MINI-REVIEW

Epidemiology of Esophageal Cancer in the High-Risk Population of Iran

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Abstract

The Iranian population includes several ethnic groups scattered throughout Iran, which differ with regard to their rates for cancer. An infamous 'Asian esophageal cancer belt' stretches to the east from the Caspian littoral in Iran via Turkmenistan to the Northern provinces of China. Apart from the eastern part of the Caspian littoral area of Iran which has the highest incidence of esophageal cancer in the world, other parts of the country have variable rates, ranging from 3 to more than 15 cases per 100,000 population, but rates have decreased sharply in the high incidence areas. Studies of the etiology of esophageal cancer in Iran and especially among the Turkmen ethnic population have indicated that several factors are behind the striking high incidence. Certain risk factors such as a family history of esophageal cancer, low socioeconomic status and poor nutritional diet are well studied and plausible evidence for their etiologic contributions exist. While thermal irritation and coarse food (physical damage to the mucosal lining of the esophagus) have attracted attention in correlational studies, conclusions about their etiologic contribution are inconclusive.

Key Words: Esophageal cancer - Iran - etiological factors

Asian Pacific J Cancer Prev, **7**, 375-380

Introduction

The Iranian population includes several ethnic groups scattered throughout Iran with varying rates for cancers. The gastrointestinal cancers are the most frequent cancer among Iranian males and second to breast cancer among females.The Turkmen in northeastern Iran have a high rate of esophageal cancer and the Turks in the north and west have a high rate of stomach cancer (Mahboubi, 1971; Hormozdiari et al., 1975). Among Iranians, esophageal cancer has attracted much interest due to its high incidence among the Turkmen of northeastern Iran, resulting in continuing investigation into its etiology by local and international scientists. The aim of this article is to review the published studies performed on the population in the high-risk area of the Caspian littoral of Iran to address the epidemiology and etiology of esophageal cancer in this population.

Materials and Methods

All published studies regarding esophageal cancer in the high-risk area of Iran were retrieved from two sources: 1) Medline with a keyword search of esophageal cancer in Iran, and 2) theses and dissertations kept in the School of Public Health of the Tehran University of Medical Sciences. The School of Public Health is one of the oldest research institutes actively investigating the etiology of esophageal cancer in Iran. Only original research papers addressing the epidemiology and etiology of esophageal cancer in the high-risk population were included in the review.

Results

The search yielded 61 papers published in English and 15 theses and dissertations, which were written in local language (Farsi). For 10 out of the 61 published papers in English, there were no full text versions available and only information from the abstracts was used. A systematic review was not possible due to the heterogeneity of published studies in terms of subjects as well as methodologies.The papers were reviewed for descriptive (incidence and time trend) and analytical (risk factors) measures.

Incidence and time trends

The incidence of esophageal cancer in Iran has variable

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Figure 1.Turkmen of Iran Reside in the Northeastern Part of the Country

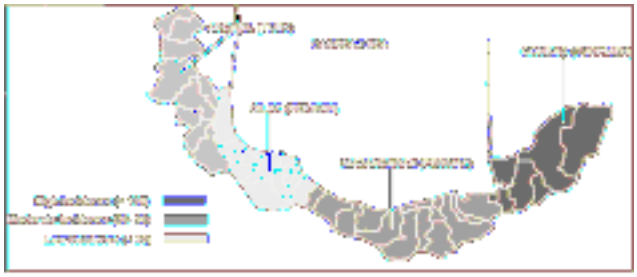

Figure 2. Distribution of Esophageal Cancer Incidence in the Caspian Littoral of Iran

rates from 3 to more than 15 cases per 100,000 population (Sadjadi et al., 2003). The high-risk area of Caspian littoral is part of an infamous 'Asian esophageal cancer belt' that stretches from the eastern part of the Caspian littoral in Iran via Turkmenistan to the northern provinces of China (Sagar, 1989). The ethnic background of the high-risk area of Iran includes Persian (including people of Sistani and Baloochi ethnicity who have migrated from south east of Iran seeking work) and the Turkmen scattered from north of Khorasan to east of the Caspian Sea (Figure 1).The first reported incidence from the area came from a cancer registry established as a collaborative research project between the IARC (International Agency for Research on Cancer) and the School of Public Health at Tehran University. This registry shut down in the late 1970's. The registry reported a very high incidence (truncated rate of 150 cases per 100,000) with a sex ratio of one and in some parts higher incidence among females (Mahboubi et al., 1973). Although there was no report of incidence according to the ethnic group living in the area, an extension of the registry in other parts of the Caspian littoral revealed that the areas closer to the central part of the Caspian littoral (Figure 2) (primarily Persian ethnicity) had a lower incidence (Hormozdiari et al., 1975).The breakdown of incidence based on ethnicity is not available, however, based on data from case-control and other analytical studies, the highest incidence is seen among those of Turkmen ethnicity (Hormozdiari et al., 1975). Descriptive measures of esophageal cancer in the high-risk population of Iran present an epidemiologic characteristic similar to other high-risk areas of the Asian esophageal cancer belt. In other countries located in the "Asian esophageal cancer belt" the incidence has decreased, with a substantial decrease in Shanghai (Zheng et al., 1993) and a moderate one in Lixin, China (Lu et al., 1985). However, due to the disruption in the cancer registry, no changes of incidence have been documented in the high-risk area of Iran. A recent Baloon cytology screening survey of the Turkmen in the high incidence area estimated a very high rate for males (140 per 100,000) and a moderate rate for females (45 per 100,000) (Saidi et al., 2000) indicating no changes in the incidence during last 30 years, at least for males. However, this recent high rate, based on a limited number of people surveyed, lacks concordance with the male-to-female ratios in other high-incidence areas of the world (a unique feature of esophageal caner in high-incidence areas is that the female-to-male ratio is almost 1 or more) (Nyren and Adami, 2002). This divergence reduces the credibility of the recent estimate among Turkmen.

Recently, a new wave of studies has been initiated by a group of scientists in the Gastrointestinal Research Center of Tehran University of Medical Sciences and the IARC. Among these studies is a survey of cancer in the area. A recently published report has estimated that the age adjusted incidence is 43.4 for males and 36.5 for females per 100,000 population, indicating a sharp decline in the incidence in the high risk area(Semnani et al., 2006). The fact that the incidence has decreased during last 30 to 40 years seems reasonable, although the amount of decline needs further scrutiny as part of this sharp decline could be attributed to differences between the practices of the registry at early studies and the current surveys. The rate of esophageal cancer in other parts of Iran (low-risk area) has decreased as much as 30% in recent years (Yazdizadeh et al., 2005).This decrease has been attributed to changes in lifestyle and rapid urbanization.

Risk factors

Since the first report of high incidence in the Turkmen of Caspian littoral in the early 1970s (Kmet and Mahboubi, 1972), several teams of investigators have explored the etiology behind the high incidence of esophageal cancer in this population. Studies on the etiology of esophageal cancer in Iran and especially among the Turkmen ethnic population have indicated that several factors are behind such striking high incidence. Investigated factors can be divided into the following categories;

I. Family history and genetic background
II. Lifestyle, environmental factors
*Habits related to food/drink preparation and consumption
*Smoking history, alcohol, and locally prepared opium products
*Low social and economic status and poor standard of living
III. Nutritional intake/deficiency
IV. Other factors (viruses, fungi, etc.)

I. The family history and genetic background

The genetic background as an etiologic factor has been addressed by measuring familial aggregation of esophageal cancer as well as the prevalence of low penetrance susceptibility genes involved in the repair of DNA and polymorphic genes involved in the metabolism of xenobiotics, and alcohol. Most studies addressing familial aggregation have found that positive family history for esophageal and other cancers has a strong risk associated with the disease (Bagheri, 1997). In early studies (Pour and Ghadirian, 1974; Ghadirian, 1985a) of 427 Turkmen with esophageal cancer, 47% had a positive family history for esophageal cancer. The age of onset for 40% of those with family history was younger than 50 years (an early onset indication). In several case-control studies done in the high-risk area, odd ratios of 1.8 to 7 for a positive family history has been reported among patients (Bagheri, 1997; Shafieizadeh Tayebeh et al., 2005; Akbari et al., 2006).

Two recent, well-planned studies of familial risk in the high-risk population, the first based on a case parent study and the second based on a cohort study, have estimated a more than two-fold increase in the risk of esophageal cancer among first degree relatives (Shafieizadeh et al., 2005; Akbari et al., 2006). Compatible with the finding in Iran, studies addressing the familial aggregation in the other parts of the Asian esophageal cancer belt have reported a higher frequency of a positive family history of esophageal cancer among patients living in high-risk areas compared to low risk areas (Ghadirian, 1985b; Wang et al., 1992).

The low penetrance polymorphic genes involved in alcohol metabolizing enzymes (alchohol dehydrogenase and aldehyde dehydrogenase) has been associated with an increased risk of esophageal cancer among Japanese patients abusing alcohol (Yokoyama et al., 1996b) but not among Chinese patients (Yokoyama et al., 1996a; Tian et al., 1998). Consumption of alcohol is very low in the high-risk area of Iran (Pourshams et al., 2005) and the frequency of this polymorphism has been reported to be lower among the high risk population(Sepehr et al., 2004b). The polymorphic genes involved in enzymatic activities in phase I (CYP-related enzymes such as CYP1A1, CYP2A6, and CYP2E1), and phase II (glutathione-S-transferases such as GSTM1, GSTP1, GSTT1) for metabolizing xenobiotics has been reported to be associated with the risk of esophageal and other cancer among different populations (Lu et al., 2005, Yang et al., 2005). There are no case-control studies addressing the risk associated with these polymorphic genes and esophageal cancer in Iranian patients, although a correlational study did not find a higher prevalence of susceptibility alleles of these genes among the high-risk Turkmen (Sepehr et al., 2004a).

II. Lifestyle, environmental factors

The second category of risks among patients in the high-risk area of northern Iran includes those risks related to lifestyle and environmental factors. It has been hypothesized that certain habits related to food and drink consumption exposes the lining mucosa of the esophagus to chronic damage and irritation that may contribute to dysplasia and malignant transformation. Two categories of risk factors have been identified for this hypothesis: 1) course foods, 2) hot beverages. In a large study (Ghadirian, 1987b) of 1501 individuals living in the high- and low-risk area of the Caspian littoral, it was found that the main staple food for the high-risk area was bread, versus rice in the low risk area.†In addition, other studies have shown that people in the high risk area eat their food very fast resulting in an unchewed and abrasive bolus passing through the esophagus, inflicting physical damage (Ghadirian et al., 1992). Moreover, in the high-risk area, bread is made from whole wheat contaminated with fine silica particles. It has been hypothesized that damage inflicted by these particles may contribute to the etiology of esophageal cancer in Iran. In China's high esophageal cancer area, fine mineral particles have been identified in the mucosa of the esophagus and a contribution to cellular growth has been postulated (O'Neill et al., 1980).

Consumption of hot beverages and food is another habit widespread in the high-risk area of the Caspian littoral. While each person drinks 20 cups of tea, five times a day, more than 50% of the people drink their tea at temperatures higher than 60 degrees centigrade (Ghadirian, 1987a; Ghadirian et al., 1988). Thermal irritation of the esophageal mucosa due to the consumption of hot beverages and food has been consistently reported to be associated with esophageal cancer (Castellsague et al., 2000), especially in the high-risk area of China as well as the high risk area of Japan (Segi, 1975) where boiled rice gruels are consumed routinely.

Studies addressing food habits are mainly correlational or case controls that are subject to measurement errors (as the measuring temperature while the beverage is in contact with mucosa can not be easily ascertained), leaving the contribution of these groups of risk factors to the high incidence of esophageal cancer controversial and inconclusive. Other categories of risk factors studied in the Iranian high-risk area are the use of tobacco, alcohol, and opium.

Case-control studies done in the high-risk population has reported ORs of less than 2 for smokers (Cook-Mozaffari et al., 1979; Bagheri, 1997), but the prevalence of smoking is very low in the area. A recent survey (Pourshams et al., 2005) found the prevalence of smoking to be just 13% among the high-risk population. A negligible number of cases can be attributed to smoking. Alcohol, a major risk factor of esophageal cancer in the western countries, is prohibited in Islam and the prevalence of its consumption is very low (Islami et al., 2004); thus it may not contribute to the high incidence of esophageal cancer in Iran.

Opium pyrolysates as putative carcinogens have been related to esophageal cancer in high-risk populations (Kmet, 1978; Hewer, 1979; Ghadirian et al., 1985).Opium use was widespread in the high-risk area; early population based studies has reported a prevalence of up to 30-60% and cases

control studies reported about a two-fold risk associated with its use (Cook-Mozaffari et al 1979, Ghadirian et al 1985; Bagheri and Nadim A, 1995). A recent study has reported a lower prevalence of opium use among people in the high-risk area (Pourshams et al., 2005) indicating a decrease in the prevalence of opium use among high-risk population. What role opium use plays in the etiology of esophageal cancer in the high-risk area is a subject of controversy. While case-control studies report an association in the high-risk area, the high prevalence of opium use among Iranians living in other parts of the country (Alemi, 1978) with a very low risk of esophageal cancer contradicts this association or dilutes its effect as a major contributing factor. Traces of other known carcinogens such as polycyclic aromatic hydrocarbons has been reported (Joint Iran/IARC, 1977) in the food of high-risk populations in early studies and a higher frequency of metabolites of PAH (Kamangar et al., 2005) have been found in the urine of people living in high-risk areas compared with low risk areas (Kamangar et al., 2005). However, the origin and contribution of these carcinogens to high incidence esophageal cancer remain uncertain.

Esophageal cancer has been associated with a lower socioeconomic status in countries where incidence is low (Cook-Mozaffari et al 1979; Brown et al., 2000;Tran et al., 2005). Most of the Asian esophageal cancer belt is includes countries considered to be underdeveloped and in the high-risk area of Iran, a low standard of living, including a poor nutritional diet and poor personal hygiene is well documented and a recent case-control study has reported a higher rate of esophageal dysplasia associated with poor oral hygiene (Sepehr et al., 2005).

Another category of suspected risk factors in the etiology of esophageal cancer in high-risk areas of Iran is nutritional factors. Correlational studies carried out in the area have shown low consumption of vegetables, citrus fruit, and animal protein among the high-risk population compared to neighboring areas with low-risk populations (Hormozdiari et al 1975; Cook-Mozaffari et al 1979; Ghadirian, 1987b). Among nutritional factors, riboflavin deficiency has been proven to be involved in cellular events in the malignant transformation to esophageal cancer (Powers, 2003). Riboflavin deficiency has been constantly reported from the area (Chaharbashi-Sobhan and Siasi , 1983). A recent study of riboflavin in the high-risk area reports a two-fold risk associated with a low intake of riboflavin (Siassi & Ghadirian, 2005) indicating low consumption of riboflavin may contribute to the high-incidence in the area. Among several trace elements studied in regard to esophageal cancer, selenium deficiency has been associated with a higher risk of the disease in several parts of the world, but no lower level of serum selenium was found among high risk population in Iran (Azin et al., 1998, Nouarie et al., 2004).

V. Other studied factors

Certain biological agents have been studied as suspected etiology of esophageal cancer in Iran; HPV has been detected in higher frequency in the tumor tissue of high-risk esophageal cancer cases in two studies (Moradi and Mokhtari, 1999; Farhadi et al., 2005). Fusarium mycotoxin (Fumonisins B) has been proven to be a carcinogen in rats (Gelderblom et al., 1992) and is a suspected etiologic factor in esophageal cancer in the high incidence area of the South African region of Transeki and in China (Marasas, 1996, Marasas, 2001). A higher concentration of contaminants in corn in Iran has been reported in the high risk area (Mazandaran province) compared to the low-risk area (Shephard et al., 2000a; 2000b; Ghyasian S et al., 2003) in Iran (Esfahan province). However, no further studies have been undertaken to address its importance in the etiology of esophageal cancer in Iran.

Conclusions

In conclusion, the incidence of esophageal cancer is still high but not as high as it was reported to be in early 1970.A wide range of environmental and lifestyle related factors may contribute to the high incidence of esophageal cancer in the high-risk population of Turkmen, certain risk factors such as family history of esophageal cancer, low socioeconomic status and poor nutritional diet are well studied and plausible evidence of their etiologic contribution exist. While thermal irritation and coarse food (physical damage to the mucosal lining of the esophagus) are vastly studied, all of these studies are based on correlational studies and, therefore, conclusions about their etiologic contribution to the high risk of esophageal cancer are inconclusive.

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Oesophageal cancer is the seventh most commonly occurring cancer in men and the 13th most commonly occurring cancer in women. There were over 500,000 new cases in 2018. The top 20 countries with the highest rates of oesophageal cancer in 2018 are given in the tables below.Â There is some evidence that being physically active might decrease the risk of oesophageal cancer (all types). Read about all the evidence in our Third Expert Report. Age-standardised rates are used in the tables. This is a summary measure of the rate of disease that a population would have if it had a standard age structure.Â Oesophageal cancer rates: both sexes. Malawi had the highest rate of oesophageal cancer in 2018, followed by Mongolia.