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Review Article

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Epidemiology of Gastroesophageal Junction Adenocarcinoma in Korea

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ABSTRACT

The incidence of gastroesophageal junction adenocarcinoma (GEJAC) in Western countries has increased in recent decades, in addition to a rise in the incidence of esophageal adenocarcinoma (EAC). Gastroesophageal reflux disease (GERD), obesity, smoking, alcohol consumption, and low *Helicobacter pylori* (HP) infection rate have been nominated as risk factors for such cancers. Among these risk factors, the increased prevalence of GERD and obesity and the decreased prevalence of HP infection are of special interest owing to the currently increasing prevalence of GEJAC in Western countries. Although similar trends in the prevalence of GERD, obesity, and HP infection are observed in Asian countries after a time lag from Western countries, it is still uncertain if the prevalence of GEJAC in Asian countries is increasing, especially in Korea. The incidence of GERD in Korea is currently increasing; it was below 3% in the 1990s. The incidence of obesity in the Korean population is increasing owing to the adoption of westernized lifestyles, including food preferences, and the HP infection rate in Korea is known to be decreasing. Therefore, based on logical extrapolation of observations of Western countries, the incidence of GEJAC will increase in Korea. However, the proportion of GEJAC among other upper gastrointestinal malignancies in Korea appears to be currently unchanged compared with that in the 1990s. Presently, there is a lack of epidemiologic studies on this issue in this region; therefore, more studies are needed to clarify the characteristics of these tumors and to improve clinical outcomes for patients with these tumors.

Keywords: Gastroesophageal junction adenocarcinoma; Prevalence; Risk factor; Asia; Korea

INTRODUCTION

Population-based studies in several Western countries have shown that the incidence of esophageal adenocarcinoma (EAC) and gastroesophageal junction adenocarcinoma (GEJAC) has rapidly increased; however, the degree of increment of EAC was less than that of the GEJAC [1,2]. Although EAC and GEJAC share common risk factors, such as gastroesophageal reflux disease (GERD), obesity, smoking, alcohol consumption, male sex, and Caucasian ethnicity [3-8], there are two distinct etiologies of GEJAC: one from severe atrophic gastritis, which is of intestinal or diffuse subtype, similar to gastric non-cardia cancer (GNCC); and

jgc Journal of Gastric Cancer

one related to GERD, which is of intestinal subtype, similar to EAC [9]. This may be the explanation for the more gradual rise in the incidence of GEJAC compared with the rapid rise in the incidence of EAC in Western countries. GERD is a major risk factor for EAC and GEJAC, which acts in a dose-dependent manner [4]. It is known to be a major clinical problem in Western countries, with a recently reported prevalence of approximately one in every three adults [10,11]. GERD is also a current rapidly emerging disease in Asian countries. In addition, a prevalence of 15% for erosive esophagitis and of up to 20% for reflux symptoms has been reported. However, the prevalence of Barrett's esophagus (BE) and EAC remains low in this region [12].

In this review, I will focus on epidemiology of GEJAC in Korea and the differences in epidemiology between Korea, Western counties, and other Asian countries.

DEFINITION AND CLASSIFICATION

The gastroesophageal junction (GEJ) forms the border between the distal esophagus and the proximal stomach and is normally where the squamous epithelium of the esophagus transitions into a columnar epithelium. However, the imprecise limit of the GEJ has made the classification of GEJAC complicated owing to the various definitions and interpretations of the site of origin. In 1996, Siewert and Stein [13] proposed a classification scheme that defined adenocarcinoma (AC) of the GEJ as tumors that have their epicenter within 5 cm proximal and distal of the anatomic gastric cardia. Three subtypes were further described, based on the location of the epicenter of the tumor: type I, between 1 and 5 cm above the GEJ; type II, between 1 cm above and 2 cm below the GEJ; type III, between 2 and 5 cm below the GEJ. Subsequently, Siewert type II cancers are considered as true GEJACs, arising from the GEJ epithelium. This classification was approved at the Second International Gastric Cancer Congress, held in Munich, Germany, in April 1997, and has since been accepted worldwide [14]. The mention of GEJAC in the American Joint Committee on Cancer (AJCC) TNM staging system first appeared in the seventh edition, in 2010. In this edition, cancers with an epicenter in the lower thoracic esophagus, GEJ, or within the proximal 5 cm of the stomach that extend into the GEJ or esophagus (Siewert type III) were stage grouped, similar to EACs [15]. However, the appropriateness of this grouping was debated by many gastric surgeons. Subsequently, it was revised in the eighth edition, in 2017, with cancers involving the GEJ that have their epicenter no more than 2 cm into proximal stomach (Siewert types I/II) staged as EAC. Cancers with the epicenter more than 2 cm distal from the GEJ, even if the GEJ is involved, were to be staged using the stomach cancer TNM and stage groupings. Siewert type II cancers not involving the GEJ are staged in the same way as stomach cancer [16]. If the tumor has an epicenter located between 2 and 5 cm below the GEJ, and does not invade the GEJ, it is classified as stomach cancer rather than GEJAC. However, the classification changes to Siewert type III when the tumor invades the GEJ by horizontal progression [17]. Alternatively, Nishi classification is used to classify GEJ cancers, including squamous cell carcinoma, in Japan [18]. A tumor with the epicenter located within 2 cm proximal or distal to the GEJ, regardless of histological type, is designated as GEJ cancer. Some Siewert type I cancers and all Siewert type II cancers are included in Nishi classification; however, squamous cell carcinomas of the GEJ are also included. Therefore, Siewert classification may provide a better basis for international communication. In this review, GEJAC is designated as a Siewert type II cancer, known to be a true GEJ cancer.

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TRENDS IN THE PREVALENCE OF GEJAC IN WESTERN COUNTRIES

The incidence of GEJAC in the USA has risen significantly since the early 1970s, stabilizing in the early 1990s after increasing by almost 2.5-fold since the early 1970s [19]. This is in contrast to the incidence of EAC, which has continued to increase to the present day, along with a significant rise in the prevalence of GERD and obesity in Western countries over the past several decades. This partly means that there is a slight difference in pathogenesis between GEJAC and EAC, even though they share many of the common risk factors mentioned above. Hansen et al. [20] reported that GEJAC was negatively associated with HP infection, but that HP-positive GEJAC was associated with gastric atrophy. The predominant histological subtype of GEJAC was intestinal and, compared with the diffuse subtype, was not associated with gastric atrophy. They concluded that there were two etiologies of GEJAC, one associated with HP atrophic gastritis, which resembles GNCC, and the other associated with non-atrophic gastric mucosa, which resembles EAC. This hypothesis was further investigated and supported by Derakhshan et al. [9]. The prevalence of HP infection and GNCC in Western countries has significantly declined in the recent several decades. The gradual rise in the incidence of GEJAC compared with the sharp rise in the incidence of EAC may be partly due to the proportion of GEJAC the pathogenesis of which resembles that of GNCC. Nonetheless, GEJAC is one of the most prevalent cancers in Western countries, and the rate of increase has exceeded that of the next most commonly increasing tumor, melanoma, by approximately three times [1,21,22].

RISK FACTORS AFFECTING THE PREVALENCE OF GEJAC

GERD

In a population-based, case-control study in Sweden, Lagergren et al. [4] reported a strong association between GERD symptoms and the risk of EAC and GEJAC; however, the association with GEJAC was weaker than that with EAC, and the severity of GERD was related to the risk of EAC and GEJAC. The adjusted odds ratio (OR) for patients with EAC was 16.7 (95% confidence interval [CI], 8.7–28.3) when the frequency of reflux symptoms was >3 times per week, 20.0 (95% CI, 11.6–34.6) when the reflux-symptom score was 4.5–6.5 points, and 16.4 (95% CI, 8.3–28.4) when the duration of reflux symptoms was >20 years; in patients with GEJAC, the adjusted ORs were 2.3 (95% CI, 1.2–4.3), 2.8 (95% CI, 1.6–5.0), and 3.3 (95% CI, 1.8–6.3), respectively. Several studies have since supported this finding [23-25]. Chronic GERD is associated with BE, a metaplastic precursor lesion that predisposes individuals to EAC. GERD has also been linked to intestinal metaplasia in the GEJ, which may arise from a multilayered epithelium transition state and is believed to represent the biological precursor of dysplasia and cancer [26].

Previously, GERD was considered a rare disease in Asia. Earlier studies on this subject, conducted between the 1970s and 1990s, revealed the low prevalence of the disease (2%–5%), with an inordinately low prevalence of reflux esophagitis (RE) [27]. However, the situation in Asia is changing. In a recent community-based study conducted in southern India, the incidence of GERD was 22.2% [28], a community-based study in Taiwan found that the prevalence of GERD in Taiwan was 25%, and an endoscopic study revealed a 2.5-fold increase in the prevalence of erosive esophagitis in Taiwanese adults from 1995 to 2002 [29]. The incidence of health check-up examinees with GERD symptoms was 1.9%–13.7% in Japan

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jgc Journal of Gastric Cancer

Table 1. The current prevalence of GERD, diagnosed by a symptom-based approach in Asian countries

Author	Year	Country	Setting	Prevalence of GERD (%)	Comments
Wang et al. [28]	2016	India	Community-based	22.2	Comparable with the rate in Western countries
Hung et al. [29]	2011	Taiwan	Community-based	25	Emerging as a common disorder in Taiwan
Murao et al. [31]	2011	Japan	Health exam program	23.5	Increasing along with lifestyle changes
Kim et al. [34]	2012	Korea	NHI claim data	7.3	Rapidly increasing

GERD = gastroesophageal reflux disease; NHI = National Health Insurance.

in the 1990s, but had risen to 4.9%–23.5% in the 2000s, suggesting that the prevalence of GERD was increasing in Japan [30,31]. Therefore, GERD is a rapidly emerging disease in Asian countries, even though the prevalence of BE, which forms the precursor lesions of EAC and GEJAC, was 0.06%–0.84% in health check-up examinees and 0.31%–2.00% in the referral hospital setting, which is still very rare compared with the incidence in Western countries [32].

The prevalence of GERD in Korea in a population-based, cross-sectional study conducted in 2000 and 2001 was 3.5% [33]. The prevalence of doctor-diagnosed GERD increased rapidly from 4.6% to 7.3% between 2005 and 2008, with a mean annual increase rate of 15.3%. Over the same period, the amount of proton pump inhibitor claims increased by 56% [34]. Similar to other Asian countries, a rapidly increasing trend in the prevalence of GERD has also been observed in Korea, although the increase is smaller than that in other Asian countries (**Table 1**).

Obesity

The rise in the prevalence of GEJAC has paralleled the worldwide obesity epidemic, with almost all epidemiological studies reporting increased body mass index (BMI) and that obesity increases the risk of GEJAC development [35]. Abnet et al. [36] reported that a BMI of ≥35 kg/m^2 was associated with a significant increase in the risk of GEJAC (hazard ratio [HR], 2.46; 95% CI, 1.60–3.80), than a BMI of 18.5–25 kg/m^2 among 480,475 cohorts in the National Institutes of Health (NIH)-American Association of Retired Persons (AARP) Diet and Health study. A population-based study in Sweden reported the OR for patients with GEJAC was 2.3 (95% CI, 1.5–3.6) for those in the highest BMI quartile compared with those in the lowest BMI quartile and 4.3 (95% CI, 2.1–8.7) among obese individuals [37]. Kubo and Corley [38] reported that a high BMI was weakly associated with the risk of GEJAC (OR, 1.5; 95% CI, 1.3–1.8; P [heterogeneity]=0.38) in their systematic review and meta-analysis. They also mentioned that the BMI-cancer association was strongest in the study that primarily included only EACs that were >2 cm from the GEJ. In a case-control study conducted in Australia, the combination of smoking, BMI, and GERD accounted for 76% of EAC cases and 69% of GEJAC cases. Individually, high BMI (≥30 kg/m^2) and frequent acid reflux (≥1 time/week) accounted for the greatest proportions of EAC (23% and 36%, respectively), and smoking and frequent acid reflux accounted for the greatest proportions of GEJAC (43% and 28%, respectively) [39]. Whiteman et al. [24] insisted that the combination of obesity and GERD was associated with considerably higher risk for GEJAC than either factor alone, although additive effects appeared most commonly, which contrasted with the synergistic effects observed in EAC. Increased body weight may predispose individuals to reflux through mechanical means but may also act through independent pathways involving inflammatory or hormonal mediators. The prevalence of overweight and obese individuals has increased significantly in recent decades in Western countries. Although this trend may partially account for the increase in the incidence of GEJAC in the late 1970s and 1980s, obesity levels have continued to increase, while the increase in GEJAC has plateaued [19].

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jgc Journal of Gastric Cancer

Table 2. The current percentages of overweight and obese individuals (BMI ≥25 kg/m²) in the USA and several Asian countries

Author	Year	Country	Sample (No.)	% BMI ≥25 kg/m²	
				Male	Female
Berrington de Gonzalez et al. [43]	2010	USA	1,460,000	64	47
Deepa et al. [40]	2009	India	2,350	43.2	47.4
Gu et al. [41]	2005	China	15,540	26.9	31.1
Sasazuki et al. [42]	2011	Japan	353,395	22.9	24.7
Park et al. [44]	2014	Korea	1,200,000	35.6*	29.8*

BMI = body mass index.
*23.9% and 26.8% in 1995, 36.4% and 30.2% in 2005, and 35.6% and 29.8% in 2009.

Traditionally, obesity has been considered a problem in Western countries. However, over the past two decades, urbanization in many Asian countries has led to sedentary lifestyle and overnutrition, which has set the stage for an epidemic of obesity. In some of the epidemiological studies in several Asian countries, the proportion of individuals with a BMI of more than 25 kg/m² was 43.2% in men and 47.4% in women in India, 26.9% and 31.1% in China, and 22.9% and 24.7% in Japan, respectively [40-42], whereas the proportion of those with a BMI of more than 25 kg/m² in Western countries was 64% in men and 47% in women [43]. In a population-based cohort study in Korea, the proportion of individuals with a BMI of more than 25 kg/m² in men and women was 23.9% and 26.8% in 1995, 36.4% and 30.2% in 2005, and 35.6% and 29.8% in 2009, respectively [44] (**Table 2**). A moderate increase was observed during the years 1995–2005, but the rate remained stable between 2005 and 2009. Obesity is a current serious health problem in both Asian countries and Western countries, but the severity of the problem is lower in some Asian countries, including Korea.

Helicobacter pylori (HP) infection

HP infection is associated with an increased risk of peptic ulcer disease and gastric cancer (GC) through the mechanisms of chronic inflammation, atrophy, and dysplasia [45]. In contrast, an inverse correlation has been reported between HP infection and the risk of EAC and GEJAC [46]. In a prospective observational study of 281 patients with BE who underwent surveillance endoscopy, Weston et al. [47] reported that HP infection rate was significantly lower in patients with Barrett's high grade dysplasia (14.3%) and adenocarcinoma (15.0%) than in patients with GERD alone (44.2%), BE alone (35.1%), or Barrett's low grade dysplasia (36.2%) (P=0.016); moreover, they insisted that HP infection appeared to have a protective effect against the development of Barrett's adenocarcinoma. A recent meta-analysis also confirmed this finding [48]. In a prospective case-control study in the USA, HP seropositivity was strongly associated with the risk of GNCC (OR, 7.9; 95% CI, 3.0–20.9) but was inversely associated with the risk of GEJAC (OR, 0.31; 95% CI, 0.11–0.89) [49]. This finding supported the hypothesis that the decrease in HP prevalence over the past century may have contributed to lower rates of GNCC and higher rates of GEJAC in Western countries. In an Australian population-based, case-control study, HP infection was associated with significantly reduced risks of EAC (OR, 0.45; 95% CI, 0.30–0.67) and GEJAC (OR, 0.41; 95% CI, 0.27–0.60), but not esophageal squamous cell carcinoma (ESCC; OR, 1.04; 95% CI, 0.71–1.50). For each cancer subtype, the risks were of similar magnitude across strata of reflux frequency and smoking status [50]. Unlike in Western countries, the relationship between HP infection rate and the risk of GEJAC has not been sufficiently well studied in Asian countries. In their case-control study, Inomata et al. [51] reported that the prevalence of HP infection in patients with GEJAC was significantly lower than that in patients with distal early gastric cancer (EGC) and it tended to be higher than that in patients with RE alone or BE. The degree of preservation of gastric acid secretion in patients with GEJAC was significantly higher than that in control subjects and patients with distal EGC, but it was comparable to that in patients with RE alone or BE, independent of HP infection

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Table 3. The association between GEJAC and HP infection in several case-control studies

Author	Year	Country	No. of GEJAC	Results	Statistics
Kamangar et al. [49]	2006	USA	61	Inverse association with HP+	OR, 0.31; 95% CI, 0.11–0.89
Whiteman et al. [50]	2010	Australia	307	Inverse association with HP+	OR, 0.41; 95% CI, 0.27–0.60
Inomata et al. [51]	2006	Japan	12	HP+ significantly lower than in early GNCC	P<0.05

GEJAC = gastroesophageal junction adenocarcinoma; HP = *Helicobacter pylori*; OR = odds ratio; CI = confidence interval; GNCC = gastric non-cardia cancer.

status. They concluded that the preservation of gastric acid secretion may be more important for the development of GEJAC in Japanese people, irrespective of HP infection status (**Table 3**).

Currently, the global prevalence of HP infection is following a rapidly decreasing trend, especially in Oceania (24.4%; 95% CI, 18.5%–30.4%), Western Europe (34.3%; 95% CI, 31.3%–37.2%), and North America (37.1%; 95% CI, 32.3%–41.9%), in association with improved standards of living, but the prevalence remains high in most developing countries, mainly because of low socioeconomic status and poor hygiene practices [52]. Reports from Asia have shown the steady decline of this infection over several years [53-56]. A study from Japan has linked the decrease in the prevalence of HP with an increase in GERD [57]. The current prevalence in the three countries in Eastern Asia is 55.8% (95% CI, 51.8%–59.9%) in China, 54.0% (95% CI, 50.1%–57.8%) in Korea, and 51.7% (95% CI, 44.7%–58.7%) in Japan. Despite the rapid decrease in pediatric HP prevalence in these countries, HP prevalence remained relatively stable and several decades are required to identify a significant change in rate [52].

TRENDS IN PREVALENCE OF GEJAC IN ASIAN COUNTRIES AND KOREA

Data on the incidence of GEJAC in Asian countries are lacking. Several reports from a single institution in Asia show no change or a slight increase in incidence [58-60]. Recently, Hatta et al. [61] reported the incidence of GEJAC in three Asian countries; gradual increases were observed in Malaysia and Japan, but the incidence in Hong Kong was stable.

GC has been the most commonly diagnosed cancer in Korea since 1999 when the Korea Central Cancer Registry first reported nationwide cancer incidence data [62]. Despite the continued decrease in the incidence of GC in Western countries, the incidence of GC is higher in Korea than in any other country, and this has remained unchanged for over a decade [63]. In addition to the decreasing prevalence of GC in Western countries, the incidence of proximal GC, including GEJAC, is increasing [1,21,22]. However, it is still a matter of debate as to whether the incidence of proximal GC is increasing in Korea, because the incidence in 2009 was 13.4%, which was only 2.2% higher than that in 1995 [64]. The reported proportion of GEJAC (Siewert type II cancer) among GCs in several Korean high-volume centers for GC are 1.7%–7.2% [65-67]. According to a retrospective study in a high-volume center in Korea, including 16,811 patients with ESCC, Siewert type I–III cancer and GNCC, the proportion of GEJAC (Siewert type II cancer) was 0.3% (47 cases). The proportion of Siewert type I–III cancers to ESCC and GNCC was unchanged in the periods 1992–1996, 1997–2001, and 2002–2006, at 3.7%, 3.4%, and 3.9%, respectively [60].

Despite the currently increasing prevalence of GERD and obesity, and the decreasing prevalence of HP infection in Asia, the reasons for the gradual or lack of change in the epidemiology of GEJAC in this region may be: 1) the relatively higher proportion of GNCC resembling GEJAC in etiology than in Western countries [68]; 2) the long time interval in

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jgc Journal of Gastric Cancer

the progression from GERD to GEJAC [69-71]. In Korea, GERD is most prevalent in patients between 30 and 40 years of age [72], and the most common age of patients with GEJAC is 55 to 60 years of age. Thus, 20–30 years may be required for the development of GERD into GEJAC [60]. Therefore, to observe the same prevalence of GEJAC in Asian countries, including Korea, as seen in Western countries, several decades may be needed.

CONCLUSIONS

A slow increase in the prevalence of GEJAC, with rapidly increasing trends in GERD and obesity, and steadily decreasing trends in HP infection in Asian countries, including Korea, has been observed. However, few epidemiologic studies have been conducted in this region and treatment strategies against these tumors are still under debate. An international collaborative study may be helpful, not only to clarify the characteristics of these tumors, but also to improve the clinical outcome for these patients.

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