—————— **Review Article** ——————

Esophageal Cancer in Northeastern Iran: A Review

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Golestan Province in northeastern Iran has one of the highest rates of esophageal squamous cell cancer in the world. This article reviews the studies conducted on esophageal squamous cell cancer in this area and summarizes the data on epidemiologic patterns, incidence trends, and etiology of esophageal squamous cell cancer in this province.

Introduction

With approximately 386,000 deaths per year, esophageal cancer is the 6th most common cause of cancer death in the world.[1, 2] The epidemiology of esophageal cancer is characterized by wide variation in annual incidence rates,[1, 2] ranging from $3/10^5$ person-years in the U.S. white population[3] to $>100/10^5$ person-years in some areas of China.[4]

Golestan Province in northeastern Iran is one of the very high-risk areas of the world,[5] and several studies have been conducted to examine the epidemiologic patterns, incidence trends, and etiology of esophageal cancer in this province. In this paper, we review the designs and objectives of these studies, summarize the currently available data on incidence patterns and etiologic factors, and outline some future steps to identify risk factors of esophageal cancer in Golestan Province.

Overview of the studies

The earliest reports of high incidence of esophageal cancer in Iran were published in the

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Accepted for publication: 13 December 2006

mid 1960s and early 1970s. Analysis of case series referred to university and private clinics in Tehran[6, 7] and Shiraz[8 – 10] showed that approximately 3 – 4% of all registered cancers were arising from the esophagus and concluded that this percentage was higher than comparable Swedish or U.S. populations. Due to lack of a population-based cancer registry system, however, determining the incidence or mortality rates was not possible.

Anecdotal reports indicated that the high rates of esophageal cancer in Iran reflected very high incidence rates in certain areas of this country, especially Mazandaran and Khorasan Provinces in northeastern Iran. These two provinces bordered Afghanistan and Turkmenistan, which were also known for high risk of esophageal cancer. Having heard of these anecdotal reports, in 1967 Janiz Kmet from the International Agency for Research on Cancer (IARC) and Ezatollah Mahboubi from the Tehran University Institute of Pubic Health Research (IPHR) made an exploratory visit to the southern Caspian littoral, in the North of Iran, during which they got the "clinical impression" that rates in the eastern part of this littoral were much higher than those in the western part.[11] They subsequently established a cancer registry and confirmed their impression,[5] and they compared the climate, soil, fauna and flora, and several other environmental factors between the high-risk and low-risk areas of the Caspian littoral and published the results of their survey in a highly-cited paper in *Science.*[11] During 1968 – 1978, several studies

were conducted to further investigate the epidemiologic patterns and causes of esophageal cancer in the Caspian littoral. IARC and IPHR established a cancer registry,[5] conducted an ecologic study to compare various factors in high-risk versus low-risk areas,[12, 13] and tested the results from this ecologic study in a subsequent case-control study.[14] We will refer to these studies as IARC-IPHR cancer registry, ecologic study, and case-control study, respectively. During the same period, other studies investigated early detection of esophageal cancer,[15, 16] or examined some suspected risk factors in more depth.[17 – 21]

Esophageal cancer studies in northeastern Iran came to a halt for approximately 16 years (1979 – 1995) due to the 1979 revolution in Iran. In 1995, faculty members and medical students of Shaheed Beheshti University of Medical Sciences resumed these studies by conducting a large-scale screening study.[22 – 24] In 2000, the Digestive Disease Research Center (DDRC) of Tehran University of Medical Sciences continued to build on this effort by establishing Atrak Clinic, a referral clinic for upper gastrointestinal (GI) tract diseases in Gonbad, one of the major cities of Golestan Province, and began collaborations with several international cancer research groups, including the U.S. National Cancer Institute (NCI), IARC,

Karolinska Institute, the University of Toronto, and Cambridge University. These collaborators are currently involved in a wide range of studies, including a cancer surveillance and cancer registry program, a case-control study, a cohort study, and a number of genetic and molecular epidemiologic studies. Thus far several reports have been published based on pilot studies for these case-control, cohort, and cancer surveillance projects, but the full-scale studies have not yet been completed. In addition to DDRC, several other Iranian groups have recently conducted smaller etiologic studies. Table 1 summarizes the most important studies conducted on the incidence and etiology of esophageal cancer in northeastern Iran.

Here, we describe the most prominent results obtained from the old (1970s) and the more recent (after 1996) studies, and describe both the incidence patterns and etiologic factors that have been described thus far.

Incidence patterns

The IARC-IPHR 1968 – 1971 Cancer Registry[5] documented for the first time the high rates of esophageal cancer in some parts of northern Iran. Similar to most other areas of the world, squamous cell cancers constituted >90% of the all esophageal cancers in northeastern Iran. Therefore, the

Table 1. Major studies on the incidence and etiology of esophageal squamous cell cancer in northeastern Iran

	Period	Organizer	Main findings
Cancer registry	1968 – 1971	IARC-IPHR	Esophageal cancer incidence rate ranged from $< 10 / 10^5$ to $> 100 / 10^5$ across the southern border of the Caspian Sea. In high-risk areas, male: female ratio was close to one.
Ecologic study	1972 – 1973	IARC-IPHR	Differences were found between high-risk versus low-risk areas in climate, fauna and flora, ethnic backgrounds, staple food, chewing of nass, tea consumption, opium consumption, and several other factors
Case-control study	1974 – 1975	IARC-IPHR	Low intake of fresh fruit and vegetables and low socioeconomic status were associated with a higher risk of esophageal cancer.
Screening study	1995 – 1996	SBUMS	Results confirmed that esophageal cancer incidence was still high in Golestan Province. Poor oral health was associated with higher risk of esophageal premalignant lesions.
Case-control study	Ongoing since 2003	DDRC-NCI	Pilot results showed that squamous type histology was still the dominant type of esophageal cancer in Golestan Province. The results also confirmed that tobacco smoking, alcohol consumption, and opium consumption are less strong risk factor for esophageal squamous cell carcinoma in this area than in the western world.
Cohort study	Ongoing since 2005	DDRC-IARC-NCI	Pilot results showed no evidence for contamination of grain samples with fumonisins. Study instruments were shown to be valid.

IARC = International Agency for Research on Cancer; IPHR = Institute of Public Health Research (Tehran University of Medical Sciences); SBUMS = Shaheed Beheshti University of Medical Sciences; DDRC = Digestive Disease Medical Research Center (Tehran University of Medical Sciences); NCI = National Cancer Institute (U.S.).

Table 2. Descriptive epidemiology of esophageal squamous cell cancer in the United States of America, in high-risk areas of China, and in northeastern Iran

	USA	Linxian, China	Golestan Province, Iran
Age-adjusted incidence (/ 10^5 person-years)	< 10	> 100	> 100 in the 1970s; now perhaps down to 50
Male to female ratio	3:1	1:1	1:1
Ethnicity	Highest in African-Americans than in Caucasians	Not applicable	Possibly higher in Turkmens than in Persians

discussions made in this paper are mainly related to esophageal squamous cell cancer (ESCC). This 3-year cancer registry included the entire southern border of Caspian littoral, and showed a 30- and 10-fold variation in esophageal cancer incidence rates among women and men, respectively, within this geographic area. In Rasht City, located in the southwestern Caspian littoral, and its surrounding areas, age-adjusted rates were as low as 10 – $20/10^5$ for men and 3 – $10/10^5$ for women.[5] Low rates and a male-dominant incidence pattern was similar to epidemiologic patterns of esophageal cancer in most of the western world. In contrast, in the southeastern part of this littoral, in areas surrounding Gonbad City and further to the East, rates were at least as high in women as in men, and were some of the highest rates for any single cancer ever reported anywhere in the world (age-adjusted rates >$100/10^5$ /year).[5] Equally high (or higher) rates among females is a rare epidemiologic feature of esophageal cancer, but it has been reported in Linxian, China, the other area

of the world with registry-reported rates >$100/10^5$ (Table 2).[4, 25, 26] Very high risks and this unusual gender incidence pattern may indicate the presence of a single very strong risk factor that is shared by both genders.

As mentioned earlier, in addition to northeastern Iran, very high rates of esophageal cancer have also been reported in several other areas of Central and East Asia, including Turkmenistan,[27] Uzbekistan,[27] Karakalpakstan,[28] Kazakhstan,[29] and certain areas of China.[4] Together these high-risk geographic areas appear to extend from northeastern Iran to China, along the path of the Silk Road, and are collectively called the "Central Asian Esophageal Cancer Belt" (Figure 1). However, there have been very few well-established cancer registries in these areas, and the presence of such a belt is not entirely certain. Indeed, there may be only certain focal areas with high rates of esophageal cancer. If such a Belt exists along the Silk Road, it may indicate the spread of environmental risk factors shared
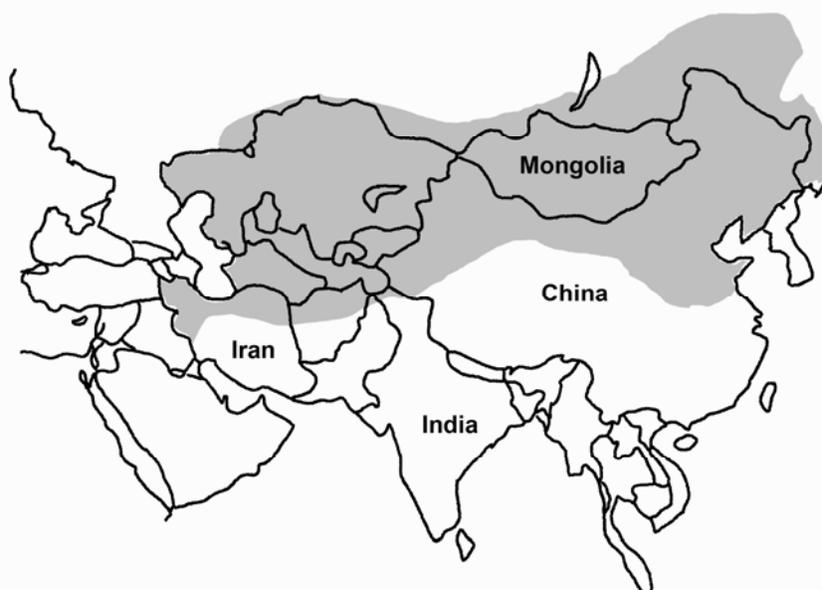
Figure 1. The Central Asian Esophageal Cancer Belt extending from Iran to China.

among the Turkic tribes and the Mongol conquerors who settled along this road, the presence of one or more high-penetrance susceptibility genes in these groups, or the presence of local carcinogens (e.g., plants, molds, or infectious agents). One epidemiologic feature suggesting increased susceptibility among Silk Road inhabitants was early reports from around Gonbad City of higher ESCC incidence among the Turkmen population compared to the Persian population or other ethic groups, but this finding has not yet been confirmed.[5, 30] Turkmens are descendants of Turkic tribes who migrated from East Asia, have East Asian facial features, and speak Turkic languages, and they and similar groups inhabit much of the Silk Road.

More recent studies have reexamined incidence rates and incidence patterns in Golestan Province. These studies have shown that the male to female ratio is still close to one and the majority of cancers are still of the squamous type.[30] Rates are still high, but they seem to have declined considerably in the past 30 years, perhaps to half of what they were in the past.[31] Lower esophageal cancer rates may partly be due to misclassification of gastric cardia cancer cases as lower esophageal cancer cases in the older studies.[30] In the 1960s and early 1970s, the majority of the cases were diagnosed by history and physical examination and/or radiologic findings. Since both cardia cancers and esophageal cancers cause dysphagia, and the radiologic features can be similar, it is possible that some cardia cancers were misclassified as esophageal cancers. Consistent with this possibility, gastric cancer rates have slightly increased in the most recent studies. Nevertheless, there is little doubt that there has been a significant real reduction in esophageal cancer rates, which probably reflects the highly improved socioeconomic status in Gonbad City and the rest of Golestan Province. Of interest, esophageal cancer rates in Cixian county, a high-risk area in China, also decreased from 1974 to 1996,[32] but at a much lower pace, which may indicate a lower rate of socioeconomic change in this area during the study period.

Risk factors

Several risk factors have been investigated as possible etiologic factors for ESCC in northeastern Iran, but very few have been shown to be associated with this disease (Table 3). The suspected risk factors include those that have been associated with ESCC in other parts of the world (e.g., smoking, alcohol consumption, low intake of fruits and vegetables, and low socioeconomic status) and those that were found to be more common in high-risk areas of the Caspian littoral compared with low risk areas (e.g., consumption of opium and hot tea).

Tobacco smoking and nass chewing

Tobacco smoking is a major etiologic factor for ESCC in western countries, where it increases the risk by approximately 3 – 5 fold.[33 – 35] However, in some high-risk areas of the world, such as Linxian, smoking plays a much less significant role in the etiology of ESCC, and the relative risk for ever-

Table 3. Strength of association for environmental factors associated with esophageal squamous cell cancer in the United States of America, in high-risk areas of China, and in north-eastern Iran

	USA	Linxian, China	Golestan Province, Iran
Tobacco smoking	Very strong	Moderate	Moderate
Alcohol consumption	Very strong	None	None
Opium use	No data	No data	Possible
Hot drinks	No data	Possible	Possible
Low socioeconomic status	Strong	Strong	Strong
Nutritional deficiency			
Low intake of fruits and vegetables	Moderate	Moderate	Moderate
Selenium deficiency	No data	Strong	None
Zinc deficiency	No data	Strong	No data
Polycyclic aromatic hydrocarbons	Possible	Possible	Possible
N-nitroso compounds	Possible	Possible	Possible
Silica fibers	No data	No data	No data
Viral agents	Unclear	Unclear	No data
Poor oral hygiene	No data	Moderate	Possible
Animal contact	No data	No data	Possible

Very strong and strong: Present evidence shows high relative risks; Moderate = present evidence shows moderately high relative risk; Possible = no data on relative risks, but circumstantial data suggest the possibility of an association; None = present evidence shows no association; Unclear = conflicting results.

smoking cigarettes is only 1.3.[26] These different risk ratios are consistent with the different incidence patterns of ESCC in these populations. In the U.S., ESCC incidence rates are highest among populations who smoke the most, i.e., black males. In Linxian, however, <1% of women versus approximately 70% of men smoke,[36] yet ESCC rates are nearly equal in the two sexes. These findings suggest that the majority of the ESCC cases in both men and women in Linxian are due to a very strong risk factor other than tobacco, and the presence of this factor results in an attenuation of the relative risk associated with smoking.

In Golestan Province, the prevalence of ever-smoking ranges from 1% in rural women to 39% in urban men,[37] and there is a weak to moderate association between smoking prevalence and ESCC incidence.[13, 37] The IARC-IPHR case-control study showed an almost 2-fold ESCC risk associated with tobacco smoking,[1, 4] and in a recent case series only 27% of ESCC cases reported having ever smoked.[30] Therefore, tobacco smoking appears to have only a limited role in esophageal carcinogenesis in Golestan.

Chewing nass, a mixture of tobacco, ash, and lime, is confined in Golestan to rural males of Turkmen ethnicity.[13, 14, 37] There was no association between nass chewing and ESCC in the IARC-IPHR case-control study.[14]

Alcohol consumption

Like tobacco consumption, alcohol use is a major cause of ESCC in western countries,[33 – 35, 38, 39] but not in Linxian[26] or Iran.[13, 37] In the West, alcohol intake is associated with a dose-response increase in ESCC risk, and heavy consumption increases risk by 5 – 15 fold.[33, 34, 39] In Linxian, alcohol consumption is associated with a mild decrease in ESCC risk,[26] possibly due to the fact that alcohol consumption in Linxian is very limited and it may be associated with higher socio-economic status. In Golestan Province, alcohol consumption is rare, especially among rural residents, and it is unlikely to be a major cause of ESCC.[13, 37]

Opium use

A role for opium in the etiology of esophageal cancer in Iran was first suggested in the IARC-IPHR ecologic study. Fifty percent (20 of 40) of the adult residents of the high-risk areas, compared to only 11% (10 of 90) of the residents of medium or low-risk areas, tested positive for urine morphine metabolites.[13] A subsequent study of 1,590 rural individuals showed that the prevalence of appreciable levels ($\geq$ 1 µg/mL) of urinary morphine metabolites was almost 6-fold higher among residents of high-risk versus low-risk areas of the Caspian littoral.[19] This latter study also compared household members of 41 cases and 41 matched controls for urinary opium metabolites and found nonsignificantly increased positivity rates among case household members (OR: 2.1; 95% CI: 0.7 – 6.5).[19] Opium use is still prevalent in Golestan Province, especially among rural men,[37] and may contribute to the high rates of esophageal cancer in this area.

It is perhaps the opium dross (the residue remaining in the pipe after smoking), rather than raw opium, that is most carcinogenic to the esophageal mucosa.[19] Opium is expensive and is normally smoked. Opium dross (called sukhteh in the local language) is less expensive and is normally ingested and swallowed by those who cannot afford crude opium. Sukhteh and smoke condensates from opium and morphine cause mutations in *S. typhimorium*,[17, 18] sister chromatid exchanges in human lymphocytes,[40] and morphologic transformations in cultured Syrian hamster embryo cells,[41] whereas opium itself is not a mutagen.[17, 18] Another possible reason for carcinogenicity in sukhteh and opium smoke condensates is the presence of pyrolysis products such as polycyclic aromatic hydrocarbons (PAH).

Notwithstanding the above results, a role for opium or its residues in esophageal carcinogenesis is not yet well-established. An ongoing active surveillance and cancer registry has shown that in Kerman Province, where opium and sukhteh consumption is very high, the incidence of esophageal cancer is low (unpublished data). Among Golestan residents, opium use carries little stigma, and a recent study showed that self-report of opium had a sensitivity of 93% and specificity of 89% versus a gold standard of urine morphine or codeine,[42] so answers to questions about opium use are probably quite accurate in this population. Questioning of esophageal cancer patients in Golestan Province showed that only 33% (48 of 144) had ever used opium.[30] Therefore, if it is eventually proven as a risk factor, opium probably contributes to causing only a proportion of esophageal cancer cases in Golestan.

Hot drinks

Hot drinks have been suggested to increase risk

of ESCC, but the evidence accumulated thus far is not convincing, partly due to the difficulty of measuring the quantity and temperature of the liquid consumed.[43]

Drinking mate, a herbal tea, which is usually consumed hot, is a main risk factor for ESCC in certain areas of South America.[44, 45] Whereas some studies have attributed the carcinogenicity of mate solely to the temperature of the consumed tea,[46, 47] other studies have suggested that there are other factors beyond temperature alone,[44, 48] or have found temperature irrelevant.[49] Another potential mechanism for carcinogenicity of mate is its PAH content.[50]

Ecologic studies from northeastern Iran[21] and Japan[51] have suggested that residents of high-risk areas consume higher quantities of tea at higher temperatures. Also, several case-control studies in Iran,[14] Singapore,[52] and Puerto Rico[53] have shown that drinking hot tea and coffee are associated with higher risk of esophageal cancer. Nevertheless, questioning esophageal cancer cases regarding their history of hot drink consumption may not be very dependable, so case-control studies may provide biased data concerning this association. In the IARC-IPHR case-control study, hot tea consumption was more strongly associated with gastric cancer than with esophageal cancer.[14] An ongoing cohort in northeastern Iran is designed to provide a more reliable answer to this question.[37]

Socioeconomic status

Throughout the world, the risk of ESCC increases markedly as socioeconomic class declines.[35, 54 – 56] Those of a higher socioeconomic class often have more access to fresh fruits and vegetables, cleaner water, and better sanitary conditions.

Results of the IARC-IPHR case-control study demonstrated a similar trend.[14] This study classified urban males and control males into three separate socioeconomic classes based either on their occupation or on the appearance of their homes relative to others in their community. Risk of esophageal cancer was significantly higher for those of low socioeconomic backgrounds when compared with the highest group (OR: 4.8; 95% CI: 2.1 – 11.1).[14] The IARC-IPHR study also demonstrated that higher levels of education and greater numbers of rooms in the home, both indirect indicators of higher socioeconomic class, were significantly associated with a lower risk of esophageal cancer.

Nutritional deficiency

Poor nutrition has been consistently associated with higher risks of ESCC in all areas of the world. To present several examples, we will review the associations between fruit and vegetable intake, selenium status, and zinc status and ESCC risk.

Low intake of fruits and vegetables

Low intake of fruits and vegetables has been consistently associated with higher risk of esophageal cancer. Several case-control studies[57 – 61] and two cohort studies[62, 63] have shown reduced risk of esophageal cancer associated with regular intake of fruits and green and yellow vegetables. The World Cancer Research Fund and American Institute for Cancer Research joint committee (WCRF-AICR) and The Committee on Medical Aspects (COMA) of Food and Nutrition Policy called the evidence for a protective association between fruit and vegetable intake and esophageal cancer *convincing* and *strongly consistent*, respectively.[64] A meta-analysis of the literature suggested that protective effects were more pronounced for fruits than vegetables.[64]

Data from northeastern Iran show similar results. Families in the regions of high incidence of esophageal cancer reported very limited intake of fruits and vegetables relative to families in the low incidence areas.[12, 13] The IARC-IPHR case-control study showed that higher intake of raw vegetables reduced the risk of esophageal cancer by 40 – 50%.[14] However, cases and controls showed little difference in the consumption of cooked vegetables.

Selenium deficiency

Selenium deficiency has also been shown to be a risk factor for upper GI tract cancers. Both observational and experimental studies have shown that higher selenium status reduces the risk of esophageal and gastric cancers in selenium deficient populations.[25, 65 – 67] In Golestan Province, however, selenium deficiency is unlikely to be a major risk factor for esophageal cancer. A study of 100 urban and rural residents who were recruited in the pilot phase of Golestan cohort study in 2004 showed that the median value (interquartile range) for serum selenium was 155 (141 – 173) μg/L,[68] which was well above 90 μg/L, the concentration at which serum selenoproteins are saturated.

Zinc deficiency

Zinc deficiency enhances the effects of *N*-

nitrosomethylbenzylamine and certain other nitrosamines in esophageal carcinogenesis in rodents.[69, 70] Studies in rodents have shown that tissue zinc is perhaps the most relevant measure of zinc in relation to carcinogenesis. The only human study investigating the association between tissue zinc and ESCC was conducted in Linxian, China, and showed that there was a significant dose-response relationship between lower levels of zinc in esophageal biopsies and increased risk of future ESCC.[71] No well-designed study for evaluating the role of zinc deficiency in esophageal carcinogenesis has yet been conducted in Golestan Province.

Polycyclic aromatic hydrocarbons (PAHs)

Polycyclic aromatic hydrocarbons (PAHs) are environmental carcinogens produced during incomplete combustion of organic materials, including tobacco and coal, which have been shown to be etiologically associated with upper aerodigestive cancers,[72] including esophageal cancer.[73] Studies in Linxian have shown histopathologic evidence consistent with high exposure to PAHs in ESCC cases,[74] presence of high levels of carcinogenic PAHs in staple foods,[75] and high concentrations of 1-hydroxypyrene glucuronide (1-OHPG), a PAH metabolite, in urine samples.[73]

PAHs have not been directly linked to ESCC in northeastern Iran. However, there is circumstantial evidence that PAHs may play an important role in esophageal carcinogenesis in this area. A study of 99 inhabitants of Golestan Province[76] showed 42% of the study participants had urine 1-OHPG levels ranging from 1 to 5 pmol/mL, indicative of moderate PAH exposure, and 41% had levels above 5 pmol/mL, indicative of very high exposure. Further analysis showed that 1-OHPG levels were high in all subgroups of the study subjects, including both sexes, rural and urban dwellers, and smokers and nonsmokers. This pattern of PAH exposure parallels the ESCC incidence pattern seen in this area. Only 15% of the variance in 1-OHPG was explained by age, sex, residence, smoking, nass, or opium consumption. Therefore, the source of this high exposure remains unknown.

N-nitroso compounds

Nitrosamines and nitrosamides, both subgroups of N-nitroso compounds, are formed by the reaction of nitrites with amines or amides, respectively. N-nitroso compounds have been shown to increase the risk of cancers of the nasal cavity, esophagus, and liver in several animal models.[77 – 80] Humans are exposed to these chemicals from diet, tobacco smoking, occupational exposure, or drinking water,[81] as well as from endogenous synthesis, which contributes to 45 – 75% of the total exposure.[82] Nitrites are directly found in sodium nitrite and various foods, and are also formed by reduction of ingested or salivary nitrates.[83 – 85] Vegetables are the main sources of exogenous nitrates but high levels of nitrates may also be found in water.[85] Reduction of nitrates to nitrites by oral bacteria is a major contributor to the formation of N-nitroso compounds, and this may be one of the reasons why poor oral health has been associated with higher risk of esophageal and gastric cancers.[36, 86] Dietary exposure to high levels of N-nitroso compounds has been shown to be more common in high-risk areas than in low-risk areas for esophageal cancer in China.[87] Jakszyn and Gonzalez have recently reviewed case-control and cohort studies associating nitrosamine and related food intake with risk of esophageal cancer.[88] This review suggests that intake of processed meat, which is a major source of nitrites and nitrosamines, has been consistently associated with higher risk of esophageal cancer.[88]

In high-risk areas of northeastern Iran, no evidence has been found for high dietary exposure to nitrosamines.[12] It has, however, been reported that despite the low intake of nitrate and nitrite, salivary nitrite levels are much higher in this Iranian population than in western countries.[89]

Silica fibers

Crystalline silica is a known human carcinogen.[90 – 92] Inhalation of silica fibers is known to increase risk for lung cancer in factory workers (OR: 1.6; 95% CI: 1.31 – 1.93) and to increase risk for upper GI cancers as a result of clearing the throat in dusty areas (OR: 2.8; 95% CI: 1.4 – 5.25).[92 – 93] Fields of wheat in northeastern Iran are known to be interspersed with the grass Phalaris minor.[90] The seeds of Phalaris minor contain a fibrous mineral comprised mostly of silica. The silica fibers detach from the Phalaris minor seeds and contaminate flour when the wheat is milled and processed.[90] The ingestion of foods prepared with this flour may be a risk factor for esophageal cancer in northeastern Iran. A similar situation was observed in a high-risk area of northern China,

where silica fibers were detected in millet bran, a common component of the diet in that region.[91]

Viral agents

Human papillomavirus (HPV) is the only viral agent extensively examined in relation to esophageal cancer. Oncogenic types of HPV, most notably HPV 16 and HPV 18, are recognized as the most significant risk factors for cervical cancer,[94] and are also important risk factors for cancers of the vulva, anus, penis, and oropharynx.[95] During the past 20 years, several studies have used a variety of techniques, including detection of HPV DNA in esophageal tumor tissues and serologic methods, to examine the association between exposure to HPV and risk of ESCC.[96] The results of HPV DNA studies have not been consistent: case series using polymerase chain reaction have found evidence for the presence of HPV in tumor tissues varying from 0% to 67%.[96] Epidemiologic studies using type-restricted serologic assays have also showed inconsistent results.[97] While some serologic studies have found a positive association between ESCC and HPV16,[98 – 100] others have found no association.[97, 101, 102]

To the best of our knowledge, no study has investigated the association between oncogenic types of HPV and ESCC in high-risk areas of northeastern Iran. The only study that examined this association in Iran[103] found a higher risk of ESCC associated with HPV16 but not with HPV18 in case and control subjects from Tehran.

Oral hygiene and tooth loss

Poor oral hygiene and tooth loss have been associated with higher risk of both gastric and esophageal cancers.[36, 86, 104 – 106] There are several mechanisms through which poor oral health might increase the risk of ESCC:[86] (a) physical irritation and damage to the esophageal epithelium due to swallowing unchewed food; (b) change in dietary patterns and nutrient intake due to poor dentition; (c) changes in oral flora with an increase in carcinogen-producing microorganisms; (d) infection of the esophageal mucosa with an oral microorganism; and (e) genetic factors that affect both oral health and ESCC. A study by Abnet and colleagues[36] in Linxian, China, suggested that formation of nitrosamines via alterations in bacterial flora was most likely to be the responsible mechanism.

In Golestan Province, poor oral health showed a dose-response association with esophageal squamous dysplasia.[24] Edentulous individuals had a 5-fold higher risk of dysplasia compared to participants with good oral health.[24]

Animal contact

Horse riding and races are common in the high-risk Turkmen area of Iran. Many people who live along the Central Asian Esophageal Cancer Belt have routine contact with horses, donkeys, and mules. Additionally, using horses and donkeys is common in the Kurdistan areas of Iran and Turkey, two other places with high rates of ESCC. These facts suggest that animal contact may be a risk factor for ESCC, and the case-control study in Golestan is currently investigating this association. If positive results are found, a search for zoonotic sources may be undertaken.

Genetic factors

As discussed earlier, the extension of high-risk areas of ESCC from China through the Central Asian republics of the former Soviet Union to northeastern Iran and the reported high incidence rates among people with the so-called "Mongolian phenotype" may suggest the involvement of genetic factors in this disease.

Thus far no high-penetrance germline genetic mutations have been associated with ESCC risk. However, somatic mutations in *TP53* and other tumor suppressor genes have been extensively studied in ESCC tumors. A study of 98 ESCC tumor samples collected from hospitals in Tehran found *TP53* mutations in 50% of the tumors.[107] The most frequent mutations were $C > T$ transitions at CpG islands, in both male and female cases, and A:T base pair mutations, predominantly in males cases. High $C > T$ mutations at CpG islands suggest a baseline inflammatory process that may be involved in the development of ESCC in Iran. The high incidence of A:T mutations, mainly in the male population, may imply the effect of opium exposure or other male-predominant behaviors.

Scores of studies have examined the association between genetic polymorphisms and ESCC. Phase I/II enzymes metabolize environmental carcinogens. Therefore, their polymorphisms have been suggested to modify cancer risk. A recent meta-analysis[108] showed a modest association between the *CYP1A1* Ile-Val polymorphism and esophageal cancer risk; the summary OR for Ile-

Val or Val-Val versus Ile-Ile was 1.44 (1.17 – 1.78). However, this meta-analysis showed no statistically significant association between other phase I/II enzyme polymorphisms, such as *CYP1A1* MspI, *CYP2E1* RsaI, *GSTM1* null type, *GSTT1* null type, or *GSTP1* Ile104Val and esophageal cancer risk.[108] Polymorphisms in enzymes that control alcohol and acetaldehyde metabolism have also been associated with esophageal cancer risk.[109, 110] After adjusting for alcohol intake, low activity polymorphisms in alcohol dehydrogenase-2 (*ADH2*1) and acetaldehyde dehydrogenase-2 (*ALDH2*2) have both been associated with a higher risk of esophageal cancer.[109, 110]

An ecologic study compared the frequencies of polymorphisms in ten genes that have been hypothesized to have a role in risk of ESCC (*CYP1A1*, *CYP2A6*, *CYP2E1*, *GSTM1*, *GSTP1*, *GSTT1*, *ADH2*, *ADH3*, *ALDH2*, and *O6-MGMT*) among three Iranian ethnic groups with highly varying rates of ESCC.[111] High-risk Turkmens from Golestan Province were compared to medium-risk Turks from Ardabil and low-risk Zoroastrian Persians from Tehran. Compared to Zoroastrians, Turkmens had higher frequencies of four alleles that are speculated to favor carcinogenesis (*CYP1A1* m1, *CYP1A1* m2, *CYP2A6*9, and *ADH2*1). These results were consistent with an influence of these allele variants on the population risk of ESCC. However, none of these four alleles had a high enough prevalence in Turkmens to explain the high rates of ESCC in this group. Three of these four alleles (*CYP1A1* m1, *CYP1A1* m2, *CYP2A6*9) were less frequent among Turkmens than in some Asian populations with lower risks of ESCC. Therefore, it is unlikely that variations in these polymorphic genes are major contributors to the high incidence of ESCC among Turkmens in Iran

Conclusions

Although rates appear to be declining, very high rates of ESCC are still observed in northeastern Iran. Several risk factors, including nutritional deficiencies and low socioeconomic status, have been associated with ESCC in this area. However, it is unlikely that the extraordinarily high rates observed in this area are solely due to these factors, as they are also reported in many areas of the world with low ESCC rates.

It is likely that one or more major risk factors, yet undiscovered, exist in northeastern Iran and in other very high-risk areas of the world such as Linxian, China. One such strong risk factor may be an unknown virus or other infectious agent. The advent of viral detection DNA microarrays composed of oligonucleotides corresponding to the most conserved sequences of all known viruses may help in identification of a viral risk factor, if it exists.[112] Such an alleged strong risk factor may explain the relatively low relative risk of ESCC associated with smoking in these regions. In western populations, where other strong risk factors are not present, smoking increases the ESCC rate from about $3/10^5$/year[3] to about $12/10^5$/year, resulting in a relative risk of approximately 4.[34] However, in Linxian, where one or more very strong unknown risk factors are probably present, the baseline rate is approximately $100/10^5$/year, and smoking increases the rate to approximately $134 /10^5$/year, resulting in a relative risk of 1.34.[26] A very similar pattern may exist in Golestan Province in Iran.

The apparent decline of ESCC rates in the past 30 years may be due to a decline in the over-riding risk factor(s) mentioned above, or may be due to easier access to fresh fruits and vegetables and a general increase in the socioeconomic levels in Golestan Province.

Result of the ongoing case-control and cohort studies conducted by DDRC, IARC, and NCI are eagerly awaited. These studies will most likely identify or confirm several modest risk factors for ESCC in this area. Because of very high rates, many cases can be attributed to risk factors that are modestly associated with ESCC in Golestan. Therefore, the results of the ongoing studies will be extremely important. However, the initial results of these studies may fail to discover the over-riding etiology of ESCC in Golestan. If so, clever use of collected biologic materials in small studies targeted toward novel risk factors may be the key to important discoveries.

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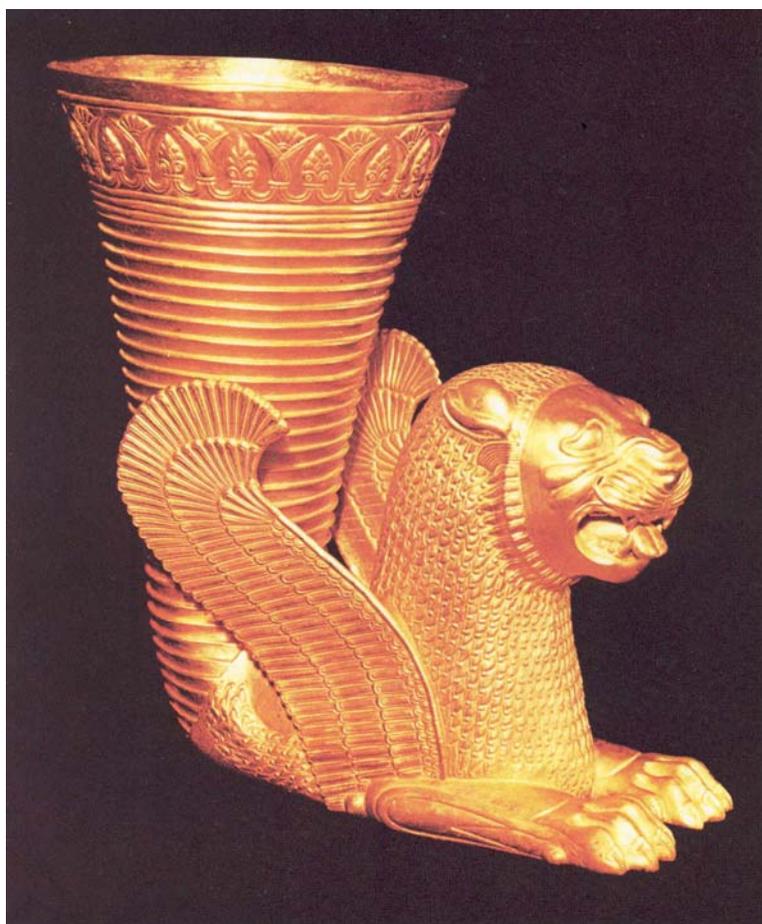
A fifth-century gold rhyton or drinking vessel with the body of a winged lion. Archaeological Museum, Tehran-Iran (Persian Mythology by J.R. Hinnells, Chancellor Press, London, 1985).

Once a rare cancer, EAC now constitutes approximately half of all esophageal cancer cases in some Western populations (11–13). Our results suggest that CagA-positive strains of H. pylori, which constitute the majority of H. pylori strains, may protect against EAC, and that increasing EAC rates may be partly due to the decline of H. pylori in human populations. . Epidemiologic features of upper gastrointestinal tract cancer in northeastern Iran. Br J Cancer 2004;90:1402–6. OpenUrl CrossRef PubMed. . Helicobacter pylori and oesophageal and gastric cancers in a prospective study in China. Br J Cancer 2007;96:172–6. OpenUrl CrossRef PubMed. A peculiar distribution of esophageal cancer was observed in the Caspian littoral of Iran, where an ad hoc cancer registry has been in operation since 1968. A very high incidence, among the hghest recorded in the world, with a higher incidence in women than in men (male: 108.8 cases per 100,000 population; female: 174.1 per 100,000), was recorded in the northeastern corner of the region; this sparsely populated, semidesert area of the central Asian type, with predominantly saline soils, was settled by Turkomans. A lower incidence with a change in the male-to-female ratio was observed in the so Although esophageal cancer (EC) is the eighth most common cancer in several European countries, it is one of deadliest worldwide. The most frequent predisposing factor implicated in its development is Barrett's esophagus (BE), an acquired metaplastic transformation of the esophageal lining cells from normal squamous epithelium into specialised or intestinal-like columnar epithelium. The major risk factor for BE is gastroesophageal reflux disease. Although BE is in itself a benign and often asymptomatic disorder, its clinical importance stems from the recognition that it represents the mai