BMJ Open

Helicobacter pylori eradication treatment for gastric carcinoma prevention in asymptomatic or dyspeptic adults: systematic review and Bayesian meta-analysis of randomised controlled trials

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To cite: Terasawa T, Hamashima C, Kato K, *et al*. *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;**9**:e026002. doi:10.1136/bmjopen-2018-026002

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-026002).

Received 13 August 2018
Revised 29 July 2019
Accepted 02 September 2019

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ABSTRACT

Objectives Recent meta-analyses of eradication therapy in *Helicobacter pylori*-infected adults reported significant reductions in gastric carcinoma risk. However, concerns about supporting unfocused screening and eradication programme in healthy, asymptomatic populations have arisen. We performed a systematic review and Bayesian meta-analysis to provide an accurate interpretation of randomised evidence on the preventive effectiveness of eradication therapy on gastric carcinoma risk.

Methods We searched databases including PubMed, Cochrane Central and Embase for reference and citation tracking without language restrictions, from inception through 31 July 2018. Paired investigators independently selected randomised controlled trials (RCTs) comparing eradication therapy with placebo or no treatment for asymptomatic or dyspeptic *H. pylori*-infected adults with no previous gastric carcinoma. The main outcome was gastric carcinoma incidence; secondary outcomes included gastric carcinoma-specific, non-gastric carcinoma and all-cause mortality.

Results A total of 5 population-based and 2 outpatient care-based RCTs involving 7303 adults were eligible. Eradication algorithms were heterogeneous, and unsuccessful eradication and reinfection were frequently observed. A Bayesian meta-analysis with competing risk outcomes found low-certainty evidence that eradication therapy might be more likely than control to reduce gastric carcinoma risk (HR=0.65; 95% credible interval (CrI) 0.41 to 1.0; I^2=11%). The CrIs included the null effects across the subgroup and sensitivity analyses, apart from those based on particular models that excluded two RCTs that enrolled subjects with specific histological findings only (HR=0.55; CrI 0.30 to 0.89; I^2=14%). The uncertainty of the average 41% risk reduction in gastric carcinoma-specific mortality included a clinically important mortality risk increase (HR=0.59 favouring eradication therapy; CrI 0.25 to 1.20; I^2=13%; low certainty).

Conclusions There is insufficient evidence to support or refute the effectiveness of eradication therapy in preventing gastric carcinoma in *H. pylori*-infected, high-risk populations. Rigorously conducted large RCTs of healthy infected adults only would provide evidence of the true efficacy of successful eradication.

PROSPERO registration number: CRD42014009245.

Strengths and limitations of this study

- ► This is the first meta-analysis of the preventive effectiveness of eradication attempts in healthy-appearing *Helicobacter pylori*-infected subjects with no previous gastric carcinoma that adopted fully Bayesian approaches to account for multiple time-to-event outcomes with competing risks and frequent censored observations.
- ► This review also performed comprehensive literature searches, obtained updated data from the trial authors and used the Grading of Recommendation Assessment, Development and Evaluation approach to formally assess the certainty of the evidence.
- ► The eligible trials included subjects with high-risk preneoplastic lesions and adopted suboptimal eradication algorithms, which precluded reliable assessments of the true efficacy of successful eradication in healthy *H. pylori*-infected adults.

BACKGROUND

Gastric carcinoma is the second most common cancer-specific cause of death worldwide and the third most prevalent cancer in East Asia.[1] Infection with *Helicobacter pylori* is a strong risk factor for gastric carcinoma.[2] Several postulated oncogenic mechanisms[3] and epidemiological evidence[4 5] supporting this association exist. Explanations for the high gastric carcinoma incidence in East Asia include environmental factors such as high sodium intake[6] and the geographically distinct predominance of *H. pylori* strains characterised by strain-specific polymorphisms in the *cagA* gene, producing a highly virulent CagA.[6 7]

Since the establishment of effective eradication treatments in the 1990s, several randomised controlled trials (RCTs) have assessed whether eradicating *H. pylori* can reduce the risk of gastric carcinoma in healthy adults. After multiple reports of inconclusive results, with the long-term follow-up of the largest RCT that showed a significant reduction in gastric carcinoma risk in the eradication group,[8] several meta-analyses that included RCTs only,[9 10] observational studies only,[11] and both RCTs and observational studies[12] reported similar findings. On this basis, clinical guidelines and consensus reports have consistently recommended screening and eradication of *H. pylori* in high-risk populations.[13–18] However, concerns about implementing unfocused screening and eradication programme in healthy, asymptomatic populations still remain because these meta-analyses had several limitations.[9–12] The evidence partly derived from studies focusing on patients treated for early-stage gastric carcinoma[10 11] cannot be directly applied to the general population. Also, concerns about the evidence obtained from cohort studies[11 12] include confounding and other sources of bias.[19 20] A recent Cochrane review, the only meta-analysis focusing on RCTs of subjects without previous gastric carcinoma,[9] relied on data reported in conference abstracts[21] and used statistical approaches that can calculate falsely narrow CIs when the number of studies is small and events are rare.[22–25] Additionally, the sensitivity analyses used for exploring the effect of censored cases on the summary estimates were for binary outcomes,[26 27] not for time-to-event outcomes with competing risks.[28]

Bayesian random-effect meta-analysis is an increasingly used flexible methodology that accounts for uncertainty by combining all available external evidence as the initial belief through the likelihood function, using new data to update the evidence.[29 30] We conducted a systematic review and Bayesian meta-analysis to provide an accurate interpretation of the currently available evidence from RCTs on the preventive effect of *H. pylori* eradication on gastric carcinoma.

METHODS

This study is an updated systematic review and meta-analysis based on an evidence report that was produced for developing the Japanese Guidelines for Gastric Cancer Screening (see online supplementary methods for details).[31]

Data sources and searches

We searched PubMed, the Cochrane Central Register of Controlled Trials and Embase from inception through 31 July 2018 using search terms including "gastric cancer", "*Helicobacter pylori*", "eradication" and their synonyms, without language restrictions. To supplement the search, we perused the reference lists of eligible studies and relevant review articles. We also examined the titles and abstracts of all articles citing at least one of the publications already included, found through the citation-tracking functions of Web of Science, Scopus and Google Scholar (see online supplementary methods).

Study selection

Paired reviewers, drawn from the group of seven investigators (TT, CH, KK, IM, TY, RT, and HN), independently screened non-overlapping sets of abstracts and full texts of potentially eligible studies. RCTs that compared eradication therapies for *H. pylori* with placebo or no treatment in asymptomatic or otherwise healthy, dyspeptic *H. pylori*-infected adults (aged ≥18 years) with no history of gastric carcinoma were eligible. We allowed for the inclusion of 'otherwise healthy, dyspeptic subjects' *post hoc* because both uninvestigated and functional dyspepsia are common in Asia,[32] and the relevant RCTs had included such subjects. Trials reporting no gastric carcinoma events were excluded. We included trials published as full text only. Disagreements were resolved by consensus. Full details of the inclusion criteria are described in the online supplementary methods.

Data extraction

One reviewer (TT) extracted trial, subject and intervention characteristics from each eligible paper; another (KK) verified the data. If the paper with the longest follow-up period did not report the relevant information but cited earlier publications, we extracted data from the cited publications (see online supplementary methods).

Our primary outcome was the incidence of gastric carcinoma; non-carcinoma tumours (eg, lymphomas or sarcomas) were excluded. Our secondary outcomes were gastric carcinoma-specific mortality, non-gastric carcinoma mortality and all-cause mortality. Two reviewers (TT, IM) independently extracted the number of randomly allocated participants as the intention-to-treat analysis population, excluding any mistakenly enrolled ineligible subjects[26 33] as well as the numbers of gastric carcinoma events, deaths from gastric carcinoma and other causes, and censored subjects as missing outcome data (MOD) for each arm from the publications with the longest follow-up. Censored subjects included those lost to follow-up for interim exclusion due to protocol deviation, non-compliance and withdrawal.[34] Disagreements were resolved by consensus. For any missing information or unresolved discrepancies, we contacted the authors of the primary studies for clarification or to request unpublished data. We considered the request rejected if two emails received no response.

Assessment of risk of bias

Two independent reviewers (TT, TY) analysed sequence generation; allocation concealment; blinding of participants; trial personnel and outcome assessment; incomplete outcome data; selective reporting and other biases using the Cochrane Collaboration's Risk of Bias tool.[35] The kappa coefficient for inter-rater agreement was

0.76, indicating good agreement.[36] Disagreements were resolved by consensus.

Data synthesis

We calculated summary HRs and their 95% credible intervals (CrIs) and prediction intervals (PrIs),[30 37] using a hierarchical Bayesian random-effect meta-analysis method for competing risk time-to-event outcomes.[38 39] For gastric carcinoma incidence, we modelled the baseline and relative hazard rates for gastric carcinoma events, non-gastric carcinoma deaths and MOD as mutually exclusive outcomes and their respective random-effect parameters in a single analysis; we assumed that no cases of gastric carcinoma later died from a cause other than gastric carcinoma. For analysing gastric carcinoma-specific and non-gastric carcinoma mortality, deaths from gastric carcinoma, deaths from all other causes and MOD were simultaneously modelled as mutually exclusive outcomes with their respective random-effect parameters. As a sensitivity analysis, we calculated summary ORs for cumulative gastric carcinoma incidence as a binary outcome. For MOD and non-gastric carcinoma deaths, we applied hierarchical Bayesian random-effect meta-analytic models using the conventional imputation methods for binary outcomes,[26] and models directly allowing for uncertainty due to missing data.[40]

After conducting the analyses based on three alternative prior distributions on the between-trial standard deviations (tau), we selected the context-specific informative prior distributions in the main analysis.[41] We determined this *post-hoc* selection since the data from only seven RCTs were deemed to be insufficient to inform multiple between-trial variance parameters using the other two conventional, less informative priors.[24 39] For each model in the Bayesian meta-analysis, we based results on 3 different chains and 100 000 iterations following a burn-in of 100 000 iterations. We considered nodes to have converged when the Brooks-Gelman-Rubin statistic was <1.010.[24] The online supplementary methods provide complete details of the methodologies, model fitting, choice of prior distributions for the parameters and the operational definitions used in the sensitivity analysis.

We assessed the certainty of evidence for each outcome using the Grading of Recommendation Assessment, Development and Evaluation approach.[42] We quantified between-study heterogeneity using the *tau* and I^2 statistics with their 95% CrIs.[43] To examine how each trial affected the summary estimate of the other RCTs, we performed a leave-one-out meta-analysis by calculating summary estimates iteratively, excluding one trial at a time.[44] We did not perform the planned tests for funnel plot asymmetry because eligible studies were <10.[45] To explore clinical heterogeneity, we performed trial-level subgroup analyses and univariable meta-regressions according to geographic location (East Asia vs other countries), research setting (community vs outpatient) and subject selection (all invited subjects regardless of baseline gastric histology vs those with specific histological subtypes).[44 46] All analyses were conducted using Stata/SE V.14.2 (Stata Corp) and WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK). P values for all comparisons were two tailed, and statistical significance was defined as p<0.05.

Patient and public involvement

Although this study had no direct patient involvement, we modified the systematic review protocol based on input and feedback from the public regarding draft guidelines containing a set of interim results.[31]

RESULTS

Literature search and eligible studies

After abstract-level screening of the main searches, citation index searches and citations identified from other sources, we reviewed the full texts of 42 potentially eligible published articles (online supplementary figure 1). After exclusions and review of unpublished data provided by the authors, 7 independent RCTs reported in 16 publications were ultimately eligible.[8 47–61] We excluded the long-term follow-up reports from one RCT[62 63] because of a possibility of treatment contamination due to crossover (64% of participants in the control group received eradication therapy after 6 years of follow-up). The online supplementary results provide full details of the study selection and excluded studies.

Study and clinical characteristics

The seven RCTs—five from China,[8 47 55 56 61] one from Japan,[60] and one from Colombia[58]—included 7303 *H. pylori*-infected adults without gastric carcinoma, as confirmed by upper endoscopic examination (online supplementary table 1). Two population-based RCTs[47 55] and one outpatient care trial[60] explicitly included participants with dyspeptic symptoms in addition to asymptomatic subjects. The other trials, three population-based[8 56 58] and one outpatient care-based RCT,[61] did not report on symptoms at enrolment. One RCT diagnosed *H. pylori* infection by serological testing only.[8] Four trials used a parallel design,[47 55 60 61] whereas the other three adopted factorial designs with cointerventions of vitamins[58]; vitamins, selenium and garlic extract[8]; or celecoxib, a cyclooxygenase-2 inhibitor.[56] Two RCTs focused on populations with specific precancerous lesions based on pre-enrolment histology results.[56 58] The follow-up duration extended beyond 10 years in only two trials.[8 55]

Gastric carcinoma incidence was the primary outcome in only one RCT.[47] Another long-term follow-up report from the largest trial cohort reported gastric carcinoma as the *post hoc* primary outcome.[8] No trials defined gastric carcinoma-specific mortality or all-cause mortality as their primary outcomes before conducting the study. Methods used to confirm the outcomes were non-uniform. Four RCTs periodically performed endoscopic gastric surveys with biopsies of multiple sites[8 55 58 60]; the other three scheduled similar routine gastric surveys only once.[47 56 61] Three trials also examined patients' clinical records, the regional cancer registry and/or death certificates to identify gastric carcinoma cases and death events.[8 47 56]

The sample sizes ranged from 236 to 2258 (median, 852) subjects with an average age of 42–53 years (online supplementary table 2). Precancerous gastric lesions at enrolment varied across trials; one trial that enrolled subjects with advanced gastric lesions reported gastric dysplasia in 54% of the participants.[56] The adopted eradication algorithms also varied. Two trials repeated first-line therapy for non-responders,[8 60] two provided no salvage therapy[55 56] and one employed dual combination therapy.[8] While the post-treatment eradication rates assessed at 1–72 months ranged from 72% to 89%, follow-up eradication rates at 7–12 years were approximately 50%, suggesting recurrence or reinfection.[8 55 62] The baseline incidence of gastric carcinoma ranged from 107 to 1802 per 100 000 person years. The two RCTs of populations with specific histological findings reported the lowest and second lowest incident rates.[56 58] Gastric carcinoma events were missing in 565 (15%) and 543 (15%) participants in the eradication and control arms, respectively.

Assessment of risk of bias

Overall, only one RCT, a long-term follow-up report of the largest trial,[8] was deemed to have a low risk of bias (online supplementary figure 2 and table 3). Only two RCTs used the proportional hazard model to analyse time-to-event outcomes—one for gastric carcinoma incidence,[56] the other for mortality.[8]

Incidence of gastric carcinoma

A total of 7 RCTs, including 7303 adults, observed 138 gastric carcinoma events (table 1). They failed to observe the primary outcome in 369 subjects who died from non-gastric carcinoma causes and in 649 subjects with MOD. Although the summary estimates showed a 35% risk reduction for gastric carcinoma associated with eradication therapy, the upper limit of the 95% CrI included 1, the null effect, suggesting inconclusive average preventive effects of eradication therapy on gastric carcinoma risk (HR=0.65 (95% CrI 0.41 to 1.0; 95% PrI 0.30 to 1.33); I^2=11% (95% CrI, 1% to 54%); *tau*=0.21; low certainty) (figure 1). The certainty of the evidence was downrated because of imprecision due to the small number of events and limited clinical applicability in current practice due to unsatisfactory eradication strategies and frequent reinfection. Wide CrIs for I^2 and *tau* also suggested the possibility of statistical heterogeneity. The online supplementary results provide detailed descriptions of the model fitting.

Gastric carcinoma-specific mortality

A total of 3 community-based RCTs (4400 adults) provided data on deaths from gastric carcinoma (table 1). Although gastric carcinoma-specific mortality was reduced on average by 41%, its uncertainty included both clinically important mortality benefit and risk increases (HR=0.59 favouring eradication therapy (95% CrI 0.25 to 1.20; 95% PrI 0.18 to 1.63); I^2=13% (95% CrI 1% to 66%); *tau*=0.26; low certainty) (figure 1). Concerns about precision due to the wide CrIs and indirectness due to the adoption of inadequate eradication strategies downgraded certainty.

All-cause mortality and non-gastric carcinoma mortality

A total of 5 community-based RCTs (6316 adults) contributed data on deaths from all and non-gastric carcinoma causes (table 1). Overall, there was no evidence that eradication therapy increased or decreased all-cause mortality (HR=0.97 favouring eradication therapy (95% CrI 0.69 to 1.28; 95% PrI 0.55 to 1.56); I^2=20% (95% CrI 2% to 68%); *tau*=0.15; low certainty) or mortality from causes other than gastric carcinoma (HR=1.03 favouring control (95% CrI 0.71 to 1.41; 95% PrI 0.54 to 1.80); I^2=21% (95% CrI 1% to 76%); *tau*=0.16; low certainty) (figure 1). Certainty was downrated because of the wide CrIs that included a clinically important mortality benefit and increase.

Subgroup analysis

The subgroup meta-analysis for trials conducted in East Asia found an average reduction in gastric carcinoma risk of 38% (six trials; HR=0.62 (95% CrI 0.37 to 0.98; 95% PrI 0.27 to 1.33); I^2=13% (95% CrI 1% to 60%); *tau*=0.22; relative HR=0.95 (95% CrI 0.19 to 6.57)). A higher risk reduction was suggested in the subgroup analysis in which the two trials of populations with specific histological findings were excluded (five trials; HR=0.55 (95% CrI 0.30 to 0.89; 95% PrI 0.22 to 1.19); I^2=14% (95% CrI 1% to 63%); *tau*=0.22; relative HR=0.54 (95% CrI 0.15 to 1.62)) (online supplementary table 4). The metaregression analyses showed no differential effects by geographic location, research setting or subject selection.

Sensitivity analysis

For gastric carcinoma incidence, the CrIs for the summary HRs generally became wider, with the upper limit crossing 1, when alternative, less informative priors for *tau* were specified except for the subgroup analysis where the two trials of populations with specific histological findings were excluded (online supplementary table 4). Similarly, the CrIs crossed 1, unless 1 of 2 RCTs for histologically selected populations was excluded in the leave-one-out meta-analysis (online supplementary figure 3). In the sensitivity analyses using the conventional Bayesian meta-analysis for binary outcomes, the summary ORs were generally congruent to the summary HRs of the main analysis. The CrIs were generally wide and crossed the null effects (ie, OR=1) regardless of the prior distributions for *tau*, the use of alternative imputation methods or models directly accounting for uncertainty to account for MOD, or exclusion of non-gastric carcinoma deaths from MOD, except for the subgroup analysis where two trials of histologically selected populations were excluded (online supplementary table 5). The summary HRs for the mortality outcomes were not materially different from the results in the main analysis when alternative priors for *tau* were used, or all seven trials were included in the sensitivity analysis (online supplementary table 4).

Table 1 Grading of Recommendation Assessment, Development and Evaluation evidence profile: *Helicobacter pylori* eradication treatment for gastric carcinoma prevention in asymptomatic or dyspeptic adults

	Quality assessment							Summary of findings					
								Number of subjects (%), event fraction			Absolute risk		
Outcome	Participants (RCTs), *n*	Median follow-up (range), *years*	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Control	Eradication therapy	HR (95% CrI)	Control, *per 100 000 person years*	Risk difference, *per 100 000 person years*	Certainty of evidence
All-cause mortality	6316 (5)	7.5 (5–14.7)	Uncertain*	Uncertain†	Serious‡	Serious§	Uncertain¶	207/3,146 (6.6)	212/3,170 (6.7)	0.97 (0.69 to 1.28)	856**	26 fewer (265 fewer to 240 more)	++◯◯*Low*
Gastric carcinoma-specific mortality	4440 (3)	10 (7.5–14.7)	Uncertain*	Uncertain†	Serious‡	Serious††	Uncertain¶	33/2,217 (1.5)	21/2,223 (0.9)	0.59 (0.25 to 1.20)	145**	59 fewer (109 fewer to 29 more)	++◯◯*Low*
Gastric carcinoma incidence	7303 (7)	6 (3–14.7)	Uncertain*	Uncertain†	Serious‡	Serious‡‡	Uncertain¶	83/3,636 (2.2)	55/3,667 (1.5)	0.65 (0.41 to 1.00)	314**	110 fewer (185 fewer to 0)	++◯◯*Low*

*Uncertainty due to large loss to follow-up relative to the small number of events, possible interaction with cotreatments and/or short follow-up.
†Uncertainty due to clinical heterogeneity (eg, inclusion of subjects with dyspepsia in addition to asymptomatic healthy adults, different recruitment sources (population based vs outpatient care based), and/or subject selection based on pre-eradication gastric precancerous lesions (subjects with specific gastric lesions only vs all participants regardless of histological results)) and possible statistical heterogeneity suggested by the broad CrIs for I^2 and *tau*.
‡Unsatisfactory eradication attempts and frequent reinfections, limiting the applicability of the results to current clinical practice.
§While the CrI for the pooled effect crossed the null effect, the plausible effects suggest both reduction and increase by 31% and 28%, respectively.
¶Not assessed due to the small number of eligible RCTs.
**Control-group incident rates based on Ma *et al* 2012.[8]
††While the CrI for the pooled effect crossed the null effect, the plausible effects suggest both reduction and increase by 75% and 20%, respectively.
‡‡While the upper boundary of the CrI reached the null effect, the plausible average effects include risk reduction by as high as 59%.
CrI, credible interval; RCT, randomised controlled trial.

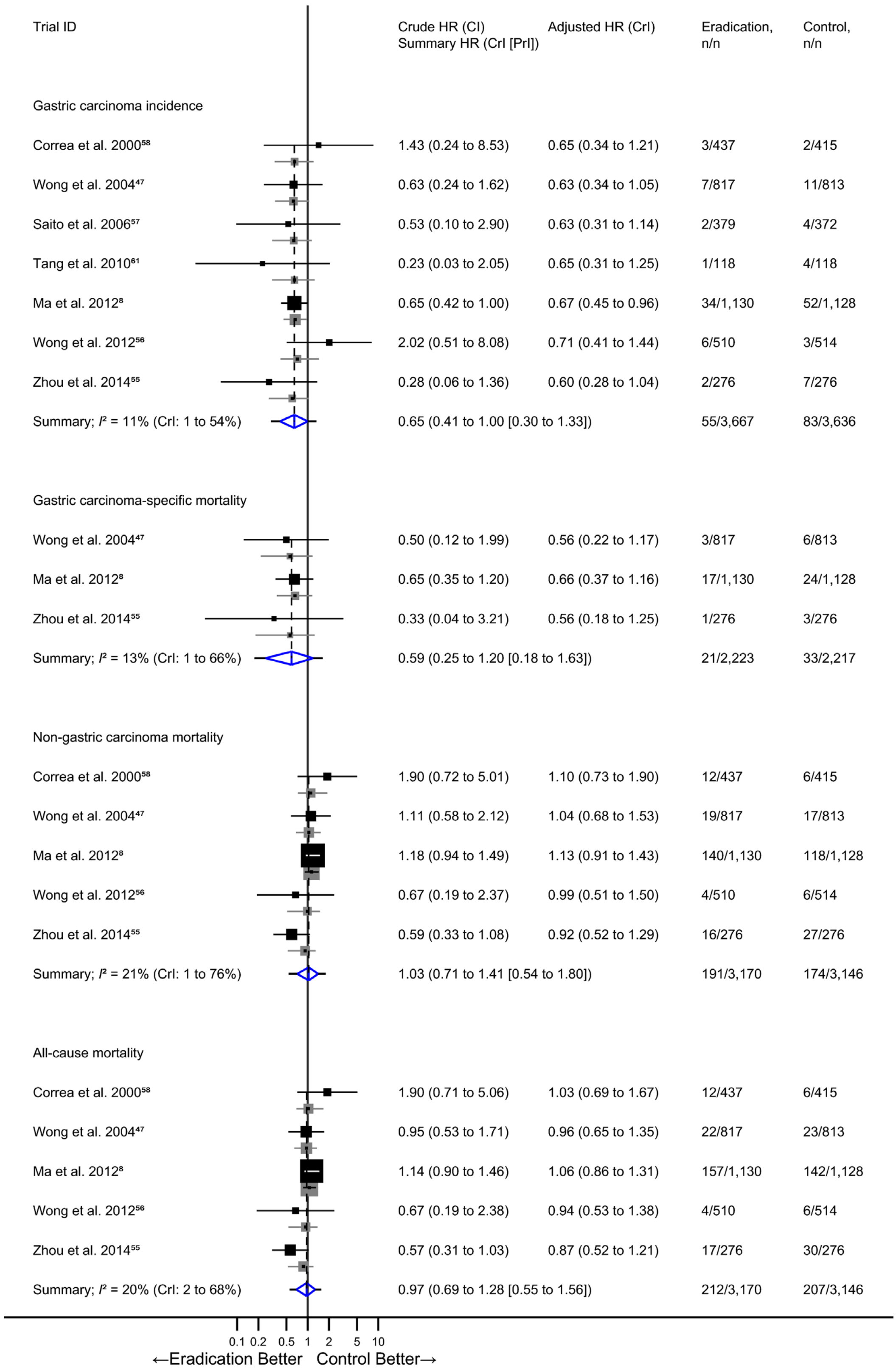

Figure 1 Effect of eradication therapy on gastric carcinoma incidence, gastric carcinoma-specific mortality, non-gastric carcinoma mortality, and all-cause mortality in asymptomatic or dyspeptic *Helicobacter pylori*-infected adults. Diamonds represent the summary HRs centred on a combined estimate and extending to 95% credible intervals (CrIs), with estimated 95% prediction intervals (PrIs) depicted as horizontal lines. Black squares and horizontal lines indicate crude 'observed' HRs and 95% CIs. Grey squares and horizontal lines indicate 'adjusted' HRs and 95% CrIs based on the posterior distribution for individual studies. The size of the square is proportional to the inverse of the variance of the logarithm-transformed HR of each study. Studies are ordered by publication year. The colours of the CIs and CrIs for non-gastric carcinoma mortality and all-cause mortality for the study by Ma *et al*[8] are inverted. PrI, prediction interval.

DISCUSSION

Main findings

Our meta-analysis found only a low strength of evidence that *H. pylori* eradication may have been more likely than control treatment to reduce gastric carcinoma development—although the average effect suggested a risk reduction by 30%, its uncertainty included the null effects. This finding was generally consistent across subgroup and sensitivity analyses except when two factorial design trials that focused on enrolees with specific histological findings were excluded. Although we calculated a similar average effect size, our wide CrIs were not congruent with those of previous meta-analyses including the Cochrane meta-analysis that reported that *H. pylori* eradication significantly reduced gastric carcinoma risk.[9] This highlights the uncertainty surrounding the effectiveness of unfocused test-and-eradicate programme, even in high-risk regions. A recently published fixed-effect meta-analysis using risk difference as the outcome measure, although naïvely conducted, reported a non-significant risk reduction associated with eradication therapy, which raised concerns about the conclusions from previous meta-analyses.[64] The results of our Bayesian meta-analysis corroborate this finding.

The preventive effects became larger and significant—an average of 45% risk reduction—when the two factorial design trials that selected more histologically advanced lesions were excluded. This suggests that eradication therapy may be more effective in non-focused, potentially lower risk populations; this is in line with the meta-analysis of a subgroup from the primary prevention RCTs conducted by Chen *et al*.[10] The fixed-effect meta-analysis of subjects with better pre-eradication histology than intestinal metaplasia or dysplasia only, comprising only 1 case who developed gastric carcinoma out of 1221 subjects in the eradication group versus 10 cases out of 1228 in the control group, although the balance between the two groups created from randomisation might no longer hold, reported a significant 78% risk reduction (relative risk=0.22 (95% CI 0.06 to 0.86)). However, the severity of the baseline precancerous lesions across the trials could not directly be compared due to variations including the histological criteria used. Furthermore, in addition to baseline histology, other factors that affected gastric carcinoma events would exist, given the lowest baseline incidence rates in the two factorial RCTs of histologically 'high-risk' populations. For example, given the subjective nature of endoscopic evaluation in particular, 'missed' cases of gastric carcinoma at enrolment and/or during the follow-up rounds are always a concern affecting the validity of gastric carcinoma research.[65] Therefore, our observation based on subgroup analysis should be viewed as hypothesis generation.

We found that evidence on gastric carcinoma-specific and overall mortality was insufficient because the RCTs were not powered to detect differences in these outcomes. The wide CrIs for the average effect suggest that while a clinically meaningful 75% reduction in gastric carcinoma-specific mortality is possible, a 20% increase cannot be ruled out.

Our meta-analysis has several strengths. We employed Bayesian approaches to account for multiple time-to-event outcomes with competing risks and frequent censored observations. Our literature search found one RCT[61] that previous meta-analyses had failed to include. We also used data extracted from full-text publications and obtained unpublished data from two RCTs,[55 60] for which previous meta-analyses had relied on the data presented in conference abstracts[9 12] or earlier short-term reports (online supplementary table 6).[10] These additional data allowed us to perform a more comprehensive analysis than was possible in previous meta-analyses that focused on RCTs only[9 10 64] regarding across-trial differences in research settings, patient symptoms at enrolment, missing outcomes and mortality events.

Limitations

Limitations of the included RCTs other than short, incomplete follow-ups, need to be noted. The RCTs employed potentially suboptimal eradication algorithms and reported frequent rates of recurrence or reinfection. These unsuccessful eradication attempts could have affected the preventive effect. In addition, as already noted, inclusion of RCTs that allowed for the inclusion of subjects with advanced preneoplastic lesions, those at high risk for progression to gastric carcinoma,[13] might have attenuated the preventive effects. Moreover, interactions with concurrent interventions, regardless of their directions, cannot be ruled out in the three factorial design trials. Similar to previous meta-analyses,[9 10 64] our Bayesian meta-analysis could not address these limitations analytically without access to individual-level data.

In the meta-analysis of gastric carcinoma incidence, our assumption that those who developed gastric carcinoma would not die from causes other than gastric carcinoma should be clinically acceptable. Nevertheless, more accurate analysis would require individual-level data or modelling with additional assumptions for the conditional risk of non-gastric carcinoma deaths.

Implications

Given the insufficient randomised evidence, rigorously conducted large RCTs adopting stringent research methodologies would be ideal if demonstration of the true efficacy of eradication therapy is the central issue. This context would include the use of more effective eradication strategies, including accurate response assessment, better salvage therapies and meticulous longer term follow-up. Implementation of high-quality pre-enrolment gastric survey, including the strict exclusion of subjects who already have preneoplastic lesions, would be particularly relevant if healthy subjects are truly targeted. Nevertheless, challenges exist when conducting de novo long-term large high-quality RCTs of rare outcomes. Hence, the analysis of the current trends using large, clinical, practice-based registries is a realistic primary research option. If feasible, conducting individual-level consortia meta-analysis of all existing RCTs remains a viable option to repurpose the already available resources. Exploring effect modifiers for identifying subgroups that benefit most (or least) from the eradication strategy should be the highest priority.[37] Further, we should not ignore all-cause and gastric carcinoma-specific mortality and long-term adverse events as important outcomes attributable to eradication.

In conclusion, there is insufficient randomised evidence to support or refute the effectiveness of eradication therapy in preventing gastric carcinoma in *H. pylori*-infected, high-risk populations. Large RCTs of only healthy *H. pylori*-infected adults adopting more stringent research methodologies will provide evidence regarding the true efficacy of successful eradication.

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Acknowledgements The authors thank Daizo Saito, Liya Zhou and Rongli Cui for providing unpublished data from their original studies; Alexander Ford for providing additional information regarding the data extraction processes used for the Cochrane meta-analysis; Yujia Cui-Tsuzuki for translating the Chinese-language publications; and Christopher Schmid for assisting with the statistical analysis.

Contributors TT and CH conceived the initial idea, performed the literature search and are the guarantors for the study. All authors designed the study, determined the eligibility of primary studies, acquired the data, interpreted the findings and read and approved the final manuscript. TT performed the statistical analyses and drafted the first version of the report, which was critically revised by all authors.

Funding This work was supported by the Ministry of Health, Labour and Welfare, Japan. TT and CH were supported in part by the Ministry of Education, Culture, Sports, Science and Technology, Japan (No. 26460755).

Disclaimer The funding sources had no role in the design or conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; or the decision to submit the manuscript for publication.

Competing interests All authors declare no conflicts of interest associated with this publication. For complete transparency, TY reports taking grants and personal fees from Chugai Pharmaceutical Co., grants and personal fees from Taiho Pharmaceutical, grants and personal fees from Yakult, personal fees from Lilly, grants from Novartis, personal fees from Ono, personal fees from Takeda, personal fees from Nippon Kayaku Co., personal fees from Covidien, personal fees from Johnson and Johnson, personal fees from Olympus, personal fees from NPO Epidemiological and Clinical Research Information Network, personal fees from NPO KSATTS, and personal fees from NPO Cancer Net Japan, outside the submitted work.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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