

The association between *Helicobacter pylori* eradication in peptic ulcer patients and gastric cancer? Investigation in an East-Asian population

Masoud Keikha^{1,2,3,*}

¹Antimicrobial Resistance Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

²Department of Microbiology and Virology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

³Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran.

Dear Editor;

Helicobacter pylori (*H. pylori*) is one of the main cause of gastric adenocarcinoma particularly non-cardia cancer (1). There are several evidence that *H. pylori* can develop to gastric cancer via induction of inflammatory response, chronic gastric atrophy, intestinal metaplasia, and dysplasia; IARC/WHO in 1994 has been declared that *H. pylori* is classified as class I carcinogen in humans (2-3). In previous reports on Mongolian gerbils model has been defined that eradication of *H. pylori* can significantly reduce the risk of gastric cancer (4). The clinically efficacy of *H. pylori* eradication in reduction of gastric cancer in human is controversial (5-6); however, there are several published meta-analysis studies has been suggested that eradication of *H. pylori* infection is benefit in prevention of gastric cancer development in asymptomatic cases and patients with history of endoscopic resection surgery (7-8). For the first time, we analyzed all available document in relation to evaluation of gastric cancer risk after *H. pylori* eradication in patients with peptic ulcer in a East-Asia population.

A systematic search of literature was conducted via PubMed, Scopus, Embase, Google scholar, and Cochrane Library databases without limitation in publication date or language due November 2020. We searched documents by keywords according to the MeSH terms including “*Helicobacter pylori*”, “*H. pylori*”, “eradication”, “peptic ulcer”, and “gastric cancer” to collected all available documents. The inclusion criteria were: 1) clinical trials, cohort studies on evaluation efficacy of *H. pylori* eradication in patients with peptic ulcer in prevention of gastric cancer development, 2) studies that evaluated incidence of gastric cancer in both *H. pylori* eradication group and *H. pylori* persistent infection, 3) studies on East-Asian population. However, 1) review, case-reports, congress abstracts, 2) duplicates, 3) studies on non-human samples, and 4) studies with insufficient data were excluded as exclusion criteria.

We pooled the data using Comprehensive Meta-Analysis (CMA) software version 2.2 (Biostat, Englewood, NJ, USA). The incidence of gastric cancer in each groups were expressed as percentage with 95% confidence intervals (95% CIs); in addition, the relationship between *H. pylori* eradication and develop to gastric cancer was measured by odds ratio (OR) with 95% CIs. Heterogeneity in studies was assessed via I² index and Cochrane Q test. The random effects-models has been applied in case of heterogeneity (I² >25% and Cochrane Q p-Value > 0.05) (9).

We collected 1,502 reports after comprehensive literature search throughout databases. However; only 5 studies were met our inclusion criteria that entered to the statistical analysis (10-14). The studies were conducted between 2005-2015. 4 studies from Japanese ethnicity and 1 study from Taiwanese popu-

Corresponding Author: Masoud Keikha, Department of Microbiology and Virology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran;
E-mail: masoud.keykha90@gmail.com

Table 1. Characteristics of included studies.

First author	Country	Year	Follow-up period	GC incidence		Ref
				successful eradication	treatment failure	
Take <i>et al.</i> ,	Japan	2005	1 years	8/944	4/176	10
Take <i>et al.</i> ,	Japan	2007	9.5 years	9/953	4/178	11
Mabe <i>et al.</i> ,	Japan	2009	5.6 years	32/2451	11/639	12
Wu <i>et al.</i> ,	Taiwan	2009	8.5 years	19/54576	23/25679	13
Take <i>et al.</i> ,	Japan	2015	1 years	21/ 1030	9/ 192	14

lation. We extracted the required data consisting 1) first author, 2) Country, 3) Year, 4) Follow-up period, 5) incidence of gastric cancer in *H. pylori* eradicated and untreated patients with history of peptic ulcer, and 6) references number in the Table 1.

We enrolled data of the 86,818 patients with history of peptic ulcer which subdivided in two groups of *H. pylori* eradicated and uneradicated.

The incidence of gastric cancer in the *H. pylori* eradicated patients and uncured cases were 1% (0.8-1.2 with 95% CIs; p-Value: 0.001; I2: 88.44; Q-Value: 34.61; p-Value: 0.01; Egger’s p-Value: 0.34; Begg’s p-Value: 0.46) and 1.6% (1.2-2.1 with 95% CIs; p-Value: 0.01; I2: 79.36; Q-Value: 19.38; p-Value: 0.01; Egger’s p-Value: 0.20; Begg’s p-Value: 0.11) respectively. The current analysis reveal that there are inverse association between *H. pylori* eradication in patients with peptic ulcer and risk of develop to gastric cancer (OR: 0.47; 0.33-0.67 with 95% CIs; p-Value: 0.01;

I2: 0.00; Q-Value: 2.45; p-Value: 0.65; Egger’s p-Value: 0.15; Begg’s p-Value: 0.33); therefore, eradication of *H. pylori* infection can reduce risk of gastric cancer development in patients with history of peptic ulcer (Figure 1).

H. pylori is Gram-negative, microaerophilic, and motile bacteria which colonized in human stomach of nearly 50% of world population; there are several evidence for chronic colonization with *H. pylori* that significantly increased the risk of gastric cancer development (15). Eradication of *H. pylori* infection can have reduced the risk of gastric cancer as well as reduction of *H. pylori* in young population as reservoir of infection (5, 10). According to literatures, the mother to child transmission is predominant rout of *H. pylori* transmission in Japanese population; therefore, eradication of *H. pylori* infection can be considered as appropriated strategy for reducing both of gastric cancer as well as *H. pylori* infection burden (16). There are several literatures in relation to efficacy of *H. pylori* eradication for prevention of

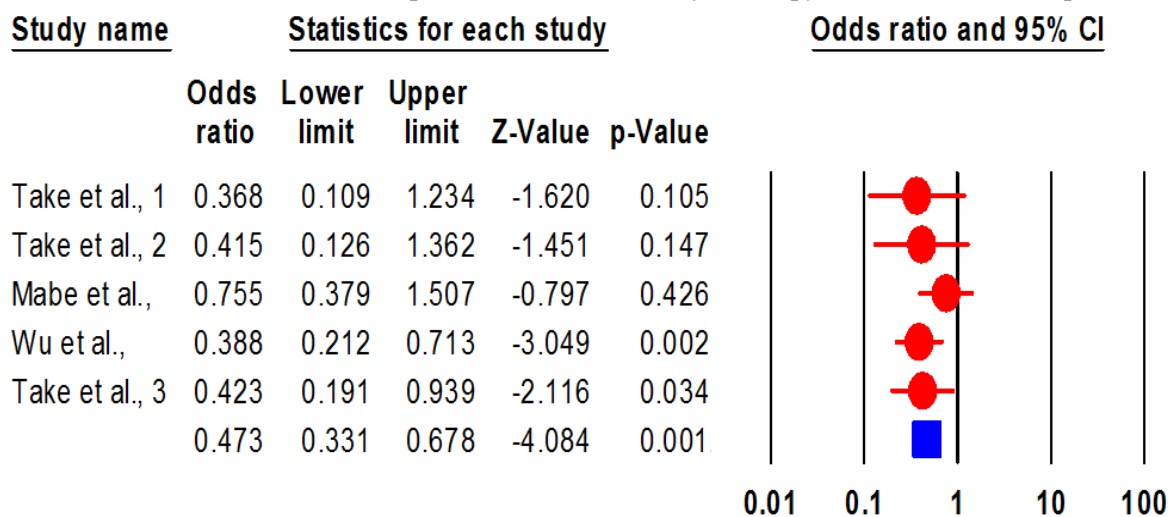


Figure 1. The clinical benefit of *H. pylori* eradication and risk of develop to gastric cancer in patients with history of peptic ulcer.

gastric cancer development in asymptomatic carrier and patients with endoscopic resections (7, 8); however, we evaluated the efficacy of *H. pylori* eradication in reduction of gastric cancer in patients with history of peptic ulcer. We are suggested that *H. pylori* infection should be eradicated in peptic

ulcer patients in order to reducing the risk of develop to gastric cancer.

Conflict of Interest

None declared.

References

1. Keikha M. Is there a relationship between *Helicobacter pylori* vacA i1 or i2 alleles and development into peptic ulcer and gastric cancer? A meta-analysis study on an Iranian population. *New Microbes New Infect.* 2020 Jul 3;36:100726. doi: 10.1016/j.nmni.2020.100726. PMID: 32714559; PMCID: PMC7378689.
2. Honda S, Fujioka T, Tokieda M, Satoh R, Nishizono A, Nasu M. Development of *Helicobacter pylori*-induced gastric carcinoma in Mongolian gerbils. *Cancer Res.* 1998 Oct 1;58(19):4255-9. PMID: 9766647.
3. Karbalaee M, Keikha M. Potential association between the hopQ alleles of *Helicobacter pylori* and gastrointestinal diseases: A systematic review and meta-analysis. *Meta Gene.* 2020:100816.
4. Nozaki K, Shimizu N, Ikehara Y, Inoue M, Tsukamoto T, Inada K, Tanaka H, Kumagai T, Kaminishi M, Tatematsu M. Effect of early eradication on *Helicobacter pylori*-related gastric carcinogenesis in Mongolian gerbils. *Cancer Sci.* 2003 Mar;94(3):235-9. doi: 10.1111/j.1349-7006.2003.tb01426.x. PMID: 12824915.
5. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniguchi K, Sasaki N, Schlemper RJ. *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med.* 2001 Sep 13;345(11):784-9. doi: 10.1056/NEJMoa001999. PMID: 11556297.
6. Wong BC, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, Lai KC, Hu WH, Yuen ST, Leung SY, Fong DY, Ho J, Ching CK, Chen JS; China Gastric Cancer Study Group. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA.* 2004 Jan 14;291(2):187-94. doi: 10.1001/jama.291.2.187. PMID: 14722144.
7. Terasawa T, Hamashima C, Kato K, Miyashiro I, Yoshikawa T, Takaku R, Nishida H. *Helicobacter pylori* eradication treatment for gastric carcinoma prevention in asymptomatic or dyspeptic adults: systematic review and Bayesian meta-analysis of randomised controlled trials. *BMJ Open.* 2019 Sep 20;9(9):e026002. doi: 10.1136/bmjopen-2018-026002. PMID: 31542733; PMCID: PMC6756423.
8. Sugimoto M, Murata M, Yamaoka Y. Chemoprevention of gastric cancer development after *Helicobacter pylori* eradication therapy in an East Asian population: Meta-analysis. *World J Gastroenterol.* 2020;26(15):1820-1840. doi:10.3748/wjg.v26.i15.1820
9. Youssefi M, Tafaghodi M, Farsiani H, Ghazvini K, Keikha M. *Helicobacter pylori* infection and autoimmune diseases; Is there an association with systemic lupus erythematosus, rheumatoid arthritis, autoimmune atrophy gastritis and autoimmune pancreatitis? A systematic review and meta-analysis study. *J Microbiol Immunol Infect.* 2020 Aug 28:S1684-1182(20)30209-7. doi: 10.1016/j.jmii.2020.08.011. Epub ahead of print. PMID: 32891538.
10. Take S, Mizuno M, Ishiki K, Nagahara Y, Yoshida T, Yokota K, Oguma K, Okada H, Shiratori Y. The effect of eradicating *Helicobacter pylori* on the development of gastric cancer in patients with peptic ulcer disease. *Am J Gastroenterol.* 2005 May;100(5):1037-42. doi: 10.1111/j.1572-0241.2005.41384.x. PMID: 15842576.
11. Take S, Mizuno M, Ishiki K, Nagahara Y, Yoshida T, Yokota K, Oguma K. Baseline gastric mucosal atrophy is a risk factor associated with the development of gastric cancer after *Helicobacter pylori* eradication therapy in patients with peptic ulcer diseases. *J Gastroenterol.* 2007 Jan;42 Suppl 17:21-7. doi: 10.1007/s00535-006-1924-9. PMID: 17238021.
12. Mabe K, Takahashi M, Oizumi H, et al. Does *Helicobacter pylori* eradication therapy for peptic ulcer prevent gastric cancer?. *World J Gastroenterol.* 2009;15(34):4290-4297. doi:10.3748/wjg.15.4290
13. 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.*

Masoud Keikha.

2009 Nov;137(5):1641-8.e1-2. doi: 10.1053/j.gastro.2009.07.060. Epub 2009 Aug 5. PMID: 19664631.

14. Take S, Mizuno M, Ishiki K, Hamada F, Yoshida T, Yokota K, Okada H, Yamamoto K. Seventeen-year effects of eradicating *Helicobacter pylori* on the prevention of gastric cancer in patients with peptic ulcer; a prospective cohort study. *J Gastroenterol*. 2015 Jun;50(6):638-44. doi: 10.1007/s00535-014-1004-5. Epub 2014 Oct 29. PMID: 25351555.

15. Karbalaei M, Khorshidi M, Sisakht-pour B, Ghazvini K, Farsiani H, Youssefi M, Keikha M, et al. What are the effects of IL-1 β (rs1143634), IL-

17A promoter (rs2275913) and TLR4 (rs4986790) gene polymorphism on the outcomes of infection with *H. pylori* within an Iranian population; A systematic review and meta-analysis. *Gene Reports*. 2020:100735.

16. Konno M, Yokota S, Suga T, Takahashi M, Sato K, Fujii N. Predominance of mother-to-child transmission of *Helicobacter pylori* infection detected by random amplified polymorphic DNA fingerprinting analysis in Japanese families. *Pediatr Infect Dis J*. 2008 Nov;27(11):999-1003. doi: 10.1097/INF.0b013e31817d756e. PMID: 18845980.