1 Epidemiology of Adenocarcinoma of the Esophagus, Gastric Cardia, and Upper Gastric Third

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Abstract The incidence of adenocarcinoma of the esophagus and esophagogastric junction (gastric cardia) has risen rapidly over the past three decades in the United States and northern Europe. This increase had been most dramatic among White males. The majority of these cancers arise from Barrett's esophagus. However, less than 10% of the patients with esophageal adenocarcinoma were known to have Barrett's esophagus before. Current evidence indicates that gastroesophageal reflux and obesity are major risk factors for adenocarcinoma of the esophagus. Abdominal obesity, more prevalent in males, and independent of body mass index, seems to be associated with an increased risk of esophageal adenocarcinoma but not of cardia adenocarcinoma. This observation may explain the high male:female ratio observed in esophageal adenocarcinoma. Tobacco use has also been found as a possible risk factor for adenocarcinoma of the esophagus and gastric cardia. Infection with *Helicobacter pylori* and the use of nonsteroidal anti-inflammatory drugs might reduce the risk. On the other hand, low intake of fruits, vegetables, and cereal fibers seem to increase the risk of esophageal adenocarcinoma. Currently, there is no evidence that strongly supports any specific strategy to screen a subgroup of the population at risk for adenocarcinoma of the esophagus or esophagogastric junction. Future strategies to decrease obesity and tobacco use might help to reduce the burden of esophageal adenocarcinoma at least partially.

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1.1 Introduction

Over the past three decades, the incidence of adenocarcinoma of the esophagus (ACE) and esophagogastric junction (EGJ) has increased rapidly in North America and Europe, whereas the frequency of squamous cell carcinoma (SCC) has remained relatively stable or declining in these geographical areas. In this review, we will discuss this epidemiological change as well as the role of different risk and protective factors that have been associated with these cancers.

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1.2 Demographics, Trends, and Geographic Variations of Adenocarcinoma of the Esophagus and EGJ

Data from the Surveillance Epidemiology and End Results (SEER) program in the United States (US) indicated that the incidence of esophageal adenocarcinoma in White males had doubled from the early 1970s to the late 1980s (Yang and Davis 1988). Blot and associates (1991) showed that the increases in the rates of esophageal adenocarcinoma in the US through the 1980s had been in the order of 5–10% per year. By 1990, adenocarcinomas accounted for nearly half of all esophageal cancers among White men (Blot et al. 1993). Based on the incidence trends available from the SEER program through 1998, Brown and Devesa (2002) described that among White males, the incidence of ACE rose from 0.72 per 100,000 population in 1974–1978 to 3.7 per 100,000 population in 1994–1998, an increase of greater than 400%. The rate of increase in esophageal adenocarcinoma in the last 25 years is greater than that of any other solid tumor in the US over the same time interval. The rates of ACE among White females, although much lower than those among White males, increased by more than 300%, from 0.11 per 100,000 population in 1974–1978 to 0.47 per 100,000 population in 1994–1998. In addition, ACE rates increased by more than 100% in Afro-American males, from 0.35 per 100,000 population in 1974–1978 to 0.81 per 100,000 population in 1994–1998; however, the rates of SCC among this population subgroup remain significantly higher (Brown and Devesa 2002). Using more recent nation-wide data (1998–2003) from US population-based cancer registries (NPCR – SEER) with substantially increased population coverage (83%) compared to previous studies, Trivers et al. (2008) found that ACE incidence increased by 2.1% per year. These results indicate a smaller magnitude of increase of ACE than those previously reported. In a recent update from the SEER program assessing the period 2001–2005, ACE represents 55.5% of all esophageal carcinomas in US (Ries et al. 2007).

In a comparison study within the U.S. SEER cancer registry for the years 1973–1998, Kubo and Corley (Kubo and Corley 2002), reported substantial regional, temporal, and ethnic differences between the incidence rates of ACE and adenocarcinoma of EGJ. These authors observed higher incidences of ACE and adenocarcinoma of EGJ in Seattle than Utah (5.3 and 4.0 vs. 2.4 and 2.8 per 100,000 person-years respectively). Association with other variables was also verified (male gender and White population were of predilection in both types of adenocarcinomas in all the studied regions). Crane et al. (2007b), using a population-based medical records database in Olmsted County, Minnesota, report that between the decades of 1971–1980 and 1991–2000 (Fig. 1.1), the incidence of ACE increased significantly from 0.4 to 2.5 per 100,000 person-years, and the incidence of adenocarcinoma of the EGJ also increased from a rate of 0.6 to 2.2 per 100,000 person-years. Similar trends have been reported from Denmark, The Netherlands, United Kingdom (UK), and other northern European countries (Levi and LaVecchia 1991; Moller 1992; Powell and McConkey 1992; Hansson et al. 1993; Reed and Johnston 1993; Powell et al. 2002; Vizcaino et al. 2002; Crane et al. 2007a; Falk et al. 2007). The incidence rates for ACE are the highest in Scotland (>9 cases per 100,000 men) compared with other countries analyzed. Using the recent data provided by the World Health Organization (WHO) over the last two decades, Bosetti et al. (2008) have confirmed a clear upward trend in the incidence of ACE in northern Europe; in Denmark and Scotland the incidence of ACE in men is now higher than that of SCC.

In South Australia, Nguyen et al. (2003) revealed that the incidence of ACE increased

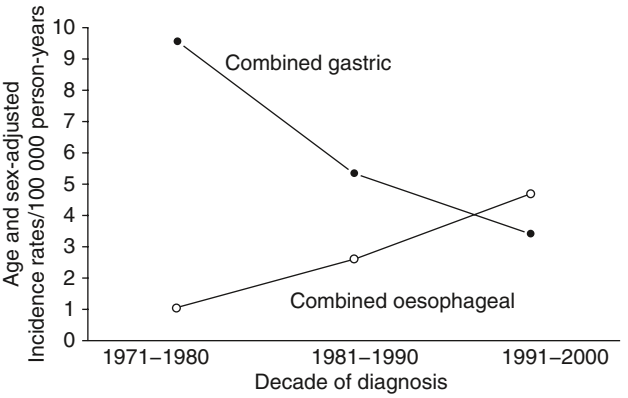

Fig. 1.1 Combined incidence of gastric (proximal, distal, and diffuse) and esophageal (esophagus and EGJ) adenocarcinoma among Olmsted County, Minnesota residents, 1971–2000. Age- and sex-adjusted (to USA white census 2000) rate are per 100,000 person–years. With permission from Crane et al. (2007b)

significantly (close to 140%) in both genders between 1977 and 2000. However, this upward trend has not been confirmed in Asian countries. Yee et al., in a population-based study, reported that in Hong Kong, though a Westernized life-style has been adopted (local prevalence of obesity similar to the US, decreased intake of vegetables, fruits, poultry, but increased consumption of processed meat, fat, beer and liquor) and with an increasing prevalence of gastroesophageal reflux disease (GERD), the incidence of ACE and the ratio of ACE vs. SCC decreased in the period from 1983 to 2003. One possible explanation is that even though the prevalence of GERD is getting more common, Barrett's esophagus (BE) is rare, and 94% of reflux esophagitis were either Los Angeles grade A or grade B esophagitis (Yee et al. 2007).

These observations of esophageal adenocarcinoma are paralleled by rising rates of adenocarcinoma of the EGJ (Blot et al. 1991; Powell and McConkey 1992; Zheng et al. 1993; Botterweck et al. 2000; Falk et al. 2007). Zheng and associates (1993) examined the incidence pattern of adenocarcinoma of the EGJ and distal esophagus in Connecticut between 1955 and 1989. Among males, adenocarcinoma of the EGJ increased during the study period from 0.6 per 100,000 population in 1955–1959 to 3.0 per 100,000 population in 1985–1989. Among females, adenocarcinoma of the EGJ was low (0.1 per 100,000 population) and unchanged during the time period between 1955 and 1969; however, the rate increased from 0.1 per 100,000 population in 1965–1969 to 0.6 per 100,000 population in 1985–1989. In the West Midlands (UK), Powell and McConkey (Powell and McConkey 1990) found that the incidence rate of EGJ tumors increased from 0.7 to 2.0 per 100,000 population between 1962 and 1981. Falk et al. (2007) found similar results in the incidence rate of adenocarcinoma of EGJ in Sweden, with an annual average increase of 2% in both genders between 1970 and 2004.

The causes for this alarming increase in the incidence of adenocarcinoma of the esophagus and EGJ are unclear. Different studies confirm that the increases in the incidence are real and the possibility of anatomic misclassification of adenocarcinoma of the gastric cardia as a possible explanation for the increases in the incidence of esophageal adenocarcinoma, could be ruled out (Devesa et al. 1998; Pohl and Welch 2005; Lindblad et al. 2006).

As we will discuss later, several risks and protective factors for esophageal and EGJ adenocarcinomas, including obesity, tobacco use,

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alcohol, dietary factors, medications, and *H. pylori* infection have been proposed. On the other hand, it is acknowledged that ACE and a portion of EGJ adenocarcinomas arise from long or short segments of BE (specialized intestinal metaplasia), a condition caused by chronic reflux of acid and duodenal contents into the esophagus (Cameron et al. 1997; Pera 2008).

1.3 Age, Gender, and Race

ACE and EGJ show similar epidemiologic characteristics that clearly distinguish them from SCC of the esophagus and from adenocarcinomas of the more distal parts of the stomach. These features include a very high male-to-female ratio at around 7:1 and a higher incidence among Whites compared with Blacks (Kalish et al. 1984; Rogers et al. 1986; Wang et al. 1986; Blot et al. 1991; Powell et al. 2002; Wu et al. 2007b).

Using data from population-based cancer registries aggregates published by the North American Association of Central Cancer Registries (NA-ACCR), Wu et al. (2007b) found that in males, the incidence of ACE in the Black non-Hispanic US population was 25% that of the White non-Hispanic US population (1.42 and 5.71 per 100,000 population, respectively), in the period 1998–2002. This proportion was 41% in females (0.32 and 0.78 per 100,000 population, respectively). They also observed that the incidence of ACE in Hispanic US population was 2.42 and 0.52 per 100,000 in males and females, respectively, with a male:female ratio of 4.6. This ratio was similar to that in Black non-Hispanic population (4.4), but minor to that of White non-Hispanic population (7.3).

Zheng et al. (1993) reported that the male: female ratio of age-adjusted incidence rates in Connecticut is approximately 5.5 for adenocarcinoma of the EGJ. The White:Black ratio for adenocarcinoma of the EGJ has been increasing, mainly due to a more rapid increase in the incidence of adenocarcinoma of the EGJ in Whites (Zheng et al. 1993). The disease, either in the distal esophagus or at the EGJ, mostly affects patients over 50 years of age with the peak at around 55–65 years (Yang and Davis 1988). Devesa et al. (1998) and Crane et al. (2007b) showed that the increasing trends for esophageal and gastric cardia adenocarcinomas varied by age, being more pronounced among older men. Below 65 years, the rates for esophageal adenocarcinoma doubled, whereas the rates for gastric cardia adenocarcinoma increased by 20%. In contrast, above 65 years, there were threefold to fourfold increase in esophageal adenocarcinoma and a 60% increase in gastric cardia adenocarcinoma (Devesa et al. 1998).

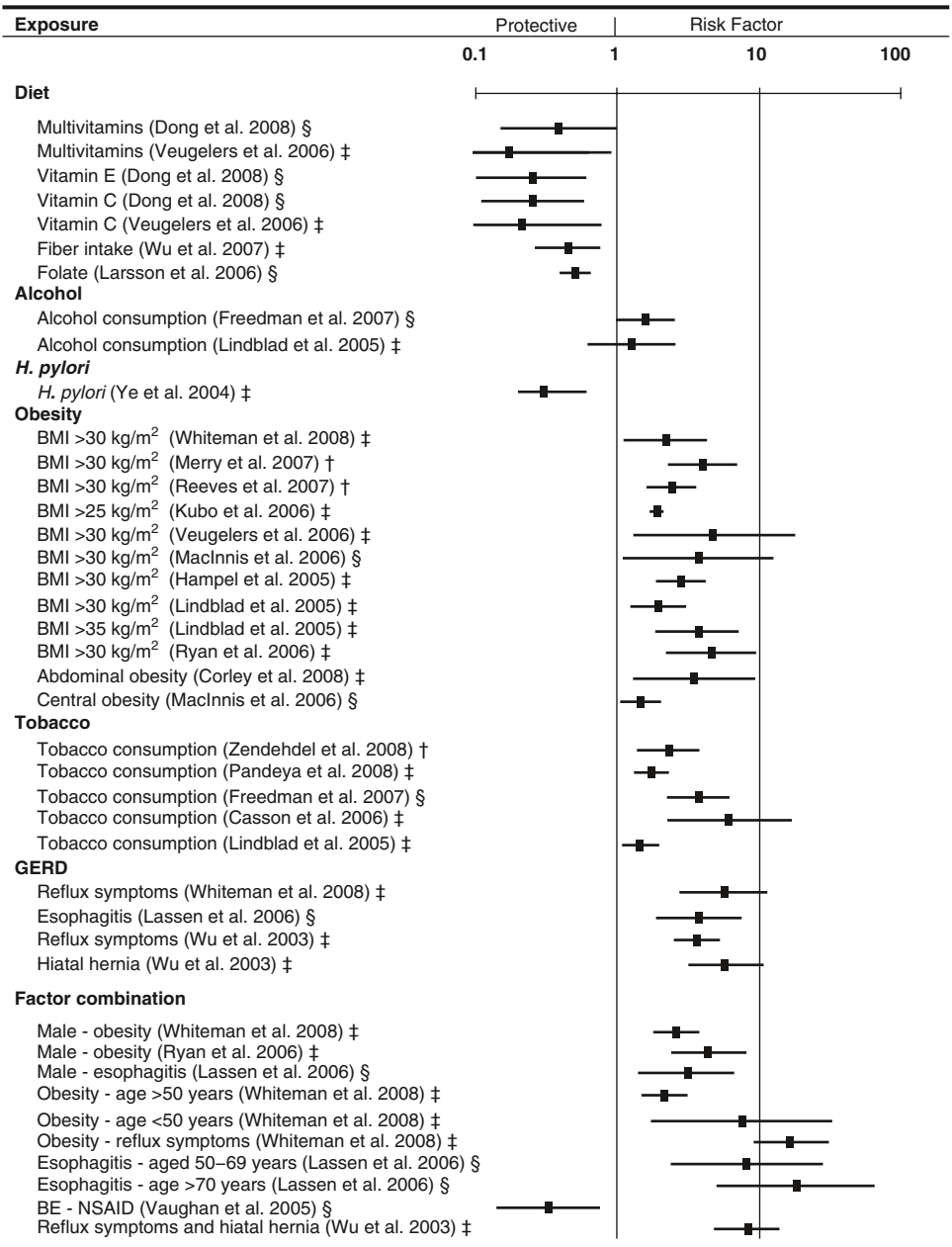
1.4 Gastroesophageal Reflux Disease and ACE and EGJ

Chow and associates (1995) compared 196 patients with ACE or EGJ with 196 matched controls. Significant twofold or greater risks of adenocarcinoma in both the locations were associated with a past history of esophageal reflux, hiatal hernia, esophagitis/ulcer, or dysphagia. The odds ratio increased with the increasing number of these conditions. A population-based, case–control study in Sweden found a strong association between symptomatic GERD and the risk of ACE (Lagergren et al. 1999a). An association, although weaker, was also found for adenocarcinoma of the EGJ, but not for SCC. Among the patients with recurrent reflux symptoms vs. those who had no such symptoms, the odds ratios were 7.7 for esophageal adenocarcinoma and 2.0 for adenocarcinoma of the cardia. In addition, the more frequent, the more severe, and longer-lasting the symptoms of reflux, the greater the risk. Among those with long-standing

severe reflux symptoms, the odds ratios were 45.5 for ACE and 4.4 for adenocarcinoma of the EGJ. The authors noted equally frequent reflux symptoms in adenocarcinoma cases with or without BE. They questioned the role of BE in the carcinogenic pathway. However, 62% of their esophageal adenocarcinomas had BE, which would expect in <1% of asymptomatic individuals and in 3–7% of patients with reflux symptoms and no cancer (Cameron and Romero 2000). In line with the findings of the Swedish Group, three studies (Farrow et al. 2000; Wu et al. 2003b; Whiteman et al. 2008) have found that both frequent GERD symptoms and a history of hiatal hernia were associated with increased risk for esophageal adenocarcinoma (Fig. 1.2). Neither reflux symptoms nor reflux conditions (hiatal hernia, esophagitis) were associated with the risk of adenocarcinoma of the EGJ in a multicenter study (Farrow et al. 2000). The cancer risk to the individual patient with GERD is low, however, because GERD is so common, some 15–20% of adults have reflux symptoms every week (Locke et al. 1997). It has been estimated that a population of 100,000 would include over 10,000 subjects with reflux symptoms, but the incidence of esophageal adenocarcinoma is only about 2.3 per 100,000 per year (Cameron and Romero 2000). BE is the intermediate stage between GERD and adenocarcinoma; progression of BE to invasive adenocarcinoma is reflected histologically by the metaplasia-dysplasia-carcinoma sequence (Cameron 1997). Lassen et al. (2006) retrieved data on endoscopies from five large population-based registers with the aim to estimate the incidence of diagnosed endoscopic esophagitis lesions, and the risk of esophageal adenocarcinoma among patients with previously diagnosed esophagitis. They found that the risk of ACE has increased fivefold in patients with previously diagnosed esophagitis, but most of the adenocarcinomas occurred among patients with BE. Likewise, Murphy et al. (2005) in a population-based cohort, have found that the risk of adenocarcinoma is not elevated in patients with histological evidence of esophagitis without BE. However, we can't, on the basis of symptoms, distinguish those with GERD, with or without BE. Shaheen et al. (2000) believes that until there is a better way of stratifying cancer risk among heartburn patients, decreasing the incidence of esophageal adenocarcinoma among those with heartburn may be difficult. It has been suggested that among 50-year-old men with symptoms of GERD, one time screening endoscopy for BE and adenocarcinoma of the esophagus is probably cost-effective (Cameron and Romero 2000; Inadomi et al. 2003).

1.5 Barrett's Esophagus and ACE and EGJ

BE, an acquired condition secondary to GERD, is a metaplastic change of the lining of the esophagus with the replacement of the normal squamous epithelium by columnar intestinal-type epithelium (Spechler and Goyal 1996; Pera 2008). It is now generally accepted that most, if not all, adenocarcinomas of the esophagus develop from areas of BE (Cameron et al. 1995). The prevalence of BE has been estimated at 3–7% in patients with frequent reflux symptoms undergoing endoscopic examination, compared with 1% in patients having endoscopy for any clinical indication (Cameron et al. 1997). It is currently unclear whether the prevalence of BE is increasing or whether this diagnosis is being made more frequently because of the widespread use of endoscopy. In a population-based study, Conio and Cameron found that the incidence and prevalence of clinically diagnosed BE have increased in parallel with the increased use of endoscopy. The rate of new diagnoses of BE increased 28-fold over the years in the study from 0.37 to 10.5 per 100,000 person-years. The rate of incidence changes of BE was similar to the 22-fold increased utilization of endoscopy over the same years (Conio et al. 2001). Prach



§Hazard Ratio; ‡Odds Ratio; †Relative Risk. Abbreviations: BMI = Body mass index; BE = Barrett's esophagus; NSAID = Non-steroidal anti-inflammatory drug; GERD = Gastroesophageal Reflux Disease.

Fig. 1.2 Protective and risk factors for adenocarcinoma of the esophagus, reported since 2003. Data are presented as mean risk (*square*) and 95% confidence interval (*line*)

(1997) in Scotland, found 1.4 BE cases per 1,000 endoscopies in 1980–1981, with a remarkable increase to 42.7 per 1,000 endoscopies 12 years later. The authors concluded that a real increase in the incidence of BE had occurred. These trends have also been confirmed in the Netherlands and Australia (van Soest et al. 2005; Kendall and Whiteman 2006). Kendall and Whiteman (2006) have reported that while the prevalence of long-segment BE remains unchanged, it is the prevalence of short-segment BE that is increasing, a phenomenon related in part to increased recognition and awareness of this condition.

BE is more common in men than in women, with a male:female ratio of about 2:1. This male predominance increases with the development of Barrett's adenocarcinoma with a ratio of at least 3:1. Mean age at diagnosis in male BE (62.0 years) is lower than that in female BE patients (67.5 years). The same applies to adenocarcinoma, mean ages at diagnosis being 64.7 in males and 74.0 years in females. A recent study in UK suggests that there is an age shift of 20 years in the onset of BE in females that may explain in part the higher incidence of adenocarcinoma in males compared to females. Many females would not survive long enough to progress to symptomatic adenocarcinoma of the esophagus (van Blankenstein et al. 2005).

Autopsy data suggest that the majority of BE cases go undetected in the general population (Cameron et al. 1990). Cameron (1993) estimates that there are about one million persons with BE in the US. Most of them (a "silent majority") do not know that they have the condition and may not be diagnosed unless complications like adenocarcinoma develop. Patients with BE are at risk of developing dysplasia and adenocarcinoma in this metaplastic epithelium. Although the precise risk remains unclear, data from retrospective and prospective studies of patients with BE suggest that the risk of cancer in BE is approximately 0.5% per year (Shaheen et al. 2000). In patients with BE and high grade dysplasia, however, the risk of developing esophageal adenocarcinoma is approximately 6 per 100 patient-years during the first few years of follow-up (Rastogi et al. 2008).

Despite the increased risk of adenocarcinoma, most patients with BE die for other causes (Van der Burgh et al. 1996). For patients with known BE, endoscopic surveillance for early detection of cancer or dysplasia is probably beneficial (Provenzale et al. 1999). However, optimal endoscopic surveillance intervals may change again based on current information showing a lower estimate of cancer incidence (Spechler 2000). Endoscopic surveillance programs are not likely to reduce the death rate from esophageal adenocarcinoma in the general population, because the majority of patients with BE remain undiagnosed. In this line, a series of patients with esophageal adenocarcinomas showed that less than 10% of them were known to have BE before seeking medical attention initially because of symptoms of esophageal cancer (Menke-Pluymers et al. 1992; Chalasani et al. 1998; Bytzer et al. 1999). The lack of GERD symptoms in patients with BE may in part contribute to this observation (GOSPE 1991).

1.6 Obesity

Obesity has assumed epidemic proportions in the US and Europe and is a risk factor for a number of chronic diseases as well as for a number of different types of cancer [colorectum, breast (postmenopausal), endometrium, gallbladder, prostate, bladder, thyroid, and connective tissue] (Carroll 1998; Jacobsen et al. 2001; Samanic et al. 2004; Kuriyama et al. 2005). Five population-based case–control (Chow et al. 1998a; Hampel et al. 2005; Lindblad et al. 2005; Corley et al. 2008; Whiteman et al. 2008), two hospital-based case–control (Ryan et al. 2006; Veugelers et al. 2006), three cohort studies (MacInnis et al. 2006; Merry et al. 2007; Reeves et al. 2007) and two meta-analyses (Hampel

et al. 2005; Kubo and Corley 2006) revealed that excess weight is a strong risk factor for esophageal adenocarcinoma (Fig. 1.2) and that the strength of the association increased with increasing body mass index (BMI). To a lesser extent, excess weight increased the risk of EGJ adenocarcinomas while no effect was seen for gastric adenocarcinoma or esophageal SCC (Chow et al. 1998a; Lagergren et al. 1999b). Kubo and Corley (2006) suggest that the association between BMI and adenocarcinoma is weakest in the EGJ and increases with increasing distance up from the gastroesophageal junction. The positive association between the risk of esophageal adenocarcinoma and the usual BMI was significantly modified by age, with the greatest increase in risk seen among the youngest group (ages <50 years), reaching an OR of 7.5 (95% C.I., 1.7–33.0) (Whiteman et al. 2008). This observation suggests that obesity is particularly important for early-onset tumors, while other risk factors may assume a more prominent role for tumors developing in later years (Chow et al. 1998a). The mechanism by which overweight might affect the risk of ACE and EGJ remains to be identified. One hypothesis suggests that obesity by increasing the risk of hiatal hernia and GERD would presumably increase the risk of BE, which in turn is a precursor lesion for esophageal adenocarcinoma (Brown et al. 1995). However, three studies have shown that obesity *per se* is a strong risk factor for ACE and gastric cardia, independent of reflux (Chow et al. 1998a; Lagergren et al. 1999b; Lindblad et al. 2005). Population-based studies and a meta-analysis have shown that the risk of esophageal and gastric cardia adenocarcinoma increased linearly with increasing BMI and reflux severity, and these risk factors combined in a multiplicative manner (Lagergren et al. 2000c; Hampel et al. 2005; Reeves et al. 2007; Whiteman et al. 2008). Lagergren et al. (2000c) observed than among obese persons (BMI >30 kg/m^2) with reflux symptoms, the odds ratio was 179.2 for esophageal adenocarcinoma and 12.2 for cardia adenocarcinoma compared with lean persons (BMI <22 kg/m^2) without reflux symptoms. However, because the incidence of ACE and gastric cardia is very low, the absolute risk of developing these tumors is still low. These authors also assessed the benefits of endoscopic screening of persons with various combinations of BMI and reflux symptoms. Despite impressive risk estimates, they found no evidence to support general endoscopic surveillance among persons with reflux symptoms. However, in the small group of very obese men with severe symptoms, surveillance might be warranted. In a multicenter population-based case–control study, Engel et al. (2003) found that BMI above the lowest quartile was associated with an attributable risk of 41.1% for developing esophageal adenocarcinoma. Both, Vaughan et al. (2002) in a cohort of patients with BE, and MacInnis et al. (2006) in a population-based cohort study, identified abdominal fat (male-pattern obesity) as a strong predictor of progression to ACE and EGJ, providing an explanation why the incidence of these cancers is substantially higher in males than in females (Lassen et al. 2006; Ryan et al. 2006; Veugelers et al. 2006; Crane et al. 2007b; Falk et al. 2007; Whiteman et al. 2008). More recently, Corley et al. (2008) in a population-based nested case–control study demonstrated that increasing abdominal diameter was strongly associated with an increased risk of ACE, but not with the risk of EGJ cancer. This association was independent of GERD and BMI. Persons with an abdominal obesity pattern have recently been shown to be at risk for BE (Corley et al. 2007; Edelstein et al. 2007). These observations support a potential link between obesity and the sequence BE-ACE. The evidence listed above may support the hypothesis that the increasing prevalence of obesity may be one of the explanations for the rising incidence of esophageal and gastric cardia adenocarcinoma in the western world (Merry et al. 2007). Alternative mechanisms for the BMI-cancer association include potential alterations in endogenous hormone metabolism, such as insulin-like

growth factor, estrogen, glucocorticoids, and insulin (Kubo and Corley 2006; Whiteman et al. 2008). Nevertheless, the case–control design of most studies makes it difficult to be emphatic about temporal association.

1.7 Additional Risk Factors for ACE and EGJ

1.7.1 Tobacco

Tobacco smoking has been found as a possible risk factor for ACE and cardia (Menke-Pluymers et al. 1993; Ahsan et al. 1997; Gammon et al. 1997; Lagergren et al. 2000b; Takesaki et al. 2001; Wu et al. 2001; Engel et al. 2003). In a multicenter, population-based, case–control study conducted in 1997, definitive evidence on the effect of smoking on the risk of esophageal and EGJ adenocarcinomas was added (Gammon et al. 1997). Risk appears to be more than doubled, with a dose-response pattern among smokers. Little reduction in risk was observed until smoking cessation for more than 30 years which is in contrast to the steady decrease in risk observed after quitting for other smoking-related cancers such as cancer of the lung and SCC of the esophagus. Gammon et al. (1997) suggest that smoking may affect an early stage in the induction of esophageal and EGJ adenocarcinomas. Although these data support the role of tobacco as an etiologic factor for adenocarcinomas of the esophagus and EGJ, it does not explain the rising incidence of these adenocarcinomas at times when SCC of the esophagus is not increasing and there is a recent reduction in the prevalence of cigarette smoking (Zhang et al. 1997). Lagergren et al. (2000b) tested the association between tobacco and the risk of ACE and EGJ cancer in a case–control study in Sweden. The risk of ACE with smoking was weak or absent. EGJ adenocarcinoma was dose-dependently associated with smoking (OR = 4.2, 95% CI = 2.5–7.0 among heavy smokers compared with never-smokers). These authors concluded that tobacco smoking does not play an important role in the etiology of ACE. Recently, many others studies (Fig. 1.2) have found an association between smoking and ACE, with an increased risk of 1.45–6.1 (Lindblad et al. 2005; Casson et al. 2006; Freedman et al. 2007; Pandeya et al. 2008; Whiteman et al. 2008; Zendehdel et al. 2008). Whiteman et al. (2008), in a case–control population-based study, found that smoking significantly increased the risk of ACE and EGJ, but there was no evidence of interaction with body mass. Casson et al. (2006) suggest that the susceptibility of some smokers to develop ACE may be genetically modulated. These authors found that this association was seen preferentially in patients with the active allele of either glutathione *S*-transferase M1 or glutathione S-transferase T1 genes.

1.7.2 Alcohol

Several observational studies have failed to find an association between alcohol consumption and risk of ACE and EGJ (Fig. 1.2) (Menke-Pluymers et al. 1993; Gammon et al. 1997; Lagergren et al. 2000c; Takesaki et al. 2001; Wu et al. 2001; Lindblad et al. 2005; Freedman et al. 2007).

1.7.3 Diet and Nutrition

Five case–control studies identified high intake of dietary calories and fat as a strong risk factor for ACE and EGJ (Zhang et al. 1997; Chen et al. 2002b; Mayne and Navarro 2002; Bahmanyar and Ye 2006; Navarro Silvera et al. 2008). Higher intake of meat, particularly red meat, is associated with an increased risk of ACE, while higher intake of meat, particularly poultry, and

high-fat dairy is associated with an increased risk of EGJ carcinoma (Navarro Silvera et al. 2008). Several studies have suggested that some nutrients could be considered as protective factors against esophageal and EGJ adenocarcinoma. This is the case of fruits and fresh vegetables, lutein, niacin, β-carotene, folate, iron, zinc, and vitamins B6, B12, C, and E (Fig. 1.2) (Brown et al. 1995; Zhang et al. 1997; Takesaki et al. 2001; Terry et al. 2001; Chen et al. 2002a; Veugelers et al. 2006; Dong et al. 2008). In the case of folate, a recent meta-analysis calculated a relative risk of 0.5 (0.39–0.65) for ACE (Larsson et al. 2006) A multicenter population-based, case–control study in England and Scotland showed that high BMI in early adulthood and low consumption of fruit are important risk factors for esophageal adenocarcinoma in women (Cheng et al. 2000). These authors found that these two factors accounted for 90% of the risk of the condition in this population. Antioxidants (vitamin C, β−carotene, alpha-tocopherol) have the potential to neutralize the harmful effects of DNA-damaging free radicals, such as those produced by smoking, and these nutrients have generally emerged as protective factors in the previous studies of esophageal SCC (Shklar 1998; Terry et al. 2000b). Terry et al. (2000b) observed that higher intake of antioxidants was associated with similarly decreased risk of esophageal adenocarcinoma. These authors also suggested that the inverse associations of antioxidants with esophageal adenocarcinoma are stronger among sufferers of GERD as well as smokers (Terry et al. 2000b). Five case–control studies showed a protective effect of dietary fiber on the risk of adenocarcinoma of the EGJ and distal esophagus (Brown et al. 1995; Zhang et al. 1997; Terry et al. 2000a; Mayne and Navarro 2002; Wu et al. 2007a). Terry et al. (2001) found a strong inverse association between fiber intake and EGJ adenocarcinoma. This inverse association was driven almost entirely by cereal fiber, and intake of fiber from fruit and vegetables was essentially unrelated to the risk (Terry et al. 2001). There was a protective trend of high fiber intake for adenocarcinoma of the esophagus, but this was not statistically significant. These authors suggest that their findings support the hypothesis that saliva and swallowed air contribute to high nitrosamine concentrations in the most proximal part of the stomach (Terry et al. 2001). Wheat fiber would act as a strong scavenger of nitrites under acidic conditions. Recent studies suggest that lower serum selenium levels may be a risk factor for esophageal adenocarcinoma and gastric cardia cancer (Rudolph et al. 2003; Wei et al. 2004). These authors speculate that selenium may act primarily at later stages of progression toward adenocarcinoma. Evidence from laboratory and population-based studies indicates that some selenium-containing compounds have anticarcinogenetic effects. Results from a cross-sectional study on patients with BE suggest that higher serum selenium levels may be associated with a reduced risk of ACE (Rudolph et al. 2003).

1.7.4 Medications

Lagergren et al. (2000a) investigated whether medications that may promote GERD by relaxing the lower esophageal sphincter (LES) increase the subsequent risk for ACE and gastric cardia. Long-term daily users (>5 years) of any of these medications had an increased risk (incidence rate ratio, 3.8 (95% CI, 2.2–6.4)) compared with persons who had never used these drugs. The association was particularly strong for anticholinergics. Adjustment for reflux symptoms almost eliminated the association, prompting the investigators to suggest that these medications may promote cancer by increasing reflux. These investigators estimated that long-term use of drugs that promote LES relaxation might be responsible for about

10% of esophageal adenocarcinomas. However, since esophageal adenocarcinoma is still a rare disease, the increment in absolute risk in the individual patient after exposure to LES-relaxing drugs is small (Eisen 2000). On the other hand, some evidence had been published in terms that the use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAID) is associated with a 50–90% reduction in the risk of ACE (Funkhouser and Sharp 1995; Corley et al. 2003; Gammon et al. 2004; Hur et al. 2004; Mehta et al. 2005). Vaughan et al. (2005) estimated a hazard ratio of 0.32 (0.14–0.76) for ACE in patients with BE who use aspirin or NSAID (Fig. 1.2). Many of the observational studies listed above have inherent limitations, mostly because not all confounding variables have been taken into account. For instance, the use of aspirin and/or NSAIDs may be associated with certain patient-led behaviors that have an influence on risk. This would then lead to a false association being established between NSAIDs and cancer prevention (Mehta et al. 2005). The role of chemoprevention itself is already being tested in a large randomized study in UK, the ASPirin Esomeprazole Chemoprevention Trial (AspECT) involving 2,500 patients with BE (Das et al. 2008).

1.7.5 *Helicobacter pylori* Infection

The results of a meta-analysis have confirmed quantitatively that *H. pylori* is an important risk factor for noncardial gastric cancer but not for cancer of the cardia (Huang et al. 1998). The risk of gastric adenocarcinoma and its precursor state, atrophic gastritis, is associated particularly with $CagA^+$ compared with $CagA^-$ strains of *H. pylori* (Parsonnet et al. 1997). On the other hand, an inverse relation between $CagA^+$ strains of *H. pylori* infection and risk of esophageal and gastric cardia adenocarcinoma has been observed (Chow et al. 1998b). It has been suggested that the increasing incidence of ACE and EGJ is linked to declining rates of *H. pylori* infection in western countries. Indeed, epidemiological evidence is accumulative that *H. pylori* infection, especially with strains $CagA^+$ is associated with a reduced risk of ACE or EGJ, although a recent population-based case–control study found negative results (Wu et al. 2003a). Recently, in the case-cohort study including 600 gastric cardia adenocarcinoma patients in Linxian (China), a population with low prevalence of BE and ACE, risk of gastric cardia cancer was increased in individuals exposed to *H. pylori* (hazard ratio = 1.64; 95% CI: 1.26-2.14) (Kamangar et al. 2007).

It will be of interest to evaluate whether variations in acidity and the content of refluxate are involved in the mechanism by which *H. pylori* strains may affect the risk of ACE and EGJ (Chow et al. 1998b). A recent study showed that infection with *H. pylori* may reduce the risk of esophageal adenocarcinoma, but these authors think that it is unlikely to do so by atrophy-reduced acidity (Fig. 1.2) (Ye et al. 2004).

1.8 Summary

ACE and EGJ is increasing in US and northern Europe; however, the reasons for this epidemiological change remain unclear. BE represents the precursor lesion for most of these tumors, but the majority of persons with this condition remain unrecognized in the general population. GERD and obesity have emerged as major risk factors for ACE and to a lesser extent for EGJ adenocarcinoma. Although fruits, cereal fibers, and vegetables intake have protective action, there is no evidence that dietary interventions can prevent these cancers. Future strategies to change life-style risk factors may be warranted to reduce at least partially the burden of esophageal adenocarcinoma.

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