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Epidemiology of Esophageal Squamous Cell Carcinoma

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Abstract

Esophageal squamous cell carcinoma (ESCC) accounts for about 90% of the 456,000 incident esophageal cancers each year. Regions of high incidence include Eastern to Central Asia, along the Rift Valley in East Africa, and into South Africa. There are many causes of ESCC, which vary among regions. Early studies in France associated smoking cigarettes and heavy alcohol consumption with high rates of ESCC, but these factors can't explain the high incidence in other regions. We discuss other risk factors for ESCC, including polycyclic aromatic hydrocarbons from a variety of sources, high-temperature foods, diet, and oral health and the microbiome—all require further research. A growing list of defined genomic regions affect susceptibility, but large genome-wide association studies have been conducted only with ethnic Chinese subjects; more studies are called for in the rest of Asia and Africa. ESCC has been understudied, but growing infrastructure in more high-incidence countries will allow rapid progress in our understanding.

Esophageal cancer, the sixth leading cause of cancer death in the world, is a complex disease with many causes which differ by histologic type and the population it is found in[1]. Esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EADC), have almost completely distinct geographic patterns, time trends, and primary risk factors. Patients with either cancer have a poor prognosis because of the late-stage at diagnosis for most patients. The causes of ESCC vary—the primary agents that cause ESCC in one population might not associated with this cancer in another. We briefly review the descriptive epidemiology of ESCC and review of confirmed and suspected risk factors.

Descriptive Epidemiology

The International Agency for Research on Cancer (IARC) estimates that there were about 450,000 cases of esophageal cancer in 2012: 88% cases of ESCC and 12% cases of EADC[2]. The geographic distribution of ESCC varies greatly, with more than 10-fold differences between countries (Figure 1). The highest incidence rates stretch from Eastern to Central Asia with another band running along the Indian Ocean coast of Africa along the Great Rift Valley. A third area with higher incidence was centralized around Uruguay in South America and encompassed the entire Gaucho Region of the continent, but lately the rates in Uruguay itself have decreased.

Although there are differences in rates among countries, there are also notable differences within countries. This is well documented in China—cancer mortality was mapped at the county level in the 1970s, and although rates have decreased in recent years, they vary among regions[3]. Within China, rates of esophageal cancer can vary 10-fold and there are sharp differences over short geographic distances (Figure 2). The most studied region of China is the North Central Taihung Mountain range. In small areas of this region, ESCC may be at or near the leading cause of death, with incidence rates exceeding 125/100,000/year[4]. The large population of China and the high rates lead to China having about half of all ESCC cases on earth. These regions often have high incidence rates of gastric cardia adenocarcinoma and ESCC; these two cancers account for up 25% of deaths in some areas. High rates of ESCC and gastric cardia adenocarcinoma are also reported in Northeastern Iran[5], but there is no clear explanation for this phenomenon.

Overall, ESCC is more common in men (69%) than women (31%). However, this ratio varies among low-risk areas, like the United States (US) where the ratio of men:women can reach 4:1, and high-incidence areas of China and Iran, where the ratio is lower, approaching or even exceeding 1:1[2]. About 12 countries are thought to have higher rates in women than men, including several in north east Africa and the Middle East. This variation in sex ratio likely reflects etiologic factors. Early studies from France[6] and later studies from Western Countries showed that risk for ESCC is increased by smoking tobacco and heavy consumption of alcoholic beverages. These behaviors were historically more prevalent in men than in women. In high-incidence areas, tobacco and alcohol may contribute little (or not at all) to ESCC incidence, because they are rarely used in the population (e.g. alcoholic beverages in Iran). In these areas, key risk factors are less well described, but seem to be less sex-dependent.

Over the last 40 years there have been large changes in the incidence in the different types of esophageal cancers, and these trends are region specific. In the US[7] (Figure 3), Europe[8], Australia, and many other Western countries, the incidence of ESCC had been decreasing for several decades, whereas the incidence of adenocarcinoma has increased. In Eastern Europe[8], Japan, and South America, ESCC still predominates[2]. In most of Asia and Sub-Saharan Africa, esophageal carcinomas occur almost exclusively as ESCCs. As noted, the co-occurrence of gastric cardia adenocarcinoma in populations with high incidence of ESCC[5, 9] creates challenges to tracking esophageal adenocarcinoma, since there is no definitive system for separating adenocarcinomas than span the esophago-gastric junction.

Within countries, the proportion of ESCC and EADC can vary greatly among population subgroups. For example, in the US, African-Americans are 7-fold more likely to be diagnosed with ESCC than EADC, whereas US whites are about 4-fold more likely to develop EADC than ESCC[7]. The reasons for this large difference are not clear and can’t be fully explained by known risk factors[10].

The ESCC incidence is decreasing in many Western countries, especially among men, probably due to decreased smoking prevalence. But these decreases are not universal. For example, the IARC projects almost no change in the rates of ESCC in Australian, Japanese, or UK men between now and 2030[11]. Incidence rates might increase in women in these

same some countries, likely due to women's later peak in cigarette smoking rates and possibly due to changing social mores regarding alcoholic beverage consumption by women. Furthermore, the number of cancer cases is unlikely to decrease even in the presence of falling rates, because of the growing and aging populations in developing countries, which have most ESCC cases.

Known and Suspected Risk Factors

The etiology of ESCC is multi-factorial and strongly population dependent. A study in the US estimated a population-attributable risk of 89% using only cigarette smoking, alcoholic beverage consumption, and low consumption of fruits and vegetables[12]. In contrast, a large cohort study conducted in a high-incidence region of China found that tobacco smoking had little role in ESCC etiology and that modest alcohol consumption was associated with lower risk of the disease than in non-consumers[13]. This lack of effects seems to be explained partly by lower exposure rates, but our understanding remains incomplete. Given these large differences in etiology, population-specific estimates are needed for all risk factors and we can draw few conclusions that apply to ESCC globally. A summary of risk factors with the strongest evidence is provided in Table 1; these have been divided into those confirmed by formal review groups and those for which the level of evidence is not yet strong enough to consider them confirmed.

Socioeconomic status (SES)

SES is a complex construct representing many aspects of the human condition, yet it is one of the most consistent risk factors for ESCC—even after comprehensive adjustment for tobacco, alcohol, age, and many other potential risk factors. In Western countries, where studies often include people with a wide range of educational histories and income, SES is still associated with larger risks than might be expected. For example, in Sweden, notable differences in risk are associated with working in a manual trade or having less than a high school education[14] and in the US a statistically significant association was evident with income[15]. What may be more surprising is that similar associations were observed in studies conducted in economically developing populations with compressed social status among participants[13, 16, 17], some which only included subsistence farmers. It can be a challenge to use SES as either a main effect or as a confounder in models that examine other exposures, given the multi-dimensional nature of the construct. One promising method uses multiple correspondence analysis to build a composite wealth score from many underlying correlated SES indicators[18]. This provides a single coherent variable and reduces the role of chance and correlation among SES indicator selection. In sum, we don't know how SES affects risk, but this is an important question that does not appear to be solely a problem of residual confounding from known risk factors.

Tobacco

Tobacco smoking and chewing are large risk factors for ESCC in economically developed countries. These account for a large proportion of population-attributable risk[12] (an approximate 3–9-fold relative risk [RR] in current smokers)[19–21]. But relatively weaker effects and lower attributable risk[22] have been reported in economically-developing

countries (RR of approximately 1.5)[13, 16, 23, 24]. In addition to cigarettes, there are other forms of tobacco for use, such as pipe, cigar, hookah, and chewing tobacco. Pipe and cigar have been demonstrated to convey risks similar risk to cigarettes[25]. Hookah and other forms of water pipe historically were predominantly used in the Middle-Eastern countries, but of late are becoming popular with young people worldwide. Meta-analyses reported pooled odds ratio of 3–4[26, 27], but there is little consistency in the risks estimates, so the true risk associated with water pipe requires further investigation. Some studies reported that certain types of chewed tobacco carry risk of a magnitude greater than cigarettes or water pipe[23, 28], but the forms of chewed tobacco and the adjuvants used in the preparations vary among countries—a complete picture of the risk will require population-specific estimates.

Both exposure intensity and duration have been reported to be relevant for risk of ESCC conveyed by smoking tobacco[13, 20, 21]. A detailed analysis of these 2 aspects of exposure showed an inverse delivery rate pattern, whereby for equal pack-years smoking more cigarettes/day for shorter duration was less harmful than smoking fewer cigarettes/day for longer duration[29], highlighting the importance of duration and the potential harm that may arise from even very modest intensity but long standing tobacco smoking[30].

Tobacco-specific nitrosamines (TSNA) and polycyclic aromatic hydrocarbons (PAH) are thought to be the major carcinogenic substances in tobacco. The Shanghai Cohort Study revealed that Chinese smokers were exposed to less TSNA compared with U.S. smokers[31]. But these investigators also reported that the urinary concentration of N'-nitrosonornicotine was very strongly linked to ESCC risk and inferred that this may the causative agent in these tobacco smokers[32].

Alcoholic beverages

Alcoholic beverage consumption has been causally linked to ESCC by IARC[33] and the World Cancer Research Fund[4]. Alcohol might increase risk for ESCC because acetaldehyde, a class 1 carcinogen, is the first metabolite of ethanol metabolism[34, 35]. Microorganisms in oral cavity also produce acetaldehyde from ethanol and could contribute to alcohol's carcinogenic effects[36–38]. Alcoholic beverages and other foods[39] can also contain acetaldehyde, leading to direct exposure without ethanol metabolism.

Most epidemiologic studies have confirmed that alcoholic beverages are a risk factor for ESCC in economically developing and developed areas, although their carcinogenic effects vary with degree of consumption. Alcohol consumption increased the risk of ESCC by 1.6- to 5.3-fold in Asian countries including China[40–47], Iran[23], Japan[40], and India[48, 49], and about 3-fold in Africa[50–53] and South America[54–57]. In many areas with low incidence rates of ESCC, however, the relationship between alcohol and ESCC is notably stronger, with about 6-fold increase in risk in Europe[58–64] and 9-fold in North America among consumers of alcohol[10, 65–67]. Drinking patterns have been understudied and the risks associated with binge drinking are important to investigate. The population-attributable fraction of ESCC due to alcoholic beverages was reported to be large (72.4%) in the US, but much lower in China (10.9%), which could be due to differences in levels of exposure[12, 22].

Even though alcohol intake is strongly associated with ESCC in most studies, a J-shaped rather than linear relationship was found between alcohol consumption and ESCC risk in many previous studies[10, 58, 68, 69]. The Million Women Study associated low alcohol intake (<70 g/week) with a decreased risk of ESCC; heavy intake of alcohol (<150 g/week) increased the risk significantly[70]. Whether this reduced risk with moderate intake is real or due to unmeasured confounders has not been established. Many cohort studies only collect data on current or recent alcohol consumption. Future studies should include data on lifetime alcohol exposure, to allow full modelling of this important exposure. Given the apparent different associations between alcohol and risk of ESCC (possible J-shaped but clearly high risk with high intake), breast cancer (modest linear increased risk), and kidney cancer (strong reduction in risks with increasing intake even at high levels), for example, it seems likely that different mechanisms are involved at different organ sites.

Tobacco and alcohol may interact to increase the risk of ESCC compared with the predicted multiplicative risk of either one alone[71]. Although many studies have reported interactions, some large cohort studies have not found evidence for this effect modification[19]. Cohort members tend to have healthier lifestyles than subjects enrolled through population-based case–control studies; the lack of interaction observed in cohort studies may be due to the low number of heavy consumers of alcohol. Nevertheless, even without an interaction, heavy consumption of alcohol paired with tobacco consumption greatly increases risk of ESCC.

PAHs

PAHs cause cancer at multiple sites through some exposure routes. Exposure to high levels of PAHs from non-tobacco sources could mask the effects of PAHs from cigarettes. So the apparently lower risk ESCC among tobacco smokers in some populations may be due to PAHs from other sources. Iranian[72], Chinese[73], and Brazilian[74] high-risk populations have high exposure to PAHs—even non-smokers. The PAHs could come from certain foods, beverages, or cooking and heating methods. This exposure seems to be a constant among populations in economically developing countries with high incidences of ESCC. A case–control study measured PAH exposure in normal esophageal tissues of cases and controls and reported odds ratios more than 25 for the most-exposed quintile[75]. This finding strongly implicates PAHs in esophageal squamous cell carcinogenesis, but confirmation in prospective studies is required.

Betel quid

Betel quid consists of a betel leaf wrapped around areca nut with or without tobacco and other additives. Chewing betel quid is common in South and South-East Asian countries. The IARC has confirmed it as a risk factor for ESCC[76]. Betel quid chewing is common in South and South-East Asian countries, with the independent relative risk values of approximate 2.2–5.6[77–80]. The combination of betel quid and tobacco increases relative risk by 2.3- to 3.5-fold compared to betel quid alone[78, 79]. Betel quid chewers in some populations are also frequently tobacco smokers[77]—betel and tobacco might have synergistic effects on ESCC risk[77, 78].

Diet

Numerous studies of many designs in different locales have examined whether diet, foods, or specific nutrients are associated with ESCC risk. Broader measures of diet quality using pre-specified indices, such as the Healthy Eating Index, may be a useful construct for assessing dietary effects within a population and adherence has been associated with lower risk of ESCC[81]. But poor diet can be strongly confounded by other important risk factors already discussed including tobacco smoking, alcoholic beverage consumption, and low SES. And given the substantial etiologic heterogeneity for ESCC, drawing strong conclusions for dietary factors is further challenged by population differences in other major risk factors.

Many cohort studies have failed to associate individual foods or nutrients with ESCC risk—even those in populations that appear to be deficient in the tested nutrients. This appears to mean that it is not poor diet in general that increases risk of ESCC. Rather, either any real effects on risk are probably mediated by a limited list of specific agents that have not been appropriately tested, or by small contributions from a wide variety of different foods. Conclusive evidence for specific nutrients could lead to prevention strategies that involve fortification, supplementation, avoidance, or reformulation. It is important to remember that regardless of whether specific dietary agents affect risk of ESCC, diet affects risk for many diseases, and except in the most highly affected populations, dietary choices should probably be based on their effect on overall health and mortality—not risks of individual cancers[82].

Vegetables and fruits

Systematic review of all studies of diet and cancer risk concluded that higher intake of fruits and vegetables probably decreases the risk of esophageal cancer. Each increment of 50 g/day of raw vegetables was associated with 31% decrease in risk of esophageal cancer, while the same increment intake of fruit was associated with 22% decrease[12]. However, these estimates for fruits and vegetables may be over-estimates because much of the evidence comes from case-control studies, which are more susceptible to bias than cohort studies. The Continuous Update Project for the esophagus concluded that the evidence supporting greater consumption of vegetables decreases the risk of ESCC is “limited”, which was downgraded from “probable” in the Second Expert Report[4]. Each increment of 100 g/day of vegetables was associated with reduced risk of ESCC by 9% (non-significant), whereas the same increment intake of fruit was associated with reduced risk by 16% (significant)[4]. Increasing variety in consumption of vegetables and fruits combined and fruit consumption alone was associated with a 12% and 24% reduction in risk of ESCC, respectively—at least among smokers[83].

Pickled vegetables

Asian pickled vegetables could contribute to development of ESCC and gastric cancer[84, 85]. In high-risk areas of China, pickled vegetables were an integral part of the diet in many families and eaten 9–12 months a year[9]. The vegetable pickling process could generate potentially carcinogenic mycotoxins and N-nitroso compounds[9, 86, 87]. The mutagenicity and carcinogenicity of pickled vegetables have been shown in some animal and in vitro studies[86, 88]. An IARC Working Group concluded that there was limited evidence from

humans and inadequate evidence from experimental animals to support the carcinogenicity of pickled vegetables[89]. A meta-analysis associated intake of pickled vegetables with a 2-fold higher risk of ESCC[90]. Well-designed prospective studies are warranted, as most data come from retrospective studies with high heterogeneity in the results.

Micronutrients

There is evidence from mechanistic and human studies that micronutrients, including vitamin A, retinol, thiamin, riboflavin, calcium, iron, zinc, pro-vitamin A carotenoids, or β-cryptoxanthin, contribute to development of ESCC[91–97]. Evidence for these exposures was judged as "limited – no conclusion". It is noteworthy that nutrient supplements are not currently recommended for ESCC prevention in the general population[94, 98]. A 6-year randomized trial conducted in China showed that multivitamins did not reduce risk in a sub-population of persons at high risk for ESCC or affected any other endpoint examined[99]. This negative result is particularly notable given the low nutrient status of this population, which should be the most likely to benefit from these agents, and the long-post intervention follow-up time, which could have detected late effects.

In contrast, there is increasing evidence that selenium and riboflavin affect risk of ESCC—at least in some populations of low nutritional status for these nutrients. High exposure to selenium has been associated with decreased risk of ESCC[100–104]. The Nutrition Intervention Trial conducted in the general population of Linxian, China, a region with epidemic rates of ESCC and nutritional deficiencies showed that riboflavin and niacin daily supplement reduced risk of esophageal cancer by 14% (non-significant) after 5.25 years intervention[105]. A 10-year follow-up study showed selenium, β-carotene, and α-tocopherol supplements significantly reduced risk of esophageal cancer death by 17%, but only among participants younger than 55 years old[106]. Analogous to the hypothesis for folate and colorectal cancer this age interaction may suggest that selenium might prevent ESCC only when it is supplemented before advanced preneoplasia is evident. An independent chemoprevention trial focused on precancerous lesion reported that selenium could increase regression and reduce regression in subjects with mild esophageal squamous dysplasia[107].

Hot food and beverages

Consumption of hot food and beverages has been associated with increased risk of ESCC in multiple studies[18]. Numerous case-control studies in Uruguay and the Gaucho Region of South America reported increased risk in subjects that drink the traditional herbal beverage maté, which is consumed in large volumes (several liters per day) at high temperature[108]. One limitation of these studies was their use of a non-validated qualitative questionnaire. Several recent studies have used quantitative measurements of temperature of drinks; these found that in several high-incidence areas, typical temperatures are extraordinarily high, including in Iran[109] and in Tanzania[110]. In Tanzania, the mean temperature at first sip exceeded 70°C, which would carry a high risk based on the study from Iran. The good news is that the adverse risk of high temperature beverages and foods might be at least partially mitigated by modestly lowering the temperature of consumption rather than avoiding consumption altogether. This would seem to be a more achievable public health goal than asking people to stop consuming beverages that have important roles in many local cultures.

Most studies of coffee have found no adverse associations, but this may be because few people in heavy coffee-consuming cultures drink it at a temperature above 60°C. Studies in animal models of ESCC showed that high-temperature water can potentiate the effects of chemical carcinogens, through thermal irritation;[111] this potentiation is thought to be the primary method of action. Several recent studies have called into question whether the adverse effects of maté on risk of esophageal cancer might also be mediated by contamination with PAHs[112]. Reports that high consumption of maté may be associated with increased risk at tumor sites without contact with the hot beverage, such as the bladder and kidney, provide support for this hypothesis[113].

Body mass index (BMI)

Increased BMI is frequently associated with a lower risk of ESCC[114, 115]. However, this association is routinely and plausibly attributed to the combined effects of undiagnosed cancer and frank or incipient dysphagia leading to weight loss. However, long-term follow-up studies of ESCC have reported this association is evident decades before cancer diagnosis[116], so reverse causation might not be an explanation. It is important to determine the association between BMI at young ages and the risk of ESCC. One study using recalled body size from youth reported an association between higher body weights and ESCC risk, but there have been few studies of this hypothesis[117].

Alternatively, BMI may reflect another physiologic process associated with an etiologically relevant exposure. BMI has a similar association with respiratory disease death that can be detected many years before death[118] and is clearly not caused by dysphagia. Fine particulate matter (such as $PM_{2.5}$) has been linked to chronic obstructive pulmonary disease.[119] Many particles carry carcinogenic substances[120]. Exposure to indoor air pollution is common and has been associated with ESCC risk in many populations with high incidence of ESCC[121, 122]. Indoor air pollution might induce weight loss linked to chronic obstructive pulmonary disease and ESCC upon exposure to carcinogens.

Reproductive factors

The male predominance of ESCC can be mostly accounted for by differences between sexes in exposure to risk factors such as tobacco smoking and alcohol consumption in Western countries, but hormonal factors should be investigated. A few studies have examined factors such as parity, breast feeding, menopause, or use of tamoxifen[123–125] and found some apparently protective effects that could be interpreted as benefit from exposure to estrogen. However, a study in Sweden showed that parity and age at first birth show the same protective associations in men and women. So, associations may be due to confounding by socioeconomic status or other non-hormonal factors[126].

Medical conditions

Several medical conditions have been associated ESCC risk, such as Plummer Vinson Syndrome (symptoms include iron deficiency anemia and webbing of esophageal membranes)[127] and Fanconi Anemia (an inherited bone marrow failure linked to several cancers)[128]. Although the relative risks may be very large, the absolute risks are low, as would be the contribution of these cases to the overall burden of ESCC. A long-term follow-

up study of 448 patients with achalasia (an esophageal motility disorder) in the Netherlands[129] found 15 patients (3.3%) had developed EC with a mean time to cancer diagnosis after presentation of 11 years. This resulted in a relative risk for ESCC of 28 and an incidence rate of 0.34%/year. Esophageal cancer risk is also increased in persons exposed to therapeutic radiation for other medical conditions, such as breast cancer[130].

Poor oral health

Poor oral health, including tooth loss, the frequency of teeth brushing, and poor periodontal health has been examined as a potential risk factor of ESCC[16, 131]. However, too few epidemiologic studies have investigated the potential association between oral hygiene and ESCC worldwide to draw final conclusions. There is evidence from case–control and cohort studies that people with more lost teeth have an approximate 1.5-fold increase in risk of ESCC. Regular tooth brushing has been reported to associate with reduced risk of ESCC in several studies[132], including studies conducted in China[16, 131], Iran[133], Kenya[53] and India[134], whereas tooth loss was not significantly associated with ESCC in the US[135] or Europe[135, 136]. Proposed mechanisms for the association between poor oral health and ESCC include the potential for inflammation associated with periodontal disease to have distant effects. Alternatively, the microbiota associated with periodontal disease and poor oral hygiene might produce secondary metabolites such as acetaldehyde and reactive nitrate and nitrite—precursors to nitrosamines,[137] which are carcinogens associated with ESCC.

Microbiome

The Human Microbiome Project and the availability of inexpensive high-throughput sequencing, has revolutionized the direct study of the role of the human microbiome on human health and disease. The richness, diversity, and exact composition of microbiota in different organs might contribute to development of ESCC. There have been a few studies of associations between the upper digestive tract microbiota and ESCC.

People with lower esophageal microbial richness and saliva microbial diversity may be more prone to develop esophageal squamous dysplasia[138] (the precursor of ESCC) and ESCC[139], respectively in China. Increased richness of *Clostridiales* and *Erysipelotrichales* in the gastric corpus might contribute to esophageal squamous dysplasia and ESCC[140] in Iran. Furthermore, *Porphyromonas gingivalis*, an important periodontal disease pathogen, was detected in 61% of ESCC tissues but not in tissues from healthy subjects. So, *P gingivalis* could affect risk for ESCC[141]. Prospective cohort studies, ideally with repeat sampling from multiple organ sites, including the mouth esophagus, stomach, and stool, will be necessary to investigate the role of the microbiota in ESCC and other gastrointestinal cancers and disease.

Human papilloma virus (HPV)

Numerous studies have attempted to assess whether HPV is an etiologic agent for ESCC. Studies that test for the presence of HPV DNA in ESCC tumor tissue have reported a wide range of prevalence estimates, ranging from 0 to nearly 70%[142], but detecting HPV DNA in the tumor does not mean that it causes tumorigenesis or tumor development.

A large international consortium performed serologic analyses of L1 and E6/E7 to assess the role of HPV in ESCC etiology[143]. Antibodies to E6/E7 are generally considered necessary to determine that a cancer is caused by HPV. This study identified only 4 ESCC samples (0.3% of those tested) that tested positive for HPV16 E6 and E7. This finding indicates a limited role, if any, for HPV in ESCC. A follow-up study of tissue samples confirmed the lack of association between ESCC and HPV DNA, HPV mRNA, or p16(INK4a) upregulation[144]. Studies that sequenced genomes of ESCC samples from diverse countries did not find evidence for integrated HPV DNA[145, 146]. Altogether, evidence indicates that if HPV is an etiologic agent for ESCC, the number of cases caused by these viruses is very low —HPV vaccines are not likely to prevent ESCC.

Genetic Factors

There is long-standing indirect evidence for an inherited component to ESCC etiology. Many studies of genetic factors have reported that a family history of ESCC increases the risk for an incident cancer[147, 148]. Of course, family history comprises a mixture of inherited genes and habits, which are partly determined by genetic factors. The clearest example is tobacco smoking, where the habit is more likely among persons raised with tobacco smokers, but there is also a genetic component to tobacco addiction.

Many diseases are caused by defects in a small number of genes, with Mendelian patterns of inheritance. For ESCC, one of the clearest links is to tylosis. Tylosis is a rare genetic disease characterized by palmoplantar keratoderma (thickening of the skin on the palms and soles of the feet). The genetic basis for tylosis has been elucidated to the point that versions with and without risk of esophageal cancer risk have now been defined. Tylosis with esophageal cancer has been linked to the autosomal dominant mutations in *RHBDF2* gene at 17q25[149]. ESCC risk is high in these subjects, with a young age at onset and penetrance estimated to be as high as 90%[150].

Other familial syndromes have also been linked to increased risk of ESCC, including the inherited bone marrow failure syndrome Fanconi Anemia[128]. Although relative risks for esophageal cancer are high in this group, competing risk for other causes of death, avoidance of high risk behaviors such as tobacco smoking and heavy alcohol drinking, and the young age at onset of these competing risks leads to low absolute risks.

The history of studies of high-prevalence but low-penetrance genetic variants that affect risk for ESCC is similar to that of most diseases. Development of inexpensive genotyping technologies has resulted in many small case–control analyses of individual single-nucleotide polymorphisms (SNPs). Most of these have not produced reproducible results, with one notable exception. Alcoholic beverage consumption and ESCC risk are associated with a well-known phenomenon known as flushing[151]. Flushing occurs in some individuals of East Asian origin when they consume alcoholic beverages. This response occurs because individuals with specific variants in the aldehyde dehydrogenase 2 family gene (*ALDH2*) and an acetaldehyde dehydrogenase gene (*ADH1B*) produce high concentrations of acetaldehyde during consumption of alcohol. The flushing response is unpleasant, so individuals heterozygous for this variant in *ALDH2* tend to avoid alcohol consumption,

whereas individuals who are homozygotes for this variant rarely, if ever, consume alcohol; they have a low risk for alcohol-linked diseases including alcoholism. If people carrying these polymorphic variants consume alcohol, their risk of ESCC increases as high as 43-fold for moderate drinkers and 73-fold for heavy drinkers[152]. Individuals with this variant in *ALDH2* who do not consume alcohol have no increase in risk for ESCC[153].

High-throughput genotyping enabled efficient characterization of the associations between common genetic variants and risk of many diseases by what has come to be known as genome wide association studies (GWAS). Three large studies of people of Chinese descent have published results alone and in combination[153–158], whereas a single study of European subjects included a moderate number of esophageal cancer cases[159]. Collectively these studies have identified several genomic regions associated with ESCC (Table 1). GWAS studies alone can't identify the functional polymorphisms, so although the nearest gene is often used to describe these findings, one should not assume that that gene is the cause of the differential risk.

The main effects from the Chinese studies have revealed several key SNPs, most notably variants in the phospholipase c epsilon 1 gene (*PLCE1*). Remarkably, this SNP is also strongly related to risk of gastric cardia cancer, increasing our understanding the co-occurrence of these tumors of different cell types that develop in adjoining organs[153, 155]. This gene has been knocked out in mice and appears to have multiple roles in modulating carcinogen effects. Mice without this gene are less susceptible to PAH-induced skin cancers[160] and genetically induced colon tumors[161]. Further elucidation of the mechanism of action of this variant is important.

Other identified variants have included genomic regions linked to other cancers including, the region of the caspase 8 gene— a complex region with cancer risk linked to variants in several in-line linkage disequilibrium blocks. One notable finding was the risk of ESCC linked to a polymorphism in the *TP53* gene region[157]. Somatic mutations in this gene are a common feature of ESCC and many other tumors, but common SNPs in the gene have not been linked to other cancers.

Another notable finding from the combined analysis of the three published Chinese GWAS[157] is the apparent association between a variant in the HLA 2 genome region and ESCC risk, at least among subjects collected in the high-incidence Taihung Mountain region of China. Few risk factors specific to this geographic region have been discovered. The HLA region has very complex and long-range linkage disequilibrium patterns that require extensive and detailed follow-up analyses. Further elucidation of this HLA region and its role in ESCC remains a research priority.

Outside these GWAS studies, there has been little progress in understanding the role of common genetic variants and ESCC risk. A few studies have re-examined these polymorphisms in other populations, including a study of polymorphisms in PLCE1 in South Africa[162], a region with high rates of ESCC. That study highlighted the complexity of translating and testing findings from one population to another, given the need to re-sequence the local region to design genotyping assays. Ideally, large GWAS will be carried

out in each high-risk population to provide local results, which can be combined to increase our overall understanding of ESCC pathogenesis. Without this sort of comprehensive assessment, we will not realize the full potential for common genetic variants to help us understand the etiology of ESCC in different populations, nor the potential for these variants to play a role in risk stratification as is being realized in breast cancer[163].

Future Directions

Many Western countries have a decreasing incidence of ESCC, likely due to decreases in tobacco consumption and some moderation in heavy consumption of alcohol. However, ESCC remains a major cause of cancer death worldwide, with greater incidence values than cancers of the pancreas, prostate, cervix, or other tissues (http://globocan.iarc.fr). The concentration of ESCC in impoverished populations with limited research infrastructure has been a major impediment to progress, but studies in Iran[164], East Africa[165], India[28], and elsewhere have added to findings from decades-long research in China. These continued studies should lead to a deeper understanding of the highly fatal and understudied cancer that primarily afflicts our poorest people.

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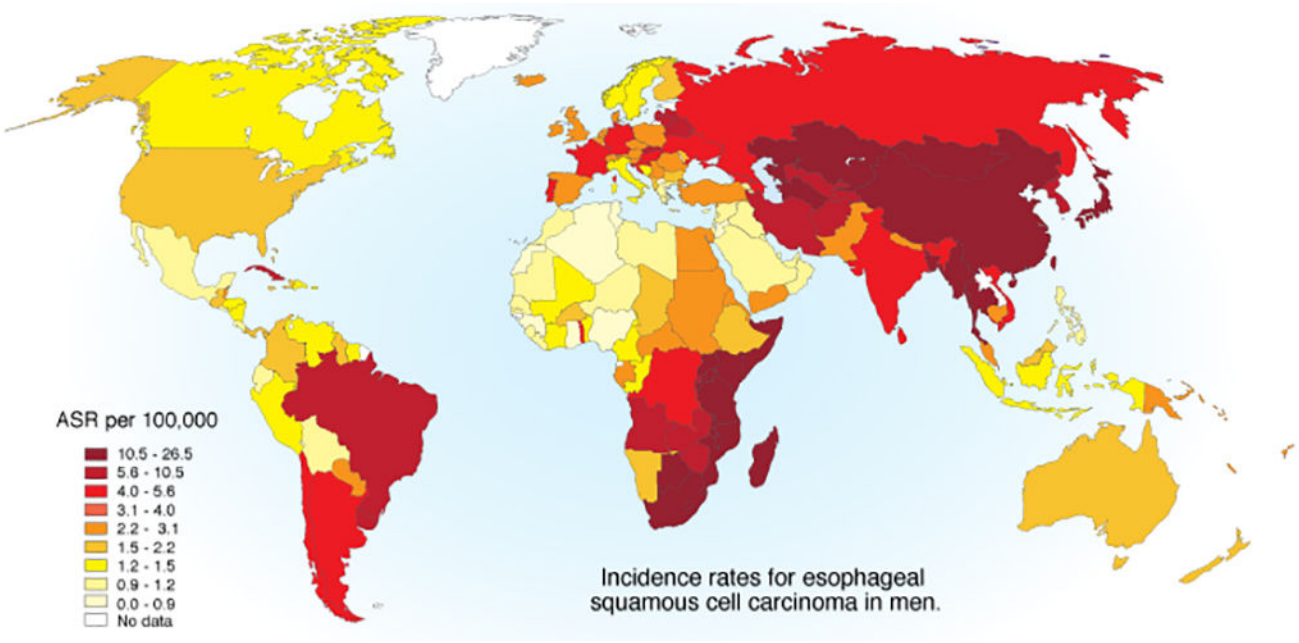

Figure 1.
Incidence rates for esophageal squamous cell carcinoma in men[1]

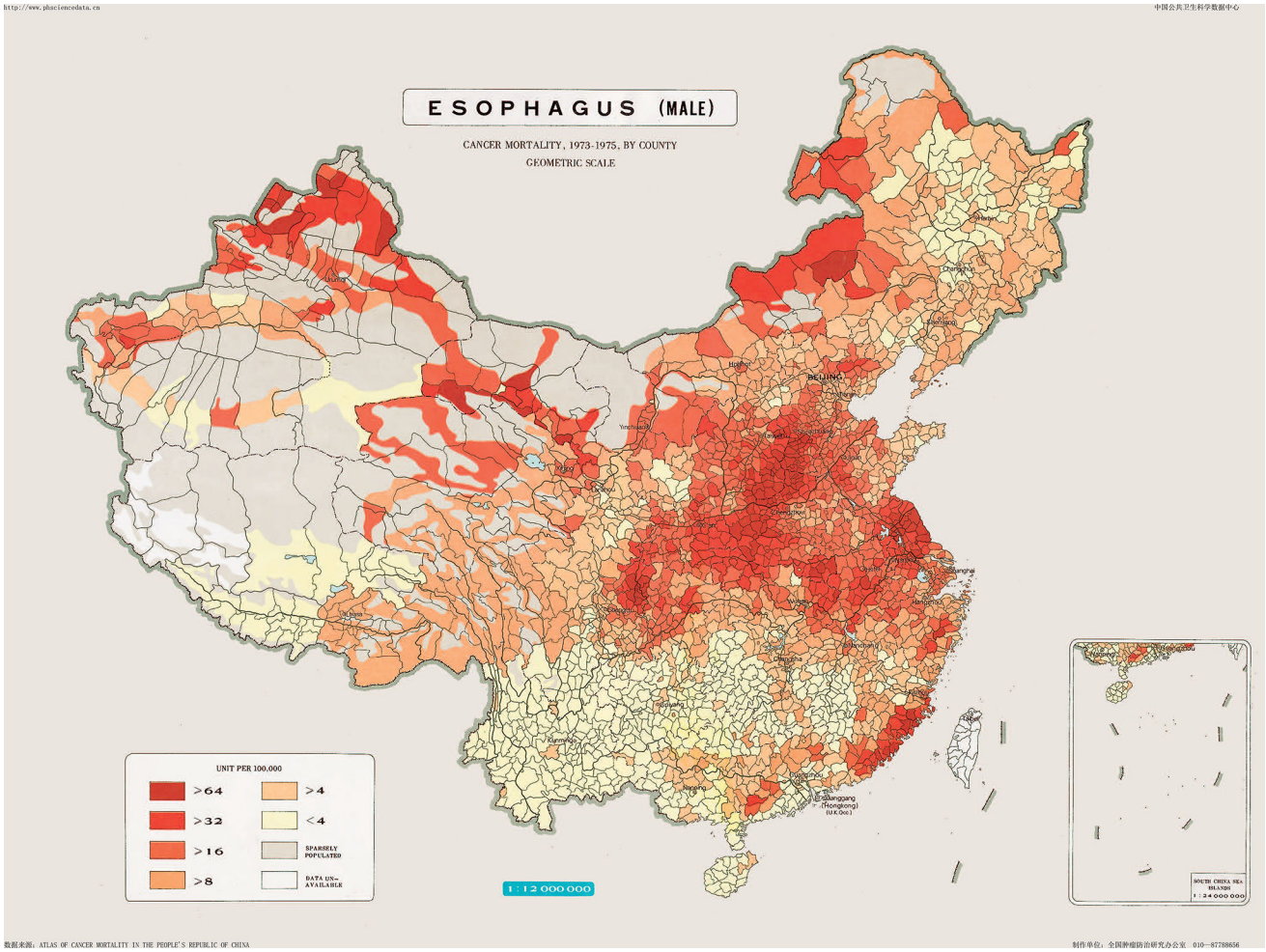

Figure 2.

Esophageal cancer mortality rates in men by county in the People's Republic of China 1973–1975. Used with permission from the National Office for Cancer Prevention and Control, National Cancer Center, Beijing, People's Republic of China

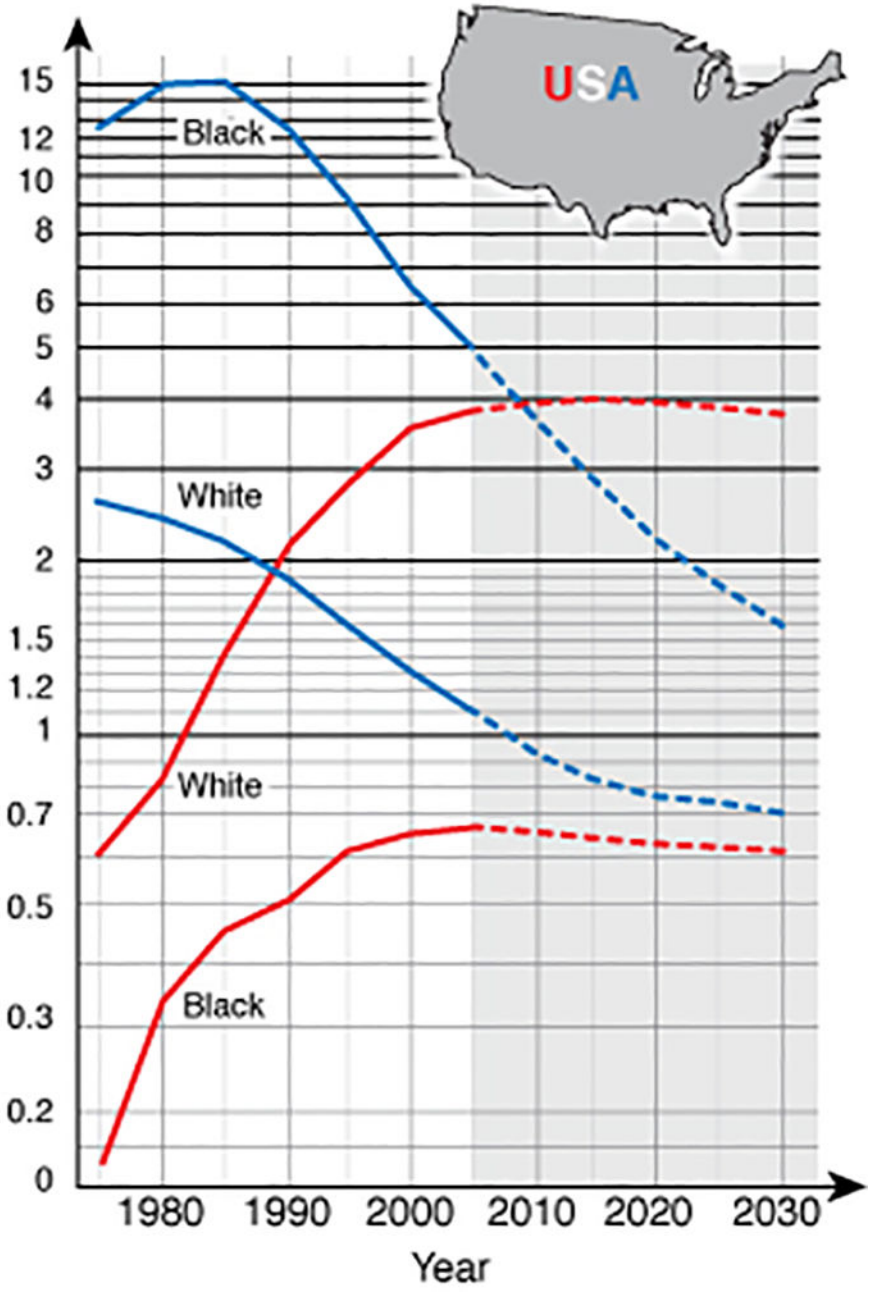

Figure 3.

Esophageal cancer rates by cell type and race in the United States. Blue lines indicate incidence rates for esophageal squamous cell carcinoma, and red lines indicate incidence rates for adenocarcinoma (adapted from[11]).

Table 1

Risk factors for esophageal squamous cell carcinoma

Exposure	Comments
Risk factors with consistent evidence for causation	
Poverty	Various markers of socioeconomic status within populations
Tobacco	Smoking cigarette, pipe, cigar, hookah, and chewing tobacco
Betel quid	Chewing with or without tobacco
Alcoholic beverages	Heavier consumption, effects of modest consumption are unclear
Pickled vegetables	Traditional Chinese methods of pickling without vinegar
Hot foods	Thermal injury from maté, tea, soup, porridge
X- and γ-radiation	Medical settings
Achalasia	High relative risks, but absolute risk may be low
Fanconi anemia	High relative risks, but absolute risk may be low
Risk factors with repeatedly reported associations, but not confirmed	
Polycyclic aromatic hydrocarbons	Strong ecologic evidence, but few studies with individual exposure metrics
Poor oral health	Includes loss of teeth and poor oral hygiene. Seen in most but not all studies where it was tested
Reproductive factors	Limited evidence and residual confounding might explain current literature
Gastric atrophy	Shown repeatedly in Nordic studies, but mixed evidence in other populations
Opium	Multiple recent reports for opium users, but unclear if other forms of opiates would be implicated