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REVIEW ARTICLE

Risk Factors for Rising Incidence of Esophageal and Gastric Cardia Adenocarcinoma

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Abstract
Introduction In the last 30 years, the incidence of esophageal and gastric cardia adenocarcinoma has steadily increased. The increase in incidence is approximately seven-fold, which is a more substantial increase than that of several malignancies, including melanoma, breast cancer, and prostate cancer.
Discussion The rising incidence has led to a steady increase in mortality from 2 to 15 deaths per 100,000 in the last three decades. The etiologic factors involved in the development of these malignancies include gastroesophageal reflux disease, Barrett's esophagus, acid-suppressive medication use, obesity, and tobacco use. This article discusses the contribution of these etiologic risk factors to this increase in incidence.

Keywords Esophageal adenocarcinoma · Risk factors · Gastric cardia adenocarcinoma

Introduction

The incidence of esophageal and gastric cardia adenocarcinoma has steadily increased over the past several decades [1]. From 1973 to 2006, the rise in incidence represents a seven-fold increase (from 3.6 to 25.6 cases per million), which is more substantial in comparison to that of other malignancies, including melanoma, breast cancer, and prostate cancer [2]. This rise in incidence rates from the 1970s have ranged from 1.5 to 17 % per year [3]. The incidence rate from 2004–2008 was reported to be 7.2 per 100,000, representing an annual average percent change of 1.7 % from 1999 to 2008 [4]. Several etiological hypotheses have emerged, and these include gastroesophageal reflux disease (GERD), acid-suppressive medication use, obesity, and possible genetic and epigenetic alterations predisposing certain patients to developing disease. This article reviews the current literature on the contribution of each of these factors to the rising incidence of esophageal and gastric cardia adenocarcinoma.

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GERD and Esophageal Adenocarcinoma

The presence of acid in the esophagus may lead to esophagitis, which results from inflammation and necrosis [5]. The state of continuous injury, inflammation, metaplasia, necrosis, and proliferation may lead to chromosomal instability and genomic alterations associated with the development of subsequent esophageal adenocarcinoma (EA) and gastric cardia adenocarcinoma (GCA) [6].

Population-based case–control series have demonstrated an association between chronic GERD and EA (Table 1). Patients with GERD have a 2- to 28-fold increased risk of EA when compared to patients without GERD. Wu et al. [7] conducted a population-based case–control study of patients with EA (n= 222) in Los Angeles County. In patients with GERD diagnosed within 3–15 years of EA diagnosis, the risk of EA increased 2.7-fold (odds ratio (OR) 2.7 (1.4–5.3)). The "diagnosis of GERD" group included all patients with a physician-based diagnosis of the condition, regardless of longevity of disease or severity of symptoms. The wide range of GERD penetrance within this group may be responsible for the relatively small observed increased risk. When longevity and severity of GERD symptoms are taken into account, the risk increased significantly with high frequency (daily: OR 4.1 (2.5–6.6)), duration (16+ years: OR 4.9 (3.2–7.5)), and severity

Table 1 Adjusted odds ratios (95 % CI) for esophageal adenocarcinoma (EA) and gastric cardia adenocarcinoma (GCA) in relation to gastroesophageal reflux disease (GERD)

	Author	Measure		EA	GCA
Any history of GERD	Lagergren[a] et al. [11]	Heartburn, regurgitation or both		7.7 (5.3–11.4)	2.0 (1.4–2.9)
	Wu[b] et al. [8]	GERD diagnosed by physician within 3–15 years of cancer diagnosis		2.7 (1.4–5.3)	1.3 (0.6–2.7)
	Garcia-Rodriguez[c] et al. [9]	Ever experienced reflux symptoms		1.7 (1.2–2.4)	1.5 (1.0–2.3)
Frequency	Lagergren[a] et al. [11]	Frequency of reflux symptoms	1×/week	5.1 (2.8–9.4)	2.0 (1.1–3.6)
			2–3×/week	6.3 (3.8–10.3)	1.9 (1.2–3.1)
			>3×/week	16.7 (8.7–28.3)	2.3 (1.2–4.3)
	Wu[b] et al. [8]	Sour stomach/regurgitation	Weekly	3.5 (2.3–5.4)	1.0 (0.6–1.7)
			Daily	4.0 (2.5–6.3)	2.6 (1.7–4.0)
		Heartburn	Weekly	3.2 (2.0–5.0)	2.6 (1.7–4.0)
			Daily	4.0 (2.5–6.7)	2.3 (1.4–3.8)
	Farrow et al. [10]	Severe heartburn or acid regurgitation	3–12×/year	1.2 (0.6–2.2)	0.6 (0.3–1.1)
			13–104×/year	2.0 (1.2–3.2)	0.6 (0.3–1.0)
			105–364×/year	3.4 (1.9–6.1)	0.9 (0.5–1.9)
			365+ ×/year	5.5 (3.2–9.3)	1.2 (0.7–2.2)
Duration	Lagergren[a] et al. [11]	Duration of symptoms, heartburn or regurgitation	3–15 years	3.0 (1.8–4.8)	1.7 (1.1–2.8)
			16+ years	4.3 (2.9–6.4)	1.5 (1.0–2.4)
	Wu[b] et al. [8]	Duration of weekly or daily symptoms: heartburn	3–15 years	2.1 (1.2–3.7)	2.2 (1.3–3.5)
			16+ years	4.9 (3.2–7.5)	2.8 (1.8–4.3)
	Farrow et al. [10]	Duration of GERD symptoms(heartburn or acid regurgitation)	<10 years	1.6 (1.0–2.4)	0.5 (0.3–0.8)
			10–20 years	2.7 (1.6–4.5)	0.4 (0.2–0.8)
			20–30 years	2.3 (1.2–4.5)	0.9 (0.5–1.9)
Severity	Lagergren[a] et al. [11]	Reflux symptom score[d]	1–2 points	1.4 (0.7–3.0)	1.7 (1.0–2.9)
			2.4–4 points	8.1 (4.7–6.1)	1.8 (1.0–3.2)
			4.5–6.5 points	20 (11.6–34.6)	2.8 (1.6–5.0)
	Wu[b] et al. [8]	Reflux symptom index[e]	1–2 points	2.9 (1.9–4.3)	1.7 (1.2–2.6)
			2.5–4 points	4.4 (2.8–6.9)	2.4 (1.5–3.7)
			4.5–5 points	6.8 (3.2–14.4)	3.2 (1.4–7.1)

[a] Data adjusted for age, sex, socioeconomic status, BMI, tobacco smoking, alcohol use, intake of fruits and vegetables, and physician activity at work

[b] Data adjusted for smoking, age, race, birthplace, and level of education

[c] Data adjusted for age, sex, smoking, alcohol consumption, BMI, hiatal hernia, peptic ulcer, and dyspepsia

[d] Reflux symptom score: heartburn only = 1 point, heartburn + regurgitation = 1.5 points, nightly symptoms = 2.0 points. Frequency: once per week = 0 point, 2–6 times per week = 1 point, 7–15 times per week = 2 points, >15 times per week = 3 points

[e] Reflux symptom index: 0–2.5 points assigned to heartburn and sour stomach/regurgitation independently and then summed: 0 = symptom less than weekly, first occurred within 2 years of reference date; 1 = symptoms at least weekly but not daily, first occurred within 3–15 years of reference date; 1.5 = symptoms at least weekly but not daily, first occurred >16 years before reference date; 2 = symptoms daily, first occurred 3–15 years before reference date; 2.5 = symptoms daily, first occurred >16 years before reference date

(maximum reflux symptom score (RSS): OR 6.8 (3.2–14.4)) of symptoms. In a later study, patients with both hiatal hernia and reflux symptoms, the risk of EA was increased 8-fold (OR 8.1 (95 % confidence interval (CI) 4.8–13.9)), while patients with reflux symptoms alone had only a 3-fold increased risk of EA (OR 3.6 (95 % CI 2.5–5.2)) [8]. Garcia-Rodriguez et al. [9] conducted a similar study with EA (n=287) in the UK and found a lower increase in the risk of EA with GERD symptoms (OR 1.7 (95 % CI 1.2–2.4)). In calculating this risk, case patients were chosen if they had "ever experienced GERD symptoms," but neither a qualification of "ever" nor a list of specific symptoms were included in the text. This loose definition of GERD may be responsible for the relatively low OR. Farrow et al. [10], who reviewed data from a previous case–control study, also cited a significant increase in the risk of EA (n=293) with GERD, which was further stratified by frequency (daily: OR 5.5 (3.2–9.3)) and duration (10–20 years: OR 2.7 (1.6–4.5)) of GERD symptoms.

Lagergren et al. [11] reported that the risk of EA (n=189) increased with higher frequency (more than three times/week: OR 16.7 (8.7–28.3)), duration (>20 years: OR 16.4 (8.3–28.4)), and severity (maximum RSS: OR 20.0 (11.6–34.6)) of GERD symptoms. Similarly, Chow et al. [12] found a slightly increased risk (OR 2.1 (1.3–3.5)) of EA/GCA (n=196) with history of GERD. A study using the General Research Practice Database in the UK reported that the relative risk for EA was elevated to 4.5 (95 % CI 1.04–19.6) among patients with esophagitis as compared to the general population [13]. Furthermore, they reported no relationship with prior diagnosis of GERD without esophagitis with subsequent risk of developing adenocarcinoma. Evidence to date does support an association of GERD with adenocarcinoma with variable natural course and, in some cases, with equivocal and unclear relationship. Up to 40 % of patients with EA have no history of regular reflux symptoms questioning the validity of such observational studies [14]. All are subject to similar limitations, including lack of direct interview data, self-reporting of symptoms, patient use of acid-suppressive drugs, which may significantly alter self-reported symptoms of GERD, and socioeconomic factors restricting patient access to physician care.

GERD and GCA

The association between GERD and GCA appears to be weaker (Table 1). Lagergren et al. [11] evaluated the risk of GCA in patients with GERD. The only significant finding was an increase in GCA in patients with long standing (>20 years: OR 3.3 (1.8–6.3) vs. <12 years: OR 1.6 (0.9–2.9)) or severe (maximum RSS: OR 2.8 (1.6–5.0) vs. minimum RSS: OR 1.7 (1.0–2.9)) symptoms of GERD. Another case–control study looked at GCA (n=277) separately from EA and cited a 1.3 OR (0.6–2.7) of GCA with prior GERD diagnosis [7]. Though these results were not significant, increased frequency (daily: OR 2.6 (1.7–4.0)), duration (16+ years: OR 2.8 (1.8–4.3)) or severity (maximum RSS: OR 3.2 (1.4–7.1)) of GERD symptoms each conferred a significant increase in the risk of GCA.

Barrett's Esophagus

Barrett's esophagus (BE) is a premalignant acquired condition characterized by the displacement of the squamocolumnar junction proximal to the esophagogastric junction as a result of mucosal injury [15]. Although the precise prevalence of BE is not known in the general population, it is estimated to be around 0.4 to 1.6 % in the adult US population [16]. It is estimated that the risk of developing cancer in a given patient with BE is approximately 0.5 to 0.7 % annually with no specific geographic predilection [17, 18]. A more recent population-based cohort study involving patients with BE in Denmark suggested that the annual risk for cancer development was 0.12 %, much lower than previously reported [19]. Evolving epidemiologic data suggest that despite the rising incidence of EA, the majority of patients with BE may never progress to cancer [20, 21], suggesting that other factors in addition to the presence of BE may compound the risk of developing dysplasia and cancer. A number of characteristics of BE have been reported to be associated with an increased risk of cancer development.

Studies to date have yielded conflicting results for segment length as a risk factor for cancer development. Observational studies have reported that prevalence of cancer is higher in longer lengths of BE [22–24]. Contrary to other published reports, a prospective cohort study by the Seattle Barrett's Esophagus Research Program found that segment length was not associated with cancer risk [25]. Weston et al. [23] reported that a segment length of 6 cm or longer was associated with an increasing risk for developing high-grade dysplasia or adenocarcinoma. Moreover, a recent meta-analysis reported a trend for decreased risk for cancer progression for short-segment BE [18]. In summary, these data suggest that the association of segment length in BE with cancer progression is uncertain.

Dysplasia, specifically high grade, has been identified as the only reliable predictor for cancer progression in patients with BE. A sequence ranging from low-grade dysplasia to high-grade dysplasia and then adenocarcinoma has been suggested, but this may not occur in a step-wise fashion, and some patients may progress to cancer without preceding high-grade dysplasia [26–28]. The data on natural history of low-grade dysplasia have been fraught with many limitations and are not well defined. Firstly, there is a high degree of inter-observer variability, even among expert GI pathologists, which can limit the accuracy of the diagnosis [29]. Majority of patients with low-grade dysplasia may not progress to high-grade dysplasia or adenocarcinoma, but a certain subset of these patients does progress. Various studies where the mean follow-up ranged from 26 to 48 months, reported that 10–28 % of subjects progressed to high-grade dysplasia or adenocarcinoma [30, 31]. A Veteran Affairs cohort study estimated that patients with low-grade dysplasia had a 1.3 % per year risk of progressing to high-grade dysplasia or adenocarcinoma as compared to 0.36 % per year for patients without low-grade dysplasia [32]. Another study reported that 31.8 % of patients (N=77) with baseline diagnosis of low-grade dysplasia progressed to cancer as compared with 68 % of patients with baseline high-grade dysplasia, at a mean follow-up of 25 months (range 1–136 months) [33]. In summary, low-grade dysplasia may have a variable natural course where some patients clearly progress while others never. Evidence based on prior studies

does suggest that this may represent an intermediate risk for subsequent adenocarcinoma development [34]. Contrary to low-grade dysplasia, there are more consensuses regarding high-grade dysplasia as posing unequivocally more risks for subsequent cancer development. Carcinoma is detected in esophagectomy specimens in approximately 40 % of patients with high-grade dysplasia [35]. A prospective study following 100 patients with high-grade dysplasia reported progression to adenocarcinoma at 1 and 3 years in 38 and 56 % of patients, respectively [36]. A recent meta-analysis reported that the incidence of adenocarcinoma in high-grade dysplasia is 6.58 % annually [37]. Thus, high-grade dysplasia represents a well-recognized risk factor for the development of adenocarcinoma.

In addition to segment length and dysplasia, a number of molecular markers may define a subset of patients at increased risk for the development of adenocarcinoma. Alterations in p53, p16, and aneuploidy by FLOW are among the most frequently encountered molecular abnormalities in BE [38–40]. Mutations of p53 and 17p loss of heterozygosity (LOH) have been detected in BE epithelium before the development of adenocarcinoma, and similar mutations have been reported in up to 92 % of cases of esophageal carcinoma [38, 41]. Moreover, p16 LOH and inactivation of the gene promoter region by hypermethylation have also been frequently reported in EA [42]. Interestingly, other epigenetic changes such as hypermethylation of RUNX3 and HPP1, are reported to be independent risk factors for adenocarcinoma progression from BE [43]. These studies highlight important observations and can be potentially utilized for further development of promising biomarkers for risk stratification. In a study, combination of 17p LOH, 9p LOH, and primary DNA abnormality was shown to predict the 10-year progression to adenocarcinoma with a relative risk of 38.7 (95 % CI 10.8–138.5) with a cumulative incidence of adenocarcinoma of 79 % over the same period, as compared to subjects with no baseline abnormalities [44]. Such biomarkers need to be validated in clinical trials to establish their utility.

Obesity

Obesity has emerged as a leading candidate risk factor for EA. A large number of studies have reported the association between obesity and EA/GCA. Current evidence suggests that an incremental association exists between obesity and EA and GCA. A population-based case–control study in Los Angeles County reported a significant increase in the risk of EA (OR 1.9 (1.3–2.9)) and GCA (OR 1.6 (1.1–2.4)) with only the highest quartile of BMI (BMI >28 kg/m^2) [7]. The trend toward an increased risk of EA (n=222) or GCA (n=277) with increasing BMI was found to be statistically significant (p<0.001 for EA and p<0.03 for GCA). In addition, a positive association was found between a BMI of greater than 28 kg/m^2 at age 20 and an increased risk of EA and GCA, suggesting that BMI may be a strong predictor of the risk for EA and GCA. Chow et al. [12] conducted a population-based case–control study in the state of Connecticut and reported similar results but found a significantly increased risk of EA with a BMI as low as 25 kg/m^2 (OR 2.0 (1.3–3.3)). This group's analysis of the trend toward an increased risk of either EA (n=252) or GCA (n=261) with increasing BMI was also found to be highly statistically significant (p<0.0001 for EA and p<0.0016 for GCA).

Vaughan et al. [45] investigated BMI as a risk factor for EA (n=133) and GCA (n=165) by separating cases into quartiles based upon the BMI distribution for controls. BMIs in the 50–89th percentile were classified as overweight, and cases whose BMIs were in the 91st–100th percentile were classified as obese, noting that the median BMI value of controls was 26.2 kg/m^2 for males and 25.4 kg/m^2 for females. Reported results showed a statistically significantly increased risk of EA, and not GCA, in obese patients (OR 2.5 (1.2–5.0)) and estimated that obesity alone may account for 18 % of cases of EA [45].

The Netherlands Cohort Study initiated in 1986 provided prospective data regarding the association of EA and obesity [46]. The results demonstrated a significant increase in the risk of EA (RR 4.0 (2.3–6.9)) and GCA (RR 2.7 (1.6–4.8)) in patients with BMI ≥30 kg/m^2. Furthermore, an increasing BMI had a linear relationship with the risk of EA (n=142) and GCA (n=173), and this trend was statistically significant (p=0.001 for EA and p=0.002 for GCA).

Lagergren et al. [47] also reported the strong association between EA and BMI. In this study, a 16.2-fold (OR 16.2 (6.3–41.4)) increased risk of EA (n=189) was observed in the cohort of patients with a BMI >30 kg/m^2, and a 4.3-fold (OR 4.3 (2.1–8.7)) increased risk of GCA (n=262) with a BMI >30 kg/m^2. A population-based case–control study from Australia found a dose-dependent relationship of obesity with EA with the highest risk encountered for BMI of 40 kg/m2 or greater as compared to a healthy BMI [48]. Moreover, a risk associated with obesity was found to be higher in men than in women. Another case–control study also reported dose-dependent relationship with abdominal girth and EA, which did not change when adjusted for BMI (OR 4.78 (95 % CI 1.1.4–20.11)) [49].

Hampel et al. [50] conducted a systematic review and meta-analysis of epidemiological studies that examined the association between obesity and several GERD-related disorders, including GERD symptoms, esophageal erosions, and EA. Investigators identified seven studies that examined the association between obesity and EA. Adjustments for race, smoking, alcohol consumption, and history of reflux symptoms did not affect the statistical significance of the unadjusted

associations. There was a dose–response relationship with an increase in pooled adjusted odds ratio for a BMI of 25–30 kg/m^2 and a BMI greater than 30 kg/m^2 .The pooled adjusted OR for BMI of 25–30 kg/m^2 and EA was reported to be 1.52 (95 % CI 1.147 to 2.009; p=0.004), and for BMI more than 30 kg/m^2, it was 2.78 (95 % CI 1.850 to 4.164; p< 0.001). This study suggested that there is approximately a 2-fold increased risk of EA in obese patients as compared to patients with normal BMI. Kubo et al. [51] conducted a meta-analysis of 14 studies evaluating the association between BMI and the risk of EA or GCA that demonstrated a positive association between high BMI (>25) and an increased risk for EA (males OR 2.2 (1.7–2.7) and females OR 2.0 (1.4–2.9)) but demonstrated only a weak association between BMI and GCA (OR 1.5 (1.3–1.8)).

The mechanisms responsible for this association between obesity and EA/GCA remain unclear. One hypothesis is that central obesity leads to higher intra-abdominal pressure and a higher likelihood of gastric reflux and consequently EA and GCA [7, 45, 46]. Another hypothesis is that the metabolic syndrome associated with obesity can contribute to the inflammatory response observed in GERD and to the development of EA and GCA. In a series reported by Ryan et al., 46 % of patients (n=102) with Barrett's esophagus had metabolic syndrome and 78 % were centrally obese [52]. Furthermore, 92 % of patients with long-segment Barrett's esophagus were centrally obese as compared to 62 % with short-segment Barrett's esophagus. A number of hormones such as adiponectin and insulin-ike growth factors are associated with obesity, and they have shown to modulate cellular proliferation and apoptosis [53]. This also provides another plausible mechanistic explanation highlighting the risk of obesity and carcinogenesis.

Dietary Factors

The association between EA/ GCA and dietary intake, glycemic index, and glycemic load is less well established. A variety of studies have analyzed diet and dietary supplements and the risk of EA. In a matched case–control series, Kubo et al. compared the dietary intake of patients with Barrett's esophagus (296), GERD (308), and control population (309). Higher intake of omega-3 fatty acids, polyunsaturated fats, and fiber was associated with a lower risk of Barrett's esophagus. On the other hand, higher *trans* fat intake was associated with a higher risk of Barrett's esophagus. Similarly, other studies have reported a lower risk of EA and GCA associated with dietary fiber, fruits /vegetables, and antioxidant intake [54–56]. Moreover, a higher intake of saturated fats and red meat have been proposed to increase cancer risk [55, 56]. Aligned with this, an ecologic study reported a correlation with a rise in carbohydrate consumption and increase in the incidence of EA [57]. It has been proposed that a diet high in carbohydrates can lead to insulin resistance and, thus, lead to elevated levels of insulin-like growth factors contributing towards carcinogenesis [52, 58].

Tobacco Use

A number of studies have linked current or past smoking as a strong risk factor for EA [7, 59, 60]. There is a proportional increase in the risk with increasing duration and intensity of smoking [61, 62]. Interestingly, a Swedish population-based case–control study failed to identify smoking as a risk factor for EA development [63]. More recently, a Chinese case–control study identified both passive and active smoking as risk factors for GCA [64]. Cook et al. [65] studied primary data from ten population-based case–control studies and two cohort studies from the Barrett's Esophagus and Esophageal Adenocarcinoma Consortium, looking into the association of cigarette smoking and EA. They reported a summary of odds ratio between cigarette smoking and EA (OR=1.96 (95 % CI= 1.64 to 2.34)), esophagogastric junctional adenocarcinoma (OR=2.18 (95 % CI=1.84 to 2.58)), and all adenocarcinoma (OR=2.08 (95 % CI=1.83 to 2.37)). Moreover, there was a statistically significant dose–response relationship between pack-years and each studied outcome (p<0.001). These studies suggest that, in addition to common knowledge on established association of tobacco use and esophageal squamous carcinoma, smoking does increase the risk of EA development.

Acid-Suppressive Therapy

Several studies show an association between the use of H2-blockers/proton pump inhibitors (PPI) and the incidence of EA and GCA. Researchers believe that this association is unlikely to be causal since the indication for use of these drugs, namely GERD, leads to significant confounding.

In several studies, the association between PPI or H2 blocker use and incidence of EA was stronger than the association between their use and GCA, yet no studies showed a clear, significant increase in the risk of EA with use of either drug. Most recently, Pandeya et al. [66] found no statistically significant evidence that use of PPIs or H2 blockers increased risk of EA or GCA, though the trend for EA suggested a possible association among patients with at least weekly symptoms of GERD who used acid suppressants (OR 7.8 (5.2–11.8), n=105) and also in patients with less than weekly symptoms who reported usage of acid-suppressive therapy (3.1 (2.1 to 4.7); n=65). The investigators found no evidence

that the risk of EA associated with reflux symptoms was altered by the use of acid-suppressive therapy.

The research on EA is more extensive than the research on GCA. After adjusting for age, sex, smoking, alcohol consumption, and body mass index, a study by Garcia-Rodriguez et al. [9] found an insignificant increase in the risk of EA with current (all durations, OR 1.5 (0.9–2.5), n=17) but not past (OR 0.8 (0.3–2.0), n=5) use of PPIs, while a significant increase in the risk of EA was found with current (all durations, OR 1.6 (1.1–2.2), n=36) and past (OR 1.5 (1.0–2.3), n=31) use of H2 blockers. However, further adjustment by logistic regression for occurrence of GERD, hiatal hernia, peptic ulcer, and dyspepsia revealed that the risk of EA with current use of PPIs (OR 0.9 (0.5–1.5)) or H2 blockers (OR 1.2 (0.8–1.8)) was insignificant. It was noted that the risk of EA with current, long-term use of PPIs did not significantly increase from shorter-term use (>3 years: OR 0.9 (0.2–3.9) vs. <1 year: OR 0.6 (0.3–1.4), adjusted for occurrence of GERD, hiatal hernia, peptic ulcer, and dyspepsia), although the risk of EA with current, long-term use of H2 blockers did significantly increase from shorter-term use (>3 years: OR 2.1 (1.2–3.7) vs. <1 year: OR 0.8 (0.4–1.5), adjusted for occurrence of GERD, hiatal hernia, peptic ulcer, and dyspepsia).

Though the study by Garcia-Rodriguez et al. [9] indicated that long-term use of H2 blockers or PPIs is a marker for increased risk for EA, investigation of the indications for their use suggested that the pathological condition, and not the drug, was responsible for this increase. That is, people who suffer from GERD consume more antireflux agents, and their risk of EA is increased because of the duration and severity of their GERD, not because of the duration or amount of antireflux medications they consume.

A recent Veteran Affairs cohort study suggested that long-term PPI therapy was associated with decreased risk of the development of dysplasia [67]. Similar results have been reported in a study conducted in Australia [68]. De Jonge et al. [69] offer a mechanistic explanation for PPIs' role in lowering the risk of dysplasia. Use of PPIs resulted in a significant decrease in the number of CD8 (+) T lymphocytes within the dysplastic tissue (p<0.05),but did not reduce oxidative damage to the tissue. This study suggests that PPI use may not, in fact, reduce the risk of progression to EA because oxidative damage has been shown to be a major mechanism for carcinogenesis in EA. Thus, the role of PPIs in reducing or exacerbating the risk for EA has yet to be definitively determined.

Farrow et al. [10] attempted to eliminate the confounding effect of GERD by including GERD symptom frequency in their logistic regression. This study found no significant increase in the risk of EA with current short-term use (1–48 months: OR 0.7 (0.4–1.3), n=26) or long-term use (48+ months: OR 1.3 (0.6–2.8), n=21) of H2 blockers, and no significant increase in the risk of EA with past H2 blocker for short- or long-term use. The investigators concluded that incomplete accounting for GERD symptoms may have confounded earlier results, and GERD was likely the source of the moderate, yet insignificant, increase in the risk of EA. Hillman et al. [70] present an interesting perspective on determining the risk of EA in patients who use acid suppressants. Their data suggest that PPIs alter the markers used to determine the risk of EA when patients are diagnosed with Barrett's esophagus, making it difficult for clinicians to assess overall risk. However, they argue that the benefit of PPIs in lowering the risk for dysplasia outweighs the difficulty in calculating the risk.

Investigation of H2 blockers and PPIs as predictors of increased risk of GCA showed similar findings across studies. When adjusted for occurrence of GERD, hiatal hernia, peptic ulcer, and dyspepsia, no significant increase in the risk of GCA was found with current (all durations) or past PPI or H2 blocker use [9]. Tamim et al. [71] who stratified results based on drug dose and studied only gastric adenocarcinomas found no significant increase in the risk of GCA with current (for at least 1 year) PPI or H2 blocker use, regardless of dose. Farrow et al. [10] studied only H2 blockers and found no significant increase in the risk of GCA with current (n=27), or past short-term (1–47 months, n=12) or long-term (>48 months, n=10) use.

Other means to achieve acid suppression and potentially defend against severe mucosal injury is by antireflux surgery. Some have suggested that perhaps antireflux surgery protects against progression from BE to EA [72]. This hypothesis has been repudiated by at least a couple of studies. A Swedish-based population cohort study of GERD patients found no such protective effect of surgery [73]. In addition, a Veteran Affairs cohort study found no cancer risk reduction associated with fundoplication as compared to medically treated GERD patients [74].

Table 2 Risk factors for esophageal adenocarcinoma

Risk factor	Esophageal adenocarcinoma
GERD	↑↑
Barrett's esophagus	↑↑↑
Obesity	↑↑↑
Dietary factors	↑↑
Tobacco use	↑
Antiacid therapy	↑
Race	Caucasian > non-Caucasian
Gender	Male > female

GERD gastroesophageal reflux disease, ↑ increased associated risk

Socioeconomic Risk Factors

Male gender is a well-known risk factor and estimates put an increase in 6- to 8-fold in the incidence of EA in men. However, recent reports suggest that the incidence of EA is increasing in both genders [58]. A recent analysis of SEERS registry reported that the average annual incidence rate for EA for white males (4.2/100,000 per year) was double that of Hispanic males (2/100,000 per year). This rate was consideraby higher in white men as compared to black, Asians, and Native Americans [75]. With clear predilection for Caucasians and male sex, a possible heritable factor has been hypothesized as supported by a number of reports of familial clustering in both BE and EA. A Swedish Family-Cancer Database study found that the standardized incidence ratio for EA was increased to 3.52 (95 % CI 1.11–9.28) among offsprings of parents with EA [76]. Another study reported that a positive family history among patients with BE, EA, and gastroesophageal junction adenocarcinoma was higher as compared to GERD controls (24 vs. 5 %) [77]. Contrary to such reports, a US case conrol study found no association between the risk of EA or any family history of digestive cancers [78]. In summary, inherited risk factors may potentially be contributory towards an incrased risk of EA, but more data are needed to clearly define the magnitude and association of these risk factors.

Conclusion

The rising incidence of EA and GCA over the last several decades is alarming. Although there is an association between GERD and risk of EA, no clear association between GERD and risk of GCA exists. It is clear that BE is perhaps the most reliable risk factor associated with EA, yet most of BE patients may never progress to adenocarcinoma. Data also suggest that treatment for GERD with PPIs or H2 blockers is unlikely to play a role in the carcinogenesis of EA or GCA. An association between obesity and increased risk of EA is clearly supported in epidemiologic studies, but the relationship between obesity and GCA remains unclear. Likewise, the mechanism by which obesity increases the risk of EA is unknown. Further studies to elucidate the causal relationship between the aforementioned risk factors (Table 2) and development of adenocarcinoma are needed to further understand the pathogenesis of this malignant entity.

The data on molecular markers as predisposing risk factors for EA and GCA are preliminary but continue to reveal new insights into the pathophysiology of these diseases. The next several decades of research will likely focus on this factor within the disease process as we continue to expand our understanding on the relationship between genetic factors and the biology of human cancers. Clearly, an in-depth understanding on risk exposures and carcinogenesis is needed to design interventions that may potentially impede this disturbing trend and rising incidence.

Conflict of Interest The authors have declared no conflicts of interest.

References

1. El-Serag HB. Time trends of gastroesophageal reflux disease: a systematic review. Clin Gastroenterol Hepatol. 2007;5:17–26.
2. Pohl H, Sirovich B, Welch HG. Esophageal adenocarcinoma incidence: are we reaching the peak? Cancer Epidemiol Biomarkers Prev. 2010;19:1468–70.
3. Desai HG, Kamani PM. Factors responsible for the increasing incidence of oesophageal adenocarcinoma. J Assoc Physicians India. 2007;55:435–7.
4. Simard EP, Ward EM, Siegel R, Jemal A. Cancers with increasing incidence trends in the United States: 1999 through 2008. CA Cancer J Clin 2012.
5. Moayyedi P, Talley NJ. Gastro-oesophageal reflux disease. Lancet. 2006;367:2086–100.
6. Kim R, Weissfeld JL, Reynolds JC, Kuller LH. Etiology of Barrett's metaplasia and esophageal adenocarcinoma. Cancer Epidemiol Biomarkers Prev. 1997;6:369–77.
7. Wu AH, Wan P, Bernstein L. A multiethnic population-based study of smoking, alcohol and body size and risk of adenocarcinomas of the stomach and esophagus (United States). Cancer Causes Control. 2001;12:721–32.
8. Wu AH, Tseng CC, Bernstein L. Hiatal hernia, reflux symptoms, body size, and risk of esophageal and gastric adenocarcinoma. Cancer. 2003;98:940–8.
9. Garcia Rodriguez LA, Lagergren J, Lindblad M. Gastric acid suppression and risk of oesophageal and gastric adenocarcinoma: a nested case control study in the UK. Gut. 2006;55:1538–44.
10. Farrow DC, Vaughan TL, Sweeney C, et al. Gastroesophageal reflux disease, use of H2 receptor antagonists, and risk of esophageal and gastric cancer. Cancer Causes Control. 2000;11:231–8.
11. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999;340:825–31.
12. Chow WH, Finkle WD, McLaughlin JK, et al. The relation of gastroesophageal reflux disease and its treatment to adenocarcinomas of the esophagus and gastric cardia. JAMA. 1995;274:474–7.
13. Solaymani-Dodaran M, Logan RF, West J, et al. Risk of oesophageal cancer in Barrett's oesophagus and gastro-oesophageal reflux. Gut. 2004;53:1070–4.
14. Chak A, Faulx A, Eng C, et al. Gastroesophageal reflux symptoms in patients with adenocarcinoma of the esophagus or cardia. Cancer. 2006;107:2160–6.
15. Sharma P, McQuaid K, Dent J, et al. A critical review of the diagnosis and management of Barrett's esophagus: the AGA Chicago Workshop. Gastroenterology. 2004;127:310–30.
16. Ronkainen J, Aro P, Storskrubb T, et al. Prevalence of Barrett's esophagus in the general population: an endoscopic study. Gastroenterology. 2005;129:1825–31.
17. Shaheen NJ, Crosby MA, Bozymski EM, Sandler RS. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? Gastroenterology. 2000;119:333–8.

18. Thomas T, Abrams KR, De Caestecker JS, Robinson RJ. Meta analysis: cancer risk in Barrett's oesophagus. Aliment Pharmacol Ther. 2007;26:1465–77.
19. Hvid-Jensen F, Pedersen L, Drewes AM, et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med. 2011;365:1375–83.
20. Moayyedi P, Burch N, Akhtar-Danesh N, et al. Mortality rates in patients with Barrett's oesophagus. Aliment Pharmacol Ther. 2008;27:316–20.
21. van der Burgh A, Dees J, Hop WC, van Blankenstein M. Oesophageal cancer is an uncommon cause of death in patients with Barrett's oesophagus. Gut. 1996;39:5–8.
22. Weston AP, Krmpotich PT, Cherian R, et al. Prospective long-term endoscopic and histological follow-up of short segment Barrett's esophagus: comparison with traditional long segment Barrett's esophagus. Am J Gastroenterol. 1997;92:407–13.
23. Weston AP, Sharma P, Mathur S, et al. Risk stratification of Barrett's esophagus: updated prospective multivariate analysis. Am J Gastroenterol. 2004;99:1657–66.
24. Avidan B, Sonnenberg A, Schnell TG, et al. Hiatal hernia size, Barrett's length, and severity of acid reflux are all risk factors for esophageal adenocarcinoma. Am J Gastroenterol. 2002;97:1930–6.
25. Rudolph RE, Vaughan TL, Storer BE, et al. Effect of segment length on risk for neoplastic progression in patients with Barrett esophagus. Ann Intern Med. 2000;132:612–20.
26. Sharma P, Falk GW, Weston AP, et al. Dysplasia and cancer in a large multicenter cohort of patients with Barrett's esophagus. Clin Gastroenterol Hepatol. 2006;4:566–72.
27. Hameeteman W, Tytgat GN, Houthoff HJ, van den Tweel JG. Barrett's esophagus: development of dysplasia and adenocarcinoma. Gastroenterology. 1989;96:1249–56.
28. van Sandick JW, van Lanschot JJ, Kuiken BW, et al. Impact of endoscopic biopsy surveillance of Barrett's oesophagus on pathological stage and clinical outcome of Barrett's carcinoma. Gut. 1998;43:216–22.
29. Montgomery E, Bronner MP, Goldblum JR, et al. Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation. Hum Pathol. 2001;32:368–78.
30. Skacel M, Petras RE, Gramlich TL, et al. The diagnosis of low-grade dysplasia in Barrett's esophagus and its implications for disease progression. Am J Gastroenterol. 2000;95:3383–7.
31. Weston AP, Banerjee SK, Sharma P, et al. p53 protein overexpression in low grade dysplasia (LGD) in Barrett's esophagus: immunohistochemical marker predictive of progression. Am J Gastroenterol. 2001;96:1355–62.
32. Dulai GS, Shekelle PG, Jensen DM, et al. Dysplasia and risk of further neoplastic progression in a regional Veterans Administration Barrett's cohort. Am J Gastroenterol. 2005;100:775–83.
33. Srivastava A, Hornick JL, Li X, et al. Extent of low-grade dysplasia is a risk factor for the development of esophageal adenocarcinoma in Barrett's esophagus. Am J Gastroenterol. 2007;102:483–93. quiz 694.
34. Sharma P. Low-grade dysplasia in Barrett's esophagus. Gastroenterology. 2004;127:1233–8.
35. Pellegrini CA, Pohl D. High-grade dysplasia in Barrett's esophagus: surveillance or operation? J Gastrointest Surg. 2000;4:131–4.
36. Buttar NS, Wang KK, Sebo TJ, et al. Extent of high-grade dysplasia in Barrett's esophagus correlates with risk of adenocarcinoma. Gastroenterology. 2001;120:1630–9.
37. Rastogi A, Puli S, El-Serag HB, et al. Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. Gastrointest Endosc. 2008;67:394–8.
38. Reid BJ, Prevo LJ, Galipeau PC, et al. Predictors of progression in Barrett's esophagus II: baseline 17p (p53) loss of heterozygosity identifies a patient subset at increased risk for neoplastic progression. Am J Gastroenterol. 2001;96:2839–48.
39. Bian YS, Osterheld MC, Fontolliet C, et al. p16 inactivation by methylation of the CDKN2A promoter occurs early during neoplastic progression in Barrett's esophagus. Gastroenterology. 2002;122:1113–21.
40. Reid BJ, Haggitt RC, Rubin CE, Rabinovitch PS. Barrett's esophagus. Correlation between flow cytometry and histology in detection of patients at risk for adenocarcinoma. Gastroenterology. 1987;93:1–11.
41. Reid BJ. p53 and neoplastic progression in Barrett's esophagus. Am J Gastroenterol. 2001;96:1321–3.
42. Wong DJ, Paulson TG, Prevo LJ, et al. p16(INK4a) lesions are common, early abnormalities that undergo clonal expansion in Barrett's metaplastic epithelium. Cancer Res. 2001;61:8284–9.
43. Schulmann K, Sterian A, Berki A, et al. Inactivation of p16, RUNX3, and HPP1 occurs early in Barrett's-associated neoplastic progression and predicts progression risk. Oncogene. 2005;24:4138–48.
44. Galipeau PC, Li X, Blount PL, et al. NSAIDs modulate CDKN2A, TP53, and DNA content risk for progression to esophageal adenocarcinoma. PLoS Med. 2007;4:e67.
45. Vaughan TL, Davis S, Kristal A, Thomas DB. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev. 1995;4:85–92.
46. Merry AH, Schouten LJ, Goldbohm RA, van den Brandt PA. Body mass index, height and risk of adenocarcinoma of the oesophagus and gastric cardia: a prospective cohort study. Gut. 2007;56:1503–11.
47. Lagergren J, Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. Ann Intern Med. 1999;130:883–90.
48. Whiteman DC, Sadeghi S, Pandeya N, et al. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. Gut. 2008;57:173–80.
49. Corley DA, Kubo A, Zhao W. Abdominal obesity and the risk of esophageal and gastric cardia carcinomas. Cancer Epidemiol Biomarkers Prev. 2008;17:352–8.
50. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. Ann Intern Med. 2005;143:199–211.
51. Kubo A, Corley DA. Body mass index and adenocarcinomas of the esophagus or gastric cardia: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006;15:872–8.
52. Ryan AM, Healy LA, Power DG, et al. Barrett esophagus: prevalence of central adiposity, metabolic syndrome, and a proinflammatory state. Ann Surg. 2008;247:909–15.
53. Moayyedi P. Barrett's esophagus and obesity: the missing part of the puzzle. Am J Gastroenterol. 2008;103:301–3.
54. Engel LS, Chow WH, Vaughan TL, et al. Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst. 2003;95:1404–13.
55. Navarro Silvera SA, Mayne ST, Risch H, et al. Food group intake and risk of subtypes of esophageal and gastric cancer. Int J Cancer. 2008;123:852–60.
56. Chen H, Tucker KL, Graubard BI, et al. Nutrient intakes and adenocarcinoma of the esophagus and distal stomach. Nutr Cancer. 2002;42:33–40.
57. Thompson CL, Khiani V, Chak A, et al. Carbohydrate consumption and esophageal cancer:an ecological assessment. Am J Gastroenterol. 2008;103:555–61.
58. Falk GW. Risk factors for esophageal cancer development. Surg Oncol Clin N Am. 2009;18:469–85.
59. de Jonge PJ, Steyerberg EW, Kuipers EJ, et al. Risk factors for the development of esophageal adenocarcinoma in Barrett's esophagus. Am J Gastroenterol. 2006;101:1421–9.

60. Lindblad M, Rodriguez LA, Lagergren J. Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. Cancer Causes Control. 2005;16:285–94.
61. Gammon MD, Schoenberg JB, Ahsan H, et al. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst. 1997;89:1277–84.
62. Brown LM, Silverman DT, Pottern LM, et al. Adenocarcinoma of the esophagus and esophagogastric junction in white men in the United States: alcohol, tobacco, and socioeconomic factors. Cancer Causes Control. 1994;5:333–40.
63. Lagergren J, Bergstrom R, Lindgren A, Nyren O. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. Int J Cancer. 2000;85:340–6.
64. Zhao DL, Chen WQ, Yu TT, et al. [A population-based matched case-control study on the risk factors of gastric cardia cancer]. Zhonghua Zhong Liu Za Zhi. 2011;33:775–8.
65. Cook MB, Kamangar F, Whiteman DC, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. J Natl Cancer Inst. 2010;102:1344–53.
66. Pandeya N, Webb PM, Sadeghi S, et al. Gastro-oesophageal reflux symptoms and the risks of oesophageal cancer: are the effects modified by smoking, NSAIDs or acid suppressants? Gut. 2010;59:31–8.
67. El-Serag HB, Aguirre TV, Davis S, et al. Proton pump inhibitors are associated with reduced incidence of dysplasia in Barrett's esophagus. Am J Gastroenterol. 2004;99:1877–83.
68. Hillman LC, Chiragakis L, Shadbolt B, et al. Proton-pump inhibitor therapy and the development of dysplasia in patients with Barrett's oesophagus. Med J Aust. 2004;180:387–91.
69. De Jonge PJ, Siersema PD, Van Breda SG, et al. Proton pump inhibitor therapy in gastro-oesophageal reflux disease decreases the oesophageal immune response but does not reduce the formation of DNA adducts. Aliment Pharmacol Ther. 2008;28:127–36.
70. Hillman LC, Chiragakis L, Shadbolt B, et al. Effect of proton pump inhibitors on markers of risk for high-grade dysplasia and oesophageal cancer in Barrett's oesophagus. Aliment Pharmacol Ther. 2008;27:321–6.
71. Tamim H, Duranceau A, Chen LQ, Lelorier J. Association between use of acid-suppressive drugs and risk of gastric cancer. A nested case-control study. Drug Saf. 2008;31:675–84.
72. DeMeester SR, DeMeester TR. Columnar mucosa and intestinal metaplasia of the esophagus: fifty years of controversy. Ann Surg. 2000;231:303–21.
73. Ye W, Chow WH, Lagergren J, et al. Risk of adenocarcinomas of the esophagus and gastric cardia in patients with gastroesophageal reflux diseases and after antireflux surgery. Gastroenterology. 2001;121:1286–93.
74. Tran T, Spechler SJ, Richardson P, El-Serag HB. Fundoplication and the risk of esophageal cancer in gastroesophageal reflux disease: a Veterans Affairs cohort study. Am J Gastroenterol. 2005;100:1002–8.
75. Kubo A, Corley DA. Marked multi-ethnic variation of esophageal and gastric cardia carcinomas within the United States. Am J Gastroenterol. 2004;99:582–8.
76. Ji J, Hemminki K. Familial risk for esophageal cancer: an updated epidemiologic study from Sweden. Clin Gastroenterol Hepatol. 2006;4:840–5.
77. Chak A, Lee T, Kinnard MF, et al. Familial aggregation of Barrett's oesophagus, oesophageal adenocarcinoma, and oesophagogastric junctional adenocarcinoma in Caucasian adults. Gut. 2002;51:323–8.
78. Dhillon PK, Farrow DC, Vaughan TL, et al. Family history of cancer and risk of esophageal and gastric cancers in the United States. Int J Cancer. 2001;93:148–52.