Epidemiological Review of Gastroesophageal Junction Adenocarcinoma in Asian Countries

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Keywords

Gastroesophageal junction adenocarcinoma · Epidemiology · Gastroesophageal reflux disease · Obesity · *Helicobacter pylori*

Abstract

Background: Similar trends in the prevalence of gastroesophageal reflux disease (GERD), obesity, and *Helicobacter pylori* infection have been observed in Asian and Western countries despite their time differences. However, it is unclear whether the prevalence of gastroesophageal junction adenocarcinomas in Asian countries is increasing. In this review, we discuss the epidemiological trends of gastroesophageal junction adenocarcinoma in Asian countries. **Summary:** The prevalence of GERD is increasing in Asian countries, but most cases are considered mild. Obesity is a serious problem worldwide, but it is considered less serious in Asia than in Western countries. In Asian countries where gastric cancer is common, both cardiac and noncardiac cancers are associated with high rates of *H. pylori* infection, which is considered a carcinogenic risk factor for both sites of cancer. The widespread use of *H. pylori* eradication therapy for chronic gastritis in several Asian countries has not directly led to an increased prevalence of esophageal adenocarcinoma. One

of the originating sites of junctional adenocarcinoma in most Asian countries is Barrett's esophagus, with short-segment Barrett's esophagus having much lower carcinogenicity than long-segment Barrett's esophagus. **Key Messages:** Considering the future trends of several risk factors for gastroesophageal junction adenocarcinoma in Asian countries, it is likely that the incidence of gastroesophageal junction adenocarcinoma will gradually increase, but not at a rate that exceeds that of squamous cell carcinoma, as in Western countries.

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Introduction

In recent decades, the incidence of distal gastric carcinoma has decreased in Western countries, whereas that of gastroesophageal junction (GEJ) adenocarcinomas has clearly increased [1]. Several risk factors, such as gastroesophageal reflux disease (GERD), obesity, smoking, and low *Helicobacter pylori* (*H. pylori*) infection rates, have been associated with an increase in the prevalence of GEJ adenocarcinoma [2–5]. Nowadays, there have been several large-scale studies on risk factors for GEJ adenocarcinomas from Asian countries [6–11]. In 1999, Blaser

proposed that the prevalence of reflux esophagitis and GEJ adenocarcinomas would increase in the future due to changes in the *H. pylori* infection rate [12]. Similar trends in the prevalence of GERD, obesity, and *H. pylori* infection were observed in Asian and Western countries, despite the time differences [13–21]. However, it is yet to be determined whether the prevalence of GEJ adenocarcinoma in Asian countries is increasing. This review article focuses on the epidemiology of GEJ adenocarcinoma in Asian countries and the differences in epidemiological trends among Japan, other Asian countries, and Western countries.

Definition of the GEJ Adenocarcinoma

GEJ carcinoma is a carcinoma in which the epicenter of the tumor is located within the GEJ region. In Japan, the Nishi classification is usually used as the definition of the GEJ region. However, the Siewert classification is widely used in Western countries. In the Nishi classification, the GEJ region is defined as the area within 2 cm above and below the GEJ, and the epicenter of the tumor located in this area is considered a GEJ carcinoma. Therefore, not only adenocarcinomas, but also squamous cell carcinomas, are included [22]. The Siewert classification is applied to adenocarcinomas located within 5 cm above or below the GEJ. The GEJ adenocarcinomas are classified as 3 types as follows. Type I which is located 1–5 cm above the GEJ is adenocarcinoma of the distal esophagus (almost the same as esophageal adenocarcinoma). Type II is true carcinoma of cardia centered between 1 cm above and 2 cm below the GEJ. Type III is subcardial carcinoma located 2–5 cm below the GEJ [23]. Barrett's esophageal adenocarcinoma is a carcinoma that originates from Barrett's mucosa and is mostly included in Siewert type II.

Epidemiology of Esophageal Adenocarcinoma and GEJ Adenocarcinoma in Asian Countries

Several population-based studies [1–5, 24] from Western countries have reported a rapid increase in the incidence of not only esophageal adenocarcinoma but also GEJ adenocarcinoma. Interestingly, the incidence of GEJ adenocarcinoma increased at a much slower rate than that of esophageal adenocarcinoma [8, 9]. These 2 types of adenocarcinomas are sometimes confused because they share common risk factors [2–5]. Furthermore, GEJ

adenocarcinomas have 2 different etiologies and should be examined carefully. One type is similar to distal gastric carcinoma and occurs in the background of severe atrophic gastritis; the other type is Barrett's esophageal adenocarcinoma [10]. GERD is considered an important risk factor for esophageal adenocarcinoma and GEJ adenocarcinoma [3]. It is obvious that the current increase in GERD cases in Western countries has contributed to the increased prevalence of esophageal adenocarcinoma and GEJ adenocarcinoma. In recent years, Asian countries have reported an increased prevalence of GERD [11], which is similar to the trend in Western countries. However, according to a large epidemiological study of Asian countries, the incidence of esophageal adenocarcinoma and GEJ adenocarcinoma is not as high as that in Western countries (Table 1) [25–31].

Differences in the Definition of Barrett's Esophagus between Japan and Other Asian Countries

Barrett's esophagus is believed to result from chronic gastroesophageal acid/bile reflux and is considered to predispose patients to esophageal adenocarcinoma and GEJ adenocarcinoma. In general, the incidence of Barrett's esophagus is lower in Asian countries than in Western countries [32]. However, its prevalence was reported to be as high as 43.0% in a series without biopsy in Japan [33], which is different from the results of studies conducted in other Asian countries. This discrepancy is attributed to the difference in the definition of the GEJ between Japan and other countries. Japan often uses the definition of the esophageal cancer treatment guidelines (10th edition) [34], which identifies Barrett's esophagus as the esophagus with Barrett's mucosa (a columnar epithelium extending continuously from the stomach into the esophagus, with or without intestinal metaplasia). Two types of endoscopic landmarks are used for GEJ as follows: (1) the lower margin of the palisade vessels and (2) the proximal extent of the gastric folds. In Japan, the lower margin of the palisade vessels is used as the landmark, while in Western countries, the proximal extent of the gastric folds is used. Depending on which of these landmarks is used, the rate of agreement on the diagnosis of Barrett's esophagus varies. A previous report that investigated differences in the definition of Barrett's esophagus in East Asian countries showed that the percentage of institutions using the presence of specialized intestinal metaplasia (SIM) as a criterion of Barrett's esophagus was <50% only in Ja-

Table 1. The incidence of esophageal adenocarcinoma and GEJ adenocarcinoma in Asian countries and in Western countries

Geographic area	Yearly incidence of esophageal adenocarcinoma per 100,000 population (year)	Yearly incidence of GEJ adenocarcinoma per 100,000 population (year)
America		
North America (white)	2.5–3.0 (1991–2000)	2.0–2.2 (1991–2010)
Europe		
UK/Ireland	4.2–4.8 (2004–2006)	5.4 (2004–2006)
South Europe	0.7–3.9 (1992–1996)	–
North Europe	1.6 (2000–2007)	4.0–7.0 (1986–2002)
West Europe	0.4–3.2 (1989–1996)	–
East Europe	0.5–0.7 (1987–1992)	–
Australia	4.8 (1993)	–
Asia		
East Asia	0.08–0.9 (1998–2014)	0.6–1.7 (2008–2014)
Southeast Asia	0.02–0.06 (1968–2002)	0.5 (2015)

North America: USA, Canada; North Europe: Denmark, Norway, Sweden, Finland; West Europe: Germany, the Netherlands, Switzerland; East Europe: Czech, Slovakia, Poland; East Asia: Japan, Korea, Hong Kong; Southeast Asia: Malays in Singapore. GEJ, gastroesophageal junction.

pan. However, the majority of endoscopists in other countries accepted this criterion for the diagnosis of Barrett's esophagus [35]. Because Barrett's esophagus is associated with Barrett's esophageal adenocarcinoma, different definitions of Barrett's esophagus result in different incidences of Barrett's esophageal adenocarcinoma.

The definition of Barrett's esophagus has not been standardized worldwide, and this issue needs to be resolved. The reasons for the differences in definitions include (1) the need for biopsy, (2) the length of Barrett's mucosa, and (3) differences in the endoscopic diagnosis of the GEJ. In particular, the definition of Barrett's esophagus in Japan differs from that in Western countries, except in the UK, in which the presence of a SIM is considered important [36]. Takubo et al. [37] conducted an in-depth examination of the background mucosa of endoscopic mucosal resection specimens of Barrett's esophageal adenocarcinoma and found that SIM was absent in 56.6% of the specimens. Even in Western countries, several reports have found epigenetic abnormalities in the columnar-lined esophagus without SIM. Considering these results, Barrett's esophageal adenocarcinoma does not necessarily develop only from SIM, and columnar-lined esophagus without SIM is also likely to be the origin of Barrett's esophageal adenocarcinoma.

Temporal Trends in Risk Factors Known to Be Associated with GEJ Adenocarcinoma in Asian Countries

To date, several risk factors, such as GERD, obesity, smoking, alcohol consumption, male sex, Caucasian ethnicity, and low *H. pylori* infection rate, have been associated with an increased prevalence of GEJ adenocarcinomas [2, 5]. Male sex and older people are also considered risk factors for GEJ adenocarcinoma, but the degree of the sex ratio varies by the 3 types in Western countries, but not in Asian countries. A previous report reviewed the differences in the incidence and clinicopathological features of GEJ adenocarcinoma between Western and Eastern countries. This report showed that the average age of the patients was similar in the 3 types of GEJ adenocarcinoma [38]. All types of tumors showed a male predominance. Siewert et al. [39] reported that the male-to-female ratio was 10.7 in type I, 4.9 in type II, and 2.2 in type III, with significant differences among these types. In their study, the male-to-female ratio of type II and type III in Eastern countries tended to be similar to those of Western countries, with a higher ratio of Type II patients, but the difference was not statistically significant. A recent multicenter prospective cohort study in Japan reported that the annual risk of Barrett's esophageal adenocarcinoma was 1.2% [40]. Additionally, congenital factors such as race and sex have been considered risk factors for Bar-

Table 2. Risk factors for GEJ adenocarcinoma

Variable	Odds ratio	95% confidence interval
Age ≥70 years	0.90	0.50–1.60
Male	2.04	0.93–4.46
Esophagitis	2.16	0.85–5.49
Hiatal hernia	2.15	1.12–4.14
Gastric atrophy	0.75	0.40–1.42
Past gastric surgery	3.58	0.92–13.96
Past cholecystectomy	6.67	0.76–58.26
Family history of digestive disease	0.55	0.24–1.26
Smoking	2.04	1.11–3.75
Drinking	0.78	0.42–1.45
Obesity (BMI QUOTE ≥25 kg/m ²)	3.35	1.62–6.93
Heart burn	0.83	0.34–2.06

GEJ, gastroesophageal junction; BMI, body mass index.

rett's esophageal adenocarcinoma, and acquired factors (environmental factors) such as smoking and obesity have also been reported. According to our recent large-scale epidemiological study, the incidence of GEJ adenocarcinoma, including Barrett's esophageal adenocarcinoma, is 0.6–1.7 per 100,000 person-years, which is lower than that in Western countries [41]. We identified hiatal hernia, obesity, smoking, and male sex as risk factors for GEJ adenocarcinoma, similar to that in Western countries (Table 2). In this review, among the identified risk factors, we focus on GERD, obesity, *H. pylori* infection rate, and Barrett's esophagus length in Asian countries and discuss their temporal trends.

Gastroesophageal Reflux Disease

In Asian countries, GERD was earlier considered a rare disease, but its incidence has clearly been increasing in recent years. In a recent population-based epidemiological study, the incidence of GERD was 22.2% in South India, 25% in Taiwan, 3.5% in South Korea, and 23.4% in a study of participants in a health examination program in Japan [42], and the number of cases has increased in the 2000s compared with that in the 1990s. The prevalence of GERD is increasing in Asian countries because of changes in several environmental factors and a decrease in *H. pylori* infection rates, but most cases are considered mild (Fig. 1). The increased incidence of GERD may be due in part to the increased interest in GERD among physicians and the improved diagnostic ability of endoscopic methods for GERD compared with that in the past. A study from Japan indicated that the rate of increase in

GERD incidence was higher in the early 2000s than in the 1990s, but the rate of increase in the past decade has not been as high as that in previous decades [43]. Currently, duodenogastroesophageal reflux of bile acids is also considered to play an important role in the development of metaplasia of Barrett's esophagus and promotion of Barrett's esophageal carcinogenesis. However, the effect of bile acid sequestrants on these conditions is unclear [44].

Obesity

Until now, obesity has been considered a problem in Western countries but not in Asian countries. However, in recent decades, as Asian countries have urbanized and transportation networks have developed, people's physical activity has diminished combined with an increase in overeating, and obesity has become a social problem that cannot be ignored. According to a recent epidemiological study in Asian countries, the percentage of obese (body mass index [BMI] >25 kg/m²) men and women was 22.9% and 24.7% in Japan [18], 43.2% and 47.4% in India, 26.9% and 31.1% in China, and 35.6% and 29.8% in Korea, respectively [10]. Cases of obesity in Asian countries are milder than those in Western countries. BMI tended to increase from 1995 to early 2000, but this has hardly changed since 2005. Thus, obesity is a serious problem worldwide, but it is less serious in Asia than in Western countries.

Helicobacter pylori

Persistent *H. pylori* infection is believed to promote the development of gastric cancer through the development of atrophic gastritis and decrease in gastric acid secretion. However, it has a suppressive effect on GERD, Barrett's esophagus, Barrett's esophageal adenocarcinoma, and GEJ adenocarcinoma. In Western countries, *H. pylori* infection rates in cardiac cancers were found to be considerably lower than those in the control group. However, in Asian countries where gastric cancer is common, *H. pylori* infection rates are high in both noncardiac and cardiac cancers, and *H. pylori* infection is considered a carcinogenic risk factor for both sites of cancer [45]. In a comparison of *H. pylori* infection rates between GEJ adenocarcinoma and distal gastric carcinoma [46], the *H. pylori* infection rate in GEJ adenocarcinoma was significantly lower, and the degree of histological gastritis in the gastric body was also significantly lower. In Asian countries, including Japan, where the incidence of gastric cancer is high, 2 types of GEJ adenocarcinoma have been reported: one that is not associated with *H. pylori* infection as in Western countries and another that is associated

Fig. 1. Trends in the incidence of GERD worldwide. GERD, gastroesophageal reflux disease.

with *H. pylori* infection. McColl described the pathogenesis of GEJ adenocarcinoma in terms of gastric acid secretion and categorized it into 2 types: one that is associated with atrophic gastritis and low gastric acid secretion (similar to distal gastric cancers) and another type that is associated with excessive acid secretion with or without *H. pylori* infection (similar to esophageal adenocarcinomas) [47].

A large number of patients with chronic gastritis have undergone *H. pylori* eradication therapy in Asian countries, including Japan. It is important to determine whether the incidence of esophageal adenocarcinoma will increase after *H. pylori* eradication therapy, especially in the context of future trends of GEJ adenocarcinoma. Although there is currently no sign of an increase in the incidence of GEJ adenocarcinoma in post-eradication cases in Japan, there is only limited evidence on this issue. Take et al. [48] followed up 2,737 patients after *H. pylori* eradication therapy for an average of 7.1 years and found 2 cases of esophageal adenocarcinoma. They concluded that although the incidence of GEJ adenocarcinoma in patients after *H. pylori* eradication is higher than that in the general population, it is still very low. A previous study also found that the prevalence of esophageal adenocarcinoma is higher with persistent *H. pylori* infection than after eradication therapy, and a recent meta-analysis suggested that *H. pylori* infection may reduce the risk of esophageal adenocarcinoma in the general population. However, these findings may be one-sided; the statement of “protection effect” may be overestimated [49]. At pres-

ent, it is reasonable to assume that the widespread use of *H. pylori* eradication therapy for chronic gastritis will not directly lead to an increase in the incidence of esophageal adenocarcinoma and GEJ adenocarcinoma, although further studies are needed to clarify this important issue.

Currently Known Underlying Molecular Mechanisms of GEJ Adenocarcinoma, Especially for Barrett’s Esophageal Adenocarcinoma

Barrett’s epithelium changes from an atypical epithelium to a morphologically cancerous epithelium. One of the genes that regulate the cell cycle is p16, and it is classified as a tumor suppressor gene. The p16 gene is frequently altered in the atypical epithelium, which is considered to be in a precancerous stage. In addition to p16, p53 mutations are frequently observed in Barrett’s esophageal adenocarcinoma [50]. In long-segment Barrett’s esophagus (LSBE) and short-segment Barrett’s esophagus (SSBE), adenocarcinoma tends to develop and is characterized by severe inflammation. This suggests the involvement of nuclear factor- κ B and activation-induced cytidine deaminase in carcinogenesis [51]. Chronic inflammation of Barrett’s epithelium caused by chronic reflux of gastric acid and/or bile acid leads to the development of Barrett’s esophageal adenocarcinoma. Additionally, there is activation of activation-induced cytidine deaminase via nuclear factor- κ B, and mutation of p53, β -catenin, c-myc, and K-ras.

Differences in the Rate of Carcinogenesis between SSBE and LSBE

There is a difference in carcinogenesis between the 2 major categories of Barrett's esophagus: SSBE and LSBE. LSBE refers to the presence of Barrett's mucosa ≥ 3 cm in circumference, whereas SSBE refers to the presence of Barrett's mucosa < 3 cm in circumference or noncircumferential size. Most cases of Barrett's esophagus in Asian countries are SSBE.

The risk of carcinogenesis of Barrett's esophagus depends on its length. A recent meta-analysis showed that the incidence of carcinogenesis, including high-grade dysplasia, was 0.24% per year for SSBE and 0.76% per year for LSBE [52]. The carcinogenesis of Barrett's esophagus involves both genetic instability and clonal expansion. A previous study measured the presence and size of p16 lesions (loss of heterozygosity, mutations, and CpG island methylation), p53 lesions (loss of heterozygosity and mutations), and ploidy abnormalities (aneuploidy and tetraploidy) in 267 patients with Barrett's esophagus who were followed for > 4.4 years. The size of clones with p53 loss or ploidy abnormalities was found to be more predictive of progression to Barrett's esophageal cancer than only the presence of such clones [53]. Although we cannot deny the possibility that the incidence of SSBE will increase in the future, it is unlikely that there will be an extreme increase in the incidence of LSBE because of the current changes in environmental factors. Therefore, unlike in Western countries, it is likely that the cases of Barrett's esophageal adenocarcinoma based on LSBE will not significantly increase in Asian countries.

Trends in the Incidence of GEJ Adenocarcinoma in Asian Countries

A review of the trends in the incidence of surgical cases of GEJ adenocarcinoma, including Barrett's esophageal adenocarcinoma, in Japan, has shown that GEJ cancers accounted for only 2.3% of all gastric cancers from 1962 to 1965, but this proportion increased to 10.0% from 2001 to 2005. This increase was mostly due to an increase in the incidence of Siewert type II esophageal adenocarcinoma [54]. Recent reports in Japan have also reported an increase in the incidence of GEJ cancer, including Barrett's esophageal adenocarcinoma [55].

In the USA, the incidence of esophageal adenocarcinoma has exceeded that of esophageal squamous cell carcinoma in the approximately 20 years since the first

report indicating its increase. In Japan, the incidence of esophageal adenocarcinoma has recently increased by 6%–7% [56], but it is not thought to increase at a faster rate than esophageal adenocarcinoma in Western countries. There are several potential reasons for this. First, although the *H. pylori* infection rate in Japan is decreasing, the corresponding increase in the capacity of gastric acid secretion is not necessarily increasing [57]. Second, although the incidence of reflux esophagitis is clearly increasing, the rate of increase over the past 10 years is not high [37]. Third, the degree of obesity in Asian countries is mild compared with that in Western countries, and the trend of BMI has remained almost unchanged in recent decades. Fourth, cases of Barrett's esophagus, one of the originating sites of junctional carcinoma, are mostly categorized as SSBE in most Asian countries, which has much lower carcinogenicity than LSBE. In consideration of arguments, the incidence of GEJ adenocarcinoma, including Barrett's esophageal adenocarcinoma, is expected to increase gradually in the future, but not as rapidly as that in Western countries.

Conclusion

In general, esophageal adenocarcinoma is positively correlated with socioeconomic development. The incidence of reflux esophagitis and GEJ adenocarcinoma has clearly been increasing in some Asian countries, including Japan, but not as rapidly as in Western countries. Because several differences have already been recognized between Asian and Western countries regarding its pathogenesis and the aforementioned risk factors, it is difficult to apply study results from Western countries directly to the Asian population. From 1988 to 2007, no clear increase in the incidence of esophageal adenocarcinoma in any Asian country has been reported [24]. To be prepared for the medical treatment of GEJ adenocarcinoma, it is necessary to determine the epidemiological trends in Asian countries while referring to those in Western countries.

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Conflict of Interest Statement

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Author Contributions

N.M. conceived the study, designed the research, and drafted the manuscript; K.M. and K.M. edited and revised the manuscript; N.M., K.M., and K.H. approved the final version of the manuscript. The authors alone are responsible for the content and writing of the article.

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