Epidemiology and Risk Factors

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1.1 Methodological Issues

The definition of esophagogastric junction (EGJ) is still debated in the current literature. For instance, the landmark for the border between the esophagus and the stomach is the proximal margin of the gastric folds according to the Prague C&M criteria, while the distal limit of the lower esophageal longitudinal or palisade vessels is mainly used in the Japanese criteria [1].

Also, the definition of EGJ or cardia cancer gave rise to many discrepancies. In most European countries, a code for cardia cancer was introduced only in the late 1970s, and a consensus on the definition of gastric cardia cancer was achieved only at the end of the 1990s [2]. As a consequence, true cardia cancer incidence, occurring between 1989 and 1994 in Sweden, could have been up to 45 % higher or 15 % lower than that reported by the Swedish Cancer Registry [2].

Of note, two studies were recently performed in the United States on the same database (SEER = Surveillance, Epidemiology, and End Results cancer registry program) over about the same period. The studies reported different trends in EGJ adenocarcinoma from 1973 to 2008 [3] and in gastric cardia carcinoma from 1978 to 2005 [4]. The World Health Organization seems to include both carcinomas in EGJ carcinomas, which are defined as tumors "*that cross the oesophagogastric junction… regardless of where the bulk of the tumours lies*" [5]. In this chapter, the term adenocarcinoma of the "esophagogastric junction (EGJ)" will be preferentially used. However, the term "cardia" cancer or "gastric cardia" cancer will also be adopted when used by the authors cited.

1.2 General Overview of Cancers from the Upper Gastrointestinal Tract

In Western countries, the decrease in the incidence of esophageal squamous cell cancer (SCC) and noncardia gastric cancers parallels a concomitant increase in the incidence of distal esophageal adenocarcinoma (AC) and EGJ/"gastric cardia" cancer. As a consequence, upper gastrointestinal tumors are decreasing overall, but concentrating around the gastroesophageal junction.

In detail, the incidence of esophageal AC has been markedly increasing in the last decades in most European regions [6] and in the United States, especially among white American men [7, 8]. On

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the contrary, the incidence of esophageal SCC is decreasing in both sexes and in all ethnic groups in the United States [7, 8], as well as in men living in Southern and Western Europe, while being on the rise in men from Northern Europe and in women from all European regions [6]. In the rest of the world, the incidence of esophageal SCC has been relatively stable or slightly decreasing [9].

Similarly, the increase in EGJ adenocarcinoma [3] and gastric cardia carcinoma [4] was more prominent in American white men and less pronounced among women and black people. In Norway, age-adjusted rates for distal gastric tumors decreased in both sexes between 1958 and 1992, while the rates of proximal gastric cancer were stable in men and decreased only slightly in females [10].

In Eastern Asia, the rise in esophageal adenocarcinoma has not occurred, despite a recent increase in the prevalence of gastroesophageal reflux disease (GERD), especially in urbanized areas. Chinese, Koreans, and Japanese seem to be more predisposed to esophageal SCC [9]. Nevertheless, the proportion of cardia cancer on overall gastric cancer has been reported to be on the rise also in Japan [11] and China [12, 13].

1.3 Incidence of EGJ Adenocarcinoma

1.3.1 Geographic Variability

Incidence of gastric cardia adenocarcinoma presents large variations among countries. According to the Five-Continent database [14], the cumulative incidence between 0 and 74 years was the lowest (about 0 %) among women in Concordia (Argentina) and the highest among Dutch men (0.52 %).

Cumulative incidence varied substantially by ethnicity, even within the same country; for instance, in the United States, cumulative incidence between 0 and 74 years was 0.37 % (95 % CI 0.35–0.39 %) among Whites and 0.25 % (0.19–0.31 %) among Blacks. An even larger discrepancy was observed in Singapore, where 0–74 years cumulative incidence was sixfold higher among Chinese men (0.29 %, 0.22–0.36 %) than among Malay men (0.05 %) [14]. Conversely, significant differences were observed even within the same ethnic group, when living in different countries; for instance, cumulative incidence doubled from Indians living in the mainland (0.08 %, 0.06–0.10 %) to Indians migrated to Singapore (0.15 %, 0.01–0.29 %) [14].

In the United States, ethnic differences are mainly restricted to men, while women present approximately the same incidence of the disease. During 1996–1998, age-adjusted incidence rate per 100,000 person-years was 3.4 among Caucasian men while being 1.9–2.1 among Hispanics, Blacks, and Asians/Pacific Islanders [15]. Among women, incidence rates ranged between 0.6 and 0.7 per 100,000 person-years among these ethnicities. At variance, Native Americans had a very low incidence, both in men and in women (0.9 and 0.2 per 100,000 person-years, respectively) [15].

1.3.2 Age and Sex Distribution

As regards sex and age distribution, in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, cardia adenocarcinoma was more common among men (37 % of all gastric adenocarcinoma) than among women (18 %), while an opposite pattern was recorded for noncardia adenocarcinoma (58 % among women vs. 41 % among men) [16]. Much higher male to female ratios were found in Spanish (6:1) [17] and British (4:1) [18] patients with gastric cardia cancer, and in American patients with gastric cardia adenocarcinoma (5:1) [19].

Age at onset did not differ between gastric cardia (63.8 ± 7.4 years, mean ± SD) and noncardia adenocarcinoma (62.5 ± 8.5 years) according to the EPIC study [16]. Likewise, median age at onset was similar in adenocarcinoma of the gastric cardia (69.3 years) and esophagus (69.6 years) in the Netherlands [20]. Of note, 75 % of gastric cardia adenocarcinomas were diagnosed after 60 years of age in the Netherlands [20], and also in the United States most patients with gastric cardia adenocarcinoma were older than 60 years at diagnosis [19].

1.3.3 Proportion of Gastric Cancer Arising from the Cardia

According to the EPIC study, cardia adenocarcinomas represent 29.4 % of all gastric adenocarcinomas in Europe. The proportion of cardia cancer was higher in Northern countries (35 %) than in Mediterranean countries (18 %) [16] (Fig. 1.1). Of note, these proportions become even higher (43.8 % and 24.7 %, respectively) if one excludes cancers from unknown site.

In the United States, the proportion of cardia cancer was 24.1 % in the SEER database from 1978 to 2005 [4], and this proportion increased to 34.2 % after excluding overlapping and nonspecified sites.

The proportion of cardia cancer was rather low in South Korea (6.9 %) [21] and Japan (10 %) [11], while in China it was comparable to that recorded in Northern Europe (33.6 %) [12] (Fig. 1.1). The proportion of proximal gastric carcinomas among small carcinomas (<=2 cm) was even higher, peaking at 45 % in 2011 in a Chinese hospital series [13].

1.3.4 Trends in Cardia Cancer

EGJ/cardia cancer reportedly increased in Western countries until the 1990s, remaining stable or declining thereafter (Table 1.1). The incidence of cardia cancer more than doubled in England [18] and Spain [17], it increased by 3.9 % every year in Sweden [26]. Interestingly in the American SEER database, the incidence of EGJ adenocarcinoma nearly doubled [3], while the incidence of cardia cancer increased only by 23 % [4].

During the 1990s, the increasing trend persisted in British Columbia, Canada [25], but in most countries it leveled off (Spain [17], the United States [3, 19, 23]), or turned into a declining trend (The Netherlands [20], Switzerland [24], Sweden [26]).

Moreover it should be reminded that gastric cancer from unspecified site also markedly decreased in the last decades, and this pattern could have amplified the rising trend in cardia cancer [18].

The increase in cardia cancer, combined with the simultaneous decrease in noncardia gastric adenocarcinoma, caused a remarkable increase in the proportion of gastric cancers arising from the cardia. In the Connecticut Tumor Registry [23], the ratio of cardia/noncardia tumors increased from 0.2 in 65–69 to 0.6 in 2003–2007. In a large Japanese series [11], the overall proportion of EGJ adenocarcinoma increased from 2.3 % (1962–1965) to 10.0 % (2001–2005). Likewise in the Gansu province of China, the proportion of cardia cancers increased from 29.6 % in 1993 to 37.1 % in 2004 [12]. Accordingly in a Chinese

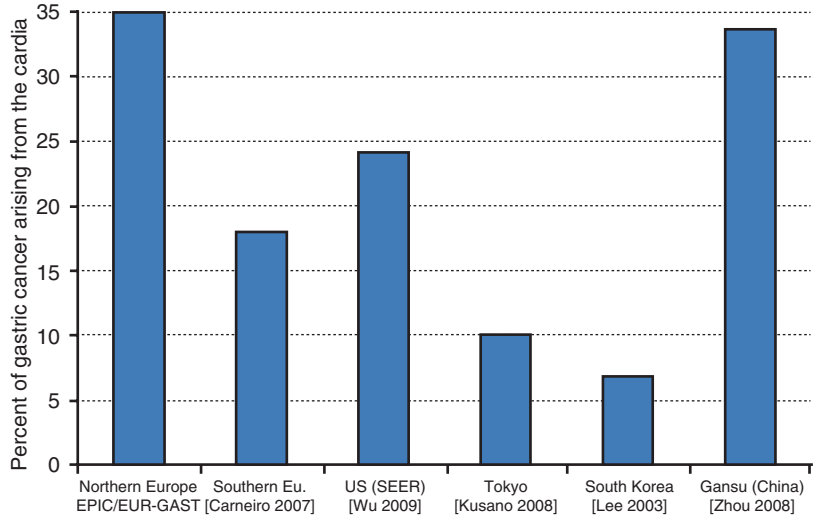

Fig. 1.1 Proportion of gastric adenocarcinomas arising from the cardia

Table 1.1 Incidence (per 100.000 person-years) of adenocarcinoma of gastroesophageal junction (GEJ) and cardia

I Author	Country		Incidence (per 100,000 pyrs)		
			Start	Middle	Final
Newnham	England	Men	**2.0 in 1971**		**5.4 in 1991**
2003 [18][a]	(cardia ca.)	Women	**0.6**		**1.4**
Crane	Olmsted	EGJ AC	**0.6 in 1971–1980**		**2.2 in 1991–2000**
2007 [22][e]	Minnesota	Cardia AC	0.9 in 1971-1980		0.8 in 1991–2000
Abrams	Connecticut	Cardia	**2.4 in 1965–1969**	**3.7 in 1988–1992**	3.4 in 2003–2007
2013 [23][d]	USA	Cancer			
Wu 2009 [4][d]	SEER USA	Gastric cardia	**1.8 in 1978–1983**	**2.2 in 1996–2000**	2.1 in 2001–2005
Buas	SEER USA	White men	**2.48 in 1973–1978**	**4.10 in 1991–1996**	3.78 in 2003–2008
2013 [3][d]	(EGJ AC)	White women	**0.40**	**0.71**	0.80
		Black men	**1.35 in 1973–1978**	**2.05 in 1991–1996**	2.01 in 2003–2008
		Black women	**0.34**	**0.68**	0.55
Aragones	Spain	Men	**1.13 in 1980–1984**	**2.71 in 1990–1994**	2.76 in 2000–2004
2010 [17][d]	(cardia ca.)	Women	**0.26**	**0.56**	0.48
El-Serag 2002 [19][c]	SEER USA	Cardia adenocarcinoma	3.3 in 1987–1991		3.1 in 1992–1996
Dikken	NL	Men	**5.7 in 1989**	**(–1.2 %/year)**	**4.4 in 2008**
2012 [20][a]	(cardia AC)	Women	1.2	(–0.2 %/year)	1.0
Schmass-	Switzerland	Men	**7.5 in 1982–1985**		**4.3 in 2006–2007**
mann 09[a] [24]	(cardia AC)	Women	**2.4**		**1.8**

I Author	Country		Start	% variation/yr	End
Bashash	British	Men	**From 1990**	**+3.8**	**To1999**
2008 [25]	Columbia (cardia ca.)	Women		**+9.2**	
Lagergren	Sweden	Cardia	**From 1970**	**+3.9 (3.2 –4.7)**	**To1990**
2011 [26][b]		adenocarcinoma	**From 1990**	**–1.0 (–1.6 – –0.3)**	**To 2008**

Significant/remarkable changes are highlighted in bold and increasing trend is further highlighted with a gray background

AC adenocarcinoma, SEER Surveillance, Epidemiology, and End Results cancer registry program in the United States
Age-standardized using [a]the European standardized population, [b]the 1989 Swedish population, [c]the 1970 US population, [d]the 2000 US standard population, [e]the 2000 US white standard population, [f]the 1996 Canadian population

series [13], the proportion of small gastric carcinomas (<=2 cm), located within 3 cm below the EGJ, increased from 16 % in 2004 to 45 % in 2011. At variance, in South Korea the proportion of gastric cardia cancer did not change from 1991 to 1995 to 1996–2000, being 6.2 % and 6.9 %, respectively [21].

The increase in cardia cancer was mainly due to an increase in the incidence of Siewert type II cancer and reflux-related subtype. In a Japanese series [11], the proportion of Siewert type II rose from 28.5 % (1962–1965) to 57.3 % (2001–2005), while that of type I remained at around 1 %. According to the Connecticut Tumor Registry [23], the reflux-related subtype markedly increased during the last 50 years, from 0.3 per 100,000 person-years in 1955–1959 to 2.4 in 2003–2007. On the contrary, *Helicobacter pylori*-related cardia cancer markedly declined during the same period, from 3.7 to 1.0 per 100,000 person-years.

1.4 Stage and Survival

As regards stage, in a national Dutch study [20] about 45 % of gastric cardia cancers, diagnosed in 2004–2008, were classified as M0, 40 % as M1, while in 15 % stage was unknown. In a multicentric US study [27], T stage was more advanced in gastric cardia adenocarcinoma than in noncardia subtype: indeed the proportion of AJCC T3-T4 tumors was, respectively, 71.8 % vs. 59.2 %. At variance, no significance difference was detected as regards the proportion of patients with nodal metastases, which was, respectively, 60.3 % and 59.2 % in gastric cardia and noncardia adenocarcinoma.

Prognosis is still poor in Western countries. In Dutch patients diagnosed with gastric cardia adenocarcinoma in 2004–2008, relative survival was 20.6 % (95 % CI 17.7–23.8 %) at 5 years in M0 patients, while it dropped to 6 % (4.6–7.7 %) at 2 years in M+ patients [20]. Likewise in the American SEER database, 5-year survival was 17 % in patients diagnosed from 1997 to 2008 [3]. Survival was substantially higher in patients undergoing surgery with curative intent, being 32.5 % 5 years after surgery in a US multicentric study [27] and 40.2 % after 3 years in an Italian series [28].

A much better 5-year survival (58.7 %) was recorded in a Japanese series [29].

Five-year survival in patients with EGJ adenocarcinoma doubled in the United States from 1973–1984 to 1997–2008 [3], and this improvement was attributed to both diagnostic anticipation and better treatment. At variance, the prognosis of gastric cardia adenocarcinoma did not improve from 1989 to 2008 in the Netherlands [20]. The authors pointed out that centralization of surgery and adoption of multimodal treatment allowed to improve prognosis in esophageal cancers, and the same interventions should be adopted also in cardia cancer treatment.

1.5 Risk Factors

According to the main risk factor involved, two distinct subtypes of cardia cancer have been identified: reflux-related and *H. pylori*-related [8, 23]. Of note, gastroesophageal reflux is the main risk factor for esophageal adenocarcinoma, while *H. pylori* infection is the main risk factor for gastric noncardia adenocarcinoma [30]. Reflux-related subtype presents an intestinal histotype, while *H. pylori*-related subtype is associated with severe atrophic gastritis and can present both an intestinal and a diffuse histotype. According to the Connecticut Tumor Registry [23], the *H. pylori*-related subtype was more common in 1955–1959 (3.7 vs. 0.3 per 100,000 person-years), while in 2003–2007 the reflux-related subtype has become predominant (2.4 vs. 1.0 per 100,000 person-years). Recent studies reported that *H. pylori* infection, one of the most important risk factors in noncardia cancer, could be even protective in cardia cancer [31].

Discrepancy exists on whether the adverse effect of gastroesophageal reflux is larger as regards the risk of adenocarcinoma of the esophagus [32] or gastric cardia [33]. In addition to gastroesophageal reflux, adenocarcinoma of the gastric cardia shares several risk factors with esophageal adenocarcinoma: obesity [34, 35],

meat and fat consumption [36], smoking [37], body posture, and occupational activities [32] (Table 1.2).

In particular, recent meta-analyses performed by the International Barrett's and Esophageal Adenocarcinoma (BEACON) consortium found that the OR associated with a BMI of >=40 relative to a BMI of <25 was 3.07 (95 % CI: 1.89–4.99) [34], while the OR of EGJ adenocarcinoma in smokers with respect to nonsmokers was 2.18 (95 % CI 1.84–2.58) [37]. Smoking was not only harmful per se but also amplified the carcinogenic effect of GERD [43].

At variance, abdominal obesity, alcohol drinking, and dietary antioxidant intake, which are strong predictors of esophageal adenocarcinoma, do not affect EGJ adenocarcinoma. Indeed, in a prospective cohort study [44], increasing waist-to-hip ratio increased the risk of esophageal but not EGJ adenocarcinoma. Another meta-analysis by the BEACON consortium reported that the OR for 7 drinks/day was 0.77 (95 % CI: 0.54–1.10) with respect to nondrinkers [45]. Moderate intake (0.5–>1 drink/day) was even protective (OR 0.78, 95 % CI: 0.62–0.99). Another meta-analysis found that dietary antioxidant intake (vitamin C, vitamin E, or beta-carotene/vitamin A) is protective against esophageal adenocarcinoma, while no consistent association has been found between antioxidant intake and the risk of cardiac carcinoma [46].

In summary, gastroesophageal reflux, obesity, and smoking may account for almost 70 % of EGJ adenocarcinoma [47]. The risk profile of

Table 1.2 Summary of risk factors for cardia cancer

Risk factor	Type of association	Study country
Demographic factors		
Gender, sexual hormones	Reduced risk in a male cohort treated with estrogens for prostate cancer	Sweden [38]
Ethnicity	Higher incidence in white men compared with the other ethnic groups studied both in England and in the United States	England [39], United States [15]
Socioeconomic factors		
Education	Higher education was associated with a reduced risk of gastric cardia cancer (HR: 0.42, 95 % CI: 0.20–0.89)	EPIC [40]
Occupation	Increased risk in gardeners, transport workers, bricklayers, and chemical process workers among men	Sweden [41]
Lifestyle factors		
Physical activity	Regular physical activity may be protective against noncardia cancer, and to a lower extent, cardia cancer	NL [42]
Meat and fat consumption	A diet high in processed meat, red meat, sweets, and high-fat dairy nearly double the risk of EGJ adenocarcinoma relative to a diet low in these foods	Sweden [36]
Obesity	OR of 3.07 (95 % CI: 1.89–4.99) associated with a BMI of >=40 relative to a BMI of <25	BEACON meta-analysis [34]
	Increased body mass index increases the risk of esophageal adenocarcinoma, and to a lower extent, the risk of cardia cancer	US [35]
Smoking	OR 2.18 (95 % CI 1.84–2.58) in smokers vs. nonsmokers	BEACON meta-analysis [37]
Pathologic factors		
Gastroesophageal reflux disease	More important role in the pathogenesis of esophageal adenocarcinoma	NL [32]
	More important role in the pathogenesis of gastric cardia adenocarcinoma	Minnesota [33]
H. pylori infection	*H. pylori* infection enhances the risk of noncardia gastric cancer but reduces the risk of cardia cancer	Finland [31]

cardia cancer is somewhat different from the risk profile of both esophageal adenocarcinoma and gastric noncardia adenocarcinoma.

1.5.1 Genetic Factors

EGJ adenocarcinoma has been associated with genes involved in DNA repair or inflammatory response. TP53 mutations were the most common abnormality, being detected in 42 % of gastroesophageal junction carcinomas [48]. Also, genes involved in Interleukin 2 and 4 metabolism were associated with gastric cardia cancer [49].

In a Japanese series of patients with Siewert type II adenocarcinoma, 18.2 % had HER2-positive tumors, which were also more prone to liver recurrence (23.7 % in HER2-positive patients vs. 7.6 % in HER2-negative patients [29].

Conclusions

The incidence of adenocarcinoma of the esophagogastric junction (EGJ)/cardia has increased in Western countries in the 1970s and 1980s, and then has either remained stable or slightly declined. In Eastern Asia, the rise in cardia cancer has been much smaller and somewhat delayed. Nowadays, cardia adenocarcinoma represents one third of all gastric cancer in Europe and in some areas of China. Prognosis is still poor in Europe and in the United States, 5-year survival being less than 20 %.

The rise in EGJ cancer during the last 50 years mainly reflected an increase in the subtype related to gastroesophageal reflux, while the *H. pylori*-related subtype declined over the same period. In addition to gastroesophageal reflux, adenocarcinoma of the EGJ shares several risk factors with esophageal adenocarcinoma: obesity, meat and fat consumption, smoking, body posture, and occupational activities. Nevertheless, the risk profile of EGJ/cardia cancer is somewhat different from the risk profile of both esophageal adenocarcinoma and gastric noncardia adenocarcinoma.

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