The epidemic of oesophageal carcinoma: Where are we now?

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A R T I C L E   I N F O

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A B S T R A C T

Since the early 1970s, the incidence of oesophageal adenocarcinoma has increased dramatically in most Western populations. In contrast, the incidence of oesophageal squamous-cell carcinoma has decreased in these same populations. Epidemiological studies conducted over the past decade have provided great insights into the etiology of oesophageal cancer. These studies have identified gastro-oesophageal reflux disease, obesity and cigarette smoking as risk factors for oesophageal adenocarcinoma, while use of nonsteroidal anti-inflammatory drugs and infection with Helicobacter pylori are associated with reduced risk of oesophageal adenocarcinoma. For oesophageal squamous-cell carcinoma, alcohol and cigarette smoking are the two major risk factors underlying most cases. This review combines a synthesis of these studies with an analysis of data from the United States National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program to discuss the change in incidence of oesophageal cancer and summarize current knowledge of risk factors.

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1. Introduction

Oesophageal cancer is a relatively common and highly fatal malignancy. Worldwide, oesophageal cancer is the eighth most common cancer (456,000 new cases in 2012; 3% of all cancers in 2012) and the sixth most common cause of cancer-related death (400,000 deaths in 2012) [1]. The highest incidence rates of oesophageal cancer are seen along two geographic belts, one from north central China through the central Asian republics to northern Iran, and one from eastern to southern Africa (Fig. 1).

There are two main histological subtypes of oesophageal cancer: oesophageal adenocarcinoma and oesophageal squamous-cell carcinoma. Worldwide, oesophageal squamous-cell carcinoma is the most common oesophageal cancer subtype (representing 87% of all cases of oesophageal cancer in 2012 [2]). While this is due largely to high rates in many developing countries, incidence rates

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of oesophageal squamous-cell carcinoma are significantly higher than rates of oesophageal adenocarcinoma in 90% of all countries presented in GLOBOCAN [2].

There has been a dramatic shift in the epidemiology of oesophageal cancer in Western populations such that oesophageal adenocarcinoma has become the predominant subtype of oesophageal cancer in North America, Australia and Europe [3–5]. Epidemiological studies have implicated gastro-oesophageal reflux disease, obesity and cigarette smoking as the main risk factors for oesophageal adenocarcinoma. Together, these three risk factors account for over 70% of all cases of oesophageal adenocarcinoma in Western populations [6,7].

Barrett’s oesophagus, a condition in which the normal squamous mucosa of the oesophagus is replaced by columnar intestinal epithelium, is the only precursor lesion for oesophageal adenocarcinoma. Barrett’s oesophagus is present in up to 15% of individuals with frequent symptoms of gastro-oesophageal reflux disease, and in 1–2% of the general adult population [8]. Compared
to the general population, patients with Barrett’s oesophagus have at least 10-fold higher risk for oesophageal adenocarcinoma [9]. Consequently, patients with Barrett’s oesophagus are entered into a program of periodic endoscopic surveillance. However, although endoscopic surveillance every 3 years is recommended for patients with known nondysplastic Barrett’s oesophagus, the absolute risk of oesophageal adenocarcinoma in Barrett’s oesophagus is relatively low (0.33% per year) [10] and it remains unclear whether these patients benefit from long-term surveillance in terms of a reduction in overall mortality or risk of death from oesophageal adenocarcinoma [11–17].

During the period when rates of oesophageal adenocarcinoma were increasing dramatically in many Western populations, rates of oesophageal squamous-cell carcinoma declined in these same populations; however, oesophageal squamous-cell carcinoma remains the predominant oesophageal cancer subtype in Asia, Africa and South America. Heavy alcohol consumption and cigarette smoking are the main risk factors for oesophageal squamous-cell carcinoma, accounting for 80% and 40% of oesophageal squamous-cell carcinomas in men and women, respectively [18]. Oesophageal squamous dysplasia is the precursor lesion for oesophageal squamous-cell carcinoma [19]. Although treatment effectiveness has improved during the past decade, survival rates for oesophageal cancer remain poor. This review will focus mainly on the descriptive epidemiology and risk factors for oesophageal adenocarcinoma.

2. Recent trends in the incidence of oesophageal adenocarcinoma in Western populations

A seminal paper published in 2005 reported that oesophageal adenocarcinoma was one of the fastest rising cancers in the United States between 1975 and 2001 [3]. In subsequent analyses using data from the United States National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program to quantify rates of change in the incidence of oesophageal cancer over time, it was shown that the incidence of oesophageal adenocarcinoma in the United States increased at a rate of 8% per year until the late 1990s, and at a rate of almost 2% per year since the turn of the century until 2008 [4].

For the purpose of this review, data were analyzed from the SEER 9 registries (covering approximately 10% of the United States’ population) where 16,597 cases of invasive oesophageal adenocarcinoma (International Classification of Diseases for Oncology, Third Edition (ICD-O-3) site codes, C15.0–C15.9; histologic codes, M8140–8573) were diagnosed between 1973 and 2012. The overall incidence rate for oesophageal adenocarcinoma during this time period was 1.8 per 100,000 person-years. As expected, the majority of cases of oesophageal adenocarcinoma occurred in men (n = 14,158, 85%) and in whites (n = 15,832, 95%). Almost 8% of all cases of oesophageal adenocarcinoma were diagnosed in persons aged <50 years. Overall, the incidence of oesophageal adenocarcinoma increased from 0.4 per 100,000 in 1973 to 2.8 per 100,000 in 2012 (rate ratio [RR], 7.67; 95% confidence interval [CI], 5.76–10.4) (Fig. 2). In white men, the incidence of oesophageal adenocarcinoma increased from 0.8 per 100,000 in 1973 to 6.3 per 100,000 in 2012 (RR, 7.65; 95% CI, 5.63–10.6). Importantly, rates of oesophageal adenocarcinoma were stable in all sex and racial/ethnicity subgroups in the most recent years. In contrast, the incidence of oesophageal squamous-cell carcinoma (histologic codes, M8050–8082) continues to decline in the United States. Between 1973 and 2012, the incidence of oesophageal squamous-cell carcinoma decreased from 2.8 per 100,000 to 1.2 per 100,000 (RR, 0.44; 95% CI, 0.38–0.51) (Fig. 2).

3. Prognosis for oesophageal adenocarcinoma

In the United States, the overall 5-year survival rate for patients diagnosed with oesophageal adenocarcinoma is less than 20% [20]. For the purpose of this review, data were analyzed from the SEER 18 registries (covering approximately 28% of the United States’ population) to examine trends in relative survival rates for patients diagnosed with oesophageal cancer in the United States between 1973 and 2007 [21]. Since the early 1970s, there has been progressive improvement in overall 5-year survival rates for oesophageal adenocarcinoma, from around 5% to almost 20% in

![Fig. 3. 5-year survival rates for oesophageal adenocarcinoma in US SEER 18 registries, overall (black), and among whites (stripes) and blacks (grey).](image)
most recent years (Fig. 3). Although the proportion of patients diagnosed with early-stage oesophageal adenocarcinoma has increased (patients diagnosed and staged between 2003 and 2007, 25% had localized disease at diagnosis), over 40% of patients are still diagnosed with distant disease. Among these patients, the 5-year survival rate is less than 3%. In the SEER 18 dataset, the 5-year survival rate for oesophageal adenocarcinoma in blacks remains lower than the 5-year survival rate for whites (Fig. 3). Except for advanced stage oesophageal adenocarcinomas, where 5-year survival rates are similar for whites and blacks (both 3%), blacks diagnosed with localized or regional oesophageal adenocarcinomas have worse 5-year survival rates than whites for the same stage (34% vs. 43% and 14% vs. 21%, respectively). The overall 5-year survival rates for oesophageal squamous-cell carcinoma in the United States are slightly lower than the rate for patients with oesophageal adenocarcinoma (patients diagnosed between 2003 and 2007, 15% for oesophageal squamous-cell carcinoma vs. 19% for oesophageal adenocarcinoma).

4. Selected risk factors for oesophageal adenocarcinoma

4.1. Demographics

The incidence of oesophageal adenocarcinoma increases with age and is rare among persons aged <50 years [22]. In the SEER 9 registries, for oesophageal adenocarcinoma diagnosed between 1973 and 2012, incidence rates were 21 times (RR, 20.8; 95% CI, 19.6–22.1) and 44 times (RR, 44.4; 95% CI, 41.8–47.1) higher among persons aged 50-69 years and ≥70 years, respectively, as that it was among persons aged <50 years (Table 1; Fig. 4). One of the most intriguing observations in oesophageal adenocarcinoma is the striking sex disparity; in all populations, incidence rates of oesophageal adenocarcinoma are significantly higher among men than women [22,23]. In our analysis of SEER 9 data, the incidence of oesophageal adenocarcinoma was 7-fold higher (RR, 7.49; 95% CI, 7.17–7.82) among men compared with women (Table 1). Interestingly, the male-to-female ratio for oesophageal adenocarcinoma has not changed over time [24]. Overall, the incidence of oesophageal adenocarcinoma was four times as high among whites as it was among blacks (RR, 4.26; 95% CI, 3.83–4.75) (Table 1). As with the sex ratio, the white-to-black ratio for oesophageal adenocarcinoma has not changed over time [24]. This has important implications for understanding the reasons for the continued rise in the incidence of oesophageal adenocarcinoma and how sex and race may influence risk of developing oesophageal adenocarcinoma.

4.2. Gastro-oesophageal reflux disease

Epidemiological studies strongly implicate gastro-oesophageal reflux disease as the primary causal factor for oesophageal adenocarcinoma. A seminal nationwide, population-based case-control study conducted in Sweden reported that the odds of oesophageal adenocarcinoma developing increase by a factor of eight for persons with recurrent symptoms of gastro-oesophageal reflux disease (i.e., weekly heartburn and/or regurgitation symptoms), as compared with individuals with less frequent symptoms of gastro-oesophageal reflux disease (at least weekly symptoms vs. <weekly symptoms, odds ratio [OR], 7.7; 95% CI, 5.3–11.4) [17]. It was also shown in this study that the risk of oesophageal adenocarcinoma was especially high for persons with more severe and longer-lasting (more than 20 years) symptoms (OR, 43.5; 95% CI, 18.3–103.5) [25]. More recently, in a pooled analysis of individual participant data from five studies (including the Swedish study [25]) participating in the international Barrett’s and Esophageal Adenocarcinoma Consortium (BEACON; involving 1128 patients with oesophageal adenocarcinoma and 4057 population-based controls), persons with recurrent symptoms of gastro-oesophageal reflux disease had 5-fold increased risk for oesophageal adenocarcinoma (OR, 4.81; 95% CI, 3.39–6.82) [18]. Compared to persons without gastro-oesophageal reflux disease symptoms, persons with daily symptoms of gastro-oesophageal reflux disease had 8-fold higher risk of oesophageal adenocarcinoma and those with symptoms longer than 30 years had 6-fold increase in risk (OR, 6.08; 95% CI, 3.26–11.34) [26]. For Barrett’s oesophagus, a known downstream consequence of gastro-oesophageal reflux disease, earlier age at onset of recurrent gastro-oesophageal reflux disease symptoms is associated with especially high risk (age <30 years, OR, 15.1; 95% CI, 7.91–28.8) [27]. Unlike oesophageal adenocarcinoma, population-based studies have not shown an association between symptoms of gastro-oesophageal reflux disease and oesophageal squamous-cell carcinoma [25].

Although studies are still needed to further understand the mechanism that link frequent, severe gastro-oesophageal reflux disease to esophageal adenocarcinoma, the prevailing hypothesis is that chronic reflux of acid or bile injures the oesophageal epithelium, inducing a cascade of cytokine responses that result in inflammation and cell proliferation, thereby initiating the metaplasia–dysplasia–carcinoma sequence [28].

4.3. Cigarette smoking

Cigarette smoking has been consistently shown to be associated with increased risks of oesophageal adenocarcinoma and oesophageal squamous-cell carcinoma. In a pooled analysis of 12 studies participating in BEACON (involving 1540 patients with oesophageal adenocarcinoma and 9453 population-based

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**Table 1**

<table>
<thead>
<tr>
<th>Age, years</th>
<th>All histologies</th>
<th>Oesophageal adenocarcinoma</th>
<th>Oesophageal squamous-cell carcinoma</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>Rate</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>&lt;50</td>
<td>2915</td>
<td>0.5</td>
<td>1.00</td>
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<td>20840</td>
<td>11.2</td>
<td>24.3 (23.4–25.3)</td>
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<tr>
<td>≥70</td>
<td>17967</td>
<td>23.3</td>
<td>50.4 (48.4–52.4)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
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<td>7.7</td>
<td>3.65 (3.57–3.73)</td>
</tr>
<tr>
<td>Women</td>
<td>10831</td>
<td>2.1</td>
<td>1.00</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
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<td>4.3</td>
<td>0.52 (0.51–0.54)</td>
</tr>
<tr>
<td>Black</td>
<td>6407</td>
<td>8.2</td>
<td>1.00</td>
</tr>
</tbody>
</table>

CI, confidence interval; RR, rate ratio. Rates are per 100,000, age-adjusted using United States 2000 standard population.
controls), Cook and his colleagues reported that the risk of oesophageal adenocarcinoma was twice as high among persons with a history of cigarette smoking as it was among persons who have never smoked (OR, 1.96; 95% CI, 1.64–2.34) [20]. While earlier studies had reported inconsistent results regarding a possible dose-response relationship, Cook and colleagues observed a strong dose-response association between pack-years of cigarette smoking and oesophageal adenocarcinoma (<45 pack-years, OR, 2.71; 95% CI, 2.16–3.40; P<0.001) [29]. For oesophageal squamous-cell carcinoma, risk among smokers is three to five times that among persons who have never smoked [30]. There is strong evidence of a synergistic effect of cigarette smoking and alcohol use on risk of oesophageal squamous-cell carcinoma [31,32].

4.4. Obesity

It is estimated that almost 4% of all cancers are attributable to overweight and obesity [2]. Evidence accumulated from epidemiological studies conducted over the past decade suggests that obesity, abdominal obesity and its associated metabolic abnormalities are associated with oesophageal adenocarcinoma [33]. Because the temporal trends in the incidence of oesophageal adenocarcinoma parallel the increasing prevalence of obesity in the United States population, some have suggested that obesity is the main driver of increased rates of oesophageal adenocarcinoma; however, the extent to which obesity has contributed to the rise in incidence of oesophageal adenocarcinoma continues to be debated [34–36]. Furthermore, there are important sex differences in fat distribution such that these differences may in part explain the sex disparity observed in oesophageal adenocarcinoma, with males more likely than females to develop abdominal obesity and its metabolic and systemic sequelae [37,38].

In a pooled analysis of data from ten case-control studies and two cohort studies (involving 1,997 patients with esophageal adenocarcinoma and 11,159 population-based controls) participating in BEACON, Hoyoe and her colleagues reported that the risk of oesophageal adenocarcinoma was twice as high among persons with a BMI of 30–34.9 kg/m² as it is among persons with a normal BMI (OR, 2.39; 95% CI, 1.86–3.06) [39]. The odds of oesophageal adenocarcinoma will develop increase by a factor of five for persons with a BMI ≥ 40 kg/m² (OR, 4.76; 95% CI, 2.96–7.66) [39]. The association between BMI and risk of oesophageal adenocarcinoma has been subsequently reported in large national European prospective cohort studies, including the European Prospective Investigation into Cancer and Nutrition study (n = 391,456 participants, of whom 124 developed oesophageal adenocarcinoma during follow-up) [40] and the Metabolic Syndrome and Cancer project (n = 578,700 participants, of whom 114 developed oesophageal adenocarcinoma during follow-up) [41]. Obesity (as measured by BMI) does not appear to explain however the sex disparity for oesophageal adenocarcinoma: the prevalence of obesity is similar for men and women [42], and the pooled analyses found that the magnitude of the association with BMI was similar for men (30–34.9 kg/m², OR = 2.47, 95% CI 1.94–3.13) and women (30–34.9 kg/m², OR = 2.66, 95% CI 1.59–4.46) [39].

Because obesity is strongly associated with gastro-oesophageal reflux disease [43], epidemiological studies examining the association of obesity with oesophageal adenocarcinoma have carefully examined for potential confounding by gastro-oesophageal reflux disease symptoms in their analyses. Regardless of these efforts, imperfect measurement of reflux events in epidemiological studies may have resulted in residual confounding. We recently used a novel study design that employed Mendelian randomization as an instrumental variables approach to causal inference and data from studies participating in BEACON to quantify the non-reflux effects (‘independent effects’) of obesity on risk of oesophageal adenocarcinoma. The results from this study provide the best evidence yet that the association between obesity and oesophageal adenocarcinoma is an independent of gastro-oesophageal reflux disease symptoms [44]. Furthermore, childhood and adolescent BMI may be more strongly associated with oesophageal adenocarcinoma than BMI in later life [45,46]. The association is stronger for abdominal obesity (e.g., as measured by waist circumference) than overall obesity, which may in part explain
why oesophageal adenocarcinoma occurs more frequently in men than in women.

In contrast, studies have consistently reported an inverse association between obesity and oesophageal squamous-cell carcinoma [47]. While many have argued that this may be due to confounding by cigarette smoking, the inverse association has been found in smokers and non-smokers [48].

4.5. Alcohol

Alcohol is strongly associated with oesophageal squamous-cell carcinoma. The risk of oesophageal squamous-cell carcinoma is three to five times as high among people who consume alcohol as it is among people who have never consumed alcohol [31]. Among smokers, the risk of oesophageal squamous-cell carcinoma is over 20 times as high among heavy drinkers as it is among never drinkers (OR, 21.9; 95% CI, 3.9–122) [31]. Unlike oesophageal squamous-cell carcinoma, epidemiological studies have not shown an association between alcohol consumption and oesophageal adenocarcinoma. In their pooled analysis of 11 studies participating in BEACON (1821 patients with oesophageal adenocarcinoma and 10,854 population-based controls), Freedman and his colleagues found no increased risk of oesophageal adenocarcinoma among persons who consumed alcohol, irrespective of duration and frequency [49]. Interestingly, they observed an inverse relationship with low-alcohol-use and moderate-alcohol-use groups.

4.6. Nonsteroidal anti-inflammatory drugs

There is consistent evidence from observational studies that frequent users of nonsteroidal anti-inflammatory drugs have lower risk of oesophageal adenocarcinoma than non-users of these medications. In their pooled analysis of individual participant data from five case-control studies and one cohort study participating in BEACON (involving 1226 patients with oesophageal adenocarcinoma and 5314 population-based controls), Liao and her colleagues found that any use of nonsteroidal anti-inflammatory drugs was associated with 30% lower risk of oesophageal adenocarcinoma (OR, 0.68; 95% CI, 0.56–0.83) [50]. The inverse association was strongest for current users (OR, 0.40; 95% CI, 0.24–0.97). Risk decreased linearly with increased frequency and duration of use [41]. A similar inverse association between use of non-steroidal anti-inflammatory drugs and oesophageal squamous-cell carcinoma has been reported [51,52].

5. Helicobacter pylori

H. pylori is a gram-negative bacterium that persistently colonizes the human stomach and causes gastric cancer [53]. In contrast, epidemiological studies have consistently observed an inverse association with oesophageal adenocarcinoma. Two recent meta-analyses both reported over 40% lower risk of oesophageal adenocarcinoma in persons infected with H. pylori [45,46]. Epidemiological studies have not shown an association between H. pylori infection and oesophageal squamous-cell carcinoma [54,55].

6. Summary

The epidemiology of the two main subtypes of oesophageal cancer is very different. While the incidence of oesophageal adenocarcinoma continues to rise in the United States and other western populations, the incidence of oesophageal squamous-cell carcinoma continues to decline. The main risk factors for oesophageal adenocarcinoma are symptoms of gastro-oesophageal reflux disease, obesity and cigarette smoking (Table 2). Use of aspirin and nonsteroidal anti-inflammatory drugs and infection with H. pylori are associated with a reduced risk of oesophageal adenocarcinoma. Increasing evidence suggests that these risk factors confer equivalent risk for men and women and thus do not explain the sex disparity for oesophageal adenocarcinoma. We have limited data on risk factors for oesophageal adenocarcinoma and Barrett’s oesophagus in non-white populations and it is unknown why oesophageal adenocarcinoma occurs more frequently in whites than non-whites [56]. Most cases of oesophageal adenocarcinoma arise from Barrett’s oesophagus; consequently, patients with Barrett’s oesophagus are entered into a program of periodic endoscopic surveillance. However, the survival benefit associated with long-term surveillance for these patients remains unclear. Efforts are underway to derive risk models that identify persons at greatest risk for oesophageal adenocarcinoma [57–61]. These models offer promise; however, they need to be externally validated before being considered for clinical application.

Conflicts of interest

I have no conflicts of interest.

Authorship contribution

APT performed all analyses and drafted the manuscript.

References


