Matsu Island of Taiwan in 2004. *H. pylori* was positive in 2598 (63 %) of the 4121 participants [38]. A total of 1762 *H. pylori* infected subjects underwent endoscopy and biopsy and eradication therapy. The cumulative eradication rate after first line 7-day clarithromycin triple therapy and second line 10-day levofloxacin triple therapy was 97.7 % [54]. By 2008, the prevalence of *H. pylori* infection has been reduced to 11.2 % (94/841) [38]. The incidence of gastric atrophy was reduced by 61 %. The

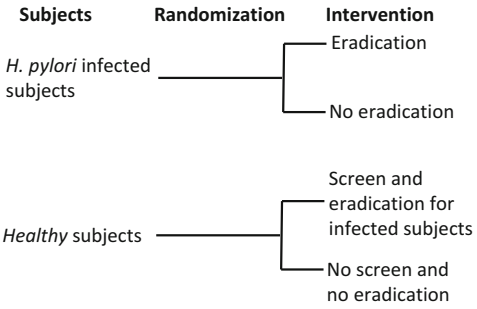

Fig. 12.4 Different designs in the interventional trials

Table 12.4 Factors to be considered for mass screening and eradication of *H. pylori*

Factors	Example 1	Example 2
Participation rate in screening	80 %	50 %
Accuracy of screening test	90 %	80 %
Prevalence of *H. pylori* infection	60 %	20 %
Participation rate in treatment	90 %	70 %
Eradication rate (ITT)	98 %	80 %
Reinfection rate	1 %/year	3 %/year
10 years (cumulative)	10 %	30 %
Prevalence of *H. pylori* 10 years later	25.8 %	17 %
% reduction in the prevalence of *H. pylori*	↓57 %	↓16 %

ITT intention-to-treat

prevalence of peptic ulcer disease was also reduced from 11 % to 3.6 % [38]. However, the prevalence of endoscopic esophagitis was increased from 13.7 % to 27.3 %. There was a trend of reduced incidence of gastric cancer, but the difference was not significant (risk ratio 0.75, 95 % CI 0.37–1.52) [38]. A longer follow-up period would be needed to reach the statistically significance.

12.6.3 Factors to be Considered in the Mass Screening and Eradication Program

Whether the strategy of screening and eradication of *H. pylori* infection may reduce the risk of gastric cancer in a region is affected by many factors, including the participation rate in the screening, the accuracy of the screening test, the prevalence of *H. pylori* infection in that region, the participation rate in the eradication therapy, the efficacy of the eradication regimen, and the reinfection (recurrence) rate in that region (Table 12.4). For example, in a region with high prevalence of *H. pylori* infection, the prevalence of *H. pylori* may be reduced by 57 % after the mass screening and eradication if the participation rate in screening and treatment are high, the regimen is effective, and the reinfection rate is low (example 1 in Table 12.4). In contrast, in a region with low prevalence of *H. pylori* infection, the prevalence could be reduced only by 16 % after the mass screening and eradication if the participation rate in screening and treatment are low, the regimen is less effective, and the reinfection rate is higher (example 2 in Table 12.4).

12.7 Regimen to be Used in the Primary Prevention of Gastric Cancer

As discussed in the previous section, regimens with high eradication rate and good compliance is anticipated in the mass eradication program. However, the intention-to-treat eradication rates in the trials conducted in the community were lower than 80 % in trials that used 7-day triple therapy or bismuth quadruple therapy (Table 12.5) [39–42, 46, 47, 54–58]. The efficacy of 14-day triple therapy was about 82 % in Latin America and in Taiwan [56–58]. This indicated that longer treatment duration, less complex and better tolerated regimens might be needed in the asymptomatic *H. pylori* infected subjects in the community. Nevertheless, more randomized trials are warranted to find out the most effective and well tolerated regimen in the community. Development of effective rescue regimens is also needed [58].

12.8 Reinfection or Recrudesces After Successful Eradication of *H. pylori*

Recurrence (reinfection or recrudesces) of *H. pylori* infection after eradication therapy is also an important issue. Reinfection is defined as infection by a new *H. pylori* strain after confirmation of successful eradication by tests that detect active *H. pylori* infection, such as urea breath test. Recrudesces is defined as reactivation of the same strains which became undetected after eradication therapy. Take et al. followed 1609 patients who had received successful eradication therapy for 4.7 years. *H. pylori* became again in 26 patients and 13 (50 %) of them became infected again within the first year [59]. The crude annual reinfection rate was 0.22 % per year. The *H. pylori* strains before eradication therapy and after reinfection or recrudesces were analyzed by random amplification of polymorphic DNA fingerprinting. Of the ten paired strains in patients who became infected again in the first year, 40 % (4/10) of the strains were different from the initial strains (reinfection), whereas another 60 % (6/10) strains were identical with the initial strains (recrudesces) [59]. Of the four paired strains in patients who became infected again after the first year, all of these four strains were different from the initial strains (reinfection). These collectively indicated that half the reinfection or recrudesces occurs in the first year. Of those whose *H. pylori* became positive again within the first year, 40 % was due to reinfection and 60 % was due to recrudesces [59]. Of those whose *H. pylori* became positive after the first year, almost 100 % was due to reinfection of new strains.

The annual reinfection and recrudesces rates vary greatly among different studies and countries [38, 60–62]. Factors that might affect the reinfection rate include the prevalence of *H. pylori* infection in that population, the hygiene status, and the socioeconomic status [38, 60–62]. The probability of recrudesces might be

Table 12.5 The eradication rates of *H. pylori* eradication regimens in the community

Study	Country	Regimen	Duration	Eradication rate
Correa et al. [39]	Columbia	Bismuth/amoxicillin/metronidazole	2 weeks	52.3 % (157/300)
Sung et al. [40]	China	Omeprazole/amoxicillin/clarithromycin	1 week	82.3 % (243/295)
Wong et al. [42]	China	Omeprazole/co-amoxiclav/metronidazole; Retreatment: bismuth/omeprazole /metronidazole/clarithromycin	2 weeks 1 week	1st: 76.4 % (624/817) 2nd: 70.6 % (60/85) Overall: 83.7 % (684/817)
Saito et al. [46]	Japan	Lansoprazole/amoxicillin/clarithromycin	1 week	85.2 % (282/331)
You et al. [41]	China	Omeprazole/amoxicillin; Retreatment: Omeprazole/amoxicillin	2 weeks; 2 weeks	1st: 62 % (703/1130); 2nd: 32.5 % (124/382); Overall: 73.2 % (827/1130)
Wong et al. [47]	China	Omeprazole/amoxicillin/clarithromycin	1 week	63.3 % (323/510)
Lee et al. [54]	Taiwan	Esomeprazole/amoxicillin/clarithromycin; Retreatment: esomeprazole/amoxicillin / levofloxacin	1 week; 10 days	1st: 86.9 % (770/886); 2nd: 91.4 % (96/105) Overall: 97.7 % (866/886)
Greenberg et al. [55]	Latin America	Lansoprazole/amoxicillin/clarithromycin	2 weeks	82.2 % (401/488)
		Lansoprazole/amoxicillin/clarithromycin/ metronidazole (concomitant)	5 days	73.6 % (360/489)
		5 days of lansoprazole and amoxicillin followed by 5 days of lansoprazole, clarithromycin, and metronidazole (sequential therapy)	10 days	76.5 % (372/486)
Pan et al. [56]	China	Bismuth/omeprazole/metronidazole/ tetracycline	10 days	72.9 % (32336/ 44345)
Liou et al. [57]	Taiwan	Lansoprazole/amoxicillin/clarithromycin	2 weeks	82.2 % (213/259)
		5 days of lansoprazole and amoxicillin followed by 5 days of lansoprazole, clarithromycin, and metronidazole (sequential therapy)	10 days	85.3 % (220/258)

attributed to the efficacy of the eradication regimen and the compliance of patients [38, 60–62]. Yet, reinfection or recrudesces could not be differentiated in almost all of the epidemiological studies that reported the reinfection/recrudesces rate due to the lack of strains before and after reinfection or recrudesces. Niv et al. searched the PubMed database up to 2007 and identified 10 and 7 prospective studies addressing on this issue in developed and developing countries, respectively [60]. Meta-analysis of these studies revealed that the annual recurrence rates were 2.7 % and 13 % in developed and developing countries, respectively [60]. In another systemic review including 77 eligible studies and a total of 43,525 follow-up patient-years after successful eradication therapy, recurrence of *H. pylori* infection occurred in 1226 cases [61]. They further showed a correlation of recurrence rate with national Human Development Index (HDI). The annual recurrence rates in countries with very high HDI, high HDI, medium HDI, and low HDI were 1.7 %, 6.1 %, 7.0 %, and 9.6 %, respectively [61].

However, most of the included studies were hospital-based researches and relatively little is known about the recurrence rate in the asymptomatic populations in the community. Recently, a randomized trial comparing the efficacy of 14-day triple therapy, 10-day sequential therapy, and 5-day concomitant therapy in asymptomatic subjects in 7 Latin American communities showed that the recurrence rate 1 year after eradication therapy was as high as 11.5 % of participants who had negative posttreatment UBT result [62]. In a community-based screening and treatment program for gastric cancer prevention in Taiwan, Lee et al. reported that the annual recurrence rate was about 1 % in asymptomatic subjects treated with 7-day triple therapy in Matsu Island [38]. Future studies to identify and block the routes of reinfection, especially in developing countries, are warranted.

12.9 Future Prospects

Elimination of this bacterium from human stomach may prevent the development of gastric cancer. Although improvement in the hygiene may reduce the prevalence of *H. pylori* infection, the implementation of screening and eradication program might hasten the reduction in the prevalence of this infection. The results from the ongoing trials on this issue are highly anticipated. Yet, although mass screening and eradication of *H. pylori* is a promising strategy to prevent gastric cancer, there are some concerns which might limit the application of such program. The most concerned issue is the potential emergence of antibiotic resistance in various bacteria in the community [63, 64]. However, very few studies have addressed on this important issue. In a small cohort study, Sjölund et al. showed a persistence of clarithromycin resistant Enterococcus in three of the five patients 3 years after *H. pylori* eradication [65]. Future randomized trials are needed to clarify the long term impact of the short term *H. pylori* eradication therapy on the antibiotic resistance. The second concern is the development or exacerbation of other diseases, such as gastroesophageal reflux disease, allergic disease, and obesity [64, 66,

67]. However, contradictory results have been reported. Well-designed randomized trials are warranted to clarify these issues. The third concern is the substantial cost of such kind of program, although it has been reported to be cost-effective in areas with high risk of gastric cancer [68–70].

12.10 Conclusion

Ecological studies showed higher cumulative incidence of gastric cancer in countries with higher prevalence of *H. pylori* infection. Meta-analysis of case–control studies nested within prospective cohort showed that *H. pylori* infection was associated with a 5.9-fold increased risk of non-cardia gastric cancer using blood samples collected more than 10 years. *H. pylori* was associated with increased risk of both diffuse type and intestinal type gastric cancer. Cag-A seropositivity was associated with higher risk of gastric cancer. Prospective cohort studies showed that gastric cancer developed in 1–3 % of *H. pylori* infected subjects. Recent meta-analysis of randomized control trials showed a significant reduction in the risk of gastric cancer in *H. pylori* infected subjects who received *H. pylori* eradication therapy. Gastric cancer was successfully induced in Mongolian gerbils and INS-GAS transgenic mice after inoculation of *H. pylori*. The incidence of gastric dysplasia and gastric cancer could be reduced in mice treated with eradication therapy. Based on these evidences, it is well agreed that *H. pylori* is a causal risk factor of gastric cancer. However, large well-designed randomized trials are highly anticipated to assess the effectiveness of the screen and treat strategy as well as the changes in the antibiotic resistance and risks in the development of gastroesophageal reflux disease, obesity, and allergic diseases after *H. pylori* eradication.

References

1. World Health Organization Internal Association of Cancer Registries. The Globocan register. http://globocan.iarc.fr/Pages/age-specific_table_sel.aspx
2. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet. 1984;1:1311–5.
3. Kuipers EJ, Lundell L, Klinkenberg-Knol EC, Havu N, Festen HP, Liedman B, et al. Atrophic gastritis and *Helicobacter pylori* infection in patients with reflux esophagitis treated with omeprazole or fundoplication. N Engl J Med. 1996;334:1018–22.
4. Parsonnet J, Hansen S, Rodriguez L, Gelb AB, Warnke RA, Jellum E, et al. *Helicobacter pylori* infection and gastric lymphoma. N Engl J Med. 1994;330:1267–71.
5. Kuipers EJ, Uyterlinde AM, Peña AS, Roosendaal R, Pals G, Nelis GF, et al. Long-term sequelae of *Helicobacter pylori* gastritis. Lancet. 1995;345:1525–8.
6. An international association between *Helicobacter pylori* infection and gastric cancer. The EUROGAST Study Group. Lancet. 1993;341:1359–62.
7. Miwa H, Go MF, Sato N. *H. pylori* and gastric cancer: the Asian enigma. Am J Gastroenterol. 2002;97:1106–12.

8. Leung WK, Wu MS, Kakugawa Y, Kim JJ, Yeoh KG, Goh KL, et al. Screening for gastric cancer in Asia: current evidence and practice. Lancet Oncol. 2008;9:279–87.
9. Hansson LE, Engstrand L, Nyrén O, Evans Jr DJ, Lindgren A, Bergström R, et al. *Helicobacter pylori* infection: independent risk indicator of gastric adenocarcinoma. Gastroenterology. 1993;105:1098–103.
10. Huang JQ, Sridhar S, Chen Y, Hunt RH. Meta-analysis of the relationship between *Helicobacter pylori* seropositivity and gastric cancer. Gastroenterology. 1998;114:1169–79.
11. 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.
12. Nomura A, Stemmermann GN, Chyou PH, Kato I, Perez-Perez GI, Blaser MJ. *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. N Engl J Med. 1991;325:1132–6.
13. Parsonnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. N Engl J Med. 1991;325:1127–31.
14. Helicobacter and Cancer Collaborative Group. Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case control studies nested within prospective cohorts. Gut. 2001;49:347–53.
15. Forman D, Newell DG, Fullerton F, Yarnell JW, Stacey AR, Wald N, et al. Association between infection with *Helicobacter pylori* and risk of gastric cancer: evidence from a prospective investigation. BMJ. 1991;302:1302–5.
16. Wald NJ, Law MR, Morris JK, Bagnall AM. *Helicobacter pylori* infection and mortality from ischaemic heart disease: negative result from a large, prospective study. BMJ. 1997;315:1199–201.
17. Lin JT, Wang LY, Wang JT, Wang TH, Yang CS, Chen CJ. A nested case–control study on the association between *Helicobacter pylori* infection and gastric cancer risk in a cohort of 9775 men in Taiwan. Anticancer Res. 1995;15:603–6.
18. Aromaa A, Kosunen TU, Knekt P, Maatela J, Teppo L, Heinonen OP, et al. Circulating anti-*Helicobacter pylori* immunoglobulin A antibodies and low serum pepsinogen I level are associated with increased risk of gastric cancer. Am J Epidemiol. 1996;144:142–9.
19. Webb PM, Yu MC, Forman D, Henderson BE, Newell DG, Yuan JM, et al. An apparent lack of association between *Helicobacter pylori* infection and risk of gastric cancer in China. Int J Cancer. 1996;67:603–7.
20. Yuan JM, Yu MC, Xu WW, Cockburn M, Gao YT, Ross RK. *Helicobacter pylori* infection and risk of gastric cancer in Shanghai, China: updated results based upon a locally developed and validated assay and further follow-up of the cohort. Cancer Epidemiol Biomarkers Prev. 1999;8:621–4.
21. Simán JH, Forsgren A, Berglund G, Florén CH. Association between *Helicobacter pylori* infection and gastric carcinoma in the city of Malmo, Sweden. A prospective study. Scand J Gastroenterol. 1997;32:1215–21.
22. Watanabe Y, Kurata JH, Mizuno S, Mukai M, Inokuchi H, Miki K, et al. *Helicobacter pylori* infection and gastric cancer. A nested case–control study in a rural area of Japan. Dig Dis Sci. 1997;42:1383–7.
23. Hansen S, Melby KK, Aase S, Jellum E, Vollset SE. *Helicobacter pylori* infection and risk of cardia cancer and non-cardia gastric cancer. A nested case–control study. Scand J Gastroenterol. 1999;34:353–60.
24. 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.
25. Shin A, Shin HR, Kang D, Park SK, Kim CS, Yoo KY. A nested case–control study of the association of *Helicobacter pylori* infection with gastric adenocarcinoma in Korea. Br J Cancer. 2005;92:1273–5.

26. Kamangar F, Dawsey SM, Blaser MJ, Perez-Perez GI, Pietinen P, Newschaffer CJ, et al. Opposing risks of gastric cardia and noncardia gastric adenocarcinomas associated with *Helicobacter pylori* seropositivity. J Natl Cancer Inst. 2006;98:1445–52.
27. Sasazuki S, Inoue M, Iwasaki M, Otani T, Yamamoto S, Ikeda S, et al. Effect of *Helicobacter pylori* infection combined with CagA and pepsinogen status on gastric cancer development among Japanese men and women: a nested case–control study. Cancer Epidemiol Biomarkers Prev. 2006;15:1341–7.
28. Palli D, Masala G, Del Giudice G, Plebani M, Basso D, Berti D, et al. CagA+ *Helicobacter pylori* infection and gastric cancer risk in the EPIC-EURGAST study. Int J Cancer. 2007;120:859–67.
29. Hansson LE, Nyrén O, Hsing AW, Bergström R, Josefsson S, Chow WH, et al. The risk of stomach cancer in patients with gastric or duodenal ulcer disease. N Engl J Med. 1996;335:242–9.
30. 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.
31. Hsu P, Lai KH, Hsu PN, Lo GH, Yu HC, Chen WC, et al. *Helicobacter pylori* infection and the risk of gastric malignancy. Am J Gastroenterol. 2007;102(4):725–30.
32. Watanabe T, Tada M, Nagai H, Sasaki S, Nakao M. *Helicobacter pylori* infection induces gastric cancer in mongolian gerbils. Gastroenterology. 1998;115:642–8.
33. Wang TC, Dangler CA, Chen D, Goldenring JR, Koh T, Raychowdhury R, et al. Synergistic interaction between hypergastrinemia and Helicobacter infection in a mouse model of gastric cancer. Gastroenterology. 2000;118:36–47.
34. Lee CW, Rickman B, Rogers AB, Ge Z, Wang TC, Fox JG. *Helicobacter pylori* eradication prevents progression of gastric cancer in hypergastrinemic INS-GAS mice. Cancer Res. 2008;68:3540–8.
35. Romero-Gallo J, Harris EJ, Krishna U, Washington MK, Perez-Perez GI, Peek Jr RM. Effect of *Helicobacter pylori* eradication on gastric carcinogenesis. Lab Investig. 2008;88:328–36.
36. Lee CW, Rickman B, Rogers AB, Muthupalani S, Takaishi S, Yang P, et al. Combination of sulindac and antimicrobial eradication of *Helicobacter pylori* prevents progression of gastric cancer in hypergastrinemic INS-GAS mice. Cancer Res. 2009;69:8166–74.
37. 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.
38. Lee YC, Chen TH, Chiu HM, Shun CT, Chiang H, Liu TY, et al. The benefit of mass eradication of *Helicobacter pylori* infection: a community-based study of gastric cancer prevention. Gut. 2013;62:676–82.
39. Correa P, Fontham ETH, 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.
40. Sung JJY, Lin S-R, Ching JYL, Zhou L-Y, To KF, Wang R-T, et al. Atrophy and intestinal metaplasia one year after cure of *H. pylori* infection: a prospective, randomized study. Gastroenterology. 2000;119:7–14.
41. You W-C, Brown LM, Zhang L, Li J-Y, Jin M-L, Chang Y-S, 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.
42. Wong BCY, 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.
43. Wu CY, Kuo KN, Wu MS, Chen YJ, Wang CB, Lin JT. Early *Helicobacter pylori* eradication decreases risk of gastric cancer in patients with peptic ulcer disease. Gastroenterology. 2009;137:1641–8.e1-2.

44. Leung WK, Lin S-R, Ching JYL, To K-F, Ng EKW, Chan FKL, et al. Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on *Helicobacter pylori* eradication. Gut. 2004;53:1244–9.
45. Zhou L. Ten-year follow-up study on the incidence of gastric cancer and the pathological changes of gastric mucosa after *H. pylori* eradication in China. Gastroenterology. 2008;134 suppl 1:A233.
46. Saito D, Boku N, Fujioka T, Fukuda Y, Matsushima Y, Sakaki N, et al. Impact of *H. pylori* eradication on gastric cancer prevention: endoscopic results of the Japanese intervention trial (JITHP-Study): a randomized multi-center trial. Gastroenterology. 2005;128 suppl 2:A4.
47. Wong BCY, Zhang L, Ma J-L, Pan K-F, Li J-Y, Shen L, et al. Effects of selective COX-2 inhibition and *Helicobacter pylori* eradication on precancerous gastric lesions. Gut. 2012;61:812–8.
48. Ma J-L, Zhang L, Brown LM, Li J-Y, Shen L, Pan K-F, et al. Fifteen-year effects of *Helicobacter pylori*, garlic, and vitamin treatments on gastric cancer incidence and mortality. J Natl Cancer Inst. 2012;104:488–92.
49. Fuccio L, Zagari RM, Eusebi LH, Laterza L, Cennamo V, Ceroni L, et al. Meta-analysis: can *Helicobacter pylori* eradication treatment reduce the risk for gastric cancer? Ann Intern Med. 2009;151:121–8.
50. Fischbach LA, Correa P, Ramirez H, Realpe JL, Collazos T, Ruiz B, et al. Anti-inflammatory and tissue-protectant drug effects: results from a randomized placebo-controlled trial of gastritis patients at high risk for gastric cancer. Aliment Pharmacol Ther. 2001;15:831–41.
51. Miehlke S, Kirsch C, Dragosics B, Gschwantler M, Oberhuber G, Antos D, et al. *Helicobacter pylori* and gastric cancer: current status of the Austrian Czech German gastric cancer prevention trial (PRISMA-study). World J Gastroenterol. 2001;7:243–7.
52. Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, et al. 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.
53. Ford AC, Forman D, Hunt RH, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. BMJ. 2014;348:g3174.
54. Lee YC, Wu HM, Chen TH, Liu TY, Chiu HM, Chang CC, et al. A community-based study of *Helicobacter pylori* therapy using the strategy of test, treat, retest, and re-treat initial treatment failures. Helicobacter. 2006;11:418–24.
55. Greenberg ER, Anderson GL, Morgan DR, Torres J, Chey WD, Bravo LE, et al. 14-day triple, 5-day concomitant, and 10-day sequential therapies for *Helicobacter pylori* infection in seven Latin American sites: a randomised trial. Lancet. 2011;378:507–14.
56. Liou JM, Chen CC, Chang CY, Chen MJ, Chen CC, Fang YJ, et al. Sequential therapy for 10 days versus triple therapy for 14 days in the eradication of *Helicobacter pylori* in the community and hospital populations: a randomised trial. Gut. 2015. doi:10.1136/gutjnl-2015-310142.
57. Pan KF, Zhang L, Gerhard M, Ma JL, Liu WD, Ulm K, et al. A large randomised controlled intervention trial to prevent gastric cancer by eradication of *Helicobacter pylori* in Linqu County, China: baseline results and factors affecting the eradication. Gut. 2015. doi:10.1136/gutjnl-2015-309197.
58. Liou JM, Chen CC, Chang CY, Chen MJ, Fang YJ, Lee JY, et al. Efficacy of genotypic resistance-guided sequential therapy in the third-line treatment of refractory *Helicobacter pylori* infection: a multicentre clinical trial. J Antimicrob Chemother. 2013;68:450–6.
59. Take S, Mizuno M, Ishiki K, Imada T, Okuno T, Yoshida T, et al. Reinfection rate of *Helicobacter pylori* after eradication treatment: a long-term prospective study in Japan. J Gastroenterol. 2012;47:641–6.
60. Niv Y, Hazazi R. *Helicobacter pylori* recurrence in developed and developing countries: meta-analysis of 13C-urea breath test follow-up after eradication. Helicobacter. 2008;13(1):56–61.

61. Yan TL, Hu QD, Zhang Q, Li YM, Liang TB. National rates of *Helicobacter pylori* recurrence are significantly and inversely correlated with human development index. Aliment Pharmacol Ther. 2013;37:963–8.
62. Morgan DR, Torres J, Sexton R, Herrero R, Salazar-Martínez E, Greenberg ER, et al. Risk of recurrent *Helicobacter pylori* infection 1 year after initial eradication therapy in 7 Latin American communities. JAMA. 2013;309:578–86.
63. Malfertheiner P, Sipponen P, Naumann M, Moayyedi P, Mégraud F, Xiao SD, et al. *Helicobacter pylori* eradication has the potential to prevent gastric cancer: a state-of-the-art critique. Am J Gastroenterol. 2005;100:2100–15.
64. 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.
65. Sjölund M, Wreiber K, Andersson DI, Blaser MJ, Engstrand L. Long-term persistence of resistant Enterococcus species after antibiotics to eradicate *Helicobacter pylori*. Ann Intern Med. 2003;139:483–7.
66. Cover TL, Blaser MJ. *Helicobacter pylori* in health and disease. Gastroenterology. 2009;136:1863–73.
67. Atherton JC, Blaser MJ. Coadaptation of *Helicobacter pylori* and humans: ancient history, modern implications. J Clin Invest. 2009;119:2475–87.
68. Ford AC, Forman D, Bailey AG, Axon ATR, Moayyedi P. A community screening program for *Helicobacter pylori* saves money: ten-year follow-up of a randomised controlled trial. Gastroenterology. 2005;129:1910–7.
69. Lee YC, Lin JT, Wu HM, Liu TY, Yen MF, Chiu HM, et al. Cost-effectiveness analysis between primary and secondary preventive strategies for gastric cancer. Cancer Epidemiol Biomarkers Prev. 2007;16:875–85.
70. 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.