**Helicobacter pylori** Eradication on the Prevention of Metachronous Lesions after Endoscopic Resection of Gastric Neoplasm: A Meta-Analysis

Da Hyun Jung¹, Jie-Hyun Kim², Hyun Soo Chung¹, Jun Chul Park¹, Sung Kwan Shin¹, Sang Kil Lee¹, Yong Chan Lee¹*

¹ Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea, ² Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

* leeyc@yuhs.ac

**Abstract**

**Background**
There is controversy about the effect of Helicobacter pylori (H. pylori) eradication on the prevention of metachronous gastric cancer after endoscopic resection (ER).

**Aims**
The aim of this study was to systematically evaluate the effect of H. pylori eradication on the prevention of metachronous gastric lesions after ER of gastric neoplasms.

**Methods**
We performed a systematic search of PubMed, EMBASE, the Cochrane Library, and MEDLINE that encompassed studies through April 2014. Our meta-analysis consisted of 10 studies, which included 5881 patients who underwent ER of gastric neoplasms.

**Results**
When we compared the incidence of metachronous lesions between H. pylori-eradicated and non-eradicated groups, H. pylori eradication significantly lowered the risk of metachronous lesions after ER of gastric neoplasms (five studies, OR = 0.392, 95% CI 0.259 – 0.593, P < 0.001). When we compared H. pylori-eradicated and persistent groups, again, H. pylori eradication significantly lowered the incidence of metachronous lesions after ER of gastric neoplasms (six studies, OR = 0.468, 95% CI 0.326 – 0.673, P < 0.001). There was no obvious heterogeneity across the analyzed studies.
Conclusions
This meta-analysis suggests a preventive role for *H. pylori* eradication for metachronous gastric lesions after ER of gastric neoplasms. Thus, *H. pylori* eradication should be considered if *H. pylori* infection is confirmed during ER.

Introduction
The incidence of early gastric cancer (EGC) has been increasing as screening upper endoscopy has become widely available in Korea. The prognosis of EGC is quite favorable, with a 5 year survival rate > 95% [1]. Therefore, endoscopic resection (ER) has been a standard treatment for select cases of EGC in Korea. ER has many advantages, such as preservation of the stomach, quality of life, and reduced health costs. However, risk of metachronous gastric cancer in the remnant stomach after ER is higher than after gastrectomy [2]. The incidence of metachronous gastric cancer within 3–5 years after ER is 2.7–14.0% [3,4]. Therefore, scheduled endoscopic surveillance has been recommended to detect metachronous lesions after ER of EGC.

*Helicobacter pylori* (*H. pylori*) infection is closely related to progression to gastric dysplasia or cancer. In 1994, the International Agency for Research on Cancer (IARC), a subdivision of the World Health Organization (WHO), defined *H. pylori* as a group I carcinogen for gastric carcinoma [5]. However, the exact role of *H. pylori* infection in development of metachronous gastric lesions after ER has not been clearly elucidated. Fukase et al. reported that eradication of *H. pylori* after ER of EGC reduced the incidence of metachronous gastric cancer (odds ratio (OR) 0.353, 95% CI 0.161–0.775, *P* = 0.009), and recommended that prophylactic eradication should be pursued after ER [6]. However, Choi et al. showed that the incidence of metachronous cancer did not differ significantly between *H. pylori*-eradicated and control groups. This study enrolled 901 patients, who underwent ER for gastric dysplasia and cancer [7]. Thus, here lies the controversy about the effect of *H. pylori* eradication on prevention of metachronous gastric cancer after ER. Therefore, we aimed to systematically evaluate the effect of *H. pylori* eradication on prevention of metachronous gastric lesions after ER of gastric neoplasms.

Methods
Meta-analysis inclusion criteria
All relevant randomized controlled trials (RCTs) and retrospective cohort studies that compared the effects of *H. pylori* eradication on prevention of metachronous gastric lesions after ER of EGC were eligible for inclusion in our analysis.

Identification of appropriate studies
PubMed (1966 to April 2014), Cochrane Library (1997 to April 2014), MEDLINE (1966 to April 2014), and EMBASE (1985 to April 2014) databases were queried during our computer-aided search. Database searches used the following terms: *Helicobacter pylori*, *H. pylori*, metachronous, second, recur, gastric dysplasia, neoplasm, and gastric cancer. We also searched references manually in order to not miss relevant articles. Two reviewers (DH Jung and J-H Kim) searched the databases independently. The primary outcome measure was the incidence of metachronous gastric lesions after *H. pylori* eradication.
Study selection
Titles and abstracts were screened by two reviewers, and studies were chosen for meta-analysis if they were relevant. Language restrictions were not considered. If there was a disagreement, it was resolved by simultaneous review.

Data extraction and quality assessment
Reviewers used standardized data extraction forms. Extracted data included baseline patient and tumor characteristics, status of *H. pylori* infection and eradication, duration of follow-up, and primary outcome measures reported by the authors. All obtained data were compared in order to minimize error.

Measures of treatment effect
We compared the incidence of metachronous gastric neoplasms after ER of gastric neoplasms between *H. pylori*-eradicated and non-eradicated groups. We also compared the incidence of metachronous gastric neoplasms after ER of gastric neoplasms between *H. pylori*-eradicated and persistent groups. The results of each study were reported as a risk ratio (RR) between *H. pylori*-eradicated and non-eradicated or persistent groups, with a 95% confidence interval (CI).

Assessment of heterogeneity
Statistical heterogeneity among trials was assessed with $\chi^2$ and $I^2$ tests. The $I^2$ test measures the percentage of variability between studies caused by heterogeneity but not chance. As values from the $I^2$ test increase, heterogeneity increases. Data were pooled according to the fixed-effects and random-effects models.

Statistical analysis
The Begg’s funnel plot and Egger’s test were used to evaluate publication bias. $P < 0.05$ suggested a significant publication bias. Data was analyzed using CMA ver. 2.0 software (Comprehensive Meta-Analysis, Englewood, NJ, USA). Weights were assigned to individual studies based on the inverse of the variance. We used the PRISMA checklist (S1 PRISMA Checklist).

Results
Study inclusion
Our literature search yielded a total of 10 studies associated with *H. pylori* eradication and metachronous gastric lesions that were included in the final analysis. Fig 1 shows the search process that resulted in the final selection of eligible studies. Of the 1590 studies identified through our search strategy, 1575 studies were excluded after review of titles and abstracts. The 15 articles that were potentially relevant were reviewed carefully. Of these, three studies were excluded because they did not explore *H. pylori* [8–10], and one study was excluded due to an insufficient description of metachronous gastric cancer [11]. The last study was excluded because it focused on patients with dysplasia [12].

Heterogeneity
There was no heterogeneity for the primary outcome between *H. pylori*-eradicated and non-eradicated or persistent groups. There was no significant heterogeneity between *H. pylori*-eradicated and non-eradicated groups ($\chi^2 = 3.11, P = 0.539$, and $I^2 = 0$). Similarly, there was no
significant heterogeneity between *H. pylori*-eradicated and persistent groups ($\chi^2 = 2.05$, $P = 0.842$, and $I^2 = 0$).

**Effect of *H. pylori* eradication on prevention of metachronous lesions after ER**

Ten studies, which included 5881 patients, compared the effect of *H. pylori* eradication on prevention of metachronous lesions after ER of gastric neoplasm (Table 1). Among these, five studies compared the incidence of metachronous lesions between *H. pylori*-eradicated and non-eradicated groups [6,7,13–15]. Six studies compared the incidence of metachronous lesions between *H. pylori*-eradicated and persistent groups [14,16–20]. One study compared the

| Study ID | Authors | Year | Ethnicity | Sample size (No receiving *H. pylori* eradication therapy) | Participant | Metachronous Recurrence | *H. pylori* Infection status (%) |
|----------|---------|------|-----------|----------------------------------------------------------|-------------|-------------------------|---------------------------------|
| 1        | Uemura et al. [15] | 1997 | Japanese  | 132 (67)                                                   | EGC         | EGC                     | 100                             |
| 2        | Nakagawa et al.[13] | 2006 | Japanese  | 2825 (2469)                                               | EGC         | EGC                     | 100                             |
| 3        | Fukase et al.[6]    | 2008 | Japanese  | 505 (250)                                                  | EGC         | EGC                     | 100                             |
| 4        | Shiotani et al. [16] | 2008 | Japanese  | 91 (0)                                                     | EGC         | EGC                     | 91.0                            |
| 5        | Maehata et al. [18] | 2012 | Japanese  | 268 (0)                                                    | EGC         | EGC                     | 100                             |
| 6        | Choi et al.[7]      | 2013 | Korean    | 880 (441)                                                  | Gastric dysplasia or EGC | Gastric dysplasia or EGC | 100                             |
| 7        | Seo et al.[17]      | 2013 | Korean    | 74 (0)                                                     | EGC         | EGC                     | 100                             |
| 8        | Kim et al.[14]      | 2014 | Korean    | 156 (88)                                                   | EGC         | EGC                     | 41.7                            |
| 9        | Bae et al.[19]      | 2014 | Korean    | 667 (N/A)                                                  | EGC         | EGC                     | 66.2                            |
| 10       | Kwon et al.[20]     | 2014 | Korean    | 283 (0)                                                    | EGC         | Gastric dysplasia or EGC | 69.0                            |

*H. pylori*, *Helicobacter pylori*
EGC, early gastric cancer

doi:10.1371/journal.pone.0124725.l001
incidence of metachronous lesions between \textit{H. pylori}-eradicated and non-eradicated or persistent groups \cite{14}. On the whole, compared with the \textit{H. pylori} non-eradicated group, results showed that \textit{H. pylori} eradication was significantly helpful in preventing metachronous lesions after ER of gastric neoplasms (OR = 0.392, 95\% CI 0.259–0.593, \textit{P} < 0.001) (Fig 2). When we compared \textit{H. pylori}-eradicated and persistent groups, \textit{H. pylori} eradication significantly lower the incidence of metachronous lesions after ER of gastric neoplasms (OR = 0.468, 95\% CI 0.326–0.673, \textit{P} < 0.001) (Fig 3). According to the Begg’s and Egger’s tests, there was no apparent publication bias on the effect of \textit{H. pylori} eradication for prevention of metachronous lesions after ER between \textit{H. pylori}-eradicated and non-eradicated or persistent groups (Egger’s test, \textit{P} = 0.090 or 0.926, funnel plot, Fig 4).

\section*{Sensitivity analysis}

A sensitivity analysis showed that the results of our meta-analysis could not be obviously influenced by removing any one study (Fig 5).

\section*{Discussion}

The effect of \textit{H. pylori} eradication on the prevention of metachronous lesions after ER is still controversial. Thus, it may be useful to combine the results of similar published studies to arrive at a meaningful conclusion. As far as we know, this is the first meta-analysis to evaluate the association between \textit{H. pylori} eradication and the incidence of metachronous lesions. Based
on our findings, \textit{H. pylori} eradication would be helpful for prevention of metachronous lesions after ER.

Nowadays, ER is widely used for local treatment of a gastric neoplasm. In Korea, the number of patients who have undergone ER for gastric neoplasm has increased annually because of the popularity of screening endoscopy \cite{21}. The \textit{H. pylori} infection rate in patients undergoing ER varies widely: 41.7–91.0\% \cite{14,16,19}. Our analysis suggests a preventive effect of \textit{H. pylori} eradication since \textit{H. pylori} eradication lowered the incidence of metachronous lesions after ER (OR = 0.392, 95\% CI 0.259–0.593, \textit{P} < 0.001). However, patients persistently infected after receiving \textit{H. pylori} treatment were included in these groups. The study by Choi \textit{et al.} showed the eradication rate of \textit{H. pylori} after ER of gastric neoplasms \cite{7}. Persistent \textit{H. pylori} infection was
found in 80 of 439 (18.2%) patients who received \textit{H. pylori} treatment and in 373 of 441 (84.6%) patients who did not receive \textit{H. pylori} treatment. We compared the effect of \textit{H. pylori} treatment between \textit{H. pylori}-eradicated and persistent groups. Successful \textit{H. pylori} eradication was associated with a significant decrease in the incidence of metachronous lesions after ER (OR = 0.468, 95% CI 0.326–0.673, \(P < 0.001\)). This means that \textit{H. pylori} eradication has a protective effect for the development of metachronous lesions. And, successful eradication of \textit{H. pylori} is very important for the prevention of metachronous lesions after ER of a gastric neoplasm.

A large, prospective, randomized study in China reported that the incidence of gastric cancer was similar between patients receiving \textit{H. pylori} eradication treatment and those receiving placebo. Subgroup analysis revealed that \textit{H. pylori} eradication significantly inhibited development of gastric cancer in patients without a precancerous lesion [22]. However, several reports have shown that \textit{H. pylori} eradication decreases the incidence of gastric cancer in high-risk patients as well [23,24]. Bae \textit{et al.} reported that \textit{H. pylori} eradication prevents development of metachronous lesions despite the presence of severe atrophy and intestinal metaplasia (IM) in the mucosal background [19].

Metachronous gastric cancer can develop after ER. Therefore, evaluating the risk factors associated with metachronous gastric cancer is important. Kwon \textit{et al.} showed that old age and persistent \textit{H. pylori} infection were independently significant risk factors for development of metachronous gastric cancer after ER of EGC [20]. Hanaoka \textit{et al.} reported that extensive atrophic fundic gastritis diagnosed by autofluorescence imaging is a significant predictor for development of metachronous gastric cancer after \textit{H. pylori} eradication [25]. According to Correa’s hypothesis, atrophic gastritis and IM caused by \textit{H. pylori} infection are closely associated with the development of gastric cancer [26]. A meta-analysis of 12 studies inferred that \textit{H. pylori}
eradication significantly improved atrophic gastritis [27]. We cannot interrupt age-related atrophic changes in gastric mucosa. Thus, *H. pylori* eradication may be a very effective intervention strategy for promoting regression of metachronous lesions after ER.

Metachronous gastric cancers are found more frequently in patients following ER than in the gastrectomized stomach. It is caused naturally by the remnant stomach, which is preserved after ER. In addition, the surrounding non-tumorous mucosa may be at high risk of developing metachronous gastric lesions because it used to share the environment with gastric cancer [28]. Therefore, eradication of *H. pylori* should be recommended to promote regression of background mucosa in patients after ER of a gastric neoplasm.

Our study has some limitations. First, the ethnicity of study participants included in this meta-analysis was Korean and Japanese. The incidence of gastric cancer and *H. pylori* infection in Eastern Asia is higher than in other areas of the world. And, ER of gastric neoplasm is performed routinely in Korea and Japan [29–31]. Therefore, reports of an association between *H. pylori* eradication and metachronous recurrence after ER might be published mostly in Korea and Japan.

Secondly, our results did not segregate dysplasia and cancer. However, dysplasia was a precancerous lesion as Correa’s hypothesis [26]. Therefore, to elucidate the effect of *H. pylori* eradication on prevention of metachronous lesions after ER is significant in patients with dysplasia or cancer.

In conclusion, the incidence of metachronous gastric cancer was higher in patients with persistent *H. pylori* infection than in those whose *H. pylori* infection was eradicated. And, eradication of *H. pylori* was helpful in decreasing the development of metachronous gastric cancer. Thus, eradication of *H. pylori* should be recommended if *H. pylori* infection is confirmed after ER.

Supporting Information

S1 PRISMA Checklist. (DOC)

Author Contributions

Conceived and designed the experiments: DHJ J-HK YCL. Performed the experiments: DHJ J-HK. Analyzed the data: DHJ J-HK. Contributed reagents/materials/analysis tools: HSC JCP SKS SKL. Wrote the paper: DHJ YCL.

References

1. Soetikno R, Kaltenbach T, Yeh R, Gotoda T. Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract. J Clin Oncol. 2005; 23: 4490–4498. PMID: 16002839
2. Choi KS, Jung HY, Choi KD, Lee GH, Song HJ, Kim do H, et al. EMR versus gastrectomy for intramucosal gastric cancer: comparison of long-term outcomes. Gastrointest Endosc. 2011; 73: 942–948. doi: 10.1016/j.gie.2010.12.032 PMID: 21392757
3. Isomoto H, Shikuwa S, Yamaguchi N, Fukuda E, Ikeda K, Nishiyama H, et al. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. Gut. 2009; 58: 331–336. doi: 10.1136/gut.2008.165381 PMID: 19001058
4. Nasu J, Doi T, Endo H, Nishina T, Hirasaki S, Hyodo I. Characteristics of metachronous multiple early gastric cancers after endoscopic mucosal resection. Endoscopy. 2005; 37: 990–993. PMID: 16189772
5. Schistosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7–14 June 1994. IARC Monogr Eval Carcinog Risks Hum. 1994; 61: 1–241. PMID: 7715068
6. 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
Kwon YH, Heo J, Lee HS, Cho CM, Jeon SW. Failure of Helicobacter pylori eradication and age are in-

10. Kato M, Asaka M, Ono S, Nakagawa M, Nakagawa S, Shimizu Y, et al. Eradication of Helicobacter pylori for primary gastric cancer and secondary gastric cancer after endoscopic mucosal resection. J Gastroenterol. 2007; 42 Suppl 17: 16–20. PMID: 17238020

11. Kikuchi S, Kato M, Katsuyama T, Tominaga S, Asaka M. Design and planned analyses of an ongoing randomized trial assessing the preventive effect of Helicobacter pylori eradication on occurrence of new gastric carcinomas after endoscopic resection. Helicobacter. 2006; 11: 147–151. PMID: 16684261

12. Chon I, Choi C, Shin CM, Park YS, Kim N, Lee DH. Effect of Helicobacter pylori eradication on subsequent dysplasia development after endoscopic resection of gastric dysplasia. Korean J Gastroenterol. 2013; 61: 307–312. PMID: 23877210

13. Nakagawa S, Asaka M, Kato M, Nakamura T, Kato C, Fujioka T, et al. Helicobacter pylori eradication and metachronous gastric cancer after endoscopic mucosal resection of early gastric cancer. Alimentary Pharmacology & Therapeutics. 2006; 24: 214–218.

14. Kim YI, Choi IJ, Kook MC, Cho SJ, Lee JY, Kim CG, et al. The association between Helicobacter pylori status and incidence of metachronous gastric cancer after endoscopic resection of early gastric cancer. Helicobacter. 2014; 19: 194–201. doi: 10.1111/hel.12116 PMID: 24612125

15. 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: 639–642. PMID: 9264278

16. Shiotani A, Uedo N, Ishii H, Yoshiyuki Y, Ishii M, Manabe N, et al. Predictive factors for metachronous gastric cancer in high-risk patients after successful Helicobacter pylori eradication. Digestion. 2008; 78: 113–119. doi: 10.1159/000173719 PMID: 19023205

17. Seo JY, Lee DH, Cho Y, Oh HS, Jo HJ, Shin CM, et al. Eradication of Helicobacter pylori reduces metachronous gastric cancer after endoscopic resection of early gastric cancer. Hepatogastroenterology. 2013; 60: 776–780. doi: 10.5754/hge12929 PMID: 23165228

18. 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. doi: 10.1016/j.gie.2011.08.030 PMID: 22018552

19. Bae SE, Jung HY, Kang J, Park YS, Baek S, Jung JH, et al. Effect of Helicobacter pylori eradication on metachronous recurrence after endoscopic neoplastic lesion. J Gastroenterol. 2014; 109: 60–67. doi: 10.1038/jaig.2013.404 PMID: 24343545

20. Kwon YH, Heo J, Lee HS, Cho CM, Jeon SW. Failure of Helicobacter pylori eradication and age are independent risk factors for recurrent neoplasia after endoscopic resection of early gastric cancer in 283 patients. Aliment Pharmacol Ther. 2014; 39: 609–618. doi: 10.1111/apt.12633 PMID: 24461252

21. Kang KJ, Lee JH. Characteristics of Gastric Cancer in Korea—with an Emphasis on the Increase of the Early Gastric Cancer (EGC). Journal of the Korean Medical Association. 2010; 53: 283–289.

22. 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: 187–194. PMID: 14722144

23. 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: 1037–1042. PMID: 15842576

24. Takenaka R, Okada H, Kato J, Makidon C, Hori S, Kawahara Y, et al. Helicobacter pylori eradication reduced the incidence of gastric cancer, especially of the intestinal type. Aliment Pharmacol Ther. 2007; 25: 805–812. PMID: 17373919

25. Hanaoka N, Uedo N, Shiotani A, Inoue T, Takeuchi Y, Higashino K, et al. Autofluorescence imaging for predicting development of metachronous gastric cancer after Helicobacter pylori eradication. J Gastroenterol Hepatol. 2010; 25: 1844–1849. doi: 10.1111/j.1440-1746.2010.06442.x PMID: 21091995
26. Correa P. A human model of gastric carcinogenesis. Cancer Res. 1988; 48: 3554–3560. PMID: 3288329

27. Wang J, Xu LJ, Shi RH, Huang XY, Li SWH, Huang ZH, et al. Gastric Atrophy and Intestinal Metaplasia before and after Helicobacter pylori Eradication: A Meta-Analysis. Digestion. 2011; 83: 253–260. doi: 10.1159/000280318 PMID: 21282951

28. Bornschein J, Toth K, Selgrad M, Kuester D, Wex T, Molnar B, et al. Dysregulation of CDX1, CDX2 and SOX2 in patients with gastric cancer also affects the non-malignant mucosa. Journal of Clinical Pathology. 2013; 66: 819–822. doi: 10.1136/jclinpath-2013-201448 PMID: 23613102

29. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011; 61: 69–90. doi: 10.3322/caac.20107 PMID: 21296855

30. Lee SY. Current progress toward eradicating Helicobacter pylori in East Asian countries: Differences in the 2013 revised guidelines between China, Japan, and South Korea. World Journal of Gastroenterology. 2014; 20: 1493–1502. doi: 10.3748/wjg.v20.i6.1493 PMID: 24587624

31. Kim MY, Cho JH, Jain P, Cho JY. ESD around the world: Asia. Gastrointest Endosc Clin N Am. 2014; 24: 283–293. doi: 10.1016/j.giec.2013.11.001 PMID: 24679239