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WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

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## Statistical proof of *Helicobacter pylori* eradication in preventing metachronous gastric cancer after endoscopic resection in an East Asian population

Mohsen Karbalaei, Masoud Keikha

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### Abstract

We conducted a comprehensive literature review and meta-analysis study on the efficacy of *Helicobacter pylori* (*H. pylori*) eradication in preventing metachronous gastric cancer after endoscopic resection among an East Asian population. Our results showed that the eradication of this pathogen significantly reduced the risk of susceptibility to metachronous gastric cancer in these patients. However, based on the available evidence, several factors such as increasing age, severe atrophy in the corpus and antrum, and intestinal metaplasia all may increase the risk of metachronous gastric cancer in *H. pylori* eradicated patients.

**Key Words:** *Helicobacter pylori*; Gastric cancer; Eradication rate; Metachronous gastric cancer

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**Core Tip:** Gastrointestinal infections caused by *Helicobacter pylori* (*H. pylori*) is one of the most well-known infections in the human digestive tract. This bacterium successfully has been colonized in the stomach of more than 4 billion people worldwide. In many developing countries, these microorganisms are colonized in childhood, which in later years may develop to severe complications, particularly gastric adenocarcinoma. In the present study, we statistically evaluated the effectiveness of *H. pylori* eradication in reducing the risk of tend to metachronous gastric cancer (MGC) in Asian populations. Our results suggested that the eradication of this pathogen significantly reduced the risk of susceptibility to MGC in these patients. However, based on the available evidence, several factors such as increasing age, severe atrophy in the corpus and antrum, and intestinal metaplasia all may increase the risk of MGC in *H. pylori* extirpated patients. Unfortunately, there is no detailed information about the location of the stomach where the reduction of gastric cancer can be achieved after *H. pylori* eradication. Therefore, in future studies, more research should be done on the recent puzzle.

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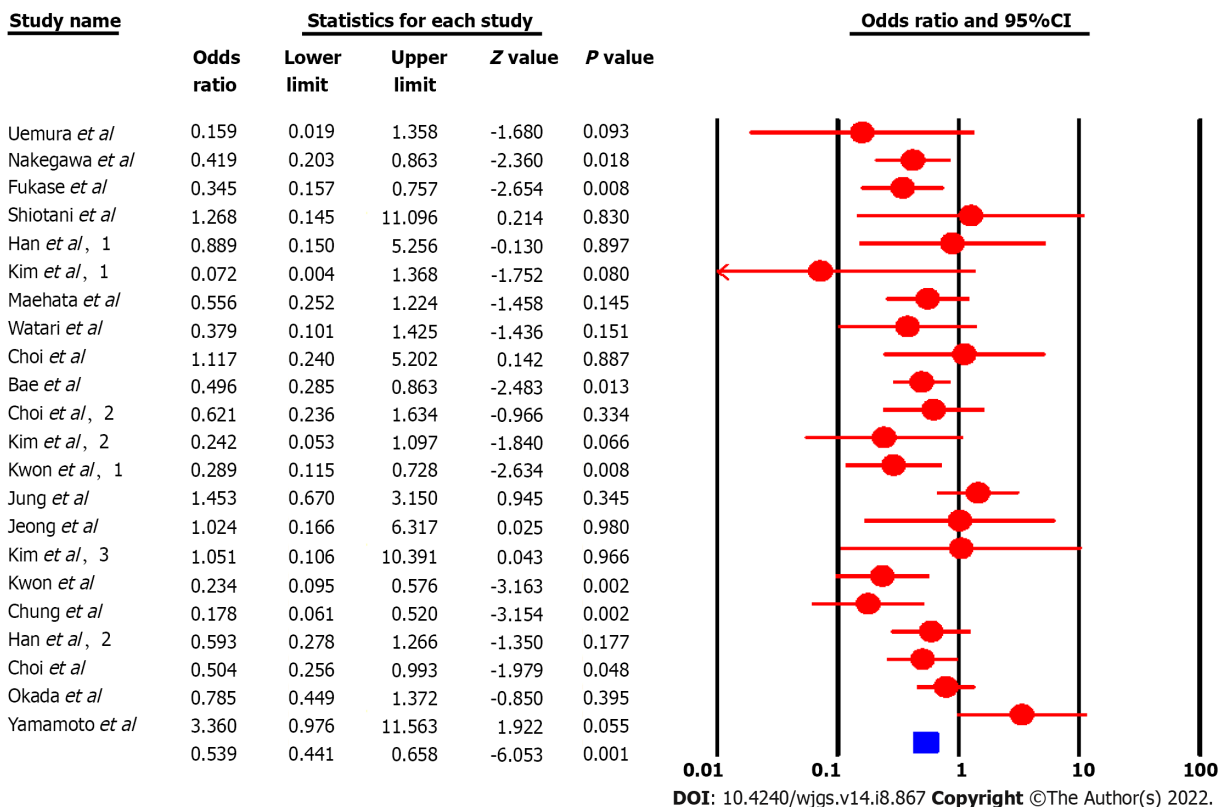
## TO THE EDITOR

*Helicobacter pylori* (*H. pylori*) is a Gram-negative, microaerophilic, and helical microorganism that colonizes the gastric mucosa in half of the world's population[1]. This bacterium is the main etiologic cause of gastritis, dyspepsia, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, gastric cancer, and peptic ulcer[1-3]. According to the literature, *H. pylori* also contributes in extragastric disorders such as insulin resistance, non-alcoholic liver disease, diabetes mellitus, coronary artery disease, and neurodegenerative disease[3,4]. In 1994, the International Agency for Research on Cancer (IARC) identified this bacterium as a group I gastric carcinogen[5]. There is ample evidence about the positive relationship between *H. pylori* infection and gastric cancer; primary infection with this bacterium has been proven to lead to cancer by inducing atrophic gastritis, intestinal metaplasia, and dysplasia[6]. According to previous randomized controlled trials (RCTs), it seems that the eradication of this pathogen is not effective in preventing the occurrence of primary gastric cancer[7-12]. Doorakkers *et al*[13] in a recent meta-analysis found that the eradication of this microorganism fundamentally reduced the incidence of primary gastric cancer.

Antrectomy (distal gastric resection) is a rare surgical procedure to treat early distal gastric cancer, in which the pyloric antrum is excised; although the presence of *H. pylori* may be decreased in the residual stomach, both untreated bacterial infection and biliopancreatic reflux damage the residual gastric mucosa, which can be considered as precursors for gastric stump cancer (GSC)[14]. Endoscopic resection (ER) procedures such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are known as accepted therapeutic strategies for treating early gastric cancer (EGC); although the effect of ER on EGC treatment is greater than that of gastrectomy, the risk of metachronous gastric lesions in the remnant stomach is higher after ER than gastrectomy[15].

Based on documents, the incidence of metachronous gastric cancer (MGC) has been estimated at 2.7%-15.6% in 3-5 years after EGC[16]. The efficacy of eradication of infection in the prevention of metachronous recurrence is controversial[15,17]. In the present study, we determined the beneficial effect of *H. pylori* eradication to prevent the recurrence of MGC after ER in an East Asian population.

We searched scientific databases such as Scopus, PubMed, Google Scholar, Cochrane Library, as well as Embase regardless of restriction in date and language by November 2020. The titles and abstracts of all papers were assessed to select the relevant articles. Then, eligible studies related to the effect of definitive treatment of infection on the recurrence of MGC after ER were collected. The inclusion criteria were: (1) RCTs or cohort studies on the effect of standard bacterial eradication on metachronous recurrence; (2) comparative studies of people with conventional *H. pylori* eradication and those who do not receive conventional eradication procedure; and (3) studies on the East Asian population. On the other hand, criteria such as (1) review articles, letters, or congress abstracts; (2) duplication studies; (3) non-clinical studies; and (4) studies with insufficient materials and findings were considered as the exclusion criteria. We collected the essential information using Comprehensive Meta-Analysis software, version 2.2. The incidence of metachronous recurrence was reported in each group as a percentage with 95% confidence interval (95%CI). Moreover, the clinical achievement of *H. pylori* eradication in reduction of metachronous recurrence was also measured using odds ratio (OR) with 95%CI. Heterogeneity was determined *via* *P* value and Cochran's *Q* test; a random-effect model was applied in high heterogeneity cases ( $I^2 > 25\%$  and Cochran's-*Q*  $P > 0.05$ ) according to the Dersimonian and Laird



**Figure 1** Forest plot for incidence of metachronous gastric cancer between *Helicobacter pylori*-eradicated group and non-eradicated group in 23 studies. 95%CI: 95% confidence interval.

method. The potential study bias was assessed by the Egger's test and Begg's test[18,19].

A total of 1753 documents were retrieved during the initial literature search. Finally, we selected 23 articles as eligible articles according to the inclusion criteria[20-42]. The demographic information such as first author, date of publication, country, follow-up years, metachronous lesions, frequency of metachronous recurrence in both eradicated and persistent cases, and references are summarized in Table 1. These studies were conducted during 1997-2019. Of all the studies, 10 were from Korea, and 10 from the Japan. In the current analysis, we evaluated the data of 9233 *H. pylori* positive cases to determine the efficacy of complete eradication in preventing metachronous events.

The frequency of metachronous recurrence in both *H. pylori* extirpated and persistently infected cases was 7.2% (95%CI: 6.4-8.1,  $P = 0.01$ ;  $I^2 = 81.68$ ,  $Q = 125.56$ ,  $P = 0.01$ ; Egger's  $P = 0.08$ , Begg's  $P = 0.05$ ) and 17.7% (95%CI: 16.1-19.5,  $P = 0.01$ ;  $I^2 = 92.68$ ,  $Q = 314.26$ ,  $P = 0.01$ ; Egger's  $P = 0.01$ , Begg's  $P = 0.54$ ), respectively.

According to the statistical analysis, there is an inverse relation between *H. pylori* elimination and metachronous recurrence (OR = 0.53, 95%CI: 0.44-0.65,  $P = 0.01$ ;  $I^2 = 39.22$ ,  $Q = 34.55$ ,  $P = 0.03$ ; Egger's  $P = 0.08$ , Begg's  $P = 0.09$ ). We showed that the eradication of *H. pylori* can significantly reduce the risk of metachronous recurrence (Figure 1).

Although most of included studies had not investigated the positive effect of *H. pylori* eradication in reducing MGC in each location of the stomach, in patients with *H. pylori* eradication, the risk of MGC was significantly associated with other conditions such as severity of corpus atrophy and intestinal metaplasia[21-23,27,39,40]. However, Han *et al*[39] showed that antrum/body atrophy and old age can meaningfully increase the risk of metachronous cancer after *H. pylori* eradication[24]. In some studies, there was no significant relationship between this cancer and the eradication of *H. pylori*[26,31,36].

Gastric cancer is one of the most prevalent cancers worldwide, especially in East Asian countries; today, the incidence of secondary gastric cancer after ER has become a major public health concern[34]. Unfortunately, in some cases, the eradication of *H. pylori* has not been able to prevent MGC in patients with ER. In general, the clinical eradication of *H. pylori* seems to be effective in preventing secondary gastric cancer and improving quality of life and survival of patients with gastric cancer[43]. In the present study, using data from 9233 *H. pylori* positive cases, we showed an inverse association between the elimination of *H. pylori* and progression to MGC in patients with a record of ER. In previous studies, we have shown that eradicating *H. pylori* in patients with gastric ulcers can reduce the risk of gastric cancer[44]. In general, it is suggested that eradicating *H. pylori* after primary gastric cancer can reduce the risk of MGC and increase survival in gastric cancer population[15,34,45].

Table 1 Characteristics of included studies

First author	Country	Year	Follow-up years	Metachronous lesions	<i>H. Pylori</i> positive samples	Frequency		Mean age (yr)		Gender		Antrum/body/cardia		Ref.
						Eradicated	Persistent	Eradicated	Persistent	Eradicated (M/F)	Persistent (M/F)	Eradicated	Persistent	
Uemura	Japan	1997	3 years	EGC	132	1/65	6/67	69.4	68.7	47/18	49/18	48/24/3	42/31/2	[20]
Nakagawa	Japan	2006	2 years	EGC	2825	8/356	129/2469	NA	NA	NA	NA	NA	NA	[21]
Fukase	Japan	2008	3 years	EGC	505	9/255	24/250	68	69	195/60	191/59	130/96/29	114/103/33	[22]
Shiotani	Japan	2008	24-48 mo	EGC	91	9/80	1/11	66		82/18		NA	NA	[23]
Han	Korea	2011	18-57 mo	EGC	116	4/94	2/22	70		NA	NA	NA	NA	[24]
Kim	Korea	2011	60 mo	EGC	55	0/28	5/27	62	60	19/10	17/9	14/10/4	15/7/5	[25]
Maehata	Japan	2012	3 years	EGC	268	15/177	13/91	68	72	128/49	66/25	70/91/16	34/48/9	[26]
Watari	Japan	2012	1 year	ER	185	3/79	10/106	NA	NA	NA	NA	NA	NA	[27]
Seo	Japan	2012	27 mo	EGC	74	0/61	0/13	NA	NA	NA	NA	NA	NA	[28]
Kim	Korea	2014	12 mo	EGC	156	2/49	16/107	59	64	39/10	73/34	39/7/3	90/12/5	[29]
Bae	Korea	2014	60 mo	EGC/dysplasia	667	34/485	24/182	62	64	380/105	145/37	NA	NA	[30]
Choi	Korea	2014	36 mo	EGC	880	10/439	17/441	59	61	291/148	305/136	325/101/13	313/113/15	[31]
Kwon	Korea	2014	3 years	EGC	283	10/214	10/69	61	60	141/73	49/20	197/10/7	63/4/2	[32]
Jung	Korea	2015	42 mo	EGC/dysplasia	675	10/169	21/506	NA	NA	NA	NA	NA	NA	[33]
Jeong	Korea	2015	NA	EGC	148	3/88	2/60	NA	NA	NA	NA	NA	NA	[34]
Kim	Korea	2016	30 mo	EGC	162	3/120	1/42	64	67	86/34	29/13	75/35/10	23/14/5	[35]
Ami	Japan	2017	53 mo	EGC	226	0/212	0/14	69		NA	NA	NA	NA	[36]
Kwon	Korea	2017	47 mo	EGC/dysplasia	395	33/368	8/27	NA	NA	NA	NA	NA	NA	[37]
Chung	Korea	2017	61 mo	EGC/dysplasia	185	17/167	7/18	67		NA	NA	NS	NA	[38]
Han	Korea	2017	60 mo	EGC	408	12/212	18/196	61	61	165/47	144/52	133/70/9	136/50/10	[39]
Choi	Korea	2018	5.9 years	EGC	396	14/194	27/202	59	59	141/53	157/45	160/25/9	166/27/9	[40]
Okada	Japan	2019	2 years	ESD	348	27/174	33/174	65	65	129/45	133/41	45/66/68	49/66/64	[41]
Yamamoto	Japan	2019	31.7 mo	Dysplasia	53	12/17	15/36	67	67	14/3	28/8	6/11/1	15/18/3	[42]



ESD: Endoscopic submucosal dissection; EGC: Early gastric cancer; ER: Endoscopic resection; *H. pylori*: *Helicobacter pylori*; NA: Not available.

Unfortunately, there is no detailed information about the location of the stomach where the reduction of gastric cancer can be achieved after *H. pylori* eradication. Therefore, in future studies, more research should be done on the recent puzzle.

## FOOTNOTES

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