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Chemoprevention of gastric cancer development after *Helicobacter pylori* eradication therapy in an East Asian population: Meta-analysis

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Abstract

BACKGROUND

Helicobacter pylori (*H. pylori*) infection is a risk factor for gastric cancer (GC), especially in East Asian populations. Most East Asian populations infected with *H. pylori* are at higher risk for GC than *H. pylori*-positive European and United States populations. *H. pylori* eradication therapy reduces gastric cancer risk in patients after endoscopic and operative resection for GC, as well as in non-GC patients with atrophic gastritis.

AIM

To clarify the chemopreventive effects of *H. pylori* eradication therapy in an East Asian population with a high incidence of GC.

METHODS

PubMed and the Cochrane library were searched for randomized control trials (RCTs) and cohort studies published in English up to March 2019. Subgroup analyses were conducted with regard to study designs (*i.e.*, RCTs or cohort studies), country where the study was conducted (*i.e.*, Japan, China, and South Korea), and observation periods (*i.e.*, ≤ 5 years and > 5 years). The heterogeneity and publication bias were also measured.

RESULTS

For non-GC patients with atrophic gastritis and patients after resection for GC, 4 and 4 RCTs and 12 and 18 cohort studies were included, respectively. In RCTs, the median incidence of GC for the untreated control groups and the treatment groups was 272.7 (180.4–322.4) and 162.3 (72.5–588.2) per 100000 person-years in non-GC cases with atrophic gastritis and 1790.7 (406.5–2941.2) and 1126.2 (678.7–1223.1) per 100000 person-years in cases of after resection for GC.

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Compared with non-treated *H. pylori*-positive controls, the eradication groups had a significantly reduced risk of GC, with a relative risk of 0.67 [95% confidence interval (CI): 0.47–0.96] for non-GC patients with atrophic gastritis and 0.51 (0.36–0.73) for patients after resection for GC in the RCTs, and 0.39 (0.30–0.51) for patients with gastritis and 0.54 (0.44–0.67) for patients after resection in cohort studies.

CONCLUSION

In the East Asian population with a high risk of GC, *H. pylori* eradication effectively reduced the risk of GC, irrespective of past history of previous cancer.

Key words: *Helicobacter pylori*; Eradication therapy; Gastric cancer; Metachronous cancer; East Asia; Prevention

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Core tip: No meta-analysis is available in the literature about the chemopreventive effects of *Helicobacter pylori* eradication therapy on the incidence of gastric cancer (GC) focused on East Asian populations living in geographical areas with high incidences of GC. We conducted a meta-analysis to reevaluate the prevention of *Helicobacter pylori* eradication therapy on the incidence of GC, irrespective of history of endoscopic or surgical treatment for GC.

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INTRODUCTION

Gastric cancer (GC) is one of the major cancers in the world, especially in East Asian countries such as Japan, South Korea, and China. *Helicobacter pylori* (*H. pylori*)-associated GC is caused by multifactorial and multistep process. The International Agency for Research on Cancer of the World Health Organization categorized *H. pylori* as a group I carcinogenic factor of GC in 1994^[1,2]. Many clinical trials have shown that *H. pylori* infection is associated with an elevated risk of GC development not only in patients with atrophic gastritis and intestinal metaplasia alone, but also in patients already treated by resection of GC (Table 1). Due to the small sample size in each report, however, it remains unclear whether the risk of GC related to *H. pylori* is similar among patients with atrophy and intestinal metaplasia alone compared with post-resection patients.

With or without *H. pylori* infection, severe gastric mucosal atrophy and intestinal metaplasia are well-known risk factors for peptic ulcers as well as GC^[3,4]. Several pathological reporting systems, including the Sydney system, its Houston-updated version, and the operative link on gastritis assessment system, as well as endoscopic reporting systems, such as the Kyoto classification of gastritis, are used to select patients at high risk for GC based on severity of pathological or endoscopic gastric mucosal atrophy and intestinal metaplasia^[4-7]. In addition, the severity of gastric mucosal inflammation, atrophy, and intestinal metaplasia has been shown to correlate with *H. pylori* virulence factors (*i.e.*, *cagA*, *vacA* and *oipA*)^[8-11]. Because > 90% of *H. pylori* isolated from East Asian populations carry the *cagA*, which is associated with increased proliferation and pro-inflammatory and pro-apoptotic gene expression, and the *vacA* s1m1 type, which is associated with enhanced production of toxin with higher vacuolating activity^[12,13], most East Asian populations infected with *H. pylori* are at higher risk for GC than *H. pylori*-positive European and United States populations. Thus, it is important to evaluate the association of *H. pylori* infection with GC risk in East Asian populations in order to formulate strategies to reduce the risk of GC.

Many clinical trials have shown that eradication of *H. pylori* infection reduces the risk of GC development (Table 1). Following *H. pylori* eradication therapy, a gradual

Table 1 Characteristics of the studies

Ref.	Country	Primary or metachronous cancer	Design	Disease at basement	Follow-up periods (yr)	Patients number	Age (yr)	Sex (male/female)	Regimen of eradication therapy	Eradication rate (%)
Fukase <i>et al</i> ^[31] , 2006	Japan	Metachronous	RCT	Gastric cancer	3	544	68 (62-73)	386/119	LPZ(30)/A MPC(750)/CAM(200), BID, 7D	75.0
Choi <i>et al</i> ^[32] , 2018	South Korea	Metachronous	RCT	Gastric cancer	5.9	396	59	298/104	RPZ(10)/A MPC(1000)/CAM(500), BID 7D	80.4
Choi <i>et al</i> ^[33,69]	South Korea	Metachronous	RCT	Gastric cancer	6	898	60.4	594/283	OPZ(20)/A MPC(1000)/CAM(500), BID 7D	82.6
Uemura <i>et al</i> ^[70] , 1997	Japan	Metachronous	Cohort	Gastric cancer	3	132	69 (44-85)	97/35	1st: OPZ(20)/CAM(400) 14D, 2nd: OPZ(20)/A MPC(1500)/MNZ(500), BID 14D	46.2
Nakagawa <i>et al</i> ^[71] , 2006	Japan	Metachronous	Cohort	Gastric cancer	2	2825	NA	NA	NA	NA
Shiotani <i>et al</i> ^[72] , 2008	Japan	Metachronous	Cohort	Gastric cancer	2.75	100	69	67/13	PPI/AMPC(750)/CAM(200), BID 7D	81.3
Han <i>et al</i> ^[73] , 2011	South Korea	Metachronous	Cohort	Gastric cancer	2.7	176	61.8 (43-83)	112/64	NA	NA
Kim <i>et al</i> ^[74] , 2011	South Korea	Metachronous	Cohort	Gastric cancer	5.1	55	60.7 (43-81)	36/19	NA	50.9
Maehata <i>et al</i> ^[75] , 2012	Japan	Metachronous	Cohort	Gastric cancer	3	268	69 (49-90)	194/74	PPI/AMPC(750)/CAM(200), BID 7D	78.2
Seo <i>et al</i> ^[76] , 2013	South Korea	Metachronous	Cohort	Gastric cancer	2.27	74	62	55/19	PPI/AMPC(1000)/CAM(500), BID 7-14D	82.4
Kato <i>et al</i> ^[77] , 2013	Japan	Metachronous	Cohort	Gastric cancer	2.23	368	70.5	953/305	NA	NA
Bae <i>et al</i> ^[78] , 2014	South Korea	Metachronous	Cohort	Gastric cancer	5	1007	63 (28-88)	785/222	PPI/AMPC(750)/CAM(200), BID 7-14D	NA
Kim <i>et al</i> ^[79] , 2014	South Korea	Metachronous	Cohort	Gastric cancer	4.3	374	64 (35-87)	278/96	PPI/AMPC(1000)/CAM(500), BID 7D	72.1
Kwon <i>et al</i> ^[80] , 2014	South Korea	Metachronous	Cohort	Gastric cancer	3.4	283	59	190/93	PPI/AMPC(750)/CAM(200), BID 7D	68.9
Jung <i>et al</i> ^[27] , 2015	South Korea	Metachronous	Cohort	Gastric cancer	3.36	1041	62.7	773/268	LPZ(30)/A MPC(1000)/CAM(500), BID 7-14D	NA
Lim <i>et al</i> ^[28] , 2015	South Korea	Metachronous	Cohort	Gastric cancer	3.1	933	63.0 ± 9.51	512/250	NA	NA
Kim <i>et al</i> ^[81] , 2016	Korea	Metachronous	Cohort	Gastric cancer	2.5	257	67	189/68	PPI/AMPC(1000)/CAM(500), BID 7D	86.3
Ami <i>et al</i> ^[82] , 2017	Japan	Metachronous	Cohort	Gastric cancer	4.47	438	69.4 ± 8.7	421/118	LPZ(30) or RPZ(10)/A MPC(750)/CAM(200), BID 7-14D	NA

Kwon <i>et al</i> ^[29] , 2017	South Korea	Metachronous	Cohort	Gastric cancer	3.725	590	63	398/192	RPZ(20)/A MPC(1000)/ CAM(500), BID 7D	81.8
Chung <i>et al</i> ^[30] , 2017	South Korea	Metachronous	Cohort	Gastric cancer	5.125	185	67.4 (45-87)	141/44	PPI/AMPC /CAM, BID 7D	NA
Han <i>et al</i> ^[33] , 2018	South Korea	Metachronous	Cohort	Gastric cancer	5	565	61	440/125	NA	NA
Cho <i>et al</i> ^[17] , 2013	South Korea	Metachronous	RCT	Gastric cancer	3	169	56	117/52	RPZ(10)/A MPC(1000)/ CAM(500), BID 7D	77
Wong <i>et al</i> ^[18] , 2004	China	Primary	RCT	Gastritis alone	7.5	1630	42.2 (35-65)	880/750	OPZ(20)/A MPC(750)/ MNZ(400), BID 14D	82.5
Ma <i>et al</i> ^[23] , You <i>et al</i> ^[84] and Li <i>et al</i> ^[85]	China	Primary	RCT	Non-gastric cancer	14.3	2258	47.1	1808/1603	OPZ(20)/A MPC(1000), BID 7D	66.2
Wong <i>et al</i> ^[19] , 2012	China	Primary	RCT	With/without metaplasia	2	1024	53.0 (35-64)	473/551	PPI/AMPC(1000)/CAM(500), BID 7D	71.3
Zhou <i>et al</i> ^[24] , 2014, Leung <i>et al</i> ^[86] , 2004	China	Primary	RCT	Non-gastric cancer	10	554	53.35 ± 8.49	268/284	OPZ(20)/A MPC(1000)/ CAM(500), BID 7D	88.9
Saito <i>et al</i> ^[22] , 2000	Japan	Primary	Cohort	Gastric adenoma	2	64	79.2 (68-92)	35/29	OPZ(20)/A MCP(1000)/ CAM(400), BID 7D	75
Uemura <i>et al</i> ^[52] , 2001	Japan	Primary	Cohort	With/without PU	7.7	1526	52.4	869/657	NA	NA
Kato <i>et al</i> ^[87] , 2006	Japan	Primary	Cohort	With/without PU	5.9-7.7	3021	54	1868/1153	LPZ(30)/A MPC(750)/ CAM(200), BID 7-14D	NA
Takenaka <i>et al</i> ^[88] , 2007	Japan	Primary	Cohort	With/without PU	3.17	1807	53.6 ± 12.4	1289/518	Dual therapy or PPI/AMPC(750)/CAM(200 or 400), BID 7D	82.9
Ogura <i>et al</i> ^[89] , 2008	Japan	Primary	Cohort	With/without PU	3.2	708	62	400/308	LPZ(30)/A MPC(750/1000)/CAM(400) or MNZ(250), BID 7D	74
Kim <i>et al</i> ^[90] , 2008	South Korea	Primary	Cohort	With/without PU	9.4	1790	46.7	1483/297	Tripotassium dicitrate bismuthate (300, QID)/MNZ(500, TID)/TC(500, QID), 5D or OPZ(20)/CAM(500)/A MPC(1000) BID 7D	NA
Mabe <i>et al</i> ^[53] , 2009	Japan	Primary	Cohort	With/without PU	5.6	4133	52.9 (13-91)	2964/1169	LPZ(30) or OPZ(20)/A MPC(750)/ CAM(200 or 400), BID 7D	64.8

Yanaoka <i>et al</i> ^[23] , 2009	Japan	Primary	Cohort	Non-gastric cancer	9.3	4129	49.8	5560/107	OPZ(20)/A MPC(750 or 500), BID 14D, OPZ(20)/A MPC(750)/CAM(200), BID 7D	87.2
Watanabe <i>et al</i> ^[26] , 2012	Japan	Primary	Cohort	Non-gastric cancer	5.4	823	NA	NA	OPZ(20, BID)/AMPC (750 or 500, BID) 14D or OPZ(20)/A MPC(750)/CAM(200), BID 7D	82.0
Lee <i>et al</i> ^[20] , 2013	China	Primary	Cohort	With/without PU or dysplasia	5	8242	49.2 ± 12.8	1888/2233	PPI/AMCP(1000)/CAM(500), BID 7D	78.7
Shichijo <i>et al</i> ^[21] , 2015	Japan	Primary	Cohort	Intestinal metaplasia	6.7 ± 4.7	659	60.1 ± 11.0	374/355	LPZ(30)/A MPC(750 or 1000)/CAM(200) or MNZ(250), BID 7D	NA
Take <i>et al</i> ^[91-94]	Japan	Primary	Cohort	Peptic ulcer	9.9	1222	49.9 ± 8.3	1087/135	Dual or Triple therapy	NA

Non-gastric cancer: patients had no history of gastric cancer, but were unknown to have peptic ulcer and dysplasia. AMPC: Amoxicillin; BID: Twice-daily dosing; CAM: Clarithromycin; D: Day; LPZ: Lansoprazole; MNZ: Metronidazole; NA: Not available; OPZ: Omeprazole; PPI: Proton pump inhibitor; PU: Peptic ulcer; QID: Four-times daily dosing; RCT: Randomized control trial; RPZ: Rabeprazole; TID: Three-times daily dosing; TC: Tetracycline.

decrease in severity of gastric atrophy in the gastric body and antrum and intestinal metaplasia in the body has been shown^[14]. In 2012, the Japanese health insurance system began to cover *H. pylori* eradication treatment in patients with endoscopically-confirmed *H. pylori*-associated gastritis. International guidelines strongly recommend eradication of *H. pylori* in patients to prevent development of GC^[15,16]. However, it remains unclear whether eradication therapy exerts the same preventive effect on GC among different groups, *e.g.*, those of different nationalities, those with a history of gastritis, those with a prior history of GC resection, *etc.*, with different risk levels for GC development.

In general, the risk of GC development differs between Western population and East Asian population, due to different life style, different genetics, and different *H. pylori* strain. Although it is important to evaluate the risk of GC separately for Western and East Asian population, previous meta-analysis did not evaluate this point and meta-analyzed all of studies, irrespective with nationalities. Thus, it is required to evaluate the association of *H. pylori* infection with GC risk in East Asian populations in order to formulate strategies to reduce the risk of GC. We conducted a meta-analysis to reevaluate the preventive effects of *H. pylori* eradication therapy on the incidence of GC, irrespective of history of endoscopic or surgical treatment for GC, especially in East Asian populations living in geographical areas with high incidences of GC.

MATERIALS AND METHODS

Search strategy and inclusion criteria

For a meta-analysis to investigate preventive effects of eradication therapy on GC development, we conducted a search of the medical literature using data of randomized control trials (RCTs) and cohort studies. Two researchers (MS and MM) independently searched both the PubMed and Cochrane Library databases using the terms "*H. pylori*," "GC," and "eradication therapy," and reviewed titles and abstracts for all potential studies (Figure 1). The inclusion criteria were: (1) RCTs or cohort studies published in English up to March 2019; and (2) Studies comparing individuals receiving *H. pylori* eradication with those not receiving eradication treatment with respect to the incidence of primary GC in East Asian non-GC patients with gastritis or metachronous cancer in patients after resection of GC, irrespective with primary outcome or secondly outcome. All GC, including gastric dysplasia, was endosco-

pically and pathologically diagnosed. Study included patients with GC or gastric dysplasia as gastric neoplasm was included as GC group in this meta-analysis. In non-GC patients with atrophic gastritis, the basement diseases before *H. pylori* eradication therapy were included atrophic gastric alone, peptic ulcer, gastric dysplasia and gastric adenoma. The full texts of potential studies were then screened to select studies meeting the inclusion criteria, and duplicated studies and multiple reports of the same study were excluded. When multiple articles were found, we used data from the latest publication date. Metachronous cancer was defined as a newly developed cancer at another site in the stomach > 1 year after resection for cancer. The exclusion criteria were (1) Non-East Asian patients; (2) Single-arm studies without a non-eradicated control group; and (3) Studies with an observation period < 1 year after eradication therapy.

Authors, publication year, country where the study was conducted, study design, numbers of treatment groups and control groups, number of patients developing GC, observation periods, patient conditions at baseline (sex and age), and pathological differentiation of GC were extracted from each study.

Statistical analysis

First, we divided studies into two kinds of clinical design: Non-GC patients with atrophic gastritis (at risk for primary GC) and patients after endoscopic and operative resection of early-stage GC (at risk for metachronous GC), because of their significantly different risk of cancer development. Subgroup analyses were conducted with regard to study designs (*i.e.*, RCTs or cohort studies), country where the study was conducted (*i.e.*, Japan, China, and South Korea), and observation periods (*i.e.*, ≤ 5 years and > 5 years). The potential study bias in each study was evaluated by funnel plots. Heterogeneity was evaluated by I^2 value and Cochran's Q. The I^2 value was used to assess the heterogeneity of the studies as follows: 0%–39%, low heterogeneity; 40%–74%, moderate heterogeneity; and 75%–100%, high heterogeneity. The relative risk (RR) and 95% confidence interval (CI) of each study were reported as the measure of effect size. All meta-analyses were conducted using open-source statistical software (Review Manager Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). All P values were two-sided, and $P < 0.05$ was considered statistically significant. Calculations were performed using commercial software (SPSS version 20, IBM Inc; Armonk NY, United States).

RESULTS

Literature search and data extraction

A total of 38 studies which investigated the chemopreventive effects of *H. pylori* eradication on GC development among East Asian populations were included in the meta-analysis (Figure 1), consisting of 16 studies (4 RCTs and 12 cohort studies) in naïve non-GC patients with gastritis and 22 studies (4 RCTs and 18 cohort studies) in patients after resection for GC. Of 22 studies investigating the risks of metachronous cancers, a study from Cho *et al.*^[17] was included for post-surgical resection cases. In naïve non-GC patients with atrophic gastritis, the basement diseases before *H. pylori* eradication therapy were included atrophic gastric alone^[18], peptic ulcer, gastric dysplasia^[19–21] and gastric adenoma^[22] or detail data not shown (but without history of GC)^[23–26].

Finally, a total of 32775 non-GC cases with gastritis (5464 cases from RCTs and 27311 cases from cohort studies) and 9605 cases after resection for cancer (2007 cases for RCTs and 7598 cases from cohort studies) were included in this analysis (Table 1).

Four studies evaluated patients included GC or gastric dysplasia as gastric neoplasm^[27–30]. The mean or median follow-up period ranged from 2.0–14.3 years, and the mean or median age of patients ranged from 46.7–79.2 years (Table 1). The ratio of males was from 46.2% to 98.1%. In most studies, *H. pylori* eradication therapy was performed using a regimen including proton pump inhibition (PPI) [*i.e.*, omeprazole (20 mg, bid), lansoprazole (30 mg, bid), rabeprazole (10 or 20 mg, bid) or esomeprazole (20 mg, bid)] and two kinds of antimicrobial agents [*i.e.*, clarithromycin (200, 400, or 500 mg, bid), amoxicillin (750 or 1000 mg, bid, or 500 mg, tid), and metronidazole (250 or 500 mg, bid)] (Table 1). In the RCTs, eradication rates were 66.2%–88.9% in studies for non-GC cases with gastritis and 75.0%–82.6% in cases after gastric resection (Table 1).

The median incidence of GC for the untreated control groups in non-GC cases of gastritis was 322.4 (68.7–1379.5) per 100000 person-years. Those in RCTs and cohort studies were 272.7 (180.4–322.4) and 467.2 (68.7–1379.5) per 100000 person-years, respectively (Table 2). In the treatment groups, median incidences of cancer in all

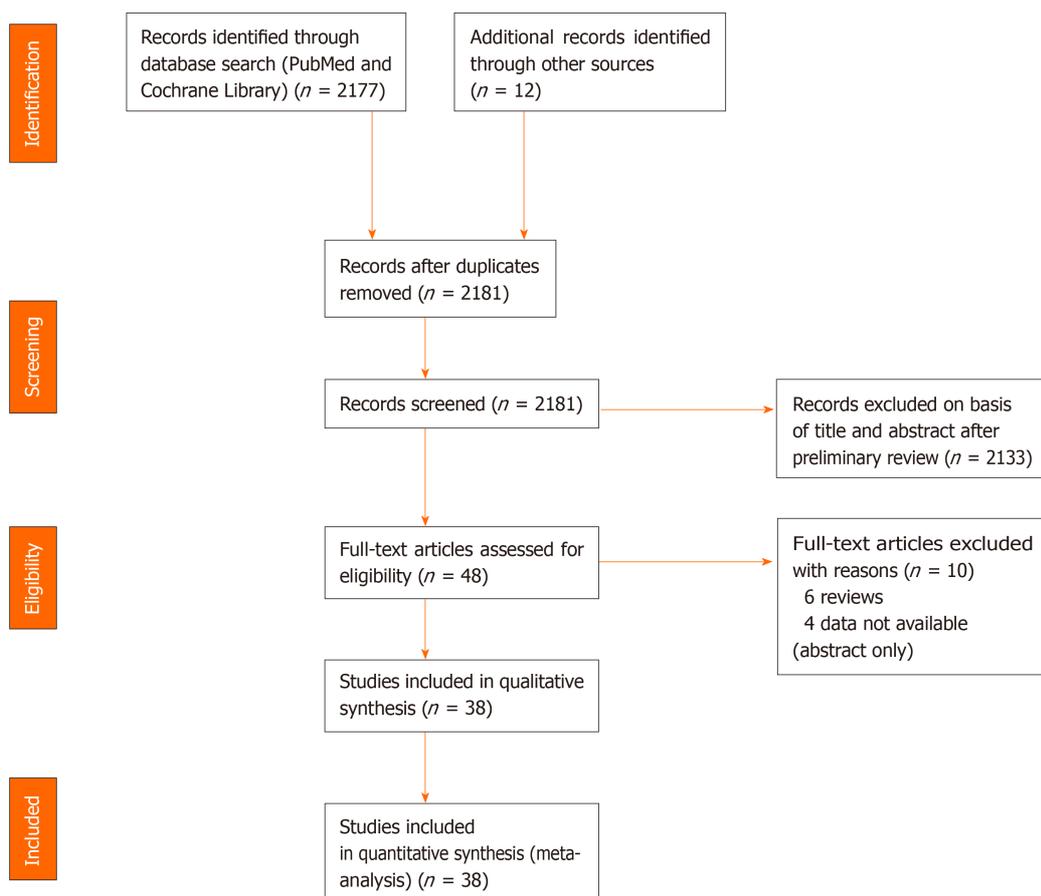


Figure 1 Study flow diagram.

studies, RCTs and cohort studies were 114.2 (0–588.2), 162.3 (72.5–588.2) and 113.7 (0–464.1) per 100000 person-years, respectively.

The median incidence of metachronous GC for the *H. pylori*-positive non-treated control groups after endoscopic and operative gastric resection was 2922.0 (406.5–10,166.0) per 100000 person-years. Those in RCTs and cohort studies were 1790.7 (406.5–2941.2) and 3117.9 (701.3–10166.0) per 100000 person-years, respectively (Table 2).

In the treatment groups, median incidence of metachronous GC in all, RCTs and cohort studies were 1229.2 (0–4333.1), 1126.2 (678.7–1223.1) and 1489.1 (0–4333.1) per 100000 person-years (Table 2).

Meta-analysis of GC risk in treated groups and untreated control group

In non-GC patients with gastritis, when combined with 4 RCTs^[18,19,23,24] and 12 cohort studies, 180 (1.0%) patients developed GC among 17300 individuals who underwent eradication, and 285 (1.8%) patients did so among 15475 individuals in the untreated control group (Figure 2A). The RR for GC in the treatment groups compared with *H. pylori*-positive controls was 0.47 (95%CI: 0.38–0.59) (Figure 2A). No heterogeneity was found among the studies.

In 4 RCTs^[18,19,23,24], GC developed in 49 (1.8%) patients among 2733 *H. pylori*-negative treated cases, and in 73 (2.7%) patients among 2731 *H. pylori*-positive controls (Figure 2B). The mean RR comparing the *H. pylori*-negative eradicated group with the *H. pylori*-positive control group was 0.67 (95%CI: 0.47–0.96) (Figure 2B). No heterogeneity was found among the studies. In addition, in the cohort studies, the mean RR in the *H. pylori*-negative eradicated group was 0.39 (95%CI: 0.30–0.51) compared with the *H. pylori*-positive controls (Figure 2C).

In studies of a combination of 4 RCTs and 18 cohort studies of patients after endoscopic and operative resection, metachronous cancer occurred in 281 (6.0%) patients among 4688 treated individuals, and in 357 (7.3%) cases among 4917 cases in the *H. pylori*-positive control groups. The RR for metachronous cancer comparing *H. pylori*-negative treated groups with *H. pylori*-positive controls was 0.53 (95%CI: 0.44–0.64) (Figure 3A). No heterogeneity was found among the studies.

Table 2 Gastric cancer development and histological characteristics

Ref.	Design	Follow-up periods (yr)	Eradicated group		Non-eradicated control group		Eradicated group		Non-eradicated control group	
			Cancer/Total	Cancer incidence, /100000 PY	Cancer/Total	Cancer incidence, /100000 PY	Intestinal type	Diffuse type	Intestinal type	Diffuse type
Patients after resection for gastric cancer										
Fukase <i>et al</i> ^[51] , 2006	RCT	3	9/272	1102.9	24/272	2941.2	9	0	23	1
Choi <i>et al</i> ^[32] , 2018	RCT	5.9	14/194	1223.1	27/202	2265.5	14	0	25	1
Choi <i>et al</i> ^[33,69]	RCT	6	18/442	678.7	36/456	1315.8	13	5	26	8
Uemura <i>et al</i> ^[70] , 1997	Cohort	3	0/65	0	6/67	2985.1	0	0	6	0
Nakagawa <i>et al</i> ^[71] , 2006	Cohort	2	8/356	864.3	129/2469	2902.7	NA	NA	NA	NA
Shiotani <i>et al</i> ^[72] , 2008	Cohort	2.75	9/80	4090.9	1/11	3305.8	9	0	1	0
Han <i>et al</i> ^[73] , 2011	Cohort	2.7	4/94	1576	2/22	3367	NA	NA	NA	NA
Kim <i>et al</i> ^[74] , 2011	Cohort	5.1	0/28	0	5/27	3631.1	0	0	NA	NA
Maehata <i>et al</i> ^[75] , 2012	Cohort	3	15/177	2824.9	13/91	4761.9	14	1	13	0
Seo <i>et al</i> ^[76] , 2013	Cohort	2.27	6/61	4333.1	3/13	10166	NA	NA	NA	NA
Kato <i>et al</i> ^[77] , 2013	Cohort	2.23	24/263	4092.1	6/105	2562.5	NA	NA	NA	NA
Bae <i>et al</i> ^[78] , 2014	Cohort	5	34/485	1402.1	24/182	2637.4	NA	NA	NA	NA
Kim <i>et al</i> ^[79] , 2014	Cohort	4.3	2/49	770.1	16/107	3250.7	NA	NA	NA	NA
Kwon <i>et al</i> ^[80] , 2014	Cohort	3.4	18/214	2473.9	13/69	5541.3	8	2	6	4
Jung <i>et al</i> ^[27] , 2015	Cohort	3.36	21/506	1235.2	10/169	1761.1	NA	NA	NA	NA
Lim <i>et al</i> ^[28] , 2015	Cohort	3.1	7/236	956.8	6/276	701.3	NA	NA	NA	NA
Kim <i>et al</i> ^[81] , 2016	Cohort	2.5	3/120	902.5	1/42	872.1	NA	NA	NA	NA
Ami <i>et al</i> ^[82] , 2017	Cohort	4.47	25/212	2638.1	1/14	1598	NA	NA	NA	NA
Kwon <i>et al</i> ^[29] , 2017	Cohort	3.725	33/368	2255.9	8/27	7454	10	6	3	2
Chung <i>et al</i> ^[30] , 2017	Cohort	5.125	17/167	1986.3	7/18	7588.1	NA	NA	NA	NA
Han <i>et al</i> ^[83] , 2018	Cohort	5	12/212	1132.1	18/196	1836.7	11	1	18	0
Cho <i>et al</i> ^[17] , 2013	RCT	3	3/87	1149.4	1/82	406.5	1	2	1	0
Patients with gastritis										
Wong <i>et al</i> ^[18] , 2004	RCT	7.5	7/817	114.2	11/813	180.4	NA	NA	NA	NA
Ma <i>et al</i> ^[23] , You <i>et al</i> ^[84] and Li <i>et al</i> ^[85]	RCT	14.3	34/1130	210.4	52/1128	322.4	NA	NA	NA	NA
Wong <i>et al</i> ^[19] , 2012	RCT	2	6/510	588.2	3/514	291.8	6	0	2	1

Zhou <i>et al</i> ^[24] , 2014, Leung <i>et al</i> ^[86] , 2004	RCT	10	2/276	72.5	7/276	253.6	NA	NA	NA	NA
Saito <i>et al</i> ^[22] , 2000	Cohort	2	0/32	0	4/32	6250	0	0	4	0
Uemura <i>et al</i> ^[52] , 2001	Cohort	7.7	0/253	0	36/993	424.4	0	0	23	13
Kato <i>et al</i> ^[87] , 2006	Cohort	5.9-7.7	23/1788	218	44/1233	467.2	19	4	32	12
Takenaka <i>et al</i> ^[88] , 2007	Cohort	3.17	6/1519	121.5	5/288	598.7	4	2	4	1
Ogura <i>et al</i> ^[89] , 2008	Cohort	3.2	6//404	464.1	13/304	1379.5	3	3	11	2
Kim <i>et al</i> ^[90] , 2008	Cohort	9.4	1/476	22.3	4/977	43.6	0	1	3	1
Mabe <i>et al</i> ^[53] , 2009	Cohort	5.6	47/3781	222	9/352	491.7	35	10	5	4
Yanaoka <i>et al</i> ^[23] , 2009	Cohort	9.3	5/473	113.7	55/3656	161.8	4	1	36	19
Watanabe <i>et al</i> ^[26] , 2012	Cohort	5.4	0/327	0	7/496	261.4	0	0	1	6
Lee <i>et al</i> ^[20] , 2013	Cohort	5	15/4121	72.8	16/4121	77.7	NA	NA	NA	NA
Shichijo <i>et al</i> ^[21] , 2015	Cohort	6.7 ± 4.7	4/260	229.6	13/203	955.8	NA	NA	NA	NA
Take <i>et al</i> ^[91-94]	Cohort	9.9	24/1133	214	6/89	681	14	10	5	1

NA: Not available; RCT: Randomized control trial; PY: Person-year.

In the four RCTs^[17,31-33], metachronous cancer occurred in 44 (4.4%) cases from 995 *H. pylori*-negative individuals, and in 88 (8.7%) cases among 1012 *H. pylori*-positive controls (Figure 3B). The RRs of the *H. pylori*-negative treated groups in RCTs and cohort studies were 0.51 (95%CI: 0.36–0.73) and 0.54 (0.44–0.67), respectively (Figure 3B and C).

Quality assessment

The funnel plot of all included studies did not suggest asymmetry in non-GC patients with atrophic gastritis and patients after resection of GC Supplementary Figure (1A and B), and statistical analysis with Egger's test also confirmed that there was no publication bias according to different set of primary outcomes.

Subgroup analysis by different countries and observation periods

A total of 16 studies of cases of gastritis-10 from Japan, 5 from China, and 1 from South Korea – were analyzed (Figure 4A and B). The RR of the Japanese studies was 0.33 (95%CI: 0.25–0.45), which was lower than that from China (0.73; 0.51–1.03) and South Korea (0.51; 0.06–4.58) (Figs 4A and B). Seven Japanese and 15 Korean studies of post-gastric resection cases were conducted (Figure 4C and D). The RRs for metachronous cancer were similar between Japan (RR 0.57; 95%CI: 0.40–0.81) and South Korea (0.51; 0.42–0.63) (Figure 4C and D). When observation periods were subgrouped into ≤ 5 years and > 5 years, the RRs were similar between the two subgroups in studies of non-GC cases of gastritis, and in studies of cases after resection of GC (Figure 5A-D).

Characteristics of GC after eradication therapy

Of non-GC patients with gastritis developing later cancer, 73.3% (85/116) of *H. pylori*-negative eradicated cases and 67.7% (126/186) of *H. pylori*-positive untreated controls were observed to be of the intestinal type ($P = 0.31$) (Table 2). Of patients developing metachronous cancers after endoscopic and operative resection of cancer, 84.0% (89/106) *H. pylori*-negative eradicated and 88.4% (122/138) *H. pylori*-positive non-treatment controls were observed to be of the intestinal type ($P = 0.31$) (Table 2).

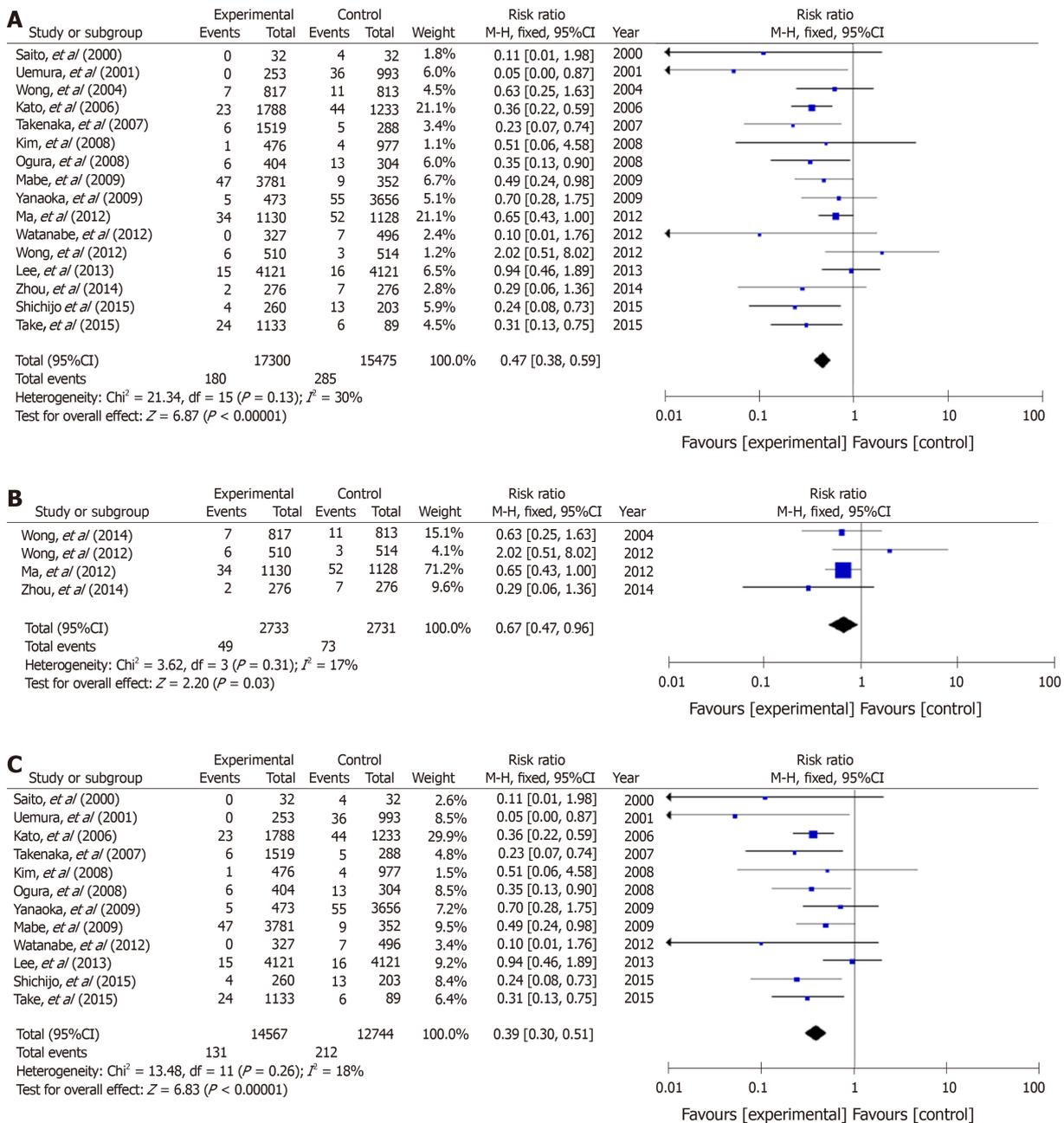


Figure 2 A forest plots for the incidence of gastric cancer between *Helicobacter pylori*-eradication group and non-eradication group in 16 studies combined with randomized control studies and cohort studies (A), 4 randomized control studies (B) and 12 cohort studies (C) in non-gastric cancer patients with atrophic gastritis. There was no heterogeneity in the total analysis ($I^2 = 30\%$, $P = 0.13$), randomized control studies ($I^2 = 17\%$, $P = 0.31$) and cohort studies ($I^2 = 18\%$, $P = 0.26$). A: Randomized control studies + Cohort studies; B: Randomized control studies; C: Cohort studies.

DISCUSSION

In this meta-analysis, we evaluated whether *H. pylori* eradication therapy effectively reduced the risk of GC development in both non-GC patients with gastritis and patients after endoscopic and surgical resection for GC, especially in East Asian populations with high incidence rates of GC. This meta-analysis of 38 studies (16 studies in non-GC patients with gastritis and 22 in patients after gastric resection) showed that eradication therapy had a significant protective effect against development of GC with mean RRs of 0.47 (95%CI: 0.38–0.75) and 0.53 (95%CI: 0.44–0.64), irrespective of study design (RCTs or cohort studies), past history of GC, countries of origin, and observation periods after eradication therapy. This efficacy was similar to the previous meta-analysis performed by Yoon *et al*^[34] (OR: 0.42; 95%CI: 0.32–0.56), Xiao *et al*^[35] (RR: 0.50; 95%CI: 0.41–0.61), and Sugano^[36] [OR: 0.46; 95%CI: 0.39–0.55]. Our observations suggest that *H. pylori* eradication therapy should be performed in all patients with *H. pylori* infection to prevent development of GC in

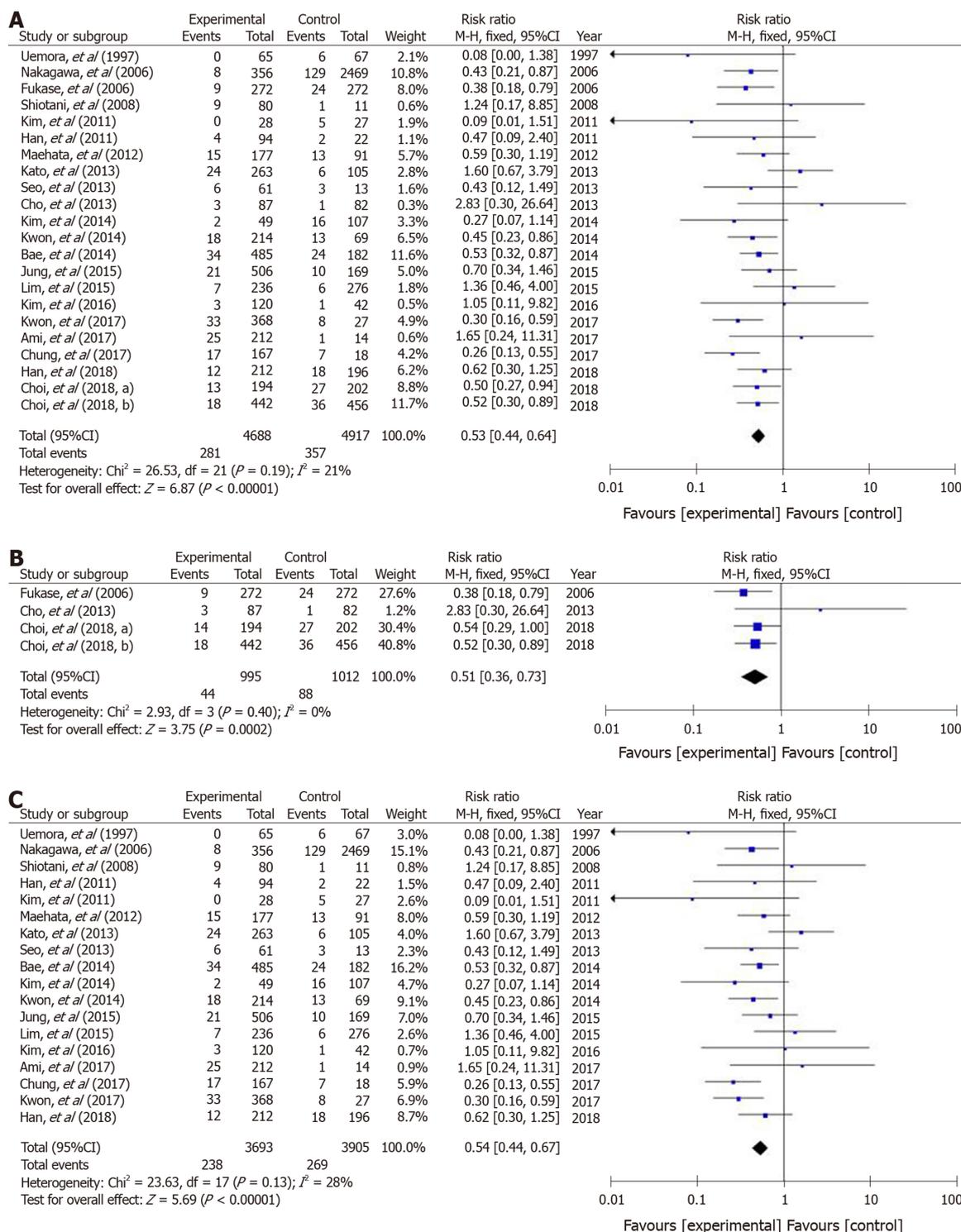


Figure 3 A forest plots for the incidence of metachronous gastric cancer between *Helicobacter pylori*-eradication group and non-eradication group in 22 studies combined with randomized control studies and cohort studies (A), 4 randomized control studies (B) and 18 cohort studies (C) in patients after endoscopic and operative resection. No heterogeneity in the total analysis ($I^2 = 21\%$, $P = 0.19$), Randomized control studies ($I^2 = 0\%$, $P = 0.40$) and cohort studies ($I^2 = 28\%$, $P = 0.13$) was shown. A: Randomized control studies + Cohort studies; B: Randomized control studies; C: Cohort studies.

East Asian populations.

Characteristics of GC risk in East Asian populations

Considered globally, East Asian countries, especially South Korea, have a high age-standardized incidence rate for GC. The age-standardized incidence rate per 100000 persons in 2018 was 39.6 in both sexes (57.8 in men and 23.5 in women) in South Korea, followed by 27.5 (40.7 and 16.0) in Japan and 20.7 (29.5 and 12.3) in China, vs a world rate in 2012 of 12.1 (17.4 and 7.5, respectively) [https://\(www.wcrf.org/dietand-cancer/cancer-trends/stomach-cancer-statistics\)](https://www.wcrf.org/dietand-cancer/cancer-trends/stomach-cancer-statistics). As observed in global trends,

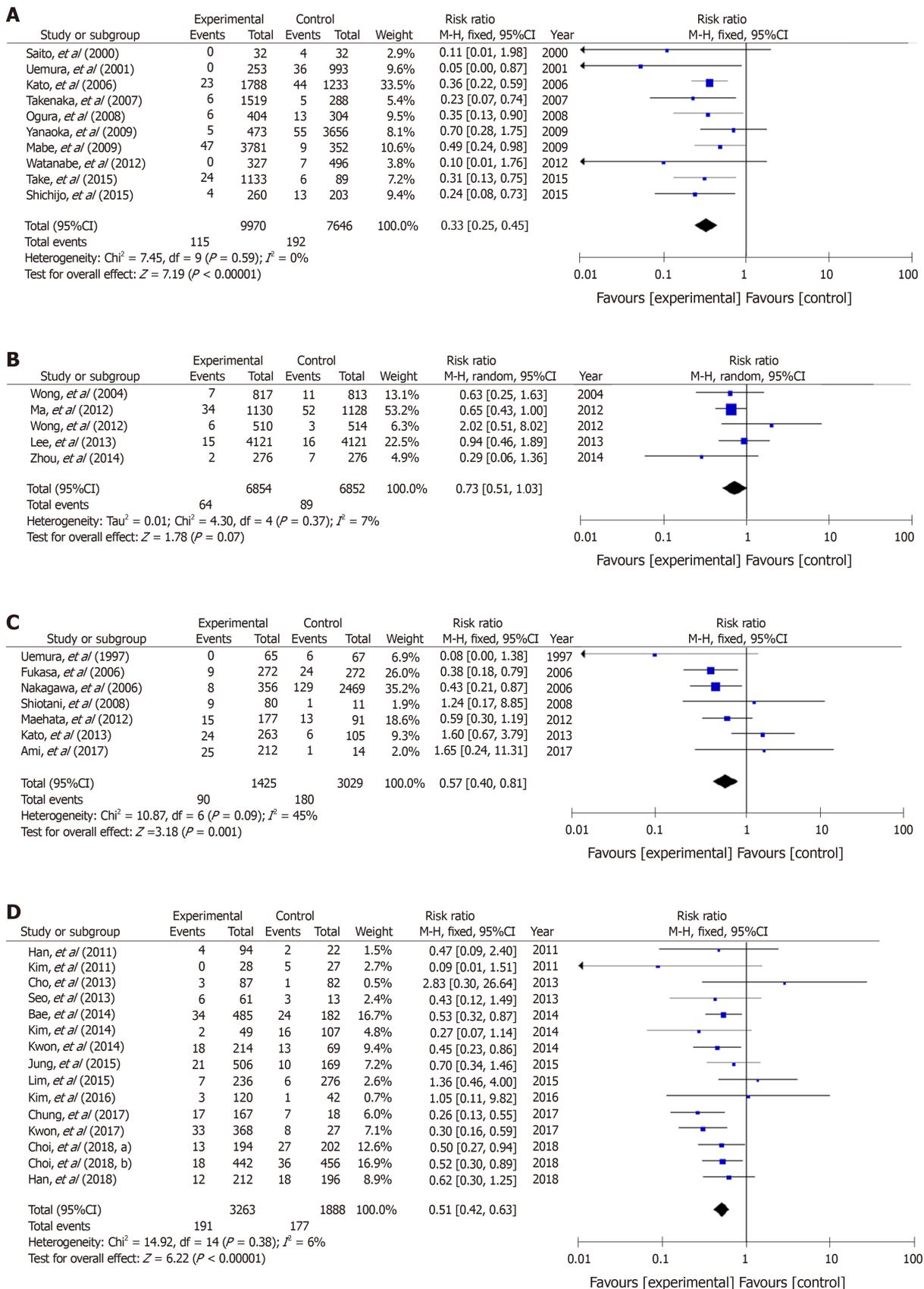


Figure 4 Forest plots of the incidence of gastric cancer between *Helicobacter pylori*-negative and positive groups with atrophic gastritis in studies published in different countries; 10 studies from Japan (A) and 5 from China (B). Forest plots of the incidence of metachronous gastric cancer between *Helicobacter pylori*-negative and positive groups presenting with gastric cancer in 7 studies from Japan (C) and 15 from South Korea (D). A: Non-gastric cancer patients with atrophic gastritis: Japan; B: Non-gastric cancer patients with atrophic gastritis: China; C: Metachronous gastric cancer: Japan; D: Metachronous gastric cancer: South Korea.

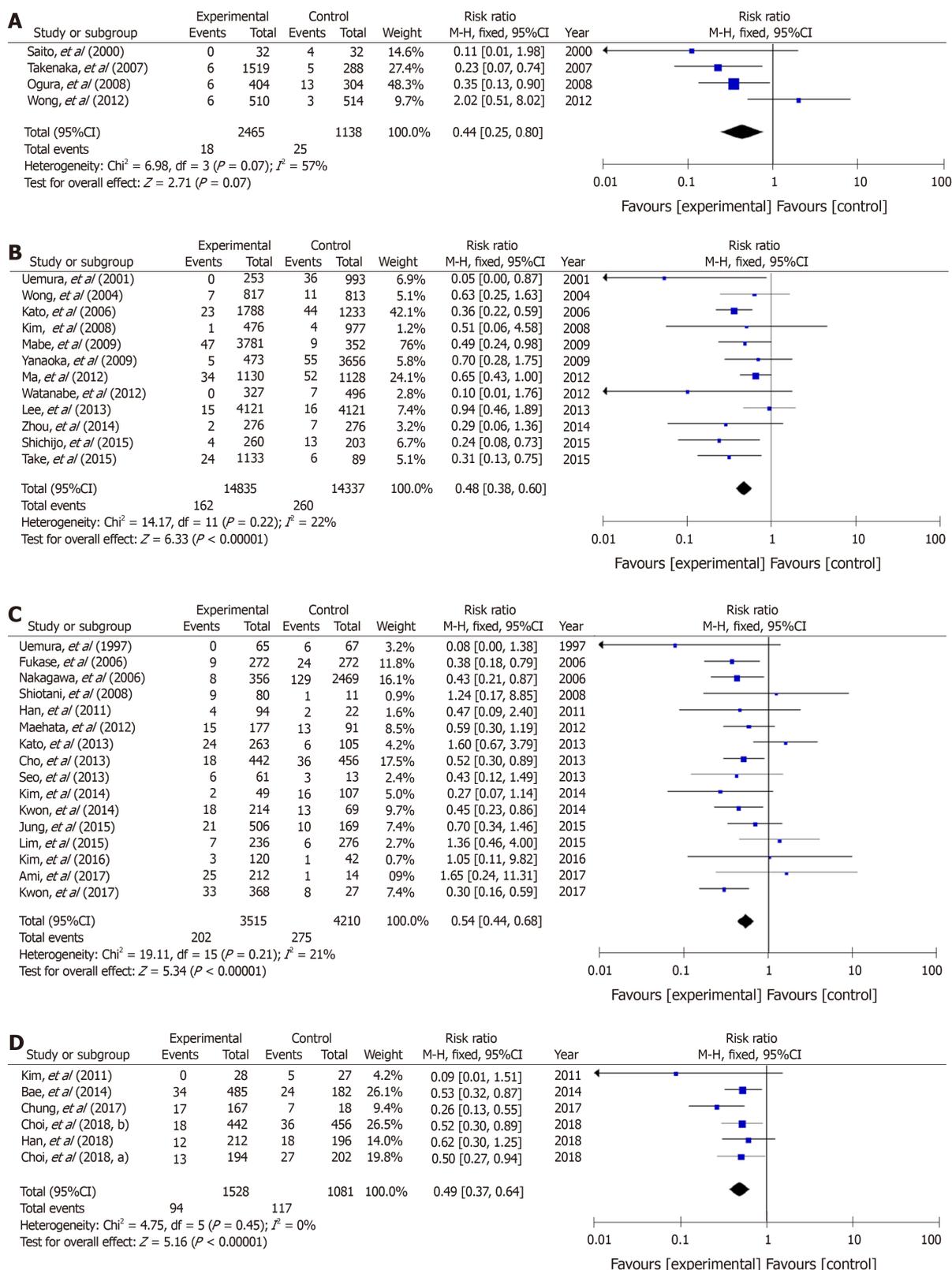


Figure 5 Forest plots of the incidence of gastric cancer between *Helicobacter pylori*-negative and -positive groups with atrophic gastritis in studies of different observation period length, < 5 years (A) and > 5 years (B). Forest plots of the incidence of metachronous gastric cancer in cases treated for gastric cancer in studies of different observation period length, < 5 years (C) and > 5 years (D). A: Non-gastric cancer with atrophic gastritis: within 5 years of resection; B: Non-gastric cancer with atrophic gastritis: more than 5 years after resection; C: Metachronous cancer: within 5 years of resection; D: Metachronous cancer: more than 5 years after resection.

however, in accordance with the increased chance of receiving *H. pylori* eradication therapy^[37] resulting in a decrease in infection rates across the population^[38] and improvement of sanitary conditions, incidence rates of GC are gradually declining,

particularly *H. pylori*-associated non-cardia GC^[37]. In Japan, although approximately 50000 GC deaths occurred annually over 40 years, deaths significantly decreased from 48427 in 2013 to 45509 in 2016 following expansion of insurance coverage for *H. pylori* eradication therapy^[37]. In addition, national GC screening programs using upper endoscopy in South Korea and Japan may have contributed to the decrease of GC mortality by decreasing the risk of diagnosis at an advanced stage and by *H. pylori* eradication therapy after endoscopic diagnosis^[39]. Currently, approximately half of all GCs in Japanese are detected at an early stage, confined to the mucosa or submucosa^[40]. Establishment of an effective screening system for GC detection and the stratification of risk for GC development are considered to be important for reducing GC development and mortality.

Chemoprevention for metachronous GC

Endoscopic resection, including endoscopic mucosal resection and endoscopic submucosal dissection for early-stage GC, are widely accepted as curative^[41]. With the development of treatment tools and endoscopy, endoscopic submucosal dissection is used as first-line treatment for early-stage GC in Japan and South Korea, because it enables *en bloc* resection of GC^[42-44]. However, the risk of metachronous cancer after endoscopic resection is expected to be higher than the risk in non-GC patients with gastritis, and a drawback of endoscopic and operative resection is the residual risk of metachronous cancer arising from severe atrophic gastritis or intestinal metaplasia in the gastric remnant. In general, metachronous GCs are characterized as small, differentiated intramucosal cancers < 20 mm in size. The incidence rate of metachronous cancer within 3–5 years after endoscopic resection has been reported to be about 2.7%–15.6%^[45]. The median incidence of metachronous cancer decreased to 1229.2 (0–4333.1) per 100000 person-years after eradication therapy from 2922.0 (406.5–10,166.0) in *H. pylori*-positive individuals in this meta-analysis. In a multicenter RCT by the Japan GAST Study Group in 2008, the cumulative incidence of metachronous cancer was 6.5% during 3-years follow-up. *H. pylori* eradication therapy decreased the incidence of metachronous cancer by approximately two-thirds in patients after endoscopic resection for early-stage GC (3.5% vs 9.6%, $P = 0.003$)^[31]. Also in an RCT from South Korea, during a median follow-up of 5.9 years, metachronous cancer developed in 7.2% of patients who underwent successful eradication therapy and 13.4% of patients receiving placebo (HR: 0.50; 95% CI: 0.26–0.94), correlating with improvement in gastric corpus atrophy^[32]. In this meta-analysis, only 36.4% of all studies (all 3 RCTs and five studies of 18 cohort studies in patients after endoscopic resection) showed significant reduction of metachronous cancer risk. This observation may have been caused by the small sample size in each report and it remains unclear whether the risk of GC related to *H. pylori* decrease after eradication therapy. The RRs with eradication therapy in RCTs and cohort studies were 0.51 (95% CI: 0.36–0.73) and 0.54 (0.44–0.67), respectively. Therefore, we recommend that all East Asian patients who remain *H. pylori*-positive after endoscopic resection for GC receive further eradication therapy to decrease the risk of metachronous cancer.

After gastrectomy, the cumulative incidence of metachronous cancer is 0.9%–3.0%, irrespective of *H. pylori* infection^[45]. One report investigated the efficacy of eradication therapy for metachronous cancer risk after surgical partial gastric resection^[17]. Cho *et al*^[17] reported that eradication for patients after surgical resection is beneficial, as reflected by milder atrophy and intestinal metaplasia at 36 mo after surgery, but did not report any effect on GC. Therefore, although *H. pylori* in the gastric remnant would be associated with more severe atrophy and intestinal metaplasia over time, the efficacy of eradication therapy in patients with gastric remnants might be limited compared with that in non-GC patients with gastritis and patients after endoscopic gastric resection.

Subgroup analysis by different countries

Significant difference of GC risk after eradication among East Asian countries is shown in this meta-analysis. GC risk is known to depend on combination of bacterial factors (*e.g.*, *cagA* status and *vacA* type), the host genetic factors (*e.g.*, inflammatory cytokine genes, detoxification-related genes and oncogenes) and environmental factors (*e.g.*, salt intake, smoking and alcohol)^[46-51]. Therefore, the preventive effect for GC after eradication is also expected to depend on above different factors. Because the host genetic factors in East Asian populations (*e.g.*, Japan, South Korea and China) is similar, different life style and different strain of *H. pylori* may cause difference for GC risk after eradication.

Chemoprevention for non-GC patients with gastritis

In this meta-analysis, although metachronous cancer incidence in *H. pylori*-positive patients after resection of GC was 2922.0 per 100000 person-years, that in non-GC

patients with gastritis was not as high (322.4 per 100000 person-years). In 2001, Uemura *et al*^[52] reported that GCs developed in 2.9% of *H. pylori*-positive patients at a mean follow-up of 7.8 years, but not in any *H. pylori*-negative patients or eradicated patients. This startling observation focused attention on the association of GC and *H. pylori* infection. This meta-analysis showed that 1 study of 4 RCTs (25.0%) and 7 studies of 12 cohort studies (58.3%) in East Asian populations had significant reduction in GC risk, with mean RRs of 0.67 (95%CI: 0.47–0.96) in RCTs and 0.39 (0.30–0.51) in cohort studies, suggesting that eradication for all *H. pylori*-positive non-GC patients with gastritis will decrease the risk of GC in East Asian populations. Further prospective studies with longer follow-up periods might help clarify the protective effect of *H. pylori* eradication against GC.

It was shown that the prophylactic effect of *H. pylori* eradication therapy was not observed in all groups of patients, but only in some ones. Longer follow-up after eradication therapy is associated with better prevention of GC development^[53] and significant reduction in cancer incidence after eradication is observed only in pepsinogen test-negative subjects^[25]. It may be important to clarify a high-risk group or a risk factor for GC development. A simple and safe method of identifying patients at increased risk of GC is necessary. As possible factors, pro-inflammatory cytokines (*e.g.* interleukin-1beta and tumor necrosis factor-alpha)^[46,54], prostate stem cell antigen gene^[55] methylation levels of any genes [*e.g.*, miR-124a-3, empty spiracles homeobox 1 (EMX1) and NK6 homeobox 1 (NKX6-1)]^[56], and *H. pylori* virulence factors (*e.g.* *cagA* and *vacA*)^[57,58], as well as endoscopic and pathological evidence of atrophy and intestinal metaplasia, have been cited. Ideally, eradication therapy should be instituted prior to the development of atrophy and intestinal metaplasia to achieve the optimal lowering of risk.

Incidence rate of GC after *H. pylori* eradication therapy between RCTs and cohort studies is the large difference: 272.7 (180.4–322.4) for RCT and 467.2 (68.7–1379.5) per 100000 person-years for cohort studies. This may be caused that patient background in each report is very heterogeneous in age, sex, disease, and severity of gastric atrophy and intestinal metaplasia. Further study will be required to clarify this problem.

High-efficacy eradication therapy and eradication regimens

In this meta-analysis, as summarized in Table 1, eradication therapy with a regimen including PPI and two kinds of antimicrobial agent (*i.e.*, clarithromycin, amoxicillin, or metronidazole) in the RCTs resulted in eradication rates of 66.2%–88.9% in non-GC patients with gastritis and 75.0%–82.6% in patients after resection. To prevent GC, it is ideal to select an eradication regimen that provides a high eradication rate^[59]. Unfortunately, however, because the frequent use of clarithromycin in general clinical situations has led to a global increase in the prevalence of clarithromycin-resistant strains, eradication rates with first-line clarithromycin-containing therapies are decreasing^[60,61]. Recently, the Maastricht V/Florence Consensus Report has recommended quadruple therapy with or without bismuth, and without clarithromycin for patients living in areas with a high prevalence of clarithromycin resistance^[62]. The new acid-inhibitory drug vonoprazan that produces rapid, strong and long-lasting gastric acid inhibition after administration of the first tablet in a dose-dependent manner has become clinically available in Japan, and vonoprazan-containing regimens have demonstrated effectiveness in patients infected with clarithromycin-resistant strains and patients living in areas where the prevalence of clarithromycin-resistant strains is > 15%^[59,63–65]. As culture-based and pharmacogenomics-based tailored treatment may have the potential to achieve an eradication rate exceeding 95%, the theoretical advantages of vonoprazan as evidenced by its potent acid inhibition during eradication therapy are considered to expedite risk reduction.

In addition, according to increase of incidence rates of antimicrobial agents-resistant *H. pylori* strains, patients refractory to eradication therapy including amoxicillin, clarithromycin, nitroimidazoles, fluoroquinolones, bismuth or tetracycline, is expected to be increasing. Recently, possible that use of new antimicrobial agents, such as rifabutin and sitafloxacin, have a potential with high eradication rate are suggested^[66,67].

Limitations

We meta-analyzed studies in East Asian populations. Therefore, it is unclear whether this preventive strategy also applies to other populations. Studies investigating efficacy in populations with lower incidence rates of GC are scarce, and more investigation is needed. In addition, this meta-analysis is insufficient to investigate any association of preventive efficacy with patient age at the time of eradication. In an animal model with Mongolian gerbils, eradication therapy was shown to have an

association with GC risk and duration of *H. pylori* infection, and a shorter duration of *H. pylori* infection due to early eradication was associated with a low risk of GC^[68]. Long-term *H. pylori* infection may result in severe atrophic gastritis with intestinal metaplasia, and the earliest possible implementation of *H. pylori* eradication therapy is likely important in preventing GC.

In conclusion^[17-33,52,53,69-94], this meta-analysis strengthens the evidence for the potential of *H. pylori* eradication therapy to reduce the risk of GC in East Asian populations with high incidence rates of GC. GC risk is known to depend on combination of bacterial factors (*e.g.*, *cagA* status and *vacA* type), the host's genetic factors (*e.g.*, inflammation-related molecule polymorphism) and environmental factors (*e.g.*, salt and smoking). Of those risk factors, because gastric mucosal change (*e.g.*, gastric mucosal atrophy and intestinal metaplasia) with risk of GC development gradually progress after *H. pylori* infection, best way is to avoid from infection of *H. pylori*, and if *H. pylori* infects, eradication therapy should be performed as soon as possible at younger age before progression of gastric mucosal atrophy in all *H. pylori* positive patients. The surveillance interval in patients after endoscopic and operative resection and non-GC patients with atrophic gastritis is important after eradication therapy. The National Comprehensive Cancer Network guidelines state that even for Tis or T1 with N0 lesions achieving R0 with endoscopic and surgical resection, all patients should be followed systematically, and that follow-up should include a complete history and physical examination every 3 to 6 mo for 1 to 2 years, every 6 to 12 mo for 3 to 5 years, and annually thereafter for all patients (http://www.nccn.org/professionals/physician_gls/PDF/gastric.pdf).

ARTICLE HIGHLIGHTS

Research background

Helicobacter pylori (*H. pylori*) infection is a risk factor for gastric cancer (GC), especially in East Asian populations. Most East Asian populations infected with *H. pylori* are at higher risk for GC than *H. pylori*-positive European and United States populations. *H. pylori* eradication therapy reduces GC risk in patients after endoscopic and operative resection for GC, as well as in patients with atrophic gastritis. However, it remains unclear whether eradication therapy exerts the same chemopreventive effect on GC among different groups, *e.g.*, those of different nationalities, those with a history of gastritis alone, those with a prior history of GC resection, *etc.*, with different risk levels for GC development.

Research motivation

We hope to up-date evidences for preventive effect on development of GC after eradication therapy in East Asian populations.

Research objectives

To clarify the preventive effects of *H. pylori* eradication therapy for development of GC in an East Asian population with a high incidence of GC.

Research methods

PubMed and the Cochrane Library were searched for randomized control trials (RCTs) and cohort studies published in English up to March 2019 using the terms "*H. pylori*," "GC," and "eradication therapy". Subgroup analyses were conducted with regard to study designs (*i.e.*, RCTs or cohort studies), country where the study was conducted (*i.e.*, Japan, China, and South Korea), and observation periods (*i.e.*, ≤ 5 years and > 5 years). The heterogeneity and publication bias were also measured.

Research results

For patients with atrophic gastritis alone and patients after resection for GC, 4 and 4 RCTs and 12 and 18 cohort studies were included, respectively. In RCTs, the median incidence of GC for the untreated control groups and the treatment groups in cases of gastritis alone was 272.7 (180.4–322.4) and 162.3 (72.5–588.2) per 100000 person-years. In RCTs, the median incidence of metachronous GC for the untreated control groups and the treatment groups was 1790.7 (406.5–2941.2) and 1126.2 (678.7–1223.1) per 100000 person-years. Compared with non-treated *H. pylori*-positive controls, the eradication groups had a significantly reduced risk of GC, with a relative risk of 0.67 [95% confidence interval: 0.47–0.96] for patients with atrophic gastritis alone and 0.51 (0.36–0.73) for patients after resection for GC in the RCTs and 0.39 (0.30–0.51) and 0.54 (0.44–0.67) in cohort studies.

Research conclusions

The current meta-analysis showed that in the East Asian population with high incidence rates of GC, *H. pylori* eradication effectively reduced the risk of GC, irrespective of past history of previous cancer. The surveillance interval in patients after endoscopic and operative resection and patients with atrophic gastritis alone is important after eradication therapy.

Research perspectives

The results of the current meta-analysis may offer gastroenterologists and endoscopists more reliable evidence in efficacy of *H. pylori* eradication therapy and importance of surveillance after eradication therapy.

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