Esophageal Cancer Crisis in Golestan Province, Iran; Focus on Risk Factors: Back to Future

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ABSTRACT

Esophageal cancer (EC) is categorized histologically to two common groups; adenocarcinomas and squamous cell carcinomas, with high incidence and mortality worldwide. Esophageal squamous cell carcinoma (ESCC) is the most prevalent (more than 90%) form of all EC cases in Golestan province. Golestan province, as the high-risk province for ESCC, is located in the eastern part of the Caspian littoral area of Iran, although in the last decades, the occurrence rates have decreased in this area. Tobacco smoking, opium consumption, low oral hygiene, drinking hot liquids, insufficient intake of fresh fruits and vegetables, and poor socioeconomic status increase the risk of ESCC in Golestan, although exposure to infections and toxic chemical compounds are also reported. Here, we summarize the previous epidemiological studies from 1970 to 2019 that have investigated the risk factors involved in ESCC in this high-risk area. More prospective cohort studies are required to assess the risk factors, categorize high-risk peoples, and evaluate early detection and involved mechanisms.

Keywords: Esophageal cancer, Esophageal squamous cell carcinoma, Environmental risk

INTRODUCTION

Cancer is a challenging, multi-factorial disease and a major public health concern worldwide (1). In 2018, the incidence and mortality rates related to esophageal cancer (EC) were reported as 572,000 new cases (seventh ranks) and 509,000 deaths (sixth ranks) worldwide, respectively (2). These statistics emphasize the necessity of more investigations on the risk factors and more effective treatments. The historical investigations on the risk factors related to EC go back to about one century ago. Based on preliminary clinical studies, the risk factors for EC were alcohol consumption, tobacco smoking, hot or mate drinks consumption, low socioeconomic status, and poor oral health (3,4). EC is histologically characterized to two principal types: squamous cell carcinoma (ESCC; frequently occurs in flat cells lining the upper esophagus) and adenocarcinoma (EAC; originates primarily from Barrett mucosa) (5). The types of EC diverge histologically based on the risk factors, ethnic pattern, incidence, and geographical regions. The risk
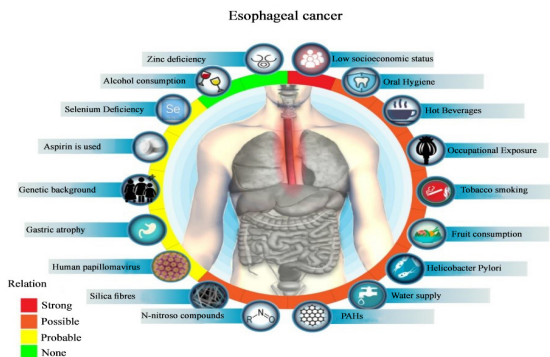
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Fig.1: The risk factors involved in Esophagus cancer in Golestan province as high-risk area
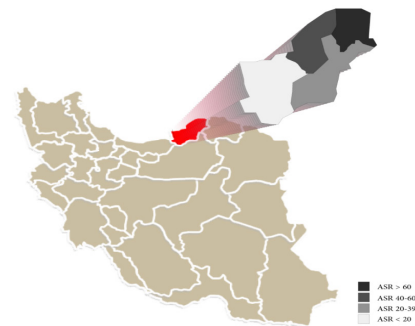

Fig.2: The distribution of esophageal cancer incidence in different regions of Golestan province based on the Golestan Cancer Registry database (14) and also the GCS database (data not published).

factors of EAC such as increased age, male sex, obesity, gastroesophageal reflux disease, cigarette smoking, and low vegetables and fruit intakes have been commonly documented; although for ESCC, cigarette smoking, alcohol use, caustic ingestion, low oral hygiene, and malnutrition are main risk factors (6,7). In the recent decades, a significant mysterious rise in the incidence and burden of EAC has been found in developed countries such as northern and western Europe, Northern America, and Oceania (46% of the total global EAC cases) (8), although ESCC is the main prevalent type of EC in less-developed or developing counties like Iran (8). Some regions in Asia, such as northern Iran, Turkey, Central Asia, and northern and central China, are known as the high-risk areas for EC ("Asian ESCC Belt") (9). The age-standardized rate (ASR) rates between the incidence of ESCC in women and men in Iran were 7.2 and 8.2, respectively (9).

Recently, the altering epidemiology of ESCC and EAC has also been documented by the high incidence of ESCC in areas such as Iran. And EAC is now increasing, especially in female sex in the central Asian area (10). In developed areas, the most predominant risk factors of ESCC are tobacco smoking and alcohol drinking, although, in ESCC high-incidence regions, the factors may be different from those seen elsewhere, and several further risk factors are possibly considered as the risk factors of EC. In this study, due to the importance of investigations on the EC risk factors to prevent and reduce the burden of cancer, we summarized all the risk factors and protective factors that have already been suggested for EC in Golestan province as a high-risk area (Figure 1).

Geographical, Geological, and Demographical Setting in Golestan Province

Golestan province (36° 30′–38° 07′ N, 53° 51′–56° 21′ E) with moderate, damp, and Mediterranean climate, which is located in the north-east of the country, south of the Caspian Sea (Figure 2), includes a region of 20,438.31 km² and has a population of 1,868,819 in 2016 (50.2% male; 48.2% female). The percentages of inhabitants who live in rural and urban areas were 45.14% and 54.75%, respectively. The north and south counties of Golestan province can be classified as high and low risk of EC, respectively (Figure 2). Turkmen, Fars, Sistani (Zaboli), Baluch, Tork, and Kurd are the most prevalent ethnic groups of Golestan province.

EC Epidemiology in Golestan Province

Surprisingly, in a population-based study done on Caspian Cancer Registry between 1969 and 1971, Golestan province was the high-risk area for EC with ASR > 100 per 100000 person-years in men and women (> 165.5/100,000 in men and 195.3/100,000 in women) (11). There is an extensive difference in the incidence of EC in several geographical areas as the results of population-based cancer registries conducted in Gilan, Ardabil, and Semnan provinces revealed that the incidence of EC in the

western parts of the Caspian littoral, and center of Iran decreased to ~ 10, 15.4, and 7.9 per 100,000 populations, respectively (12). Additionally, the significant sex difference (a striking discrepancy of 3-fold) in men to women ratio of ASR was observed in Gilan province compared with Golestan, Ardabil, and Semnan provinces. In a retrospective study conducted over a period of 9 years (from March 1994 to March 2003) in Eastern Azerbaijan (north-west Caspian littoral), a low incidence rate of EC 5.9 (4.6 for ESCC; 0.7 for EAC) per 105 persons-years with an average incidence rate of 11.4 and 14 per 105 person-years in men and women were reported, respectively (13). There is a marked high incidence of EC in the north of Golestan province, which mainly Turkmens reside, and is a plain called Turkmen Sahra. However, an association between Turkmen ethnic and the high incidence of EC has not been established yet. A report of prospective cancer surveillance in an ongoing population-based cancer registry in Golestan province, which was conducted for 4 years from 2004 to 2008, reported a clear drop in the incidence rate of ESCC (24.3/100,000 in men and 19.1/100,000 in women) (14,15). Although, the ASRs of ESCC have remained high in males and females, especially in Kalaleh district (situated in the eastern region of the province). Although the reason for the striking decline trend in ESCC was mainly unknown, the overall improvement in socioeconomic status may be a factor. Thus, more accurate risk stratification and further larger-scale or other screening/surveillance modalities for EC control are required in this area. The risk factors of ESCC in Golestan province are shown in Figure 1. Previous investigations on risk factors of EC in Golestan province since the 1970s are presented in Table 1.

Risk factors

Many risk factors of EC have been proposed, and according to two histological types of EC (ESCC & EAC), they may be slightly varied. Since Golestan province is a high-risk area for ESCC, the results reported in this review are mainly focused on ESCC.

Environmental risk factors

Habits—tobacco, opium, and alcohol use, consumption of hot tea and mate drinks

Historically, the surgeon general's report in 1979 stated that cigarette smoking is a significant cause of EC (16). International Agency for Research on Cancer (IARC) has characterized tobacco use as an active factor in EC. Tobacco smoking is a major risk factor for ESCC, demonstrating a dose- and time-dependence trend (17). The risk of ESCC among current smokers is 3-7 fold higher worldwide (18). Among 1057 participants in a cohort study, in which the populations were randomly selected from both rural and urban regions, 30% of rural men, 39% of urban men, 1% of rural women, and 3% of urban women had ever smoked cigarettes (19). Several other forms of tobacco use, with little information about them, such as using a water pipe (hookah also known as the qalyân) and nass (a combination of lime, ash, and tobacco), are mostly consumed in the Middle East that can also increase the risk of EC (20). In Golestan province and China (in the Taihang mountain area), which is a high-risk area for EC, there is a slight association between cigarette smoking and ESCC with a relative risk of approximately 1.5 (20,21). The cause of this association is unclear, but the only hypothesis is that there is another major cause in these areas, which is more critical than cigarette smoking (22).

Tobacco use

The IARC categorized cigarettes as a leading etiologic cause of ESCC (23). Cigarette smoking can be a cause for ESCC through several mechanisms. For example, carcinogens formed by smoked cigarettes could be responsible for altered p53 gene alterations and p53 overexpression may be a critical factor in carcinogenesis, as well as in EC development (24). Another example is polycyclic modules as one of the ingredients related to cigarette smoke, which may be associated with esophageal carcinogenesis (24). Compared with non-smokers, smokers have a 3-7 fold rise in their risk of developing cancers (25). This factor increases the risk of ESCC in western countries to about 3-5 fold (20). However, the significance of this factor is different in various parts of the world. For example, in Linxian (China) where 10% of women and approximately 70% of men smoke, and it is one of the high-risk areas in the world, smoking does not have a substantial role

in ESCC (26). In Golestan province, there is a low to moderate association between cigarette smoking and ESCC (27). Around 1% of rural women and 39% of urban men are ever smoking in this province. A case-control study (28) stated a nearly 2-fold risk of ESCC association with tobacco smoking. The relative risk for ever cigarette smoking is only 1.47, which confirms a weak association in Golestan province. A case-control study (20) reported a high risk of ESCC in those who used tobacco (cigarettes, qalyân, and nass chewing) (2.35, 1.50 – 3.67), thus more research are required to evaluate the exact role of tobacco use as an etiological factor for EC in this area.

Alcohol Consumption

IARC characterized alcoholic beverages as group 1 carcinogens to humans (29). A series of epidemiological reports have established that alcohol drinking had a significant role in various cancers such as breast, colorectum, liver, esophagus, and oral cavity (30). As stated above, alcohol use is known as one of the major risk factors for EC (31-33). Although there are a few data about the correlation between alcohol and the risk of EC in Iran, it typically can increase the risk by 3-5 fold. Alcohol use is related to a dose-response rise in ESCC risk, and heavy intake raises the risk by 5-15 fold (29). Some mechanisms for alcohol carcinogenicity have been recommended, including having a number of carcinogenic compounds (ethanol, acetaldehyde, aflatoxins, and ethyl carbamate), reduced saliva flow, and specific nutritional deficiencies, particularly in folates and other vitamins (34). However, in Golestan province, alcohol is not considered as an essential factor because it is prohibited in Islam and it is rarely consumed in Iran; thus, it cannot impact on the high frequency of EC in Iran (20).

Opium use

Opium consumption is frequent among rural men of Golestan province, and it has a critical role in ESCC (35). One important reason is that opium is traditionally used for the treatment of pain, diarrhea, and insomnia in this area (27). It is thought that maybe the remaining of opium is more effective in ESCC. Consuming opium in pure form has less mutagenicity and genotoxicity, but transformed products known as "shireh and sukhteh" are more effective because of their components such as pyrolysis and polycyclic aromatic hydrocarbons (PAHs) (20). Of course, the role of opium and its compounds have not been well defined (36,37). In the research studies conducted by the IARC in 1977s, the use of opium, and in specific of opium dross ("shireh and sukhteh") has been supposed to be a significant etiological factor for ESCC in Golestan province (28). In the Golestan cohort study, crude and refined opium consumption were related to 1.6-fold and 3.4-fold rises in the risk of ESCC (36,37). In a study in Golestan province, 32% of men and 13% of women had consumed opium. This difference is conflicting with the insignificant dominance of ESCC incidence in men compared with women, which was shown in another study (20). Although still, the incidence rate of ESCC in Golestan province is high, different factors led to a decline in the last few decades, such as socioeconomic status, more availability to piped water, and more consumption of fresh vegetable and fruits due to the greater availability of refrigerators (35).

Consumption of hot tea and mate drinks

Some studies showed that both black and green tea that consists of several compounds and antioxidants such as flavonoids, have cancer prevention properties in animal models, but several ways have been suggested for thermal injury and EC (38). Researchers have proposed that local hyperthermia and the chronic inflammatory process can cause chronic irritation of the oesophageal mucosa and formation of reactive nitrogen species (RNS), and consequently, N-nitroso complexes. Another way is the damage of esophageal epithelium and sensitivity to carcinogenic compounds such as polycyclic aromatic hydrocarbons (PAHs) that are shown in the food and opium dross of Golestan people (39). Consuming tea and other drink can cause the EC in two ways: First, the use of hot tea and other drinks can cause inflammation in the esophageal tract and cancer. Second, aromatic hydrocarbon in some drinks can cause EC, but some chemical compounds in the drinks have an anti-cancer effect. Strict detection of these is very hard and should be detected in cohort studies (4). In Golestan province, people similar to other areas in Iran, drink a large amount of tea every

Table 1: Summary of previous studies on risk factors involved in EC in Golestan province, Iran

Risk factors	Author/Year/ Type of study	Methods	Outcome	Relation with EC
Nutritional deficiencies	Semnani et al/2010/ Cross Sectional (263)	135 soil samples investigated by FAAS from the high and low-risk areas.	A considerable positive association between soils Se level and EC rates.	Possible
Nutritional deficiencies	Keshavarzi et al/2012/ Ecological (264)	663 samples (206 cultivated soils, 247 sediments, 45 loess deposits, and 165 grain) investigated by ICP/MS method in the 45 villages of high EC areas.	Increase total Se concentrations (0.18 to 3.1 mg kg−1) in soil samples. Much higher of Sb and Sr content in samples in high EC area. Decrease total Zn content samples from the low to the high EC regions .	Probable
Nutritional deficiencies	Fazeltabar Malekshah et al./ 2010/ Cohort (265)	Food consumption information was collected from 30,463 healthy participants Using an FFQ.	Decrease of Vitamin A and C intake in the majority of participants. Higher insufficiency in vitamin use among women and rural inhabitants.	Probable
Ethnicity	Marjani et al/2010/ Sectional (266)	A structured questionnaire used to investigate role environmental risk factors among 171 (57.0%) Turkmen and 129 (43.0%) non-Turkmen ESCC cases.	No significant difference between Turkmen and non-Turkmen ESCC cases in the prevalence of exposure to tobacco, nass, and opium use, hot and extremely hot tea consumption, and decreased levels of education.	None
Chemical carcinogens	Kamangar et al/2005/ pilot (24)	Urine 1-OHPG in 99 inhabitants of Gonbad and its surrounding area measured using IC and SFP.	The median urine 1-OHPG was 4.2 pmol/ml. 41 (41%) inhabitants were very high exposure (> 5 pmol/ml).	Possible
Consumption habits (tobacco, alcohol, opium, mate and hot drinks use)	Islami et al/2004/ cohort (70)	245 of ESCC patients were interviewed by a physician using a structured questionnaire and underwent physical examination followed by esophageal-gastro duodenal video endoscopy.	It also shows that smoking is not a major risk factor. Tobacco, nass, alcohol and perhaps opium use is not the main etiological factors for ESCC.	Probable
Consumption habits (tobacco, alcohol, opium, mate and hot drinks use)	Pourshams et al/2005/cohort (19)	1349 rural and urban inhabitants invited to undergo extensive lifestyle interviews. Fumonisin contamination testing performed on samples of rice, wheat, and sorghum.	A total of 1057 subjects (610 women and 447men) participated. Tobacco smoking was linked with urinary cotinine. No fumonisins were found in the samples..	Probable
Consumption habits (tobacco, alcohol, opium, mate and hot drinks use)	Nasrollahzadeh et al/ 2008/ Case-control (20)	A validated structured questionnaire administered to investigate role environmental risk factors in 300 ESCC cases and 571 controls.	Higher risk of ESCC was in those who used tobacco only (OR, 95% CI: 1.70, 1.05 − 2.73), in those who used opium only (2.12, 1.21 − 3.74), and in those who used both tobacco and opium (2.35, 1.50 − 3.67).	Probable
Consumption habits (tobacco, alcohol, opium, mate and hot drinks use)	Islami et al/ 2009/ case-control (41)	Patterns of tea consumption and temperature at which tea was drunk were considered among 300 EC cases and 571 controls.	An increased risk of EC with consumption hot tea (OR: 2.07, CI: 1.28 to 3.35) or very hot tea (8.16, 3.93 to 16.9). A strong association was found between consumption of hot tea with a higher risk of EC.	Possible

Risk factors	Author/Year/ Type of study	Methods	Outcome	Relation with EC
Low socio-economic status	Islami et al/ 2009/case–control (267)	Conditional logistic regression used to compare 300 cases and 571 controls for individual SES indicators.	Compared with no education, the adjusted odds ratios for primary education and high school or beyond were 0.52 and 0.20, respectively. A potent inverse correlation between SES and ESCC risk.	Strong
Chemical carcinogens	Islami et al/2012/ cross-sectional (106)	Investigated the patterns of 111 randomly selected never-smoking women (structured questionnaire), genotyping polymorphisms (SBE method), and measuring levels of 1-OHPG related to PAH metabolism in urine samples was made with SFS.	High exposure of the general population to PAHs. Certain foods, cooking methods, and genetic polymorphisms increase exposure to PAHs.	Possible
Chemical carcinogens	Hakami et al/2008/ case-control (97)	Assessment of the daily consumption of food and water in 3 groups: 40 ESCC cases, 40 healthy individuals from the same area, and 40 healthy individuals from a low-risk area in Southern Iran using a dietary questionnaire and BaP concentration measured by HPLC-FL.	The daily consumption of BaP was higher in controls from the high-risk region than in controls from the low-risk region (91.4 vs. 70.6 ng/day, $p < 0.01$). PAHS could, along with other risk factors, contribute to the high risk of ESCC.	Possible
Water supply	Keshavarzi et al/2012/ Ecological (52)	183 drinking water samples from 45 villages with EC mortality rates are collected and analyzed using portable measuring devices. Also, trace element concentrations were measurement using ICP/MS.	NO_3^-, SO42-, Sb, and Sr exceed the recommended MCL in drinking water. A potential relation between EC occurrence and water quality. Se deficiency does not act a main role in the etiology of EC.	Possible
Nutritional deficiencies	Nouraie et al/2004/ (268)	Serum selenium measured in 300 healthy adults from Ardabil (n = 100), Mazandaran (n = 50), Golestan (n = 100), and Kerman (n = 50), using ICP-DRC-MS.	A very different in median serum selenium concentrations in the four Provinces. Selenium deficiency is not a significant contributor to the high incidence of EC in northeast ern Iran.	None
Genetic studies	Zendehdel et al/ 2009/ (171)	Genetic polymorphisms of GSTP1Ile105Val, GSTM1, GSTT1 analyzed using pyrosequencing, and multiplex PCR in 96 EA and 79 SCC cases, 126 cardia cancer cases, and 471 controls.	An increased risk of ESCC (OR=1.7; 95% CI 1.0–2.9) relation with Variant GSTP1Val105 allele. GSTP1 polymorphism seems to be linked with the risk of ESCC (OR = 1.4; 95% CI 1.0–2.2).	Possible
Genetic studies	Abedi-Ardekani et al/2012/ (269)	152 cases ESCC from Iran and north India has been analyzed for EGFR mutation by direct sequencing.	A rare activating mutation (4/152 cases, 2.6%) but frequent EGFR protein over-expression (65%).	Probable
Nutritional deficiencies	Hashemian et al/2015/ Cohort (46)	Consumptions of minerals were measured with a validated FFQ in 201 ESCC patients.	A important reverse link between calcium and zinc consumption and ESCC risk. There was no association between dietary consumption of manganese and the risk of ESCC.	Probable

Risk factors	Author/Year/ Type of study	Methods	Outcome	Relation with EC
Fungus contamination	Alizadeh et al/2012 [87]	The levels of FB1 were assessed by TL-PLC and HPLC in 66 rice and 66 corn samples from 22 geographical subdivisions of Golestan province.	FB1 contamination was discovered in 50% and 40.9% of corn and rice samples, respectively. An important FB1 rate (43.8 µg/g) was from a high EC-risk region ($p = 0.01$). An important positive link between FB1 contamination in rice and the risk of EC.	Possible
Nutritional deficiencies	Hashemian et al/2017/ case–control [270]	The concentration of selenium, zinc, chromium, mercury, and scandium using INAA in toenail samples collected from 222 cases of ESCC and 222 controls.	Median nail selenium, zinc, chromium, and mercury levels were 1.01, 74.59, 0.77, and 0.018 µg/g in cases and 1.02, 75.71, 0.71, and 0.023 µg/g in controls, respectively. No support of any link between selenium or chromium concentrations and risk of ESCC.	NONE
Genetic studies	Keeley et al/2014/ case-control [271]	A panel of inflammatory biomarkers in 159 individuals (81 controls, 36 EC cases, 28 LC cases, and 14 HNC cases) measured using Luminex assay in serum samples collected at least 2 years prior to cancer development.	A significant increase of inflammatory biomarkers in future EC and LC patients compared to controls. A significant association between IL-1Ra, IFN-a2, FGF-2, and IL-12p70 for the future development of EC.	Probable
Genetic studies	Aghcheli et al/2012 [200]	Assessment of serum hyaluronic acid and laminin levels using enzyme-linked immunosorbent assay in 20 GCC, 23 GNCC, and 20 ESCC cases and 25 controls for potential tumor markers.	A higher mean serum hyaluronic acid and laminin in cancer cases compared with controls. A significant correlations between hyaluronic acid levels and GNCC (Beta-coefficient = 0.390; $p = 0.01$) and ESCC (Beta coefficient = 0.332;$p = 0.05$) in multivariate models.	Probable
Nutritional deficiencies	Hashemian et al/2018/ Cohort [272]	Assessment of intake of peanuts, walnuts, and mixed nuts (including seeds) using a validated food frequency questionnaire at baseline in a cohort study in 50,045 subjects between 2004 and 2008.	Important inverse relationship between nut use and the risk of ESCC compared with non-consumers (HR = 0.60, 95% CI = 0.39–0.93, p-trend = 0.02, and HR=0.52, 95% CI = 0.32–0.84, p trend = 0.002, respectively).	Probable
Genetic studies	Sahebi et al/2016 [273]	Determination of the expression patterns of linc-ROR and its two novels spliced variants ESCC using qrt PCR assay in 30 tumor biopsy samples and 30 normal tissue biopsies.	A significant up-regulation of linc-ROR ($p = 0.0098$) and its variants 2 ($p = 0.0250$) and 4 ($p = 0.0002$) in tumor samples of ESCC, compared with non-tumor tissues.	Possible
Genetic studies	Ghasemi et al./ 2018/[274]	Determination of the expression level of miR-371–373 clusters analyzed in biopsies of tumor and tumor margin in 36 ESCC cases using qrt PCR.	Significant up-regulation of miR-371, miR-372, and miR-373 in ESCC compared with their adj acent healthy cells ($p < 0.05$).	Probable

Risk factors	Author/Year/ Type of study	Methods	Outcome	Relation with EC
Genetic studies	Khazaei et al./ 2017 [275]	Evaluation of miR-451 expression in serum (n;39) and tissue (39) samples from ESCC patients using qRT-PCR. Assessment of exosomal miR-451 secretion into the cell lines normal human fibroblasts (HFSF-PI3) and esophageal cancer cell line (KYSE-30).	Over-expression of miR-451 in serum samples of ESCC cases. An important induction of miR-451 exosomal secretion into the conditioned medium and important induce. miR-451-over-expressing fibroblasts considerably induced migration tendency in KYSE-30 cell line.	Possible
Nutritional deficiencies	Joshaghani et al/ 2017/ ecological [276]	Measurement concentrations levels of zinc, copper, magnesium, and manganese in 227 serum samples in the high-risk and low-risk regions for EC using an atomic absorption spectrometer.	A significant decrease of the mean serum level of zinc in the high-risk area compared with the low-risk area. No important divergence in serum levels of copper, magnesium, and manganese in the low-risk and high-risk areas.	Probable
Low socio-economic status	Islami et al/ 2013/ case-control [277]	Conditional logistic regression form data of 297 ESCC cases (149 women) and 568 controls (290 women) calculated odds ratios (ORs) and corresponding 95% confidence intervals (CIs).	An inverse correlation between the number of children in women and ESCC risk. In contrast, a correlation between the number of miscarriages/stillbirths and ESCC risk. The protective influence of female hormonal factors on ESCC risk.	Probable
Nutritional deficiencies	Golozar et al/ 2016/ case-control [53]	Investigation on food preparation methods, sources of drinking water, and dietary habits from 300 cases and 571 controls using a structured questionnaire and a semi-quantitative FFQ.	A significant reduction and rise in ESCC odds with fish intake and red meat consumption, respectively (0.4, 0.8). A 4-fold increase in the odds of ESCC with drinking unpiped water (2.2, 8.1).	Probable
Nutritional deficiencies	Rahimzadeh-Barzoki et al/2014/ ecological [278]	Investigation of Se concentrations in 69 rice samples using the voltammetric method.	An important positive association between the levels of Se in rice and the incidence rate of EC from high EC rate regions ($p = 0.03$).	Probable
Genetic studies	Sepehr et al/2004/ ecological [279]	Analysis of genetic polymorphisms in ten genes risk of EC (CYP1A1, CYP2A6, CYP2E1, GSTM1, GSTP1, GSTT1, ADH2, ADH3, ALDH2, and O6-MGMT) among Turkomans, Turks, and Zoroastrian Persians using either Sequenom w or APLP assays.	A high frequency of four alleles (CYP1A1 m^1, CYP1A1 m^2, CYP2A6*9, and ADH2*1) in Turkomans compared with Zoroastrians.	Probable
Fungus contamination	Ghasemi-Kebria et al/ 2013/ cross-sectional [91]	Measurement of aflatoxins levels in wheat flour samples obtained from low and high-risk areas of EC using the HPLC method.	A significant increase levels of total AF ($p = 0.03$), AFG2 ($p = 0.02$), and AFB1 ($p = 0.003$) in high-risk area. The humidity of silos was the most significant determinant of AF contamination of WF.	Possible

Risk factors	Author/Year/ Type of study	Methods	Outcome	Relation with EC
Chemical carcinogens	Kamangar et al./ 2008 (280)	Measurement of the concentrations of PAHs was in dry leaves of eight commercial brands of yerba mate and in infusions made with hot (80°C) or cold (5°C) water using GC/MC assay.	A high concentration of carcinogenic PAHs in yerba mate leaves and in hot and cold mate infusions.	Probable
Genetic studies	Biramijamal et al/2001 (281)	Analysis of 34 ESCC patients for the presence of mutations in exons 5–8 of the p53 gene by PCR and the direct sequencing method.	62% (21/34) had one or more p53 gene point mutations. Over one-third (38%) of the 21 mutations, we identified were transitions at CpG sites	Possible
Genetic studies	Taghavi et al/.../ case-control (188)	Detection of the p21 polymorphism in the 3'UTR and codon 31 of samples from 126 ESCC cases and 100 controls using the PCR-RFLP method.	Non-significant association of p21 genotypes with the risk of ESCC. synergistic interaction between the presence of these polymorphisms and cigarette smoking in ESCC carcinogenesis ($P = 0.02$, OR=8.38; 95% CI:1.03-67.93)	Probable
Physiologic or pathologic predisposing conditions	Nasrollahzadeh et al/2012/ case-control (261)	Measurement of serum pepsinogen I (PGI) and pepsinogen II (PGII) among 293 OSCC cases and 524 controls using enzyme-linked immunosorbent assays	A two-fold increased risk of OSCC with gastric atrophy (PGI < 55 mg/dl -1) (OR = 2.01, 95% CI: 1.18, 3.45). Poor dental health and gastric atrophy increased the risk of OSCC (OR = 4.15, 95% CI: 2.04, 8.42).	Possible
Diet, low socioeconomic status, chewing of nass	Cook Mozaffari et al/1979/ case-control (28)	Investigation on the use of sheep's milk and yogurt, sesame oil, chewing of nass, making of carpets, use of pregnancy diets, salting and sun-drying of meat, and use of wild spinach from 344 cases and 181 controls using a questionnaire.	No association between the use of sheep's milk and yogurt, sesame oil, with EC. The strong correlation between low socioeconomic status and low consumption of fresh fruit and vegetables with the risk of EC.	Possible
Infections	Moradi et al/ 2006/ case-control (63)	Examination presence of HPV in 85 patients with ESCC and 31 non-cancerous of the esophagus using PCR based-sequenced.	Non-important divergence between the rate of HPV positive in cancerous and non-cancerous tissues. HPV is a probable etiologic agent in EC.	Probable
Consumption habits (tobacco, alcohol, opium, mate and hot drinks use)	Ghadirlan et al/1985/case-control (35)	Determination of morphine metabolites and AP-T I /2 in 1590 urine and saliva samples in regions of the very high, high, and moderately low incidence of EC using a Gilford Stasor spectrophotometer and radioimmunoassay.	Much high morphine metabolites in regions of the high and very high incidence of EC than in low-incidence regions. A high prevalence of positive urinary morphine metabolite in members of households with a case of EC. Opium use is one of the factors implicated in the etiology of EC.	Possible

Risk factors	Author/Year/ Type of study	Methods	Outcome	Relation with EC
Genetic studies	Marjani et al/ 2010/ case-control (282)	Determination of NQO1 C609T genotypes in 93 ESCC cases and 50 control subjects by PCR-based assay. Also, immunohistochemical techniques were used to identify PAH-DNA adducts in ESCC and normal esophageal tissues.	No important divergence in distributions of NQO1 genetic polymorphism between cases and the control group. A significant increase of the level of PAH-DNA adducts in ESCC tissues of cases than in healthy tissues adjacent to tumor tissues and in normal esophageal tissues of healthy controls. No important association between cigarette smoking and PAH-DNA adducts.	Possible
infections	Moradi et al/2002 (283)	Molecular analysis of HPV (HPV L1 gene) in 85 SCC samples using PCR based-sequencing.	HPV-16 is the most common (54.7%) type of HPV.	Possible
Physiologic or pathologic predisposing conditions	Abnet et al/2008/case-control (256)	Investigation on socioeconomic status, life-long history of tobacco uses, tooth loss and oral hygiene, and dietary data from 283 cases and 560 controls using a structured questionnaire and FFQ.	A significant association between ESCC and more decayed, missing, or filled teeth with a median (interquartile range) of 31 (23-32) ($P = 0.0045$). A significant association between the larger number of decayed, missing, or filled teeth and lack of daily tooth brushing, and risk of ESCC.	Possible
Nutritional deficiencies	Islami et al/2009/ pilot cohort study (284)	Assessment of nutrient intake in 131 healthy participants in RDAs and LTIs. Also, compare the intake of 27 food groups and nutrients among several population subgroups, using mean values from the twelve recalls.	Rigorous inadequacy in vitamin consumption among women and rural dwellers and clear changes in nutrient consumption between rural and urban inhabitants.	Possible
Genetic studies	Abedi-Ardekani et al/ 2011/ case-control (285)	TP53 mutation analysis by direct sequencing in 119 ESCC cases.	The highest rate (89.9%) of TP53 mutations ever reported in any cancer anywhere.	Possible
Consumption habits (tobacco, alcohol, opium, mate and hot drinks use)	Shakeri et al/2012/ Case-Control (286)	Investigation on demographics, family history of cancer, history of tobacco, opium and alcohol use, drinking tea habits, oral health, and socioeconomic variables from 300 cases and 571 hospital/ neighborhood controls using a structured questionnaire.	No considerable divergences in exposure data for tobacco-related variables such as cigarette smoking, chewing Nass, and hookah usage. Neighborhood controls were higher to hospital controls in assessing the risk of ESCC related to opium exposure.	Possible
Genetic studies	Taghavi et l/2010/ Case-Control (178)	Investigation of expression of p53 and p21 proteins in tumor tissue from 80 ESCC patients and 60 paraffin-embedded blocks of adjacent healthy specimens from the cases, along with normal esophageal tissue from 80 healthy subjects using immunohistochemically.	An association between the over-expression of p53 with cigarette smoking in ESCC carcinogenesis. p21 an association between over-expression with poor prognosis.	Possible

Risk factors	Author/Year/ Type of study	Methods	Outcome	Relation with EC
Consumption habits (tobacco, alcohol, opium, mate and hot drinks use)	Islami et al/2019/ population-based prospective (42)	50,045 individuals aged 40–75 years subjects were followed-up for a median duration of 10.1 years (505,865 person-years) to assessed tea consumption temperature using validated methods and collected data on several other tea consumption habits and potential confounders.	A definite link was shown between consumption hot tea with a risen risk of ESCC. Furthermore, High frequency and high amounts of hot tea consumption could make the Golestan population significantly susceptible to ESCC.	Strong

Abbreviations: Flame Atomic absorption spectrometry (FAAS), antimony (Sb), strontium (Sr), and zinc (Zn), EC, FFQ, polycyclic aromatic hydrocarbons (PAHs), 1-hydroxypyrene glucuronide (1-OHPG), Immunoaffinity chromatography (IC), Synchronous fluorescence spectroscopy (SFS), ESCC ..., †Alcohol consumption was not associated with ESCC risk., OSCC, PAHS …, single base extension (SBE), Benzo(a)pyrene BaP, high-performance liquid chromatography combined with fluorescence (HPLC-FL), inductively coupled plasma/mass spectrometry (ICP/MS), maximum concentration level (MCL), Esophageal adenocarcinoma (EA) and Squamous cell carcinoma (ESCC), Fumonisin B1 (FB1), thin layer and high pressure liquid chromatographies (HPLC/TLPLC), instrumental neutron activation analysis (INAA), lung cancer (LC), head and neck cancer (HNC), interleukin (IL), fibroblast growth factor (EGF), interferon (IFN), gastric cardia cancer (GCC), gastric noncardia cancer (GNCC) and 20 esophageal squamous cell carcinoma incident, quantitative real-time PCR (qRT-PCR), amplified product length polymorphism (APLP) cases, gas chromatography/mass spectrometry (GC/MC), Salivary antipyrine half-life (AP-T I /2), Human Papillomavirus (HPV), Daily Allowances (RDAs) and Lowest Threshold Intakes (LTIs).

day, and this is a common habit in this region. It has been shown in a meta-analysis that drinking hot tea is one of the significant etiological risk factors for ESCC in Golestan province (40). A research study in Golestan province showed that in high-risk areas of EC, people consume more tea and hot drinks. Another cohort study showed that consuming tea with high temperature increases the risk of EC for 2-3 fold (19). However, the evidence is too sparse to analyze the preference for stronger or lighter tea or chemical components of tea. It seems that further investigations are needed about the heterogenicity of the chemical constituents of tea in this area. The probable link between hot tea consumption and EC in Golestan province have been considered in previous case–control studies (28,41), but a drawback of both of these studies is their retrospective design and that they used only self-perceived reporting of tea drinking temperature. In a prospective cohort study in Japan, it was shown that drinking hot tea was linked with a 1.5-fold intensified risk of EC death. In the recent, large, prospective Golestan Cohort study, Islami and colleagues (42) have examined the correlation between measured tea drinking temperature, as well as subjective preference for hot tea drinking, time from pouring tea to drinking, and other tea-drinking habits, and risk of ESCC. A definite link was shown between the consumption of hot tea and a raised risk of ESCC. In addition, a high rate and high amounts of hot tea consumption could make the Golestan population significantly susceptible to ESCC. So, they recommend the community to postpone rinks to cool

to < 60°C before drinking. Additional investigation is required to find the correlations between mechanisms, amount of tea used, or consumption tea at more moderate temperatures and ESCC risk.

Nutritional Deficiencies

Vitamin and Micronutrient Deficiency
Insufficient intake of fruits and vegetables clearly increase the risk of ESCC (43). Regular use of vitamins A, C, E, riboflavin, zinc, selenium, and insufficient intake of fresh fruits and vegetables decreases the risk of EC. Dietary factors seem to be the leading cause of ESCC in Golestan province (43). A meta-study indicated fruits to be more useful than vegetables. Similar results were reported by the Japan Public Health Center-based Prospective Study Group (44). Tumor formation could prevent the antioxidant effects of some vitamins in people of several regions with extremely high-risk of EC; for example, people in Linxian (a high-risk region of EC in China), had acute insufficiencies in some vitamins and minerals (45). The consumption of vitamin C was under the suggested value in 41% of men and 64% of women in urban regions and 97% of men and 100% of women in rural regions of Golestan province (46). These insufficiencies in nutrient use may impact on the higher risk of ESCC, primarily in rural areas (28). One of the significant risk factors of upper gastrointestinal tract cancers is selenium deficiency. It has been shown that high selenium status decreases the risk of EC in selenium-

inadequate people (28, 47, 48). Studies showed that in Golestan province, the blood level of selenium is in the recommended range; therefore, this risk factor may not be necessary for Golestan province (28,47,48). Some studies showed severe insufficiency in vitamin consumption among rural populations and women in Golestan and the highest insufficiency among rural women, but protein consumption in this region is upper than the recommended values (19,49). The data from the Golestan Cohort Study (50) conducted on 505,865 person-years of follow-up, characterized multiple risk factors such as thermal injury (from hot drinks), exposure to PAHs (from opium and indoor air pollution), and nutrient-inadequate diets. Insufficient consumption of fruits (HR 1.48; 95% CI 1.07–2.05) and vegetables (HR 1.62; 95% CI 1.03–2.56), were considerably related to the increased risk of ESCC, in a dose-dependent manner. Thus, their results strongly suggested that ESCC in this area is a multifactorial problem, necessitating multiple risk factors for its development.

Water supply

A possible association between the source of drinking water and ESCC has been reported from Iran and China (51-53). The potential and possible risk factors may be associated with the occurrence of carcinogenic complexes, such as nitrates, phosphates, oil, and heavy metals, or lack of protective elements, such as specific trace elements, in the drinking water (54,55). In an ecological study conducted on 45 villages in high-risk areas including a broad spectrum of EC mortality rates in Golestan province, it was observed that in comparison to low-risk areas, drinking water comprises extra nitrate, sulfate, antimony, and strontium concentrations in the high-risk areas of Golestan (52) and also are above the maximum concentration level recommended by the environmental protection agency (EPA). An inverse association has also been suggested between piped drinking water with improved hydrogeochemical characteristics and the incidence and mortality rates of EC in Golestan province and Linxian in China (56). However, researchers suggested that the declared association cannot be only due to access to piped safe drinking water.

Infections

Historically, based on histological surveys by Syrjänen and colleagues in 1982, a correlation between HPV infection and ESCC was observed (57). On the other hand, in a series of surveys through immunohistochemistry and molecular methods, a link between HPV and ESCC in low and high-incidence areas has also been reported (43,58,59). In addition, in many case series from different parts of the world, including Africa, South America, Europe, and Asia, the frequency of HPV detection was between 0% to 54% (60,61). In a systematic review (62) including 61 studies on a variety of HPV-associated cancers in Iranian populations, HPV occurrence in ESCC was 23.1%, and HPV16 was the most frequent (40.9%) HPV types involved in ESCC. Additionally, the pooled data of this analysis propose that HPV may have a main role in the development of ESCC. Some cross-sectional and case-control studies conducted in Golestan using polymerase chain reaction have been already found the high frequency ($\geq$ 43.7%) of HPV in ESCC samples (63). Although, several reports have been declared no link between HPV and ESCC (64-66), the major reasons for these discrepancies, inconsistency, and incoherency in immunohistochemistry, and serological and molecular findings in ESCC may be due to geographic variation, type of study design, and absence of standardized testing methods (67,68). Because of these inconsistencies and conflicting results, the IARC suggested that more, continuous, and nationwide epidemiological surveillance investigations are highly required to prove the carcinogenicity of HPV in ESCC (69). Therefore, the exact association between HPV and ESCC carcinogenesis is unknown and remains controversial (70). *Helicobacter pylori (H. pylori)* is a gastrointestinal bacterial pathogen considered as the causative agent in infection-related cancers (71). This bacterium has frequently seemed to have a precancerous role in gastroesophageal cancers, most notably ESCC (71). Nevertheless, the results of the published studies have shown substantial heterogeneity (72,73), and mostly the exact role of *H. pylori* in ESCC carcinogenesis is not clear and controversial. Surprisingly, *H. pylori* has shown a diverse pattern of correlation with two histological types of EC (positive association with ESCC and protective association with EAC). A meta-analysis showed a protective relationship between *H. pylori* and EAC (OR = 0.41, 95% CI: 0.28-0.62) and no correlation with ESCC (OR = 1.08, 95% CI: 0.76–1.53) (72). But some reports have

shown a significant role of *H. pylori* colonization in the stomach and ESCC (2-fold increased risk of ESCC) (74,75). A study conducted in China has revealed a link between bacterial microbiota of saliva and risk of ESCC in patients with ESCC (76).

Mycotoxin contamination

Mycotoxins are secondary metabolites with low molecular weight produced by some filamentous fungi, including Aspergillus, Alternaria, Penicillium, Fusarium, etc., and may develop on various foods, causing severe risks to human and animal health (77-79). Human exposure to mycotoxins occurs via direct contact (consumption of plant-derived foods and animal products) and inhalation (exposure to air and dust containing toxins) (80). These mycotoxins are known to be either carcinogenic (e.g., aflatoxin B1, ochratoxin A, fumonisin B1), estrogenic (zearalenone), neurotoxic (fumonisin B1), nephrotoxic (ochratoxin), dermatotoxic (trichothecenes), or immunosuppressive (aflatoxin B1, ochratoxin A, and T-2 toxin) (81). Some studies have reviewed the health hazards of mycotoxicosis for humans or animals (78,82). Fumonisin B1 (FB1) is the most predominant member of the fumonisin family of mycotoxins, and previously published studies in the 90s in China and South Africa (the high risk of EC areas) have established its relation to the development of EC (83-86). The exact mechanisms for carcinogenesis remained controversial. A strong association between fumonisin contamination of foods and some environmental factors included humidity, drought stress, temperature, and rainfall has been documented in different geographical regions (87). Ecologic studies in Asia and Africa have shown higher exposure to fumonisins in high-risk areas of EC (88, 89). There is scarce data about the association between FB1 and the occurrence of EC in Golestan province. Consistent with other published epidemiological studies (83, 84, 90), Alizadeh and co-workers (87) in a population-level ecological study have also shown a significant positive association between the use of FB1 contaminated foods and the risk of EC. In addition, a possible correlation between aflatoxin (AF) contamination level of wheat flour samples and the risk of EC in Golestan province reported in a cross-sectional study by Ghasemi-Kebria and others (91). Compared to low EC-risk area, the levels of AFB1 was considerably higher in samples obtained from high risk area in Golestan province (*p* = 0.003). They Also found that humidity of silos was the significant cause of AF contamination of wheat flour samples. However, a case-control study conducted in high-risk areas of EC (Linxian, China) observed no correlation between fumonisin exposure and risk of EC (92), although the indices of fumonisin exposure used were unclear, and the outcomes were not definite. More epidemiological studies are needed to ascertain or reject a link between fumonisins and EC.

PAHs

PAHs contain three or more fused aromatic rings (for example to be human carcinogens: benzo-a-anthracene, benzo b-fluoranthene, benzo j- fluoranthene, benzo k- fluoranthene, benzo-a-pyrene, dibenz-a,h-anthracene, indeno-1,2,3-c,d-pyrene) and are produced by carbonization (coal, crude oil, petroleum, gas, charcoal, and wood stove), incomplete combustion of organic matter, and metal production processing (aluminum, iron, and steel) (93). They are existed in soil due to deposition from sewage, particular wastes such as oil or gasoline spills, urban run-off, and atmospheric fallout. PAHs are proposed as the critical risk factor for developing EC (94). Contamination happens through inhalation, ingestion, or percutaneous penetration. Direct contact with the external environment happens in more than half of the cancers in the surface epithelium, such as the esophagus epithelium (95). Various risk factors, including the route of exposure, the chemical composition of the mixture, the presence of co-exposures, and genetic susceptibility might be conferring in the carcinogenicity of PAHs (95). There are epidemiological similarity features of ESCC in both Golestan province (Iran) and Linxian (China) (high-risk areas of ESCC). According to the previous epidemiological published data in Linxian and Golestan, the occurrence of high levels of PAHs or PAHs metabolite in ESCC cases, staple foods, urine, and esophageal tissue samples have been documented (24,94,96); nevertheless, the previous data from Golestan province showed low levels of PAHs in staple food samples (24,97). Remarkably, PAHs exposure pattern was shared in all subgroups of the study, including both sexes, both urban and rural areas, and in smokers and non-smokers (94). A case (ESCC carcinoma)-control study in Golestan province showed a higher level of PAH DNA-

adducts in the case group than the healthy group (98). Extremely high concentrations of carcinogenic PAHs (benzo[a]pyrene) recovered from yerba mate leaves, and in hot and cold mate drinks, endorse the hypothesis that the carcinogenicity of mate may be associated with its PAHs content. Significant amounts of PAH existed in: smoked foods (such as charbroiled foods, pizza prepared in a wood-burning oven, and in barbecued meat), tobacco smoking, opium and nass consumption (high urinary level of 1-OHPG; a stable PAH metabolite), occupation (foundry workers, chimney sweeps, blast furnace, and coke-oven workers, vendors of broiled food, steel plant and waste incineration workers, and coke-oven exposure), indoor air pollution (combustion of solid fuels), and environmental air pollution (car exhaust, industrial emissions, and smoke) (99-103). Polymorphisms variations in genes encoding the enzymes in the metabolic pathways of PAHs, including cytochrome P450 such as CYP1A1/2&1B1 and glutathione S-transferases such as GSTM1, GSTP1, and GSTT1 might affect the levels of PAHs metabolites (104,105). Islami and colleagues (106), in a cross-sectional study, considered the patterns of non-smoking associated exposure to PAHs in Golestan province. They showed that mutations in some CYP genes were related to lower levels of 1-OHPG, although deletions in GSTM1 and GSTT1 were related to higher levels of 1-OHPG. Food processes such as whole grilled chicken, meat burgers, and grilled vegetables were significant dietary sources of PAHs. In Golestan province, the amount of PAHs is in the high level, because the use of smoked foods such as charbroiled foods and opium and nass consumption is in the high level in the people's life style (95). It is suggested that in high-risk areas, decreasing the levels of PAHs might be an active policy for controlling ESCC.

N-nitrous compounds (NNCs)

Mostly, NNCs, including nitrosamines and nitrosamides, are potent carcinogens in animals and cause various cancers, including cancers of nasal cavity, esophagus, and stomach (107). Nitrosamines commonly used in industries (pesticides and some cosmetics), most rubber products, latex products such as balloons, and various foods and other consumables (108). They naturally exist in many materials such as foods (protein resources: meat, fish,

dried and pickled vegetables), water, and tobacco. The principal direction is exposure to nitrosamines through cigarette smoke (109). Bacteria in saliva convert nitrate to nitrite; thus, high concentrations of nitrite occur in the mouth and esophagus. Swallowing of saliva results in nitrite reaction to acidic gastric juice and conversion to nitrosating species (110). High temperatures that occurred during frying can also increase the formation of nitrosamines (111). An association between the amount of NNCs in gastric acid with dysplasia and neoplastic changes in the esophageal epithelium has been revealed (112). Nitrate (NO_3) and nitrite (NO_2) are frequently consumed as food additives in processed meats such as ham, bacon, sausages, and hot dogs to prevent microbial spoilage, and preserve meat products' recognizable appearance and flavor. High use of processed meats is related to increased gastric cancer risk, and it seems that nitrates/nitrites are the leading cause for that (113). In Cixian, China, as a high-risk area, the presence of N-nitro compounds and precursors have been described in salted vegetables and preserved fish (114). In Golestan province, because of the high uses of smoked and salting methods for drying foods and also the use of pickles and black pepper, especially in fish foods, the nitrosamines level is higher than the maximum. Kamangar and colleagues (115) showed that the amount of nitrosamine in the saliva of Gonbad population (high risk area in Golestan province) was 4 times more than Germany.

Acetaldehyde

The main route of exposure to acetaldehyde in humans is drinking alcohol (116). The other source of acetaldehyde exposure, include incomplete wood combustion in woodstoves and fireplaces, the roasting of coffee, tobacco burning, vehicle exhaust fumes, and coal and waste refining (117). Acetaldehyde is the first and more toxic metabolites derived from alcohol by oxidization from ethanol with mediate alcohol dehydrogenase enzyme (ALDH) (118,119). IARC characterized acetaldehyde in the group I carcinogenic substances for EC (120). Mutation in ALDH coding genes such as ADH1B and ALDH2 increases the incidence of ESCC (121). Maybe the consumption of alcohol increases the risk of cancers in upper aerodigestive tracts (oral cavity, throat, pharynx, larynx, and esophagus), liver, colon, rectum, and breast (29,122). Carcinogenic

acetaldehyde affects the esophagus epithelium via intrinsic (cellular metabolism such as inflammation, oxidative stress, and infections, as well as from chemicals derived from complex interaction with oral microbiome) and extrinsic (water contaminants, air pollutants, diet, and drugs) pathways (119,123). The In vitro effects of acetaldehyde including human lymphocyte mutations, mutagenic DNA-adducts, sister chromatin exchange, cellular proliferation exposure to reactive oxygen species (ROS), and prevention of DNA repair (124). In contrast with a case-control study in Spain (125), alcohol drinking was not considered to be related with ESCC in rural high-risk areas of China (56) and Golestan province (115). Low alcohol consumption in Golestan province led to this observation.

Socioeconomic Status (SES)

It is a long time thought that EC is a disease of the poor and socially deprived. Although SES is not an exact biological risk factor, it can impact the health status via behavior and lifestyle, environmental exposure, and access to health care (107). Historically, the first possible correlation between low SES with EC risk was noted in 1939 by Watson (4). Currently, a series of epidemiological studies with diverse designs, diverse SES indices, and diverse geographical regions have established a positive correlation between low SES and EC risk (126-128). SES has been determined as an essential factor of the incidence of cancer, cancer stage at diagnosis as well as treatment choices in developed countries (129). SES factors, including sexual activity, living area, educational level, marriage, and wealth affect the incidence of EC (130). A significant association between low SES and higher risk of ESCC has been established (107,131-137). Although, the low relation SES with an increased risk of EAC is unknown (138). In a recent cross-sectional association study by Wong and co-workers (9) the incidence ratio between EAC and ESCC and its association with SES improvement (Gross Domestic Product [GPD] and Human Development Index [HDI]) across 41 countries on a global basis was reported. Results of their study presented that countries with higher SES had higher EAC: ESCC ratio in association analyses, and mainly EAC was positively associated with SES development. These findings could be elucidated by the capacities and accessibility of

healthcare services, which are fundamental for early diagnosis and management. Some studies conducted in Scotland (139), Swedish (138) displayed the significance of various SES factors and risk of EC. The risk of both EAC and ESCC significantly increased (> 2-fold) with low SES and a life without a partner for long periods of time. The higher use of tobacco or alcohol, opium, nass, and nutritional deficiencies probably involved in increasing EC (107). SES could be affected by the cancer stage diagnosis, longer health care delay, and varying receipt of treatment for EC (140). A population-based study (141) included 20,488 cancer patients diagnosed in 2002 in Taiwan studied the link between SES (individual and neighborhood) and mortality rates for primary cancers. They indicated that cancer patients with low individual SES have the highest risk of mortality, even under a universal health-care system. Wu and colleagues in recent population-based study (142) conducted of 4097 patients diagnosed with EC during 2002 to 2006 in Taiwan investigated the correlation between SES and the survival of working-age patients with EC. Their results showed a notable decreased risk (39%) of mortality in working-age patients with high individual SES than patients with low individual SES (OR 0.61, 95% CI 0.48–0.77). A recent published data (129) conducted on patients diagnosed with primary EC in China showed a significant association between health-care delay > 2 months in patients with lower SES (OR 2.271; 95% CI 1.069-4.853). In addition, SES was found to be related to health-care delay, tumor stage and treatment modalities in EC. Only two case-control studies (110) conducted in Golestan province have surveyed the link between SES and ESCC, and they proposed an inverse relationship consistent across studies (25). In line with the results of a previous case-control study conducted in Golestan, the findings of a population-based case-control study (110) conducted in Golestan province in 2009 showed a strong inverse link between ESCC and SES factors (education level, marriage status). Interestingly, residing in rural areas for a long time > 20 years showed the considerable increase (3-fold) risk of ESCC (OR = 2.79, 95% CI 0.97–8.03). Nevertheless, the exact association between educational level and risk of ESCC remains mainly controversial. The researchers suggested that public health, more health education, improved early detection, and disease resection, greater access to

medical resources, the institution of social welfare programs, and also national health insurance are highly necessary to efficiently improve the overall outcomes of EC in patients with low individual SES.

Families studies

Many studies demonstrated that having EC in a family may increase the risk of this disease up to 3 fold, especially among first-degree relatives (FDRs) (143-147). In this regard, a positive correlation has been observed in high-risk areas like China and Iran. Several case-control studies during 1997-2007 conducted in northern Iran has been described as a positive correlation between family history (FH) and EC among patients (odds ratios of 1.8 to 7.6) (145,148). On the other hand, a considerable increase > 2-fold in the EC risk among FDRs in the high-incidence population has been documented (145,148), which is in line with the previously published data in the other parts of the Asian EC belt (149,150). A cohort study in China showed that the EC-related mortality ratio was 2.36 among people with FH-FDR of this disease (143). Also, some previous epidemiological studies conducted in endemic areas of China have reported a higher risk of such cancer in people with an FH of EC. Frequently, family members have a common genetic background. Thus, an FH-FDR of cancer can be considered as a marker in the etiology of EC (151). When considering the genetic effects on the progress of cancer, the same risky habits may be seen within the same family members, indicating an exact association between FH and cancer occurrence (144,151). Some valid reasons have been reported to support this hypothesis that FH-FDR plays an important role in the incidence of EC. First of all, persistent familial risks have been seen among individuals who were not exposed to lifestyle risk factors; for example, those who never smoke and infrequently drink alcohol. Secondly, an apparent dose-response relationship has been reported with multiple affected relatives (152). In addition, the higher risk was declared in younger affected relatives, indicating the role of genetic background in EC rather than environmental effects (153). Finally, other environmental- and lifestyle-related cancers such as stomach cancer (dietary factors-related), liver cancer (alcohol-related), and lung cancer (smoking-related) have no significant effects on the risk of EC occurrence in individuals with an FH-FDR. In Iran, it has been found a hazard

ratio of 2.3 among individuals whose EC was attributed to FDR (145). In a study (149) conducted in the 1970s, 47% and 15% of 427 patients with EC of Turkmen ethnicity reported a positive family history of EC or of other cancers, respectively. In another study conducted in Golestan province (145), on 167 ESCC cases and 200 controls of Turkmen race, the risks of FDR-EC of cases and controls were 34% and 14%, respectively (relative risk = 2.3). The risk of disease is monotonically increasing by a growing number of affected relatives, particularly if both parents were affected, which cause an 8-fold more risk of ESCC for their offspring. By the age of 75, it was approximately calculated that about %12 of the first-degree relatives of ESCC patients might progress towards the malignancy, while this number was %7 for those relatives of the healthy control groups (154). The relation between FH-FDR and EC were less consistent in Western countries such as the United States (155) and Sweden (156), contrary to high-risk regions. This discrepancy in different regions might be due to differences in the frequency of esophageal susceptibility alleles and variation in major attributable lifestyle and environmental risk factors.

Genetic studies

The development and progression of EC is a multistage process that can be identified with genome-wide association studies (GWAS). It will occur because of some mutations, deletions or chromosomal abnormalities (157-159). Some of them are discussed in the following; GWAS is a tool for finding genetic markers for various diseases. The development of EC is a multifactor and multistage process involving the activation of oncogenes and dysfunction of tumor suppressor genes (160), such as mutations and deletions of Rb, p53, p16, APC, MCC, and DCC or chromosomal abnormalities such as amplification of C myc, Cyclin D, epidermal growth factor receptor gene, and int-2 gene (157-159). Single nucleotide polymorphisms (SNPs) associated with EC have been identified in the PLCE1 gene, TP53 gene, and HLA class II genes (161,162). Phospholipase CE1 (PLCE1) is an isozyme of phospholipase C family regulating cell growth, differentiation, apoptosis, and angiogenesis (163). So, it is involved in the development and progression of EC (164). PLCE1 gene polymorphism rs2274223, which is located in 26th exons are one of the most studied loci, which is

a risk factor of carcinoma of the esophagus, is able to make PLCE1 mRNA and upregulate its expression in EC. The PLCE1 rs2274223 and rs11599672 SNPs were related to susceptibility to ESCC in northern China (165).

SNPs (single nucleotide polymorphisms)

The occurrence of SNPs in phospholipase CE1 (PLCE1) and the gene loci rs2274223 that has a role in its upregulation will impact on apoptosis, and cell growth, which resulted in EC, has been reported (161,164). In a study in china rs2274223 and rs11599672 SNPs were reported as risk factors for EC (165). These SNPs have also been identified in TP53 and HLA class II genes that can be associated with the disease (161,162). The SNP alteration (A to G at position 313) the 105th amino acid from isoleucine to valine (Ile/Val 105; rs1695) of the GSTP1 gene has been linked with changed differential metabolism of various toxicants and increased risks of various cancers in epidemiological studies (166-168). The pooled results data extracted in a recent meta-analysis (169) included 20 case-control studies (2,992 cases and 4,758 controls), proposed that GSTP1 Ile105Val polymorphism drastically increased the risk of developing EC in Caucasians populations nevertheless no significant association was observed in other (Asians, African) or mixed ethnicities and different histological types. The GSTP1Ile 105Val polymorphism in association with EC risk has been addressed (170). However, the results were very inconsistent with odds ratios ranging between 0.1 and 4.6 (171). Glutathione S-transferase Pi 1 (GSTP1) can play as a marker of malignancy or anticancer drug resistance in some cancers. On the other hand, Ogino and colleagues reported that GSTP1 considerably related to malignant potential and maybe a novel predictor of drug resistance in ESCC patients (172).

Genetic polymorphisms of enzymes

The glutathione S-transferases (GSTs), characterized into four main groups including GSTA (a), GSTM1 (l), GSTT1 (h), and GSTP1 (p) are concerned in the metabolic detoxification of many carcinogenic reactive electrophilic compounds including benzo(a)pyrene and other carcinogens in tobacco smoke, and alcohol dehydrogenases (AdHs)/ aldehyde dehydrogenases (ALds) (169). It has been investigated that genetic polymorphisms such as

XRCC1, XRCC5, XRCC6, ALDH2, and CYP1A1 can be striking in the onset of EC (173-175). Polymorphism may take place in different situations and will play a role in pathogenesis. They may affect the enzymes and produce substances that can make people more or less exposed to cancer. The development of polymorphism in Interleukin-10 (IL-10), which is an immunoregulatory cytokine, is noticeable when the inflammation begins to appear in esophageal tissues (176). In a Chinese population three SNPs (-1082G/ A rs1800896, -819T/C rs1800871, and -592A/C rs1800872) that are related to its polymorphism had been identified (177). Also, a polymorphism in the aldehyde dehydrogenase-2 gene, which has roles on blood acetaldehyde concentration, the methylenetetrahydrofolate reductase gene, a central enzyme in folate metabolism, and the CYP1A1 gene can affect EC. In previously published data in Iran, there is a hypothesis that possibly 10 polymorphisms may cause EC (58). In an ecologic study (178), Sepehr and colleagues evaluated the frequency of genetic polymorphisms of enzymes in genomic DNA at high-risk, medium-risk, and low-risk groups included Turkomans, Turks, and Zoroastrian Persians, respectively. Turkomans had a higher occurrence of CYP1A1 m^1, CYP1A1 m^2, CYP2A6*9, and ADH2*1 alleles that are hypothesized to favor carcinogenesis compared with Zoroastrians ($p < 0.001$). However, none of these four alleles had a high enough occurrence in Turkomans to explain the high rates of EC in this group. Compared to some Asian populations in lower-risks of EC, Turkomans had lower frequency of CYP1A1 m^1, CYP1A1 m^2, CYP2A6*9 alleles. Thus, it might be possible that these variants play a key role in the risk of EC among Turkomans in Iran.

Tumor suppressor genes (P53, P21)

P53 and p21 are important proteins that are involved in EC in northeastern Iran (178). More than 83% of people with EC have a mutation in TP53, which is revealed by whole-exome sequencing and array hybridization. The TP53 tumor suppressor gene is implicated in the control of cell growth, DNA replication, and DNA repair. Some environmental factors induce TP53 mutations (179). It was found that p53 overexpression was related to cigarette smoking habit in EC subjects among high-risk populations (178). Other studies focused on this issue that this mutation may be caused by cigarette smoking carcinogens

(180,181). One of these carcinogen components is PAH (polycyclic aromatic hydrocarbon), which has been shown in a study in Golestan province that people are exposed moderately to highly that can be due to their lifestyle. The presence of mutations in exons 5 to 8 of TP53 gene in EC cancer was investigated in Tehran and northern Iran (161,182). In both studies, more than half of the cases had at least one TP53 mutation. The incidence of p53 mutation in EC is about 50%, and the frequency of changes appears to be higher in high incidence regions. A study in Japan found that the prognosis of patients with p53 mutation was poorer than patients whose tumors had no p53 mutations. Although some results showed that patients with p53 changes were likely to have shorter survival, its relevance as a prognostic factor is still controversial (160,183). P21 protein is a cell cycle regulator that acts when DNA damage occurred and leads to DNA repair or apoptosis. It was suggested that p21 polymorphisms might have a role in susceptibility to cancer (184,185). Of these polymorphisms that may occur, two of the most important ones are in codon 31 (p21 C98A, dbSNP rs1801270), which affect the DNA-binding zinc finger motif and in the 3'UTR (p21 C70T, dbSNP rs1059234) that occurs in the 3'-UTR. 3'-UTR is a central site for cell differentiation, proliferation, and tumor suppression (184,186). It affects mRNA stability by inducing rapid message degradation, leading to an alteration in the protein expression level (184,187). In a study, the effect of both polymorphisms of p21 gene in codon 31 and the 3'UTR on the risk of EC in northeastern Iran was investigated, and there was no association between these two polymorphisms and EC development. But it became clear that cigarette smoking not only is a risk factor for ESCC but also it interacts with p21 polymorphisms in susceptibility to EC (188). It was also observed that the evaluation of expression of p21 could support valuable data on the prognosis of the disease among the populations at risk (188).

BRCA2

Breast cancer type 2 susceptibility protein (BRCA2) has a significant role in the repair of DNA, especially in cases that the damage is caused by different carcinogenic factors. The presence of mutations in this gene cause chromosomal instability, and abnormal changes can lead to EC (189). It is also demonstrated that BRCA2 is strongly related to a genetic susceptibility to familial EC (190). Six mutations have been detected in the coding region of BRCA2 gene in Turkmen patients with EC in Golestan province (58).

Fanconi anemia genes (FANC)

Fanconi anemia (FA) is an abnormality and an autosomal disorder caused by genomic instability and bone marrow failure (191). FA can occur because of mutations in regulators of the FA pathway (192).

Several mutations, such as FANCD2 and FANCD1, have been detected in patients with a familial history of EC (193). In Golestan province, several FANC predisposing genes are related to an increased risk of ESCC (194).

Hyaluronic acid and laminin

Hyaluronic acid and laminin are components of the extracellular matrix, which play their role in some cellular activities such as cell adhesion, migration, and proliferation (195). There are some reports about the association between their high serum levels and the types of cancers (196). This increase in serum levels in addition to cancer also has been identified in various liver diseases (197,198). Very few studies have been conducted on their use as markers with both positive and negative outcomes (199). But eventually, these studies concluded that serum hyaluronic acid and laminin levels in EC are high. Hyaluronic acid and laminin levels may be useful in finding high-risk groups or closer follow-ups. In Golestan province, mean serum hyaluronic acid and laminin concentrations in incidental cancer cases were higher than in controls in crude analyses, and strong associations were shown between hyaluronic acid levels and ESCC (beta coefficient = 0.332, P = 0.05) in multivariate models (200).

MicroRNAs (miRNA)

MicroRNAs (miRNAs) are non-coding RNAs that play a role in regulating gene expression (201). They bind to 3UTR of target mRNAs and repress their translation (202). miRNAs have been stated in different cancers, including EC (203-205). Some of miRNAs, which were associated with poor prognosis of ESCC are miR-103/107, miR-21, and MiR-27a (203-205).

Occupational Exposure

In general, EC is not occupational cancer (206). The relationship between silica and EC was first reported in 1968 among the population of South Africa's Transkei, where it was thought that contaminated diet by silica was partly responsible for the high EC rates (207). The carcinogenic action of silica was reviewed by IARC, and crystalline silica was classified as group 1 carcinogen in 1997 for lung cancer (208). Several findings suggested that silica particles might play a role in the etiology of EC. In reality, a different result is available about the statistically important association between EC and silica exposure, some of them are in line and assume that silica plays a vital role in EC etiology, and others disagree.

O'Neill and colleagues described that contamination with fibrous silica in the diet is high, and there is a relationship between silica fibers in the millet bran and esophageal tumors. Contamination of wheat with sand and weed and its low quality is considered as essential features. Golestan province, is of the northern provinces of Iran, is located on the hot spots of the EC. Turkmen Sahra, as an area in the northeast of Iran, is recognized to have the highest rates of EC and to be one of the highest regions worldwide (209-212). Although EC in northeast Iran has a high incidence, there were no considerable changes between silica and wheat flour of this region and standard unit of measurement. It appears that silica could not play a vital role in the etiology of EC or is a risk factor when we consume it. Probably orally inhaled absorption of silica can be important on carcinogenicity when this scientific theory becomes acceptable that we pay attention to the major component of the Earth's crust. Silica that is in contact with the skin is an abundant mineral that is found in soil, sand, and rocks, but it is not assumed as a predisposing or carcinogenic factor (212). A historical study in Hong Kong showed an increased risk of mortality of EC among people in contact with silica (213). That previous data suggested that a significant amount of silica in the flour produced in this region may contribute to EC (209). But Jabbari and colleagues reported that no high level of silica in the flour of Golestan province was found (212). Selikoff and others in 1964 and 1978 (214, 215), followed by Miller in 1978 (216), put forward the association between asbestos as occupational exposure and some digestive cancers. However, the connection between exposure to asbestos and EC remains a controversial topic. In fact, on the report of IARC (217), the association between them is uncertain. However, several studies have shown that occupational asbestos exposure could increase the risk of EC up to 16-fold (218-226). Li and co-workers in a meta-analysis reported that high amounts of asbestos might lead to a high risk of mortality from EC, and demonstrated an increased risk in the pooled estimate for mortality of EC in correlation with asbestos (222).

Physiologic or Pathologic Predisposing Conditions

Gastroesophageal acid reflux

Gastroesophageal acid reflux (GERD) is probably the most potent risk factor for EAC. It seems that the risk to be higher in people with more frequent symptoms (206,227). The risk of EAC in people with regurgitation, heartburn, or both at least once a week, was approximately eight times more than people without these symptoms (228). Lagergren and colleagues in Sweden reported a robust dose-response relationship of both duration and frequency of reflux with EA. Also, in this study, any reflux was related to almost 8-fold increased risk, but increased risk up to 20-fold in persons with frequent or constant reflux (228). In studies from the USA, a higher prevalence of GERD symptoms in patients with EA compared to control populations was reported (229, 230). Also, some studies reported the dose-response relationship between reflux and EA had been an approximately 4-fold increase in total and 8-fold for individuals having the highest frequencies (231-234). GERD can also be the cause of Barrett's esophagus. Patients with Barrett's esophagus are at more risk than people without this state to develop EA (235). Unlike EA, ESCC is reported not to be associated with GERD.

Achalasia

Achalasia is a chronic esophageal motility disorder caused by impaired lower esophageal sphincter (LES) relaxation and generally peristalsis of the distal esophagus. People with untreated achalasia, frequently complain of reflux symptoms (heartburn and regurgitation), and this leads to food stasis and fermentation in the esophagus, which may increase the risk for inflammation and EC (236,237). The incidence of achalasia in EC is reported to range from 0.4% to 9.2% (238-242). The relationship between

achalasia and EC was first reported as long ago as 1872. There have been some studies addressing them since then, with useful but limited information (243). In most cases, EC develops 10-15 years after the diagnosis of achalasia or 20-25 years after the start of the symptoms of achalasia. There is a significant discrepancy in the reported risk of EC in achalasia, and several authors have shown an increase in EC up to 50 times higher than in control people (244, 245). Meijssen and others evaluated the incidence of EC in patients with achalasia who were treated. The risk of EC was about 33 times more than in the control people (245). Tustumi and co-workers reported an incidence of EC of 312.4 per 100,000 patient-years at risk. The prevalence of EC in patients with achalasia was 26 in 1,000 with an absolute risk increase for EC of 308.1 per 100,000 patients per year (246).

Gastric Atrophy

Gastric atrophy has been linked to gastric cancer as a risk factor for a long time (247). However, detection of a relationship between gastric atrophy and EC is a relatively recent finding. For the first time, Ye in 2003 showed that patients with pernicious anemia had a three-fold higher risk of EC than the healthy population. Because gastric atrophy is an important feature of pernicious anemia, it was assumed that gastric atrophy might also cause EC (248). Gastric atrophy can be indicated either by measuring serum pepsinogen concentrations or by direct histologic analysis of the gastric biopsies. Low serum pepsinogen-I (PGI) or the ratio of low serum pepsinogen I/ pepsinogen II (PGI/II) detect atrophy (249,250). Ye and colleagues reported a 4-fold increased risk of EC in patients with a low serum PGI (251). In addition, Iijima and colleagues found that gastric atrophy increases the risk of superficial EC by over 4-fold (252). In gastric atrophy, the gastric glands vanish, and acid secretion is reduced, leading to bacterial proliferation in the stomach, and thereby gastric atrophy can increase the risk of EC. In turn, these bacteria may increase the production of carcinogenic nitrosamines and acetaldehyde, which may clarify the link between gastric atrophy and esophageal neoplasia (206).

Hiatal Hernia

A hiatal hernia can increase the risk of EC by increasing the gastroesophageal acid reflux (232).

Several studies reported the link between hiatal hernia and EC, and all have found that the risks have increased with relative risks up to 6 folds (231,232,253,254). In addition, people with Barrett's esophagus that have high hiatal hernia have an increased risk of EC. In comparison with esophageal adenocarcinoma (EA), the risk of esophageal squamous cell carcinoma (ESCC) by the presence of a hiatal hernia is not increased (206).

Poor oral hygiene and tooth loss

Research studies from 1970 led to the hypothesis that poor oral health or tooth loss could increase the risk of EC (255). The relationship between poor oral hygiene and EC have been described in studies from some high-risk regions including Iran (256), China (26,255), India (257), and other regions such as Japan (258) and Latin America (259). In addition, poor oral hygiene was reported as the risk factor for esophageal squamous dysplasia, and as a synergistic factor with other risk factors, such as gastric atrophy, to increase the risk of EC (260,261). The associations found between poor oral health or tooth loss with EC could be confounded by low socioeconomic status, alcohol drinking, smoking, or other factors. Abnet and others, in Golestan province, examined the links between oral hygiene and tooth loss and the risk of EC, and the results did not differ materially in persons who have never smoked tobacco or drank alcohol; also, they found important relationships between poor oral health and lack of brushing tooth daily and risk of EC in people at high-risk of EC where frequently occur in never-smokers (256). In another study by Abnet in Finland, no relationship was reported between tooth loss and risk of EC (262). Also, various factors such as low SES, salivary bacterial microbiota, and rapid swallowing or incomplete chewing of large pieces of food that might cause damage or inflammation to the squamous esophageal epithelium, may be related with poor oral health, and increase risk of EC (255). Often studies of the relationship between poor oral hygiene and the risk of EC have been done in regions that ESCC constitutes the vast majority of cases, and there have been no studies particularly evaluating a relationship between poor oral hygiene and EA.

In conclusion, in the last decades, the Golestan Cohort Study stated an obvious reduction in the incidence rate of ESCC (24.3/100,000 in men and 19.1/100,000 in women). However, the ASRs of

ESCC has remained still high in both sexes. The etiology of the striking decline trend in ESCC was mainly unidentified, but the overall development in SES may be considered for the decrease rates of ESCC. Thus, more accurate risk stratification, further larger-scale or other screening/surveillance modalities, and prospective cohort studies for EC control are required in this area.

CONFLICT OF INTEREST

None of the authors declare any conflict of interest.

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