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*Guest editorial**

Esophageal cancer in Kashmir – an assessment

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Introduction

Epidemiological data show a wide variation in the geographical distribution of human cancers and, therefore, suggest an important contribution of the local environment in influencing the incidence of the disease (Doll 1978). Several studies in recent years have implicated dietary habits and life-style in increasing the risk of certain cancers in different parts of the world (Joint Iran-IARC Study Group 1977, Yang 1980; Day and Munoz 1982). It is now believed that a majority of human cancers are of environmental origin (Doll 1977; Higginson and Muir 1979), and thus in principle can be prevented to a considerable extent, provided the specific risk factors are identified and proper intervention measures are introduced.

Among the cancers which are considered to be etiologically linked to the human environment, esophageal cancer presents the most unusual epidemiology (Tuyns et al. 1985). First, high incidences of esophageal cancer are found in populations having diverse life-styles with differing environmental conditions, and secondly, a sharp decline is observed in the incidence of this disease in neighbouring areas (Dowlatshahi and Mobarhan 1984). These contrasting epidemiological features indicate that the causal and contributing factors that may be necessary for the disease are intrinsic to the milieu of susceptible populations. While the presence of an unknown common causal agent can not be ruled out, different predisposing and promoting factors could be involved in high-risk areas of esophageal cancer in different regions.

High occurrences of esophageal cancer have been observed in the Linxian province in China (Yang 1980), the Caspian Littoral of Iran (Mahboobi et al. 1973), the Transkei region in South Africa (Burrell 1962), and Brittany in France (Tuyns and Masse 1973). Low to moderate incidences of this cancer have also been reported from several other regions (Dowlatshahi and Moharban 1984). In recent years intensive epidemiological as well as analytical studies have been conducted in some of these areas (Coordinating Group for Research on Etiology of Esophageal Cancer in North China 1975; Joint Iran-IARC Study Group 1977). Despite little success in identifying specific etiological risk factors, such studies have certainly strengthened the view that food habits and other practices of life-style are closely associated with the disease (Lu and Lin 1982; Preussmann 1987; Pera et al. 1987). Thus, the consumption of alcohol (Tuyns et al. 1979), hot beverages (Day and Munoz 1982; Ghadirian 1987), tobacco (Martinez 1969) and the use of mouldy foodstuffs (Li et al. 1980) have been suggested as major risk factors for esophageal cancer in different places. Furthermore, lack of animal proteins (Hormozdiari et al. 1975; Tuyns et al. 1985), fresh fruits and vegetables (Cook-Muzaffari et al. 1979) and deficiency of zinc (Fong et al. 1977) and vitamin B_1 (Van Rensburg 1981; Thurnham et al. 1985) have also been considered as vital contributing factors for a high occurrence of the disease. While some of these factors may be primarily involved in inducing a favourable predisposition to the disease, others may act as sources of causative or promotional agents necessary for initiation and development of the organ-specific malignancy.

We report here our preliminary assessment of a high-risk area for esophageal cancer in Kashmir (India). Some of the unique environment features that may have strong bearing on the incidence of esophageal cancer in the region are discussed.

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The geography and population

Kashmir is a valley at high altitude in the Jammu and Kashmir province of India, situated in the extreme north of the Indian subcontinent. There are three geographically different regions in the province inhabited by populations with diverse sociocultural backgrounds and life-styles.

The Jammu region is located at an altitude of 300–3000 m having a warm tropical climate. It has a population of 2.9 million, of which nearly 95% people are Hindus. Kashmir is situated at 1800–4000 m above sea level on the northern borders of Jammu and has a population of 3.1 million, of which nearly 95% are Muslims. It has a temperate climate with a severe winter and a moderate summer. The Ladakh region is situated further north at an altitude of 3000–6000 m and has a predominantly Buddhist population among its 130000 inhabitants. Thus, the three geographical segments of Jammu and Kashmir province are inhabited by people of differing socioreligious backgrounds and life-styles, a feature which could be advantageous in studying environmentally related disease patterns.

Evidence for esophageal cancer

In the past two decades, improved diagnostic and medical facilities in this area have been responsible for emergence of information concerning an apparently high rate of esophageal cancer among the Kashmiri population. The region has no cancer registry and the hospital statistics are largely unclassified. We have, therefore, based our assessment primarily on published and unpublished hospital data available from medical professionals working in the area.

It has been reported that esophageal cancer accounted for 21.5% of the patients diagnosed histopathologically for various malignancies at the Government Medical College Hospital, Srinagar (Kashmir), during 1962–1970 (Mattoo and Kaul 1974). In a retrospective study of cancer patients attending the same hospital for radiological investigations between July 1980 and December 1982, 494 cases of esophageal cancer were observed out of a total of 1076 diagnosed cases of different malignancies (B. Sanyal, personal communication). In a 5-year study on 480 diagnosed cases of esophageal cancer patients aged between 21 and 76 years, Maqbool and Ahad (1976) report a male : female ratio of 2 : 1. Dietary habits of these patients showed that 70%–80% of them used excessive amounts of red chillies and spices in their food and consumed about 15–20 cups of hot salted tea per day. Prevalence of esophagitis has also been observed in the normal population of Kashmir (A. G. S. Pathania, personal communication). In addition, a high rate of gastric cancer has also been reported in Kashmir (Durrani 1982).

Table 1. Occurrence of esophageal cancer in India

Place	All sites	Esophagus	Frequency (%)
Bangalore[a]	2137	131	6.1
Madras[a]	2297	115	5.0
Chandigarh[a]	2455	139	5.6
Dibrugarh[a]	1226	188	15.3
Trivandrum[a]	3493	134	3.8
Ahmedabad[a]	7740	582	7.5
Bombay[b]	18690	1660	8.8
Kashmir	1413[c]	304	21.5
	2808[d]	826	29.4

[a] Data for 1982 (Perkin 1986)
[b] Data for 1978–1982 (Waterhouse et al. 1982)
[c] Data for 1962–1971 (Mattoo and Kaul 1974)
[d] Data for 1980–1982; 1984–1985 (B. Sanyal, personal communication)

Considering the low to moderate rates of occurrence of esophageal cancer in various regions of India (Table 1), the Kashmiri data appear to be remarkably high, therefore emphasising the need for a planned epidemiological study to determine the incidence rates of the disease in this region.

Absence of known risk factors for esophageal cancer

The consumption of alcohol and smoking of tobacco have been shown to be major risk factors in Europe and the United States (Tuyns et al. 1985), whereas chewing of tobacco, use of betel-nut, opium and special dietary habits have been related to the high occurrence of this disease in Asia and Africa (Dowlatshahi and Mobarhan 1984). Deficiency of Zn and vitamin B_1 as well as a lack of intake of fresh fruits, vegetables and animal proteins have also been linked with increased risk of esophageal cancer in developing countries (Hormozdiari et al. 1975; Cook-Muzaffari et al. 1979).

In Kashmir, however, the situation appears to differ with respect to some of these risks related to lifestyle. The population is almost entirely non-vegetarian with sufficient intake of lamb meat and fish. The area is devoid of alcohol consumption since the people are predominantly Muslims. Although the use of water pipes ('hukka') has been quite common in rural areas, cigarette smoking is only now becoming popular in the towns; chewing of tobacco or betel-nut is practically unknown to the local inhabitants. Moreover, Kashmir being one of the highest fruit-producing regions in the country, the local inhabitants in general have an adequate intake of locally grown fruits. Thus, the consumption of alcohol, the use of chewing tobacco or betel-nut, lack of animal proteins

and low intake of fruits, which are normally associated with esophageal cancer, do not seem to be related with the high occurrence of this disease in Kashmir. Zinc and vitamin B_1 deficiency has not been studied in the local population and needs investigation.

Dietary style of local inhabitants

The Kashmiris, mainly because of climatic constraints and distinct sociocultural traditions, have an exclusive dietary style. The ingredients used in food and beverages as well as the method of preparation are entirely different from those found in neighbouring areas or in the rest of the country. Owing to the short growing season and long severe winter, locally grown foodstuffs are preserved for storage. Plant-based foods are either sun-dried or pickled, whilst fish is preserved by sun-drying or by smoking on grass. Preserved foodstuffs may be stored for several years because of the uncertainty of the harvest and their availability prior to being consumed. A brief description of some of the food practices in Kashmir is given below.

Salted tea (noon chai). Salted tea is the most popular and freely consumed beverage in Kashmir. The method of preparation is typical and exclusively practiced in this region. Green tea leaves (not grown in Kashmir) are brewed in the presence of sodium bicarbonate until a thick red-brown coloured extract is obtained. The extract is then diluted with water according to personal preference, and salt and milk are added prior to consumption. The tea, which has a pink colour on addition of milk and tastes strong and salty, is repeatedly boiled or kept hot in 'samawar' before it is served. The per capita daily consumption is quite large (approximately up to ten cups a day).

Spiced green tea (kehwa). The 'kehwa' is prepared by boiling green tea leaves in water in the presence of cardimom, cinnamom and saffron. Kehwa is taken without milk and has a mild taste with spicy flavour. Its consumption is moderate and occasional.

Dried and pickled vegetables (hohk siun and anchar). Locally grown fresh vegetables, which include aubergine, gourd, tomato, and turnip, are sliced and preserved by sun-drying in the open. Dried spinach leaves are also frequently consumed. Several vegetables are also pickled by addition of salt, mixed spices, food colourant from flowers and mustard oil prior to their curing in the sun. Dried and pickled vegetables are generally stored in large earthen pots for periods extending up to several years.

Sun-dried and smoked fish (hokh gaard and phari). Fish constitutes an important component of the Kashmiri diet. Besides fresh fish, sun-dried and smoked fish are consumed quite commonly. The process for sun-drying is simple and similar to that practiced in many other places. However, the method of preparation of smoked fish appears to be unique to Kashmir. The fishes are not cleaned or gutted prior to smoking which is carried out on slow-burning green grass. Both sun-dried and smoked fish are preserved in earthen pots for prolonged periods.

Mixed spice cake (wur). A mixture of commonly used dried spices with food colorants, mashed onions, garlic and red chillies, which is held together by addition of mustard oil and compressed into flat circular cakes, is dried and stored. The dried spice cake ('wur') is a ready source of spices and is used as a base for most Kashmiri food dishes.

Food colourants (mawal *and* zafran). A red-coloured aqueous extract from the flowers of *Celosia argentea*, locally known as 'mawal', is widely used as colouring material in various food preparations, pickled vegetables and spice cake. Saffron ('zafran') is also widely used as food colourant.

Brassica olerecea (haak). A cruciferous leafy vegetable of the *Brassica* genus, locally known as 'haak', forms an important component of the staple diet of the native population. It is available throughout the year as it is not susceptible to cold weather.

In addition to the food items described, there is a large consumption of locally grown rice, red chillies and lotus stem. Lamb meat and yoghurt are also frequently consumed.

Diet and etiology of esophageal cancer

On the basis of comparative epidemiology, several dietary factors have been shown to be intimately associated with a high occurrence of esophageal cancer in different parts of the world. While the exact mechanism of their action remains unknown, it appears that certain dietary factors can exert their influence at different stages in the development of this disease (Pera et al. 1987). The observation that asymptomatic individuals in high-risk areas show premalignant lesions (Crespi et al. 1984) indicates that the presence or lack of substances in diet may be responsible for a continuous injury to the esophageal epithelium leading to chronic esophagitis. This has been suggested to be a predisposition for the development of esophageal cancer (Munoz and Crespi 1986). An overall malnutrition, leading to the deficiencies of riboflavin, vitamin A and zinc (Peto et al. 1981; Munoz et al. 1982; Ghadirian 1987), due to inadequate or deficient dietary

composition is shown to be responsible for such precursor lesions. Progression of the putative premalignant state of the esophageal epithelium is believed to be further enhanced by factors such as coarse or abrasive food (O'Neill et al. 1980), hot beverages (Ghadirian 1987) and irritant dietary components.

In addition to factors which may favour initiation of a reversible preneoplastic stage, several dietary components specifically prevalent in high-risk areas may act as cocarcinogens or promoters of the neoplastic process. A widespread contamination of foods with fungi producing T-2 toxin (Hsia and Tsao 1978), high intake of alcohol (Tuyns et al. 1985), excessive use of red chillies (Bhatia and Bhide 1983) and exposure to foodstuffs containing diterpene esters (Weber and Hecker 1978; Hecker et al. 1983) are some of the risk factors implicated in human esophageal cancer with potentially cocarcinogenic or promotional properties.

It may be noted, however, that while being an important link in the etiology of esophageal cancer, the risk factors outlined above need not necessarily be involved in initiation of the carcinogenic process per se. As some of these factors are also encountered in areas of low cancer risk, it is logical to assume that their role may be limited to the induction of reversible precancerous lesions (Thurnham et al. 1985; Pera et al. 1987) or to merely promoting the progression of a malignant state. Thus, the search for causal agents in the human environment, whether they originate in diet or lifestyle, or the host factors which may potentiate the endogenous formation (metabolism) of such agents is vital for our understanding of the etiology of human esophageal cancer.

Involvement of *N*-nitroso compounds

The carcinogenicity and organotropy of *N*-nitroso compounds in experimental animals is well established (Druckery et al. 1967; Preussmann and Stewart 1984). A widespread occurrence of these compounds in the human environment (Preussmann and Tricker 1988) and the possibility of their formation under in vivo conditions from nitrosatable precursors in the diet have led to suggestions of their potential role in human carcinogenesis (Bartsch and Montesano 1984). Evidence from population studies in high-risk areas provides encouraging indications for a possible involvement of *N*-nitroso compounds in human cancers and in particular in those of the upper respiratory tract (Hoffmann and Hecht 1985; Preston-Martin 1987) and bladder (Hicks et al. 1982). Several *N*-nitrosamines, especially the asymmetric ones, have been found to induce esophageal cancer in a number of animal species (Preussmann and Stewart 1984). An association between human esophageal cancer and exposure to *N*-nitroso compounds, therefore, has been strongly suspected. However, mainly because methods are lacking for the accurate measurement of human exposure to these compounds, no convincing evidence has so far been available.

Our initial assessment of the possible environmental risk factors in Kashmir reveal several unique dietary habits and life-style features that may provide interesting clues to our understanding of human esophageal carcinogenesis. For sociocultural reasons, by and large the present-day Kashmiri population is non-migratory, having uniform and stable dietary habits. As already mentioned it is evident that the risk provided by the habits of consuming alcohol, tobacco and betel-nut are not valid in Kashmir. The large consumption of hot tea is a local feature common to several high-risk areas for esophageal cancer (Ghadirian 1987). However, the use of sodium bicarbonate at the time of boiling the tea leaves and the further addition of common salt to prepared tea makes one suspect that the tea does more than cause thermal injury to the esophageal epithelium. Common salt (NaCl) is a well-known irritant of gastric epithelium and has been considered a risk factor for stomach cancer (Correa 1987). Its effects on esophageal epithelium have not been fully explored. Our studies on salted tea, prepared according to the method practiced in Kashmir, has shown the presence of preformed *N*-nitrosodimethylamine as well as the formation of high amounts of *N*-nitrosopipecolic acid with several as yet unidentified non-volatile *N*-nitroso compounds on nitrosation of tea extracts under conditions simulating the fasting human stomach (Siddiqi et al. 1988 a, b). Although we detected no mutagenic of tea extracts using Ames test, tannins isolated from salted tea have been found to give a positive result in ribosomal degranulation tests (Minocha et al. 1986). In preliminary experiments, the tea extracts were found to exhibit genotoxicity to rat hepatocytes in alkaline elution assays (Siddiqi, Pool and Preussmann, unpublished data).

Whereas, sun-drying of spices and vegetables is common practice in tropical countries, it is more widely used as a device for preservation and storage of foodstuffs in Kashmir. Staple raw foodstuffs are routinely sun-dried and stored for prolonged periods. In addition, pickled vegetables and smoked fish are also widely used. We have recently shown the presence of trace levels of several volatile and non-volatile *N*-nitroso compounds in a variety of stored foodstuffs from Kashmir (Siddiqi et al. 1988 a), in particular, the presence of *N*-nitrosodimethylamine and *N*-nitrosopyrrolidine in dried and smoked fish, dried and pickled vegetables, red chillies and spice cake. *N*-Nitrosodimethylamine was also detected in 'mawal' a

plant-based food colourant. Our results indicate that a considerable human exposure to *N*-nitroso compounds may result through the consumption of staple dietary items in Kashmir. The practice of drying raw foodstuffs in open sun (or shade) under humid conditions, and storage procedures that may be subject to bacterial or fungal growth, appear to be the main reason for the presence of preformed *N*-nitroso compounds in preserved foods.

Besides the exposure provided by preformed compounds in the diet, the intragastric formation of *N*-nitroso compounds from dietary precursors has been considered to be another potential risk in the etiology of human carcinogenesis (Bartsch and Montesano 1984; Chen et al. 1987). The in vivo formation of specific *N*-nitroso compound(s) depends on several interacting parameters in the human stomach that are influenced by the dietary source of nitrosatable amino compounds and the presence of both inhibitors and/or activators of nitrosation (Bartsch et al. 1986). These variables in the staple diet of a population seem to be critical for the endogenous formation of *N*-nitroso compounds. Using in vitro nitrosation of individual foodstuffs under simulated gastric conditions as an indirect measurement of their in vivo nitrosation potential, we have shown the additional formation of *N*-nitrosodimethylamine (20–69 μg/kg) from dried fish, vegetables and *Brassica olerecea* leaves ('haak') (Siddiqi et al. 1988 b). Several plant-based foodstuffs, particularly red chillies and spice cake ('wur') yielded *N*-nitrosopipecolic acid as well as several unidentified non-volatile compounds. These results were supported by our data showing high concentrations of precursor compounds to *N*-nitrosodimethylamine, *N*-nitrosopyrolidine and other volatile and non-volatile *N*-nitroso compounds in several raw food items (Siddiqi, Tricker and Preussmann, unpublished results).

Thus, the preliminary analytical studies on Kashmiri foods indicate the possibility of substantial exposure to *N*-nitroso compounds in the local population, from exogenous as well as endogenous dietary sources. Apart from the consumption of unusual food, there are other features of the life-style (Table 2) that need careful examination for their adverse biological effects in the local population. The most notable of these being the use of copper utensils for cooking. In a recent study, high blood copper and ceruloplasmin levels have been shown in patients suffering from gastrointestinal cancer in Kashmir (Narang et al. 1987). Although copper has not been implicated in human esophageal cancer so far, its role in causing zinc deficiency through its preferential binding to metallothioneins can not be ruled out.

Table 2. Notable features of life-style in Kashmir

No alcohol consumption
No habit of chewing tobacco or betel-nut
Sufficient fruit intake
Non-vegetarian population
Exclusive dietary habits
Preserved and stored foodstuffs
Large intake of salted green tea
Use of food colourants from plants
Excessive consumption of spices

Conclusion

Kashmir, with its culturally distinct population with uniform and stable dietary habits, provides an interesting field area for studying the relevance of diet in human esophageal carcinogenesis. In the absence of several features of life-style normally associated with increased incidence of the disease, the local food habits appear to be critical factors in the etiology of this cancer in Kashmir. Evidence from our preliminary studies shows a considerable dietary exposure to preformed *N*-nitroso compounds in the local population. In addition, the potential endogenous formation of *N*-nitroso compounds, caused by high precursor contents in certain foodstuffs, enhances the relevance of these compounds as possible risk factors for esophageal and other gastrointestinal cancers in this region. The quantitative assessment of total human exposure to *N*-nitroso compounds and their exact significance to the high cancer incidence in Kashmir requires carefully planned environmental monitoring and prospective epidemiological studies.

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