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Meeting Report

Esophageal and Cardia Cancers Summit: Report of the First Meeting

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Cancers of the esophagus (squamous cell carcinoma and adenocarcinoma) are among the most deadly cancers with a five-year survival of less than 10%. Esophageal squamous cell carcinoma (ESCC) is decreasing rapidly in western countries and adenocarcinoma rising significantly. Gastric cancer (GC) epidemiology is changing as well, with distal GCs decreasing and proximal GCs, especially at the cardia region on the rise.

ESCC claims about 335,000 lives worldwide each year with over 90% occurring in developing countries. It is the 6th most common fatal cancer in men and 9th in women with a male/female ratio of 1-3:1. There is a great variation in incidence between and within countries. Most of the hotspots are located along a presumptive belt starting from northern China, extending along the southern parts of the former Soviet Union, and ending in the Caspian littoral in northern Iran. Genetic and familial factors play their role in addition to environmental, nutritional, and habitual factors.

The first esophageal and cardia cancers summit (ECCS-1) was held on December 13 – 14, 2005 in Tehran, Iran. The meeting was sponsored by the Digestive Disease Research Center (DDRC) of Tehran University of Medical Sciences. Co-sponsors were the Center for International Collaboration and Research (ISMO) of the Iranian Ministry of Higher Education, the International Agency for Research on Cancer (IARC, Lyon, France), and the National Cancer Institute (NCI, NIH, Bethesda, USA). This meeting aimed to gather scientists dealing with various aspects of these deadly cancers (i.e., squamous cell carcinoma (SCC), adenocarcinoma of the esophagus, and adenocarcinoma of the cardia) from all around the world in order to: 1) review the current knowledge in the field, 2) provide an opportunity for investigators to get familiar with the details of ongoing studies in different areas, and 3) set the stage for closer collaboration between these scientists for joint field and bench research and avoiding parallel works. Clinical and basic scientists from China, France, Iran, Japan, South Africa, Sweden, the United Kingdom, and the USA met in Tehran and participated in a compact two-day program. Speakers briefed the audience for 20 – 30 minutes followed by discussions of 60 – 90 minutes with effective contribution by all the participants. On the evening of the second day, a concluding session was held, a sum-up of all the discussions was provided and a plan for future collaboration sketched. This group came to the following conclusions:

- Elucidating risk factors for these cancers is of prime importance in order to understand them effectively. This mandates using large sample sizes in studies of comparable designs and methods to achieve an acceptable level of precision and inundate low prevalence or low penetrance risk factors, and gene-environment interactions. Considering the heterogeneous nature of these cancers and the heterogeneity of their risk factors in different parts of the world and even in different regions of the same country, low- and intermediate- risk populations should also be enrolled in the collaborative studies. This is achievable only through close scientific exchange and collaboration between major research centers involved.
- Collaborations can be in different ways: holding periodical meetings, performing pooled analyses of available data, and designing and implementing multicenter studies. Regarding the

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vast cultural, ethnic, genetic, and environmental differences between different areas where these cancers are prevalent, design of these joint studies will be rather challenging and this should be elaborated from the very beginning.

Establishing an "Esophageal and Cardia Cancers Consortium (E3C)" seems timely. This should be a multidisciplinary consortium promoting etiologic, epidemiologic, clinical, and biologic (including the molecular aspects) research on these cancers especially in high-risk populations. The E3C will have branches to deal with: a) nutrition, b) biomarkers, c) pathology, including molecular aspects, and d) clinical issues, e) epidemiology and misclassification.

The scientific committee of the ECCS-1 took the responsibility of launching the initial steps for establishing the E3C with collaboration of the DDRC, IARC, NCI, and the Chinese Academy of Medical Sciences (CAMS).

- Other institutions and people who were not able to join the ECCS-1 will be most welcome to collaborate.

The next meeting (i.e., the ECCS-2) will happen in Beijing in 2007, CAMS being the main sponsor. The following is a brief summary of presentations at this meeting. A more detailed report, published as a book, is available at the DDRC (sianm@ams.ac.ir).

Descriptive Review of Esophageal Cancer Research in North Central China

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Esophageal malignancies have been known since about 200 BC in the North Central China. Even today Barrett's esophagus and esophageal adenocarcinoma are nonexistent in this area. "Linxian" in "Henan" Province harbors the highest rates (165 per 10^5 in men and 103 per 10^5 in women). Corn, millet, and wheat are the main food in Linxian with very little fruits, vegetables, or meat.

Nitrosamines and their precursors are high in the food and drinking water and local people's saliva, gastric juice, and urine.

In a nested case-control study looking at 1,079 esophageal and GCs and 1,053 controls of the same cohort, low serum selenium correlated with increased rates of esophageal SCC and cardia adenocarinoma, while low vitamin E (α-tocopherol) was associated with increased incidence of SCC. Abnet et al, following a cohort for 16 years, found lower tissue zinc levels in those developing SCC. Those in the highest quartile had a 5-fold lower risk of developing esophageal cancer. An association between *Helicobacter*

pylori (HP) infection and gastric cardia cancer has been found in Linxian.

In "The General Population Trial (GPT)", 29,594 adults (40 – 69 yr) were randomized to either receive one of the four different vitamin/mineral combinations (factors A-D) or placebo and were followed up for a mean of 5¼ years. Again esophageal cancer incidence and mortality rates were looked at. The GPT revealed that beta-carotene, vitamin E, and selenium combination (factor D) significantly reduces the total mortality rate (9%), the total cancer mortality rate (13%), and the GC mortality rate (21%). This effect was more pronounced in those who were younger at enrollment. A 15-year follow-up of this population showed a continued posttrial benefit and no harmful long-term effects. The benefits were consistently greater in participants who were younger at enrollment. Therefore, according to the GPT, selenium and vitamin E are beneficial for prevention of upper GI cancers in Linxian as well as decreasing all-cause mortality. In another study, selenomethionine decreased dysplastic changes in 360 endoscopically-screened people with low grade dysplasia (LGD) while celecoxib had no benefit. In an endoscopic study with 13 years of follow-up on 682 asymptomatic subjects, the only histologic lesion significantly associated with the development of esophageal SCC was squamous dysplasia.

Esophageal Cancer-Former Transkei Region, Eastern Cape Province, South Africa

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Esophageal cancer is one the most common cancers in Transkei region, South Africa (age standardized incidence rates (ASIR): 40 and 25 per 10^5 population for men and women, respectively). Fungal contamination of maize, the major dietary staple in this region, has been associated with high incidence of esophageal cancer in the region. We are currently evaluating the eating habits, fumonisin exposure, and other oesophageal cancer risk factors in this region utilizing a multipurpose epidemiologic questionnaire and a local tool called the "Ratio and Portion Size Picture" (RAPP) tool (a culture-specific semiquantitative food frequency questionnaire to assess nutrient intake). In addition, home-grown and commercial maize samples were collected and the fumonisin levels were determined. Our data (unpublished) show intakes well above the permitted provisional maximum tolerable daily Intake (PMTDI) limit of 2 μg/kg/day set by the WHO.

Esophageal Cancer in South America

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Uruguay has the highest ASR for esophageal cancer in South America (14.5 and 5.9 per 10^5 population for males and females, respectively, Globocan 2002). Tobacco (especially black) smoking is a major risk factor in this area and giving up smoking decreases the risk of SCC. Alcohol (especially hard liquor in higher amounts) is another risk factor for esophageal cancer in the area. "Mate" is a local drink usually consumed hot and in unusually high amounts. Consuming salted or boiled meat imposes a greater risk for developing such cancers while raw vegetables and fruits may be protective. Castellsagué et al found that both hot coffee and tea are associated with increased risk for esophageal cancer with the hot tea being a stronger risk factor.

Esophageal Squamous Cell Carcinoma and Gastric Cardia Cancer in Iran

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The Golestan Province in the North-East has the highest rate of esophageal cancer (ASR: 43.4 and 31.2 per 10^5 population for males and females, respectively). GC is the second most common cancer in males (ASR: 27.8 per 10^5 population) and the third among females (ASR: 8.3 per 10^5 population). Data from early 70s showed a rather higher incidence of esophageal cancer in Gonbad (ASR of 93.1 and 110 per 10^5 population for males and females, respectively). In Ardabil, another high-risk area in the North-West, GC is more prevalent (ASR: 49.1 and 25.1 per 10^5 population for males and females, respectively) followed by esophageal cancer (ASR: 15.4 and 14.4 per 10^5 population for males and females, respectively). In contrast in Kerman Province, in South Central Iran, gastric (ASR: 11.4 and 5.3 per 10^5 population for males and females, respectively) and esophageal cancers (ASR: 3.5 and 1.8 per 10^5

population for males and females, respectively) are much less common. We have established two clinics, the "Atrak" Clinic in Gonbad and the "Aras" Clinic in Ardabil, to serve cancer patients, meanwhile providing a base for cancer studies. We have launched a cohort of 50,000 people to be followed for 10 years and a case-control study (300 cases and 600 age- and sex-matched neighborhood and hospital controls) in Gonbad. We have also established a precise cancer registry covering the high and low risk areas. Family history and consanguinity are risk factors in the area.

Earlier studies found opium to be a risk factor for ESCC. Our data also supports this finding. We found a good correlation between self-reported opium use and the amount of morphine and codeine found in the subjects' urine. Our data show that selenium deficiency is not a major contributor to ESCC in north-eastern Iran, but it may play a role in the high incidence of GC in Ardabil. Polycyclic aromatic hydrocarbons (PAH) seem to be a possible carcinogen in Gonbad. The role of N-nitroso compounds in carcinogenesis of the upper GI cancers in the region is controversial. Poor oral hygiene and tooth loss are other risk factor in the region. We did not find any fumonisin contamination of grain samples from 10 different areas. Our data show that most of the junctional cancers are located on the right side of the cardia. This may be explained by the concept of Magenstrasse (canalis gastricus). On entering the stomach, nonsolid material proceeds down the lesser curve i.e., right side, following the "Magenstrasse" or "canalis gastricus" formed by the arrangement of inner oblique musculature and outer longitudinal mucosal folds of the esophagus and lesser curve of the stomach.

Present Situation of Gastric and Esophageal Cancers in Japan

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Mortality from malignant neoplasms has increased in Japan over the past five decades. One of the most common killing cancers has been GC. (ASR: 78 and 33 per 10^5 population for males and females, respectively). Nation-wide mass-screening programs for early detection of GC among Japanese older than 40 years have been in work since early 60s. Endoscopy is an accurate method and enables biopsy taking for histologic diagnosis of the lesion. Mass-screening programs with endoscopy have been launched. Over half of the GC diagnosed nowadays are early GC and potentially amenable to surgical or endoscopic cure.

For screening endoscopy, the patient should be adequately sedated, the stomach should be completely clear from secretions, and in a state of minimal peristalsis. Careful evaluation of the mucosa with high quality endoscopic imaging followed by Indigo Carmine dying of the mucosa is the current standard used in Japan. Careful examination of the mucosa has replaced blind biopsies. Targeted biopsies are used in suspicious lesions. Endoscopic submucosal dissection (ESD) instead of piecemeal resection of the malignant lesions has the advantage of more accurate examination not only of the margins and the submucosa but also of final histologic staging.

Noncardia vs. Cardia Gastric Cancers

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The incidence of noncardia GCs (NCGCs), associated with HP, have decreased worldwide, while the incidence of cardia cancers is on the rise. The latter has no definite correlation with HP. In a population with 50% prevalence of HP, 75% of NCGCs are attributable to HP. Genetic predisposition (e.g., autosomal dominant, E-cadherin germline mutation) plays a minor role. HP-positive peptic ulcer disease patients are protected from developing GC. In addition, higher serum gastrin levels and pepsinogen I/II ratios are associated with increased risk of developing GC. Atrophic gastritis, associated with hypochlorhydria and colonization of the stomach by various bacteria, may cause decreased vitamin C concentrations and increased nitrites. Normally, nitrates have an entero-salivary recirculation and nitrites are removed by the gastric acid and vitamin C. In the atrophic stomach, the retained nitrites are reduced by bacteria to N-nitroso compounds (potent carcinogens). Bacterial strain of HP, host's genetic make-up (e.g., IL-1 polymorphism), and environmental and dietary factors (e.g., smoking, amount of salt, and fruit intake) are known determinants of HP-related GC. HP infection, dietary factors, and smoking are reversible risk factors for NCGC. HP eradication may be effective in decreasing the incidence of

NCGC especially in younger people. This strategy has its own attractions (relatively safe and cheap, reducing ulcers as well) and draw-backs (antibiotic side effects and resistance, concern for increased incidence of gastroesophageal reflux disease (GERD) and esophageal adenocarcinoma, whether precancerous lesions reverse after HP eradication, a long lag-time between the treatment and its possible benefit, and whether this is useful in western countries where the incidence of HP and NCGC are already decreasing).

There are two types of GCCs: Type-A (associated with HP, atrophic gastritis, and achlorhydria) and Type-B (usually HP negative with normal acid secretion). Type-B is common in the West and its incidence is increasing. Adenocarcinoma of the lower esophagus is associated with GERD. Up to now the link of GERD with adenocarcinoma of the cardia has been controversial. The issue of short and long segment specialized intestinal metaplasia (SIM) of the lower esophagus and SIM of the cardia and their relation to GCC are controversial. The "short segment reflux" theory for cardia inflammation is appealing. In addition, a recently described "unbuffered acid pocket" at the cardia may play its role in development of cancer in this region. The refluxate itself is not mutagenic but leads to local inflammation. Under these conditions the dietary nitrite is transformed into nitrosating agents (potential carcinogens). In addition, "acid catalyzed nitrosation" potential is highest at the cardia before and after nitrate meals. Therefore, the "short segment reflux" and the "nitrosative stress" seem to act in concert at the gastroesophageal junction (GEJ) to make this site suitable for mutagenesis.

This theory can also explain the change in the pattern of GCs seen in the West. In the "achlorhydric stomach" (HP infection, proton pump inhibitor PPIs) nitrosation, by colonization of nitrosating bacteria, occurs throughout the stomach, while in the "healthy acidic stomach" nitrosation by acidification of the salivary nitrite occurs at the gastric cardia and the GEJ.

Genetic and Hereditary Susceptibility to Esophageal and Gastric Cancers: Polymorphism

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Hereditary diffuse gastric cancer (DGC) is caused by truncating germline mutations in the E-cadherin gene (CDH1, autosomal dominant, penetrance: 70%). Germline truncating CDH1 mutations are found in 48% of families with multiple cases of GC and at least one documented case of DGC in an individual under 50 years of age.

The "GC phenotype" may be described as severe inflammation, corpus predominant pattern, gastric atrophy, hypo/achlorhydria, and bacterial overgrowth. The relative risk (RR) of developing GC in corpus-dominant HP gastritis is 34.5 (95% CI: 7.1 – 166.7) as compared with the antral-dominant HP gastritis. Host factors and acid inhibition may determine this phenotype. Genes controlling the proinflammatory cytokines, HP infection, and gastric acid physiology may also play a role. IL-1β and TNF-α polymorphisms affect the level of gastric mucosal IL-1β in HP-infected subjects. Important host genetic factors include cytokine gene polymorphisms such as IL-1β-31/-511 C/T, TNF-A-308 G/A, IL-10 ATA/ATA haplotype, IL-8-251, TLR4 Asp299Gly, and Mannose Binding Lectin (MBL). A combination of these polymorphisms may have an additive effect on development of NCGC. Synergistic effect of HP virulence factors and host genetic factors have also been shown. There is also interaction between these gene polymorphisms and GERD. An interplay of host genetic factors, especially the proinflammatory cytokine gene polymorphisms, the innate immune response, and HP genetic characteristics determine whether a given individual will develop the cancer phenotype.

Molecular and Cellular Mechanisms of Formation of Barrett's Metaplasia and of Adenocarcinoma of the Oesophagus

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Recent data show that "cardia mucosa" exists from birth and has a limited extension of a few millimeters. Misclassification is a major source of variable results in studying junctional cancers. The Siewert classification is useful (Type-I: adenocarcinoma [ADC]) of the esophagus characterized by presence of Barrett's epithelium, 75% of the tumor mass in the tubular esophagus, presence of direct periesophageal invasion, and clinical symptoms of esophageal obstruction, and

Type-II: no macro/microscopic evidence of Barrett's within 2 cm of the junction, and predominantly invading the gastric part). Barrett's ADC is more common among male smokers. TP-53 (a growth regulator specialist) is also more common in Barrett's ADC than the GEJ-ADC and the reverse is true for cytokeratin 7. TP-53 mutations may vary according to the geographic area and the possible etiology. In SCC from Tehran, Iran, the TP-53 mutation pattern is consistent with a role for chronic inflammation, and resembles the pattern observed in high-incidence areas from China, while in SCC from Atrak Clinic (Gonbad, Iran), the TP-53 mutation pattern is suggestive of a role for carcinogen(s) generating bulky DNA adducts.

A model can be proposed for development of Barrett's metaplasia and further progression to ADC: a decrease or loss of p63 expression is induced by acid-bile reflux and this prevents normal squamous differentiation. This in turn induces cells to differentiate into columnar, intestinal-type cells i.e., the Barrett's mucosa. Pro-inflammatory conditions in the Barrett's mucosa activate p53 followed by over-expression of Cox-2. This occurs as part of a survival mechanism that allows columnar cells to escape p53-dependent apoptosis. Mutation of TP53 abrogates this apoptotic pathway as well as the dependency of cells on Cox-2 expression.

Nutritional Risk Factors for Esophageal and Gastric Cancers in High-Risk Populations

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ESCC is rather common in Gonbad, Iran. Assessing the role of dietary patterns on development of ESCC, Cook and Mozaffari showed that ESCC in Gonbad is not associated with sheep milk, sesame oil, use of pregnancy diet, salting, and sun-drying, but highly associated with low socioeconomic status, and low intake of fresh fruits and vegetables. Siassi and Ghadirian reported a low dietary intake of phosphorus and niacin among households of ESCC cases. In a more recent study, they pointed to a possible role for riboflavin deficiency. Currently, food frequency questionnaires, validated against 24-hour recalls, are being used for case-control studies in the area.

Higher levels of manganese, nickel, magnesium, calcium, and potassium and lower levels of aluminium, iron, and organic matter have been shown in the soil in South Africa. Leaf analysis in high- and low-risk areas revealed a higher manganese, potassium, calcium, and iron content and lower phosphorus levels. Cytologic lesions are related to intake of green vegetables, fruits, and animal proteins and associated with lower plasma concentration of vitamins A, E, and B12. Low serum selenium was significantly associated with the risk for esophageal cancer. Exceptionally low whole blood selenium level (58 – 72 ng/mL) and a relationship between its concentration and degree of cytologic abnormalities were also shown.

People in Linxian (China) depend mostly on white yams, a symbol of multiple nutrient deficiencies. In addition, they take large amounts of pickled vegetables which are potential dietary carcinogens (nitrates). Intervention trials in this region have shown that a combination of selenium, beta-carotene, and vitamin E significantly reduces GC, total cancer, and all-cause mortality in this region, especially in individuals less than 55 years of age. Mild, moderate, and severe dysplasia are associated with incremental risks of ESCC.

All these should be looked at with interest and caution as they may not be generalizable to other populations at high risk for ESCC. For instance, median serum selenium concentration in Linxian is 71 μg/L, while that in the US is 124 μg/L, and in Golestan (Iran) is 155 μg/L.

According to present available data, it can be concluded that higher consumption of fruits and vegetables protects against ESCC, both in high- and low-risk areas, micronutrient deficiencies increase the risk for ESCC and may be responsible for a large number of ESCC cases in certain parts of the world. In addition, findings in one high-risk area are not necessarily generalizable to other high-risk areas.

Molecular Genetics and Epigenetics in Upper GI Cancers

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The genome contains information in two forms, genetic and epigenetic. The genetic information provides the blue print for manufacture of all the

proteins necessary to create a living thing, while the epigenetic information provides additional instructions on how, where, and when the genetic information should be used. Every form of sporadic cancer has both genetic and epigenetic events that lead to the disease. Mutations in key genes that regulate cellular growth (i.e., P53, P16, c-myc, Ras), DNA repair (i.e., hMLH1, hMSH2), and programmed cell death (i.e., bcl-2) are known pathways toward tumorigenesis. However, it is estimated that up to 65% of some cancers have an epigenetic basis. Histone deacetylation and DNA methylation are important epigenetic changes.

The major form of epigenetic information in mammalian cells is DNA methylation. While DNA methylation clearly enhances the ability of cells to regulate and package the genetic information, it also adds an additional level of complexity. Genomic methylation patterns are frequently altered in tumor cells, with global hypomethylation accompanying region-specific hypermethylation events. Hypermethylation within the promoter of a tumor suppressor gene silences its expression and provides the cell with a growth advantage (akin to deletions or mutations). Genetic and epigenetic alterations of multiple cancer-related genes and molecules are implicated in the development and progression of human gastric and esophageal carcinomas. To date, more than 600 genes (tumor suppressor genes, oncogenes, and cancer-associated viral genes) have been reported to be regulated by epigenetic mechanisms. The search for genetic and/or epigenetic factors or methods for early detection of cancer are on the way. Previous studies have revealed that tumor DNA is released into the circulation and that a significant amount of circulating tumor DNA may be isolated from the serum of cancer patients. Assays based on the detection of tumoral DNA can prove to be potential diagnostic tools for cancer.

Risk Factors of Esophageal and Cardia Cancer in High-risk Areas

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Currently established risk factors for ESCC include genetic predisposition, tobacco smoking and chewing, alcohol drinking, human papilloma virus (HPV) infection, occupational factors, and some medical conditions. Family history of esophageal cancer, Tylosis, and polymorphism in genes involved in tobacco and alcohol metabolism and DNA repair are known genetic predisposing factors.

A study from northern Iran showed consanguinity of parents in 9.6% of cases and 2.5% of controls (OR: 4.1, $P = 0.006$). Calculated lifetime risk of EC was 14%, while having affected parents and siblings it increased to 50%. There was no association with other cancers. The increased risk was present with any of the parents or siblings being affected. Another study in Linxian (China) revealed similar findings.

Studies from Europe, and North and South America have shown tobacco smoking to increase the risk of EC (RR: 3 – 6). There is a strong dose-response relationship and interaction with alcohol drinking. High-tar cigarettes, hand-rolled cigarettes, and black-tobacco products may increase the risk even further. Previous studies in Golestan, Iran pointed to slightly increased risk of EC among smokers. In Linxian, tobacco smoking slightly increased the risk of cardia cancer among low-risk people, but had no effect in high-risk individuals as well as on esophageal cancer. Wang et al did not find any relation between tobacco smoking and risk of esophageal cancer in Shanxi. They found a borderline increased risk of EC among high-risk individuals consuming alcohol.

In addition to conventional tobacco, smokeless tobacco and nontobacco products may affect the risk of EC and cardia cancers. Betel chewing with and without tobacco in India, "Nass" chewing in central Asia, and chewing and swallowing of smoking residues in Transkei, South Africa have been suggested as probable risk factors.

In high-risk areas such as Linxian, no links have been found and the prevalence of drinking is rather low in northern Iran.

Older studies have raised opium use as a possible risk factor in northern Iran. The prevalence of opium use has apparently decreased over time (9% prevalence in pilot cohort study of Golestan).

Fumonisin concentrations are much higher in the home-grown healthy and moldy corns in high-incidence areas as compared with similar products of low-incidence areas in Africa. Results are inconsistent with high levels detected in Linxian and low levels in North-East Italy and Golestan. Despite the high levels found in Linxian, no association could be found in a case-control study.

Thermal irritation, as in hot mate drinking in South America, is a risk factor for EC. Older data

from northern Iran have found a possible link between drinking hot tea and EC. On the other hand, Guo et al did not find any link between hot tea drinking and EC in China. Other supportive evidence comes from intermediate-risk areas such as Scotland, Japan, China, Hong Kong, Singapore, and Russia.

Association between lower education and EC have been reported from Iran and China. Other etiologic hypotheses of ESCC in high-risk areas include: silica fragments from millet bran (Iran and China), carpet making (Iran), animal ownership (Iran), use of kerosene for cooking (Iran), water contamination (China), oral health (China), and iron overload (South Africa). In intermediate- and low-risk areas other etiologic hypotheses such as ionizing radiation (atomic bomb survivors), occupational exposures (asbestos, polycyclic aromatic hydrocarbon [PAH]), broken fern [Japan], and medical conditions (Plummer-Vinson syndrome, celiac disease, hemo- chromatosis, pernicious anemia) have been put forward. Exposure to PAH and nitrosamines can play a major role in esophageal carcinogenesis.

To conclude, it can be said that risk factors for ESCC in high-risk areas are rather heterogeneous and subject to temporal changes in exposure patterns. A shift from traditional to modern lifestyle also affects these risk factors.