Gastric Cancer Risk of Intestinal Metaplasia Subtypes: A Systematic Review and Meta-Analysis of Cohort Studies

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INTRODUCTION:	Intestinal metaplasia (IM) is an independent risk factor for gastric cancer (GC). However, the subtypes of IM as a risk factor for GC remain controversial. We performed a systematic review and meta-analysis to evaluate the relationship between IM subtypes and GC risk.
METHODS:	Systematic searches were conducted in PubMed, EMBASE, and the Cochrane Library for published cohort studies of patients with complete IM (type I) or incomplete IM (type II or type III) from inception to May 15, 2021. We extracted relevant data and calculated pooled risk ratios (RRs) and 95% confidence intervals (CIs) comparing the GC risk with IM subtypes.
RESULTS:	Twelve cohort studies comprising 6,498 individuals were included in the study. Compared with complete IM, the pooled relative risk of GC risk of patients with incomplete IM was 5.16 (95% CI, 3.28–8.12), and the GC risk of type III IM was the highest, with a pooled relative risk of 2.88 (95% CI, 1.37–6.04) compared with that of type II. Compared with complete IM, the pooled relative risk of dysplasia risk in patients with incomplete IM was 3.72 (95% CI, 1.42–9.72), and the dysplasia risk of type III IM was 11.73 (95% CI, 2.08–66.08) compared with that of type I.
DISCUSSION:	Patients with incomplete IM, especially type III, were at a higher risk of GC and dysplasia than those with complete IM. The current evidence indicates a potential correlation between IM subtypes and GC risk, which may support the use of IM subtypes in GC surveillance.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A676, http://links.lww.com/CTG/A677

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INTRODUCTION

Gastric cancer (GC) remains a major health problem in many countries, with more than 1.22 million incident cases of GC occurring worldwide in 2017, with nearly half of the global incident cases occurring in China (1). GC is the third leading cause of cancer mortality, causing an estimated 783,000 deaths globally in 2018 (2). High mortality in GC is closely related to its silent nature (3). Therefore, early detection and treatment are important approaches to improve the survival of patients with GC.

Intestinal-type gastric adenocarcinoma is the final stage of what is known as the Correa cascade, which pertains to the carcinoma sequence of chronic gastritis to atrophy gastritis, then intestinal metaplasia (IM), to the final dysplasia (4). The stepwise progression of intestinal-type gastric adenocarcinoma allows for the early detection and resection of neoplastic lesions. Histologically confirmed IM is a precancerous condition of GC that has been suggested to be an independent risk factor for GC and is recommended as the most reliable marker of gastric mucosal atrophy in the management of epithelial precancerous conditions and lesions in the stomach (MAPS II) (5).

IM can be classified according to histologic subtypes: complete IM (type I) and incomplete IM (type II or type III) (6). Previous reviews and meta-analyses found that incomplete IM was associated with a higher risk of GC compared with complete IM (7–9); however, additional studies are required before subtyping can be routinely recommended. Previous reviews and meta-analyses were limited to descriptive reviews or subgroup analyses of IM subtypes based on multiple observational studies, including cross-sectional studies; however, incomplete IM is not always found in the gastrectomy specimens of patients with GC (10–12). Instead, a cohort study, where an outcome or disease-free study population is first identified and monitored in time until the disease or outcome of interest occurs, can provide powerful prognostic-related results (13). Thus, we aimed to systematically

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assess the relationship between IM subtypes and GC risk in cohort studies.

METHODS

The protocol for this systematic review was based on the Meta-Analysis of Observational Studies in Epidemiology (14). The protocol was prospectively registered at PROSPERO (CRD42020176936).

Search strategy

Two reviewers (S.D. and S.F.) independently searched electronic databases, including PubMed, EMBASE, and the Cochrane Library, from inception to May 15, 2021. The search equations were "intestinal metaplasia" AND "(gastric cancer) OR (gastric neoplasm) OR (gastric carcinoma) OR (stomach cancer) OR (stomach neoplasm) OR (stomach carcinoma)" AND "(cohort) OR (follow-up)." In addition, the references of identified articles were also searched for potentially missed articles.

Study selection

After excluding duplicate studies, the 2 reviewers (S.D. and S.F.) screened the titles and abstracts of all retrieved articles to exclude irrelevant studies and then read the full text of the remaining studies to include eligible studies. Disagreements were resolved through discussion or by involving a third reviewer (S.G.) when necessary.

The inclusion criteria were as follows: patients (individuals diagnosed with IM), intervention (being diagnosed with incomplete IM), comparator (being diagnosed with complete IM), outcome (GC and dysplasia incidence in patients with IM sub-types confirmed by pathologic diagnosis or records from government registration), and study design (cohort studies). The exclusion criteria were as follows: (i) insufficient data in original studies, (ii) duplicate publications, (iii) conference abstracts, and (iv) studies published in a non-English language.

Data extraction and quality assessment

Two reviewers (G.S. and C.X.) independently screened all the included studies to extract the following data: name of the first author, publication year, study design, country, study period, sample size, age, sex, duration of follow-up, number of patients with IM subtypes, and numbers of GC and dysplasia. They independently assessed the quality of the included studies according to the Newcastle-Ottawa Quality Assessment Scale. Disagreements were resolved through discussion or by involving a third reviewer (S.D.) when necessary.

Outcomes

The primary outcome was the incidence of GC in patients with IM subtypes. The secondary outcomes were the incidence of dysplasia in patients with IM subtypes and the incidence of GC and dysplasia among patients with IM subtypes in different countries and pathological quality control.

Statistical analysis

We calculated the risk ratios (RRs) and 95% confidence intervals (CIs) using 2×2 table data extracted from the original studies. We pooled the results with RRs and 95% CIs using a fixed-effects or random-effects model, depending on study heterogeneity. Heterogeneity in the included studies was assessed using the Cochran Q test and quantity I^2 . An I^2 greater than 50% suggested

significant heterogeneity (15). To explore the source of heterogeneity, sensitivity and subgroup analyses were further performed according to the potential effect modification of factors, including country and pathological quality control. Funnel plots were generated to evaluate the possibility of publication bias (16). All statistical analyses were conducted using Review Manager, version 5.3 (Cochrane Reviews).

RESULTS

Literature search

As shown in Figure 1, 928 articles were identified using a search strategy from PubMed, EMBASE, and the Cochrane library, of which 295 were duplicated articles. In the remaining 633 articles, 604 irrelevant articles were excluded after reviewing the titles and abstracts; hence, 29 articles remained. Subsequently, 19 articles were excluded for the following reasons: insufficient data (n = 2), conference abstracts (n = 9), cross-sectional studies (n = 6), no diagnosis of IM subtype (n = 1), and no comparator (n = 1). Two potential articles were included from the reference list. Finally, 12 articles were included in this meta-analysis (17–28).

Study characteristics and quality assessment

The main characteristics of the 12 articles are summarized in Table 1. Among the 12 cohort studies, 10 were prospective cohort studies (18–20,22–28) and 2 were retrospective cohort studies (17,21); 4 studies were conducted in Asia (20,22,25,28), 7 were conducted in Europe (17–19,21,23,24,26), and 1 was conducted in South America (27). In total, 6,498 individuals were included in this meta-analysis, and the sample size of the included studies ranged from 62 to 2,980. All studies included both male and female patients. All the included studies presented the numbers of IM subtypes at baseline and GC at end point, whereas 8 studies presented the numbers of IM subtypes, GC, and dysplasia of the included articles are listed in Table 2. Quality assessment is also summarized in Table 1, where all studies obtained 6 or more stars.

Based on the 12 studies, the fixed-effects estimated pooled prevalence of incomplete IM among patients with IM was 42% (95% CI, 34%–49%) and complete IM was 58% (95% CI, 50%–66%), presented as forest plots in Supplementary Figures 1 and 2 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A676). In patients with incomplete IM, the fixed-effects estimated pooled prevalence of type II IM was 45% (95% CI, 41%–49%) and type III IM was 55% (95% CI, 51%–59%), presented as forest plots in Supplementary Figures 3 and 4 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A676).

Outcomes

A total of 12 studies with 6,498 participants were included in this meta-analysis to evaluate GC risk in patients with IM subtypes. Compared with complete IM, the pooled relative risk of GC in patients with incomplete IM was 5.16 (95% CI, 3.28–8.12), and GC risk of type III IM was highest with a pooled relative risk of 2.88 (95% CI, 1.37–6.04) compared with type II and 6.42 (95% CI, 3.03–13.62) compared with type I. In addition, GC risk of type II IM was not significantly higher than type I (RR, 2.37; 95% CI, 0.84–6.72). Forest plots of GC risk in the IM subtypes are shown in Figure 2.

A total of 7 studies with 1,473 participants were included in this meta-analysis to evaluate dysplasia risk in patients with IM subtypes. Compared with complete IM, the pooled relative risk of



Figure 1. Flow diagram of literature search and study selection.

dysplasia in patients with incomplete IM was 3.72 (95% CI, 1.42–9.72), and the pooled relative risk in type III IM was 11.73 (95% CI, 2.08–66.08) compared with type I but not significantly higher than type II. Moreover, dysplasia risk of type II IM was not significantly higher than that of type I. Forest plots of GC risk in IM subtypes are shown in Figure 3.

Subgroup analysis was also performed according to the country of origin and pathological quality control (Table 2). According to the country of origin, the GC risk of incomplete IM was higher in Asia (RR, 8.83; 95% CI, 3.05–25.56), Europe (RR, 4.23; 95% CI, 2.51–7.14), and South America (RR, 8.16; 95% CI, 1.02–65.32) compared with that of complete IM. In addition, 5 studies performed pathological quality control, which indicated a significantly higher GC risk of incomplete IM compared with that of complete IM (RR, 5.45; 95% CI, 3.02–9.84). Forest plots of the subgroup analysis are shown in Figure 4. According to the country of origin, the dysplasia risk of incomplete IM was higher in Europe (RR, 4.05; 95% CI, 1.65–9.93) and South America (RR,

8.16; 95% CI, 1.89–35.14) compared with that of complete IM. Three studies performed pathological quality control, which indicated a significantly higher dysplasia risk of incomplete IM compared with that of complete IM (RR, 4.67; 95% CI, 1.11–19.63). Forest plots of the subgroup analysis are shown in Figure 5.

Publication bias

For the risk of GC of incomplete IM vs complete IM, a funnel plot (Figure 6) suggested that publication bias may exist. The results may be related to the small sample size of some included studies and the exclusion of non-English articles and conference abstracts. However, because the abstracts do not contain complete original data, publication bias is inevitable.

DISCUSSION

IM is an independent risk factor for GC, with an annual incidence of 12.4 (95% CI, 10.7–14.3) cases of GC per 10,000 persons with

First author	Year	Design	Country	Study period	Sample size	Age, y	Sex	Follow-up, mo	Quality assessment
Ramesar ¹⁷	1987	RC	UK	1976–1987	174	Mean 60.8	53% M	120–132	7
Sossai ¹⁸	1990	PC	Italy	None	112	Mean 64.2	57% M	12–88	7
Silva ¹⁹	1990	PC	Portugal	1982–1988	124	31–76	71% M	12–72	7
Fang ²⁰	1991	PC	China	1982–1987	112	18–70	80% M	15–70	6
Filipe ²¹	1994	RC	Slovenia	1967–1986	1,281	NR	65% M	126–234	8
Sun ²²	2009	PC	China	1989–2003	62	NR	NR	60–168	6
Gonzalez ²³	2010	PC	Spain	1988–1994 2005–2007	478	Mean 50	47% M	Mean 153.6	8
Gonzalez ²⁴	2016	PC	Spain	1995–2004 2011–2013	649	Mean 52	54% M	Mean 144	8
Pittayanon ²⁵	2017	PC	Thailand	2004–2014	91	63 ± 13.3	51% M	48.6 ± 30	8
Chapelle ²⁶	2020	PC	France	2000–2015	79	Mean 61	44% M	Mean 66	7
Piazuelo ²⁷	2021	PC	Colombia	1991–2011	356	69 ± 8	45% M	240	8
Lee ²⁸	2021	PC	Singapore	2004–2010	2,980	59.1 ± 6.7	52% M	Mean 52.8	8

Table 1. Characteristics of studies included in the meta-analysis

NR, not reported; PC, prospective cohort; RC, retrospective cohort.

IM (9). The Operative Link on Gastritis Assessment (29) and Operative Link on Gastritis Intestinal Metaplasia Assessment (OLGIM) (30) systems have been proposed for staging of atrophy and IM. A meta-analysis revealed that stage III/IV OLGIM system was indeed associated with an increased risk of GC (31). Management of epithelial precancerous conditions and lesions in the stomach II recommended that patients with advanced stages of atrophic gastritis (Operative Link on Gastritis Assessment/ OLGIM III/IV) should be followed up with a high-quality endoscopy every 3 years (5). The key issue is that the use of OLGIM has some limitations when only a few biopsies are available for examination, which always happens in clinical practice; thus, other reliable GC risk assessment systems or markers are urgently needed.

The IM subtype may be an easier way to assess the risk of GC. Since the 1970s, investigators have found that there are variants of IM that differ based on morphology and mucin secretion, and they found that some variants were more strongly associated with

Table 2. Characteristics of the IM subtypes and GC of studies included

					No. of GC			No. of dy			
		No. of CIM	- No. of IIM		No. of CIM at baseline	No. of IIM at baseline		No. of CIM at baseline	No. of base	IIM at eline	
First author	Year	Type I	Type II	Type III	Туре І	Type II	Type III	Type I	Type II	Type III	Pathological quality control
Ramesar ¹⁷	1987	16	14	14	0	1	1	NR	NR	NR	NR
Sossai ¹⁸	1990	71	22	19	0	0	2	9	7	5	NR
Silva ¹⁹	1990	101	12	11	0	0	1	0	0	3	NR
Fang ²⁰	1991	47	34	31	0	0	5	NR	NR	NR	NR
Filipe ²¹	1994	518	197	275	6	5	15	NR	NR	NR	NR
Sun ²²	2009	19	22	21	0	1	3	6	4	3	NR
Gonzalez ²³	2010	104	88		1	16		0	()	Yes
Gonzalez ²⁴	2016	248	219		8	15		9	1	3	Yes
Pittayanon ²⁵	2017	81	10		0	3		1	2	2	Yes
Chapelle ²⁶	2020	60	13		0	2		2		3	NR
Piazuelo ²⁷	2021	134	115		1	7		2	1	4	Yes
Lee ²⁸	2021	302	244		2	13		NR	Ν	R	Yes
CIM, complete	intestina	l metaplasia	a; GC, gas	tric cance	r; IIM, incomplete intes	tinal meta	plasia; NR	, not reported.			

REVIEW ARTICLE



Figure 2. Forest plots of gastric cancer risk in IM subtypes. IIM, incomplete intestinal metaplasia; CIM, complete intestinal metaplasia; CI, confidence interval; M-H, Mantel-Haenszel.



Figure 3. Forest plots of dysplasia risk in IM subtypes. IIM, incomplete intestinal metaplasia; CIM, complete intestinal metaplasia; CI, confidence interval; M-H, Mantel-Haenszel.

the risk of intestinal-type gastric adenocarcinoma (32–36). According to the general pathological classification criteria proposed by Jass and Filipe, IM can be classified as complete IM (type I) and incomplete IM (type II or type III) (6). In complete IM (type I), sialomucins are present in goblet cells with no mucins in columnar cells. In type II IM, sialomucins are present in goblet cells. In type III IM, sulfomucins predominate in columnar cells, and goblet cells may contain sialomucins or sulfomucins (37).

Our study provided a comprehensive summary of the relationship between IM subtypes and GC risk and included only cohort studies with high scores of quality assessment (7.33 on average) to ensure the overall quality of evidence. This metaanalysis of cohort studies included 12 studies with 6,498 participants to evaluate the relationship between IM subtypes and GC risk. Compared with complete IM, the pooled relative risks of GC and dysplasia risk of patients with incomplete IM was 5.16 (95% CI, 3.28–8.12) and 3.72 (95% CI, 1.42–9.72), respectively, and the risk of type III IM was the highest. The abovementioned results are more significant in high-incidence areas of GC (Asia and South America). In addition, interobserver agreement between pathologists can improve the accuracy of pathological diagnosis, and research has gradually found that it is poor for AG but moderate or strong for IM (38–40). As reported in the included

Study or Subgroup	Incomplet Events	te IM <u>Tota</u> l	Complet Events	e IM <u>Tota</u> l	Weight	Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio M-H, Fixed, 95% Cl
2.1.1 Asia							
Fand 1991	5	65	0	47	3.0%	8 00 00 45 141 251	
Sun 2009	1	12	ñ	10	3 504	4 NG IN 22 72 411	
Dittouonon 2017	4	40	0	13	0.00	4.03 [0.23, 72.41]	
Pillayanon 2017	3	10	U	81	0.6%	52.18 [2.88, 944.18]	
Lee 2021	13	244	2	302	9.1%	8.05 [1.83, 35.31]	
Subtotal (95% CI)		362		449	16.2%	8.83 [3.05, 25.56]	
Total events	25		2				
Heterogeneity: $\chi^2 = 1.3$ Test for overall effect:	74, df = 3 (F Z = 4.01 (P	e = 0.63 < 0.001	3); /² = 0% 01)				
2.1.2 Europe							
Domocor 1007	2	20	0	16	2.20%	2 0 2 10 15 57 521	
Ramesar 1907	2	20	0	10	3.270	2.93 [0.15, 57.52]	
Sossal 1990	2	41	U	- 11	1.9%	8.57 [0.42, 174.31]	
Silva 1990	1	23	0	101	1.0%	12.75 [0.54, 303.41]	
Filipe 1994	20	472	6	518	29.2%	3.66 [1.48, 9.03]	
Gonzalez 2010	16	88	1	104	4.7%	18.91 [2.56, 139.75]	
Gonzalez 2016	15	219	8	248	38.3%	2.12 [0.92, 4.91]	+-∎
Chapelle 2020	2	13	0	60	1.0%	21.79 [1.11.429.04]	│ →
Subtotal (95% CI)	-	884	Ŭ	1118	79.1%	4,23 [2.51 7 14]	•
Total events	50	504	15			1120 [210 1, 1114]	· ·
Loteregensity w ²	00 75 df 0 /5	2 - 0 2 4	10				
Heterogeneity: $\chi = 6.1$	7-642/0	1 = 0.34	9;/*=11% 001\				
restion overall effect.	z = 0.42 (P	~ 0.00I	001)				
2.1.3 South America							
Piazuelo 2021	7	115	1	134	4 7%	8 16 (1 02 65 22)	
Subtotal (05% CI)	· ·	115		134	4.7 %	0.10[1.02, 05.32]	
Subtotal (95% CI)	-	115		134	4.1 70	0.10[1.02, 05.32]	
i utal events	· · · · · · · · · · · · · · · · · · ·		1				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z= 1.98 (P	= 0.05))				
Total (95% CI)		1361		1701	100.0%	5 16 [3 28 8 12]	
						0.10[0.20, 0.12]	
Total events	90		18			5.10 [5.20, 6.12]	•
Total events Heterogeneity: $\chi^2 = 11$	90 04 df=11	(P = 0	18 44): /²= 0	%		5.10 [5.20, 5.12]	· · · · · · · · · · · · · · · · · · ·
Total events Heterogeneity: $\chi^2 = 11$ Test for overall effect:	90 .04, df = 11 Z = 7.09 /2	(<i>P</i> = 0. < 0.000	18 .44); /²= 0 001)	%		5.10 [5.25, 517]	0.01 0.1 1 10 100
Total events Heterogeneity: χ ² = 11 Test for overall effect: Test for subgroup diff.	90 1.04, df = 11 <i>Z</i> = 7.09 (<i>P</i>	(<i>P</i> = 0. < 0.001 = 1.70	18 .44); /² = 0 001) df = 2 /8 -	% - 0.42\	/ 3 - 0%	5115 [5125, 5112]	0.01 0.1 1 10 100 Higher risk of CIM Higher risk of IIM
Total events Heterogeneity: χ ² = 11 Test for overall effect: Test for subαroup diffe	90 .04, df = 11 Z = 7.09 (P erences: x ²	(P = 0. < 0.000 = 1.70.	18 .44); /² = 0 001) . df = 2 (P =	% = 0.43).	/² = 0%	Diek Datia	0.01 0.1 1 10 100 Higher risk of CIM Higher risk of IIM
Total events Heterogeneity: χ ² = 11 Test for overall effect: Test for subαroup diffe Study or Subαroup	90 .04, df = 11 Z = 7.09 (P erences: χ ² Incomplet Events	(P = 0. < 0.000 = 1.70. te IM Total	18 .44); / ² = 0 001) . df = 2 (<i>P</i> : Complet Events	% = 0.43). e IM Total	/² = 0% Weight	Risk Ratio	0.01 0.1 1 10 100 Higher risk of CIM Higher risk of IIM Risk Ratio M-H, Fixed. 95% CI
Total events Heterogeneity: $\chi^2 = 11$ Test for overall effect: . Test for subdroup diffect Study or Subgroup 2.2.1 Pathological gue	90 1.04, df = 11 Z = 7.09 (P erences: χ^2 Incomplet <u>Events</u> ality contro	(P = 0. < 0.000 = 1.70. te IM <u>Total</u>	18 .44); / ² = 0 001) . df = 2 (<i>P</i> = Complet Events	% = 0.43). e IM Total	/² = 0% Weight	Risk Ratio M-H, Fixed, 95% Cl	0.01 0.1 1 10 100 Higher risk of CIM Higher risk of IIM Risk Ratio M-H, Fixed, 95% CI
Total events Heterogeneity: $\chi^2 = 11$ Test for overall effect: . Test for subgroup Study or Subgroup 2.2.1 Pathological que Gonzalez 2010	90 1.04, df = 11 Z = 7.09 (P erences: χ^2 Incomplet Events ality contro 16	(P = 0. < 0.000 = 1.70. te IM <u>Total</u> I:Yes	18 .44); <i>I</i> ² = 0 001) df = 2 (<i>P</i> : Complet <u>Events</u>	% = 0.43). e IM Total	/² = 0% Weight	Risk Ratio M-H, Fixed, 95% CI	0.01 0.1 1 10 100 Higher risk of CIM Higher risk of IIM Risk Ratio M-H, Fixed, 95% CI
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Total events Heterogeneity: χ ² = 11 Test for overall effect. Test for subαroup diffi Study or Subgroup 2.2.1 Pathological qua Gonzalez 2010 Gonzalez 2016	90 1.04, df = 11 Z = 7.09 (<i>P</i> erences: χ^2 Incomplet Events ality contro 16 15	(P = 0. < 0.000 = 1.70. te IM Total I:Yes 88 219	18 .44); <i>I</i> ² = 0 001) df = 2 (<i>P</i> : Complet <u>Events</u> 1 8	% = 0.43). e IM <u>Total</u> 104 248	/ ² = 0% <u>Weight</u> 4.7% 38.3%	Risk Ratio <u>M-H, Fixed, 95% CI</u> 18.91 [2.56, 139.75] 2.12 [0.92, 4.91]	0.01 0.1 1 10 100 Higher risk of CIM Higher risk of IIM Risk Ratio M-H, Fixed, 95% CI
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Total events Heterogeneity: χ^2 = 11 Test for overall effect: Test for subgroup Study or Subgroup 2.2.1 Pathological que Gonzalez 2010 Gonzalez 2010 Gonzalez 2016 Pittayanon 2017 Piazuelo 2021 Lee 2021	90 1.04, df = 11 Z = 7.09 (<i>P</i> erences: χ^2 Incomplet Events ality contros 16 15 3 7 13	(P = 0. < 0.000 = 1.70. te IM <u>Total</u> I:Yes 88 219 10 115 244	18 .44); <i>I</i> ² = 0 001) .df = 2 (<i>P</i> : Complet Events 1 8 0 1 2	% = 0.43). e IM Total 104 248 81 134 302	/ ^z = 0% <u>Weight</u> 4.7% 38.3% 0.6% 4.7% 9.1%	Risk Ratio M-H, Fixed, 95% CI 18.91 [2.56, 139.75] 2.12 [0.92, 4.91] 52.18 [2.88, 944.18] 8.16 [1.02, 65.32] 8.05 [1.83, 35.31]	0.01 0.1 1 10 100 Higher risk of CIM Higher risk of IIM Risk Ratio M-H, Fixed, 95% CI
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Total events Heterogeneity: χ^2 = 11 Test for overall effect: Test for subgroup 2.2.1 Pathological qua Gonzalez 2010 Gonzalez 2016 Pittayanon 2017 Piazuelo 2021 Lee 2021 Subtotal (95% CI) Total events	90 1.04, df = 11 Z = 7.09 (P erences: χ^2 Incomplet Events ality control 16 15 3 7 13 54	(P = 0. < 0.000 = 1.70. te IM Total I:Yes 88 219 10 115 244 676	18 .44); / ² = 0 001) df = 2 (<i>P</i> : Complet <u>Events</u> 1 8 0 1 2 1 2	% = 0.43). e IM Total 104 248 81 134 302 869	/ ² = 0% <u>Weight</u> 4.7% 38.3% 0.6% 4.7% 9.1% 57.4%	Risk Ratio <u>M-H, Fixed, 95% CI</u> 18.91 [2.56, 139.75] 2.12 [0.92, 4.91] 52.18 [2.88, 944.18] 8.16 [1.02, 65.32] 8.05 [1.83, 35.31] 5.45 [3.02, 9.84]	0.01 0.1 1 10 100 Higher risk of CIM Higher risk of IIM Risk Ratio M-H, Fixed, 95% CI
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Figure 4. Forest plots of subgroup analysis of gastric cancer risk in IM subtypes according to country of origin and pathological quality control. IIM, incomplete intestinal metaplasia; CI, confidence interval; M-H, Mantel-Haenszel.

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	Incomple	to IM	Comple	to IM		Dick Datia	Dial/ Datia
Study or Subaroup	Fuente		Comple	Total	Moight	M H Bandom 05% CL	RISK Rauo
3 1 1 Agia	Events	Total	Events	Total	weight	M-H, Kandom, 95% CI	M-H, Kandom, 95% Ci
Difference 2047	2	40	4	04	0.00	46 00 14 64 460 041	
Pillayanon 2017	2	10	1	81	9.0%	10.20 [1.01, 103.01]	
Sun 2009 Subtatal (05% CI)		43	6	19	27.5%	0.52 [0.20, 1.33]	
Subtotal (95% CI)		55	7	100	21.3%	2.45 [0.08, 71.10]	
l otal events	9 5 4 0 m ²			0070.07	0.000		
Heterogeneity: Tau*=	5.16; $\chi^{-} = 1$	7.36, at =	= 1 (P = 0)	.007);7*	= 86%		
l est for overall effect:	Z = 0.52 (F	² = 0.60)					
3.1.2 Europe							
Chanelle 2020	3	13	2	60	13.0%	6 9 2 1 2 2 2 3 3 6 9	
Gonzalez 2020	13	210	â	248	19.7%	1 64 (0 71 3 75)	
Gilvo 1000	12	213	a	101	10.7%	5 26 (2 20 12 22)	
Coccoi 1000	2	41	0	71	7 200	12.00 [2.00, 12.22]	_
Subtotal (05% CI)	3	206	0	490	59.0%	12.00 [0.04, 220.08]	-
Total evente	21	230	20	400	30.070	4.05 [1.05, 5.55]	-
Hotorogonoity: Tou?	0 41 . 2 -	GEA de	- 2/0 - 0	001.12.	- 5 4 04		
Telefoyenelly. rau -	7-206/6	0.04, ul-	- 3 (r - 0 N	.09),7 -	- 34%		
restion overall ellect.	z = 3.00 (r	0.002	2)				
3.1.3 South America							
Piazuelo 2021	14	115	2	134	14.4%	8.16 [1.89, 35.14]	
Subtotal (95% CI)		115		134	14.4%	8.16 [1.89, 35.14]	
Total events	14		2				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z= 2.82 (F	P = 0.005	5)				
Total (95% CI)		464		714	100.0%	3.72 [1.42, 9.72]	
Total events	54		29				
Heterogeneity: Tau ² =	$1.11; \chi^2 = 1$	24.05, di	f=6(<i>P</i> =	0.0005)	; <i>l</i> ²= 75%)	0.01 0.1 1 10 100
Test for overall effect:	$Z = 2.68 (F_{2})$	P = 0.007	7)				Higher risk of CIM Higher risk of IIM
Test for subaroup diff	erences:X	² = 0.80.	df = 2 (P	= 0.67).	/²= 0%	D: 1 D ()	21 B - C
Ct	Incomple	ete IM	Comple	te IM		Risk Ratio	Risk Ratio
Study or Subgroup	Events	lotal	Events	lotal	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
3.2.1 Pathological qu	ality contro	ol:yes					
Gonzalez 2016	13	219	9	248	18.7%	1.64 [0.71, 3.75]	
Piazuelo 2021	14	115	2	134	14.4%	8.16 [1.89, 35.14]	
Pittayanon 2017	2	10	1	81	9.6%	16.20 [1.61, 163.01]	
Subtotal (95% CI)		344		463	42.7%	4.67 [1.11, 19.63]	
Total events	29		12				
Heterogeneity: Tau ² =	1.04; χ ² =	5.93, df:	= 2 (<i>P</i> = 0	.05);/*=	= 66%		
Test for overall effect:	Z= 2.10 (F	° = 0.04)					
3.2.2 Pathological gu	ality contro	ol:NR					
Chanelle 2020	3	13	2	60	13.0%	6 9 2 11 28 27 361	_
Silva 1990	12	22	á	101	19.0%	5 86 [2 80 12 22]	
Soccoi 1990	2	41	0	71	7 2%	12 00 0 84 228 89	_
Qup 2000	7	42	6	10	17.0%	0 52 10 20 1 220	_
Subtotal (95% CI)	(120	0	251	57.3%	3 31 [0.60, 16,03]	
Total overto	25	120	17	231	57.570	5.51 [0.05, 10.05]	
Hotorogonoity: Tou?-	1 05: v ² -	10 21 4	11 f= 2/D-	0.0004	· /Z - 0 4 04		
Telefoyenelly. rau -	7-140/0	10.21, u	1-3(0.0004	1,1 - 04%	0	
rest for overall effect.	Z = 1.49 (F	- = 0.14)					
Total (95% CI)		464		714	100.0%	3.72 [1.42, 9.72]	
Total events	54		29				
Heterogeneity: Tau ² =	$1.11; \chi^2 =$	24.05, d	f=6(P=	0.0005	; <i>1</i> ² = 75%		
Test for overall effect:	Z= 2.68 (F	P = 0.007	7)				U.UT U.T T 10 100
Test for subaroup diff	erences: x ²	$^{2} = 0.10$	df = 1 (P)	= 0.75).	$l^{2} = 0\%$		Higher fisk of CIM Higher fisk of IM

Figure 5. Forest plots of subgroup analysis of dysplasia risk in IM subtypes according to country of origin and pathological quality control. IIM, incomplete intestinal metaplasia; CIM, complete intestinal metaplasia; CI, confidence interval; M-H, Mantel-Haenszel.

studies, the abovementioned subtype staining results are easy to identify and distinguish, so the level of interobserver agreement for the IM subtype is likely similarly high. In our study, we conducted a subgroup analysis on whether to perform pathological quality control, which showed that the pooled relative risk (5.45, 95% CI, 3.02–9.84) of pathological quality control was



Figure 6. Funnel plots for the analysis of publication bias.

similar to the total pooled results, which proved that the IM subtypes have a high coincidence rate in the pathological diagnosis.

González et al. (7) conducted a review of the evidence including 14 cross-sectional studies and 10 follow-up studies assessing the risk of GC among subjects with different types of IM, and the results showed that the relative risks of GC were 4- to 11fold higher for the presence of incomplete IM in comparison with complete IM or the absence of incomplete IM. Similarly, Shao et al. (8) observed that incomplete IM (pooled OR = 9.48, 95% CI, 4.33–20.78), but not complete IM (pooled OR = 1.55, 95% CI, 0.91–2.65), was significantly associated with a higher GC risk in a meta-analysis of GC risk among patients with gastric IM. The results of our systematic review and meta-analysis are consistent with the abovementioned research conclusions.

In addition, we found that the fixed-effects estimated pooled prevalence of incomplete IM among patients with IM was 42% (95% CI, 34-49) and complete IM was 58% (95% CI, 50-66), which is consistent with previous research results (41). The widespread distribution of incomplete IM further illustrates the necessity of clinical subtype diagnosis; however, we believe that the main barrier to clinical implementation is the limited reliable evidence-based data, which is mainly caused by the heterogeneity of the research with different study designs, periods, endoscopic and biopsy protocols, and variable follow-up statuses. Fortunately, in recent years, reports of related long-term cohort studies have gradually increased. We, therefore, chose cohort studies for the meta-analysis to obtain more objective results. In clinical practice, Correa et al. (42) suggested that a diagnosis of incomplete IM should be followed by endoscopic topographic mapping to evaluate its extension and rule out more advanced lesions, such as dysplasia or early adenocarcinoma. Shah et al. (37) also promoted the utility of the IM subtype for potential prognostic value and cost-effective pathological operation. In addition, the diagnosis of mixed complete and incomplete IM has not vet been unified, and consensus on pathological diagnosis needs to be formed later.

Our systematic review and meta-analysis had several limitations. First, only 3 electronic databases were searched, and only studies published in English were included, which may have missed potential studies in other databases or those published in other languages. Second, the included studies were from Asia,

Europe, and South America; the limited generalizability to global populations cannot be ignored. Third, all the included studies were cohort studies, of which 10 were prospective cohort studies; several biases could not be avoided, particularly follow-up bias. Fourth, we calculated the RRs and 95% CIs by using the 2×2 table data extracted from the original studies; hence, confounding factors could not be excluded or matched, such as sex, age, family history of GC, and Helicobacter pylori infection. Finally, all the included studies presented the numbers of IM subtypes at baseline and GC at the end point; only 2 studies reported the hazards ratio of progression to GC for patients with incomplete IM compared with that for patients with complete IM (see Supplementary materials, http://links.lww.com/CTG/A677). However, RR and hazards ratio cannot be pooled even if we calculate the RRs of the remaining 10 studies because the absolute risk of GC in patients with IM is not low (43). A technical review reported that the annual incidence of GC is 12.4 cases per 10,000 persons with IM (9), and a Japanese study reported a higher cumulative incidence of GC at 5 years, reaching 5.3%-9.8% in patients with IM (44). Considering the abovementioned factors, we calculated the RRs and 95% CIs by using the 2 \times 2 table data extracted from all the original studies and pooled the results with RRs and 95% CIs.

In conclusion, our systematic review and meta-analysis indicated that the GC risk of incomplete IM, especially type III, was higher than that of complete IM. The current evidence indicates a correlation between IM subtypes and GC risk, which may support the use of IM subtypes in GC surveillance. More populationbased prospective cohort studies are warranted to confirm our findings.

CONFLICTS OF INTEREST

Guarantor of the article: Wei Wei, MD.

Specific author contributions: S.D., S.F., P.Z., and W.W: conception and design. S.D. and S.G.: analysis and interpretation of the data. S.D. and Y.Y: drafting of the article. S.D.: critical revision of the article for important intellectual content. all authors: final approval of the article.

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