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Literature review

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Risk Factors for IM Development and Progression: A Systematic Review

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1. Abstract

1.1. Background: IM has been established as a significant risk factor for gastric cancer (GC). Understanding the risk factors for the development and progression of IM is critical for identifying high-risk individuals and implementing preventive interventions for gastric cancer.

1.2. Objective: This systematic review aims to examine the current literature on the risk factors associated with intestinal metaplasia (IM) and to evaluate their impact on the development and progression of this condition.

1.3. Methods: A systematic literature search was conducted on PubMed, Scopus, and ScienceDirect databases, for articles published from database inception to 1st June 2023. The identified articles were then subjected to a study selection process. Thematic analysis was employed to examine how each risk factor (as a theme) affected IM incidence and progression.

1.4. Results: The initial search identified 2655 articles from databases and only 28 articles were included in this systematic review. The significant risk factors for IM incidence are H. pylori infection, older age, male gender, higher BMI, active smoking, consumption of spicy food and being of an African-American ethnicity. Some of the risk factors that did not reach statistical significance are, having a smoking history, GERD, having a family history of gastric cancer (GC), diabetic mellitus, hypertension, consumption of salty foods, and consumption of dairy products. Some of the risk factors for IM progression are older age, H.pyori infection, male gender, smoking and alcohol consumption. Being a relative to a gastric cancer patient did not reach statistical significance as a risk factor for IM progression. Being older (> 50 years, especially those > 60 years) and being male were significantly liked to the severity of IM. This review also reports some protective factors like consumption of soft drinks, fruits and vegetables and having duodenal ulcer illness.

1.5. Conclusion: People who have H.pylori infection, are older, are male in gender, are active smokers and consume alcohol are at substantial risk for both IM incidence and progression. Also, people who have a smoking history, consume spicy foods, consume salty foods, have a family history of gastric cancer (GC), have higher BMI, or have GERD are also at risk. This review calls for consideration of these cohorts as high-risk populations when formulating IM and GC intervention measures.

2. Introduction

Intestinal metaplasia (IM) is a pathological condition in which the normal gastric epithelial cells are replaced by cells of intestinal morphology. The condition is attributed to the presence of goblet cells, paneth cells and absorptive cells (de Vries et al., 2007). This metaplastic transformation happens due to bacterial-induced and persistent inflammation of gastric epithelial cells and the subsequent immune response of the individual. This inflammatory insult causes the degeneration of gastric glands followed by the replacement of gastric mucosa by intestinal epithelium (Correa & Houghton, 2007). In clinical settings, IM is classified according to histologic subtypes as either complete IM (type I) or incomplete IM (type II or type III) (Jass & Filipe, 1981). In 1988 Correa first described the series of events by which IM progresses to gastric cancer (Correa, 1988), for a while now IM has been considered an important precursor for gastric cancer (GC) (Du et al., 2021) (Jiang et al., 2017). According to Uemura et al. (2001) and Gomez and Wang (2014), patients with histologically confirmed gastric intestinal metaplasia have a 6 times more increased risk of developing gastric cancer compared to the general population. Understanding the risk factors for the development and

progression of IM is critical for identifying high-risk individuals and implementing preventive interventions for gastric cancer. There are several studies independently looking at individual risk factors, but a synthesis of all available evidence is required to identify consistencies and disagreements regarding the effect of identified risk factors. This systematic review, the first on this topic, aims to examine the current literature on the risk factors associated with intestinal metaplasia (IM) and to evaluate their impact on the development and progression of this condition.

3. Methods

This systematic review is reported following guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement (Page et al., 2021).

3.1. Information Sources and Study Selection

A systematic literature search was conducted on PubMed, Scopus, and ScienceDirect databases, for articles published from database inception to 1st June 2023. The query employed search strings detailed in (Table 3) in Appendix. The identified articles were then subjected to a study selection process.

3.2. Inclusion and Exclusion Criteria

Inclusion criteria were: (1) Articles written in English language, (2) peer-reviewed articles, (3) original research articles, (4) randomized controlled trials, and (5) observational studies. Exclusion criteria were: (1) qualitative studies, (2) systematic review and meta-analysis, (3) conference papers, and editor comments.

3.3. Review of Methodological Quality

Critical appraisal for both cohort and cross-sectional studies was done using the quality assessment tool for observational cohort and cross-sectional studies. Case-control studies were appraised using the quality assessment tool of case-control studies. Both of these tools were published by the National Heart, Lung, and Blood Institute (NHLBI) (National Heart, Lung, and Blood Institute (NHLBI), 2013). The second version of the Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to appraise the randomized trials (Sterne et al., 2019).

3.4. Data Extraction

Each article included in the review was summarized in a study descriptor table. The data extracted were study author(s), publication year, study type, study country, participant demographics, type of intestinal metaplasia and risk factor assessed.

4. Results

4.1. Search Results

The initial search identified 2655 articles from databases. 1041 from PubMed, 1364 from Scopus and 250 from ScienceDirect. 301 duplicates were removed. During the title and abstract screening, 2282 articles were excluded following the eligibility criteria, and the remaining 72 articles were subjected to a full-text review. 44 of these articles were excluded because they did not fully satisfy the inclusion criteria. Only 28 articles were included in this systematic review. The reasons for exclusion are shown in Figure 1 (PRISMA flowchart).

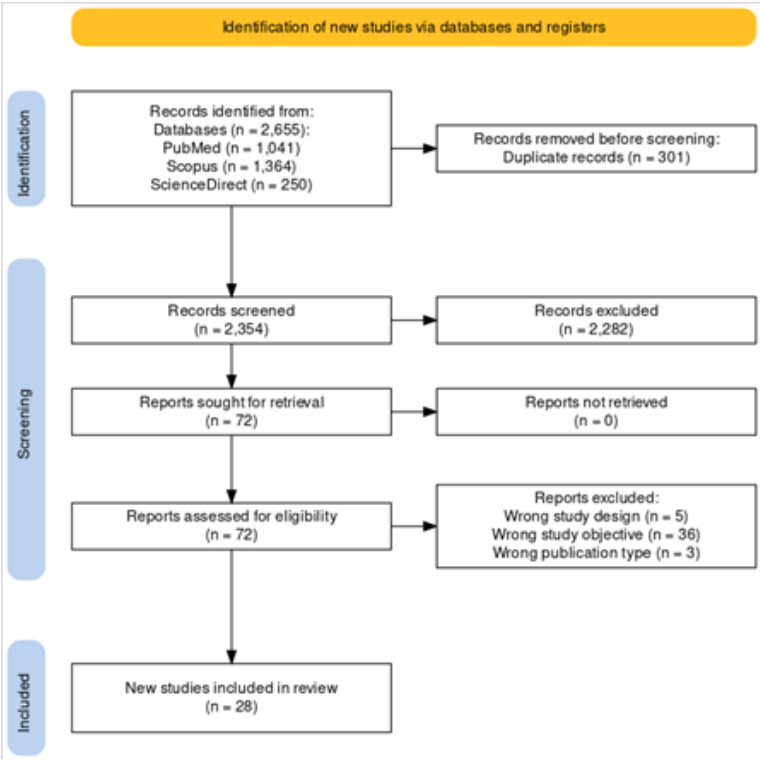

Figure 1: PRISMA flowchart showing the study selection process.

4.2. Results of Quality Assessment

The randomized trial (Leung et al. 2004) scored a low risk of bias. The cohort and cross-sectional studies overall scored well, with most studies scoring 'good'. All of the case-control studies scored 'good' in overall quality.

5. Results of Data Extraction

5.1. Characteristics of Included Studies: Summary

This systematic review included 28 studies; 6 cohort studies, 14 cross-sectional studies, 7 case-control studies and 1 randomized trial. Most of the studies were done in USA or Asia. Most of the studies looked at the risk factors for the incidence of IM, but only 4 looked at IM progression (Aumpan et al. 2021), (Huang et al. 2020), (Kneller et al. 1992), (Nieuwenburg et al. 2021). The total study population is 439, 210.

5.2. Number of Biopsies in Studies

Histological examination of biopsy samples was done in all included studies except Joo et al. (2013), Kim et al. (2019) and Kim et al. (2020). The number and location of biopsies varied across studies. Despite performing biopsy, Tan, Jamali, et al. (2021) did not report the location and number of samples taken.

6. Results of Included Studies

6.1. H.Pylori Infection

In most studies, current H.pylori infection or having a history of H.pylori infection was a significant risk factor for the development and progression of IM (Aumpan et al. 2020) (Aumpan et al. (2021), (Felley et al. 2012), (Hong et al. 2014), (Goldblum et al. 1998), (Kim et al. 2008) (Holmes et al. 2021), (Huang et al. 2020), (Pieramico and Zanetti 2000), (Joo et al. 2013), (Oh et al. 2013), (Leung et al. 2005), (Ohkuma et al. 2000), (Tsukui et al. 2001), (Jiang et al. 2017) (Thrift et al. 2020). In some of the studies, this positive association was however non-significant (Felley et al. 2012), (Nieuwenburg et al. 2021), (Tan, Jamali, et al. 2021).

In Aumpan et al. (2020), H. pylori infection rates were significantly higher for IM patients compared to those with chronic gastritis. The study also reported a difference in the H.pylori infection rates for complete and incomplete IM. The rate for patients with incomplete IM was slightly lower than those with complete IM, at 58.6% compared to 66.5%. Holmes et al. (2021) reported a 52.5% H. pylori infection rate in people with IM of non-cardia, compared to a 21.9% prevalence in the control group. Huang et al. (2020), Thrift et al. (2020), and Pieramico and Zanetti (2000) reported a significantly higher prevalence of GIM in those with H.pylori infection compared to those without, the rates were 29.9% vs 11.0%, and 53.2% vs. 21.7%, and 27% vs 13%, respectively. Additionally, in Pieramico and Zanetti (2000), 59% of patients with IM of the cardia had an H. pylori infection compared to 41% who didn't. In Hong et al. (2014), H. pylori infection was detected in 81.7% of IM patients compared to 68% of the control group. This would in regression analysis translate to an Odds Ratio of 2.338 (95% CI, 1.573–3.474), acknowledging H.pylori as a significant risk factor for the development of IM. Using regression analysis Aumpan et al. (2021), Huang et al. (2020), Joo et al. (2013), Ohkuma et al. (2000), and Tsukui et al. (2001) arrived at the same statistical findings as In Hong et al. (2014). Felley et al. (2012), Kim et al. (2008) and Oh et al. (2013) looked at how H.pylori infection affected the occurrence of IM at specific gastric locations i.e. in the antrum and the corpus. Kim et al. (2008) found H. pylori to be a risk factor for IM in the antrum (OR 8.22, 95% CI 3.27–20.7) and for IM in the body (OR 3.65, 95% CI 1.51–8.87). In Oh et al. (2013), the odds ratios for developing IM of the antrum were 7.81 (95% CI 3.72–16.40) and 2.86 ($P<0.001$) in the body. In Leung et al. (2005), which used only first-relatives of gastric cancer patients as study subjects, H. pylori infection, was associated with an OR of 5.4 (95% CI, 2.8-10.43) to the incidence of IM. Felley et al. (2012), Goldblum et al. (1998), Huang et al. (2020) and Jiang et al. (2017) reported a strong association between active H.pylori infection and the occurrence of GIM. The association reported by Felley et al. (2012) was however limited only to IM in the antrum and the fundus.

In Tan, Jamali, et al. (2021) having an H. pylori infection (current or history) was not significantly associated with GIM (AOR 1.14; 95% CI 0.86-1.51). The same study also reported that the prevalence of H.pylori infection was not different between IM patients and controls. Felley et al. (2012), also reported that H. pylori infection showed no significant association with IM of the cardia (IMC). It however played a pivotal role in the incidence of metaplasia of the antrum and the fundus, with odds ratios reaching 7.4 and 11.2 respectively (Felley et al. 2012).

Leung et al. (2004) took a different analytical step and instead of looking at the risk factors for IM incidence, looked at the risk factors for IM progression. After performing a logistic regression analysis, subjects who had persistent H pylori infection (with five years of follow-up) had a significantly higher risk of IM progression than those with successful eradication (AOR = 2.13 (95% CI 1.41–3.24). Aumpan et al. (2021), which also looked at IM progression, found a significant association with an OR of 2.64(95%CI 1.13–6.18). This is because 15.2% of H.pylori-positive patients recorded progression of IM to dysplasia compared to 2.1% of H. Pylori-negative people. Nieuwenburg et al. (2021) also looked at factors for IM progression but found no significant association with H.pylori. The study reported a Hazards ratio of 1.1(95%CI, 0.6–1.7, $P=0.953$).

6.2. Age

In most included studies the incidence and severity of IM increased with age (Aumpan et al. 2020), (Felley et al. 2012), (Holmes et al. 2021), (Chitapanarux et al. 2023), (Hong et al. 2014), (Huang et al. 2020), (Jiang et al. 2017), (Joo et al. 2013), (Kim et al. 2008), (Leung et al. 2005), (Oh et al. 2013), (Ohkuma et al. 2000), (Tan et al. 2020), (Russo et al. 2001), (Tan, Jamali, et al. 2021), (Tan, Niharika Mallepally, et al. 2021), (Tsukui et al. 2001). Only one study, (Stemmermann et

al. 1990) found no significant association between age and incidence of IM.

The age of 50 years and older (Aumpan et al. 2020), (Chitapanarux et al. 2023), (Hong et al. 2014) (Russo et al. 2001) and especially that of 60 years and older(Joo et al. 2013), (Ohkuma et al. 2000), (Tan, Jamali, et al. 2021), (Tan, Niharika Mallepally, et al. 2021), (Aumpan et al. 2021) seemed to have the highest risk. From the studies where age group categories were used, older age groups always had higher OR compared to younger age groups.

In Aumpan et al. (2020), people with age >50 years were significantly more in the IM group than in the chronic gastritis group. Aumpan et al. (2020) also looked at the difference in the occurrence of complete and incomplete IM according to age. The study reported that the prevalence of incomplete IM increased with age and doubled in the age group of 41–50 and 51–60 years compared to the group of ≤40 years. In Felley et al. (2012) age was a potential factor associated with intestinal metaplasia of the cardia (IMC). Age was significantly greater in patients with IMC than in patients with normal cardiac mucosa. Also in Tan, Jamali, et al. (2021), Tan et al. (2020) and Tan, Niharika Mallepally, et al. (2021), which categorized subjects into those with IM and those without (case-control studies); the case group were much older on average compared to the control group. In Hong et al. (2014), patients with IM were significantly older than those without IM (52.4±11.8 vs. 45.4±13.6 years). The study also looked at the association between age and severity of IM. In the study, the mean age of the patients with moderate and severe IM was 56.0±10.1 years, which was slightly older than that of the patients with mild IM (51.8±12.0) (Hong et al. 2014). A Cochran– Armitage test By Jiang et al. (2017) also revealed that not only the incidence rate but also the degree of severity of IM increased notably with age. In Holmes et al. (2021), compared to controls, cases with non-cardia gastric IM were significantly more likely to be aged ≥60 years at study enrollment. In Leung et al. (2005), which looked only at first-relatives of gastric cancer patients, subjects with gastric IM were significantly older than those without metaplasia (45.8 ± 7.9 versus 39.9 ± 8.8). In Chitapanarux et al. (2023), the prevalence of IM increased from 9% in those under 50 years to 30% in those above 60. People who were aged above 61 years in Oh et al. (2013) showed more than 30% prevalence (Tables 1-6).

In Aumpan et al. (2021), age >50 years, was significantly associated with IM with OR of 1.67 (95% CI 1.15–2.42). Analysis results in Chitapanarux et al. (2023) showed that the older age group of 50–59 years (OR, 2.18; 95% CI, 1.20–3.95) and above 60 years old (OR, 4.46; 95% CI, 2.51–7.93) were at significant risk for IM incidence. Hong et al. (2014) identified age ≥50 years as a significant independent risk factor for the development of IM with the Odds Ratio at 2.606 (95% CI=1.889–3.597). Joo et al. (2013) also showed that older age groups of 40 to 59 (OR, 3.16; 95% CI, 2.11 to 4.72) and above 60 years old (OR, 3.25; 95% CI, 2.05 to 5.15) were significant independent risk factors for IM. In Oh et al. (2013), analysis was done using the age group 26–30 years set as the reference. The distribution of IM was reported to increase with age. The odds ratio was about 1.2 per a 5-year period. Ohkuma et al. (2000) reported an odds ratio of 5.5, (95% CI; 1.7–17.6) for those aged 60 years and older. In Russo et al. (2001), which only had subjects with H. pylori infection, there was a significant association between age and IM. The OR was 2.1 (95% CI, 1.0–4.6) for the subjects aged 50–59 years and 3.8 (95% CI, 1.1–13.0) for those aged at least 60 years. In Tan, Jamali, et al. (2021), age 40-60 years (OR= 2.02; 95%CI 1.17-3.29) and >60 years (OR 4.58; 95%CI 2.61-8.03) were significant risk factors for incident IM. This is compared to <40 years as a reference. Tan, Niharika Mallepally, et al. (2021) used an older age group, 60 years, as a reference but found the same results. Ages of 60–69 years (OR=1.50; 95% CI, 1.17–1.93) and >70 years (OR, 2.12; 95% CI, 1.48–3.04), were independently associated with gastric intestinal metaplasia. Kim et al. (2008) looked at the risk factors for antral and body IM separately. The risk factors of IM in the antrum were age 48 to 60 years (OR= 2.28, 95% CI 1.04–4.98) and ages ≥ 61 years with OR= 3.02 (95% CI 1.34–6.78) (Kim et al. 2008). The risk factors of IM in the body were age ≥ 61 with OR = 9.98 (95% CI 3.78–26.3). In Tsukui et al. (2001), age was reported as an independent risk factor for intestinal metaplasia of the gastric corpus. There was a significant correlation between age and IM scores (r = 0.298, P = 0.0002). The study also reported that the odds of a patient having IM increases by 2.94 within 20 years, suggesting that the risk for intestinal metaplasia becomes almost threefold after a 20-year period. This was specific to H. pylori-positive subjects, showing that a combination of old age and H. pylori infection is substantially risky.

In Leung et al. (2004) which looked at the factors for IM progression, the age group of 45 years and above was a significant risk factor (AOR=1.92 (95% CI 1.18–3.11). The rate of progression was highest, at 62.8%, among ages of 45 years or older with persistent H pylori infection (Leung et al. 2004). Once again showing the substantial risk arising from an H.pylori infection in old age. In Aumpan et al. (2021), being age >65 years, was significantly associated with persistent IM or IM progression to dysplasia with OR 2.47(95%CI 1.33–4.61).

Table 1: Study Descriptor table

Study	Study Design	Study Area	Type of Participants	Participant Demographics	Type of Intestinal Metaplasia	The Risk Factor Been Assessed	Risk Factors Analysis for Incidence or Progression
Aumpan et al. (2020)	CS	Thailand	subjects from a low prevalence area of gastric cancer	1370 patients, 45% male, mean age of 60.7 ± 13.3 years, range of 16–96 years	GIM	age, BMI, H.pylori infection, underlying health e.g. diabetes mellitus, family history of gastric cancer, smoking, alcohol	incidence
Aumpan et al. (2021)	CS	Thailand	subjects from a low prevalence area of gastric cancer	2025 patients, 44.2% male, mean age of 61.3± 13.4 years, age range of 16–96 years	GIM	age, BMI, H.pylori infection, underlying health e.g. diabetes mellitus, family history of gastric cancer, smoking, alcohol	incidence and progression
Chitapanarux et al. (2023)	CSS	Thailand	patients with dyspepsia	947 subjects, 60% male, mean age of 53.61 ± 9.73 years	GIM	age, H.pylori infection, dietary habits	incidence
Felley et al. (2012)	CSS	Finland	general population	217 people, 45% male, mean age of 45.3 ± 15.3 years	IM of the cardia (IMC)	Helicobacter pylori (H. pylori), gastroesophageal reflux disease (GERD), age, smoking and BMI	incidence
Goldblum et al. (1998)	CCS	USA	patients with GERD	85 patients, mean age of 63 years	IM of the cardia (IMC)	GERD and H. pylori infection	incidence
Holmes et al. (2021)	CSS	USA	U.S. Veterans population	2084 participants, 92% male, mean age was 60.2 years	GIM	alcohol use	incidence
Hong et al. (2014)	CSS	China	patients with concomitant gastric and duodenal ulcer (CGDU) disease	2149 cases, 75% males	GIM	age, gastric ulcer, H.pylori infection, gender	incidence
Huang et al. (2020)	CCS	USA	general population	36799 cases, 46% males	GIM	age, gender, ethnicity, H pylori status	incidence and progression
Jiang et al. (2017)	CSS	China	general population	28745 cases, mean age of 50.98 ± 13.33 years	GIM	age, sex, H. pylori infection rate, atrophic gastritis, GDP per capita	incidence
Joo et al. (2013)	CSS	South Korea	general population	4023 subjects, 58.6% males, mean age of 48.7±11.3, age range from 15 to 98 years	antral and corpus IM	age, male gender, H. pylori IgG positivity, AG, BMI, relatives to gastric cancer, smoking, alcohol, low education, and consumption of dairy product	incidence
Kim et al. (2019)	CS	South Korea	subjects free of endoscopic IM and AG	142832 subjects, 56.3% males, mean age of 37.3 ±6.3 years	IM	BMI	incidence
Kim et al. (2020)	CS	South Korea	adults free from AG and IM	202675 subjects, 55.4% males, mean age of 36.1 ±6.4 years	GIM	alcohol use, smoking	incidence
Kim et al. (2008)	CSS	South Korea	population without gastroduodenal disease	389 subjects, 30.1% male, mean age of 51.3 years	antral and corpus IM	age, sex, H. pylori, Smoking, Alcohol, source of current drinking water, Education, Occupation, Salty food, Spicy food	incidence
Kneller et al. (1992)	CSS	China	general population at high risk for stomach cancer (China is a high GC risk area)	3104 participants, 53% males, median age was 44 years	GIM	smoking tobacco, alcohol intake, diet, family medical history	progression
Leung et al. (2004)	RT	China	H pylori infected subjects	587 participants, mean age of 52.0±8.1 years	GIM	duodenal ulcer, H pylori infection, age, alcohol use, source of drinking water	incidence
Leung et al. (2005)	CSS	China	First-degree relatives (FDRs) of gastric cancer patients	270 subjects,47% male, median age of 42 years	antral and corpus IM	age, male sex, H. pylori infection, alcohol use	incidence
Nieuwenburg et al. (2021)	CS	Netherlands, Norway	people from areas with low GC incidence	308 patients, 48.4% male, median age of 61 years	GIM	Alcohol use, BMI, history of H. pylori infection, family history of gastric cancer, smoking	progression
Oh et al. (2013)	CCS	South Korea	First-degree relatives (FDRs) of gastric cancer patients	564 patients, mean age of 51 years	antral IM	age, sex, ethnicity, smoking status, current H. pylori, diet	incidence
Ohkuma et al. (2000)	CSS	Japan	general population	163 patients, 47.2% male	GIM	Helicobacter pylori infection, Sex, Alcohol, Smoking, Coffee	incidence

Pieramico and Zanetti (2000)	CCS	Italy	patients with gastroesophageal reflux disease (GERD)	171 patients	cardia IM	degree of chronic gastritis, Helicobacter pylori colonization	incidence
Russo et al. (2001)	CCS	Italy	H. pylori-positive subjects	344 subjects, 81.3% male	GIM	smoking, alcohol, dietary habits	incidence
Stemmermann et al. (1990)	CS	USA	a cohort of Hawaii Japanese men	350 patients, 100% men	GIM	diet, smoking	incidence
Taborda and Prolla (2012)	CCS	Brazil	functional dyspeptic patients	320 patients	GIM	nutritional factors and dietary habits	incidence
Tan, Jamali, et al. (2021)	CSS	USA	general population	2106 participants, 39.7% male	GIM	age, sex, ethnicity, smoking status, current H. pylori status	incidence
Tan et al. (2020)	CSS	USA	US Veterans	2219 participants	GIM	dietary factors	incidence
Tan, Niharika Mallepally, et al. (2021)	CSS	USA	US Veterans	2219 patients, 91.9% male	non-cardia IM	age, sex, ethnicity, smoking status, alcohol status, H.pylori infection	incidence
Thrift et al. (2020)	CCS	USA	US Veterans	1962 participants, 92% male	non-cardia IM	smoking	incidence
Tsukui et al. (2001)	CSS	Japan	patients with dyspepsia	154 patients, 71.4%, male, mean age of 57.1 ± 1.1 years, age range of 23–89 years	corpus IM	age, gender, duodenal ulcer, H.pylori infection	incidence

CS-cohort study; CSS-cross-sectional study; CCS-case-control study; RT-Randomized trial

Table 2: Number and location of biopsy

Study	Sites and Number of Biopsies Per Site
Aumpan et al. (2020)	antrum (n=1), corpus (n=1), and incisura (n=1) plus from any macroscopic targeted lesion (n=2)
Aumpan et al. (2021)	antrum (n=1), corpus (n=1), and incisura (n=1)
Chitapanarux et al. (2023)	antrum (within 3 cm from the pylorus) (n=2), angulus (n=1), body (n=2).
Felley et al. (2012)	esophagus (2 cm above the Z-line) (n=2), esophagogastric junction (n=4), cardia (10 mm below the Z-line) (n=2), fundus (greater and lesser curvature) (n=2), antrum (greater and lesser curvature) (n=2), angulus (n=1)
Goldblum et al. (1998)	distal esophagus (5 cm above the squamo-columnar junction) (n=2), gastric antrum (n=2), fundus (n=2), cardia (n=2)
Holmes et al. (2021)	at least 10 biopsies, the antrum (both greater and lesser curvature), corpus (proximal greater curvature, proximal lesser curvature, distal greater curvature, distal lesser curvature), and cardia
Hong et al. (2014)	antrum (n=2), body mucosa without the ulcer (n=2), body mucosa at edge of each ulcer (n≥2)
Huang et al. (2020)	antrum and body
Jiang et al. (2017)	from 2 to 10 biopsies per case….. Antrum (greater or lesser curvatures) and areas of suspected lesion
Kim et al. (2008)	the lesser curvature of the mid-antrum (mid-portion between the pyloric ring and the angularis incisura) (n=3), the greater curvature of the mid-antrum (mid-portion between the pyloric ring and the lower end of mucosal folds) (n=2), the mid-body of the stomach (mid-portion between the angularis incisura and upper line of high body (n=3), mid-body (mid-portion between the lower end of mucosal folds and upper line of high body) (n=2)
Kneller et al. (1992)	upper and lower stomach
Leung et al. (2004)	three antrum (greater and lesser curvatures 2–3 cm from the pylorus) (n=3), Corpus (lesser and the greater curvature at the mid corpus) (n=3)
Leung et al. (2005)	antrum (greater and lesser curvatures in the distal and proximal) (n=4), corpus (greater and lesser curvature of the proximal and distal) (n=4)
Nieuwenburg et al. (2021)	antrum (n=4), incisura (n=2), lesser curvature (the concave side of the stomach) (n=2), greater curvature (the convex side of the stomach) (n=2), cardia (n=2) and from any visible lesion
Oh et al. (2013)	mid antrum (n=2), mid body (n=2), the lesser curvature of the antrum (n=3), the lesser curvature of the body (n=3)
Ohkuma et al. (2000)	Antrum (anterior and posterior wall, at approximately 3 cm from the pylorus) (n=3), body (anterior and posterior wall) (n=3)
Pieramico and Zanetti (2000)	antrum (within 2 cm of the pylorus) (n=2), corpus (greater curvature) (n=2), cardia (1 cm below the squamo-columnar junction) (n=2)
Russo et al. (2001)	antrum (n=2), angulus (n=1), corpus/fundus (n=2), areas of suspected of lesions
Stemmermann et al. (1990)	antrum, corpus, incisura
Taborda and Prolla (2012)	antrum (n=3), body(n=2), incisura angularis (n=2)

Tan et al. (2020)	at least 10 biopsies, the antrum (both greater and lesser curvature), corpus (proximal greater curvature, proximal lesser curvature, distal greater curvature, distal lesser curvature), and cardia
Tan, Niharika Mallepally, et al. (2021)	at least 10 total biopsies, the antrum (both greater and lesser curvature), corpus (distal greater curvature, distal lesser curvature, proximal greater curvature, and proximal lesser curvature), cardia
Thrift et al. (2020)	at least 10 biopsies, antrum (both greater and lesser curvature), corpus (proximal greater curvature, proximal lesser curvature, distal greater curvature, distal lesser curvature), cardia
Tsukui et al. (2001)	gastric corpus (2 cm below the esophageal-cardia junction), the middle portion of the lesser curvature of the corpus , the gastric anglular region, lower portion of the greater curvature of the gastric corpus (n=2)

Table 3: Search String

Database	Search string
PubMed	("risk factor"[Title/Abstract] OR determinants[Title/Abstract] OR contributors[Title/Abstract] OR predictors[Title/Abstract] OR "causal factor"[Title/Abstract] OR "predisposing factor"[Title/Abstract]) AND ("intestinal metaplasia"[Title/Abstract] OR IM[Title/Abstract] OR GIM[Title/Abstract] OR "epithelial metaplasia"[Title/Abstract] OR "mucosal metaplasia"[Title/Abstract] OR "Intestinalized gastric mucosa"[Title/Abstract])
Scopus/ ScienceDirect	"risk factor" OR contributors OR predictors OR "causal factor" OR "predisposing factor" AND "intestinal metaplasia" OR "epithelial metaplasia" OR "mucosal metaplasia" OR "Intestinalized gastric mucosa"

In Scopus and ScienceDirect, the search was limited to title, abstract and keywords. No date limits or any other filters were applied in any of the databases.

Table 4: Risk of bias in a randomized trial

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall bias
Leung et al. (2004)	some concerns	low risk	low risk	low risk	some concerns	low risk

Table 5: Quality assessment for cohort and cross-sectional studies

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Quality Rating
Aumpan et al. (2020)	Yes	Yes	Yes	Yes	No	No	Yes	NA	Yes	Yes	Yes	Yes	CD	No	Good
Aumpan et al. (2021)	Yes	Yes	Yes	Yes	No	No	Yes	NA	Yes	Yes	Yes	Yes	CD	No	Good
Kim et al. (2019)	Yes	Yes	Yes	Yes	No	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Kim et al. (2020)	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CD	Yes	Good
Nieuwenburg et al. (2021)	Yes	Yes	Yes	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	NR	CD	Good
Stemmermann et al. (1990)	Yes	Yes	NR	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Good
Chitapanarux et al. (2023)	Yes	Yes	NR	Yes	No	No	NA	Yes	Yes	No	Yes	Yes	NA	No	Fair
Felley et al. (2012)	Yes	Yes	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Good
Holmes et al. (2021)	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Yes	Good
Hong et al. (2014)	Yes	Yes	CD	Yes	Yes	No	No	No	Yes	No	Yes	Yes	NA	Yes	Fair
Jiang et al. (2017)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Good
Joo et al. (2013)	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	CD	Good

Kim et al. (2008)	Yes	Yes	CD	Yes	Yes	CD	CD	Yes	Yes	Yes	Yes	Yes	NA	Yes	Good
Kneller et al. (1992)	Yes	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Fair
Leung et al. (2005)	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Good
Ohkuma et al. (2000)	Yes	Yes	Yes	Yes	No	No	NA	NA	Yes	No	Yes	Yes	NA	Yes	Fair
Tan et al. (2020)	Yes	Yes	CD	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	NA	Yes	Good
Tan, Niharika Mallepally, et al. (2021)	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Good
Tan, Jamali, et al. (2021)	Yes	Yes	NR	Yes	No	No	NA	Yes	Yes	No	Yes	Yes	NA	Yes	Fair
Tsukui et al. (2001)	Yes	Yes	CD	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	NR	Yes	Good

Item 1: Was the research question or objective in this paper clearly stated? Item 2: Was the study population clearly specified and defined? Item 3: Was the participation rate of eligible persons at least 50%? Item 4: Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants? Item 5: Was a sample size justification, power description, or variance and effect estimates provided? Item 6: For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? Item 7: Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? Item 8: For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? Item 9: Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? Item 10: Was the exposure(s) assessed more than once over time? Item 11: Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? Item 12: Were the outcome assessors blinded to the exposure status of participants? Item 13: Was loss to follow-up after baseline 20% or less? Item 14: Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?
NA = Not applicable, NR = not reported, CD =cannot determine

Table 6: Quality assessment of case-control studies

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Quality Rating
Goldblum et al. (1998)	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Good
Huang et al. (2020)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CD	Yes	Good
Oh et al. (2013)	Yes	Yes	No	Yes	Yes	Yes	Yes	CD	Yes	Yes	Yes	Yes	Good
Pieramico and Zanetti (2000)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CD	CD	Good
Russo et al. (2001)	Yes	Yes	No	Yes	Yes	Yes	Yes	CD	Yes	Yes	Yes	Yes	Good
Taborda and Prolla (2012)	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Thrift et al. (2020)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

Item 1: Was the research question or objective in this paper clearly stated and appropriate? Item 2: Was the study population clearly specified and defined? Item 3: Did the authors include a sample size justification? Item 4: Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)? Item 5: Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants? Item 6: Were the cases clearly defined and differentiated from controls? Item 7: If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible? Item 8: Was there use of concurrent controls? Item 9: Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case? Item 10: Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants? Item 11: Were the assessors of exposure/risk blinded to the case or control status of participants? Item 12: Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?
NA = Not applicable, NR = not reported, CD =cannot determine

6.3. Sex

From the findings of included studies, the male gender was reported to be at a higher risk for incidence and progression of IM (Aumpan et al. 2020), (Jiang et al. 2017), (Holmes et al. 2021), (Tan et al. 2020). In Tan et al. (2020) and Tan, Jamali, et al. (2021) IM cases, compared to healthy patients, were more likely to be male 97.2% vs. 90.8% and 47.6% vs 38.6% respectively. Being male in Aumpan et al. (2020), Joo et al. (2013) Tan, Niharika Mallepally, et al. (2021), was linked to a significant risk factor of OR= 1.43 (95%CI 1.01–2.03), OR= 1.88; 95% CI, 1.39 to 2.54 and OR, 2.76; 95% CI, 1.50–5.10, respectively.

In Aumpan et al. (2021), Huang et al. (2020), and Ohkuma et al. (2000), male gender was a risk factor but did not reach statistical significance. In Hong et al. (2014) there was no significant difference in the incidence of IM between males and females (8.0 vs. 9.6%). The odds ratio for the male gender was OR=0.809 (95% CI=0.577–1.134) (Hong et al. 2014). Also, concerning the relationship between male gender and IM severity, moderate and severe IM was more frequently detected in males than in females 18.8% vs. 5.8% (Hong et al. 2014). The incidence rate of IM in the male population in Holmes et al. (2021) was 30.84% compared to 28.21% in the female population. The odds ratio for the male gender was OR = 1.12 (95% CI 1.07–1.18). In concurrence to Hong et al. (2014), the degree of severity of IM in male patients tended to be more severe than in female patients. In Leung et al. (2005), which looked at first-relatives of gastric cancer patients, male gender (OR, 2.09) was significantly associated with the presence of IM.

Only one study, Russo et al. (2001) found no relationship between gender and the incidence of IM.

6.4. Body Mass Index

In Aumpan et al. (2020), Felley et al. (2012) and Kim et al. (2019) the risk of IM increased as the BMI category increased. In Aumpan et al. (2020), overweight patients i.e. BMI ≥23 kg/m2 were significantly associated with higher risk for the development of incomplete IM (OR 3.25; 95%CI 1.14–9.27, p = 0.027). The association with complete IM was however not significant.

In Aumpan et al. (2021), Tan, Jamali, et al. (2021) and Tan, Niharika Mallepally, et al. (2021) BMI did not significantly affect the incidence of intestinal metaplasia.

Regarding the progression of IM, Nieuwenburg et al. (2021) report that BMI showed no association with the progression of GIM.

6.5. Smoking

People with IM of non-cardia in Holmes et al. (2021) were more likely to have a history of cigarette smoking (80.7%). In Thrift et al. (2020), 80.8% of cases with gastric intestinal metaplasia were current or former smokers compared to 71.0% in control. In Tan et al. (2020) and Tan, Jamali, et al. (2021), IM cases compared to controls were more likely to be ever-smokers, 76.4% vs. 66.3% and 25.5% vs 18.7%, respectively.

In Kim et al. (2008) smoking history had a risk factor of OR=3.49, (95% CI 1.39–8.75) for IM in the antrum and OR =7.10, (95% CI 2.48–20.3) for IM in the body. In Tan, Jamali, et al. (2021), and Tan, Niharika Mallepally, et al. (2021), current smoking status was an independent risk factor with an odds ratio of OR=2.04 (95%CI 1.39-3.00) and OR = 1.78 (95% CI, 1.29–2.48), respectively. In Russo et al. (2001), which included only subjects with H. pylori infection, current smokers of over 20 cigarettes per day had a 4-fold risk of IM (OR, 4.75, 95% CI, 1.33– 16.99). The odds ratio for smokers of fewer than 20 cigarettes was 1.88 (95% CI 0.91–3.89). Non-smokers were used as references in this study. In Thrift et al. (2020), compared to never-smokers, current smokers had a 2-fold increased risk for gastric IM (OR, 2.05; 95% CI, 1.47–2.85). Among ever smokers, increasing duration and total dose were significantly associated with increased risk for gastric intestinal metaplasia. Among former smokers, the risk for gastric intestinal metaplasia decreased over time and was no different to never smokers after 15 years of smoking cessation (Thrift et al. 2020).

In Nieuwenburg et al. (2021), smoking (HR 1.6; 95%CI 0.9–2.7, P=0.079) was associated with an increased risk of progression of GIM, but statistically non-significant.

In Aumpan et al. (2020), Aumpan et al. (2021), Felley et al. (2012), Ohkuma et al. (2000), Nieuwenburg et al. (2021), Stemmermann et al. (1990), and Taborda and Prolla (2012), smoking status did not reach statistical significance. In Kneller et al. (1992), cigarette smoking was found to be a mild risk factor for intestinal metaplasia. The ORs associated with smoking were similar for lesions occurring in both the upper (cardia) and the lower (antral) stomach (Kneller et al. 1992).

6.6. Alcohol

In Leung et al. (2005), a history of alcohol use was significantly associated with the presence of IM. Holmes et al. (2021) found that individuals who consumed on average ≥28 drinks per week had no elevated risk for gastric intestinal metaplasia (adjusted OR, 1.27; 95% CI, 0.74–2.19), compared to non-drinkers. The study found no demonstrable association between cumulative lifetime alcohol consumption and risk for gastric IM. In Kim et al. (2020) an increase in alcohol intake was positively associated with an increased risk of IM in adose–response manner. After adjustment for confounders, the Hazard ratios (95% CIs) for incident IM comparing alcohol intake of <10, 10–19.9, 20–39.9, and ≥40 with lifetime abstainers as a reference were, 1.27 (1.03–1.57), 1.35 (1.08–1.68), 1.50 (1.20–1.87), and 1.54 (1.23–1.93), respectively. Kim et al. (2020) also reported that drinking frequency (higher frequency of drinking), quantity (higher quantity of alcohol consumption per drinking day), and binge drinking (higher frequency of binge drinking) were consistently associated with increased risk of IM in adose–response manner. Former drinkers were also at a higher risk for IM compared with lifetime abstainers. A significant risk of incident IM was observed for fre-

quencies from 1 to 2 times drinking per week and quantities of 1 to 2 drinks per day. In Kneller et al. (1992), associations between drinking alcoholic beverages and intestinal metaplasia were less pronounced, although the risk of intestinal metaplasia among those consuming 400 mL per week or more was slightly elevated.

In Aumpan et al. (2021), Ohkuma et al. (2000), Tan, Jamali, et al. (2021), and Taborda and Prolla (2012) alcohol consumption was a risk factor but did not reach statistical significance. In Taborda and Prolla (2012), it was noted that the consumption of alcohol was not statistically different between the patients with IM and those without. Holmes et al. (2021), Russo et al. (2001), and Tan, Niharika Mallepally, et al. (2021), found no association between alcohol drinking status and risk of non-cardia gastric IM.

In Leung et al. (2004) alcohol use was an independent risk factor associated with IM progression with an OR = 1.67 (95% CI 1.07–2.62). In Aumpan et al. (2021) and Nieuwenburg et al. (2021), alcohol use showed no association with the progression of GIM.

6.7. Dietary Habits

In Kim et al. (2008) the consumption of strong spicy food was a risk factor with OR of 2.38 (95% CI 1.16–4.88). Also in Oh et al. (2013), spicy food increased the risk of antral IM by 2.28 fold (95% CI 1.36–3.84). However, regression analysis in Chitapanarux et al. (2023) showed that consuming spicy food (OR, 0.62; 95%CI, 0.44–0.89) was a significant protective factor for IM. In Stemmermann et al. (1990), nitrite-rich salty foods (e.g. cured meats) were directly related to metaplasia. In Taborda and Prolla (2012) and Oh et al. (2013), no significant effect of salt consumption was detected.

Multivariate analysis by Joo et al. (2013) showed that consumption of dairy products at least five times per week (OR, 1.40; 95% CI, 1.12 to 1.76) was a risk factor. In Russo et al. (2001) high butter consumers had a two-fold increased risk for IM (OR, 2.17; 95% CI, 1.14–4.11). In the study, no effect was noted for milk, processed meat, wholemeal cereals, and traditional nonalcoholic beverages such as tea and decaffeinated coffee. Instead, a moderate association was found for coffee consumption (OR, 2.14; 95% CI, 0.61–7.54) (Russo et al. 2001). A moderate positive risk was also reported by Ohkuma et al. (2000). In Russo et al. (2001), fish and cheese were directly associated with IM, though not statistically significant. In Leung et al. (2004) drinking water from a well was an independent risk factor associated with IM progression.

In Russo et al. (2001), soft drink consumption was inversely related to IM (OR, 0.44, 95% CI, 0.23–0.85). Raw vegetables, fresh fruits, carrots, eggs, and olive oil were also inversely associated, though not significant. In Taborda and Prolla (2012), the analysis of the patients with IM showed a higher frequency of canned and smoked foods consumption in the IM group and higher consumption of fruits and vegetables in patients without intestinal metaplasia. In Tan et al. (2020) GIM cases had lower fat intake (43.6% vs. 33.4%) and higher carbohydrate intake (41.8% vs. 33.3%) compared to controls. Tan et al. (2020) concluded that high carbohydrate intake was associated with an increased risk of GIM in US populations, independent of H. pylori or smoking.

Regarding eating habits, Kneller et al. (1992) reported that the prevalence of severe IM did not vary with eating fast or slowly or with a preference for hot or warm food.

6.8. Relation to Gastric Cancer Patients

Multivariate analysis by Joo et al. (2013) showed that having a relative with gastric cancer (OR, 1.48; 95% CI, 1.12 to 1.96) was a significant risk factor. In Kneller et al. (1992), the odds ratios for IM due to a parent having stomach cancer were 1.17 (95% CI = 0.75-1.82). Also, no excess risk of IM was associated with a parental history of other cancers. In Aumpan et al. (2020), a family history of GC did not reach statistical significance as a risk factor.

In Aumpan et al. (2021) and Nieuwenburg et al. (2021) family history of gastric cancer did not reach statistical significance for IM progression. In Nieuwenburg et al. (2021), having a family member (first- and/or second-degree) with gastric cancer had a hazard ratio of HR 1.5 (95% CI 0.9–2.4). 50 subjects had a first-degree relative with GC (48.0% showed progression of IM), 26 had a second-degree relative with GC (50.0% showed IM progression), and 190 did not have a family history of GC (36.3% showed IM progression) (Nieuwenburg et al. 2021). In Oh et al. (2013) relative of GC-patients had an adjusted OR of 2.69 (95% CI 1.06–6.80, P=0.037) for antral IM in the male population and OR of 1.68 in the total population.

6.9. Health Factors

In Aumpan et al. (2021), diabetes mellitus was significantly associated with persistent IM or its progression to dysplasia, with an odds ratio (OR) of 2.54 (95% CI 1.16–5.54, p = 0.019). Having hypertension, as an underlying disease was also significantly associated with IM, with an OR of 1.31 (95% CI 1.02–1.69, p = 0.036). Having pulmonary disease as a comorbidity was a risk factor that did not reach statistical significance in the same study (Aumpan et al. 2021).

Felley et al. (2012) found no significant association between gastroesophageal reflux disease (GERD) and intestinal metaplasia of the cardia (IMC). The study by Goldblum et al. (1998) had two groups, patients with GERD and those without (control). The observed difference in cardia IM between control and GERD patients was 18.8%. Of 27 patients in the control group, 6 (22%) had intestinal metaplasia of the cardia compared with only 2 (3%) in the GERD group. Pieramico and Zanetti (2000) also observed no difference in the prevalence of cardia IM between patients with gastroesophageal reflux disease (GERD) and controls. Tan, Niharika Mallepally, et al. (2021) reported that gastroesophageal reflux disease symptoms were not associated with the risk of gastric intestinal metaplasia. These findings suggest that GERD may not be strongly linked to IMC.

Jiang et al. (2017) reported an extremely high positive correlation between atrophic gastritis (AG) and IM, with an IM incidence rate of 97.07% in cases with AG compared to 23.34% in cases without AG.

Multivariate analysis by Joo et al. (2013) also identified AG as a significant independent risk factor for IM (OR 3.68, 95% CI 2.95–4.60).

In Hong et al. (2014), gastric ulcers at the gastric incisura were identified as substantial risk factors for the development of IM (OR 2.644, 95% CI 1.926–3.630). Bile reflux was also found to be positively correlated with the incidence of IM by Jiang et al. (2017).

Leung et al. (2004), conducted stepwise logistic regression analysis and found that duodenal ulcer patients were less likely to have IM progression (adjusted OR 0.25, 95% CI 0.09–0.66). Tsukui et al. (2001) found that duodenal ulcer disease reduced the risk of IM, suggesting a protective effect.

6.10. Ethnicity

In Huang et al. (2020), whites demonstrated a significantly lower prevalence of GIM compared with African Americans, Hispanics, and Asian/Pacific Islanders in all age groups. The odds ratios (ORs) for developing GIM were 2.49 (95% CI 2.15-2.89) for Black/African American individuals, 4.94 (95% CI 4.03-6.05) for Hispanics, and 5.21 (95% CI 4.60-5.91) for Asian/Pacific Islanders. In Tan et al. (2020), IM cases were more likely to be non-white individuals. Similarly, in Tan, Jamali, et al. (2021), black race was identified as a risk factor for GIM compared to non-Hispanic whites (NHW) with an adjusted odds ratio of 2.17 (95% CI 1.31-3.62). Tan, Niharika Mallepally, et al. (2021) also found that non-White race/ethnicity, specifically Hispanic and black individuals, were independently associated with gastric intestinal metaplasia compared to non-Hispanic whites (NHW). The adjusted odds ratios were 2.66 (95% CI 1.89–3.76) for Hispanics and 2.36 (95% CI 1.85–3.02) for blacks. Controls in this study were more likely to be non-Hispanic white (NHW) compared to cases.

6.11. Other Factors

Jiang et al. (2017) reported that the incidence of IM showed a positive correlation with the gross domestic product (GDP) per capita. Through linear correlation analysis, a significant correlation was observed between the incidence of IM and GDP per capita, with a correlation coefficient (r) of 0.66 ($p = 0.0039$). In Joo et al. (2013), a multivariate analysis was conducted to identify independent risk factors for IM. The study found that low education below college was a significant independent risk factor, with an odds ratio (OR) of 1.47 (95% CI, 1.06 to 2.00). In Kim et al. (2008), risk factors for IM in the body were explored. The study found that having a nonprofessional job compared to a professional job was associated with an increased risk of IM, with an odds ratio (OR) of 3.53 (95% CI 1.17–10.7). Similarly, being unemployed compared to having a professional job was also identified as a risk factor for IM, with an odds ratio (OR) of 3.79 (95% CI 1.28–11.2) (Kim et al. 2008).

7. Discussion

The role of H. pylori infection as a risk factor for gastric intestinal metaplasia (IM) was extensively studied, with several studies consistently reporting a significant positive association (Aumpan et al. 2020; Aumpan et al. 2021; Felley et al. 2012; Hong et al. 2014; Goldblum et al. 1998; Kim et al. 2008; Holmes et al. 2021; Huang et al. 2020; Pieramico and Zanetti 2000; Joo et al. 2013; Oh et al. 2013; Leung et al. 2005; Ohkuma et al. 2000; Tsukui et al. 2001; Jiang et al. 2017; Thrift et al. 2020). Some of these studies arrived at this conclusion by using regression models (Aumpan et al. 2021; Joo et al. 2013; Huang et al. 2020). There are studies, however, which found no significant positive association (Felley et al. 2012; Nieuwenburg et al. 2021; Tan, Jamali, et al. 2021). According to Kim et al. (2008), the antrum and body had an elevated risk of IM due to H. pylori. Furthermore, H. pylori infection was linked to IM progression (Leung et al. 2004; Aumpan et al. 2021). These results were unexpected since H.pylori has already been identified as a risk factor for GIM development and progression by the AGA Institute Technical Review (Altayar et al., 2020). The lack of association in some studies may be due to methodological differences, specifically the site of biopsy removal. As detailed by Felley et al. (2012), H.pylori can be responsible for IM in the antrum and the fundus but not the cardia. The location of the IM may then play a role to consider when deciding if H.pylori is a risk factor or not.

Across studies, age consistently appeared to be a significant risk factor for IM incidence and progression. Numerous studies, those by Aumpan et al. (2020), Felley et al. (2012), Holmes et al. (2021), Chitapanarux et al. (2023), showed that the prevalence and severity of IM increased with age. Individuals aged 50 and up, especially those aged 60 and up, had the highest likelihood of developing IM, according to Aumpan et al. (2020), Hong et al. (2014), Joo et al. (2013), Russo et al. (2001). Furthermore, age was found to be an independent risk factor for IM progression, with those 45 years and older exhibiting a higher risk of progression, as observed by Leung et al. (2004) and Aumpan et al. (2004).

Most studies reported that men were at a higher risk of IM development and progression. Tan et al. (2020, 2021), Aumpan et al. (2020), Joo et al. (2013), and Tan, Niharika Mallepally, et al. (2021) all reported a male predominance among IM cases. Holmes et al. (2021) discovered that males had a greater incidence rate of IM than females, additionally, Leung et al. (2005) discovered a strong connection between male gender and IM presence in first-degree relatives of stomach cancer patients. Huang et al. (2020), Ohkuma et al. (2000), and Hong et al. (2014), on the other hand, discovered no statistically significant differences or relationships between gender and IM.

Several studies reported that having a higher BMI increased the chances of developing IM. According to Aumpan et al. (2020), Felley et al. (2012), and Kim et al. (2019), as the BMI category increased, so did the risk of IM. Aumpan et al. (2021), Tan, Jamali et al. (2021), and Tan, Niharika Mallepally et al. (2021) did not find a significant effect of BMI on IM progression.

Several studies examined the association between smoking and gastric intestinal metaplasia (IM). Holmes et al. (2021) and Thrift et al. (2020) observed a higher prevalence of smoking in individuals with IM. Kim et al. (2008) observed that a history of smoking was a major

risk factor for IM in specific stomach regions. Current smoking was established as an independent risk factor by Tan, Jamali et al. (2021) and Tan, Niharika Mallepally et al. (2021). However, the association reported in some studies (Nieuwenburg et al., 2021; Aumpan et al., 2020, 2021; Felley et al., 2012; Ohkuma et al., 2000; Stemmermann et al., 1990; Taborda & Prolla, 2012) did not reach statistical significance. One cause for this variation may be due to the inconsistencies among studies to differentiate between current, prior and non-smokers (used as reference).

In included studies, alcohol use was found to be an independent risk factor for stomach (IM). Leung et al. (2005) discovered a link between alcohol use and IM in first-degree relatives of stomach cancer patients. Kim et al. (2020) also discovered a dose-response relationship, with higher alcohol intake associated with increased IM risk after controlling for covariates. However, Holmes et al. (2021) discovered no increased risk among heavy drinkers, showing a lack of agreement. The effect of alcohol on IM progression is uncertain, as Leung et al. (2004) observed a link between alcohol usage and progression, whereas Aumpan et al. (2021) and Nieuwenburg et al. (2021) suggested no significant associations. Other studies found alcohol use to be a risk factor but found it to be statistically insignificant (Aumpan et al., 2021; Ohkuma et al., 2000; Tan, Jamali, et al., 2021; Taborda & Prolla, 2012).

Dietary factors showed inconsistent associations in their relation to IM. Consumption of spicy foods was found to be both a risk factor (Kim et al., 2008; Oh et al., 2013) and a protective factor (Chitapanarux et al., 2023). Nitrite-rich salty food was linked to IM (Stemmermann et al., 1990), although salt consumption had no significant effect (Taborda and Prolla, 2012; Oh et al., 2013). Consumption of dairy products (Joo et al., 2013) and a high butter intake (Russo et al., 2001) were found as risk factors. Soft drink consumption was found to be inversely related to IM (Russo et al., 2001).

Joo et al. (2013) reported a substantial risk of IM with a GC relative, although Kneller et al. (1992) observed no significant risk. Aumpan et al. (2020) and Nieuwenburg et al. (2021) found no significant connection between the two variables. Nieuwenburg et al. (2021) observed a greater risk of IM progression in those with GC relatives, and Oh et al. (2013) identified an association in males. Based on these contradictory findings, having a family history of gastric cancer (GC) does not appear to be a substantial risk factor for IM, its significance may be influenced by the presence of other risk factors. Giving rise to a scenario where the magnitude of a risk factor becomes substantially effective when it is coupled or combined with another factor.

Several health conditions were examined to see their association with gastric IM. Aumpan et al. (2021) found a correlation between diabetic mellitus and chronic IM or its progression to dysplasia. Hypertension was also found to be substantially associated with IM. In the same study, however, pulmonary illness did not approach statistical significance as a risk factor. GERD showed mixed results, with Felley et al. (2012) and Tan et al. (2021) showing no significant association, while Goldblum et al. (1998) and Pieramico and Zanetti (2000) reported varying prevalence rates for IM in GERD patients. Jiang et al. (2017) and Joo et al. (2013) found a significant positive correlation between atrophic gastritis (AG) and IM. In Hong et al. (2014) and Jiang et al. (2017), gastric ulcers and bile reflux were found as independent risk factors. Surprisingly, duodenal ulcer illness appeared to have a protective effect in studies by Leung et al. (2004) and Tsukui et al. (2001).

Based on the findings from multiple studies, ethnicity showed to be a significant predictor for gastric IM. Huang et al. (2020) reported a lower prevalence of GIM in whites compared to African Americans, Hispanics, and Asian/Pacific Islanders across all age groups. Tan et al. (2020) and Tan, Jamali, et al. (2021) further supported these findings using regression analysis. Specifically, black race was identified as a significant risk factor.

8. Conclusion

H. pylori infection was a significant risk factor for the occurrence and progression of IM. Across studies, age consistently appeared to be a significant risk factor for IM incidence and progression. Several studies demonstrated that men were at a higher risk of IM development and progression. Having a higher BMI was related to an increased chance of developing IM. Among the included studies active smoking was a significant risk factor and having a smoking history was a risk factor dependent on the number of years of cessation. The studies in this review show that alcohol is a risk factor for the incidence of IM but not the progression. The strength of this association is influenced by drinking frequency, quantity, and frequency of binge drinking (Kim et al. 2020). The topic of dietary habits was wide due to the large variability of foods included. In summary, the consumption of spicy foods, salty foods, dairy products, and high butter intake are risk factors. While the consumption of soft drinks, fruits and vegetables offers a protective effect against IM. Having a family history of gastric cancer (GC) seems to not be a significant risk factor for IM. Regarding health factors, diabetic mellitus showed to be a risk factor for the occurrence of IM and its progression to dysplasia. Hypertension is also a risk factor for the occurrence of IM. GERD showed a positive correlation with IM occurrence but none of the studies reached statistical significance. Duodenal ulcer illness had a protective effect against IM incidence. Ethnicity showed to be a significant predictor for gastric IM and specifically being African-American proved to be a significant risk factor.

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