AGA Institute Technical Review on Gastric Intestinal Metaplasia – Part 1

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BACKGROUND

Gastric cancer is the third leading cause of cancer-related mortality and the fifth most common cancer globally.[1] There is clear racial and ethnic and geographic variation in disease burden worldwide with populations and regions of high and low incidence.[1,2] An estimated 26,240 new cases of gastric cancer and 10,800 related deaths occur annually in the United States (US), representing 1.5% and 1.8% of all new cancer diagnoses and deaths, respectively.[3] Recent estimates confirm that the incidence and mortality rates of gastric cancer are increasing in the US among some groups, including minority populations.[3–5]

Gastric adenocarcinoma is classified by anatomic location as cardia versus noncardia and by the Lauren histologic classification as intestinal-type and diffuse-type.[6] Intestinal-type

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noncardia gastric adenocarcinoma (NCGA) develops as a stepwise progression of discrete histopathologic stages from normal mucosa to chronic nonatrophic gastritis to chronic atrophic gastritis (AG) to gastric intestinal metaplasia (GIM) and dysplasia, prior to final malignant transformation (Figure 1). Infection with *Helicobacter pylori (H. pylori)* is accepted to be the primary driver for this progression, termed the Correa cascade, although other triggers such as autoimmunity, are possible.[7–10] Risk factors for advancement along the Correa cascade are incompletely understood given that only a minority of individuals (~1–2%) will develop cancer.[11] By contrast, no precursor lesions are definitively identified for diffuse-type gastric adenocarcinoma, although mixed intestinal- and diffuse-type histology is noted in up to 10% of patients.[11] The recent NIH-funded Cancer Atlas Genome Project (TCGA) delineated molecular subtypes of gastric and confirmed both the intestinal and diffuse subtypes as distinct, as well as two lesser subtypes (EBV-associated, and Microsatellite Instability).[12] AG and GIM are precancerous lesions and are associated with an increased risk of intestinal-type NCGA (hereafter referred to as "NCGA").[13] The combination of identifiable precancerous stages and stepwise neoplastic progression offers the potential opportunity for screening and surveillance with the goal of early detection of neoplasia and opportunity for endoscopic resection, to thereby reduce disease-related morbidity and mortality.

Current US-based guidelines do not recommend endoscopic screening for NCGA nor do they recommend universal surveillance of gastric precancerous lesions for the purpose of early NCGA detection.[14]GIM is usually encountered incidentally in patients undergoing esophagogastroduodenoscopy (EGD) and biopsy for nonspecific symptoms (e.g. dyspepsia). Limited awareness of risk factors for NCGA, uncertainty regarding the risk factors for neoplastic progression of GIM, and unadjudicated risk versus benefit of GIM surveillance, have resulted in wide clinical practice variability in the evaluation and management of patients with GIM.[15,16] The American Society for Gastrointestinal Endoscopy (ASGE) and the European Society for Gastrointestinal Endoscopy (ESGE) have position statements on the management of gastric precancerous lesions, with the European guidelines based on a comprehensive review of the literature at the time (through November 2010) and expert consensus vote.[14,17] By contrast, the ASGE position statement is limited in its recommendations on GIM management without a formal systematic review of the available literature.[14] There is an unmet need for updated comprehensive guidelines for GIM management that are practical and relevant for the US population, particularly given the diversity of the population and potentially variable risk profiles for NCGA.[18,19] Our aim is to provide a systematic and comprehensive synthesis of the literature to inform the AGA guideline panel in formulating evidence-based recommendations on the management of GIM in the absence of concurrent neoplasia (dysplasia or cancer), with a focus on the potential role of *H. pylori* eradication and endoscopic surveillance.

METHODS

Overview

The technical review team systematically synthesized the literature to inform pre-defined questions proposed by the AGA guideline panel using standard systematic review

methodology. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to evaluate the certainty of evidence (also known as quality of evidence).[20] The technical review team included a GRADE methodologist (RM), and six clinical domain experts (three gastroenterologists, one pathologist, and two gastroenterology fellows with outcomes research expertise).

The AGA guideline panel identified four clinically relevant questions and the technical review team used the PICO format (population (P), intervention (I), comparator (C), and outcomes (O)) to guide the evidence synthesis. Table 1 summarizes the PICO questions, patient important outcomes, and direct and indirect evidence needed to inform the systematic review and the AGA guideline statement. The primary objective of the first PICO question ("PICO 1") was to synthesize the data assessing the need to empirically test for *H. pylori* infection (and treat if positive) in patients with GIM. The primary objectives of PICO 2 and PICO 3 were to synthesize the data informing the need for surveillance upper endoscopy once GIM is diagnosed in groups at otherwise low versus high risk for NCGA, respectively, in the US. The primary objective of PICO 4 was to synthesize the data informing the need for short-term follow up with EGD and histologic assessment in patients with GIM diagnosed incidentally on EGD.

After finalizing the PICO questions, the technical review team and the guideline panel ranked outcomes by importance and prioritized outcomes critical for decision making (Table 1). Patient important outcomes of interest included both benefits and harms such as early NCGA detection, reduced morbidity/mortality from NCGA, complications associated with endoscopy, psychological outcomes (e.g. anxiety and stress related to endoscopic surveillance, coping with a precancerous condition), and resource implications (e.g. cost of surveillance).

A comprehensive list of direct and indirect evidence needed to inform the questions was developed (Table 1). The desired evidence included incidence and prevalence data for GIM, incidence of NCGA in individuals with GIM, and risk factors associated with progression to NCGA in patients with GIM compared to individuals without GIM. This "wish list of needed evidence" guided the systematic literature search. Given the presumed paucity of robust direct data on GIM in the US, evidence from all regions of the world was considered relevant in the evidence-gathering phase. Details related to the management and natural progression of dysplasia were considered outside the scope of this technical review, unless there was clear discernible clinical relevance to outcomes of GIM.

The Systematic Review Process

We reported the systematic review and the related meta-analyses results in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statements.[21,22] The technical review team scheduled weekly meetings to conduct the systematic review and develop the GRADE evidence profiles for each PICO question.[20] The weekly meetings clarified and addressed issues that arose during the review process. Decisions were documented and input from the guideline panel was requested for key decisions.

Literature Search Strategy—In collaboration with a medical librarian, we defined a systematic search strategy and searched three electronic databases including Ovid MEDLINE ® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® from 1946; Embase Classic+Embase from 1947; and Wiley's Cochrane Library. The initial search was conducted in July 2017 and updated in September 2018. The primary search terms included "stomach," "precancerous conditions," "neoplasms," "gastric/stomach mucosa," and "metaplasia." The full literature search strategy is provided in Supplementary Table 1. Additionally, we checked the references of prior systematic reviews and guidance documents to identify additional studies that met our inclusion criteria.

Inclusion / Exclusion Criteria—We included randomized controlled trials (RCTs), prospective and retrospective cohort studies, case-control studies, and cross-sectional studies as long as they informed any PICO question. We excluded studies without data on GIM or if we were not able to separate the results by GIM status. We excluded studies that were not performed in humans or those that did not include primary data (e.g. narrative reviews, opinion pieces, letters). We excluded studies in pediatric only populations, studies conducted to evaluate the diagnostic accuracy of *H. pylori* tests, studies that compared different *H. pylori* treatment regimens, and studies that focused solely on gastric dysplasia or cancer without data on GIM. For studies that informed the incidence or prevalence of GIM, we included studies with at least 100 patients. After the data gathering phase, the threshold was modified to 250 patients due to the large number of studies identified in our search; prior to this modification, we performed a sensitivity analysis calculation that confirmed the unlikelihood that the prevalence estimates would be affected if smaller studies were included. For studies that informed the risk or rate of progression from GIM to NCGA, we included studies with at least 20 GIM patients.

We also obtained and searched the full texts of potentially relevant abstracts. If the abstract was published before 2015 and no accompanying publication was identified, we excluded the reference. For abstracts published in or after 2015, we contacted the authors to inquire about publication status and additional data; we excluded the reference if we received no response.

Study Screening and Selection—Two technical review committee members independently screened the search results for articles based on titles and abstracts. The full text-article was retrieved for any citation considered potentially relevant by any investigator. Each of the investigators then independently assessed the eligibility of each article by using a pilot-tested, standardized form with written instructions generated and maintained on the Research Electronic Data Capture (REDCap®) platform[23] hosted at The University of Kansas. If at least one of the prespecified inclusion criteria was not met, the article was excluded. Any disagreement was resolved by consensus or arbitration.

Data Items and Definitions—Due to the vast amount of literature focused on gastric cancer and *H. pylori*, but not specifically GIM, it was necessary to agree upon definitions of certain concepts prior to data abstraction in order to limit confusion and disagreement. Box 1 summarizes the definition of different concepts that were used for this review.

Histologic Staging and Scoring Systems—Gastric histologic staging and scoring systems are primarily used in research settings, since issues such as pathologist time investment and interobserver variability in histopathologic grading (e.g. differentiating moderate versus severe) limits routine clinical use. Importantly, the systems require biopsies of both the antrum and corpus *a priori*. Two systems are prominent in the literature: OLGA/OLGIM and the Correa histopathology score.

The OLGA and OLGIM are histopathologic staging standards that incorporate both the severity (mild, moderate, severe) and extent (antrum/incisura, body) of AG and GIM, respectively, and range from Stage 0 to IV.[29] Stage III/IV, which necessitate both antrum and corpus involvement (with the exception of Stage III, severe antral atrophy), are considered higher risk for neoplastic progression.[25,30–32] These stages are derived from the semiquantitative scoring of AG or GIM on a Sydney System-compliant set of gastric biopsies, including biopsies from at least the gastric corpus and antrum. Epidemiology data as well as a recently published meta-analysis of prospective case-control studies support an increased risk of gastric cancer in OLGA/OLGIM Stage III/IV.[32]

The Correa histopathology score has been shown to correlate with the OLGA/OLGIM system.[33] It is an ordinal system that incorporates data on GIM extent and complete/incomplete GIM status. The Correa histopathology score is useful for progression/regression analyses in cohort studies.

Categorization of Population Subgroups—We defined certain population subgroups to assess risk of developing GIM and of GIM progression. The subgroups were selected *a priori* based on discussion with the guidelines panel and established risk factors for NCGA. These categorical subgroups included: race and ethnicity, first-degree family history of gastric neoplasia, smoking history, concomitant autoimmune gastritis, concomitant pernicious anemia, histologic features (e.g. incomplete versus complete GIM), topographic extent of GIM (extensive versus limited), and specific biomarkers. Given the limited and highly heterogeneous biomarker data, the technical review team in consultation with the guidelines panel unanimously agreed to formally evaluate only biomarkers with potential clinical relevance; this ultimately included established *H. pylori* virulence factors (CagA, VacA) and pepsinogen. These determinants were used to inform risk stratification into "high risk" and "low risk" groups for PICO 3 and 4; having at least one risk factor was considered "high risk".

Data Collection Process—We abstracted data using a separately constructed, pre-piloted and standardized form generated and maintained on the REDCap platform. The form was tailored according to study design and tailored to abstract data relevant to the PICO questions. We abstracted the following data: baseline demographics and characteristics of the patients included in the studies, the management they received, clinically relevant outcomes and outcome measures.

We assessed methodologic quality. We also abstracted data for the pre-defined subgroups above. Two investigators independently abstracted all relevant data from each included study. The results of data abstraction were then compared and any discrepancies were

resolved by discussion and consensus or arbitration. When the same results were presented in more than one publication, we collated and summarized the data from all relevant publications and available time points. If results were incomplete or unclear, we contacted study authors for additional information. In cases of non-response, we included the study in the systematic review but not in the statistical pooling in the meta-analyses. Data abstraction for dysplasia or gastric cancer were beyond the scope of this technical review.

Summary Measures—For comparative binary outcomes, such as the risk of developing NCGA in patients with GIM who were treated versus not treated for *H. pylori* infection, we used relative risks (RR) to compare the different interventions. When the outcomes were reported as person-time, we used the incidence rate ratio (IRR). For estimating the incidence of progression from GIM to NCGA, we used the incidence rate (number of events per person-time unit) and, if not reported, the cumulative incidence (number of events over a specified period). The prevalence of GIM was reported as the proportion of patients with GIM in the population of interest (population at risk) for each study.

Statistical Analysis and Synthesis of Results—For comparative studies, we expected these to originate from heterogeneous populations and therefore used the DerSimonian-Laird random-effects model to pool the relative risks and incidence rate ratios. [34] For prevalence and incidence data, we used the Freeman-Tukey transformation and then pooled the results using the inverse variance fixed-effects model. [35,36] We elected to use the fixed-effects model despite our anticipation of heterogeneity between the studies, as we presumed that larger studies would likely be more representative and inclusive versus smaller studies. To assess the robustness of our model, we performed sensitivity analyses using the generalized linear mixed models and random-effects models. [37] We used the I^2 statistic to quantify statistical heterogeneity. [38] When subgroups were presented as binary outcomes in individual studies, we pooled them as RR or IRR as appropriate. When the subgroups were presented as proportions of the population of interest, we pooled them as proportions and compared them using interaction tests. [38] If sufficient studies were available for an outcome with no significant statistical heterogeneity, we assessed for publication bias using asymmetry tests and visual inspection of funnel plots. [38] The statistical analyses were conducted using the package meta in R version 3.4.4. [38]

Risk of Bias and Quality of Evidence—We used the Cochrane Collaboration's tool for assessing the risk of bias in RCTs. [39] For comparative non-randomized observational studies, including cohort studies, case-control studies, and cross-sectional studies, we used a modified Newcastle-Ottawa Scale for quality assessment. [40] For studies of prevalence or incidence, we used the pertinent Joanna Briggs Institute tool. [33] We used RevMan statistical software to produce risk of bias summaries and tables. [40]

We used the GRADE framework to evaluate the certainty (quality) of the body of evidence for each outcome. The quality assessment is a reflection of certainty and confidence in the evidence and can be categorized as: very low, low, moderate, and high certainty. Evidence from RCTs starts as high certainty and then can be downgraded according to the risk of bias, inconsistency, imprecision, indirectness, or publication bias. [41] Evidence originating from observational studies starts as low certainty, and can be downgraded according to the same

domains as RCTs. The certainty of evidence from observational studies, with no concerns about study validity, can also be upgraded if there is dose-response relationship, large magnitude of effect or if all plausible confounders and bias would reduce a demonstrable effect. The quality of evidence for studies of prevalence or incidence starts as high, regardless of study design, and follows the same gradation rubric as detailed above.

RESULTS

A total of 3716 articles were identified in the literature search, from which 3136 articles were excluded after removal of duplicates, conference abstracts without full text publication and title/abstract screening. The full texts of 580 articles were reviewed for eligibility. Of these, 329 studies were excluded for not meeting full inclusion criteria. Thus, we abstracted data from 121 articles. Figure 2, summarizes the PRISMA flow diagram of the studies screened and included in this review. The baseline characteristics and risk of bias of the individual studies, the results of the meta-analyses, and the quality of evidence are summarized below according to the relevant PICO question(s). Detailed risk of bias summaries for all studies are available in Supplementary Figure 1, Supplementary Figure 2, Supplementary Figure 3, Supplementary Figure 4, Supplementary Figure 5, Supplementary Figure 6.

PICO 1: In patients with GIM does testing and treating for *H. pylori* vs no testing and treating affect patient-important outcomes?

The benefit of *H. pylori* testing and treatment has been established and addressed previously for NCGA prevention and for the management of dyspepsia.[42] The specific focus of PICO 1 was to identify direct evidence to assess the effects of testing for and treating *H. pylori* infection, when diagnosed, in *patients with GIM* when compared to a no empiric testing and treatment strategy. Among *H. pylori*-related studies meeting inclusion criteria, only those studies which specifically included patients with GIM were included to answer this question. Studies which assessed the effect of *H. pylori* treatment on the different outcomes (e.g. NCGA incidence) but did not specify the inclusion of GIM patients, were excluded to limit heterogeneity and potential for bias. We acknowledge that the analysis focuses on the efficacy of the primary intervention of an *H. pylori* treatment regimen versus placebo, but not necessarily *H. pylori* infection status over the entire time course nor at the time of the endpoint of interest. To this end, confirmation of eradication following *H. pylori* treatment was variably documented. Table 2 summarizes the included studies that informed PICO1.

Of the 121 studies included for this technical review, 22 studies informed PICO 1 (Figure 2). This included 7 RCTs and 3 cohort studies.[43–55] Three large studies with multiple related publications and timepoints were included, and due to their complexity, warrant further description below:

1. Shandong Intervention Trial

   This RCT was conducted in China (Linqu County) across 14 villages.[43,44,48] Individuals were invited to participate in a gastric cancer screening program with EGD and gastric biopsies (antrum and corpus). Participants (N=4326) age 35–64

years were randomized in a 2^3 factorial design to one of three interventions: treatment for *H. pylori* infection vs. vitamin C/vitamin E/selenium dietary supplementation vs. garlic dietary supplementation.

2.   Yantai County Trial

This RCT was conducted in 11 rural villages in Yantai County, China.[49–52] Individuals age 16–75 years were invited to participate in a gastric cancer screening program with EGD and gastric biopsies (antrum and corpus). Participants (N=587) were also randomized to *H. pylori* treatment vs. placebo.

3.   Colombia Chemoprevention Trial

This RCT included individuals (N=852) from Colombia with gastric precancerous lesions who were randomized to receive *H. pylori* treatment with vs. without antioxidant supplementation.[56–58] At the end of six years of intervention, those who did not receive *H. pylori* treatment were offered treatment. After the intervention, 795 adults were followed prospectively. Endoscopy with gastric biopsies (antrum and corpus) was performed at study entry and at 3, 6, 12 and 16 years of follow up. Although the publications did not specify the number of patients with GIM in each arm, the authors provided us with the necessary data for risk estimates when we contacted them.

A summary of the pooled estimates of effect for *H. pylori* testing and treatment is shown in Table 3 and Figures 3–6 according to patient outcomes. These are further summarized below:

Mortality (All cause and gastric cancer-related)

Among patients with *H. pylori* infection, including patients with or without GIM, based on data from three RCTs (N= 2199), the relative risk of all-cause mortality was 1.07; 95% CI: 0.88–1.31 for those patients who received *H. pylori* treatment compared to placebo) (Figure 3a, low certainty in evidence).[43,44,48,53,54] Conversely, based on data derived from 2 RCTs (N=1941), among patients with *H. pylori* infection including patients with or without GIM, the relative risk of gastric cancer-related mortality was 0.67; 95% CI: 0.38–1.17 compared to placebo (Figure 3b, low certainty in evidence).[43,44,48,53]

Risk of incident gastric cancer

Data were available from 6 total studies[43,44,49–54,56,59] that each included patients with or without GIM (N=8,532); 3 studies[43,44,48,54,56] reported results limited only to patients with GIM (N=1,613). Among patients with *H. pylori* infection with or without GIM, *H. pylori* treatment was associated with a lower risk of incident gastric cancer compared to placebo (RR 0.68, 95% CI: 0.48–0.96) (Figure 4a, moderate certainty in evidence).

Among patients with *H. pylori* infection and confirmed GIM, compared to placebo, *H. pylori* treatment trended toward a lower risk of incident gastric cancer but this was not statistically significant (RR 0.76; 95% CI: 0.36–1.61) (Figure 4b, low certainty in evidence).

Risk of progression to worse global histology (from baseline)

Data were available from 4 studies that reported discrete data on progression to worsened global histology (based on the Correa histopathology cascade) from baseline enrollment; 3 of these studies included patients with or without GIM (N=3,019)[43,44,46,48,54] and 2 studies included data limited only to patients with GIM (N=1,044).[43,44,48,60] Among patients with *H. pylori* infection with or without GIM, *H. pylori* treatment trended toward lower risk of histological progression, but this was not statistically significant (RR 0.91; 95%CI: 0.83–1.00) (Figure 5a, moderate certainty in evidence).

Conversely, among patients with *H. pylori* infection and confirmed GIM, *H. pylori* treatment was associated with a 17% higher risk of progression to worse histology compared to placebo (RR 1.17; 95%CI: 1.01–1.36) (Figure 5b, moderate certainty in evidence). Notably, these estimates were driven by data from the same trial, the Shandong Intervention Trial.

Risk of regression to improved global histology (from baseline)

Data were available from 3 studies that reported discrete data on regression to improved global histologic diagnosis from baseline enrollment; 2 of these studies included all patients with or without GIM (N= 3,019) and 1 study included data limited only to patients with GIM (N=992).[43,44,46,48,54] Among patients with *H. pylori* infection with or without GIM, *H. pylori* treatment, *H. pylori* treatment was associated with a higher likelihood of regression compared to placebo (RR 1.29; 95%CI: 1.12–1.48) (Figure 6a, moderate certainty in evidence).

Similarly, among patients with *H. pylori* infection and confirmed GIM, *H. pylori* treatment was associated with a higher likelihood of regression compared to placebo (RR 1.55; 95%CI: 1.03–2.33) (Figure 6b, low certainty in evidence). Notably these estimates were informed by a single trial, the Shandong Intervention Trial.

Summary

The evidence profiles and effect estimates for PICO 1 were driven mainly by the three large RCTs, all of which were conducted in countries of high *H. pylori* prevalence and high NCGA incidence. Due to the few number of events (gastric cancer development in patients with GIM) the confidence intervals are wide. However, there were protective effects for the key outcomes of gastric cancer-related mortality (irrespective of histology) and incident gastric cancer (irrespective of histology as well as among patients confirmed to have GIM) in patients who received treatment for *H. pylori* infection versus placebo. It is important to acknowledge that the *H. Pylori* test sensitivity varies for each modality and depends both on the test itself but other factors including the use of proton-pump inhibitors and the density of H pylori colonization, for example. One recent small study found that of 19 subjects who had gastric biopsies containing H pylori DNA, only 12 tested positive for H pylori by conventional testing.[61]

Further analyses of surrogate outcomes such as progression to worse global histology or regression of GIM after *H. pylori* treatment showed inconsistent results. Specifically, among patients with GIM in a single trial, eradication of *H. pylori* was associated with both

increased risk for progression to worse histology (RR 1.17; 95%CI: 1.01–1.36) as well as increased risk of regression to *improved* histology (RR 1.55; 95%CI: 1.03–2.33). These paradoxical findings leave uncertainty with regard to the potential mechanisms of the observed reduced risk for incident gastric cancer among patients with GIM, and contribute to the moderate quality of evidence to support our recommendations for *H. pylori* testing and eradication. One hypothesis could be that the higher risk estimate for global histologic progression among patients with GIM who receive *H. pylori* treatment versus placebo, which is distinct compared to the protective risk estimate among all patients irrespective of histology, supports the generally accepted theory that some patients with GIM are "past the point of no return" in the Correa cascade (Figure 1); for reasons that are poorly understood, these patients remain at risk for neoplastic progression irrespective of *H. pylori* infection status. For similarly poorly understood reasons, regression to improved histology does appear possible in a subset of patients with GIM.

PICO 2: In patients with GIM who are identified as low risk for NCGA, does subsequent surveillance upper endoscopy with biopsies vs no follow up affect outcomes?

PICO 3: In patients with GIM who are identified as high risk for NCGA, does subsequent surveillance upper endoscopy with biopsies vs no follow up affect patient-important outcomes?

GIM is an established precancerous precursor lesion for intestinal-type gastric adenocarcinoma; unfortunately, it is currently not possible to definitively predict who will progress to gastric neoplasia. Surveillance of people with GIM might allow for the earlier diagnosis of neoplasia when endoscopic or surgical resection is curative. Whether GIM surveillance is associated with this and other patient important outcomes, particularly in a low incidence region, such as the US, is not established. Furthermore, whether outcomes of GIM surveillance are distinct for patients deemed higher risk versus lower risk for NCGA is also not established but would be important for informing surveillance recommendations and intervals. Because categorization as "high-risk" or "low-risk" is somewhat arbitrary, a complementary focus of PICO 2 and PICO 3 was to provide evidence-based guidance for risk-stratification based on predefined risk determinants (e.g. family history, racial / ethnicity background, smoking history, pernicious anemia or autoimmune gastritis, GIM topographic extent, GIM histologic subtype, predictive biomarkers), and the magnitude of association with progression of GIM to neoplasia.

The ideal studies to inform these two questions would be RCTs or prospective cohort studies with comparator arms. Unfortunately, our comprehensive systematic literature search yielded no studies that compared patient important outcomes of endoscopic GIM surveillance versus no surveillance among patients considered low-risk (PICO 2) or high-risk (PICO 3) for gastric cancer. Therefore, the technical review team and guidelines panel reached consensus regarding which indirect evidence would be informative including:

- The overall prevalence of GIM in order to determine the population burden of GIM.

- The overall risk of neoplastic progression (or global regression) of GIM without concomitant dysplasia.

- The overall risk of neoplastic progression (or global regression) of GIM without concomitant dysplasia stratified by presence or absence of predefined risk determinants.

Risk of progression of GIM to any dysplasia, high grade dysplasia, or gastric cancer (overall)

A total of 3 cohort studies,[62–64] which included 1184 patients with GIM with 8439 patient-years of follow up time, reported on the global progression of GIM to any dysplasia. The fixed-effects pooled incidence rate was 97.9 (95% CI: 77.3–120.0) dysplasia cases per 10,000 person-years follow-up time (Figure 7, low certainty of evidence). No studies were available from the US.

The cumulative incidence of dysplasia at 3-years and 5-years were both 15% based on studies from outside the US.[43,44,48,60,62,65–67] (Figure 8, very low certainty of evidence) In the Shandong Intervention Trial, among patients with GIM, the cumulative incidence of dysplasia at 7-years was 38%. One study from the US which enrolled 79 patients with GIM at the outset, reported no cases of dysplasia in 36 patients followed out to 8 years (cumulative incidence 0; 95% CI: 0.0–9.7%).[28] The cumulative incidence of high-grade dysplasia or gastric cancer among GIM patients at 5-years was 2.7% (95% CI:1.8–3.8) based on 2 non-US studies.[66,67] (Figure 9, very low certainty of evidence)

A total of 10 cohort studies, which included 25,912 patients with GIM with 159,756 patient-years of follow-up time, reported on the natural progression of GIM (without concomitant diagnosis of dysplasia) to gastric cancer. The fixed-effects pooled incidence rate was 12.4 (95% CI 10.7–14.3) gastric cancer cases per 10,000 patient-years' time (Figure 10a, low certainty in evidence). Two of these studies included US populations only (Reddy 2016, Li 2016); the rate of gastric cancer among US-based patients with GIM was 8.2 cases (95% CI: 5.1–12.0) per 10,000 patient-years' time (Figure 10b, low certainty of evidence). We performed a sensitivity analysis excluding gastric cancer cases diagnosed within 1 year of GIM diagnosis as these could be considered to be prevalent cases missed at the prior endoscopy. Of the two US-based studies, only one reported a case of gastric cancer at 7 months after the endoscopy diagnosing GIM, with all other cases being diagnosed after 1 year.[68] Exclusion of this patient from the events and total number of patients with GIM resulted in no significant change to the pooled estimates.

Among patients with GIM, the cumulative incidence of gastric cancer at 3-years, 5-years, and 10-years was 0.4%, 1.1%, and 1.6%, respectively (Figure 11, 3-years: very low certainty of evidence; 5-years: low certainty of evidence; 10-years: very low certainty of evidence). Only one of these studies was from the US (0.9% 5-year cumulative incidence).[68]

Risk of progression of GIM to dysplasia or gastric cancer (subgroup analyses)

We identified comparative studies which informed the risk of neoplastic progression among patients with GIM in the presence versus absence of our pre-specified risk determinants (i.e.

race and ethnicity, first-degree family history of gastric neoplasia, smoking history, concomitant autoimmune gastritis, concomitant pernicious anemia, histologic features (e.g. incomplete versus complete GIM), topographic extent of GIM (extensive versus limited), and specific biomarkers) as available based on the systematic literature search.

For progression of GIM according to race and ethnicity, we considered studies that were from North America and that reported on GIM progression to gastric cancer stratified by racial and ethnic background (non-Hispanic white, black, Hispanic, Asian, and other). One study from Canada reported only on Asian populations and included mostly immigrant populations[69], while the two studies from the US included Asian, non-Hispanic white, black, Hispanic, and "other" racial or ethnic subgroups. Meta-analysis of these studies revealed no significant difference in GIM progression according to race or ethnicity on subgroup interaction test. (Figure 12, very low certainty of evidence).

Four studies[60,68–70] reported data on GIM progression to gastric cancer according to family history, only one of which was from the US. Among patients with GIM, having a history of a first-degree relative with gastric cancer was associated with over 4.5-fold higher odds (OR 4.53, 95% CI: 1.33–15.46) of gastric cancer compared to patients with GIM and a negative family history (Figure 13, very low certainty of evidence).

Seven studies, all non-US based, reported data on GIM progression to dysplasia or cancer according to histologic subtype. Among patients with GIM, incomplete GIM was associated with a 3.3-fold (RR 3.33, 95%CI: 1.96–5.64) higher risk of incident gastric cancer compared to complete GIM during follow-up ranging from 3–12.8 years (Figure 14a, low certainty of evidence). Four studies[60,65,71,72] reported on the risk of dysplasia in a total of 472 patients with incomplete versus complete GIM; overall, there was a 1.7-fold higher risk of progression to dysplasia in patients with incomplete versus complete GIM (RR 1.7, 95% CI: 0.8–3.7) (Figure 14b, low certainty in evidence). As noted, histologic subtyping for GIM is not routinely done in the US and is reflected in the dearth of US-based studies on the topic.

Two studies[68,73] informed the relative risk of neoplastic progression in patients with extensive versus limited topographic extent of GIM according to our prespecified definitions, with extensive GIM associated with a nonstatistically significant 2-fold increased risk of progression compared to limited GIM (RR 2.07, 95% CI: 0.97–4.42) (Figure 15, very low certainty of evidence). Only one study, which was from the US, informed the risk of GIM progression to gastric cancer among patients with versus without a history of tobacco use and found no difference in risk of progression, albeit based on limited data (RR 1.03; 95% CI: 0.26—4.08) and with no other details for smoking status provided (Figure 16, very low certainty in evidence).[68]

Other than for histologic subtype of GIM, no data on progression of GIM to *dysplasia* according to the pre-defined subgroups were available.

No data were available for risk of progression according to history of pernicious anemia or autoimmune gastritis. Biomarker data were abstracted but significant heterogeneity precluded meaningful meta-analysis; currently no biomarkers are approved nor readily available for the purpose of gastric preneoplasia diagnosis, prognosis, and management. One

study by Plummer et al. did report on the severity of gastric mucosal lesions according to *H. pylori* CagA[+] versus *H. pylori* CagA- status, as well as compared to uninfected patients. Among 268 *H. pylori* infected patients, CagA seropositivity showed a 'dose-response' as the grade of the lesion increased; that is, there was a 2.7-fold (OR 2.71, 95% CI: 1.46–5.04), 3.2-fold (OR 3.15, 95% CI: 1.71–5.82), 7.4- (OR 7.35, 95% CI: 3.45–15.6) to 14-fold (OR 14.0, 95% CI: 6.22–31.4) and 16.7-fold (OR16.7, 95%CI: 7.75–35.9) higher odds of atrophic gastritis, complete intestinal GIM (type I), incomplete GIM (type II/III), and dysplasia, respectively, among patients infected with *H. pylori* CagA+ versus *H. pylori* CagA-. Notably, a similar magnitude of 'dose-response' was seen in *H. pylori* CagA+ infected patients compared to uninfected controls; however, among *H. pylori* CagA- infected patients, there was a higher likelihood of chronic gastritis but not more advanced lesions compared to uninfected controls.[62]

Global histologic regression of GIM to normal mucosa or (non)atrophic gastritis

A total of 15 cohort studies reported on the global regression of GIM to normal mucosa or non-atrophic gastritis. The fixed-effect cumulative risk of regression in patients with GIM at 1-year, 3-years, 5-years, and 10-years was 29.7% (95% CI: 24.5–35.2%), 19.4% (95% CI: 17.4–21.4%), 25.9% (95% CI: 23.7–28.2%), and 19.4% (95% CI: 7.9–34.2%), respectively. Only one study was from the US, which reported similar estimates overall (Figure 17, very low certainty of evidence). There were no data on risk of regression according to the predefined risk determinants.

PICO 4: In patients with GIM without dysplasia, does short-term follow up (< 1 year) to determine the extent of gastric preneoplasia (using biopsies) vs no short-term follow up affect patient-important outcomes?

The histologic extent of gastric preneoplastic lesions (AG, GIM) is generally accepted to be an important risk factor for neoplastic progression, although robust supporting data and effect estimates are limited. Accurate histopathologic staging necessitates biopsies from both the antrum and corpus. Non-targeted biopsies of the antrum and corpus increases the sensitivity of the endoscopic evaluation for the detection of GIM and allows more accurate determination of histologic extent of disease as well as histologic subtype (e.g. complete versus incomplete). The prior and recently updated European (ESGE) guidelines for GIM surveillance emphasize the extent of mucosal involvement to delineate a higher risk GIM population, and advocate endoscopic surveillance for extensive GIM (i.e. antrum and corpus involvement) at a 3-year surveillance interval; surveillance is not recommended if corpus biopsies are negative and GIM is limited to the antrum.[74,75] The ESGE acknowledges the mucosal subtlety and patchiness of GIM and state that at least four non-targeted biopsies from the antrum and corpus labelled in separate biopsy jars are needed for adequate assessment. While some higher incidence regions, such as East Asia, customarily diagnose GIM using image-enhancing techniques such as magnification chromoendoscopy with or without formal pathologic assessment, these technologies and expertise are in routine use in the US. Similarly, while serologic markers of gastric atrophy, such as pepsinogen I and pepsinogen I:II ratio, are used variably in some European and Asian countries,[76,77] there are currently no validated noninvasive biomarkers for GIM, GIM topographic extent, or GIM

progression risk in clinical use in the US. Thus, the accurate diagnosis and staging of GIM in the US hinges on EGD with biopsies of the corpus and antrum. This is potentially problematic in the US as an overall low incidence country, and has led to wide clinical practice variation, since the diagnosis of GIM is usually made incidentally on limited biopsies taken for other clinical indications.

Thus, the motivation for PICO 4, which is most relevant for populations where NCGA incidence is overall low and the topographic extent might not have been assessed *a priori*, was to determine whether a repeat short-term follow up (<12 months) endoscopy with biopsies of antrum and corpus in patients diagnosed incidentally with GIM and no dysplasia is associated with improved patient-important outcomes compared to patients who do not undergo short-term follow up examination.

Unfortunately, no studies provided direct evidence to inform PICO 4. That is, no studies compared patient important outcomes in patients with GIM and no dysplasia who underwent a repeat short-interval endoscopy (<12 months) to define the topographic extent of GIM with those who did not. Therefore, the technical review team and guidelines panel reached consensus regarding the indirect evidence that would be needed to inform PICO 4, which includes:

- The overall prevalence of GIM in order to quantify the magnitude of the potentially at-risk population.

- The risk of progression of GIM to incident dysplasia or NCGA in patients with limited versus extensive GIM.

- Identification of high-risk subgroups who might benefit from short-interval endoscopy to define the topographic extent of GIM.

- The risk of having high-grade dysplasia or NCGA diagnosed within the first year of follow up after GIM diagnosis, as these are very likely to be prevalent cases not identified on the initial endoscopy diagnosing GIM (i.e. "missed neoplasia").

Prevalence of GIM

We identified six studies that reported data on GIM prevalence in the US and included at least 250 people.[78] Among 897,371 people, the pooled prevalence of GIM was 4.8% (95% CI: 4.8% - 4.9%). Individual studies ranged from 4.9% up to 19.1%. Further details regarding the prevalence of GIM and the associated predisposing risk factors are detailed in the second part of the technical review.[78]

Risk of progression of GIM to incident gastric neoplasia among patients with limited versus extensive GIM

As noted above, we identified two retrospective cohort analyses—one from Japan[73] and one from the US[68] — that specifically reported the risk of progression to gastric cancer among patients who underwent antral and corpus biopsies and were found to have limited GIM (total N=156) versus extensive GIM (total N=66), according to the definitions decided *a priori* for this technical review. We have provided the context of these studies and highlighted key considerations below. Extensive GIM was associated with higher risk of

progression to gastric cancer compared to limited GIM (RR 2.07; 95% CI: 0.97–4.42), although this was statistically nonsignificant (Figure 15, very low certainty in evidence). Discrete data on the progression of GIM to dysplasia according to topographic extent of GIM were not available for analysis.

The Shichijo et al. study reported the incidence of gastric cancer among 573 patients from Japan following *H. pylori* eradication according to presence and topography of GIM over a follow up period of 6.2+/−4.8 years.[79] No patients had dysplasia or cancer at the outset, but over 30% had gastric ulcers (24% gastric ulcers only, 6.3% gastric and duodenal ulcers). Annual EGD was recommended for all patients although the adherence and time between EGDs was not explicitly stated in the study. For this cohort, the cumulative incidence of gastric cancer at 1 year was 0.3% in patients without GIM, 0% in patients with antral GIM only, and 5.6% in patients with GIM of the corpus (1.5%, 3.7%, and 9.8% at 5-years; and 1.5%, 11%, and 16% at 10-years, respectively). After adjusting for age and sex, there was a 3.6- (95%CI: 1.2–11.0) and 3.7-fold (95% CI: 1.1–12.0) increased risk of gastric cancer in patients with antral GIM only and corpus GIM, respectively, compared to patients without GIM.

Using a retrospective cohort design and concomitant nested case-control analysis, Reddy et al. reported the outcomes of 923 patients with GIM from the US Kaiser Health System.[68] The definitions of extensive versus limited GIM that we defined *a priori* for this technical review differed from the definitions in their study; the authors defined extensive GIM as moderate/marked GIM in at least 2 biopsy specimens (which could have been from the same gastric anatomic location) or GIM in at least 2 anatomic gastric locations (which could have included cardia GIM, notably), while limited GIM was not explicitly defined. Notably, it was not clear if all included patients in the cohort analysis had antral and corpus biopsies obtained. Among the 25 patients diagnosed with gastric cancer, only 32% (N=8) were incident gastric cancers following the GIM diagnosis, whereas the remaining 68% were diagnosed at the time of GIM diagnosis. Of these 8 incident cases, 6 occurred at least 2 years after the index endoscopy diagnosing GIM, while two cases occurred at 7 months and 13 months of follow up. Four of these patients had extensive GIM according to our definition. Using a nested case-control design (8 gastric cancer cases matched with 40 age- and sex-matched controls without gastric cancer selected from the cohort of patients with GIM), the authors reported that extensive GIM, according to their definition, was associated with over 9-fold higher likelihood for gastric cancer (OR 9.4, 95% CI: 1.8–50.4); however, they also report that the specific anatomic location of GIM was not statistically significantly associated with risk of gastric cancer. Importantly, the location of the gastric cancers (cardia versus non-cardia) was not specified.

Additional studies do report on the risk of neoplastic progression in extensive GIM, but the studies are heterogeneous with respect to reference group, definitions of extensive GIM, and protocol (e.g. not all patients had biopsies taken from both antrum and corpus for adequate determination of GIM extent), among other factors that limit the quality and interpretability of available data for PICO 4 specifically. A descriptive analysis of these studies is provided here, as they are still informative. A recent prospective cohort study from the Netherlands and Norway, both low risk geographic regions, found that among 279 patients undergoing

endoscopic surveillance (87% with varying severity of GIM), 4 (1.4%) progressed to high-grade dysplasia or invasive neoplasia, with these 4 cases occurring at 11, 43, 58, and 80 months following the baseline endoscopy; GIM (N=3) and HGD (N=1) were the most severe lesions in these patients at baseline.[67] The one case that was diagnosed at 11 months was notably in a 53-year-old woman with a first-degree relative with gastric cancer who had a low-risk baseline OLGIM (I) score and no visible endoscopic lesions; histopathology from gastrectomy confirmed diffuse-type adenocarcinoma and not intestinal-type adenocarcinoma. Although it was not possible to isolate neoplastic progression outcomes according to extensive versus limited GIM specifically, a nonstatistically significantly higher percentage of patients with high OLGIM scores (Stage III-IV) had progression to HGD or gastric cancer compared to the group with low OLGIM scores (Stage 0-II) (2/56 [3.6%] vs. 1/155 [0.6%, P=0.11) on follow-up.

Benefit of short-interval endoscopy in high-risk subgroups

We did not identify any studies that specifically compared the rate of neoplastic progression in patients with limited versus extensive GIM stratified by additional potential risk factors for progression. The study by den Hollander et al. reported that adjunctive use of the pepsinogen biomarker (PG I/II ratio) with OLGIM score appropriately identified a low- and high-risk group in this cohort (as defined by histopathologic OLGIM stage and PG I/II ratio) overall.[67] Other studies reported neoplastic progression for subgroups variably defined as high- and low-risk based on risk factors other than extensive versus limited GIM; these studies were used for indirect evidence informing PICO 2 and 3.

Risk of gastric neoplasia diagnosis within the first year following a diagnosis of GIM

In addition to determining the topographic extent of GIM, a repeat short interval endoscopy allows for a "second look" in the context of knowing a patient is at higher risk and potentially the opportunity to diagnose a previously missed lesion at a stage when curative resection is still possible. Early gastric neoplastic lesions are often subtle and might be overlooked, particularly in the absence of a careful systematic examination and clinical protocols such as magnification chromoendoscopy. In higher-risk populations, such as patients with preneoplasia, there is higher pretest probability for synchronous gastric neoplasia, although the exact risk is not known and depends on the population and presence of endoscopic findings.[80,81] With adherence to appropriate quality metrics, including full mucosal visualization, adequate air insufflation, photo-documentation, and duration of focused luminal examination[82–84] the risk of missed lesions is lower. No studies which reported the endoscopic miss rate for gastric neoplasia specifically in the setting of GIM were identified in our search. As indirect evidence, we analyzed the risk of gastric neoplasia within the first year of a GIM diagnosis. It should be noted that there is potential for unmeasured bias since it is not uncommon for cancer incidence studies to exclude patients who are diagnosed with cancer at enrollment or within a certain time interval thereafter; these potentially prevalent or short interval incident cases would thus not be captured. Based on 4 cohort studies,[28,68,85,86] the cumulative incidence of gastric cancer at one year in patients with GIM was low (5 per 1000 persons; 95% CI: 0.004–0.006) (Figure 18, low certainty of evidence), with the estimate driven primarily by a large study from the Netherlands, a low incidence nation, which included 60,488 patients with GIM.[86]

Summary and Conclusions

The comprehensive literature search, review, and data abstraction process showed that there was direct evidence to inform only one of four *a priori* PICO questions—i.e., PICO 1, which focused on the benefit of empiric *H. pylori* testing and treatment in patients with GIM. We relied on indirect evidence to inform PICO 2–4. Extensive work was done to determine if indirect evidence, including data on pertinent patient subgroups, could further inform the evidence profiles for PICO 2–4 to inform the AGA guidelines. Overall, the results highlight the limited published literature about patients with GIM without concurrent neoplasia, particularly with respect to the utility of an endoscopic surveillance program.

The diagnosis of gastric cancer in the curable stage prior to submucosal invasion is uncommon in the US since early-stage gastric cancer is typically asymptomatic or associated with nonspecific symptoms such as dyspepsia. The goal of surveillance of preneoplastic lesions at defined intervals is to diagnose early-stage cancer and facilitate endoscopic or surgical resection with curative intent. That the overall 5-year survival rates for gastric cancer have improved to nearly 70% in East Asian countries with gastric cancer screening and cancer surveillance programs validates this approach and is in marked contrast to the 31% 5-year survival rate for gastric cancer in the US.[87] Because the US is a low incidence nation, population-based gastric cancer screening and surveillance has been neither recommended nor commonly performed in clinical practice. Focused screening strategies in high-risk populations, with or without biomarkers, also has not been recommended due to the lack of evidence.

The impact of established risk factors for NCGA on the natural course of GIM are not well-established; these include age, gender, race/ethnicity, host genetics and family history, dietary factors (e.g., salt intake, processed meats), smoking, and *H. pylori* infection with considerations for genetic variants, timing of infection, and cumulative duration of infection. Up to 10% of the risk of gastric cancer is attributed to germline mutations and familial clustering, while less than 1–3% of all gastric cancer cases are inherited as part of specific familial syndromes, including hereditary diffuse gastric cancer, Lynch syndrome, and Peutz-Jeghers syndrome.[67,88] Germline mutations are increasingly recognized as a factor in intestinal-type gastric cancer. The importance of the interface between these germline mutations and the natural course of GIM are unknown. Many uncertainties similarly exist as to the relative contribution of non-genetic determinants on the natural history of GIM. Because NCGA results from cumulative exposure of disease determinants and their interaction over time, it is difficult (if even possible) to isolate the effect of a single determinant on GIM regression or progression. Risk factors will also vary by populations and geographic regions. For example, because it is consistently demonstrated that *H. pylori* eradication reduces the risk of incident and metachronous intestinal-type NCGA overall,[89] *H. pylori* eradication in the presence of GIM has been recommended if there are no competing contraindications.[74] However, the actual effect of *H. pylori* eradication or persistence on the natural course of GIM alone is unknown and highlighted by the evidence profile for PICO 1. That neoplastic progression occurs even *after* the resolution of *H. pylori* infection implicates *H. pylori*-independent factors. A better understanding of the biology of

progression has implications for improved risk stratification, patient counseling, and disease prevention.

One key strength of this technical review is its comprehensiveness, including organized efforts to identify and analyze indirect evidence and the consistent application of GRADE methodology. In order to ensure high fidelity of the data, every step of the data selection process was performed in duplicate with adjudication when disagreements arose. In addition, we were able to obtain previously unpublished data related to GIM from the Colombia Chemoprevention study[56] and cohort for this technical review. An obvious limitation of this review is related to the dearth of published evidence that is specific to GIM in the absence of neoplasia, manifest by our inability to provide direct evidence to inform three of the PICO questions proposed by the AGA. The *indirect* evidence we abstracted to inform these questions was heterogenous and of variable quality.

In conclusion, we achieved the primary objective of this technical review and qualitatively and quantitatively summarized the available evidence to inform the AGA guidelines panel on GIM management for cancer surveillance, with a prespecified focus on the intestinal-type gastric adenocarcinoma pathway. Our extensive systematic literature review and data synthesis identified direct evidence to inform one of four PICO questions, and indirect evidence to inform the remaining three. In general, empiric *H. pylori* testing and treatment in patients with confirmed infection (with or without GIM) favored a protective effect against incident gastric cancer, and was also associated with improved gastric cancer-related mortality when compared to patients who received placebo. Based on low quality evidence, family history of gastric cancer, extensive GIM and incomplete GIM on histology are associated with increased risk of progression to gastric cancer in patients with GIM. This technical review has highlighted the paucity of direct evidence to inform endoscopic surveillance of GIM, but also provides enormous opportunity for future work and efforts. Future work on GIM should use standardized protocols and definitions for defining outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Acronyms

NCGA	Intestinal-type noncardia gastric adenocarcinoma
AG	atrophic gastritis
H. Pylori	Helicobacter pylori
TCGA	Cancer Atlas Genome Project

GIM	gastric intestinal metaplasa
EGD	esophagogastroduodenoscopy
ASGE	American Society for Gastrointestinal Endoscopy
ESGE	European Society for Gastrointestinal Endoscopy
GRADE	Grading of Recommendations Assessment, Development and Evaluation
PICO	population (P), intervention (I), comparator (C), and outcomes (O)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
RCT	randomized controlled trial
REDCap	Research Electronic Data Capture
OLGA	Operative Link on Gastritis Assessment
OLGIM	Operative Link on Gastric Intestinal Metaplasia Assessment
RR	Relative Risk
IRR	incidence rate ratio
ROB	risk of bias
HGD	high drade dysplasia
US	United States

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Box 1. Definitions used throughout the process of the systematic reviews.

Global histologic progression or regression of GIM were deemed to be the more clinically relevant outcome, since scoring and staging systems are not used routinely in clinic practice and their implications are not well-defined. Similarly, we focused on incomplete versus complete as the most clinically relevant histologic classification for GIM.[24–26] We acknowledge another classification system utilized predominately for research that divides GIM into three types: Type I GIM (non-secretory absorptive cells and sialomucin secreting goblet cells), Type 2 GIM (few absorptive cells, columnar cells secreting sialomucin, and goblet cells secreting mainly sialomucin but some sulphomucin), and Type 3 GIM (columnar cells secreting predominantly sulphomucin and goblet cells secreting sialomucin or sulphomucin).[26] In accordance with the literature, Type I GIM was categorized as complete GIM, while Type II and Type III were categorized as incomplete GIM.[26–28]

Normal gastric mucosa

Chronic gastritis

Gastric atrophy

Intestinal metaplasia

Dysplasia **Cancer**
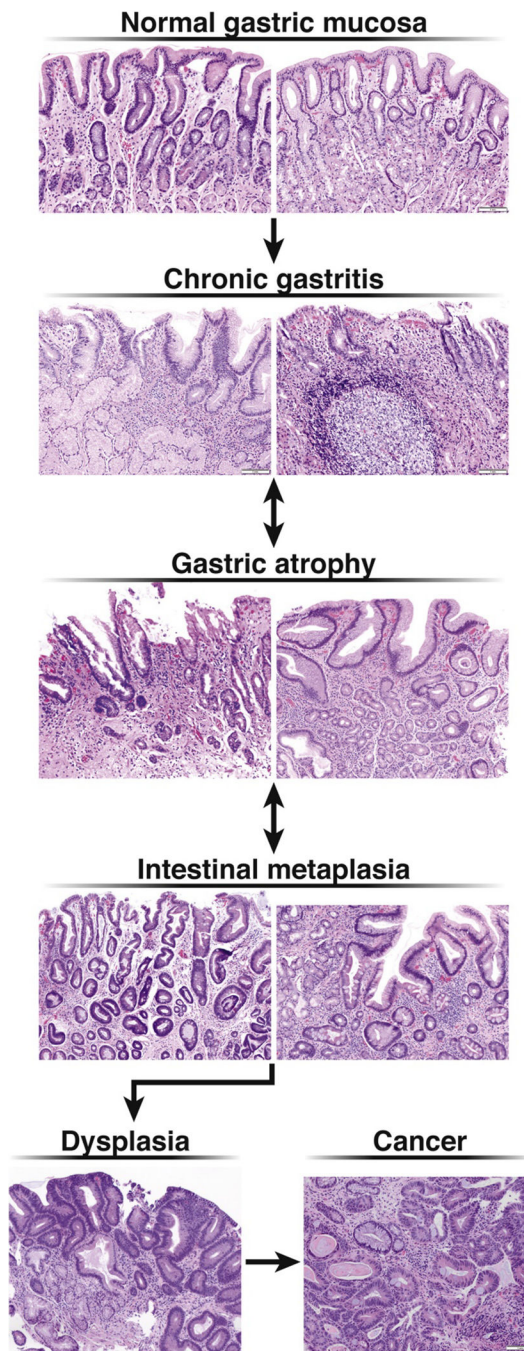
Figure 1:
Correa Cascade with histology

Figure 2:
PRISMA flow diagram

a

Study	Country	Follow-up	Hp Erad. Death	N	Placebo Death	N	Risk Ratio	RR 95% CI	Weight
Wong, 2012	China	5	1	255	4	258		0.25 [0.03; 2.25]	0.8%
Wong, 2004	China	7.5	22	817	23	813		0.95 [0.53; 1.69]	11.8%
Shandong Intervention Trial	China	15	157	1130	142	1128		1.10 [0.89; 1.36]	87.4%
Random effects model			180	2202	169	2199		1.07 [0.88; 1.31]	100.0%

Heterogeneity: I^2=0%, Tau²=0, P=.38
Test for overall effect: Z=0.69 (P=.49)

0.1 0.5 1 2 10
Favors Hp eradication   Favors placebo
Mortality in *H pylori* infected patients

Figure 3a:

Relative risk of all-cause mortality among patients with *H. pylori* infection after *H. pylori* treatment versus placebo (all patients, with or without GIM)

b

Study	Country	Follow-up	Hp Erad. Death N		Placebo Death N		Risk Ratio	RR 95% CI	Weight
Wong, 2004	China	7.5	3	817	6	813		0.50 [0.12; 1.98]	16.6%
Shandong Intervention Trial	China	15	17	1130	24	1128		0.71 [0.38; 1.31]	83.4%
Random effects model			20	1947	30	1941		0.67 [0.38; 1.17]	100.0%

Heterogeneity: I^2=0%, Tau²=0, P=.65
Test for overall effect: Z=-1.41 (P=.16)

0.2 0.5 1 2 5

Favors Hp eradication   Favors placebo
Gastric cancer-related mortality in *H pylori* infected patients
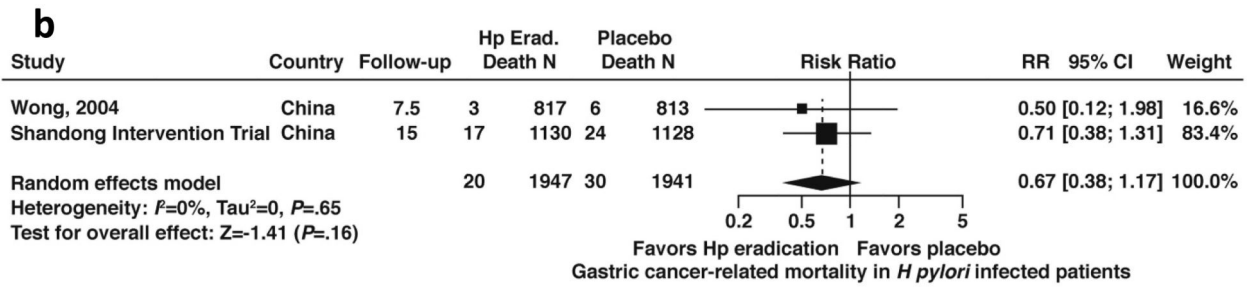
Figure 3b:

Relative risk of gastric cancer-related mortality among patients with *H. pylori* infection after *H. pylori* treatment versus placebo (all patients, with or without GIM)

a

Study	Country	Follow-up	Hp Erad. GC N		Placebo GC N		Risk Ratio	RR 95% CI	Weight
Lee, 2013	Taiwan	4	1	841	2	1762		1.05 [0.10; 11.54]	2.1%
Wong, 2012	China	5	3	255	1	258		3.04 [0.32; 28.99]	2.4%
Wong, 2004	China	7.5	7	871	11	813		0.63 [0.25; 1.63]	13.9%
Yantai County Trial	China	10	2	276	7	276		0.29 [0.06; 1.36]	5.0%
Shandong Intervention Trial	China	15	34	1130	52	1128		0.65 [0.43; 1.00]	68.4%
Colombia Chemoprevention Trial	Colombia	16	5	491	5	485		0.99 [0.29; 3.39]	8.1%
Random effects model			52	3810	78	4722		0.68 [0.48; 0.96]	100.0%

Heterogeneity: I^2=0%, Tau^2=0, P=.64
Test for overall effect: Z=-2.19 (P=.03)

0.1 0.5 1 2 10
Favors Hp eradication   Favors placebo
Risk of gastric cancer in *H pylori* infected patients

Figure 4a:

Relative risk of incident gastric cancer among patients with *H. pylori* infection after *H. pylori* treatment versus placebo (all patients, with or without GIM)

b

Study	Country	Follow-up	Hp Erad. GC	GIM	Placebo GC	GIM	Risk Ratio	RR 95% CI	Weight
Wong, 2012	China	5	1	59	0	63		3.20 [0.13; 77.07]	5.5%
Shandong Intervention Trial	China	7.3	10	495	13	497		0.77 [0.34; 1.74]	83.6%
Colombia Chemoprevention Trial	Colombia	12	1	246	3	253		0.34 [0.04; 3.27]	10.9%
Random effects model			12	800	16	813		0.76 [0.36; 1.61]	100.0%

Heterogeneity: I^2=0%, Tau^2=0, P=.53
Test for overall effect: Z=-0.71 (P=.48)

0.1 0.5 1 2   10
Favors Hp eradication   Favors placebo
Risk of gastric cancer in *H pylori* infected patients with GIM
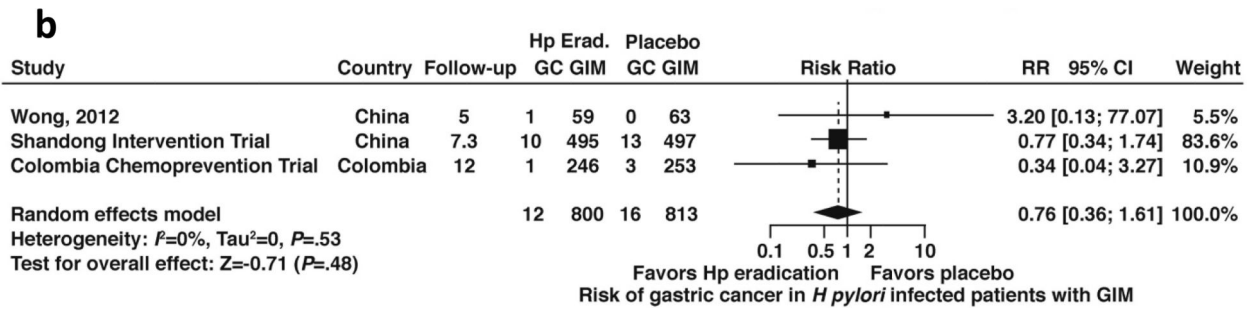
Figure 4b:

Relative risk of incident gastric cancer among patients with *H. pylori* infection and confirmed GIM after *H. pylori* treatment versus placebo

a

Study	Country	Follow-up	Hp Erad. Prog. N		Placebo Prog. N		Risk Ratio	RR 95% CI	Weight
Ley, 2004	Mexico	1	11	122	11	126		1.03 [0.47; 2.29]	1.4%
Wong, 2012	China	2	52	255	57	258		0.92 [0.66; 1.29]	8.0%
Shandong Intervention Trial	China	7	440	1130	486	1128		0.90 [0.82; 1.00]	90.6%
Random effects model			503	1507	554	1512		0.91 [0.83; 1.00]	100.0%

Heterogeneity: I^2=0%, Tau²=0, P=.94
Test for overall effect: Z=-2.03 (P=.04)

0.5   1   2
Favors Hp eradication   Favors placebo
Risk of global histological diagnosis progression in *H pylori* infected patients
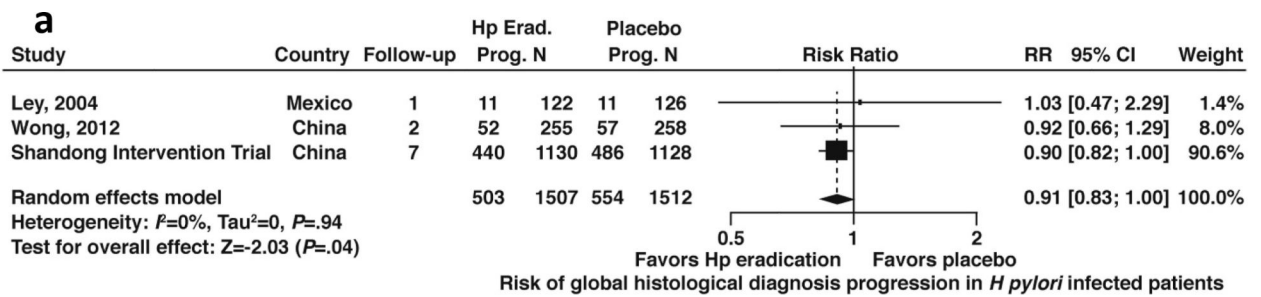
Figure 5a:

Relative risk of progression to worse global histology from baseline among patients with *H. pylori* infection after *H. pylori* treatment versus placebo (all patients, with or without GIM)

b

Study	Country	Follow-up	Hp Erad. Reg. GIM	Placebo Reg. GIM	Risk Ratio	RR 95% CI	Weight

Risk of global histological diagnosis progression in *H pylori* infected patients with GIM
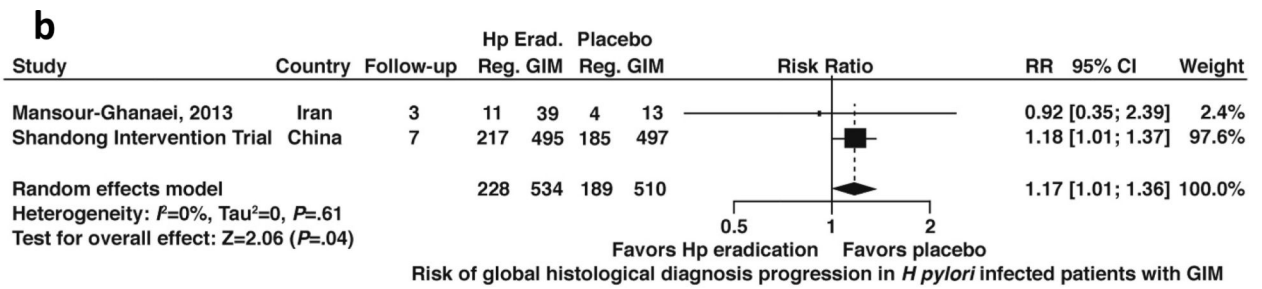
Figure 5b:

Relative risk of progression to worse global histology from baseline among patients with *H. pylori* infection and confirmed GIM after *H. pylori* treatment versus placebo

a

Study	Country	Follow-up	Hp Erad. Reg. N		Placebo Reg. N		Risk Ratio	RR 95% CI	Weight
Ley, 2004	Mexico	1	31	122	31	126		1.03 [0.67; 1.59]	10.5%
Wong, 2012	China	2	126	255	99	258		1.29 [1.06; 1.57]	49.4%
Shandong Intervention Trial	China	7	165	1130	120	1128		1.37 [1.10; 1.71]	40.1%
Random effects model			322	1507	250	1512		1.29 [1.12; 1.48]	100.0%

Heterogeneity: I^2=0%, Tau^2=0, P=.51
Test for overall effect: Z=3.59 (P<.01)

0.75   1   1.5
Favors placebo   Favors Hp eradication
Risk of global histological diagnosis regression in *H pylori* infected patients
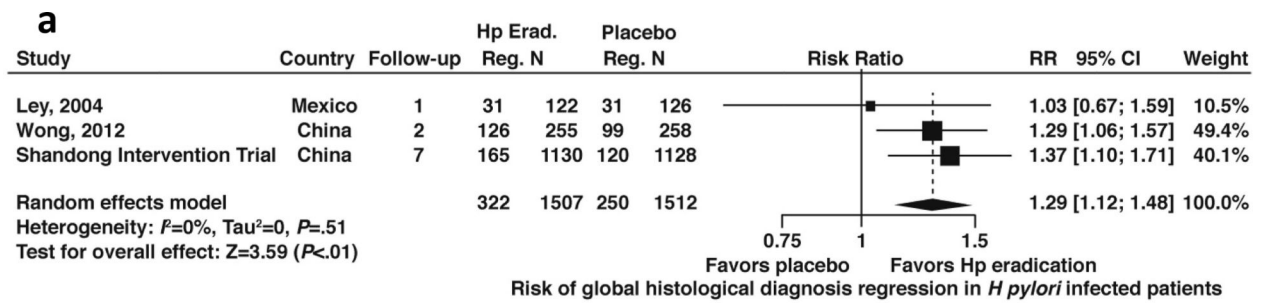
Figure 6a:

Relative risk of regression to improved global histology from baseline among patients with *H. pylori* infection after *H. pylori* treatment versus placebo (all patients, with or without GIM)

b

Study	Country	Follow-up	Hp Erad. Reg. GIM		Placebo Reg. GIM		Risk Ratio	RR 95% CI
Shandong Intervention Trial	China	7	54	495	35	497		1.55 [1.03; 2.33]

Test for overall effect: Z=2.11 (*P*=.03)

0.5　　1　　2

Favors placebo　　Favors Hp eradication

Risk of global histological diagnosis regression in *H pylori* infected patients with GIM
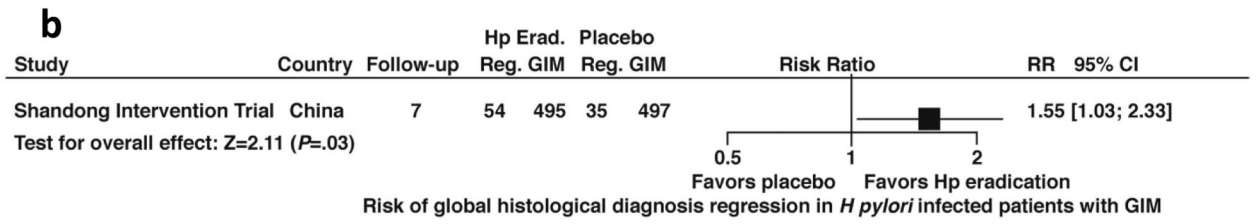
Figure 6b:

Relative risk of regression to improved global histology from baseline among patients with *H. pylori* infection and confirmed GIM after *H. pylori* treatment versus placebo

Study	Country	GIM	Follow-up	Person-years	Dysplasia	Events per 10,000 person-years	Events	95% CI	Weight
Plummer, 2007	Venezuela	419	3	1342.3	32		238.4	[162.3; 328.8]	15.9%
Correa, 1990	Colombia	298	5	1593.7	50		313.7	[232.4; 407.2]	18.9%
Gonzalez, 2016	Spain	467	12	5502.7	22		40.0	[24.8; 58.6]	65.2%
Fixed effect model				8438.7	104		97.6	[77.3; 120.0]	100.0%

Heterogeneity: I^2=98%, Tau^2=0.0047, P<.01

50 100 150 200 250 300 350 400

Incidence rate of progression from GIM to gastric dysplasia
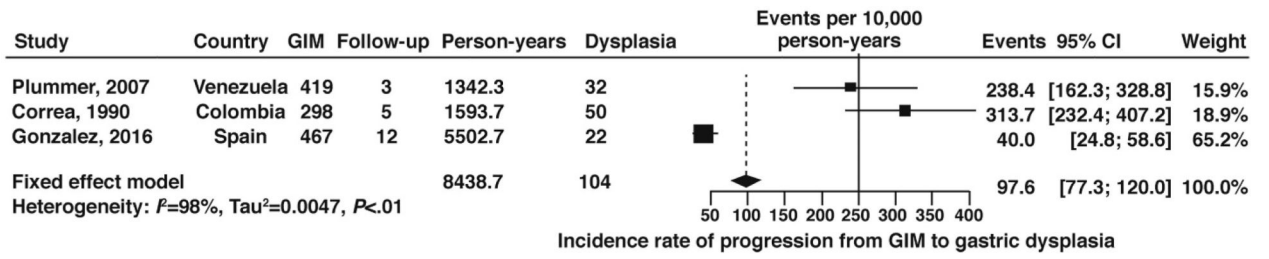
Figure 7:
Incidence rate per 10,000 person-years of any dysplasia in patients with GIM

Study	Country	Dysplasia	GIM		Proportion	95% CI
Duration of follow-up (years) = 3						
Mansour-Ghanaei, 2013	Iran	17	71		0.239	[0.146; 0.355]
Sossai, 1990*	Italy	21	112		0.188	[0.120; 0.272]
Plummer, 2007	Venezuela	32	419		0.076	[0.053; 0.106]
Shandong Intervention Trial	China	177	992		0.178	[0.155; 0.204]
Fixed effect model		247	1594		0.150	[0.132; 0.168]
Heterogeneity: I^2=91%, Tau²=0.0090, P<.01						
Duration of follow-up (years) = 5						
den Hollander, 2018	Netherlands	4	244		0.016	[0.004; 0.041]
Correa, 1990	Colombia	50	298		0.168	[0.127; 0.215]
You, 1999*	China	171	842		0.203	[0.176; 0.232]
Fixed effect model		225	1384		0.150	[0.132; 0.170]
Heterogeneity: I^2=98%, Tau²=0.0269, P<.01						

0.05 0.1 0.15 0.2 0.25 0.3 0.35
Cumulative incidence of progression from GIM to dysplasia

Figure 8:

Cumulative incidence of any dysplasia at 3-, 5-year, and 8-years in patients with GIM

Cumulative incidence of progression from GIM to dysplasia

Study	Country	HGD/GC	GIM		Proportion	95% CI
Duration of follow-up (years) = 5						
den Hollander, 2018	Netherlands	3	244		0.012	[0.003; 0.036]
You, 1999*	China	28	842		0.033	[0.022; 0.048]
Fixed effect model		31	1086		0.027	[0.018; 0.038]
Heterogeneity: I^2=69%, Tau²=0.0015, P=.07						

0.01 0.02 0.03 0.04

Cumulative incidence of progression from GIM to high grade dysplasia or gastric cancer

Figure 9:

Cumulative incidence of HGD or gastric cancer at 5-years in patients with GIM

a

Study	Country	GIM	Follow-up	Person-years	GC	Events per 10,000 person-years	Events	95% CI	Weight
Plummer, 2007	Venezuela	419	3	1342.3	0		0.0	[0.0; 12.8]	0.8%
Correa, 1990	Colombia	298	5	1593.7	1		6.3	[0.0; 27.0]	1.0%
Lee, 2016	Taiwan	6778	5	40730.0	63		15.5	[11.9; 19.5]	25.5%
Reddy, 2016	USA	906	5	4651.2	8		17.2	[7.0; 31.5]	2.9%
Li, 2016	USA	4146	7	23658.0	17		7.2	[4.1; 11.1]	14.8%
Song, 2015	Sweden	11530	8	68122.0	76		11.2	[8.8; 13.8]	42.6%
Kim, 2008	Korea	249	9	2134.0	4		18.7	[4.0; 42.7]	1.3%
Filipe, 1994	Slovenia	990	10	10738.1	26		24.2	[15.7; 34.5]	6.7%
Sadjadi, 2014	Iran	129	10	1284.0	25		194.7	[125.1; 279.3]	0.8%
Gonzalez, 2016	Spain	467	12	5502.7	23		41.8	[26.3; 60.8]	3.4%
Fixed effect model				159756.0	243		12.4	[10.7; 14.3]	100.0%

Heterogeneity: I^2=91%, Tau^2=0.0002, P<.01

0   50   100   150   200   250

Incidence rate of progression from GIM to gastric cancer

Figure 10a:

Incidence rate of gastric cancer per 10,000 person-years in patients with GIM (all geographies)

b

Study	GIM	Follow-up	Person-years	GC	Events per 10,000 person-years	Events	95% CI	Weight
Reddy, 2016	906	5	4651.2	8		17.2	[7.0; 31.5]	16.4%
Li, 2016	4146	7	23658.0	17		7.2	[4.1; 11.1]	83.6%
Fixed effect model			28309.2	25		8.2	[5.1; 12.0]	100.0%

Heterogeneity: I^2=73%, Tau^2<0.0001, P=.05

Incidence rate of progression from GIM to gastric cancer – USA studies only

Figure 10b:

Incidence rate of gastric cancer per 10,000 person-years in patients with GIM (US geography only)

Study	Country	GC	GIM		Proportion	95% CI
Duration of follow-up (years) = 3						
Mansour-Ghanaei, 2013	Iran	0	71		0.000	[0.000; 0.051]
Sossai, 1990	Italy	2	112		0.018	[0.002; 0.063]
Plummer, 2007	Venezuela	0	419		0.000	[0.000; 0.009]
Shandong Intervention Trial	China	9	992		0.009	[0.004; 0.017]
Fixed effects model		11	1594		0.004	[0.001; 0.008]
Heterogeneity: I^2=66%, Tau^2=0.0017, P=.03						
Duration of follow-up (years) = 5						
Wong, 2012	China	1	216		0.005	[0.000; 0.026]
den Hollander, 2018	Netherlands	1	244		0.004	[0.000; 0.023]
Correa, 1990	Colombia	1	298		0.003	[0.000; 0.019]
You, 1999	China	18	842		0.021	[0.013; 0.034]
Reddy, 2016	USA	7	905		0.008	[0.003; 0.016]
Lee, 2016	Taiwan	63	6778		0.009	[0.007; 0.012]
de Vries, 2008	Netherlands	726	60488		0.012	[0.011; 0.013]
Fixed effects model		817	69771		0.011	[0.010; 0.012]
Heterogeneity: I^2=57%, Tau^2=0.0001, P=.03						
Duration of follow-up (years) = 10						
Whiting, 2002	UK	10	93		0.108	[0.053; 0.189]
Sadjadi, 2014	Iran	25	129		0.194	[0.130; 0.273]
Filipe, 1994	Slovenia	26	990		0.026	[0.017; 0.038]
de Vries, 2008	Netherlands	1089	60488		0.018	[0.017; 0.019]
Fixed effects model		1150	61700		0.016	[0.015; 0.017]
Heterogeneity: I^2=96%, Tau^2=0.0074, P<.01						

0   0.05   0.1   0.15   0.2   0.25

Cumulative incidence of progression from GIM to gastric cancer

Figure 11:

Cumulative incidence of gastric cancer at 3-, 5-, and 10-years in patients with GIM

Study	Follow-up	GC	GIM		Proportion	95% CI
Race = Asian						
Abadir, 2012	4	4	222		0.018	[0.005; 0.045]
Reddy, 2016	5	1	159		0.006	[0.000; 0.035]
Li, 2016	7	2	943		0.002	[0.000; 0.008]
Fixed effects model		7	1324		0.003	[0.001; 0.008]
Heterogeneity: I^2=69%, Tau^2=0.0018, P=.04						
Race = Black						
Reddy, 2016	5	2	126		0.016	[0.002; 0.056]
Li, 2016	7	1	367		0.003	[0.000; 0.015]
Fixed effects model		3	493		0.004	[0.000; 0.014]
Heterogeneity: I^2=55%, Tau^2=0.0016, P=.13						
Race = Hispanic						
Reddy, 2016	5	3	259		0.012	[0.002; 0.033]
Li, 2016	7	7	727		0.010	[0.004; 0.020]
Fixed effects model		10	986		0.010	[0.004; 0.017]
Heterogeneity: I^2=0%, Tau^2=0, P=.69						
Race = White						
Reddy, 2016	5	2	332		0.006	[0.001; 0.022]
Li, 2016	7	5	1717		0.003	[0.001; 0.007]
Fixed effects model		7	2049		0.003	[0.001; 0.006]
Heterogeneity: I^2=0%, Tau^2=0, P=.32						
Race = Other						
Reddy, 2016	5	0	33		0.000	[0.000; 0.106]
Li, 2016	7	2	392		0.005	[0.001; 0.018]
Fixed effects model		2	425		0.001	[0.000; 0.009]
Heterogeneity: I^2=0%, Tau^2=0, P=.94						
Interaction test: χ_4^2=5.37, df=4 (P=.25)						

Scale: 0 0.02 0.04 0.06 0.08 0.1

Cumulative incidence of progression from GIM to gastric cancer

Figure 12:

Cumulative incidence of gastric cancer in GIM patients according to race and ethnicity (4–7 years followup)

Study	Country	Follow-up	(+) GC FHx		(-) GC FHx		Risk Ratio	RR	95% CI	Weight
			GC	GIM	GC	GIM				
Leung, 2006	China	2	0	66	0	147		1.00	[0.01; 68.61]	8.4%
Mansour-Ghanaei, 2013	Iran	3	0	28	0	43		1.00	[0.02; 53.65]	9.5%
Reddy, 2016	USA	4.6	3	69	5	837		6.30	[1.62; 24.43]	82.1%
Random effects model				163		1027		4.53	[1.33; 15.46]	100.0%

Heterogeneity: I^2=0%, Tau²=0, P=.50

0.1 0.51 2 10

Higher risk with (-) GC FHx   Higher risk with (+) GC FHx
Progression from GIM to gastric cancer

Figure 13:
Relative risk of progression to gastric cancer in GIM patients with versus without a family history of gastric cancer

a

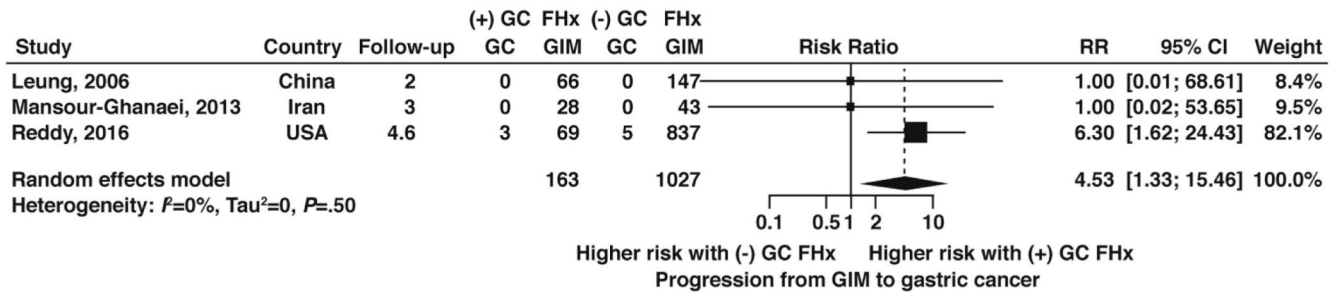| Study	Country	Follow-up	Incomplete IM		Complete IM		Risk Ratio	RR	95% CI	Weight
			GC	GIM	GC	GIM				
Mansour-Ghanaei, 2013	Iran	3	0	21	0	50		1.00	[0.01; 71.13]	1.5%
Fang, 1991	China	4	5	65	0	47		9.62	[0.43; 216.66]	2.9%
Silva, 1990	Portugal	4	1	23	0	101		6.39	[0.39; 103.48]	3.6%
Sossai, 1990	Italy	4	2	41	0	44		5.15	[0.27; 99.78]	3.2%
Filipe, 1994	Slovenia	10	20	472	6	518		3.44	[1.44; 8.24]	36.6%
Gonzalez, 2016	Spain	12	15	219	8	248		2.05	[0.91; 4.64]	41.8%
Gonzalez, 2010	Spain	12.8	16	88	1	104		12.62	[2.48; 64.16]	10.5%
Random effects model			59	929	15	1112		3.33	[1.96; 5.64]	100.0%

Heterogeneity: I^2=0%, Tau^2=0, P=.52
Test for overall effect: z=4.47, (P<.01)

0.01 0.1 1 10 100

Higher risk in complete GIM   Higher risk in incomplete GIM
Progression from GIM to gastric cancer

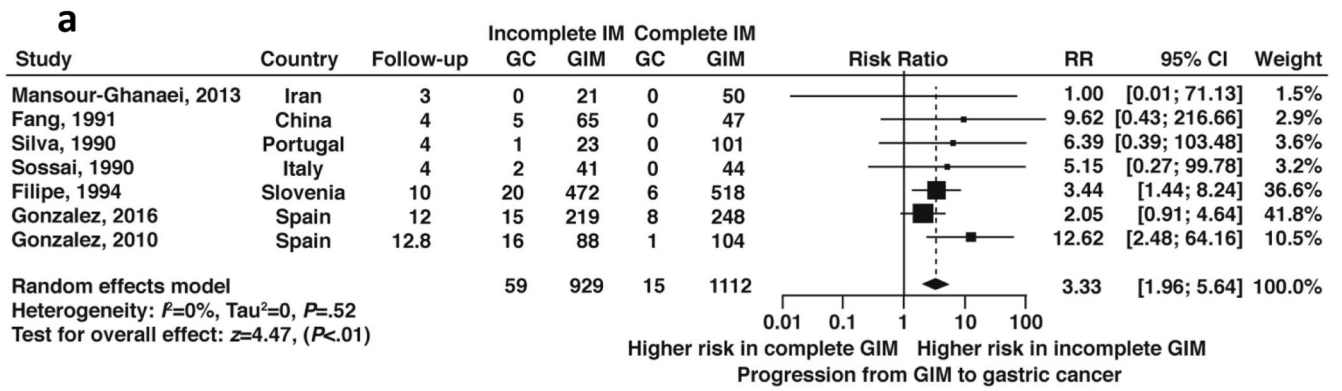**Figure 14a:**

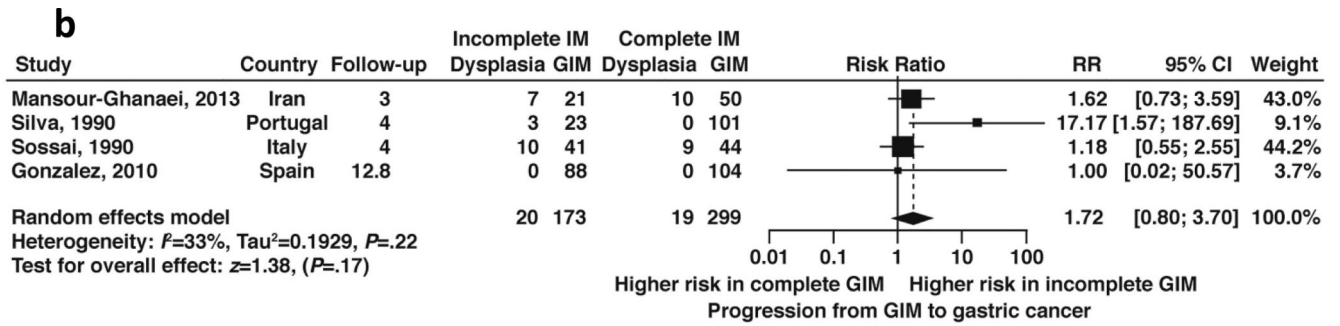Relative risk of progression to gastric cancer according to incomplete versus complete GIM on baseline histology

b

Study	Country	Follow-up	Incomplete IM Dysplasia	Incomplete IM GIM	Complete IM Dysplasia	Complete IM GIM	Risk Ratio	RR	95% CI	Weight
Mansour-Ghanaei, 2013	Iran	3	7	21	10	50		1.62	[0.73; 3.59]	43.0%
Silva, 1990	Portugal	4	3	23	0	101		17.17	[1.57; 187.69]	9.1%
Sossai, 1990	Italy	4	10	41	9	44		1.18	[0.55; 2.55]	44.2%
Gonzalez, 2010	Spain	12.8	0	88	0	104		1.00	[0.02; 50.57]	3.7%
Random effects model			20	173	19	299		1.72	[0.80; 3.70]	100.0%

Heterogeneity: I^2=33%, Tau^2=0.1929, P=.22
Test for overall effect: z=1.38, (P=.17)

0.01   0.1   1   10   100

Higher risk in complete GIM   Higher risk in incomplete GIM
Progression from GIM to gastric cancer

Figure 14b:

Relative risk of progression to any dysplasia according to incomplete versus complete GIM on baseline histology
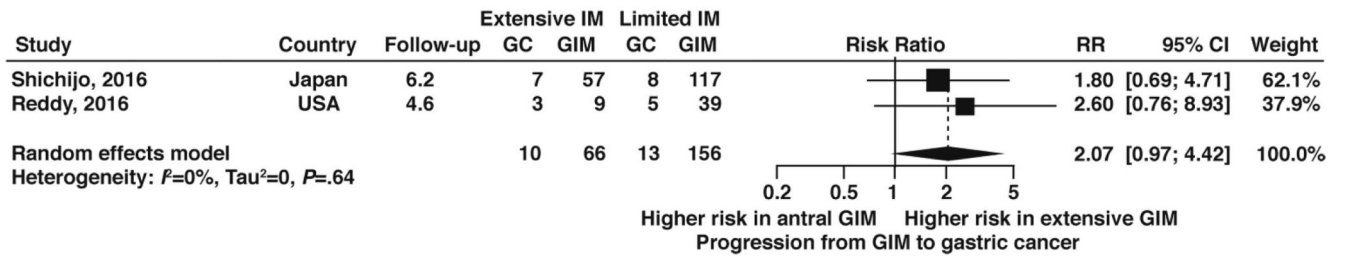
Study	Country	Follow-up	Extensive IM		Limited IM		Risk Ratio	RR	95% CI	Weight
			GC	GIM	GC	GIM				
Shichijo, 2016	Japan	6.2	7	57	8	117		1.80	[0.69; 4.71]	62.1%
Reddy, 2016	USA	4.6	3	9	5	39		2.60	[0.76; 8.93]	37.9%
Random effects model			10	66	13	156		2.07	[0.97; 4.42]	100.0%
Heterogeneity: I^2=0%, Tau²=0, P=.64										

0.2 0.5 1 2 5

Higher risk in antral GIM   Higher risk in extensive GIM
Progression from GIM to gastric cancer

Figure 15:
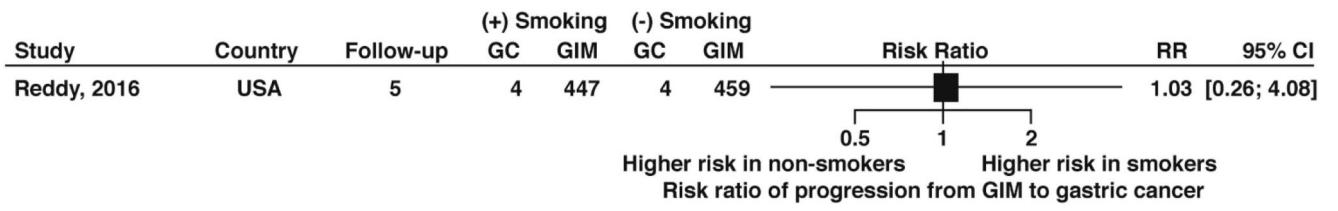Relative risk of progression to gastric cancer according to topographic extent of GIM, extensive versus limited[1]

| Study | Country | Follow-up | (+) Smoking | | (-) Smoking | | Risk Ratio | RR | 95% CI |
			GC	GIM	GC	GIM			
Reddy, 2016	USA	5	4	447	4	459		1.03	[0.26; 4.08]

0.5　　　1　　　2

Higher risk in non-smokers　　　Higher risk in smokers

Risk ratio of progression from GIM to gastric cancer

Figure 16:

Relative risk of progression of GIM to gastric cancer according to tobacco smoker versus non-smoker status
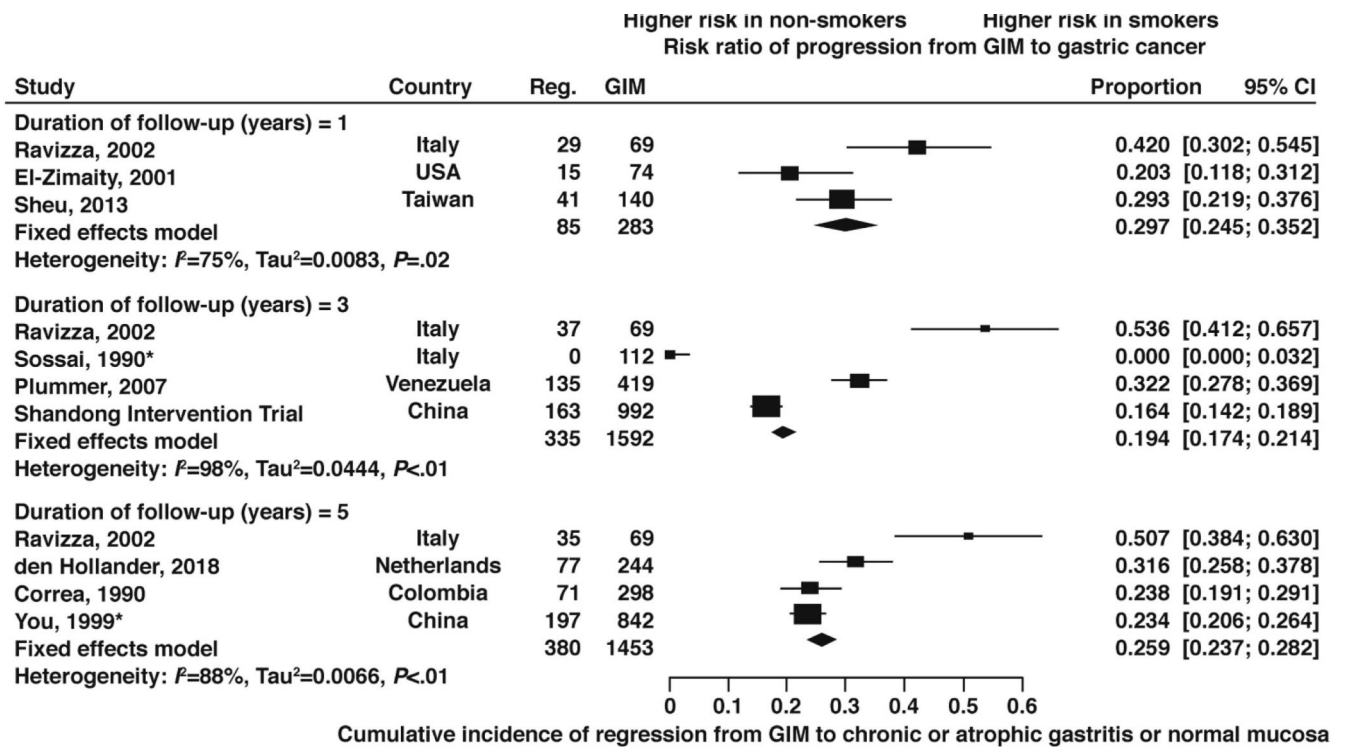
Figure 17:

Cumulative risk of regression to improved global histology at 1-year, 3-year, and 5-year follow up in patients with GIM
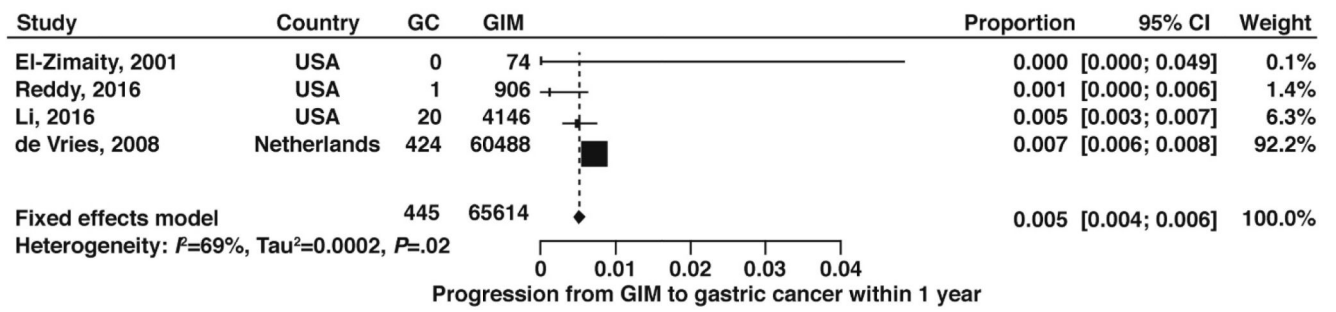
Study	Country	GC	GIM		Proportion	95% CI	Weight
El-Zimaity, 2001	USA	0	74		0.000	[0.000; 0.049]	0.1%
Reddy, 2016	USA	1	906		0.001	[0.000; 0.006]	1.4%
Li, 2016	USA	20	4146		0.005	[0.003; 0.007]	6.3%
de Vries, 2008	Netherlands	424	60488		0.007	[0.006; 0.008]	92.2%
Fixed effects model		445	65614		0.005	[0.004; 0.006]	100.0%

Heterogeneity: I^2=69%, Tau²=0.0002, P=.02

0   0.01   0.02   0.03   0.04

Progression from GIM to gastric cancer within 1 year

Figure 18:
Cumulative incidence of gastric cancer at 1 year in patients with GIM

Table 1:

PICO questions, outcomes, and evidence needed to inform PICO questions

PICO Question	Patient-Important Outcomes	Evidence needed to inform PICO questions
1. Among patients with GIM, does testing for *H. pylori* and treating if positive vs no testing affect outcomes?	Early cancer detection Reduced gastric cancer morbidity/mortality Endoscopy complications Costs Psychological harms	1. Incidence and prevalence of GIM in the US population 2. Incidence of stomach cancer in the general population 3. Prevalence of concurrent stomach cancer in patients with GIM 4. Incidence of stomach cancer in patients with GIM after GIM diagnosis 5. Risk of progression to gastric cancer in patients with GIM *Subgroups*: Family history of gastric cancer, Race/Ethnicity, smoking status, histologic features, extent of GIM, biomarkers. 6. Potential adverse consequences of performing surveillance upper endoscopy for patients with GIM 7. Benefits of performing surveillance upper endoscopy for patients with GIM
2. Among patients with GIM who are identified as low risk, does subsequent upper endoscopic surveillance vs no follow up affect outcomes?		
3. Among patients with GIM who are identified as high risk, does subsequent upper endoscopic surveillance vs no follow up affect outcomes?		
4. Among patients with GIM without dysplasia does short term upper endoscopic follow up (< 1 year) to determine the extent (using biopsies) of GIM vs no short term follow up affect outcomes?		

Table 2:

Study characteristics, objectives, patients characteristics, intervention, comparison and outcomes (PICO 1)

Study / reference	Design and Objectives	Intervention and Comparison Group	Total subjects (N), full study	Countries / (Ethnicity)	Mean Age, yrs (SD and range)	% Males	Follow up protocol and GIM-specific Outcomes
Colombian Chemoprevention Trial[56–58]	RCT To determine if treatment of *H. pylori* infection and/or supplementation with ascorbic acid and β-carotene prevents gastric precancerous lesion progression	Intervention: *H. Pylori* treatment with or without-long term supplements of ascorbic acid and β-carotene. Comparison: Placebo	852	Colombia (Hispanic)	51.1 (SD 8.5)	46.1%	Endoscopy at 3, 6, 12, and 16 yrs with biopsies to determine the prevalence of precancerous lesions and progression to gastric cancer HP eradication confirmed: Yes
Shandong Intervention Trial[43–45,48]	RCT To test the effects of one-time *H. pylori* treatment and long-term vitamin or garlic supplements in reducing the prevalence and progression of gastric precancerous lesions.	Intervention: *H. Pylori* treatment, 7 years of oral supplementation with garlic, or with a mixture of vitamin C, vitamin E, and selenium. Comparison: Placebo	4326	China	47.2 Range 35–64	51.4%	Endoscopy with biopsies to determine the prevalence of gastric precancerous lesions and incidence of cancer at 3 and 7 yrs. HP eradication confirmed: Yes
Yantai County Trial[49–52]	RCT To determine if H. pylori screening and treatment improves histologic severity and decreases risk of gastric cancer progression	Intervention: *H. pylori* screening and treatment if positive Comparison: Placebo	587	China	52 (SD 8.1) Range (16–75)	48%	Endoscopy with biopsies 1, 5, 10 yrs to determine who developed or died of gastric cancer HP eradication confirmed: Yes
Ley, 2004[46]	RCT To determine if *H. pylori* eradication is associated with regression of gastric pre-neoplastic conditions over 1 year	Intervention: *H. pylori* treatment Comparison: Placebo	316	Mexico (Hispanic)	Intervention: 51.0 (SD 9.2) Control: 52.0 (SD 9.8)	36.7%	Endoscopy with biopsies at 6wks and 12 mo to assess regression vs progression of gastric precancerous lesions HP eradication confirmed: Yes
Wong, 2004[53]	RCT To determine whether *H. pylori* eradication is associated with reduced gastric cancer incidence	Intervention: *H. pylori* screening and treatment if positive Comparison: Placebo	1630	China	42.2 (SD 9.0)	54%	Endoscopic follow up at 7.5 yrs, to determine incidence of gastric cancer HP eradication confirmed: Yes
Wong 2012[54]	RCT To assess whether celecoxib alone or combined with H. *pylori* treatment is associated with progression or regression of gastric precancerous lesions	Intervention: *H. pylori* screening and treatment if positive, with or without celecoxib. Comparison: Placebo	1024	China	53 (SD 6.5)	46%	Endoscopic follow up at 5 yrs to assess change in progression/regression of gastric precancerous lesions and gastric cancer incidence HP eradication confirmed: Yes
Massarrat, 2012[55]	RCT To evaluate histologic change and topography of precancerous lesions after H. *pylori* eradication	Intervention: *H. pylori* testing and treatment if positive Comparison: Placebo	521	Iran	47.8 Range (38–70)	49%	Endoscopic follow up at 2.5 or 4.5 yrs to assess regression or progression of GIM HP eradication confirmed: Yes
Kuipers, 2004[47]	RCT	Intervention:	234	Netherlands, France, UK,	Intervention: 61.8 (SD 12.3)	54.5%	Endoscopic follow up with biopsies at 1 and 2 yrs to

Study / reference	Design and Objectives	Intervention and Comparison Group	Total subjects (N), full study	Countries / (Ethnicity)	Mean Age, yrs (SD and range)	% Males	Follow up protocol and GIM-specific Outcomes
	To determine if H. pylori eradication in patients with GERD on long-term omeprazole therapy influences gastritis progression	H. pylori positive patients treated omeprazole based triple therapy followed by omeprazole only Comparison: H. pylori positive patients treated with omeprazole only		Denmark,Sweden, Australia, Germany	Control: 62.4 (SD12.0)		determine severity and extent of gastric pathology HP eradication confirmed: Yes
Lee, 2013[59]	Cohort To evaluate the effect of H. pylori eradication on the prevalence of gastric precancerous lesions, and secular trends in the incidence of gastric precancer and cancer.	Intervention: H. pylori screening and treatment if positive Comparison: 1995–2003 (pre-HP eradication campaign) vs. 2004–2008 (post HP eradication campaign)	Total 1762, 841 with endoscopic follow up	Taiwan	49.2 (SD 12.8)	46%	Endoscopic follow up with biopsies to determine incidence of GIM pre versus post treatment HP eradication confirmed: Yes
Ciok, 1997[90]	Cohort To evaluate the effect of H. pylori eradication on antral GIM	Intervention: H. pylori treatment if positive Comparison: Eradicated vs. Not eradicated	35	Poland	44 Range (29–63)	54.3%	Endoscopic follow up with biopsies at 2 yrs to determine presence and severity of antral GIM HP eradication confirmed: Yes
Salih, 2005[91]	Cohort 1) To evaluate the effect of H. pylori and H. pylori genotypes on gastric histology 2) To evaluate the effect of H. pylori eradication on histology	Intervention: H. pylori positive, treated Comparison: H. pylori positive, not treated	28	Turkey	46 Range (24–66)	57.1%	Endoscopic follow up with biopsies at 1 and 12 mo to determine change in average histologic score HP eradication confirmed: Yes
Lu, 2005[92]	Cohort To evaluate the effect of H. pylori eradication on atrophic gastritis and GIM	Intervention: H. pylori positive, treated Comparison: Untreated cohort (all HP +)	179	China	Range (30–74)	45.8%	Endoscopic follow up with biopsies at 3 years_ to determine change in histology score HP eradication confirmed: Yes
Mansour-Ghanaei, 2013[60]	Case series To determine histology change in GIM over 1 year	Intervention: H. Pylori treatment Comparison: H Pylori eradicated vs. not eradicated after treatment	71	Iran	48 (SD 12) Range (21–79)	56%	Endoscopic follow up with biopsies at 1 year to determine progression to dysplasia in GIM HP eradication confirmed: Yes
Yamada, 2003[93]	Cohort To evaluate the effect of H. pylori eradication on atrophic gastritis	Intervention: H. Pylori treatment Comparison: eradicated vs. infected	116	Japan	Intervention: 52.6 (SD 1.2) Control: 57.1 (SD 2.1)	61.2	Endoscopic follow up with biopsies at 10–49 mo to determine if gastric atrophy improves HP eradication confirmed: Not reported

Table 3:

Evidence profile and pooled effect estimates to inform PICO 1 (*H Pylori*)

No of studies	Design	Certainty Assessment					No of Patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Test/Treat for H Pylori	No Test/Treat	Relative (95% CI)	Absolute (95% CI)		
Relative risk of death (All-cause mortality) among patients with *H. pylori* infection after *H. pylori* treatment versus placebo (all patients, with or without GIM)												
3	RCTs	Not serious	Not serious	Serious[2]	Serious[3]	None	180/2202 (8.2%)	169/2199 (7.7%)	RR=1.07 (0.88–1.31)	5 more per 1000 (from 9 fewer to 24 more)	⊕⊕OO Low	Critical
Relative risk of gastric cancer-related mortality among patients with *H. pylori* infection after *H pylori* treatment versus placebo (all patients, with or without GIM)												
2	RCTs	Not serious	Not serious	Serious[2]	Serious[3]	None	20/1947 (1.0%)	30/1941 (1.5%)	RR=0.67 (0.38–1.17)	5 fewer per 1000 (from 3 more to 10 fewer)	++ Low	Critical
Relative risk of incident gastric cancer among patients with *H. pylori* infection after *H pylori* treatment versus placebo (all patients, with or without GIM)												
6	RCTs and cohort[1]	Not serious	Not serious	Serious[2]	Not serious	None	52/3810 (1.4%)	78/4722 (1.7%)	RR=0.68 (0.48–0.96)	6 fewer per 1000 (1 fewer to 9 fewer)	+++ Moderate	Critical
Relative risk of incident gastric cancer among patients with *H. pylori* infection and confirmed GIM after *H pylori* treatment versus placebo												
3	RCTs	Not serious	Not serious	Not serious	Very serious[3]	None	12/800 (1.5%)	16/813 (2.0%)	RR=0.76 (0.36–1.61)	3 fewer per 1000 (from 14 fewer to 20 more)	++ Low	Critical

CI: Confidence interval; RR: Risk Ratio

[1] 4 RCTs and 2 observational cohort. Results are driven by RCTs findings

[2] Data considered in all patients, not just patients with GIM

[3] Few events, confidence intervals are wide encompassing both considerable benefit and harm.

Table 4:

Evidence profile and pooled effect estimates to inform PICO questions 2–4

Outcome		Estimate (95% CI)	Certainty of Evidence	Risk of Bias	Inconsistency	Imprecision	Indirectness
Incidence rate of any dysplasia in patients with GIM		97.6/10,000 p-y (77.3 – 120.0)	⊕⊕⊕◯ Low	Not serious	Serious	Not serious	Serious
Cumulative incidence of any dysplasia in patients with GIM	at 3 years	15.0% (13.2 – 16.8)	⊕◯◯◯ Very low	Serious	Serious	Not serious	Serious
	at 5 years	15.0% (13.2 – 17.0)	⊕⊕◯◯ Low	Not serious	Serious	Not serious	Serious
Cumulative incidence of HGD or gastric cancer in patients with GIM at 5 years		2.7% (1.8 – 3.8)	⊕◯◯◯ Very low	Not serious	Not serious	Very serious	Serious
Incidence rate of gastric cancer in patients with GIM	all geographies	12.4/10,000 p-y (10.7 – 14.3)	⊕⊕⊕◯ Low	Serious[1]	Serious[1]	Not serious	Serious
	US geography only	8.2/10,000 p-y (5.1 – 12.0)	⊕⊕◯◯ Low	Serious	Not serious	Serious	Not serious
	within 1 year	0.5% (0.4 – 0.6)	⊕⊕◯◯ Low	Serious	Not serious	Not serious	Serious
Cumulative incidence of gastric cancer in patients with GIM	at 3 years	0.4% (0.1 – 0.8)	⊕◯◯◯ Very low	Not serious	Not serious	Very serious	Serious
	at 5 years	1.1% (1.0 – 1.2)	⊕⊕◯◯ Low	Serious	Not serious	Not serious	Serious
	at 10 years	1.6% (1.5 – 1.7)	⊕◯◯◯ Very low	Serious	Serious	Not serious	Serious
	Asian	0.3% (0.1 – 0.8)	⊕◯◯◯ Very low	Serious	Not serious	Very serious	Not serious
	Black	0.4% (0.0 – 1.4)	⊕◯◯◯ Very low	Serious	Not serious	Very serious	Not serious
Cumulative incidence of gastric cancer in patients with GIM based on race/ethnicity	Hispanic	1.0% (0.4 – 1.7)	⊕◯◯◯ Very low	Serious	Not serious	Very serious	Not serious
	White	0.3% (0.1 – 0.6)	⊕◯◯◯ Very low	Serious	Not serious	Very serious	Not serious
	Other	0.1% (0.0 – 0.9)	⊕◯◯◯ Very low	Serious	Not serious	Very serious	Not serious
Relative risk of incident gastric cancer in patients with GIM and first degree family history of gastric cancer vs. no first degree family history		4.5 (1.3 – 15.5)	⊕◯◯◯ Very low	Serious	Not serious	Very serious	Not serious
Relative risk of incident gastric cancer in patients with incomplete vs. complete GIM on histology		3.3 (2.0 – 5.6)	⊕⊕◯◯ Low	Not serious	Not serious	Serious	Serious

Outcome		Estimate (95% CI)	Certainty of Evidence	Risk of Bias	Inconsistency	Imprecision	Indirectness
Relative risk of incident gastric dysplasia in patients with incomplete vs. complete GIM on histology		1.7 (0.8 − 3.7)	⊕⊕○○ Low	Not serious	Not serious	Serious[2]	Serious
Relative risk of incident gastric cancer in patients with extensive vs. limited GIM		2.1 (1.0 − 4.4)	⊕○○○ Very low	Serious	Not serious	Very serious	Not serious
Relative risk of incident gastric cancer in patients with GIM who smoke(d) tobacco vs. none smokers		1.0 (0.3 − 4.1)	⊕○○○ Very low	Serious	Not serious	Very serious	Not serious
Cumulative risk of GIM regression to improved global histology	at 1 year	29.7% (24.5 − 35.2)	⊕○○○ Very low	Serious	Not serious	Serious	Serious
	at 3 years	19.4% (17.4 − 21.4)	⊕○○○ Very low	Serious	Serious	Not serious	Serious
	at 5 years	25.9% (23.7 − 28.2)	⊕○○○ Very low	Serious	Serious	Not serious	Serious

[1] we rated down one level only for both risk of bias (few studies lacked protocolized biopsies) and inconsistency (most of the evidence was consistent except two small studies) together.

[2] despite the narrow confidence interval, we elected to rate down for imprecision due to the small number of events.

Abbreviations: GIM, gastric intestinal metaplasia; HGD, high grade dysplasia.