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Environmental Causes of Esophageal Cancer

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Synopsis

This articles reviews the environmental risk factors and predisposing conditions for the two main histological types of esophageal cancer, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EA). Tobacco smoking, excessive alcohol consumption, drinking maté, low intake of fresh fruits and vegetables, achalasia, and low socioeconomic status increase the risk of ESCC. Results of investigations on several other potential risk factors, including opium consumption, intake of hot drinks, eating pickled vegetables, poor oral health, and exposure to human papillomavirus, polycyclic aromatic hydrocarbons, *N*-nitroso compounds, acetaldehyde, and fumonisins are also discussed. Gastroesophageal reflux, obesity, tobacco smoking, hiatal hernia, achalasia, and probably absence of *H. pylori* in the stomach increase the risk of EA. Results of studies investigating other factors, including low intake of fresh fruits and vegetables, consumption of carbonated soft drink, use of H_2 blockers, non-steroidal anti-inflammatory drugs, and drugs that relax the lower esophageal sphincter are also discussed.

Keywords

esophageal cancer; risk factor

Esophageal cancer (EC) is the 8th most common incident cancer in the world and, because of its high fatality rate, ranks 6th among all cancers in mortality [1,2]. It is not surprising, therefore, that the etiology of EC has been investigated for over a century. Based on clinical observations, Craver in 1932 and Watson in 1939 list excessive use of alcohol and tobacco, low socioeconomic status, poor oral health, and consumption of hot drinks as risk factors for EC

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[3,4]. They also cite papers on EC etiology published decades earlier. For example, Craver cites a 1920 article from Argentina that suggests maté drinking as a risk factor for EC.

Etiology of EC differs by histology. EC can be histologically classified into two main types: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EA). These two cancer types differ not only histologically, but also with respect to their incidence trends, populations that they affect, and risk factors. One could call EA "an emerging disease". Until the 1970s, ESCC constituted the large majority (over 90%) of all EC cases in all parts of the world. Since then, however, incidence rates of EA have sharply increased in many countries in the Western World [5–9], so that this cancer type now constitutes approximately half of all EC cases in some Western countries. In contrast, ESCC continues to be the dominant type in the rest of the world.

Most etiological studies conducted before the 1980s did not distinguish between ESCC and EA, but their results were mainly relevant to ESCC, because EA was uncommon before then. Also, results of the more recent studies from Asia, South America, or Africa that do not report histology are mainly applicable to ESCC because EA is still relatively uncommon in these areas [10–12]. Extensive investigations into the etiology of EA started only in the 1990s, mainly in Western countries, where larger numbers of this cancer began to be diagnosed.

Some parts of the world have distinct epidemiologic patterns of ESCC. In most parts of the world, incidence rates of ESCC, adjusted to the 1970 World Population, are lower than $15/10^5$ person-years and ESCC is 2–3-fold more common in men than in women [13]. However, in certain areas of China (in the Taihang mountain region) and Iran (in Golestan Province), a completely different pattern is observed: incidence rates above $100/10^5$ person-years have been reported, and men and women have similar incidence rates [13]. As we shall see below, ESCC risk factors in these areas may be different from those seen elsewhere. For example, unlike almost everywhere else, tobacco smoking and alcohol consumption play a minor role [14,15].

ESCC and EA have known precursor lesions, esophageal squamous dysplasia (ESD) and Barrett's esophagus (BE), respectively. Compared to subjects with no ESD, those with mild, moderate and severe ESD have an increased risk of ESCC of approximately 3-, 10- , and 30-fold, respectively [16]. Presence of BE substantially increases EA risk; risk of progression to EA is 0.5 – 1% per year [17,18]. Therefore, ESD and BE have been used as surrogate endpoints for ESCC and EA, respectively.

With this background, we review some factors that increase or decrease EC risk. Where data are available, we discuss the effect of each factor separately for ESCC and EA. Many factors have been investigated in relation to EC, among which we have chosen those that are established risk factors, or those for which there is substantial data, or those for which there is currently strong research interest. These factors include habits (tobacco use, alcohol consumption, opium consumption, maté drinking, consumption of hot drinks, consumption of carbonated soft drinks, eating pickled vegetables), nutritional deficiencies (low intake of fresh fruit and vegetables, vitamin and mineral deficiencies), medications (non-steroidal anti-inflammatory drugs, medications that relax lower esophageal sphincter, H_2 receptor antagonists), infections (*Helicobacter pylori*, Human papillomavirus), chemical carcinogens (polycyclic aromatic hydrocarbons, nitrosamines, acetaldehyde), physiologic or pathologic predisposing conditions (gastroesophageal acid reflux, hiatal hernia, achalasia, gastric atrophy, poor oral health), occupational exposure (to silica and asbestos), and low socioeconomic status (Table 1).

Habits

Tobacco use

As early as 1979, the Untied States Surgeon General reported that: “Cigarette smoking is significant causal factor in the development of EC. The risk … increases with the amount smoked.”[19]. The 1989 Surgeon General report added that: “The proportion of EC deaths attributable to tobacco use in the United States is estimated to be 78 percent for men and 75 percent for women” [20]. Since the publication of these reports, a large number of case-control and cohort studies have confirmed these statements.

Cigarette smoking is more strongly associated with ESCC than with EA. Studies have shown that ESCC risk is increased by approximately 3–7-fold in current smokers [21–25]. Smoking cigars or a pipe confer risks similar to cigarette smoking [26]. The International Agency for Research on Cancer (IARC) has concluded that chewing betel quid that includes tobacco, which is common in South and South-East Asia, can also cause ESCC [27]. There is less data available for other forms of tobacco use, such as using waterpipe (hookah) and chewing nass (a mixture of lime, ash, and tobacco), which are predominantly used in the Middle-East. However, these forms of tobacco also seem to increase ESCC risk [28]. The only exceptions to strong association with tobacco have been reported from the very high-risk regions of China (in the Taihang mountain region) and Iran (in Golestan Province). In these areas, cigarette smoking is minor risk factor for ESCC, with relative risk of approximately 1.5 [12,28,29]. It is unclear why the association is much weaker in these areas than what has been observed in the rest of the world. One hypothesis is that other strong risk factors may exist in these high-risk areas that account for the majority of the cases, and therefore the effect of smoking is diluted [30].

Although smoking is less strongly associated with EA, there is now little doubt that smoking is a risk factor for EA. At least 10 population-based case-control studies [31–40] and a large-scale cohort study [25] have evaluated the association between cigarette smoking and EA, and almost all of these studies have found an increased risk of nearly 2-fold. Several of these studies have also shown a dose-response relationship. The consistency of association and the dose-response relationship both indicate a causal relationship. Further supporting this causal relationship are the effect of smoking in causing cancers in other organs [41,42], and the presence of a large number of carcinogens, such as polycyclic aromatic hydrocarbons, nitrosamines, and acetaldehyde in tobacco smoke [43]. Also, because smoking starts years before tumor formation, there is no doubt about the direction of temporal relationship. Indeed the 2004 report of the Untied States Surgeon General on health consequences of smoking concluded that there is sufficient evidence for a causal relationship between cigarette smoking and EA [41].

Alcohol consumption

Like tobacco use, alcohol consumption has long been known to be a major cause of EC in most areas of the world. Classic ecologic and case-control studies by Tuyns and others in the 1970s and 1980s [44–47] established alcohol as a strong cause of EC in many countries, and showed that alcohol drinking and tobacco smoking interact to increase EC risk in a multiplicative manner. IARC has classified alcohol drinking as a known cause of EC [48].

The increased risk of EC associated with alcohol use is perhaps limited to ESCC. When used in excessive amounts (3 or more drinks per day), alcohol has almost universally been associated with an elevated risk of ESCC; it typically increases risk by 3–5 fold [25,49–51]. In contrast, there is little evidence for an association between alcohol drinking and EA. The majority of the case-control and cohort studies that have investigated this association have found no overall relationship between alcohol consumption and EA, or have found relatively weak associations,

both direct and inverse [25,31–33,35,36,38,39,52]. Some studies have suggested that only certain types of alcohol may be associated with EA. For example, one study [32] suggested that drinking straight liquor could increase risk and another one [33] suggested that drinking wine may reduce risk. These results need to be confirmed in other studies.

The exact mechanism of carcinogenicity of alcohol is not known, because alcohol itself does not bind DNA, is not mutagenic, and does not cause cancer in animals [53]. However, several mechanisms for its carcinogenicity have been suggested, including its conversion to acetaldehyde (see below, under acetaldehyde), acting as a solvent for other carcinogens, and causing nutritional deficiency [53].

Opium use

A role for opium as a potential cause of EC was first suggested when ecologic studies showed very high rates of opium consumption in high risk areas of northeastern Iran. In a study of 1,590 rural individuals, the prevalence of appreciable levels ($\geq$ 1 μg/ml) of urinary morphine metabolites was almost 6-fold higher among residents of high-risk vs. low-risk areas [54]. This study also compared household members of 41 cases and 41 matched control for urinary opium metabolites and found a non-significantly 2-fold increased risk among case household members [54]. The results of a recent case-control study in this same area also showed that opium use was associated with a 2-fold increased risk of EC [28].

Crude opium, itself, is not mutagenic in the Ames test [55,56]. However, smoking opium may produce polycyclic aromatic hydrocarbons or other carcinogenic compounds. Opium dross and smoke condensates from opium and morphine cause mutations in *S. typhimorium* [55,56], sister chromatid exchanges in human lymphocytes [57], and morphological transformations in cultured Syrian hamster embryo cells [58].

Although the results of the studies conducted thus far suggest that opium use could increase EC risk, the level of evidence for this association is not yet strong enough to be convincing. Data from case-control studies may be subject to recall or observer biases, and associations found in these studies may be due to reverse causation. The results of an ongoing cohort study in northern Iran will provide further evidence to evaluate this potential association [59].

Drinking maté

Maté, an infusion of the herb *Ilex paraguayensis* (also known as yerba maté) is commonly consumed, sometimes in large volumes (1–2 liters/day), in some areas of South America, including southern Brazil, northeastern Argentina, Uruguay, and Paraguay [60,61]. These areas also have the highest risks of EC are seen in South America [62]. Therefore, several case-control studies in these countries have examined the association between drinking maté and EC, and nearly all have found an increased risk [63–69]. A combined analysis of five of these studies showed a dose-response association with amount, duration, and temperature of maté and drinking, with a relative risk of 3 in those who drank over 3 liters of maté per day [61].

Two independent mechanisms may explain the carcinogenicity of maté: repeated thermal injury, resulting from drinking hot maté, and exposure to polycyclic aromatic hydrocarbons (PAHs) that are found in maté [70]. Maté is often consumed hot or very hot, but it also can be consumed warm or cold. In 1991, IARC classified hot maté as a probable (Group 2A) carcinogen to humans [71], implying that repeated thermal injury was the probable mechanism of carcinogenicity. However, several studies have now suggested that contaminants, especially PAHs, may also be involved. Studies have found large amounts of PAHs in processed yerba maté leaves [70,72,73] and high concentrations of urinary markers of PAHs in maté drinkers [74]. Maté has also been shown to have mutagenic effects in bacterial assays and to cause

chromosomal aberrations in human peripheral lymphocytes treated *ex vivo* [75]. These lines of evidence, in addition to finding associations between maté drinking and smoking-related cancers in other organs (lung [76], larynx [77], oral cavity and oropharyx [78], kidney [79], and bladder [80,81]) suggest that PAHs may play an important role. Further evaluation of the role of PAHs in the carcinogenicity of maté is of public health significance [70] because the PAH content of maté can potentially be modified.

The large majority of EC cases in high-risk regions of South America are ESCC; there is no evidence yet with which to evaluate the association between maté drinking and EA.

Hot foods and drinks

Although recurrent thermal injury from intake of hot foods and drinks has long been hypothesized as a cause of EC [4], it is still unclear whether this association exists. Some have doubted a causal association because of its biological implausibility. For example, in 1956 Steiner suggested that the temperature of hot foods and drinks fall so rapidly in the upper digestive tract that they cannot cause injury to the esophageal mucosa [82]. However, later De Jong and colleagues showed that intake of hot drinks could substantially increase the intraesophageal temperature, and this increase was a function of the initial drinking temperature and more importantly, the size of the sip [83]. For example, drinking 65 °C coffee increased the intraesophageal temperature by 6–12 °C, depending on the sip size [83].

The results of epidemiologic studies have shown little consistency on the role of hot drinks in esophageal carcinogenesis. Around 50 case-control studies and 2 cohort studies have investigated the association of drinking hot tea (green, black, and other types), coffee, maté, and other hot foods and drinks with EC. Except for maté, for which most studies have shown an increased risk (see above), other hot drinks have been found to be associated with EC only in a minority of studies. There are several problems in establishing or refuting an association between hot drinks and EC: 1) most of the evidence comes from case-control studies, which are prone to several biases, including recall bias and interviewer bias; 2) in some studies, consuming various types of hot drinks have been asked or analyzed together; 3) little has been done to measure sip size or the actual temperature of the drinks -- at best, the study questionnaire has asked whether the study participants drink their tea or coffee hot, warm, or cold, which may not produce reliable results; and 4) these drinks have chemicals that may cause or prevent cancer, which may confound the effect of thermal irritation. To overcome some of these problems, an ongoing cohort study in northern Iran has measured the tea drinking temperature in approximately 50,000 subjects, but the data are not available yet [59].

Consumption of carbonated soft drinks

It has been suggested that carbonated soft drinks may have contributed to the rising incidence of EA, because these drinks are acidic and may increase reflux by causing gastric distension [84]. Also, per capita consumption of these drinks increased approximately 20 years prior to the rise of EA rates [84]. However, case-control studies have found no association [85,86] or even an inverse association [87] between consuming soft drinks and EA risk. Likewise, case-control studies have found no association [87,88] or an inverse association [86] between soft drink consumption and ESCC risk. Therefore, the current data show no evidence that soft drinks increase EA or ESCC risk.

Consumption of pickled vegetables

Eating pickled vegetables was once very common in high-risk areas of China and was thought to be a major risk factor for EC in those areas [89]. As reviewed by CS Yang, ecological studies showed higher risk of EC in areas that used higher amounts of pickled vegetables [89]. Fungi and yeasts grow in pickled vegetables and they may release potentially carcinogenic

compounds such as *N*-nitrosamines, Roussin red methyl ester, and mycotoxins [89–91]. Studies have shown that samples of pickled vegetables are mutagenic in the Ames test, can cause sister chromatid exchanges in Syrian hamster, and can also cause cancer when fed to rats [89,92, 93]. However, the results of epidemiologic studies have been inconsistent. Whereas some case-control studies have shown an association between pickled vegetable intake and EC [94–99], typically with relative risks of 2–3, other case-control or cohort studies have shown no association [12,100,101]. Lack of a consistent association could partly be due to the fact that in the past the large majority of people in some high-risk areas ate pickled vegetables, which might have resulted in lack of variance. Also, a public health campaign by the government of China, which aimed to reduce pickled vegetable consumption, may have led to reporting bias in high-risk populations subject to the campaign. Therefore, further investigation of this hypothesis may be of interest. It is noteworthy that an IARC evaluation in 1993 concluded that traditional Asian pickled vegetables are *possibly carcinogenic to humans (Group 2B)* [102].

Nutritional deficiencies

Low intake of fresh fruit and vegetables

Low intake of fresh fruit and vegetables has long been considered as a possible risk factor for EC. A review of the evidence by World Cancer Research Fund and American Institute for Cancer Research (WCRF-AICR), published in 2007, identified 4 cohort studies (all from China), 36 case-control studies, and 7 ecological studies of the association of fruit intake and EC. The large majority of these studies found inverse associations between intake of fruits, especially citrus fruits, and EC risk. These protective associations were stronger in the case-control studies. The panel concluded that “the evidence … though mostly from case-control studies, is consistent with a dose-response relationship … Fruits probably protect against esophageal cancer” [103]. The WCRF-AICR panel also identified 5 cohort studies, 37 case-control studies, and 6 ecological studies that had investigated the association of non-starchy vegetables and esophageal cancer. Most case-control studies found inverse associations but cohort studies, which were mostly from China, overall found a weak inverse association. The panel’s final comment was: “Non-starchy vegetables probably protect against esophageal cancer” [103].

Since the WCRF-AICR review was conducted, at least three additional cohort studies have published their results on fruit and vegetable intake and risk of EC [104–106]. The results of all three of these cohort studies provided support for a protective association of both fruit and vegetable intake with EC [104–106]. Putting all evidence together, high intake of fruit and vegetables probably decreases EC risk by approximately 20% per 50 gram of fruit or vegetable intake per day [103].

The large majority of data on the association of fruit and vegetable intake with risk of EC comes from studies that have mainly investigated ESCC, so the results of these studies may apply only to ESCC. To our knowledge, only one cohort study has had a large enough number of ESCC and EA cases to study the effect of fruits and vegetables on these tumor types separately [104]. This study found decreased risk of ESCC, but not EA, associated with higher intake of both fruit and vegetables.

Vitamin and mineral deficiencies

By the early 1980s, both epidemiologists and basic scientists had obtained intriguing evidence that vitamin and micronutrient deficiencies may play important roles in the etiology of EC and several other cancers. Low intake of fruit and vegetables, which contain vitamins, were inversely associated with EC risk in most studies conducted until then; *in vitro* studies had shown that antioxidant effects of some vitamins could prevent tumor formation; and people in

some areas with very high risk of EC, such as Linxian (a county in the Taihang mountains region of China), had severe deficiencies in some vitamins and minerals [107]. These findings led to the conduct of two large chemoprevention trials in Linxian. One of these studies, the Linxian Dysplasia Trial, randomized approximately 3,300 subjects cytologically diagnosed with esophageal squamous dysplasia (ESD) to receive a combination of 26 vitamins and mineral or a placebo [108]. The other trial, the Linxian General Population Trial, enrolled approximately 30,000 people from Linxian to test four nutrient factors: Factor A (retinol, zinc), Factor B (riboflavin, niacin), Factor C (ascorbic acid, molybdenum), and Factor D (selenium, α-tocopherol, β-carotene) [109]. There was no risk reduction for EC in either trial using any of these nutritional supplements after 5–6 years of intervention. Longer term follow-up (through 10 years after ending the intervention) in the General Population Trial, however, showed Factor D reduced EC risk in younger subjects by 17% but increased risk in older individuals by 14% [110]. These findings, along with disappointing overall mortality and cancer incidence results from some other vitamin chemoprevention trials [111,112] and the results of some meta-analyses [113,114] have largely discouraged scientists from pursing the micronutrient hypotheses further. However, selenium and zinc deficiency may play a role in the etiology of ESCC.

Selenium deficiency has been shown to be a risk factor for upper gastrointestinal tract cancers. Both observational and experimental studies have shown that higher selenium status reduces the risk of esophageal and gastric cancers in selenium deficient populations [109,115–117]. In the Linxian General Population Trial, Factor D, which included selenium, reduced overall mortality, morality from gastric cancer, and also mortality from EC in younger individuals [110]. And, in another randomized chemoprevention trial in Linxian, selenium increased regression and reduced progression of mild ESD [118].

Zinc deficiency enhances the effects of *N*-nitrosomethylbenzylamine and certain other nitrosamines in esophageal carcinogenesis in rodents [119,120]. Tissue zinc is perhaps the most relevant measure of zinc in relation to carcinogenesis [121]. The only human study investigating the association between tissue zinc and EC showed that there was a significant dose-response relationship between lower levels of zinc and increased risk of EC [121].

Medications

Non-steroidal anti-inflammatory drugs

A meta-analysis of 9 studies, published in 2003, concluded that Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) reduced risk of EC in a dose-response manner. More frequent use was associated with lower risk, with an overall risk reduction of approximately 40% [122]. This meta-analysis also showed that these drugs had similar inverse associations with ESCC and EA. Several other studies published since then, mostly focused on EA, have shown similar results [123–127]. This association may be due to reverse causation; people with a history of upper gastrointestinal symptoms, who are also at higher risk of cancer, may limit their use of Aspirin and other NSAIDs. However, some studies stratified their results by having or not having upper gastrointestinal disorders and did not find a difference in results in these two groups of patients [127]. If the associations are causal, aspirin and NSAIDs may reduce risk by reducing inflammation and affecting the inflammation-metaplasia-cancer sequence at its early stages.[124]

Results of a short-term randomized trial in Linxian showed that celecoxib did not have any effect on regression or progression of ESD [118]. The protective effect of aspirin against the progression of BE to EA is being tested in a large, long-term trial [128].

Medications that relax the lower esophageal sphincter

Reflux of acid from the stomach to the esophagus is usually blocked by the lower esophageal sphincter. Certain medications such as asthma drugs (β-adrenergic agonists and drugs containing theophylline), calcium channel blockers, nitroglycerin, and benzodiazepines relax the lower esophageal sphincter and hence may promote acid reflux and higher risk of BE and EA. The fact that use of many of the aforementioned treatments increased rapidly after the mid-1950s and the plausibility of their relation to reflux and EA led to the hypothesis that these treatments may be responsible for the EA epidemic that started in the mid-1970s [129].

Case-control studies, however, have provided conflicting results. Whereas some studies have found no overall association with LES-relaxing drugs [126,130] others have shown increased overall BE or EA risk [125,131,132]. Among these studies, some showed increased risk with only one or two groups of medications. For examples, although Vaughan and colleagues found no overall association, they found increased EA risk with β-adrenergic agonists [130]. The most consistent association has been seen with asthma medications, but this association may be confounded by acid reflux, which causes both asthma and EA [133]. Other subgroup analyses have suggested that only younger individuals may be susceptible [131]. Overall the results are not entirely consistent and further studies are warranted.

H_2 receptor antagonists

H_2 receptor antagonists (H_2 blockers), such as cimetidine and ranitidine, are a class of drugs that reduce acid production in the stomach. These drugs were first marketed in 1977 and have been highly prescribed since then. One the one hand, these medications may reduce EA risk by reducing the acid content of gastroesophageal reflux. On the other hand, they may increase EA risk via neutralizing the gastric pH, which allows bacteria to proliferate in the stomach and thus may result in increased production of carcinogens such as nitrosamines and acetaldehyde. In addition, cimetidine can be nitrosated in the stomach to form nitrosocimetidine, which has a chemical structure similar to the potent carcinogen N-methyl-N′-nitro-N-nitrosoguanidine [134]. At least 5 epidemiologic studies have investigated the association of H_2 blocker use with EC [135–139] but the results are inconclusive. Two of these studies showed increased risk of EC [136] or EA [139] with H_2 blocker use but they did not adjust for acid reflux symptoms, which is an important indication for using these treatments. Two other studies that adjusted for acid reflux symptoms found a statistically non-significant increased risk of EA, but they acknowledged that this non-significant increase might have been due to residual confounding from acid reflux [135,137]. Another study from Sweden classified the results by indication of medication use and found an increased risk of EA in the group that received H_2 blockers for “esophageal indications”, rather than other indications, suggesting that the increased risk was confounded [138]. Only one of these studies [137] looked for an association between H_2 blockers and ESCC, and it did not find an association.

Infections

Helicobacter pylori

H. pylori is a known cause of noncardia gastric adenocarcinoma and gastric MALT lymphoma [140]. The association of this gram-negative bacterium with other gastrointestinal cancers, most notably EC, has also been evaluated in several studies.

H. pylori has shown a consistent pattern of association with EA. The large majority of epidemiologic studies have found a protective association, and the results of three recently published meta-analyses showed that *H. pylori* colonization of the stomach is associated with a nearly 50% reduction in risk [141–143]. One of these meta-analyses also tested and showed an inverse association of *H. pylori* with BE [142]. *H. pylori* may decrease risk of EA by reducing

gastric acid production and hence reducing acid reflux from the stomach to the esophagus [144]. It may also reduce EA risk by decreasing the production of ghrelin, a hormone that is mostly produced in the stomach and stimulates appetite [145]. A reduction in the level of ghrelin may lead to lower rates of obesity, an important risk factor for EA [40].

In the past few decades, advances in sanitation and the widespread use of antibiotics have caused a rapid decline in *H. pylori* colonization prevalence in human populations [146], especially in Western countries. In the United States, for example, data from the National Health and Nutritional Examination Survey 1999–2000 indicated the presence of *H. pylori* in only 5% of children who were born in the 1990's [147], which was far lower than that seen in older people of the United States [147] or than children of other countries with lower socioeconomic status [148]. Therefore, it is conceivable that the steep decline in *H. pylori* colonization rates in the past few decades may be partly responsible for the recent increase in EA incidence in Western countries.

In contrast to its association with EA, *H. pylori* has not shown a consistent association with ESCC. Whereas some studies have found a 2-fold increased risk of ESCC with *H. pylori* colonization in the stomach [98,149], others have found no association [150] or even reduced risk [151]. Three recent meta-analyses that summarized the association of *H. pylori* with ESCC found no overall association, with summary odds ratios very close to unity, but they showed substantial heterogeneity in results of the published studies [141–143].

Human papillomavirus

Oncogenic types of HPV, most notably HPV 16 and HPV 18, are necessary causes of cervical cancer [152,153], and also play an important role in the etiology of the epithelial cancers of the vulva, anus, penis, and oropharyngeal cavity [153,154]. However, despite 25 years of research and well over 100 studies of EC, the role of HPV in the etiology of this cancer remains controversial [153].

HPV was first suspected to have a role in the etiology of EC in 1982, when histological findings suggesting the presence of HPV were observed in benign esophageal epithelia and malignant esophageal tumors [155]. Since then, two major approaches have been used to investigate a possible role of HPV in causing EC: searching for the presence of HPV DNA in tumors using polymerase chain reaction (PCR), and comparing cases and controls in case-control or cohort studies for serum antibodies against HPV. PCR-based methods can detect DNA from the carcinogenic HPV types in nearly all cervical cancers [153]. In contrast, PCR results have been very inconsistent in esophageal cancers [153,156]. While many studies have found no evidence of HPV in esophageal tumors [157–163], others have found HPV in up to 75% of them [164]. This inconsistency may be due to true geographic variation [156] or it may simply reflect contamination during sample preparation or conducting the PCR. The results of case-control or cohort studies that have used serologic assays against HPV virus-like particles have also been inconsistent. Whereas some studies have found very strong (relative risks of 5 or more) [165,166], moderate to strong (relative risks of 2–5) [167], or weak (relative risks of 1–2) associations between HPV 16 or HPV 18 and EC, others have found no association [168–170] or even inverse associations. The inconsistency of these results may be due to differences in study design (case-control versus cohort studies), geographic variation (high-risk versus low-risk areas), differences in positivity cutpoints used in different studies, lack of appropriate adjustment for tobacco use or alcohol consumption, or simply chance fluctuation due to the small number of cases in some studies. Efforts to find the source of heterogeneity have so far been inconclusive [170]. Because of these conflicting results, a recent report by IARC concluded that "*there is inadequate evidence in humans for carcinogenicity of HPV in the esophagus*"[153].

Chemical carcinogens

Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are produced during incomplete combustion of organic materials. The major sources of exposure to PAHs are smoking tobacco [43], eating charbroiled meat and other food products [171], air pollution [172], and occupational exposure [173].

PAHs have long been suspected to be human carcinogens. In 1755, Percivall Pott found that exposure to soot, which contains high amounts of PAHs, causes scrotal cancers in chimney sweeps [174]. In 1915, Yamagiwa, a Japanese pathologist, induced cancer for the first time by applying coal to the ears of rabbits [175]. Kennaway and his colleagues at Royal Cancer Hospital in London found dibenz(a, h)anthracene and benzo(a)pyrene, two PAHs, to be the active carcinogenic compounds in coal tar capable of inducing skin cancer in mice [175].

A causal link between PAHs or PAH-containing substances and cancer has been established for cancers of the skin, lung, and bladder [176]. Tobacco smoke, which contains significant amounts of PAHs, is causally linked to EC. However, evidence linking other PAH-containing substances or individual PAHs to EC is based only on ecologic studies and is therefore only circumstantial. Studies in Linxian have shown histopathologic evidence in EC cases consistent with high exposure to PAHs [177], presence of high levels of carcinogenic PAHs in staple foods [178], and high concentrations of urinary markers of PAHs [179]. Studies in Golestan Province of Iran have also shown very high concentrations of urinary markers of PAHs in a majority of the residents [180]. Therefore, further evaluation of this association is of significant interest. Evaluating the association of PAHs with EC or other cancers, however, has proven to be difficult, partly because there are no valid and reliable markers of long-term PAH exposure that can be used in epidemiologic studies. Urinary markers of PAHs reflect exposure only in the 24 – 72 hours prior to urine collection [181]. Using PAH-DNA adducts or PAH-protein adducts as markers of exposure in epidemiologic studies have also been hampered by other limitations [182,183], such as lack of sensitivity to low exposures, non-linearity at high exposures, use of surrogate tissues (such as blood lymphocytes) instead of the target tissue of interest, and high cell turnover rates in many tissues, which make it impossible to measure long-term exposure. Nevertheless, adducts have been useful in establishing causal links between some carcinogens and cancer, such as the causal relationship between tobacco smoking and cervical cancer, and better assays may help future research evaluation of a PAH link to EC.

N-Nitroso compounds

N-nitroso compounds (NNCs) are strong animal carcinogens and have been shown to cause cancers of the nasal cavity, esophagus, and stomach in several animal models [184–187]. The role of these compounds as human carcinogens is less well established.

The relevance of NNCs to human cancer has been difficult to assess because humans are exposed to these compounds in many different ways and because no valid and long-term integrated biomarker of exposure has been developed. Humans can be exposed to NNCs from tobacco smoking, occupational exposure, and many food sources [188] and also from endogenous synthesis, which contributes to 45–75% of the total exposure [189]. Nitrosamines and nitrosamides, two major subgroups of NNCs, are formed by the endogenous reaction of nitrites with amines or amides, respectively. Nitrites are directly found in sodium nitrite and various foods, and are also formed by reduction of ingested or salivary nitrates [190–192]. Vegetables are the main sources of exogenous nitrates but high levels of nitrates may also be found in water [192]. Reduction of nitrates to nitrites by oral bacteria is a major contributor to

the formation of N-nitroso compounds and may be one of the reasons why poor oral health has been associated with higher risk of EC and gastric cancer [193,194]. To date, no NNC-DNA adducts are available that are easily measurable and accurately represent long-term exposure to NNCs.

Despite these challenges, there is some indirect evidence linking NNCs to EC. Jakszyn and Gonzalez recently conducted a systematic review of case-control and cohort studies associating nitrosamine exposure and foods that are direct or indirect sources of these compounds with EC risk [195], and found that eating processed meat, a major source of nitrites and nitrosamines, was consistently associated with higher risk of EC [195].

Acetaldehyde

Humans can be exposed to acetaldehyde in several ways, most notably by drinking alcohol. Ethanol is converted to acetaldehyde by alcohol dehydrogenase (ADH) enzymes and then to acetate by acetaldehyde dehydrogenase (ALDH) enzymes [196]. Therefore, higher alcohol consumption and genetic polymorphisms that enhance the activity of ADHs or decrease the activity of ALDHs result in higher acetaldehyde exposure [196]. In addition to alcohol drinking, humans are exposed to acetaldehyde by smoking cigarettes, eating moldy food, burning wood and coal, and also by *in vivo* metabolism of sugars by oral and colonic bacteria [197,198]. In vitro, acetaldehyde causes point mutations in human lymphocytes, sister chromatic exchanges, cellular proliferation, and inhibits DNA repair. In 1999, IARC classified acetaldehyde as a known carcinogen for animals but only a possible carcinogen for humans [197], mostly because there was little human data at the time this IARC evaluation was done. Since then, genetic polymorphisms in ADH genes and ALDH2 that favor the accumulation of acetaldehyde have been observed to increase ESCC risk [196], thus adding to the evidence of acetaldehyde carcinogenicity in humans. In addition, acetaldehyde may link alcohol drinking, tobacco smoking, eating moldy foods, and poor oral health to ESCC [198]. Therefore, further studies in humans are warranted.

Fumonisins

Fumonisins are toxins secreted from *Fusarium verticillioides* (formerly *Fusarium moniliforme*), a fungus that grows mostly on maize. Fumonisin B_1 is a known animal carcinogen and has been shown to cause tumors of the liver and kidney in mice and rats [199,200]. Evidence for the carcinogenicity of fumonisins in humans, however, is circumstantial, and is mostly limited to ecologic studies. Ecologic studies in China, Iran, and South Africa have shown higher exposure to fumonisins in areas with higher risk of EC [201–203]. The only case-control study that examined fumonisin exposure in relation to EC risk was conducted in Linxian, China, and found no association between exposure and risk [204]. However, the biomarkers of exposure used in this study were of uncertain value and the results were not conclusive. Further epidemiologic studies are needed to establish or refute an association between fumonisins and EC.

Predisposing conditions

Gastroesophageal acid reflux

Symptomatic gastroesophageal acid reflux is perhaps the strongest known risk factor for EA. In a population-based case-control study from Sweden, Lagergren and colleagues showed a strong dose-response association of both frequency and duration of reflux with EA [205]. In this study, any reflux was associated with approximately 8-fold increased risk, but risk was increased up to 20-fold in those with very frequent and severe reflux [205]. Several other studies published since then have confirmed a dose-response association between reflux and EA [39, 40,137,206], but the relative risks have been almost half as strong as those reported in

Lagergren's original study (approximately 4-fold overall and 8-fold for those having the highest frequencies).

Consistency of the results across studies, dose-response relationship, and strength of association all implicate a causal relationship between reflux and EA. There is also a strong association between acid reflux and BE [207]. Recurrent acid reflux may cause EA by inducing metaplasia in the mucosa of the lower part of the esophagus and changing the local squamous tissue into BE. Unlike EA, ESCC is not caused by acid reflux.

Obesity

Two meta-analyses [208,209] have summarized the association of overweight (body mass index from 25 to < 30 Kg/m^2) and obesity (body mass index of 30 Kg/m^2 or higher) with EA. The more recent of these two [209] identified 14 studies and found that EA risk increased approximately 2–3-fold in overweight and obese individuals. It also observed a dose-response relationship; risk was slightly higher in obese than in overweight people. Since the publication of this meta-analysis, several additional population-based or cohort studies of obesity and EA risk have been published, which have also shown 2–3-fold increased risks and dose-response relationships [39,40,210,211].

Since this association is consistent across a large number of studies, is moderately strong, and has a dose-response pattern, it is highly likely that it is causal. In fact, increasing weight trends in the United States and other Western countries may be partially responsible for increasing incidence rates of EA in these countries. Several mechanisms have been suggested to explain the causal link [212]. Obesity increases intra-abdominal pressure which in turn could increase risk of gastroesophageal reflux and BE. In fact, obesity has been convincingly linked to GERD [208,213], and measures of central obesity, such as waist-to-hip ratio and abdominal circumference, have been linked to BE [214,215]. In addition, adipose tissue is physiologically active and may increase risk via modulation of levels of polypeptides such as ghrelin, leptin, adiponectin, and insulin-like growth factors [212].

Hiatal Hernia

Hiatal hernia can increase EA risk by increasing gastroesophageal acid reflux. Many studies have investigated the association of hiatal hernia with EA, and all have found increased risks, with relative risks ranging 2–6-fold [135,137,138,206]. Also, among people with BE, having a large hiatal hernia increases the risk of high grade dysplasia and EA [216,217]. In contrast to EA, the risk of ESCC is not increased by the presence of a hiatal hernia.

Achalasia

Achalasia is a motility disorder of the esophagus characterized by aperistalsis in the distal esophagus and loss of LES relaxation. This lead to stasis and fermentation of food in the esophagus, which may cause increased inflammation and higher EC risk [218].

Most case series have reported EC in 3–7% of achalasia patients [219], which is far higher than the rates seen in normal population. Follow-up studies of achalasia patients have consistently shown substantially increased risk of EC [220–223], but because the size of achalasia cohorts have been small, different magnitudes of relative risks have been reported. One of the largest of these cohorts that has had a long-term follow-up is conducted in Sweden. The latest results from this cohort [223] showed a 10-fold increased risk of both ESCC and EA in achalasia patients compared to the rest of the population.

Substantial increases in risk of EC have also been reported in patients with other benign diseases that cause esophageal obstruction, including patients with esophageal webs and lye stricture [224].

Gastric atrophy

Atrophy of the gastric mucosa has long been known to be a precursor lesion for gastric cancer [225]. However, finding an association between gastric atrophy and ESCC is a relatively recent finding.

A Swedish study showed for the first time that pernicious anemia patients had a 3-fold higher risk of ESCC than the general population [226,227]. Because a main feature of pernicious anemia is gastric atrophy, it was hypothesized that gastric atrophy may also cause ESCC.

Gastric atrophy can be detected either by direct histologic examination of gastric biopsies or by measuring serum pepsinogens, pro-enzymes that are secreted by the gastric epithelial cells; low serum pepsinogen I (PGI) or low serum pepsinogen I/pepsinogen II (PGI/II) ratio indicate atrophy [228,229]. Ye and colleagues published the first case-control evaluation of the association between serum pepsinogens and ESCC risk and found a 4-fold increased risk of ESCC in patients with low serum PGI [230]. These findings were confirmed by a case-control study from Japan that found gastric atrophy, diagnosed serologically or histologically, was associated with a 4-fold or higher increased risk of superficial ESCC [231]. Also, a case-control study from Linxian showed an almost linear association between the lower serum PGI/II and risk of ESD [232]. A recent study from Netherlands found that patients with gastric atrophy had a 2-fold higher risk of ESCC than the general population [233] but ESCC risk did not increase with increasing severity of atrophy, which suggested that the association of gastric atrophy and ESCC may be confounded by other factors such as smoking. There is no evidence for an increased risk of EA associated with atrophy [227,230].

How could gastric atrophy increase the risk of ESCC? Because gastric glands disappear in atrophy, acid secretion is reduced, which results in a proliferation of bacteria in the stomach [234]. These bacteria, in turn, may increase the production of carcinogens such as nitrosamines and acetaldehyde, which may explain association between gastric atrophy and gastric and esophageal neoplasia.

Poor oral hygiene and tooth loss

Like several other etiological hypotheses, the hypothesis that poor oral health could potentially be a risk factor for EC dates back at least seven decades [3,89]. American physicians earlier in this century suggested that patients with EC had poorer dental hygiene than the general population [3]. Chinese scientists also found that the prevalence of dental caries was higher in people from high-risk areas than other Chinese people, and oral hygiene was poorer in patients with EC or ESD than other people (reviewed by CS Yang [89]). More recently, a long-term prospective cohort study conducted in Linxian showed that tooth loss was associated with a small but statistically significant increase in ESCC risk (relative risk of 1.3, comparing above versus lower than median) [193,235]. Subsequent case-control studies in South America [236], Central Europe [236], Japan [237], and Iran [238] also showed that tooth loss was associated with a 2–3-fold increased risk of EC. Furthermore, other studies from China and Iran showed a significantly increased risk of ESD associated with poor oral health [239,240].

The associations found between tooth loss or poor oral hygiene with EC could be confounded by smoking, alcohol consumption, low socioeconomic status, or other factors. Some of the aforementioned studies have extensively addressed these issues. For example, Abnet et al. [238] examined the associations in people who never smoked or drank and the results did not

change materially. Other issues still exist. In some studies, clear dose-response associations were not observed and, in some, associations were seen with some markers of oral health but not with others. In a small study in Finland, no association was seen between tooth loss and EC risk [194]. Nevertheless, the accumulated data are definitely intriguing.

If these associations are indeed causal, there are several mechanistic hypotheses [194]: (a) changes in oral microbial flora which result in both poor oral health and in increased production of carcinogens such as nitrosamines and acetaldehyde; (b) physical irritation and damage to the esophageal epithelium due to swallowing unchewed food; (c) change in dietary patterns and nutrient intake due to poor dentition; (d) infection of the esophageal mucosa with an oral microorganism; (e) genetic factors that affect both oral health and EC. Among these, the first proposed mechanism seems most intriguing and could be tested in several ways, for example by comparing nitrosamine and acetaldehyde production among people with and without ESD.

Nearly all studies of the association between poor oral health and EC risk have been done in areas that ESCC constitutes the large majority of the cases, so the results are most relevant to ESCC. To date, there have been no studies specifically evaluating an association between poor oral health and EA.

Occupational exposure

EC is generally not considered an occupational cancer. However, several studies have suggested that occupational exposure to asbestos could increase EC risk between 2-fold and 16-fold [241–245]. Other studies have found increased EC risk in relation to occupational exposure to silica [246–249]. However, other studies have shown no or only very slight increased risk with these occupational exposures. For example, Kang found only 8% increased risk of EC in relation to asbestos exposure [250]. Further research is required in this area.

IARC has classified crystalline silica and asbestos as a carcinogenic to humans (Group 1 carcinogen), mostly because of their effect in causing lung cancer and mesothelioma [251, 252].

Low socioeconomic status

It has long been known that EC is a disease of the poor and the socially disadvantaged. In his 1939 paper, Watson writes "… it should be noted that a large percentage of the patients in this series [of 771 EC cases] are … of station in life definitely below average, and further, that 9 out of 10 patients with this disease are in the lower middle class socially, and on the whole financially insecure" [4].

Since then, a large number of epidemiologic studies have confirmed that EC risk is higher in populations with lower socioeconomic status (SES) [12,29,31,51,240,253–260]. These studies have had different designs (case-control, cohort, and comparisons of incident cases with the general population), used different SES indicators (e.g., income and education), and were from all parts of the world (North America, Europe, East and South Asia, the Middle East, and Africa). Therefore, the finding that EC is more common in lower SES groups is nearly universal.

It is difficult to assign an approximate relative risk to SES, partly because SES itself is not a well-defined entity, and various SES indicators, such as education and income, may have different meanings in different populations. However, using various indicators, most studies have reported an increased risk of 2–4-fold among those with lower compared to those with higher SES.

Low education and low income are not direct biologic causes of EC. Attempts have been made to identify more direct causal mechanisms, such as higher use of tobacco or alcohol or poorer nutrition among people with lower SES. However, these attempts have not yielded consistent results.

The majority of studies of SES and EC have been conducted in populations with high risk of ESCC, so there is little doubt that ESCC is inversely associated with SES. There is less data available for EA; three recent studies suggested that SES is inversely associated with EA too [31,256,257] but one study did not find an association [261].

Summary and conclusions

Over the past century, a large number of factors have been tested for their potential association with EC risk. Whereas older studies mainly investigated the etiology of ESCC, the newer studies in Western countries have also investigated the causes of EA.

The results of these studies have established excessive use of alcohol, tobacco use, low intake of fresh fruit and vegetables, low socioeconomic status, and drinking maté as risk factors for ESCC. Also, certain physiologic or pathologic conditions, such as gastric atrophy and achalasia, may predispose people to higher risk of ESCC. There are other potential but as yet unsubstantiated risk factors. For example, PAHs and acetaldehyde may play an important role in the etiology of ESCC in high-risk areas of Iran or China, but this remains to be verified in future studies.

Three important risk factors have been identified for EA: gastroesophageal acid reflux, obesity, and smoking. Absence of *H. pylori* in the stomach is also becoming increasingly recognized as a risk factor. Other factors, such as the use of LES-relaxing medications need to be further studied.

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Table 1

Environmental risk factors and predisposing conditions for esophageal cancer

Habits	
Tobacco use	• There is strong evidence for a causal association between tobacco use and both ESCC and EA. • Tobacco use is more strongly associated with ESCC (3–7-fold increased risk) than EA (2-fold increased risk).
Alcohol consumption	• Excessive alcohol use (>3 drinks/day) is a strong risk factor for ESCC, increasing risk by 3–5-fold. • There is little evidence for an association between alcohol use and EA risk.
Opium use	• Studies point toward an association with ESCC (2-fold increased risk), but the level of evidence is not yet strong.
Drinking maté	• Epidemiologic studies have consistently shown an increased risk of EC associated with drinking maté, especially hot maté. • Most studies have been conducted in areas with high prevalence of ESCC.
Ingestions of high-temperature foods and drinks	• A large number of epidemiologic studies have investigated the association of hot foods and drinks with EC, but the results are still controversial.
Consumption of carbonated soft drinks	• Results from epidemiologic studies have shown no evidence for an increased risk of EA or ESCC associated with drinking carbonated soft drinks.
Eating pickled vegetables	• Eating pickled vegetables was once considered an important risk factor for EC in China, but the results of epidemiologic studies have been controversial.
Nutritional deficiencies	
Low intake of fresh fruits and vegetables	• There is a large body of evidence linking low intake of fresh fruits and vegetables to higher risk of EC, especially ESCC. • Eating 50 additional grams of fruits and vegetables per day may decrease EC risk by 20%.
Vitamin and micronutrient deficiency	• Most vitamins and minerals do not change EC risk. However, intake of selenium in selenium-deficient populations may decrease ESCC risk, especially in younger people.
Medications	
Non-steroidal anti-inflammatory drugs (NSAIDs)	• There is evidence that intake of aspirin and other NSAIDs may decrease both ESCC and EA by approximately 40%.
Medications that relax lower esophageal sphincter (LES)	• LES-relaxing drugs have been suggested to increase EA risk by increasing acid reflux. However, the results of epidemiologic studies have been controversial.
H2 receptor antagonists	• Although some studies have shown an increased risk of EA associated with taking these drugs, these results may be confounded by inadequate adjustment for acid reflux.
Infections	
Helicobacter pylori	• Presence of *H. pylori* in the stomach is associated with a 50% reduced risk of EA. • There is no clear pattern of association between *H. pylori* and ESCC.
Human papillomavirus (HPV)	• A large number of epidemiologic studies have investigated the association of HPV with EC, but the results are still controversial.
Chemical carcinogens	

Polycyclic aromatic hydrocarbons (PAHs)	• There is circumstantial evidence linking PAHs to EC, but there is no convincing evidence from case- control or cohort studies.
N-nitroso compounds (NNCs)	• Intake of processed meat, which contains large amounts of NNCs, has been consistently linked to higher EC risk, but more evidence is required to make a causal link between NNCs and EC.
Acetaldehyde	• Acetaldehyde may be the common denominator linking alcohol consumption, poor oral health, and gastric atrophy to EC. • The most convincing evidence for an association between acetaldehyde and EC comes from ADH and ALDH polymorphism studies, but more evidence is needed to make a causal link.
Fumonisins	• Ecologic studies have linked fumonisin exposure to increased risk of EC, but additional individual based epidemiologic studies are needed to establish or refute this association.
Predisposing conditions	
Gastroesophageal acid reflux	• Acid reflux is one of the main risk factors for EA, increasing its risk by approximately 5-fold.
Obesity	• There is strong evidence for a causal association between obesity and higher risk of EA.
Hiatal hernia	• Hiatal hernia increases EA risk by 2–6-fold, most likely by increasing gastroesophageal acid reflux.
Achalasia	• Achalasia increases the risk of both EA and ESCC by approximately 10-fold.
Gastric atrophy	• A few studies have shown that gastric atrophy could be a risk factor for ESCC but more studies are needed to confirm these results. There is no evidence for an association between gastric atrophy and EA.
Poor oral health	• Several epidemiologic studies have linked poor oral health to higher risk of EC, especially ESCC, but more evidence is required to conclude that there is a causal association.
Others	
Occupational exposure	• A number of studies have linked occupational exposure to silica and asbestos to higher risk of EC, but the results have not been entirely consistent.
Low socioeconomic status	• Low socioeconomic status is a risk factor for EC. It is a definite risk factor for ESCC, but it may also increase risk of EA.

EC: esophageal cancer; ESCC: esophageal squamous cell carcinoma; EA: esophageal adenocarcinoma