Esophageal Adenocarcinoma: Pathogenesis and Epidemiology

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Abstract

Over the past 40 years, the incidence of esophageal adenocarcinoma (EAC) has increased more than six-fold in Western countries. The increase incidence of EAC has been attributed to the rising prevalence of obesity and gastroesophageal reflux disease (GERD). GERD affects an estimated 20% of the population in the US, and its prevalence is increasing worldwide. About 10% of patients with GERD will develop Barrett's esophagus (BE). This metaplastic lesion due to the chronic injury produced by repeated reflux episodes involves genetic mutations that can lead to a malignant transformation. The development of EAC is characterized by the progression from BE metaplasia to dysplasia, and ultimately invasive carcinoma.

Keywords

Esophageal adenocarcinoma · Epidemiology · Pathogenesis · Gastroesophageal reflux disease · Barrett's esophagus

Epidemiology

Esophageal cancer is the 8th most common cancer worldwide, with an estimated 604,000 new cases and 544,000 deaths in 2020 [1]. About 85% of all esophageal cancers globally are squamous cell carcinomas (SCC), with the highest incidence rates in populations within South-Eastern and Central Asia, Eastern Africa, and South America. Although only 14% of all esophageal cancers are esophageal adenocarcinomas (EAC), it is the dominant subtype particularly in male individuals in 21 mostly developed countries, with an elevated burden seen in Northern and Western Europe, Oceania, and Northern America (Fig. 1) [1, 2]. In these regions, the continuing declines in incidence rates of SCC are offset by rapid increases in the incidence of EAC since the late 1980s, surpassing the rate of SCC since the early 1990s [3]. Over the past 40 years, the incidence of EAC has increased more than six-fold in Western countries. EAC rates are substantially higher in men than in women, with a male to female ratio of 8.5 in Northern America [4].

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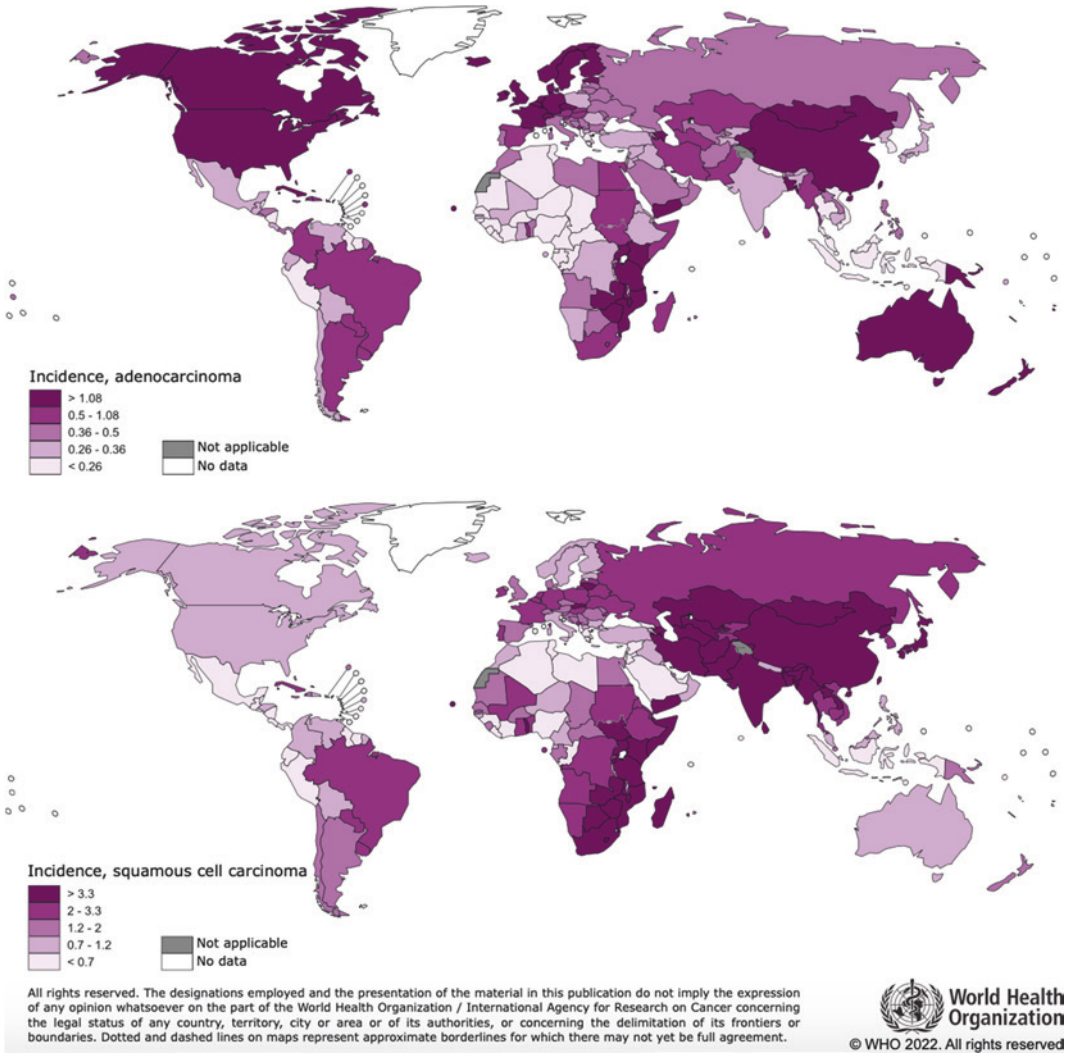

Fig. 1 Worldwide incidence of esophageal adenocarcinoma and squamous cell carcinoma in 2020 (age-adjusted according to the world standard population, per 100,000). Obtained with permission from the International Agency for Research on Cancer/World Health Organization (IARC/WHO)

The increase incidence of EAC has been attributed to the rising prevalence of obesity and gastroesophageal reflux disease (GERD). In fact, the strongest known risk factor for EAC is GERD, together with its more severe manifestation, Barrett's esophagus (BE). Although the real incidence of GERD is unknown due to its underdiagnosis, it is estimated that this disease affects around 20% of the adult population in the US, and its prevalence is increasing worldwide [5, 6]. It has been reported that high levels of urbanization may contribute to increased prevalence of GERD, such as in North America and Europe, compared to regions where rural areas predominate, such as in Asia, Latin America and the Caribbean [6]. While medical therapy has shown excellent results in controlling GERD symptoms, it has not averted the malignant complications of this disease. Increases in the prevalence of overweight and obesity have paralleled rises in the incidence of EAC in most countries. Although obesity also favors the development

and severity of GERD, it has been shown to act as an independent risk factor for EAC, with a 52% increase in risk for every five units in body mass index [2, 4, 7, 8].

The total number of new EAC cases is expected to increase substantially. The United States and The United Kingdom are predicted to have the largest annual number of EAC diagnoses by 2030, with about 15,000 new cases in the US and about 8600 cases in The United Kingdom. By 2030, one in 100 men may be diagnosed with EAC in The United Kingdom and The Netherlands (Table 1). Globally, the estimated number of cases of esophageal cancer is expected to scale to 957,000 by 2040, with deaths uprising to 880,000 in the same year [1, 9].

Pathophysiology: From GERD to Barrett's Esophagus

About 10% of patients with GERD will develop BE. BE has been traditionally defined as the presence of at least 1 cm of metaplastic columnar epithelium that replaces the stratified squamous epithelium normally lining the distal esophagus. Currently, the presence of intestinal metaplasia (i.e. columnar epithelium with goblet cells) is also needed for the diagnosis of BE in the US [10]. The reason why intestinal metaplasia is mandated in the definition of BE is related to the higher risk of developing cancer in columnar epithelium containing goblet cells, as compared to columnar epithelium without intestinal metaplasia [11, 12].

The transformation of normal esophageal squamous mucosa into a simple columnar epithelium is thought to be due to the chronic injury produced by repeated reflux episodes. In fact, in patients with GERD, symptom duration has been shown to be a risk factor for the presence of BE. Lieberman [13] showed that compared with patients with GERD symptoms for less than one year, the odds ratio for BE in patients with GERD symptoms for 5 years was 3.0 and increased to 6.4 in patients with symptoms for more than 10 years. Interestingly, columnar mucosal metaplasia is also seen in the esophageal remnant in patients with a gastric pull-up following an esophagectomy, where the reflux of gastric contents into the residual esophagus is common because there is no lower esophageal sphincter. Oberg et al. [14] reported that 46.9% of patients had metaplastic columnar mucosa within their cervical esophagus following an esophagectomy, and the length of that metaplastic mucosa was significantly correlated with the degree of esophageal acid exposure. O'Riordan et al. [15] reported similar findings with 50% of patients developing columnar metaplasia in the remnant esophagus, with the duration of reflux being the most important factor influencing that transformation. Similarly, Dunn et al. [16] in a series of 134 patients, reported an

Table 1 Estimated number of new esophageal cancer cases in 2030, as compared to 2005 (Data extracted from "Pred icting the Future Burden of Esophageal Cancer by Histological Subtype: International Trends in Incidence up to 2030. Am J Gastroenterol 2017")

Country	Population (million)		EAC		SCC		Total	
	2005	2030	2005	2030	2005	2030	2005	2030
Australia	19.9	28.5	537	1420	486	706	1023	2126
Canada	32.2	40.4	770	2043	462	379	1233	2423
France	61.1	68.0	1193	2863	3116	1930	4309	4793
Japan	126.8	120.1	670	1037	13,646	20,084	14,316	21,121
Netherlands	16.3	17.6	875	2652	514	714	1389	3366
UK	60.1	70.1	4278	8603	2708	3773	6986	12,376
US	277.5	316.8	8167	15,081	4736	4976	12,903	20,057

EAC Esophageal adenocarcinoma, *SCC* Squamous cell carcinoma, *UK* The United Kingdom, *US* The United States

incidence of 36% without any cases of progression to dysplasia.

The molecular pathway by which the normal squamous mucosa of the distal esophagus is transformed into a columnar mucosa remains uncertain. Tobey and colleagues [17] showed that acid damage of the esophageal epithelium produces dilated intercellular spaces, which in turn reduces the trans-epithelial resistance and increases trans-epithelial permeability. This change in permeability permits molecules as large as 20 kD to diffuse across the epithelium, exposing stem cells in the basal layer to refluxate. The intercellular acidification exposes the squamous basolateral membrane to acid, initiating a cascade of events leading to loss of cell osmoregulation, cell edema, and ultimately cell death [18]. Cell death is counterbalanced by tissue reparative processes, including restitution and replication. It is worth mentioning that during the normal growth process of the embryo, the esophageal cells undergo a columnar to squamous transition under the influence of a combination of active prosquamous and inactivated procolumnar homeobox genes. The cellular phenotype may reverse if the opposite set of cell patterning genes is reactivated. An acidic milieu, combined with other components of refluxate, may induce phenotypic transformation of squamous cells into columnar mucosal cells. The reason why pluripotent esophageal stem cells turn into columnar cells in this "acid environment" may be related to the better adaptability of this epithelium due to its acid resistance. Nevertheless, the origin of BE remains obscure. There are several hypotheses regarding the origin of stem cells that will give rise to BE [18–20]:

(1) Migration and differentiation of stem cells from the gastric cardia.
(2) Differentiation of stem cells residing in the crypts of the esophageal mucosal glands.
(3) Migration of stem cells from the bone marrow (circulating stem cells that can hone in to areas of injury to repair damaged tissue).

While the transition between squamous and columnar epithelium likely occurs within a few years, the development of intestinal metaplasia may take over 5–10 years [21]. Once the columnar epithelium is established, two possible pathways are observed. The first one, "*gastric differentiation*", implies the formation of parietal cells within glands and may represent a favorable change, as this mucosa is not thought to be premalignant. The second one, "*intestinal differentiation*", induces the expression of intestinalizing genes, causing the formation of goblet cells within the columnar epithelium. The development of intestinal metaplasia is considered a detrimental change because this mucosa is capable of further progression to epithelial dysplasia and adenocarcinoma.

The specific cellular event(s) that induce the "intestinalization" of the columnar epithelium is unknown. However, it is likely to occur in response to multiple noxious luminal contents rather than to acid reflux only. In fact, previous studies have demonstrated the association between BE and the exposure of a mixture of acid and bile salts on the esophagus [22–24]. The role of refluxed bile in the development of intestinal metaplasia was suggested by Oberg et al. [25] as patients with intestinal metaplasia had similar esophageal acid exposure to those with GERD and no BE, but significantly higher frequency of abnormal bilirubin exposure. It has been hypothesized that in a weakly acidic environment (pH 3–5), certain bile acids become non-ionized and are able to cross the cell membrane. Once inside the cell (pH 7) they become ionized and remain trapped causing mitochondrial injury, cellular toxicity, and mutagenesis [26]. The molecular mechanism by which bile acids promote the development of goblet cells may be related to the activation of the Caudal-related homeobox 2 (Cdx2) promoter via nuclear factor kappa B (NF-κB) with the consequent production of Cdx2 protein in esophageal immature keratinocytes, resulting in the production of MUC2 (intestinal-type protein found in Barrett's metaplasia) [27]. Further,

bile acids have shown to enhance cytoplasmic expression of the signaling ligand Delta-like 1 (Dll1) which facilitates the intestinal metaplasia in conjunction with Cdx2 expression [28]. It was found that COX-2, an enzyme that plays a major role in inflammatory responses, has a substantially higher expression in human BE tissues than that in adjacent squamous cells and control tissues. Also, its presence was considerably higher in EAC tissues. Inhibition of NF-κB in esophageal squamous cells inhibits cell proliferation, followed by decreased COX-2 expression. Inhibition of NF-κB expression in EAC cells reduces the expression of COX-2 and CDX-2, and improves apoptosis of EAC cells. This suggests that COX-2 may be involved in the development of BE [29].

Pathophysiology: From Barrett's Esophagus to Esophageal Adenocarcinoma

BE is a premalignant mucosa with increased proliferation rates and decreased apoptosis rates compared to normal epithelium [30]. In fact, it is the only known precursor of EAC. However, only a small percentage of patients with BE will develop cancer, and more than 90% of patients with diagnosis of EAC have no prior history of BE [31, 32]. The question as to why some cases of BE progress to EAC and some do not remains unanswered. Currently, the presence and grading of dysplasia is the most important predictive factor for the development of adenocarcinoma. Known risk factors for development of dysplasia in BE include: increasing length of BE, advancing age, central obesity, tobacco usage, lack of nonsteroidal anti-inflammatory agent use, lack of proton-pump inhibitors (PPI) use, and lack of statin use [11]. Recently, caffeine intake and presence of colonic adenomas have been also described as risk factors for progression of BE to high grade dysplasia [33].

Gopal and colleagues [34] showed that the prevalence of dysplasia was strongly associated with age and length of BE. Patients with BE without dysplasia were younger than those with dysplasia (62 ± 0.8 years vs. 67 ± 1.7 years, $p = 0.02$), and the risk of dysplasia increased by 3.3%/year of age. Patients with BE length ≥ 3 cm also had a significantly greater prevalence of dysplasia compared to length < 3 cm (23% vs 9%, $p = 0.0001$), and the risk of dysplasia increased by 14% per cm of increased length. Hampel et al. [35] reported that obesity was associated with a significant increase of GERD complications and EAC. Interestingly, Singh et al. [36] found that, compared with patients with normal body habitus, patients with central adiposity had a higher risk of BE, even after adjusting for body mass index and presence of GERD, suggesting a reflux-independent association between truncal obesity and BE. Added to this, central adiposity was associated with higher risk of adenocarcinoma (OR 2.5, 95% CI 1.54–4.06) compared with normal body habitus. The relationship between BE and cigarette smoking was reported by Andrici and colleagues [37] who found that having ever smoked was associated with an increased risk of BE compared with non-GERD controls but not when compared with patients with chronic GERD, suggesting that the increased risk of BE associated with tobacco usage may be due to the increased incidence of GERD in cigarette smokers.

The presence of colonic adenomas and caffeine intake have been recently described as risk factors for high grade dysplasia in patients with BE. This could be explained by common genetic alterations between BE, EAC, colonic adenomas, and colonic adenocarcinomas such as a higher expression of COX-2 and other inflammation-mediators that can induce dysplasia. Additionally, the presence of a colonic adenoma may represent a genetic predisposition to the development of dysplasia. Caffeine intake stimulates gastric acid secretion and relaxes the LES, which ultimately aggravates GERD [33].

Some medications have shown to reduce the risk of progression to dysplasia or esophageal cancer in patients with BE. Singh and colleagues described that PPI use was associated with a substantial reduction in risk of high-grade dysplasia and/or esophageal adenocarcinoma

in patients with BE (OR 0.29 95% CI 0.12–0.79) [38]. There was also a trend towards a dose–response relationship with PPI use for > 2–3 years. On the contrary, a population-based study from Sweden showed an increased risk of esophageal carcinoma among PPI users, reporting that 5.4% of the esophageal cancer in the population could be attributed to PPI use. This could correlate with a disruption in the gastrointestinal microbiome, bacterial colonization and increase production of nitrosamines, which are all well-known gastric (and probably esophageal) cancer risk factors [39]. Albeit these findings, the relationship between esophageal cancer and PPIs intake remains controversial and needs further investigation.

Another meta-analysis reported that aspirin use also reduced the risk of high-grade dysplasia/adenocarcinoma, as well as non-aspirin cyclooxygenase inhibitors in patients with BE [40]. The chemopreventive effect seemed to be independent of duration of therapy. Finally, statin usage was also associated with a significant (41%) decrease in the risk of EAC within patients with BE [41]. Alexandre et al. also reported a meaningful reduction in esophageal cancer-specific mortality and all-cause mortality (39% and 37%, respectively) in patients with EAC taking statins [42]. In line with these findings, a multicenter retrospective study including 308,793 patients showed that the use of COX-2 inhibitors, statins, metformin, and PPIs may help preventing EAC [43].

There are four categories to stratify the dysplastic process: (1) no dysplasia; (2) indefinite for dysplasia; (3) low-grade dysplasia; (4) high-grade dysplasia. The development of EAC is characterized by the progression from BE metaplasia to dysplasia, and ultimately invasive adenocarcinoma (Fig. 2). Patients with non-dysplastic BE have very low risk for malignant progression and a meta-analysis of 24 studies and 2694 patients reported that the pooled annual incidence of adenocarcinoma was 0.2–0.5%. For patients with low-grade dysplasia, they described a pooled annual incidence of 0.5% for adenocarcinoma (95% CI 0.3–0.8). The annual incidence of either EAC or high-grade dysplasia was 1.73% (95% CI, 0.99–2.47%) [44]. Patients with high-grade dysplasia present an annual incidence of adenocarcinoma of 7% (95% CI 5–8) [10, 45, 46].

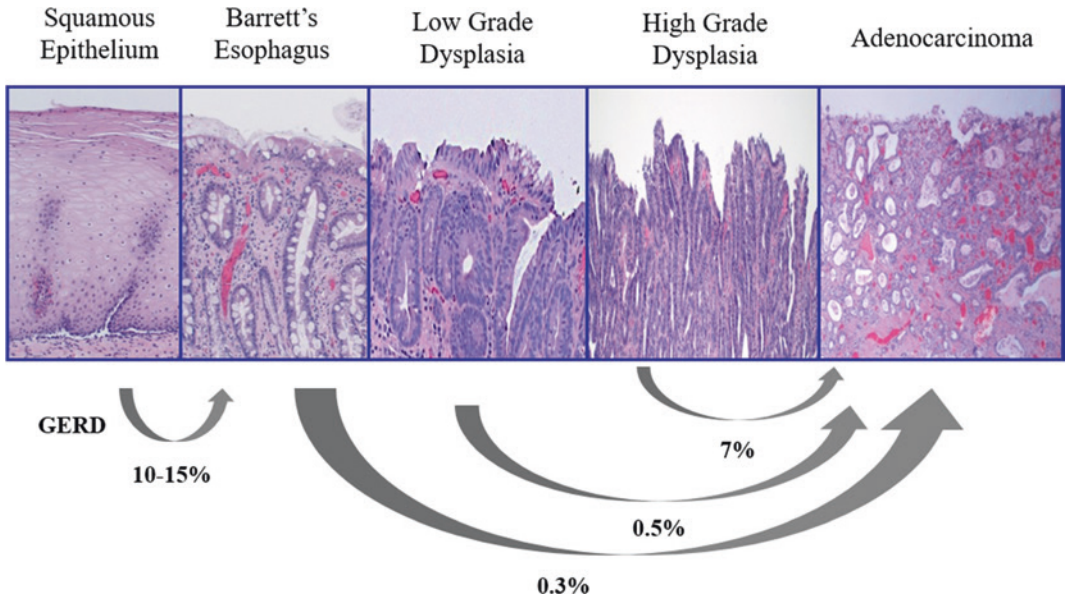

Fig. 2 Pathological progression from normal esophageal squamous epithelium to adenocarcinoma

Conclusions

The increase incidence of EAC has been attributed to the rising prevalence of obesity and GERD. The latter is considered the strongest risk factor for EAC, together with its more severe manifestation, Barrett's esophagus. This metaplastic lesion due to chronic injury produced by repeated reflux episodes involves genetic mutations that can lead to a malignant transformation. Therefore, the pathophysiology of EAC can be depicted by the progression from Barrett's esophagus metaplasia to dysplasia, and ultimately invasive adenocarcinoma.

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