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REVIEW ARTICLE



# Epidemiology and prevention of oesophageal adenocarcinoma

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**ABSTRACT**

Oesophageal adenocarcinoma (OAC) develops from columnar metaplasia of the distal oesophagus, Barrett's oesophagus (BO), secondary to chronic gastro-oesophageal reflux disease (GORD). In the present review, the stepwise development of GORD, BO and OAC is presented and the evidence of OAC prevention, including treatment with proton pump inhibitors (PPIs). PPIs are the main treatment of GORD and BO, with some evidence of prevention of OAC in these patients. However, as about 40% of OAC patient do not report a history of GORD and fewer than 15% of OAC cases are detected in individuals during BO surveillance, prevention of OAC is limited by PPI use in GORD and BO patients.

**Abbreviations:** BMI: body mass index; BO: Barrett's oesophagus; CI: confidence interval; GORD: gastro-oesophageal reflux disease; H2RA: histamine-2 receptor antagonists; HGD: high-grade dysplasia; LGD: low-grade dysplasia; NSAID: non-steroid anti-inflammatory drug; OAC: oesophageal adenocarcinoma; OR: odds ratio; PPI: proton pump inhibitor; TR: time ratio

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## Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease (GORD) is recognized by the cardinal symptoms of heartburn and acid regurgitation [1]. According to the consensus-based Montreal definition, GORD is defined as 'a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications' [2]. In epidemiological research, GORD is usually defined as at least weekly symptoms of heartburn and/or acid regurgitation. Complications of GORD include oesophagitis, benign strictures, Barrett's oesophagus (BO), and oesophageal adenocarcinoma (OAC), including adenocarcinomas of the oesophogastric junction.

GORD is highly prevalent in the Middle East, followed by Western countries and less prevalent in East Asia [3–5]. The most recent systematic review and meta-analysis of 102 studies published through June 2018 found a pooled global prevalence of 13.98% (95% confidence interval (CI) 12.47–15.56%) [5]. Comparing continents, the pooled prevalence ranged from 12.88% (95% CI 3.83–25.62%) in Latin America and Caribbean to 19.55% (95% CI 15.60–23.83%) in North America. However, the prevalence varied substantially within the continents, as the pooled prevalence ranged from 4.16% (95% CI 3.35–15.05%) in China to 22.40% (95% CI 18.53–126.53%) in Turkey.

In the meta-analysis, the risk of GORD was slightly increased in women compared to men (odds ratio (OR) 1.18, 95% CI 1.15–1.20), but there was no clear association with age (Table 1) [5]. The risk difference by sex is small and conflicting between studies and possible reasons for this difference is unclear. The risk of GORD increased with increasing body mass index (BMI) (OR 1.73, 95% CI 1.58–1.89 for BMI $\geq$30 compared to BMI 18.5–29.9), while tobacco smoking was not associated with GORD. Low socioeconomic status, represented by a low educational level was also associated with increased risk of GORD (OR 2.11, 95% CI 1.99–2.24), compared to medium and high educational level. Use of non-steroid anti-inflammatory drugs or aspirin was also associated with increased risk of GORD (OR 1.46, 95% CI 1.33–1.60).

## Barrett's oesophagus

BO is a premalignant condition which appears after chronic acid exposure of the distal oesophagus [6]. Prolonged acid exposure induces an inflammatory response and metaplasia of the normal squamous epithelium of the oesophagus to a columnar epithelium to adapt to the acidic environment. BO can be recognized by endoscopy, but the diagnosis is verified by biopsy of the mucosa. American guidelines define BO as the presence of intestinal metaplasia, with the presence of goblet cells [7,8], while British guidelines consider all metaplasia above the gastro-oesophageal junction as BO [9].

BO is prevalent in the general population, both in Western and Eastern populations [10–12]. In a Swedish population-based study from the early 2000 of 3000 randomly selected individuals, BO with intestinal metaplasia was present in 1.6% (95% CI 0.8–2.4) [10]. In an Italian population-

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Table 1. Risk factors (+) and protective factors (−) of gastro-oesophageal reflux disease (GORD), Barrett's oesophagus (BO) and oesophageal adenocarcinoma (OAC).

| Factor | GORD | BO | OAC |
|---|---|---|---|
| GORD | N/A | ++ | ++ |
| BO | N/A | N/A | +++ |
| Sex (men) | − | + | ++ |
| Age | 0 | 0 | + |
| Obesity | + | + | + |
| Tobacco smoking | 0 | + | + |
| Education (low) | + | 0 | 0 |
| PPIs | N/A | N/A | − |
| NSAIDs/aspirin | + | 0 | − |
| Helicobacter pylori | 0 | − | − |

PPIs: proton pump inhibitors.
NSAIDs: non-steroid anti-inflammatory drugs.

based study from 2000 to 2004 of 1033 individuals, 1.3% had BO with intestinal metaplasia [11]. In a systematic review and meta-analysis of 51 studies from Asian countries through September 2014, the pooled prevalence of BO with intestinal metaplasia was 1.3% (95% CI 0.7–2.2) [12]. This review also found a trend towards increasing prevalence of BO over time from 1991 to 2014.

GORD is the strongest risk factor of BO (Table 1). In a Swedish prospective population-based study from the early 2000 of 284 participants, erosive esophagitis increased the risk of BO fivefold (relative risk ratio 5.2, 95% CI 1.2–22.9) after 5 years follow-up [13]. BO is more frequent in men. A systematic review and meta-analysis of studies from 1980 to 2004, found an overall pooled ratio of 1.96/1 (96% CI 1.77/1–2.17/1) for men over women [14]. As for GORD, obesity and especially central obesity increases the risk of BO. In a systematic review and meta-analysis of 17 studies through March 2013, the risk of BO increased with central obesity (OR 1.98, 95% 1.52–2.57) [15]. The association persisted also after adjustment for BMI (5 studies, OR 1.88, 95% 1.20–2.95). Tobacco smoking is also associated with increased risk of BO. In an analysis of 5 case-control studies of 1059 BO patients and 1143 population controls, the risk of BO was increased in ever-smokers (OR 1.67, 95% CI 1.04–2.67) [16]. Increasing number of pack-years of smoking, increased the risk dose-dependently until about 20 pack-years, when the association plateaued. Infection with *Helicobacter pylori*, which may lead to decreased gastric acid production due to a pan-gastritis with atrophy of the acid producing oxyntic mucosa, is associated with reduced risk of BO [17,18]. In a case-control study of 613 men including 150 with BO from the United States between 2008 and 2011, *Helicobacter pylori* infection was associated with a reduced risk of BO (OR 0.53, 95% CI 0.29–0.97) [17]. In a second case-control study of 1308 BO patients and 1388 population controls, *Helicobacter pylori* infection was associated with a similar reduced risk of BO (OR 0.44, 95% CI 0.36–0.55) [18].

BO increases the risk of OAC, but the risk is dependent on type of metaplasia (intestinal or gastric), length of metaplasia and grade of dysplasia (low-grade dysplasia [LGD] or high-grade dysplasia [HGD]) of the BO mucosa. Overall, the annual risk of OAC progression in BO range between 0.12% and 0.18% [19–22]. Compared to intestinal metaplasia, gastric metaplasia has lower risk of OAC development. In a population-based study of 8522 BO patients with mean 7.0 years follow-up and 131 cases of OAC/HGD, the annual risk of OAC/HGD was 0.38% (95% CI 0.31–0.46) with intestinal metaplasia and 0.07% (95% CI 0.04–0.11) with gastric metaplasia [19]. In a prospective study of 108 BO patients from the United States, increasing length of metaplasia was associated with increased risk of OAC/HGD at follow-up, but OAC/HGD occurred in Barrett's mucosa of all lengths [23]. In a nationwide population-based cohort study of all 11,028 BO patients in Denmark from 1992 through 2009 including 66 new OAC cases, 0.5% of BO patients without dysplasia developed OAC (1.0/1000 person-years [95% CI 0.7–1.3]) and 2.3% of BO patients with LGD developed OAC (5.1/1000 person-years [95% CI 3.0–8.6]) [20]. In a systematic review and meta-analysis of 24 studies including 2694 BO patients with LGD and 119 new OAC cases, the pooled annual risk of OAC was 0.54% (95% CI 0.32–0.76) [24]. In a systematic review and meta-analyses of 4 studies including 236 BO patients with HGD and 69 new OAC cases, the annual risk of OAC was 6.58% (95% Ci 4.97–8.19) [25]. However, the degree of dysplasia in BO is often difficult to determine accurately and some biopsies are classified as indefinite for dysplasia, with a risk of OAC somewhere between BO without dysplasia and BO with LGD [26].

## Oesophageal adenocarcinoma

The incidence of OAC has increased considerably the last decades, from being a rarity a few decades ago to 52,000 new cases worldwide in 2012 [27,28]. The prognosis in OAC is poor, mainly due to few symptoms in early disease and late presenting symptoms, as dysphagia and weight loss, with advanced disease in >75% of cases [29]. In Europe and the United States, the overall 5-year survival is between 10% and 20% [30,31].

The main risk factors of OAC follows from the cancer's development from BO (Table 1). GORD is the strongest risk factor of OAC and the increasing incidence of OAC mirrors the increasing prevalence of GORD. A systematic review and meta-analysis of 5 population-based studies, found that at least weekly GORD symptoms increased the risk of OAC fivefold (OR 4.92, 95% CI 3.90–6.22) and daily symptoms increased the risk seven-fold (OR 7.40, 95% CI 4.94–11.1) [32]. However, 40% of patients with OAC do not report GORD symptoms [33]. As for GORD and BO, obesity increased the risk of OAC, and the increasing prevalence of obesity parallels the increasing incidence of OAC. In a systematic review and meta-analysis of 6 studies through March 2013, central obesity was associated with increased OAC risk (OR 2.51, 95% CI 1.54–4.06) [15]. Tobacco smoking is also associated with increased risk of OAC. In a pooled analysis of 10 population-based case-control studies and two cohort studies including 2990 OAC cases and 9453 controls, smoking increased the risk of OAC (OR 2.08, 95% CI 1.83–2.37) with a strong dose-response relationship with number of pack-years of smoking [34]. In contrast to GORD, OAC has a striking predominance in men, with a ratio of 4.4 for men over women globally, ranging from 1.7 to 8.5 [28]. As shown by the meta-

analysis of the sex ratio for BO, this predominance cannot only be explained by higher rates of BO in men [14]. The reasons for this are mainly unclear, but increased severity of GORD due to more abdominal obesity and high rates of tobacco smoking in men compared to women are suggested. Sex hormone factors may also contribute [35]. As for BO, infection with *Helicobacter pylori* is associated with reduced risk of OAC. A systematic review and meta-analysis of studies through February 2007, found an inverse relationship between *Helicobacter pylori* prevalence and OAC risk (pooled OR 0.52, 95% CI 0.37–0.73) [36].

In contrast to the increased risk of oesophageal squamous cell carcinoma with increased alcohol consumption, alcohol is not an important risk factor in the sequence of GORD-BO-OAC, although some studies find a weak association. A meta-analysis of 24 studies including 5500 OAC cases found no association between alcohol consumption and OAC risk, even at higher levels of consumption [37].

## Prevention of oesophageal adenocarcinoma

Due to the increased risk of malignant transformation, BO patients are enrolled in surveillance programs to detect dysplasia or early adenocarcinoma [7–9,38]. If no dysplasia is found, the BO patients are followed every 3–5 years, while more rigorous follow-up or endoscopic treatment are indicated if dysplasia is present. BO patients in surveillance programs are diagnosed with an earlier tumour stage and has improved survival [39–43]. However, earlier detection (lead time bias) and detection of slow progressing tumours (length time bias) might explain some of the apparent survival benefit of surveillance [43,44]. Moreover, a large proportion (>85%) of patients diagnosed with OAC never had a diagnosis of BO, so surveillance have little impact on the overall incidence and prognosis of OAC [20,40,45,46].

Patients with BO are usually treated with daily PPI, regardless of symptoms. The main purpose of this is to reduce the risk of OAC and HGD. PPIs are antagonists of the H+/K+ ATPase on the gastric parietal cells, blocking the release of H+ to the gastric lumen, reducing acidity of the gastric content and tissue damage to the oesophageal epithelium. Typically, treatment with PPIs is divided into low-dose (e.g., esomeprazole 20–40 mg once daily or equivalent) or high-dose (e.g., esomeprazole 40 mg twice daily or equivalent). Acid exposure also upregulates cyclooxygenase-2 (COX-2) which is implicated in carcinogenesis in BO [47]. PPIs have also been found to have anti-oxidant properties and anti-inflammatory properties by direct effects on neutrophils, monocytes, endothelial and epithelial cell [48].

Observational studies have shown evidence of reduced risk of neoplastic progression in BO with PPIs. A systematic review and meta-analysis from 2014 of seven observational studies of 2813 BO patients and 317 OAC/HGD cases, found a pooled risk reduction of 71% with PPI use (OR 0.29, 95% CI 0.12–0.79) [49]. There was also a trend towards a dose-response relationship between duration of PPI treatment and reduced risk of OAC/HGD. The estimated number of BO patients needed to treat with PPIs to prevent one case of HGD or OAC was 147. None of the included studies showed increased risk of OAC with PPI use. In contradiction to this, a nationwide population-based study using Swedish health registries of 796,425 adults exposed to maintenance PPI use, found increased risk of OAC after >5 years of PPI treatment (standardized incidence ratio 1.91, 95% CI 1.48–2.43). However, only 25% of this cohort used PPIs due to GORD and the risk in this sub-cohort was not reported. Two studies in the review reported the association between H2RA and OAC/HGD, but found no preventive effect of H2RA. A more recent nested case-control study from the United States from 2018 used a cohort of 29,536 male veterans with BO and identified 300 OAC cases and matched them to 798 BO controls without OAC [50]. In this study, PPI use was associated with a 41% reduced risk of OAC (OR 0.59, 95% CI 0.35–0.99). The risk reduction was stronger with high-dose PPI use, but there was no association with duration of treatment. H2RA was also associated with a 30% reduced risk of OAC (OR 0.70, 95% CI 0.50–0.99). In a randomised trial of esomeprazole and aspirin treatment of 2557 BO patients with median follow-up of 8.9 years and 313 endpoints (all-cause mortality, OAC or HGD), high-dose esomeprazole was superior to low-dose esomeprazole (time ratio [TR] 1.27, 95% CI 1.01–1.58) [51]. Combining high-dose esomeprazole and standard dose aspirin (300 mg in the UK and 325 mg in Canada) had the strongest effect, compared to low-dose esomeprazole and no aspirin (TR 1.59, 95% CI 1.14–2.23). However, the study included no participants without PPI treatment, but the dose-response relationship argues for a valid conclusion. NSAIDs are also found to reduce the risk of HGD or OAC development in BO, which may be greater if the NSAID is combined with a statin. In a prospective study of 570 BO patients, combined use of NSAIDs and statins reduced the risk of HGD or OAC by 78% (hazard ratio 0.22, 95% CI 0.06–0.85), while the risk was reduced by 54% among the BO patients using only an NSAID (hazard ratio 0.46, 95% CI 0.22–0.99) [52].

In theory, anti-reflux surgery with fundoplication could be better than PPIs in OAC prevention in BO patients, as surgery also stops the potentially carcinogenic bile acids and not only reduces acidity. However, two randomized trials [53,54], one meta-analysis [55], one systematic review [56] and a nationwide cohort study from Sweden [57] have not been able find any difference in OAC incidence between medically and surgically treated GORD or BO patients.

In recent years, LGD in BO patients is usually managed with endoscopic eradication treatment. In a systematic review and meta-analysis of eight studies including 619 BO patients with LGD, radiofrequency ablation of the metaplastic mucosa reduced the risk of progress to OAC/HGD compared to surveillance (OR 0.07, 95% CI 0.02–0.22) [58]. Most BO patients with HGD or early OAC also undergo endoscopic treatment with resection of the dysplastic or early OAC lesion and ablation of the remaining metaplastic mucosa. In a systematic review of 11 studies, complete eradication of dysplasia/early OAC was achieved in 95% (95% CI 87–99%) and complete eradication of all metaplastic mucosa was achieved in 89% (95% CI 79–95%) of patients [59]. However, most

studies are performed in highly specialized centres and studies of long-term follow-up (>5 years) after endoscopic treatment of BO is still lacking.

## Conclusion

PPIs have some evidence of prevention of OAC in patients with GORD and BO. However, the clinical significance of this prevention of OAC is limited as about 40% of OAC patient do not report a history of GORD and fewer than 15% of OAC cases are detected in individuals during BO surveillance. Prevention of OAC should also include assessment and intervention of modifiable risk factors, such as BMI and tobacco smoking, in patients with GORD and BO. The risk factors of OAC could also be used to target high-risk individuals and help select these for endoscopic screening or defining the interval of endoscopic surveillance of BO in future studies. In addition, future studies could also assess if the preventive effect of PPIs is related to the additional risk factors of OAC or if PPI should be used irrespective of additional risk. As long-term PPI treatment is also associated with negative outcomes, inappropriate use should be avoided. The optimal dose of PPIs for OAC prevention should also be clarified in future studies. As NSAIDs/aspirin has common and potentially serious side effects, widespread use to prevent OAC which has a low absolute risk is probably not warranted. However, the use of NSAIDs/aspirin in high-risk individuals should be assessed in future studies. Due to increased risk of gastric adenocarcinoma, *Helicobacter pylori* infections should still be treated. Never the less, the main challenge is to identify the large group of patients that develop OAC without known GORD or BO. A future strategy could be to identify high-risk individuals of OAC based on the traditional risk factors, as sex, age, BMI and smoking, and screen these for GORD and BO.

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