76975_Auto_Edited-check.docx

WORD COUNT	1880	TIME SUBMITTED	15-JUL-2022 11:14PM
		PAPER ID	88449520

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

Mohsen Karbalaei, Masoud Keikha

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 reduces 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 corpus and antrum, as well as 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

Karbalaei M, Keikha M. Statistical proof of *Helicobacter pylori* eradication in preventing metachronous gastric cancer after endoscopic resection in East Asian population. *World J Gastrointest Surg* 2022; In press

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 on

reducing the risk of tend to metachronous gastric cancer (MGC) in Asian populations. Our results suggested that the eradication of this pathogen significantly reduces the risk of susceptibility to MGC in these patients. However, based on the available evidence, several factors such as increasing age, severe atrophy in corpus and antrum, as well as 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 reduction of gastric cancer in stomach after *H. pylori* eradication. Therefore, in future studies, more research should be done on the recent puzzle.

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 extragastrointestinal 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 resected stomach, but 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 gastrectomy, but the risk of metachronous gastric lesions in the remnant stomach is higher after ER than gastrectomy[15].

Based on documents, the incidence of M 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 determine the beneficial effect of *H. pylori* eradication to prevent the recurrence of metachronous after ER in an East Asian population.

We searched scientific databases such as Scopus, PubMed, Google Scholar, Cochrane Library, as well as Embase regardless 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 metachronous after ER were collected. The inclusion criteria were: (1) RCTs or cohort studies on the effect of standard bacterial eradication in metachronous recurrence; (2) comparison 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, 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 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 a 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* I^2 value and Cochran's Q test; the random-effect model was applied in high heterogeneity cases (I^2 > 25% and

Cochran's-*Q* *P* value > 0.05) according to Dersimonian and Laird method. The potential study bias was assessed by two 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 inclusion criteria[20-42,46]. 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, thirteen were from Korea, as well as 10 from the Japanese population. In the current analysis, we evaluated data of 9233 *H. pylori* positive cases to determine the efficacy of complete eradication in preventing metachronous event.

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

According to the statistical analysis, there is an inverse relation between *H. pylori* elimination and metachronous recurrence (OR: 0.53; 0.44-0.65 with 95%CI; *P* value: 0.01; I^2: 39.22; *Q*-value: 34.55; *P* value: 0.03; Egger's *P* value: 0.08; Begg's *P* value: 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 on reducing metachronous gastric cancer (MGC) in each location of gastric cancer, however, in patients with eradicated infection, 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 the 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 effect 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 on preventing secondary gastric cancer, modifying current guidelines, 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 metachronous gastric adenocarcinoma 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].

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

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

Table 1 Characteristics of included studies

First author	Country	Year	Follow-up years	Metachronous lesions	*H. Pylori* Positive samples	Frequency in		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	[46]
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.

76975_Auto_Edited-check.docx

ORIGINALITY REPORT

22%
SIMILARITY INDEX

PRIMARY SOURCES

1	Shiyu Xiao, Sizhu Li, Liya Zhou, Wenjun Jiang, Jinzhe Liu. "Helicobacter pylori status and risks of metachronous recurrence after endoscopic resection of early gastric cancer: a systematic review and meta-analysis", Journal of Gastroenterology, 2018 Crossref	62 words — 3%
2	Parvin Askari, Mohsen Karbalaei, Kiarash Ghazvini, Masoud Keikha. "Severe clinical outcomes of infection with babA2-positive Helicobacter pylori strains in the Iranian population: A systematic review and meta-analysis", Meta Gene, 2021 Crossref	38 words — 2%
3	Mohsen Karbaalei, Amirhossein Sahebkar, Yoshio Yamaoka, Masoud Keikha. "Helicobacter pylori cagA Status and Gastric Mucosa-associated Lymphoid Tissue Lymphoma: a Systematic Review and Meta-analysis", Research Square Platform LLC, 2021 Crossref Posted Content	36 words — 2%
4	Kwon, Y. H., J. Heo, H. S. Lee, C. M. Cho, and S. W. Jeon. "Failure of Helicobacter pylori eradication and age are independent risk factors for recurrent neoplasia after endoscopic resection of early gastric cancer in 283 patients", Alimentary Pharmacology & Therapeutics, 2014. Crossref	35 words — 2%

5	Bae, Suh Eun, Hwoon-Yong Jung, June Kang, Young Soo Park, Seunghee Baek, Ji-Hoon Jung, Ji Young Choi, Mi-Young Kim, Ji Yong Ahn, Kwi-Sook Choi, Do Hoon Kim, Jeong Hoon Lee, Kee Don Choi, Ho June Song, Gin Hyug Lee, and Jin-Ho Kim. "Effect of Helicobacter pylori Eradication on Metachronous Recurrence After Endoscopic Resection of Gastric Neoplasm", The American Journal of Gastroenterology, 2014. Crossref	25 words — 1%
6	www.ncbi.nlm.nih.gov Internet	25 words — 1%
7	www.wjgnet.com Internet	24 words — 1%
8	Masoud Keikha, Hossein Kamali, Kiarash Ghazvini, Mohsen Karbalaei. " Conceptual framework of antibiotic stewardship programs in reducing ESBL-producing : a systematic review and meta-analysis ", Journal of Chemotherapy, 2022 Crossref	23 words — 1%
9	Masoud Keikha, Mohsen Karbalaei. " A Comprehensive Survey of the Relationship between Infection and Atherosclerosis in the Iranian Population: A Systematic Review and Meta-analysis ", Archives of Iranian Medicine, 2022 Crossref	22 words — 1%
10	Christophe Genisset, Cesira L. Galeotti, Pietro Lupetti, David Mercati et al. " A Vacuolating Toxin Mutant That Fails To Oligomerize Has a Dominant Negative Phenotype ", Infection and Immunity, 2006 Crossref	21 words — 1%

11	Takeshi Seta, Yoshimitsu Takahashi, Yoshinori Noguchi, Satoru Shikata et al. "Effectiveness of Helicobacter pylori eradication in the prevention of primary gastric cancer in healthy asymptomatic people: A systematic review and meta-analysis comparing risk ratio with risk difference", PLOS ONE, 2017 Crossref	21 words — 1%
12	synapse.koreamed.org Internet	20 words — 1%
13	Reina Ohba, Katsunori Iijima. " Pathogenesis and risk factors for gastric cancer after eradication ", World Journal of Gastrointestinal Oncology, 2016 Crossref	19 words — 1%
14	assets.researchsquare.com Internet	19 words — 1%
15	hdl.handle.net Internet	14 words — 1%
16	www.spandidos-publications.com Internet	14 words — 1%
17	mafiadoc.com Internet	10 words — < 1%
18	Hidekazu Suzuki. "Helicobacter pylori and gastric cancer", Gastric Cancer, 06/2009 Crossref	9 words — < 1%
19	Seyed-Abolfazl Hosseininasab-nodoushan, Kiarash Ghazvini, Tannaz Jamialahmadi, Masoud Keikha, Amirhossein Sahebkar. "Association of Chlamydia and Mycoplasma infections with susceptibility to ovarian cancer: A	9 words — < 1%

systematic review and meta-analysis", Seminars in Cancer Biology, 2021
Crossref

20 www.helicojournal.org
Internet
9 words — < 1%

21 Kim, Sang Gyun, Hye-Kyung Jung, Hang Lak Lee, Jae Young Jang, Hyuk Lee, Chan Gyoo Kim, Woon Geon Shin, Ein Soon Shin, and Yong Chan Lee. "Guidelines for the diagnosis and treatment of Helicobacter pylori infection in Korea, 2013 revised edition : Guideline for the management of H. pylori infection in Korea 2013", Journal of Gastroenterology and Hepatology, 2014.
Crossref
8 words — < 1%

22 bmcgastroenterol.biomedcentral.com
Internet
8 words — < 1%

23 Luigi Basso, Gaetano Gallo, Daniele Biacchi, Maria Vittoria Carati et al. "Role of New Anatomy, Biliopancreatic Reflux, and Helicobacter Pylori Status in Postgastrectomy Stump Cancer", Journal of Clinical Medicine, 2022
Crossref
6 words — < 1%

EXCLUDE QUOTES	OFF	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	OFF	EXCLUDE MATCHES	OFF