Gastric Cardia Cancer: How Much Is It from Fat?

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The overall age-adjusted incidence of gastric cancer has decreased in the United States from 11.7 to 7.1 persons per 100,000 from 1975 to 2008 according to the surveillance epidemiology and end results (SEER-9) database [1]. Similar trends have been observed worldwide. Although the incidence of gastric non-cardia adenocarcinoma (GNCA) has decreased worldwide the incidence of gastric cardia adenocarcinoma (GCA) has steadily increased over the last three to four decades along with a rise in esophageal adenocarcinoma (EAC) incidence [2, 3].

It is possible that the incidence of GCA has increased due to better understanding and appropriate classification of distal esophageal and GCA rather than a true increase in cancer incidence rate [4]. Current studies, however, are not completely devoid of the error of misclassification and hence concluding that the increase reflects a prior false underestimation is not completely justified. There is room for error even in studies that have selected patients based on standardized classifications. Various studies have used the International Statistical Classification of Diseases and Related Health Problems (ICD-9) and International Classification of Diseases for Oncology (ICD-O) codes [5–7]. Misclassification in the ICD-9 coding system could lead to incorrect estimation of cancer incidence (Table 1). First, EAC and cardio-esophageal junction cancers were classified under one group (ICD-9-151.0). Second, GCA could be misclassified under “unspecified gastric cancers” (ICD-9-151.9) or “overlap sites of stomach” (ICD-9-151.8) [8]. In the ICD-O 2/3 system GCA tumors are

classified under C16.0 but they could be incorrectly labeled as “overlapping lesions of esophageal cancer” (C15.8) [9] (Table 1). Nyrén et al. in 1999 studied the possibility of misclassification in the Swedish cancer registry from 1989 and 1994 and reported that the incidence of GCA could be 45 % higher or 15 % lower than that reported [10].

The Siewert classification sorts tumors as esophageal tumor (type I), true cardia tumor (type II) and subcardial tumor (types III). This is based on the location of the cancer with respect to the cardia, which is defined as oral end of the typical longitudinal gastric mucosa folds. This might be a better way of differentiating junctional cancers [11] (Table 2; Fig. 1).

Obesity as a Risk Factor for Cardia Cancer

Among the risks factors for EAC and GCA, obesity stands out as an important modifiable factor (Table 3). The prevalence of obesity has increased from 13 to 32 % between the 1960s and 2004. Currently, 68 % of US adults aged 20 and over are overweight or obese and 34 % are obese [12]. With the rise in the epidemic of obesity in the Western world there has been an increase in the incidence of GCA. One study calculated that the attributable risk percentage of GCA due to obesity has increased steadily in the United States to 21 and 10 % in men and women, respectively [13].

Several case control studies and meta-analysis have shown a positive association between higher BMI, ECA and GCA. The association appears to be much stronger for EAC. A UK-based case-control study in 2005 showed a positive association between BMI > 25 kg/m² and EAC (OR 1.67, 95 % CI 1.22–2.30), and GCA (OR 1.46, 95 % CI 0.98–2.18). Of note the data for GCA was not

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Table 1 International Classification of Diseases for Oncology (ICD-O) coding for stomach and esophageal cancer

ICD code	Term
ICD-9 (2009) stomach cancer	
151	Malignant neoplasm of stomach
151.0	Cardia
	Cardiac orifice
	Cardio-esophageal junction
151.1	Pylorus
151.2	Pyloric antrum
151.3	Fundus
151.4	Body of stomach
151.5	Lesser curvature
151.6	Greater curvature
151.8	Other specified sites of stomach
	Anterior wall not classifiable
	Posterior wall not classifiable
	Malignant neoplasm of contiguous or overlapping sites of stomach whose point of origin cannot be determined
ICD-O 2/3 stomach cancer	
C16.0	Cardia, NOS
C16.1	Fundus of stomach
C16.2	Body of stomach
C16.3	Gastric antrum
C16.4	Pylorus
C16.5	Lesser curvature of stomach, NOS
C16.6	(Not classifiable to C16.1–C16.4)
C16.8	Greater curvature of stomach, NOS
C16.9	(Not classifiable to C16.1–C16.4)
	Overlapping lesion of stomach
	Stomach, NOS
ICD-O 2/3 esophageal cancer	
C15.0	Cervical esophagus
C15.1	Thoracic esophagus
C15.2	Abdominal esophagus
C15.3	Upper third of esophagus
C15.4	Middle third of esophagus
C15.5	Lower third of esophagus
C15.8	Overlapping lesion of esophagus
C15.9	Esophagus, NOS

statistically significant [14]. Several other case control and population-based studies have shown similar association. In 2006, a review of two cohort and 12 case-control studies by Kubo et al. [15] showed that there was a weak association between BMI and GCA (OR 1.5, 95 % CI 1.3–1.8, $P_{\text{heterogeneity}} = 0.38$). A Netherlands-based study showed that the relative risk (RR) for GCA in overweight (BMI 25–29.9 kg/m²) and obese (BMI ≥ 30 kg/m²) subjects was 1.32 (95 % CI 0.94–1.85) and 2.73 (95 % CI 1.56–4.79),

Table 2 Siewert classification

Siewert classification type	Description
Type I	Adenocarcinoma of the distal esophagus, which usually arises from an area with specialized metaplasia of the esophagus (i.e. Barrett's esophagus) and may infiltrate the esophagogastric junction from above
Type II	True carcinoma of the cardia arising immediately at the esophagogastric junction
Type III	Subcardinal gastric carcinoma that infiltrates the esophagogastric junction and distal esophagus from below

Fig. 1 Topographic-anatomical classification of adenocarcinoma of gastro-esophageal junction based on their relationship to the cardia, which is defined as the oral end of the typical longitudinal gastric mucosa folds (reproduced with permission from Siewert et al. [1])

respectively, as compared to normal weight subjects (BMI 20–24.9 kg/m²). This study also showed that an increase in BMI in adulthood since age 20 was associated with significantly increased risk of ECA and GCA (P_{trend} 0.001 and 0.02, respectively) [16]. A US-population-based cohort study of half a billion people from 1995–1996 to 2003 was consistent with the earlier case-control studies and reported a hazard ratio (HR) of 2.46 (95 % CI 1.6–3.8) for GCA with BMI ≥ 35 kg/m² as compared to BMI of 18.5–25 kg/m². In EAC, where the HR for BMI ≥ 35 kg/m² was 2.27 (95 % CI 1.44–3.59) they even found that higher BMI was associated with increased risk, even in the normal BMI range [8]. The above data clearly showed a strong association of obesity and GCA in a dose-dependent manner.

It is interesting to note that the racial distribution of obesity and GCA do not follow the same trends. Obesity has increased in the African-American population in the United States whereas GCA is more common in white men

Table 3 Risk factors for esophageal adenocarcinoma and gastric cardia cancers

EAC	GCA
Risk factors	
Barrett's esophagus [31]	Barrett's esophagus [31]
GERD [32]	GERD [32]
White race [3]	White race [3]
Male sex [3]	Male sex [3]
Obesity [14]	Obesity [14]
Tobacco [33, 34]	Tobacco [33, 34]
Protective factors	
NSAIDs [35]	Cag A+ strain of <i>H. pylori</i> ^a
Vitamin C [36]	
β -carotene [36]	
Raw fruits and vegetables [36]	
Cag A+ strain of <i>H. pylori</i> ^a [37, 38]	

^a Controversial

[12]. It is possible that other measures of assessing obesity like visceral body fat, waist to height ratio (WHR) or waist circumference (WC) better correlate with and hence help explain the mechanism behind obesity-related increase in cancer incidence [7]. A nested case-control study by Corley et al. [17] showed that abdominal diameter was associated with increase of EAC independent of BMI. A similar association was observed but was not statistically significant in GCA (OR 1.28, 95 % CI 0.38–4.25; diameter ≥ 25 vs. < 20 cm) in this study. A population-based cohort study from O'Doherty et al. [7] showed that WC was associated with increase in GCA and EAC. WHR was positively associated with EAC risk only and this association was seen even in patients with normal BMI (18.5 to < 25 kg/m²). A report from Australia also supported the finding of increase in risk of GCA and EAC with increase in WC. They reported a HR of 1.46 (95 % CI 1.05–2.04) per 10 cm increase in WC for GCA and EAC in a cohort of around 41,000 people between the ages of 25 and 75 years observed over 11 years [6].

What Does the Current Study Add?

The current article from Cho et al. [18] from Korea is in concordance with the BMI data observed in prior studies from the Western population. Data from prior Asian studies have been inconsistent with regard to the incidence of GCA. Some showed an increase in incidence in Japanese, Chinese, Korean, Singaporean and South Indian populations while others showed no change [19–24]. A meta-analysis by Corley et al. showed that there was no clear association between GCA and obesity in the Asian

population and one study had even showed negative correlation [15, 25]. This latest Korean study however focuses on the difference in risk factors for GCA and GNCA and shows a positive association of obesity with GCA in the Korean population even when measured by Western standards [18].

The role of *Helicobacter pylori* and cagA+ strains in GCA has been controversial. Some studies show no association with GCA while others show a protective effect and even argue that the increase in incidence of GCA and ECA might be related to a decrease in the prevalence and hence protective effect of *H. pylori* [26, 27]. Cases from Cho et al. study did not show any difference between GCA and GNCA in *H. pylori* detection. Evaluation of the cagA+ strain might have been more helpful as compared to histological detection of *H. pylori* in post resection specimens. Misclassification as mentioned above has always been an issue in GCA cases. The authors classified cases based on the location of tumor in surgical specimens, which is likely to be more accurate than the ICD classification. Of note, although the tumor classification was not totally consistent with the Siewert's classification (with respect to distance from GEJ), it appears more reasonable with less chances of missed or misclassified GCA.

In conclusion, GCA and EAC are associated with obesity as measured by BMI and additional parameters like WC and visceral fat [7, 28]. The rising incidence of these cancers has been associated with the epidemic of obesity, especially in the Western world; however, race and age cannot completely explain the trend. Other parameters of measuring obesity like WC and visceral fat might have a better chance of explaining the correlation. The underlying mechanism is unclear. It has been shown that various adipokines and hormones like TNF- α , adiponectin, leptin, insulin, and interleukin-6 may play a role in development of EAC, Barrett's esophagus and GCA [28–30].

It has also been shown that not only does obesity increase the risk of cancer, the increase in BMI with age in adulthood is associated with increase in incidence of GCA and ECA [16]. Hence it would be interesting to see if weight reduction leads to a decrease in incidence of GAC or EAC. Large cohort studies are needed to assess this effect.

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