Review paper

Epidemiology of Barrett's oesophagus and oesophageal adenocarcinoma

Epidemiologia przełyku Barretta i gruczolakoraka przełyku

Nancy Perez, William Taylor

Department of Gastroenterology, St. Joseph Medical Center, University of Washington, WA, USA
Head of the Department: Prof. Walter Brown

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Słowa kluczowe: choroba refluksowa żołądkowo-przełykowa, czynniki ryzyka, gruczolakorak przełyku, epidemiologia, przełyk Barretta.

Abstract

Barrett's oesophagus is a condition characterised by metaplastic changes in the oesophagus and is a precursor to oesophageal adenocarcinoma. Oesophageal adenocarcinoma is recognised as being responsible for an increasing number of cancer-related deaths, especially in the western world. A deluge of risk factors have been described in the literature. Some of the important ones include gastroesophageal reflux disease, Helicobacter pylori infection, lifestyle factors like alcohol consumption, smoking, and dietary factors, and metabolic diseases like obesity. It also poses challenges in diagnosis and treatment despite recent advances in diagnostics, surgery, and other therapies. This is a narrative review of the findings of multiple studies that were retrieved from electronic databases like PubMed, Google Scholar, Scopus, Medline, Embase, and Cochrane. We summarise the current knowledge regarding the epidemiology and various risk factors for the development of Barrett's oesophagus and oesophageal adenocarcinoma.

Streszczenie

Przełyk Barretta charakteryzuje się występowaniem zmian metaplastycznych w przełyku i jest stanem przedrakowym przełyku. Gruczolakorak przełyku odpowiada za coraz większą liczbę zgonów z powodu raka, zwłaszcza na Zachodzie. W piśmiennictwie wskazano wiele czynników ryzyka. Do najważniejszych z nich należą: choroba refluksowa przełyku, zakażenie *Helicobacter pylori*, czynniki związane ze stylem życia, takie jak spożywanie alkoholu, palenie tytoniu i czynniki żywieniowe, oraz choroby metaboliczne, takie jak otyłość. Schorzenie to stwarza problemy w zakresie diagnostyki i leczenia pomimo dokonanych ostatnio postępów w dziedzinie diagnostyki, leczenia operacyjnego i innych terapii. W artykule przedstawiono przegląd wyników wielu badań, które pobrano z elektronicznych baz danych, takich jak PubMed, Google Scholar, Scopus, Medline, Embase i Cochrane. Podsumowano także aktualną wiedzę na temat epidemiologii i czynników ryzyka rozwoju przełyku Barretta i gruczolakoraka przełyku.

Introduction

Barrett's oesophagus (BO) is a medical condition that encompasses metaplastic changes in the epithelial lining of the lower oesophagus, whereas the normal stratified squamous epithelium is replaced by simple columnar with goblet cells [1]. The principle aetiology behind BO is gastro-oesophageal reflux disease (GORD), which is globally defined as reflux of stomach contents leading to troublesome symptoms and/or complications [2]. Of them, the two main complications are BO and reflux oesophagitis [3, 4]. In addition, males, obese persons, and those over 50 years old have a possible risk of developing BO [5–7]. However, patients may complain of heartburn, difficulty swallowing, vomiting blood, pain beneath the sternum, and less commonly weight loss [1]. The diagnosis of BO can be made by upper gastrointestinal endoscopy, and histological examination of the biopsy discloses the metaplasia [8].

It has been estimated that patients with BO progress to oesophageal adenocarcinoma (OAC) 30–125 times more than the general population [9–11]. During the 1960s and 1970s, only about 5% of OAC patients survived at least 5 years after being diagnosed, whereas now the 5-year survival rate is about 20%

[12]. The mortality rate of OAC is 85%, and in many regions of the western world, the incidence has been rising at a worrisome rate [13–16]. Screening and surveillance programs are vital to identify the high-risk population and to understand the epidemiology of the disease. Thus, several studies have been investigating the epidemiology of BO and OAC [2, 17–19]. Our study aimed to thoroughly review the incidence, prevalence, and risk factors associated with BO and OAC.

Incidence and prevalence of Barrett's oesophagus

First of all, patients with BO may complain of reflux symptoms such as heartburn, difficulty swallowing, haematemesis, and pain below the sternum. Nevertheless, the precise evaluation of the incidence and prevalence of BO and OAC is unattainable because patients with BO may report no symptoms. Therefore, the number of endoscopic autopsy-dependent diagnosis studies has been increasing dramatically over the years. In the United States, this has been emphasised in a prospective study including a volunteer population, in which patients who were primarily involved for colonoscopy agreed to undergo upper endoscopy. This may implicate selection bias. However, about 8% of subjects with previous history of heartburn exhibited the finding of BO through endoscopic examination. In contrast, only 6% with no history of reflux symptoms were diagnosed with BO [20–24].

Similarly, in another study in the United States but with more robust methodology through randomised screening procedures, patients with BO were recognised and considered for inclusion [25]. Interestingly, the overall incidence rate of BO in patients with no reflux symptoms was 20% compared to 15% in patients reporting no symptoms [26, 27]. In a population based study in the United States, the incidence of clinically diagnosed BO increased 28-fold between 1965 and 1997 compared to endoscopic autopsy-dependent diagnosis, which increased 22-fold in the same time frame. In the same study, the incidence of OAC increased 10-fold, and most cases reported no previous history of BO, suggesting that many patients with BO experienced no symptoms [21]. They deduced that the incidence and prevalence of BO with clinical signs had increased concurrently with the mounting application of endoscopic examinations [21, 28]. In another study in the Netherlands including 100,000 patients, and irrespective of the mounting number of upper endoscopic examinations being carried out, the incidence of BO raised from 14.3% of subjects in 1997 to 23.1% of subjects in 2002. Also, the incidence of adenocarcinoma remarkably increased from 1.7% person-years in 1997 to 6% person-years in 2002 [29].

Regarding the prevalence, the long-segment BO prevalence was detected in 376/100,000 cases, suggesting that only a few cases could be recognised clinically [9, 30–34] In Sweden, researchers carried out upper gastrointestinal endoscopy on 1000 randomly allocated participants, aiming to estimate the prevalence of BO in the general Swedish population. Among them, 16 (1.6%) cases were diagnosed with BO, and 5 (0.5%) cases exhibited long-segment BO [18]. In another European study, 1533 Italian adults were counted for upper gastrointestinal endoscopy, and the prevalence rate was 1.3%. Out of them, around 46.2% experienced no reflux symptoms [2]. In contrast to western countries, the prevalence of BO in the Far East is relatively low. However, in a Korean study, and among 992 patients allocated, 108 cases were diagnosed as short-segment BO, and only three cases were diagnosed as long-segment BO. As usual, the diagnostic method comprised of upper endoscopy. However, only 36 (3.6%) subjects met the histological standards of BO [17].

Age, sex, and ethnicity variations in patients with Barrett's oesophagus

Barrett's oesophagus is diagnosed on average in the sixth to seventh decade of life but may develop far earlier. Males are more commonly diagnosed with BO compared to females, with a ratio of 2.5 : 1 [35, 36] A study by van Blankenstein *et al.* showed that males on average developed BO about 20 years earlier when compared to females, with a ratio of males to females 2 : 1. However, the ratio of men to women approached 4 : 1 in younger adults [35].

Recently, in a case-control study 237 endoscopy-dependent diagnosed patients were examined to inspect the effect of waist-to-hip ratio (WHR) on the risk of BO. This study revealed that more patients with BO had a high WHR (92.4%) when compared to endoscopy controls (79.5%). The WHR was not high in black or Hispanic participants. However, a significant association with BO was discovered in whites (OR = 2.5; 95% CI: 1.2–5.4) [37] In the UK, one cross-sectional study was carried out to explore the risk of BO with regard to ethnicity. A total of 20,310 patients were included in the statistical analysis and revealed that BO is more common in white Caucasians (2.8%, n = 14,095) than in South Asians (0.3%, n = 5190) [38]. Moreover, in a cross-sectional analysis, white Caucasians had a remarkably higher association with BO (6.1%, n = 792) compared to Hispanics (1.7%, n = 466), and the results were statistically significant (p = 0.0002) [39].

Epidemiology of oesophageal adenocarcinoma

Oesophageal cancer ranks seventh in terms of incidence and sixth in mortality overall (Figure 1). The global distribution of oesophageal cancer differs markedly from that of most other adult tumours. Men

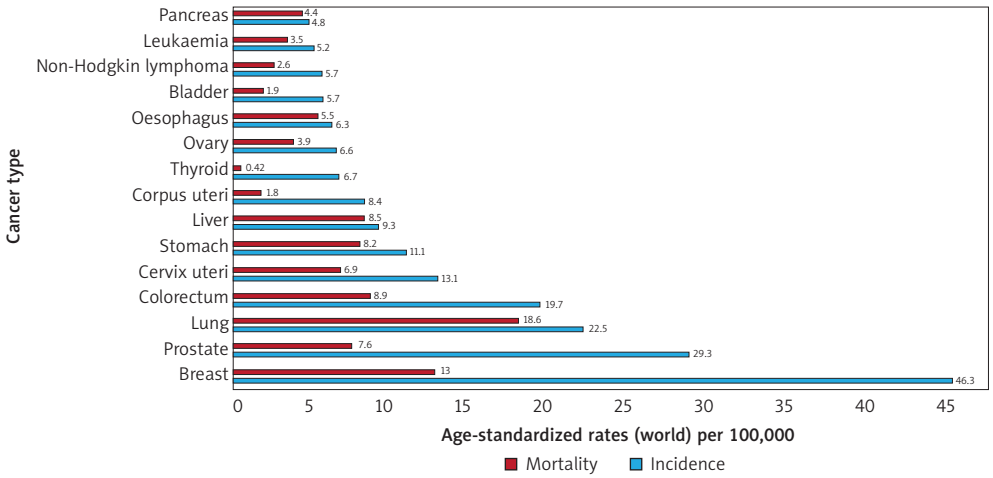

Figure 1. Estimated age-standardised incidence and mortality rates in 2018, worldwide, for both sexes, at all ages

account for 70% of cases of oesophageal cancer. Compared to females, males have a 2–3-fold increase in incidence and mortality [40–43].

About 87% of all oesophageal cancers globally are squamous cell carcinoma (SCC) of the oesophagus [44]. Only 11% of all oesophageal cancers are OACs, with an increased burden seen in Northern America, Northern and Western Europe, and Oceania [44, 45]. The OAC represents the majority of oesophageal cancer cases in high-income countries, with GORD and obesity being the key risk factors [41]. Smoking and heavy drinking of alcohol are the main risk factors for SCC of the oesophagus. The incidence of SCC of the oesophagus is decreasing worldwide, mainly due to a decline in smoking and alcohol consumption in high-income countries and dietary improvements in high-risk Asian countries. However, in those same countries, the incidence of OAC is on the rise, mainly due to increased obesity, increased GORD, and possibly due to reductions in H. pylori infections [46].

Caucasian men have the highest incidence of OAC, with a male-female ratio approaching 8 : 1 in Caucasians [47]. The same ratio in African-Americans was 3 : 1 and in Latinos 7 : 1 [48]. Surveillance, Epidemiology, and End Results (SEER) Program data suggest that the ratio of OAC cases in Caucasians when compared to African-Americans is approximately 5 : 1 [49].

Improvement in overall survival has been substantial in patients with invasive OAC over the last few decades [50]. A study in the US showed that the overall increase in 5-year survival in patients with oesophageal cancer from the 1990s to the 2000s increased from 18% to 22% [51]. Another study based on the European registry (EUROCARE-5) also showed that 5-year overall survival of oesophageal cancer patients increased from 10% in 1999–2001 to 13% in 2005–2007 [52]. In another study in China, the 5-year relative age-standardised survival rate for oesophageal cancer was 21% in 2003–2005 [53]. Patients who underwent oesophagectomy had increased survival for all stages. Patients aged < 65 years had better survival when compared to patients aged ≥ 65 years [50] A recent population-based, nationwide study in Sweden has shown that from 1990–1994 to 2010–2013, the relative 5-year survival increased from 12% to 15% for OAC [54].

Overview of the risk factors of Barrett's oesophagus and oesophageal adenocarcinoma

Several epidemiological studies examined the predisposing factors for BO and OAC, and they have shown fundamental unanimity on multiple modifiable and non-modifiable risk factors. Herein, we seek to recapitulate the evidence from the enormous literature and discuss the important risk factors that predispose to BO and OAC [55, 56].

Gastro-oesophageal reflux disease

The main risk factor for OAC is GORD. Approximately 10–15% of patients with GORD will develop BO. The chronic injury produced by repeated reflux episodes leads to this metaplastic transformation and involves genetic mutations that can lead to a malignant transformation. The sequence of BO metaplasia–dysplasia–invasive carcinoma ultimately leads to the development of OAC [57, 58]. A meta-analysis of five studies showed that at least weekly symptoms of GORD increased the odds of OAC 5-fold, and daily symptoms increased the odds seven fold, when compared with individuals without symptoms or with less frequent symptoms [59]. A pooled analysis from the *Barrett's and Esophageal Adenocarcinoma Consortium* (BEACON) study showed that increasing heartburn duration was associated with increasing OAC

risk with odds ratios of 2.80, 3.85, and 6.24 for the duration of symptoms of < 10 years, 10 to < 20 years, and ≥ 20 years, respectively [60]. Earlier age at onset of recurrent GORD symptoms is associated with high risk for BO, especially if the first reported symptoms are at age < 30 years (odds ratio (OR) 15.1, 95% confidence interval (CI): 7.91–28.8) [61]. Endoscopic screening to detect dysplasia is recommended for patients with BO.

Smoking

Smoking has been shown to increase the risk of OAC, particularly in patients with BO [62]. A pooled analysis of 12 studies from the BEACON study showed that the risk of OAC or cancer of the oesophagogastric junction was 2.08 times higher in smokers than in a control group [60]. The risk increased with the number of pack-years smoked, and it was reduced after smoking cessation but not to the level of non-smokers. Compared with never-smokers, the pooled relative risk (RR) for oesophageal and gastric cardia adenocarcinoma was 1.6 for ever-smokers, 2.32 for current smokers, and 1.62 for ex-smokers [63]. However, a recent meta-analysis of 52 studies showed that the risk of OAC was only slightly lower among former smokers (RR = 1.66, 95% CI: 1.48–1.85) than among current smokers (RR = 2.34, 95% CI: 2.04–2.69) by non-smokers as a reference. It also showed that smoking cessation for 20 years or more strongly decreases the risk of oesophageal SCC in a time-dependent manner, particularly in western populations, while it has limited influence on the risk of OAC (RR = 0.72, 95% CI: 0.52–1.01) [64].

Alcohol

Unlike oesophageal SCC, where alcohol is a strong risk factor, studies have not shown an association between the amount of alcohol consumed and the risk of OAC development. A meta-analysis of four cohorts and 20 case-control studies concluded that there was no association between alcohol consumption and OAC risk, even at higher levels of consumption. The RR for drinkers versus non-drinkers was 0.96 vs. 0.87, respectively [65]. Findings from the BEACON study showed that alcohol consumption was not a risk factor for BO or progressing from BO to OAC [66, 67].

Obesity and metabolic syndrome

The incidence of BO and OAC has increased rapidly in the past 40–50 years in western countries, parallel with rapid increases in the rate of obesity [68, 69]. Obesity has been linked to a higher risk for OAC and to BO, a predisposing lesion for OAC [70, 71]. For every 1 kg/m^2 increase in body mass index (BMI) OAC risk increased by 16% and BO risk increased by 12% [71]. A pooled analysis from the International BEACON Consortium showed that the association of OAC and oesophagogastric junction adenocarcinomas increased directly with increasing BMI. Compared to a BMI of < 25 kg/m^2 a BMI of 30.0–34.9 kg/m^2 was associated with a two-fold increased risk of OAC and 4- to 5-fold risk with BMI ≥ 40.0 kg/m^2 [72, 73].

Analysis of the SEER database in the United States found OAC to be significantly associated with metabolic syndrome (OR = 1.16, 95% CI: 1.06–1.26) compared with population controls [74]. Being overweight in early adulthood (age 20 years) and weight gain later in life were each associated with increased risks of OAC [75]. Obesity may represent an indirect risk factor for both OAC and BO because it increases the risk of GORD by mechanical mechanism effects, which include disruption of the gastro-oesophageal junction reflux barrier [76, 77]. Kubo *et al.* found that waist circumference a risk factor for BO among both men and women, even after adjustment for BMI [78, 79]. This was supported by a study that used CT scans to measure adipose tissue and showed that a large amount of visceral abdominal adipose tissue is associated with a significant increase in the risk of BO when compared to subcutaneous adipose tissue [80].

Helicobacter pylori infection

The prevalence of H. pylori infection has decreased in populations where the incidence of OAC has increased, suggesting a potential inverse relationship. A meta-analysis of 28 studies showed that there was a significant inverse association between H. pylori infection (pooled OR = 0.57; 95% CI: 0.44–0.73) and OAC (pooled OR = 0.57, 95% CI: 0.44–0.73) [81]. In people who had frequent GORD symptoms, BO risk was almost 80% lower among H. pylori-positive patients than in those negative for H. pylori [61]. Studies have shown an inverse statistically significant relationship of H. pylori infection with both OAC and BO, which might suggest a protective role of the infection in these entities, although this has been controversial [82]. The BEACON study showed that H. pylori infection was inversely associated with the risk of BO [83].

Medications

Multiple studies have shown that aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) reduced the risk of OAC [84]. A study by Liao *et al.* showed that individuals who used NSAIDs had a statistically significant reduced risk of OAC, with an approximately 40% reduction in those who used it frequently (daily or more frequently) and for a longer duration (≥ 10 years) [85]. However, a recent study by Thrift *et al.* showed that regular (at least once weekly) use of any NSAIDs was not associated with the risk of BO [86]. Studies have shown that regular statin use was

inversely associated with the development of OAC and BO [87–90]. Studies have also shown that use of lower oesophageal sphincter relaxing drugs like nitroglycerin, anticholinergics, and β-adrenergic agonists was positively associated with risk for OAC [91, 92]. A meta-analysis of seven observational studies showed that the use of proton pump inhibitors was associated with a decreased risk of OAC and/or high-grade dysplasia in patients with BO [93–95]. A recent meta-analysis of nine studies showed that long-term use of proton-pump inhibitors in patients with BO had no protective effects against the development of OAC or high-grade dysplasia [96]. Use of oral bisphosphonates has been linked to OAC and SCC of the oesophagus in post-marketing surveillance in one study [97]. However, a large cohort study done in the United Kingdom found that the use of oral bisphosphonates was not significantly associated with incident oesophageal cancer [98].

Conclusions

The OAC is recognised as being responsible for an increasing number of cancer-related deaths, especially in the western world. Significant global strides have been made in the global prevention and treatment of OAC. While prevention efforts are focused on BO screening and surveillance, the main challenge is to identify BO patients at highest risk of progression to OAC, so that they can be offered appropriate follow-up and therapy. Diet and lifestyle modification are also the most effective means of preventing OAC, especially in the developed world. Analysis of OAC and BO epidemiology may be the cornerstone of developing future cancer control strategies.

Conflict of interest

The authors declare no conflict of interest.

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Address for correspondence:

Nancy Perez MD
Department of Gastroenterology
St. Joseph Medical Center
University of Washington
WA, USA
E-mail: nancyper365@gmail.com