

Some Aspects of the Epidemiology of Esophageal Cancer

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Summary

The worldwide occurrence of esophageal cancer is reviewed, together with the epidemiological information on its causation. The data strongly suggest that factors associated with poverty and specific limitations of dietary intake increase susceptibility for this disease.

Introduction

The epidemiology of esophageal cancer presents many unusual features. There is a large variation in incidence found even over short distances, a variation usually more marked among females than among males. In some communities, which are often those one might regard as suffering from particularly modern forms of deprivation, the incidence appears to be rising more or less rapidly. In contrast, in areas where poverty is a consequence of the environment, the disease would seem to have been common for many centuries. A considerable array of external factors have been associated with the disease, but none strongly enough or with sufficient consistency between countries for their etiological role to be basic. The 1 characteristic of the disease that occurs consistently in different populations is its propensity for the lower socioeconomic groups.

This paper gives a short review of the epidemiology of esophageal cancer to illustrate the points made in the previous paragraph. No attempt will be made to be exhaustive; attention will be confined to populations where the frequency of the disease is well documented and where systematic investigation into the etiology have been conducted.

The Esophageal Belt of Central Asia

The Caspian Region of Iran. Extremely high rates have been reported (13) from the semidesert northeast region of Mazandaran province (Gonbad and Gorgan regions), bordering on Soviet Turkmenia, with a sharp downward gradient to the much lower incidence rates found in the rice-growing region of Gilan on the southwest of the Caspian (Table 1). The incidence, moving further west, is again high in Iranian Azerbaijan, although not as high as in Gonbad. As can be seen, the female rates vary more than the corresponding male rates. Another paper (11) at this conference discusses the situation in greater detail; it will suffice here to say that neither alcohol nor tobacco nor consumption of tea can account for the changes in incidence

and that the diet of the inhabitants of the high-incidence area is highly restricted.

That the disease in this area is not of modern origin is supported by the early Persian medical literature. Jurjani, writing from the Gorgan area in the year 1100 A.D. (9), gave the 1st description of dysphagia and esophageal cancer.

Data from the rest of Iran and from Afghanistan will not be considered, because the figures available are mainly pathology series, and such series often grossly underrepresent esophageal cancer (13).

The USSR. Incidence rates (approximately age standardized) for the various republics of the Soviet Union are given in Table 1 (20). The high rates in Turkmenia, Kazakhstan, and Uzbekistan form the central portion of the belt of high incidence running from northern China to Iran. The incidence is much higher in the indigenous former nomadic central Asians, the Kazakhs, Turkomen, and Uzbeks, than it is in immigrant Russians. These people have a Moslem tradition in which alcohol plays little part, and there is no evidence that tobacco can account for the high incidence in females, although the chewing of tobacco (nass) has been suggested as a possible cause for the disease in males. The drinking of large quantities of hot tea has been proposed as a cause in both men and women.

The tendency for the female rates to vary more than the male rates is shown more clearly by a finer subdivision, which also shows the exceedingly high rates to be found in the Caspian region. Thus, in the Guryev oblast of Kazakhstan, the rates are similar to those in Gonbad in Iran (see Table 1).

People's Republic of China. A report has been published (4) on incidence rates of esophageal cancer in northern China, for the provinces of Honan, Hopei, and Shansi. The results are somewhat difficult to interpret, but in the highest-incidence regions the age-standardized incidence is of the order of 130/10⁶/year in both sexes. The male:female sex ratio is lowest (about 1.0) in areas of highest incidence and highest (about 2.0) in the lower-incidence areas. This high-incidence region in northern China is the eastern end of the belt running from the Iranian Caspian littoral through Soviet central Asia, characterized by high incidence of esophageal cancer, with steeper incidence gradients in women than in men. The incidence data from the Chinese in Singapore suggest that, moving south from Honan to Fukkien and on to Kwantung province, one encounters an incidence gradient similar to that on the Caspian littoral, the gradient being sharper in females and being reflected in a change of staple cereal from wheat to

Table 1
Annual incidence rates per 10⁵ population of esophageal cancer, adjusted to the world population

Area	Male	Female
U.S.S.R. ^a		
Turkmenia	51.1	33.2
Kazakhstan	47.8	26.3
Uzbekistan	28.5	13.7
Azerbaijan	18.3	9.0
Russia	12.4	5.2
Ukraine	4.4	1.4
Georgia	3.4	1.7
Armenia	7.0	3.6
Estonia	4.3	1.3
Lithuania	2.6	1.4
Iran ^b		
Gonbad region	114.6	130.8
Gorgan region	67.7	57.8
Rest of Mazandaran	24.3	14.5
Gilan	20.1	6.2
India ^c		
Bombay	13.0	11.3
Singapore ^d		
Indians	5.5	5.7
Malays	1.9	3.7
Chinese (total)	19.4	7.0
Hokkien	26.3	10.6
Teochew	30.7	9.9
Cantonese	4.1	3.3
South Africa		
Transkei ^e	70.4	33.3
Natal: Africans ^f	40.9	12.3
Rhodesia		
Bulawayo ^g	75.6	36.1
Nigeria		
Ibadan ^h	0.8	0.5
Jamaica ⁱ	10.1	6.2
Puerto Rico ^j	17.5	6.9
United States ^k		
Whites	4.1	1.2
Blacks	15.6	3.6

^a Taken from Tuyns (21).

^b Taken from Mahboubi *et al.* (13).

^c Taken from Paymaster *et al.* (15).

^d Taken from Shanmugaratnam and Wee (18).

^e Taken from Rose (16).

^f Taken from Doll *et al.* (7).

^g Taken from Third National Cancer Survey (19).

rice. There are as yet no well-supported hypotheses on the etiology, but alcohol and tobacco are not of major importance. As in Japan and Singapore, consumption of hot drinks or gruel has been proposed as a possible predisposing factor.

Other Regions in Asia

Singapore. The outstanding feature in Singapore is the

high rate among Chinese males (Table 1). There is an equal incidence in Indian females as compared to Indian males and a slight excess in Malay females compared to Malay males. Among the Chinese, there are considerable variations in incidence. Those speaking the dialects of Hokkien and Teochew, who originate from Fukkien province or the Swatow region in northern Kwantung province, have elevated rates (Table 1) especially in males, whereas the rates for Cantonese speakers, from the rest of Kwantung, are relatively low (18). A case-control study of esophageal cancer among the Chinese in Singapore (6) indicated further that those born on mainland China, irrespective of dialect group or sex, had a 3-fold increase in risk as compared to those born in Singapore and that duration of schooling was inversely related to risk. The latter is an indication of an increased incidence among the lower socioeconomic groups; the former is probably an indicator of the high risk associated with traditional life styles, and it is also perhaps related to the many periods of famine suffered in mainland China before liberation in 1949. Neither tobacco nor alcohol played a significant role in causing the relatively high incidence, the 1 factor that appeared to stand out being the temperature at which people claimed to drink their beverages. There are difficulties, however, in obtaining retrospectively accurate information on the beverage temperatures at which people drink.

India. Incidence rates are available for the Greater Bombay population that show relatively high rates in both males and females (Table 1) (10). The frequency in Gujarat, to the north of Bombay, appears particularly high. Although tobacco in its various forms is clearly associated with the disease, it does not provide an explanation of the sex ratio. In fact, when the effect of tobacco has been removed, the incidence in the Bombay region in females is considerably higher than in males (15). Alcohol would seem to be not involved. In Bombay, the Parsis have lower rates than do other religions.

Africa

High incidence of esophageal cancer is found in many regions of East and South Africa, but in West Africa esophageal cancer is very rarely seen (17), and there is no evidence of high incidence in North Africa (N. Murali, personal communication). The latter is particularly interesting because the desert conditions and use of wheat as a staple food parallel some of the features of the central Asian esophageal belt. The varied pattern of incidence in eastern and southern Africa has been reviewed extensively (3, 22). A high male incidence is found in western Kenya and in south Malawi, among the rural population, and a high male rate is found among the urban African populations in South Africa. The latter feature appears to be a recent phenomenon, reflecting perhaps a specifically urban type of deprivation (see the section on the United States). Tobacco in particular and alcohol perhaps to the same extent are closely associated with the urban male incidence in South Africa (1).

The most interesting feature of the distribution of esopha-

geal cancer in southern Africa is the very high incidence in both males and females found in parts of the Transkei. The high incidence again seems to be of recent origin. A severe and lengthy drought occurred in the Transkei in the 1930's, with subsequent extensive degradation of the soils. Suggestions have been made that molybdenum deficiencies in the soil, due to erosion and runoff, could lead to accumulation of nitrite in plants consumed by humans. No evidence has yet been produced that the possible molybdenum deficiency is related to human disease (16, 22).

The Caribbean

Relatively high incidence rates are reported from Puerto Rico and Jamaica (7) and a high frequency is reported from Curaçao. In both Jamaica and Puerto Rico, the sex ratio is approximately 2.5:1. A case-control study was conducted in Puerto Rico to test the hypothesis (14) that "upper alimentary tract epidermoid carcinomas are associated with an interplay of some factors operating in undernourished epithelium, secondary to a diet mildly, but chronically, deficient." The study showed, in keeping with evidence from most other regions, that the lower socioeconomic groups were most affected and that there was evidence that these lower socioeconomic groups had a diet deficient in good quality protein, calories, vitamin A, riboflavin, and calcium. The relationship between deficiency and esophageal cancer was not demonstrated on an individual basis. Heavy consumption of alcohol and tobacco, together with hot beverages and spices, was associated with the disease.

The United States

A case-control study conducted in New York (23) clearly incriminated heavy alcohol consumption and tobacco, when associated with alcohol, as predisposing factors for esophageal cancer. The education level of the esophageal cancer cases was considerably lower than that of the controls, indicating poorer socioeconomic status. An increased incidence among the lower income groups was also found by Dorn and Cutler (8). A further feature of the disease in the United States is the sharp increase observed in the incidence among both male and female blacks (19). This increase appears most marked among the urban blacks in the north. It is unknown at present how much this increase can be attributed to alcohol or tobacco or whether it is related to specifically modern, urban impoverishment of the diet.

Europe

The incidence of esophageal cancer is low in most of Europe, and some evidence exists that it has decreased in the present century. The main exceptions are France and Switzerland, where the rates in males are moderately high. The situation in France has been studied in some detail. The high incidence is confined mainly to the northwest region of

Brittany and Normandy; an age standardized annual rate of 29.4/10⁵ has been reported for males in the department of Ille-et-Vilaine. The corresponding female rate is 1.2, showing an extreme male predominance. Both alcohol and tobacco have been shown to be predisposing factors (17). However, when the incidence of esophageal cancer is related to consumption of alcohol by department, it is clear that the type of alcohol is at least of as great importance as the quantity, the apple-based drinks apparently carrying greater risk. The other feature of esophageal cancer rates in Europe is the slightly elevated female rates in the British Isles and Finland, for which alcohol and tobacco are unlikely to be the cause. In the United Kingdom there is an inverse relationship between socioeconomic status and female esophageal cancer incidence (2). The etiology of the disease among these groups would seem more probably related to the Swedish experience, where esophageal cancer in females appeared to be associated with the Plummer-Vinson syndrome, a complex of deficiencies that is discussed in detail in another paper at this conference (12).

Discussion

The data presented in the previous section attempt to display the main epidemiological features of esophageal cancer. The change of incidence with age follows the normal pattern of epithelial tumors in western countries, and elsewhere the deviations could well be ascribed to differential reporting. There does not appear to be a general familial predisposition to the disease; the only indications of such predisposition are 2 unusual families from Liverpool and a report from Kazakhstan that is difficult to interpret. A variety of conditions such as achalasia, the swallowing of lye, or other external traumas can increase the risk for esophageal tumors. Their effect on the overall epidemiology of the disease is minimal, but it is established that injury to the esophagus increases risk for a tumor.

The main features of the epidemiology of the disease would thus appear to be sharp geographic gradients in incidence, often more marked in females, with exceptionally high rates being found in some areas, and among most populations a higher incidence among the lower socioeconomic groups. Most of the groups or populations with a high incidence come from the poorer of the world's populations.

Tobacco and heavy alcohol consumption increase the risk for the disease, as probably do hot food and drink. The 1st 2 factors, especially in combination, also tend to increase the risk for tumors for the oral cavity, larynx, and hypopharynx. In western Europe and the United States, the risk of a 2nd primary tumor in a separate part of the upper digestive tract after an initial upper digestive tract tumor is considerably elevated (5). Thus the etiologies of these different tumors have much in common in these countries. However, in much of the rest of the world high incidences of esophageal cancer are not associated with high rates for the mouth or hypopharynx, and alcohol and tobacco are not factors of major importance. There are evidently more basic factors to be identified. One could postulate that there is a

group of environmental carcinogens that are associated with the poorer strata of many different populations with totally distinct cultures and that, in many of these populations, as the overall exposure rises the women are relatively more exposed than the men. However, it seems more plausible to argue that the association with the poorer socioeconomic groups and the propensity of a damaged esophagus to develop a tumor indicate that much of the variation in incidence in the world is due to variation in susceptibility, the increases in susceptibility arising either from exogenous trauma, such as by hot drinks or from endogenous tissue damage due to dietary imbalances. Experimental evidence demonstrates that dietary deficiencies can alter the tumor incidence in the esophagus. The epidemiological data suggest that such a process is operating in humans.

The immediate objection to such a hypothesis is that there are many populations that suffer severe nutritional deficiencies but do not have a high incidence of esophageal cancer. This objection, however, would carry weight only if the deficiency alone were sufficient to cause the disease. However, the more likely mechanism would be that the deficiency, whatever it may be, increases susceptibility to the carcinogenic potential of an external agent. Both deficiency and carcinogen must be present.

Other papers at this conference will consider the association between alcoholism and nutritional status and the role of nutritional imbalances in the pathogenesis of esophageal lesions. This paper has attempted to show only that the epidemiological evidence would suggest that nutritional imbalances are of importance in the etiology of esophageal cancer.

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