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ORIGINAL ARTICLE

Helicobacter pylori eradication cannot reduce the risk of gastric cancer in patients with intestinal metaplasia and dysplasia: evidence from a meta-analysis

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Abstract

Background The effect of Helicobacter pylori (*H. pylori*) eradication on gastric cancer (GC) prevention is controversial. Intestinal metaplasia (IM) seems to be a "point of no return" in the precancerous cascade. We performed a meta-analysis of randomized controlled trials (RCTs) to illustrate this issue.

Materials and Methods The MEDLINE, EMBASE, Cochrane Library were searched for relevant RCTs that were published in any language up to March 2014. By dividing participants into subgroups based on their baseline diagnoses as group <IM (normal, non-atrophic gastritis, atrophic gastritis) and group ≥IM(intestinal metaplasia, dysplasia), the relative risk (RR) of GC in each study compared treatment group with control group were pooled using Mantel–Haenszel fixed-effect model and publication bias analyses were performed.

Results Ten studies from eight RCTs were included in this analysis, for a total of 7,955 participants. *H. pylori* treatment compared with control significantly reduced the risk of GC, with a pooled RR of 0.64 (95 % CI, 0.48–0.85). Subgroup analysis for patients with non-atrophic gastritis, atrophic gastritis (<IM) yielded a similar results (RR = 0.25, 95 % CI, 0.08–0.81). But this difference was not observed in patients with intestinal metaplasia, dysplasia (≥IM) (RR = 0.88; 95 % CI, 0.59–1.31).

Conclusions Our results suggested that patients with Intestinal metaplasia or dysplasia could not benefit from the *H. pylori* treatment on the risk of GC.

Keywords Gastric cancer · Helicobacter pylori treatment · Precancerous lesions

Introduction

According to the model of gastric carcinogenesis, the consecutive precancerous lesions (PL) is usually represented as normal, non-atrophic gastritis (NAG), atrophic gastritis (AG), intestinal metaplasia (IM), dysplasia (DYS) and gastric cancer (GC).Cure of *H. pylori* is proven to be effective in halting the progression of the PL and has been recommended to prevent GC [1–6]. However, the preventive effect was still controversial considering that most RCTs failed to directly demonstrate a significant decreasing on the incidence of GC after *H. pylori* treatment [3, 7–10]. A major consideration for the inconsistent results is a hypothetically existed time-point in the carcinogenesis process, when the histological change reached a certain degree of PL, the GC would progress anyway. Several studies have already showed that the progression of PL was more likely to be observed in individuals with a baseline

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diagnosis ≥IM (IM, DYS), compared with those <IM (Normal, NAG, AG). Thus, the presence of IM seems to be the "point of no return" in the process, regardless of *H. pylori* eradication [12–14]. However, to our knowledge, no conclusions concerning the effect of GC prevention after *H. pylori* eradication in these two subgroups of patients has been drawn so far.

Our study was aimed to describe the association between *H. pylori* eradication and GC incidence. By dividing participants from relevant RCTs into 2 subgroup based on their baseline of histological diagnoses (<IM or ≥IM), we performed a meta-analysis to compare the effect of *H. pylori* eradication in these two subgroups, from the perspective of preventing GC and halting PL respectively.

Methods

Search strategy

The MEDLINE, EMBASE, Cochrane Library were searched for relevant studies that were published in any language up to March 2014. The further websites were also searched, including Google Scholar, ClinicalTrials.gov, and Chinese Biomedical Literature Database (up to March 2014). We searched the literature by using the following key words and/or medical subject headings (Mesh) terms: "Helicobacter pylori"[Mesh], eradication, treatment, "Stomach Neoplasms"[Mesh], gastric cancer, gastric atrophy, intestinal metaplasia, and dysplasia. In addition, the reference lists of all included studies were reviewed carefully to identify additional eligible studies.

Study selection

Studies met the following pre-specified criteria were included as the potentially relevant studies: a design of randomized trials; contained intervention group (*H. pylori* treatment) and control group (placebo or not); with a duration of follow-up no less than 24 months; including participants confirmed *H. pylori* infection before treatment; endoscopic biopsy was performed at baseline; provided the information of GC in each group.

Two authors (Chen, Wang) independently examined all included studies in full-text, and disagreements were resolved by discussion of all authors. Duplicate publications were identified when multiple articles present common author names, locations or baseline data. Reports from the same trial were linked together and the more informative articles were selected with supplemented data from related reports. Ongoing and unpublished studies were not included in this review because of insufficient information and potential risk of bias.

Quality assessment

Two authors independently evaluated the quality of each study mainly based on the methods and results, in accordance with the assessing criteria suggested by Cochrane collaboration [15]. The quality of each study was assessed by evaluating the following item: method to generate the random sequence and conceal the treatment allocation, blinding of participants, blinding of personnel, blinding of outcome assessment (in this study, namely, the endoscopist and pathologist), whether placebo was offered, whether incomplete outcome data were described, and intention-to-treat analysis.

Data extraction

Two authors independently extracted data on the following items from the selected trials: author name; year of publication; country; study design; duration of follow-up; age range of participants; ratio of male to female; primary outcome; total number of participants enrolled; number of participants in each intervention group; number of participants with complete follow-up in each intervention group; GC in each intervention group; diagnostic criteria of *H.pylori* infection; histologic details (baseline of histological diagnosis, biopsy numbers, biopsysites); outcome definition (histological evaluation system); *H. pylori* treatment/eradication (name, dosage, and duration of treatment); the status of *H. pylori* infection in each intervention group.

Data synthesis and statistical analysis

The measure of effect of interest is the relative risk (RR) with 95 % confidence interval (CI).To estimate the effects of allocating the *H. pylori* treatment, data were generally extracted in an intention-to-treat manner, except that participants refused the allocation in each study were not counted.

The crude RRs were extracted from all studies with the raw data of GC in each intervention group and pooled in an analysis to give an estimate of the effect of *H. pylori* eradication in GC prevention. Subgroup analyses was performed based on study population (whether including patients with a history of GC). When anintervention group of a study contains no event, we added 0.5 to each cells of the 2 × 2 table for the study to provide a more conservative estimate of effect size [16].

Participants from studies providing individual histological data were divided into two subgroups based on their baseline diagnoses (≥IM or <IM). The cancer preventive effect of H.pylori eradication was evaluated by pooling the RR of GC development in two subgroups. Impacton halting

PL was expressed as the RR of the progression of PL in treatment group compared with control group, and these RRs were pooled in two separate analyses as previously described.

The Cochran's Q statistic and the I^2 statistics were used to assess heterogeneity among all studies. For the Q statistic, a p value of less than 0.1 was considered statistically significant. Random-effects model was used if the heterogeneity exists, otherwise the Mantel–Haenszelfixed-effect model was preferred. Publication bias was assessed by the Egger's/Begg's test weighted regression method; a p value of less than 0.1 was considered representative of statistically significant publication bias. All analyses were performed with Stata (version 12.0; StataCorp, College station, TX).

Results

Literature Search

A total of 6,330 records were retrieved based on the search strategy: 3,467 from Medline, 2,737 from EMBASE, 5 from Cochrane Library, and 121 from other sources (Google scholar, ClinicalTrials.gov, Chinese Biomedical Literature Database). There were 5,016 records remained after duplicate records removed. Of these, 4,991 records were excluded based on abstracts or titles. The remaining 25 articles were reviewed in full-text. Fifteen articles were excluded for the reasons listed in Supplemental material 1, leaving a total of 10 articles from 8 trials included in this review. The study by Sung et al., which is from the same trial of Leung, was included to provide supplemental data of histological change [3, 17]. Similarly, the study by You was also included for the same reason with the article by Ma [4, 18].

Study characteristic

Characteristics of the 10 studies from 8 trials were shown in Table 1. The selected studies were published between 2000 and 2013. Four trials were conducted in China [3, 7, 9, 18], 2 in Korea [10, 19], 1 in Japan [6], and 1 in Colombia [1]. Duration of follow-up in each study ranged from 2 to 15 years. Mean age of participants ranged from 42 to 69 years. The male–female ratios were approximately 1:1 in 6 trials, 2:1 in 1 trial [10] and 3:1 in another [6]. The association between *H. pylori* eradication and GC was the primary outcome of interest for 5 studies, whereas it was a secondary question in the other 5 studies. The number of participants per study ranged from 169 to 2,258, for a total of 7,953 participants across all study. The proportion of participants with complete follow-up in each study ranged

Table 1 Characteristics of studies included in the meta-analysis

Study	Country	Enrollment period	Follow-up (years)	Age range	Male–female ratio	Primary outcome	Total number of patients	Treatment group	Control group	Treatment complete	Control complete	Treatment cancer	control cancer
Correa et al. [1]	Colombia	1991	6	29–69	1:1	PL	852	437	415	320	311	3	2
Sung et al. [17][a]	China	1996	5	16–75	1:1	PL	587	295	292	219	214	NA	NA
Leung et al. [3][a]	China	1996	5	16–75	1:1	PL	587	295	292	220	215	4	6
Wong et al. [7]	China	1994	7.5	35–65	1:1	GC	1,630	817	813	735	703	7	11
You et al. [b][4]	China	1995	9	35–64	1:1	PL	2258	1130	1128	1,008	1,002	19	27
Ma et al. [18][b]	China	1995	15	35–64	1:1	GC	2,258	1,130	1,128	NA	NA	34	52
Fukase et al. [6]	Japan	2001	3	20–79	3:1	GC	542	271	271	255	250	9	24
Wong et al. [9]	China	2002	2	35–64	1:1	PL	1,024	510	514	453	466	4	3
Cho et al. [19]	Korean	2003	3	18–70	1:1	PL	169	87	82	80	71	3	1
Choi et al. [10]	Korean	2005	3	20–75	2:1	GC	891	444	447	439	441	10	17

PL precancerous lesions, *GC* gastric cancer

[a] The study by Sung et al. which is from the same trail of Leung, was included to provide supplemental data of histological change

Table 2 Histologic details of studies included in the meta-analysis

Study	HP diagnosis	Baseline	Biopsy numbers/sites	Histological evaluation system	Outcome comparison (GC/PL)	Histological diagnosis of PL	Definition of PL progression n
Correa et al. [1]	HIS	AG-DYS	4; 2*antrum; 1*corpus; 1*angulus	USS	GC; PL	Most advanced lesion	Step[a]
Sung et al. [17]	RUT and HIS	NAG-IM	4; 2*antrum; 2*corpus	USS, PIC	PL	Antral and corpus	Score[b]
Leung et al. [3]	RUT and HIS	NAG-IM	4; 2*antrum; 2* corpus	USS, PIC	GC; PL	Most advanced lesion	Score[b]
Wong et al. [7]	RUT + HIS	NAG-DYS	4; 2*antrum; 1* corpus; 1* angulus	USS	GC	NA	NA
You et al. [4]	Ser	NAG-DYS	7; 4*auntrum; 3*corpus	CHGC	GC; PL	Most advanced lesion	Step[a]
Ma et al. [18]	Ser	NAG-DYS	7; 4*auntrum; 3*corpus	CHGC	GC; PL	Most advanced lesion	Step[a]
Fukase et al. [6]	RUT or HIS	AG-IM, GC	5; 2*antrum; 3*corpus	USS, VC	GC	NA	NA
Wong et al. [9]	UBT	AG-DYS	5; 2* antrum; 2*corpus; 1*angulus	USS, PIC	GC; PL	Most advanced lesion	Score[b]
Cho et al. [191	RUT or HIS	AG-IM, GC	6; 2*antrum; 4*corpus	USS, TNM	GC; PL	Lesser and greater curvature of corpus	Score[b]
Choi et al. [10]	RUT or HIS	NAG-DYS, GC	4; 2* antrum; 2*corpus	USS, VC	GC	NA	NA

AG atrophy gastritis, *CHGC* Chinese histopathology grading criteria, *DYS* dysplasia, *GC* gastric cancer, *HIS* histology, *IM* intestinal metaplasia, *NAG* non-atrophic gastritis, *PIC* Padova international classification, *PL* precancerous lesion, *RUT* rapid urease test, *TMN* American Joint committee on cancer TNI\ classification system, *UBT* urea breath test, *Ser* serologic test, *USS* updated Sydney system, *VC* Vienna classification

[a] Progression was defined by comparing the histologic diagnoses at baseline and outcome based on the histological step

[b] Progression was defined as higher score at outcome compared with baseline

from 64.7 to 97.7 %. Raw data of GC in each intervention group was determined for 8 studies.

The methods to diagnose the *H. pylori* infection and other histologic details in each trial were shown in Table 2. Five trials chose two methods to confirm the infection while three trials used one. Participants in each study had a similar baseline of histology diagnosis, ranging from NAG to DYS, except that 3 studies included patients who had a history of GC and received endoscopic or surgical resection [6, 10, 19].

Specimens were generally obtained from antrum and corpus, except additional specimens were obtained from angulus in 3 studies [1, 7, 9]. The updated Sydney system (USS) was selected as the stipulation for the histological evaluation system of specimens in all trials except one, which used the Chinese histopathology grading criteria [4]. In most studies, GC was diagnosed once tumors invaded the lamina propria or muscularis mucosae [1, 3, 7, 9, 18]. Among studies regarded metachronous GC as outcome, two of them defined GC as either noninvasive or invasive tumor corresponding to Vienna classification [6, 10]. One used American Joint Committee on Cancer TNM classification system [19].

Five studies [1, 3, 4, 9, 18] chose the most advanced biopsy as the baseline diagnosis and two [17, 19] made the diagnosis in different sites separately, while three studies did not describe the method explicitly [19]. Regarding the definition of progression of PL, two trials [1, 4] compared the baseline and outcome histologic diagnoses based on the consecutive step of PL, two [9, 17, 19] applied a histological score comparison between baseline and outcome (e.g. progression was defined as higher score at outcome compared with baseline), while four did not provide the relevant data.

As conducted in different times, eradication therapy was not unified among the 8 serious trials (Table 3). Generally, Proton pump inhibitor triple therapy was prescribed as the initial strategy, except one, in which bismuth subsalicylate combined two kinds of antibiotics was chosen [1]. Only three trials described a design of remedies to increase the chance of successful eradication [1, 7, 18]. The mean eradication rate ranged from 46.0 to 82.5 %.

Quality assessment

The quality evaluation of included studies was shown in Table 4. Random sequence generation was explicitly specified in all trials. Allocation concealment was reported in five of the included trials. Two trials used a double-blinded design and one used a single-blinded design. Six trials explicitly specified the blinding to pathological assessment. And blinding to the endoscopist was described in four trials and was not mentioned in two trials. Half of

Table 3 Treament strategy of studies included in the meta-analysis

Study	H.pylori treatment	Repeat treatment	Eradication rate (%)	Persist-infection rate (%)
Correa et al. [1]	A(500 mg) + M(375 mg) +B(262 mg); tid*14d	O(20 mg)/L(30 mg) + A(1000 mg) + C(500 mg); bid*14d	74	84.8
Sung et al. [17]	O(20 mg) + A(1000 mg) + C(500 mg); bid*7d	NA	76.6	83.9
Leung et al. [3]	O(20 mg) + A(1000 mg) + C(500 mg); bid*7d	NA	74.5	90.7
Wong et al. [7]	O(20 mg) + AC(750 mg) + M(400 mg); bid; 7d	O(20 mg) + M(600 mg) + C(500 mg) + B(240 mg); bid*7d	82.5	91.8
You et al. [4]	O(20 mg) + A(1000 mg); bid*14d	O(20 mg) + A(1000 mg); bid*14d	46	90
Ma et al. [18]	O(20 mg) + A(1000 mg); bid*14d	O(20 mg) + A(1000 mg); bid*14d	NA	NA
Fukase et al. [6]	L(30 mg) +A(750 mg) +C(200 mg); bid*7d	NA	75	95
Wong et al. [9]	O(20 mg) + A(1000 mg) + C(500 mg); bid*7d	NA	71.3	NA
Cho et al. [19]	R(10 mg) + A(1000 g) + C(500 mg); bid*7 d	NA	75	59.2
Choi et al. [10]	O(20 mg) + A(1000 mg) + C(500 mg); bid*7d	NA	81.8	84.6

A am oxicillin, *AC* am oxicillin+clvulanate potassium, *M* metronidazole, *O* omeprazole, *R* raeprazole, *L* lansoprazole, *C* clarithromycin, *B* bismuth

the trials provide the placebo control to compare with *H. pylori* treatment. All included trials described the incomplete outcome data in each intervention group and 5 of them performed the intention-to-treat analysis. Studies included in this research present a high level of homogeneous, except three trials included patients with a history of GC. To avoid a potential risk of bias, a subgroup analysis based on these trials was performed.

Cancer preventive effect of *H. pylori* eradication

Among the 8 selected trials, only 2 trials suggest that *H. pylori* eradication can reduce the incidence of GC [6, 18]. The raw data of GC development in each intervention group were extracted from 8 studies, the crude RR ranged from 0.38 to 2.83. Overall, there were 74 cases of GC in treatment group (1.9 %, 3,992 patients) compared with 116 cases in the control group (2.9 %, 3,963 patients). In our pooled analysis, the treatment group had a reduced risk of GC development compared with control group (RR = 0.64; 95 % CI, 0.48–0.85). The impact of eradication was more pronounced on metachronous gastric cancer (RR = 0.52; 95 % CI, 0.31–0.87), compared with gastric cancer (RR = 0.70; 95 %/CI, 0.49–0.99). However, there was no significant heterogeneity between subgroups of different study population (whether including patients with a history of GC) ($I^2 = 0.0$ %, $p = 0.609$) (Fig. 1). Funnel plot asymmetry was observed (Egger's test, $p = 0.137$ and Begg's test, $p = 0.035$), suggesting publication bias or "small study effects", which was most likely caused by one small study [19].

Of the eight studies comparing treatment group with control group, six reported individual baseline diagnosis in 6,873 patients [4, 7, 9–11, 19]. These patients were divided into a subgroup of ≥IM (including 4,211 patients with IM or DYS) and a subgroup <IM (including 2,662 patients with NAG or AG).In the subgroup ≥IM, 44 (2.1 %) of 2,115 patients assigned to *H. pylori* eradication developed GC compared with 50 (2.4 %) of 2,096 patients allocated to control group (RR = 0.88; 95 %CI, 0.59-1.31) (Fig. 2), with no significant heterogeneity between studies ($I^2 = 0.0$ %, $p = 0.702$). In the subgroup of <IM, there was 1 (0.1 %) of 1,337 patients assigned to *H. pylori* eradication who developed GC, compared with 11 (0.8 %) of 1,325 patients allocated to control group (RR = 0.25, 95 % CI, 0.08–0.81), with no significant heterogeneity observed ($I^2 = 0.0$ %, $p = 0.843$).Similar results were obtained in another meta-analysis with only studies of primary-prevention cohort included (Supplemental material 2).

Effect of *H. pylori* eradication on gastric precancerous lesions

Complete individual data of histologic change between baseline and outcome were provided by 4 studies [1, 4, 17, 19]. Patients from these four studies were divided into two groups in the same way as previously described. Eventually, there were 2,217 patients with a baseline diagnosis ≥IM (IM, DYS) and 1,623 patients <IM (NAG, AG). The RR of progression was pooled in two separate analyses with a subgroup analysis based on the definition of PL progression.

In patients with a baseline diagnosis ≥IM, results varied based on the different definition of progression, the pooled RR of progression was 1.18 (95 % CI, 1.02–1.36) in studies compared the histological step and 0.81 (95 % CI, 0.64–1.03) in studies applied a histological score

Table 4 Quality assessment of studies include in the meta-analysis

Study	Random	Concealment	Binding				Placebo	Incomplete[a]	ITT
			Participant	Therapist	Endoscopist	Pathologist			
Correa et al. [1]	+	+	−	−	?	+	−	+	−
Sung et al. [17]	+	+	?	?	?	+	+	+	−
Leung et al. [3]	+	+	?	?	?	+	+	+	−
Wong et al. [7]	+	+	−	−	+	+	+	+	+
You et al. [4]	+	+	+	+	+	+	+	+	+
Ma et al. [18]	+	+	+	+	+	+	+	+	+
Fukase et al. [6]	+	?	−	−	−	−	−	+	+
Wong et al. [9]	+	+	+	+	+	+	+	+	+
Cho et al. [19]	+	?	+	?	+	+	?	+	+
Choi et al. [10]	+	?	−	−	−	−	−	+	−

ITT intention-to-treat analysis, + sufficient, − insufficient, ? not provided

[a] Whether incomplete outcome data were described

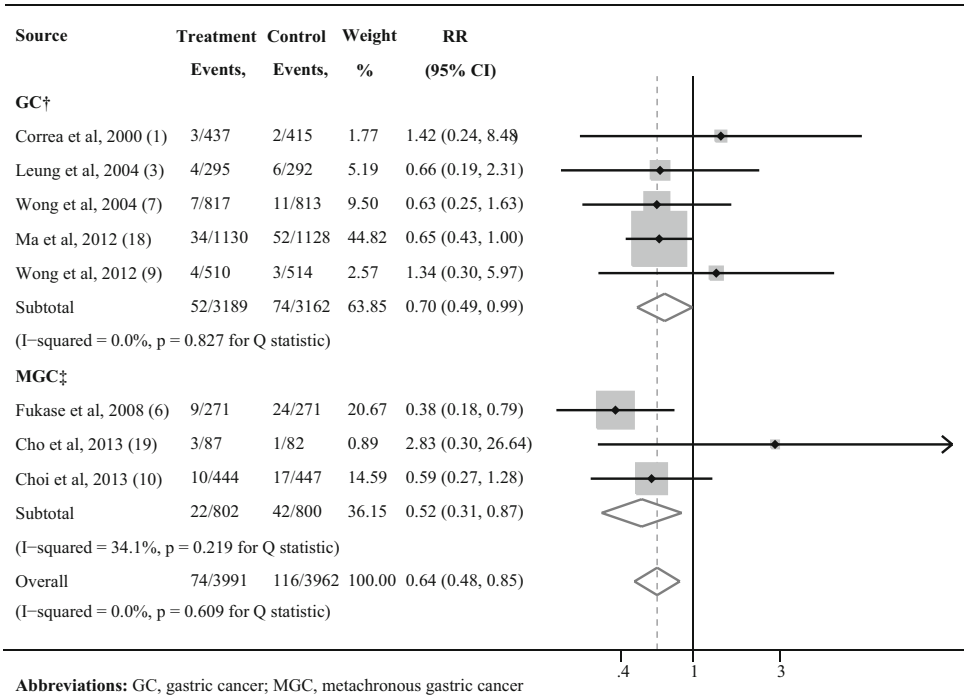


Fig. 1 Forest plot of studies reporting gastric cancer in treatment group and control group (subgroup analysis was performed based on studies regarded gastric cancer or metachronous gastric cancer as outcome, namely whether patients with a history of GC was included)

Abbreviations: GC, gastric cancer; MGC, metachronous gastric cancer

† Participants in studies regarded GC as outcome had a similar baseline diagnoses, ranging from non-atrophic gastritis to dysplasia.

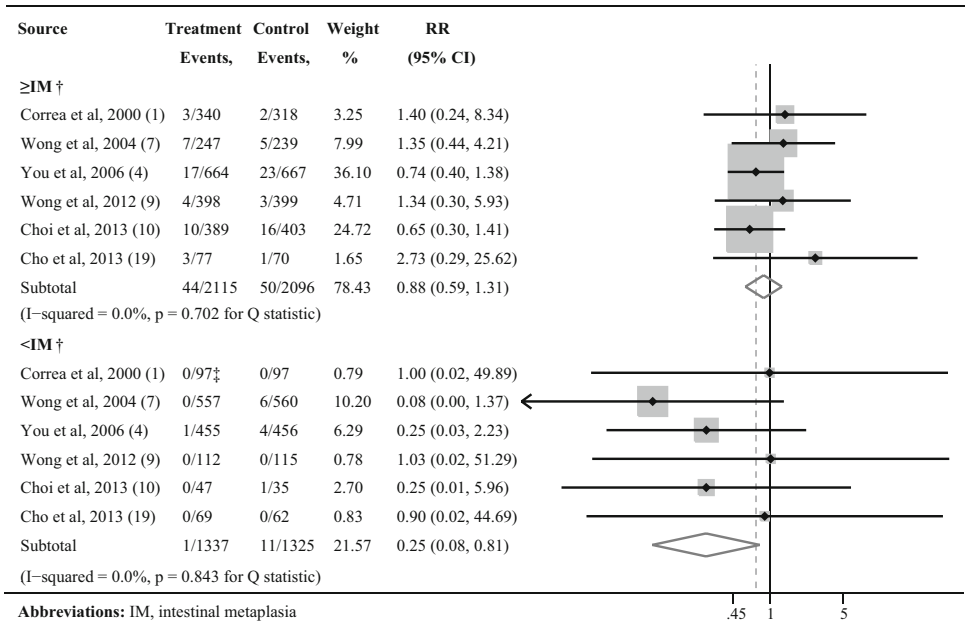
‡ Participants in studies regarded MGC as outcome had a history of gastric cancer and received endoscopic or surgical resection. Baseline diagnoses for these participants were still similar , ranging from non-atrophic gastritis to dysplasia.

comparison, with no significant heterogeneity observed ($I^2 = 0.0$ %, $p = 0.999$; $I^2 = 0.0$ %, $p = 0.539$) (Fig. 3a).

In patients with a baseline diagnosis <IM, the treatment group had a reduced risk of progression compared to the control group in studies applied a histological score comparison, with a pooled RR of 0.82 (95 % CI, 0.68–0.99). A similar but not statistically result was observed in studies compared the histological step, with a pooled RR of 0.96 (95 % CI, 0.85–1.07). There was no evidence of statistical heterogeneity of RRs across studies ($I^2 = 0.0$ %, $p = 0.787$; $I^2 = 0.0$ %, $p = 0.930$) (Fig. 3b).

Discussions

H. pylori has been given much importance in the process of gastric carcinogenesis. By including the related RCT, our meta-analysis suggests that *H. pylori* eradication may



Abbreviations: IM, intestinal metaplasia

† The consecutive steps of histological changes are usually represented as normal, non-atrophic gastritis (NAG), atrophic gastritis (AG), intestinal metaplasia (IM), dysplasia (DYS) and gastric cancer (GC). Participants were divided into two subgroups based on their baseline dignoses, ≥IM (IM, DYS) and <IM (NAG, AG).

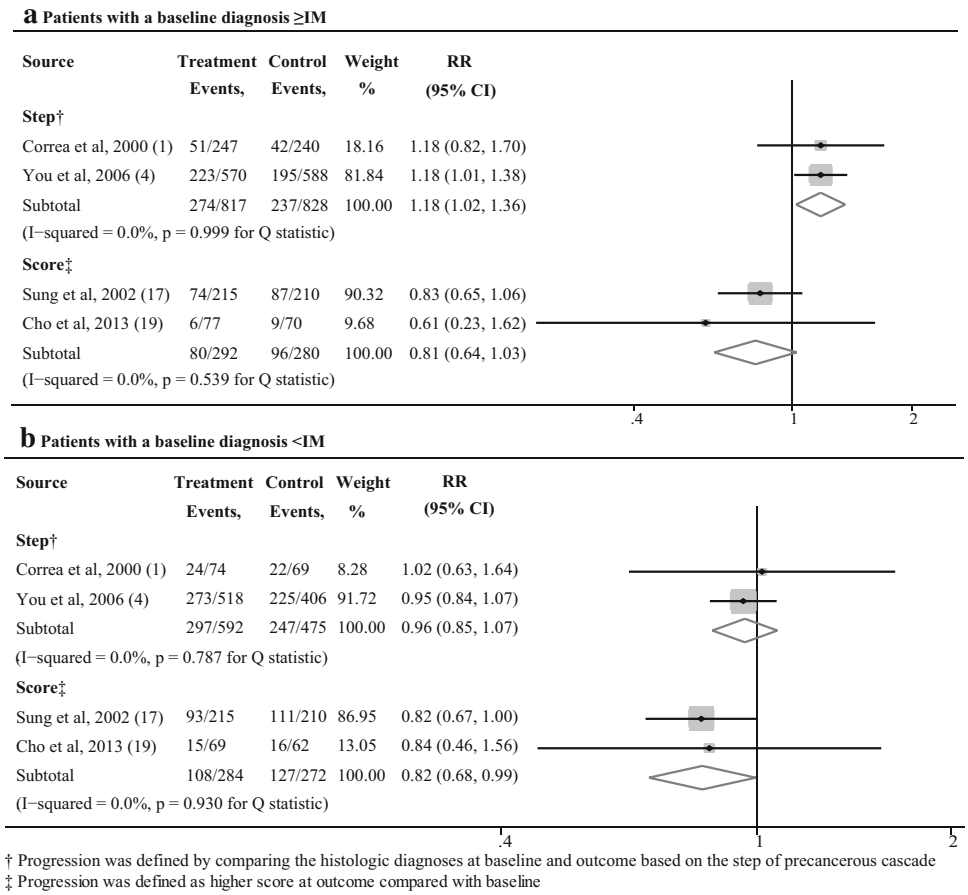
‡When an intervention group of a study contains no event, we added 0.5 to each cells of the 2×2 table for the study to provide a more servative estimate of effect size.

Fig. 2 Forest plot of studies reporting gastric cancer in treatment group and control group (subgroup analysis was performed by dividing participants based on their baseline diagnoses (≥IM or <IM))

reduce the incidence of gastric cancer (both in primary- and secondary- prevention).In particular, for patients with a baseline diagnosis <IM, *H.pylori* eradication may halt the PL progression and reduce the risk of gastric cancer. However, when PL of IM or DYS present, no preventive effect was observed after eradication, neither in the risk of gastric cancer nor the PL progression.

A previous meta-analysis has already shown a reduced risk of GC after eradication. However, its result has been questioned because of redundant data [20]. We corrected it in our analysis and also included studies evaluated the effect of eradication therapy on the risk of metachronous GC (secondary preventive effect).It cannot be denied that patients with a history of GC are different from participants of other primary-prevention cohorts, with regard to genetic susceptibility, possibility of undetected malignant lesion or other unrecognized reasons. The reason why we included these secondary-prevention cohorts is that we believe the development of GC at another site of stomach could also reveal the role of *H.pylori* infection in the carcinogenesis. As we expected, an overall reduction of GC was observed after *H. pylori* eradication as well as metachronous GC, and the prophylactic power against on metachronous GC was even more obvious. Thus, we still considered the occurrence of metachronous GC as part of our analysis.

Although these conclusion have been supported by several meta-analyses [21], the controversies still exist regarding whether *H. pylori* eradication would be sufficient to prevent GC. For example, even with a similar research design, opposite conclusions were still drawn from these RCTs [6, 10, 19]. The baseline histological diagnosis at time of eradication is one of the major explanations for the inconsistent results, which assume that treatment before the "point of no return" in the PL may be very important. Two meta-analyses of relevant studies revealed the effect of *H. pylori* eradication could halt the PL progression in individuals with a baseline diagnosis <IM compared with those ≥IM, which indicated the presence of IM seems to be the "point of no return" [12, 13]. In present study, we directly compared the occurrence of GC and the results suggested that patients with IM or DYS may not benefit from the *H. pylori* treatment on the risk of GC. Similar results indicating that the baseline of IM was a prior risk factor of GC development after eradication can be obtained in other studies [22–24].In the aspect of primary-prevention, Mera et al. [8] prescribed eradication therapy to participants allocated in placebo group and prolong the follow up duration from 6 to 12 years, and all 9 GC patients had a baseline diagnosis of IM or DYS. A large population-based study with 4,121 participants showed the 5-year average incidence of GC decreased from 40.3 to 30.4 per 100 000 person-yearsafter eradication treatment. The incidence of AG decreased from 59.9 to 13.7 %, while the incidence of both IM and DYS increased from 40.1 to 56.1 % [14]. On the other hand, in patients without history of GC, several reports have shown the close correlation between *H. pylori* infection and metachronous GC occurrence [21, 25–27], however, most of them also emphasized that limited effect



† Progression was defined by comparing the histologic diagnoses at baseline and outcome based on the step of precancerous cascade
‡ Progression was defined as higher score at outcome compared with baseline

Fig. 3 Forest plot of studies providing individual histological progression in treatment group and control group for patients with a baseline diagnosis (A) ≥ IM; (B) < IM.(subgroup analysis was performed based on the definition of precancerous lesion progression)

of eradication therapy in prevention of metachronous GC, especially in patients with IM nor DYS [28].Therefore, we believed that overall reduction of GC incidence is mainly due to the retaining of progression in patients with baseline diagnosis <IM, and malignancy transformation could hardly be prevented in those with IM or DYS.

Prospective studies, especially RCTs, which regarded the occurrence of GC as primary outcome were few, because the gastric carcinogenesis was time-consuming process which need long-term follow-up. Instead, based on the theory of consecutive progression process, many prospective studies evaluated the effect of *H. pylori* treatment in the PL to indirectly reflect the GC preventive effect [2, 29–36]. Though, meta-analyses [12, 13] has already concluded *H. pylori* treatment was succeed in halting progression of PL, we believe the retrospective design and inconsistent definitions of PL progression utilized might have a large extent influence to the pooled results. This is why most of previous RCTs assigned a single pathologist to evaluate the individual histological changes before and after eradication [1, 2, 31, 34, 37, 38].Therefore, to make a more reliable investigation, we performed an analysis only included RCTs with individual histological change provided and further conducted subgroup analyses based on the definition of PL progression (histological step or histological score).In our results, the halt effect was more obviously observed in studies applied histological score comparison with studies compared histological step. Additional, in studies used a histological step comparison, eradication seems to promote the deterioration in those with a baseline diagnosis ≥IM. As the two studies included in this analysis were both large sample randomized controlled trials, it is unlikely this result is just an incidence. We noted that both of these two studies [1, 4] have a 2^3 factorial design with multiple interventions given to participants, so the interaction between the *H. pylori* treatment and other interventions may be one explanation for this result. When we excluded other cross-over intervention groups in the study by Correa, a benefit effect was observed in the treatment group with a RR of 0.90 (95 % CI, 0.43–1.87), which may partially support our hypothesis. Anyway, regardless of the histological evaluation system used, patients with ≥IM could not benefit from *H. pylori* treatment.

There are three limitations of our study as shown below. Firstly, the number of studies was relatively small, and the duration of follow-up in each study varied. But all included studies were of high quality and large sample size. Second,

participants included in our analysis received multiple interventions to serve as control group, such as antioxidant supplements and cyclo-oxygenase-2 inhibitor. Though our data implies the potential interaction between the *H. pylori* treatment and other interventions, this hypothesis is far from proved. So far, these interventions is not considered has any additional efficiency if combined with eradication treatment. Third, only the intestinal-type gastric adenocarcinoma progresses through a relatively well-defined series of histological steps. Diffuse-type gastric adenocarcinoma does not form glandular structures and is not associated with IM. Giving the low incidence of GC in these trials, further analysis focused on the histologic type of GC seems impractical. Whether different conclusion would be drawn in diffuse-type gastric adenocarcinoma need further studies.

As conclusion of the study, our results supported the effect of H. pylori eradication on both primary- and secondary- prevention. Moreover our findings suggested that patients with IM or DYS may not benefit from the H. pylori treatment on the risk of GC. Frequent endoscopic monitoring and early treatment should be considered for these patients.

Author contribution CHN and WZ drafted the article, LX and ZZG made the study design and approved of the article. CHN and WZ contributed equally to this work

Conflicts of interest The authors declared that they have no conflicts of interest to this work.

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