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The epidemiology of esophageal cancer

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Summary. - The present paper examines the epidemiological aspects of cancers of the esophagus. Esophageal cancer is the sixth most common cancer in the world. Large geographical and temporal variations in its incidence, even within small areas, suggest that environmental exposure is causally important. Smoking and alcohol consumption are major risk factors for esophageal cancer, and alcohol has been identified as a major cause of this neoplasm in industrialised countries. In addition to smoking and alcohol consumption, dietary habits are important risk determinants of this disease. Epidemiological evidence suggests that nutritional deficiencies and, possibly, ingestion of mycotoxins and nitrosamines are factors for the development of esophageal cancer.

Key words: esophageal cancer, epidemiology.

Riassunto (*Epidemiologia del carcinoma dell'esofago*). - Il presente lavoro esamina gli aspetti epidemiologici delle neoplasie dell'esofago. Il carcinoma dell'esofago è il sesto tumore in termini di frequenza al mondo. Le ampie variazione geografiche e temporali in termini di incidenza, talvolta anche nell'ambito di piccole aree, suggeriscono l'importanza causale delle esposizioni ambientali. I consumi di fumo e alcool sono le principali cause del tumore dell'esofago nei paesi industrializzati. Oltre a fumo e alcool, le abitudini alimentari sono importanti determinanti di rischio per questa neoplasia. Evidenze epidemiologiche indicano che le deficienze nutrizionali e, forse, l'ingestione di micotossine e nitrosammine sono importanti fattori di rischio per lo sviluppo del tumore esofageo.

Parole chiave: cancro dell'esofago, epidemiologia.

Introduction

Cancer of the esophagus is one of the tumours which shows the widest geographical variation in incidence and mortality, i.e. a 300-fold variation in incidence across the world. In certain locations, the disease attains an incidence unequalled by any other fatal tumours anywhere in the world, yet, within a few hundred kilometres, the disease may have become rare again. In some regions, the frequency of this cancer is rising over time (e.g. East Europe) [1].

The identification and quantification of major risk factors derive from a series of case-control and cohort studies. Alcohol, tobacco and dietary habits are important risk factors for esophageal cancer [2-5]. Most of this review will deal with more common squamous cell carcinoma of the esophagus (92% of cases) although some aspects of the putative aetiology of adenocarcinoma will be mentioned too.

Geographical distribution

Survival rates are uniformly poor [6], so that mortality and incidence rates are very similar (Figs 1 and 2). Esophageal cancer shows high or very high incidence rates among male blacks in both South Africa and North America, intermediate or high rates in South America, high rates in the Indian sub-continent, and very high rates in southern Soviet Union, Iraq, Iran, some areas of China and in migrant Chinese populations. Such well localised excesses are the salient aspect of the epidemiology of esophageal cancer [7].

The aetiology of esophageal cancer (i.e., higher use of tobacco and alcohol among men) largely explains the low rates among females in many populations. The male/female ratio for mortality from these cancers ranges between 12.5, in Transkey, South Africa, and 1.2, in Scotland.

The geographical variation does not parallel any known source of specific carcinogens. Cancers of esophagus, can be divided into cancers essentially due to alcohol and tobacco, and those in which these two factors do not appear to play an important role. The joint effect of tobacco and alcohol exposure accounts for 80% of cases of this disease in North America, South America, Europe, South Africa and in some Asian countries [8].

However, in areas with extremely high incidence such as Iran and some parts of former USSR and China, alcohol and tobacco appear to play a minor role and the main risk factors remain to be identified, since individually-based epidemiologic studies have provided little explanation [1, 7].

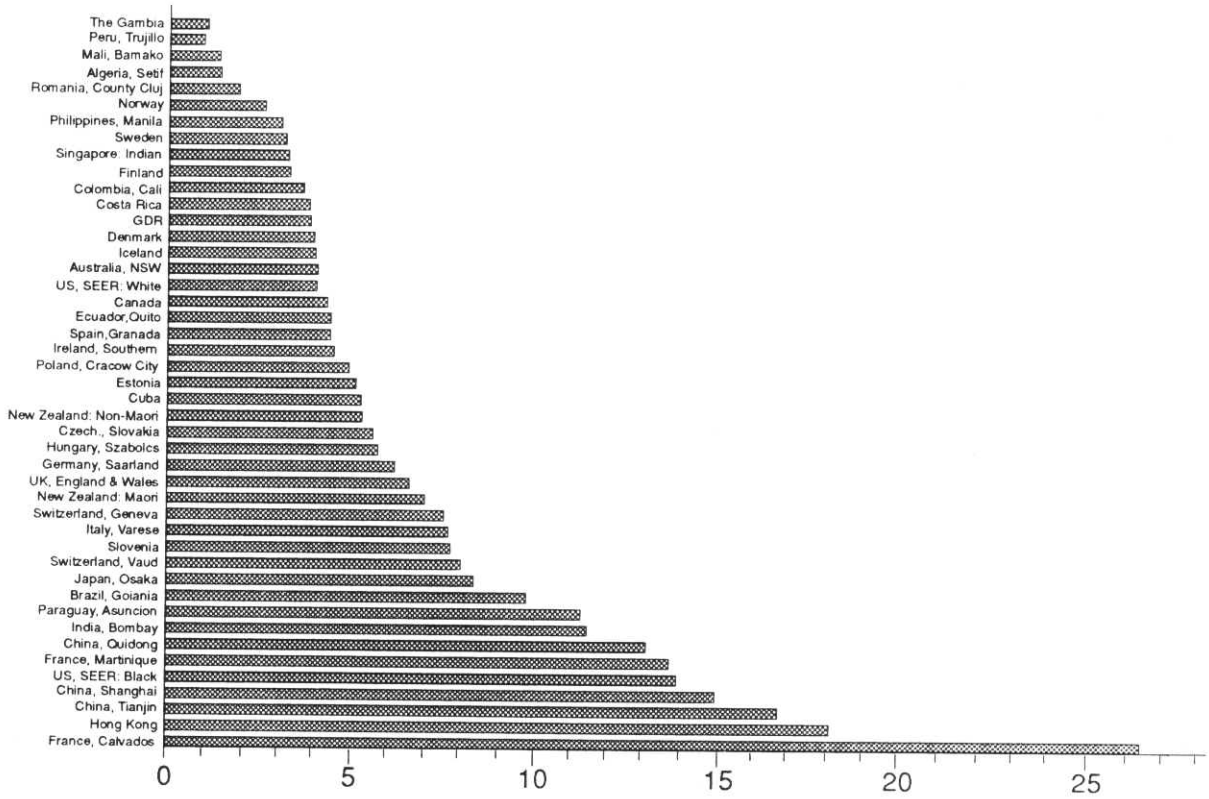

Fig. 1. - Age standardized incidence rates per 100,000 (world standard population) in different cancer registries, worldwide, 1985-1990. Males.

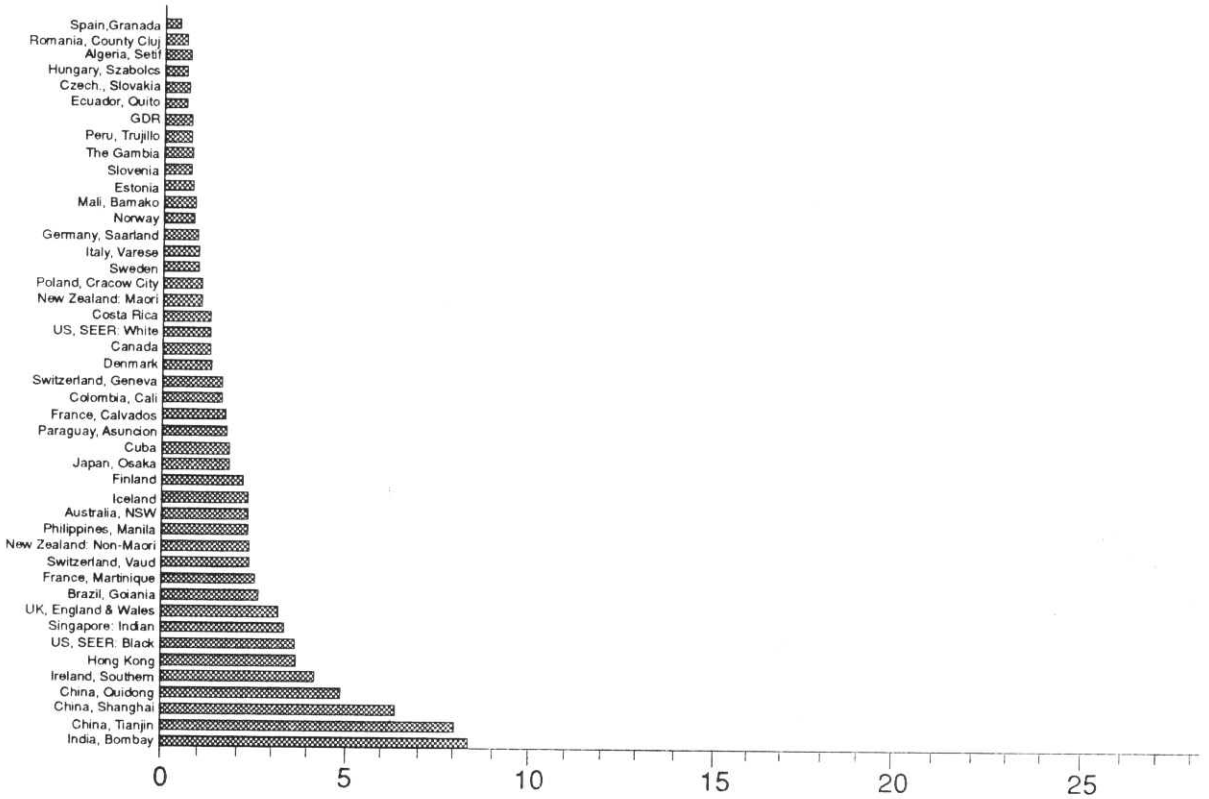

Fig. 2. - Age standardized incidence rates per 100,000 (world standard population) in different cancer registries, worldwide, 1985-1990. Females.

Time trends

Upward trends were observed in some European regions. In males, mortality rates increased approximately 10% overall (from 1955-'59 to 1985-'89) [1]. Substantial rises have been observed in the last three decades in Belgium, Czechoslovakia, Denmark, Germany, Hungary, The Netherlands, Spain and United Kingdom. Conversely, mortality rates have remained approximately stable in Austria, Italy and France and even decreased in Finland and Switzerland (Figs 3 and 4). In north-east Italy, a high-risk area, over the past two decades, an increase of 27% in mortality has been observed among men [9]. Adenocarcinomas represents approximately 5% of cases, but showed a steady increase over the last decades. This upward trend may reflect a possible true change in the disease occurrence due to the increase in one or more determinants of the disease, or an artefact due to other changes, as for instance, modifications in classification of tumours arising in the gastroesophageal junction [10].

Analytical epidemiology

Progression from normal mucosa to development of cancer of the esophagus is a multi-step process [11]. In the first step disruption or breakdown of the mucosa lining of the esophagus occurs. The second step is characterised by the delayed repair of damaged cells and tissues as well as mucosal replacement, while the third step would be the stimulation of the exposed cells by carcinogenic substances. Eventually, a variety of cancer-prone genotypes develop. It is clear that no single factor is responsible for the aetiology of esophageal cancer and the different carcinogens play a different role in the various steps.

Alcohol and tobacco

The role of alcohol and tobacco has been clearly demonstrated in most places (Fig. 5) [12, 13]. Alcohol and tobacco act approximately multiplicatively [14]. Under this assumption, the attributable risk for the combined exposure is nearly 90% [2-4]. Consumption of alcoholic beverages has been identified as a major cause of esophageal cancer in industrialised countries; the risk increases with increasing alcohol intake, with a clear dose-response relationship. The most frequently used alcoholic beverage in each area (e.g., wine in Italy, whiskey in the United States, etc.) is generally associated in each area with the highest relative risks [15]. In contrast with the lack of experimental evidence in alcohol carcinogenesis [12], some epidemiological studies showed that alcohol clearly increases the risk of esophageal cancer, even among non-smokers [16, 17]. It has long been suggested that alcohol may act as a solvent

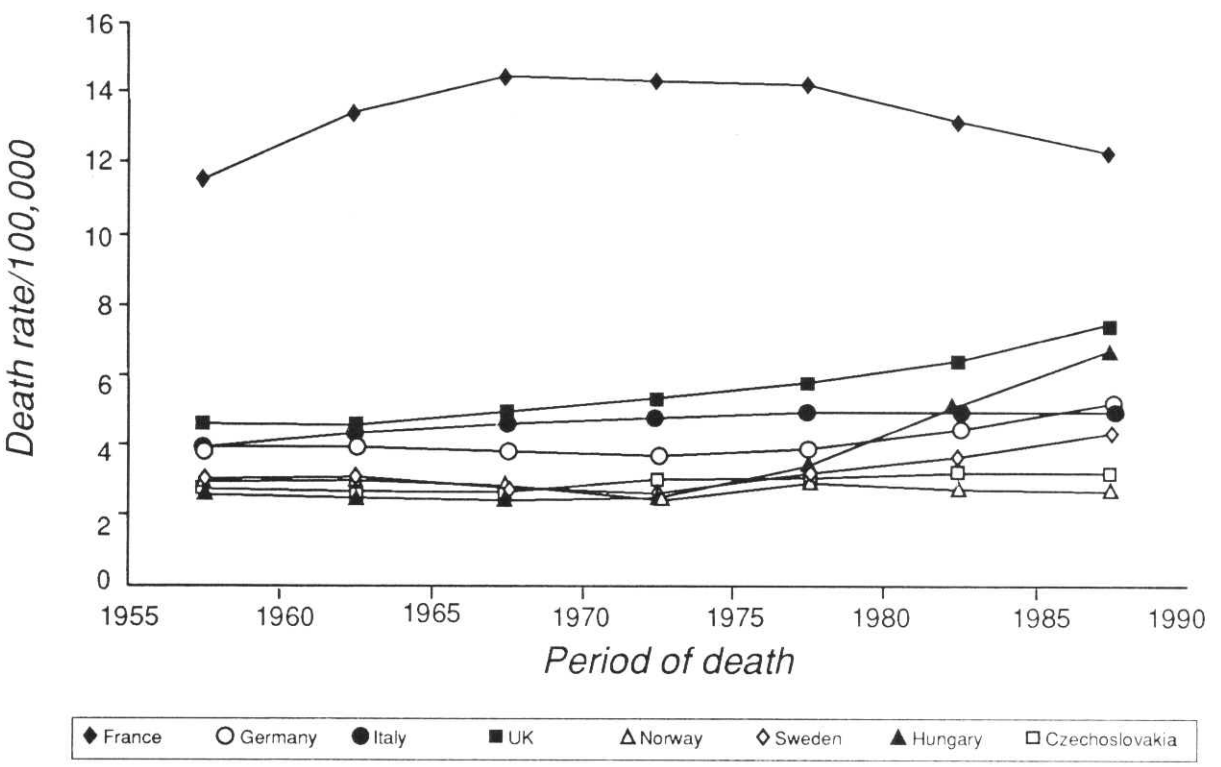

Fig. 3. - Time trend of esophageal cancer in Europe 1955-1990. Age-adjusted mortality rates (world standard population). Males.

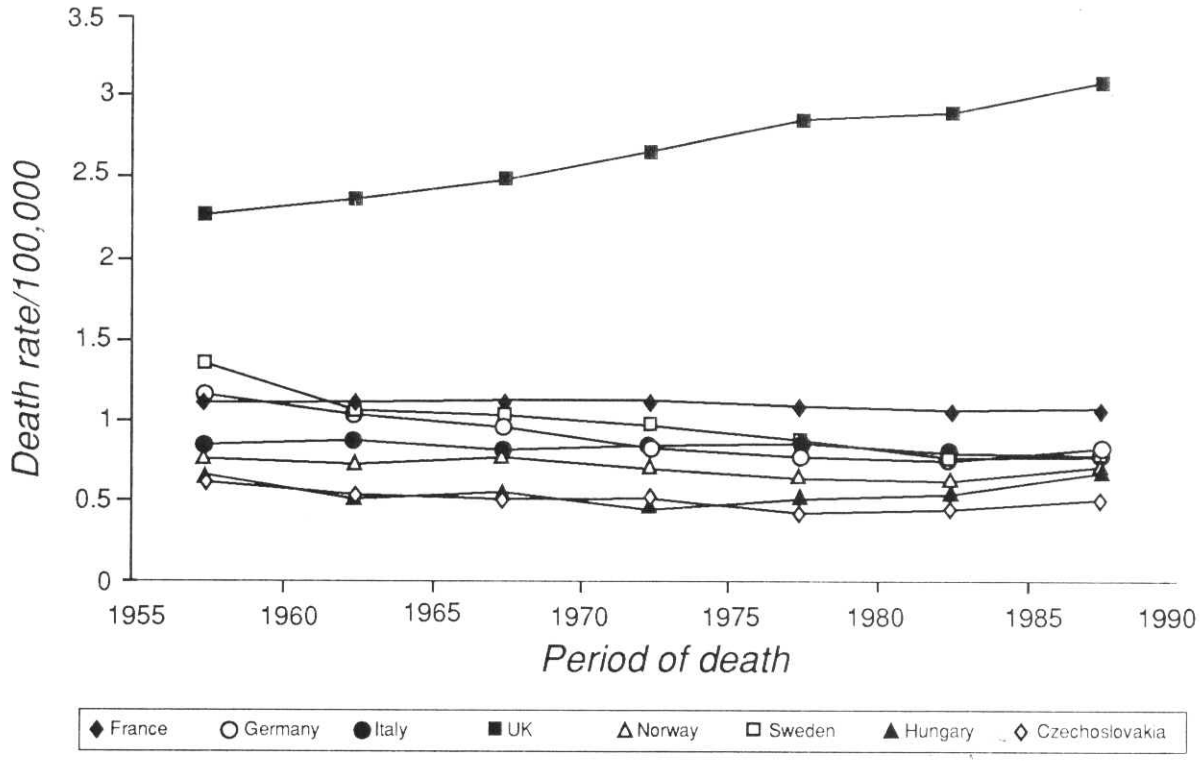

Fig. 4. - Time trend of esophageal cancer in Europe 1955-1990. Age-adjusted mortality rates (world standard population). Females.

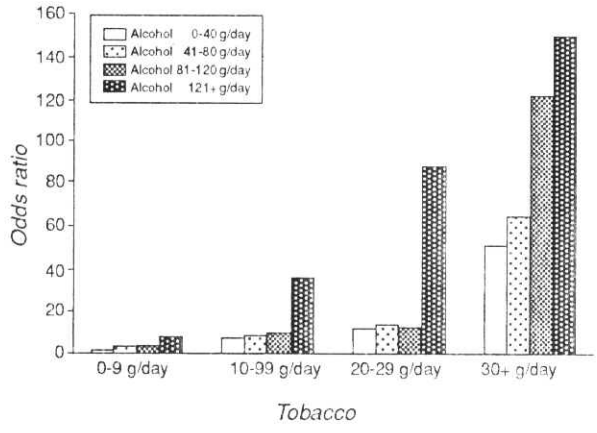

Fig. 5. - Relative risk of esophageal cancer by alcohol and tobacco consumption.

facilitating the transport of carcinogens through the esophageal mucosa, but it is also a chronic irritant which stimulate mitosis (wound healing) thus favouring the contact between the carcinogens and the dividing target cells. Some results also show that ethanol is an effective modulator of esophageal carcinogenicity by nitrosamine bioactivation. High alcohol intake could thus increase the rate of replication of cells already initiated to malignant transformation by previous exposure to nitrosamines.

Tobacco consumption is regarded as a major risk factor for esophageal cancer. The risk increase significantly with increasing number of cigarette smoked per day and duration of smoking. For smokers of only pipe or cigars, risk is more elevated than for cigarette smokers, suggesting that the course of action of tobacco may be related to the swallowing of smoke condensate [3].

Diet

An increased risk of esophageal cancer has long been reported in Plummer Vinson syndrome, which is associated with iron and vitamin deficiencies [8].

An increased risk of esophageal cancer due to poor nutritional status has been described in several epidemiological studies, and, generally, the interaction between poor nutrition and alcohol intake is approximately multiplicative. Several case-control studies and cohort studies have demonstrated an association between reduced consumption of vegetables and fresh fruits, particularly citrus fruits, (Table 1) and esophageal cancer [8,18-20]. Several correlation studies [21] have shown an association between indices of exposure to N-nitrous compounds and esophageal cancer mortality. Salt and salt-preserved foods were also associated with increased risk in developing countries [21].

Table 1. - Main results from case-control studies on diet and cancer of the esophagus in developed countries

Study	Risk factors *(a)*	Protective factors *(a)*	Interaction with alcohol intake *(a)*
United States of America			
Wynder and Bross [8]		Milk, green and yellow vegetables and citrus fruit	–
Ziegler *et al.* [41]	Bacon, canned meat, canned fish and sausages	Frozen meat and fish, dairy products and eggs (OR = 0.5)*, fruit and vegetables (0.5)*, micronutrients indeces less strongly associated than broad food groups	Multiplicative. Only 5 cases did not drink
Morris Brown *et al.* [42]	Liver (2.2)* Retinol (1.9)*	Fruits (0.5)*, especially citrus, dairy products and eggs, all vegetables. Vitamin C (0.5)*	–
Graham *et al.* [43]	Total calories (2.0)* Total fat (2.5)*, Calcium (2.2)*, Sodium (2.7)*, Retinol (3.0)*	Beta-carotene(0.6)*	–
Europe			
Tuyns *et al.* [44]	Offal*, smoked fish*, pulses*, potatoes*, butter*, carbohydrate*, proteins*, total calories*,	Meat*, chocolate*	–
Tuyns *et al.* [45]	Offal (2.2)*, canned meat (1.3)*, wholemilk (1.5)*, potatoes (2.0)*, butter (3.2)*, retinol (3.1)*, Vitamin B12*,	Fresh meat (0.2)*, skim milk (0.1)*, cakes (0.6)*, fresh vegetables (0.6)*, citrus fruit (0.3)*, fruit (0.7)*, oils (0.2)*, proteins (0.3)*, beta-carotene (0.5)*, vitamin E (0.3)*, vitamin C (0.5)*, vitamin PP (0.5)*	Multiplicative. Poor nutrition is detrimental also in light drinkers
Decarli *et al.* [24]	Fats, retinol (2.3)*, Eggs	Carrots (0.5)*, green vegetables (0.4)*, fresh fruit (0.3)*, meat, beta-carotene (0.2)*	Multiplicative with beta-carotene. Effect of beta-carotene also in light drinkers
Franceschi *et al.* [46]	Maize (2.1)*,		Lack of effect in abstainers and light drinkers
Negri *et al.* [47]		Green vegetables (0.2)*, and fresh fruit (0.3)*	–

(a) Odds ratios after allowance for major confounding factors.
* Significant.

Among micronutrients, vitamin A, C, E and riboflavin are known to be necessary to maintain the integrity of the esophageal mucosa; low intake of these nutrients is associated with an increased risk [22]. A 100-mg increase of vitamin C per day lowered the risk by about 40%. Several studies also suggested a modifying effect of vitamin C and beta-carotene on risk associated with smoking [23-25].

Thermal injury from ingestion of hot food and drinks

Ingestion of hot beverages has been shown to increase the risk of esophageal cancer in Puerto-Rico, Singapore, Iran, Uruguay and Brazil [26, 27]. A subjective report of preference for hot drinks also carried an increased risk, with an attributable risk of about 14%. The high temperature of meals and beverages was thus a strong risk indicator in these populations.

Fungi

Other sources of exposure to carcinogens may account for some of the variations in esophageal cancer risk, and epidemiological evidence suggests that ingestion of mycotoxins combined with nutritional deficiencies may be important [28]. Although it is uncertain whether fungi can produce mycotoxins that induce esophageal cancer, the tumourgenicity of fungi isolated from grain, in an area of high incidence of esophageal cancer, has been strongly suggested [29]. Risk increase has been attributed to fungal contamination of Alternaria alternata and Fusaria moniliformis. Extracts of A. alternata induced reverse mutation in *Escherichia coli*, chromosomal aberrations and sister chromatin exchanges in human peripheral blood lymphocytes [29].

Other potential risk factors

Barrett's esophagus

Barrett's esophagus is a condition where columnar mucosa extends upwards from the lining of the stomach into the distal esophagus. This disorder carries an increased risk for the development of adenocarcinoma of the esophagus (approximately 30-folds). Epithelial dysplasia in Barrett's epithelium appears thus to be a cancer precursor, but the potential value of this marker for predicting and preventing subsequent risk of adenocarcinoma is not well established. Nevertheless, persistent high grade dysplasia appears to be a sensitive indicator for the development of adenocarcinoma [30]. Bacterial infection of the digestive tract by *Helicobacter pylori* has been linked to ulceration as well as Barrett's mucosa, but its potential role in the aetiology of esophageal carcinoma is still unclear [31]. Smoking and alcohol play a less important role, if any, in the onset of adenocarcinoma than squamous-cell carcinoma of the esophagus [32].

Genetic factors

The risk associated with celiac disease and idiopathic steatorroea has been documented: for the former, HLA-B8 and HLA-DW3 seem to be important. It is possible, however, that the risk lies with the nutritional disturbances associated with these diseases [33].

An increasing risk for esophageal cancer of at least 90% was reported in tylosis [34], a hyperkeratotic condition with autosomal dominant transmission pattern and high degree of penetrance. Preliminary results suggested that this syndrome may be related to abnormal vitamin A metabolism and elevated levels of EGFR [34, 35].

HPV

Epidemiological and experimental evidences (based on search for viral DNA in tumour tissue) have lent some support to the possibility of Human Papillomavirus (HPV) playing an etiologic role on the onset of the upper aerodigestive tract cancers [36]. A more recent work on esophageal cancer suggests, however, a rather low prevalence of HPV at this cancer site [37] and does not suggest that HPV plays an important etiologic role in cancer of the esophagus, at least, in developed countries [37, 38].

Conclusions

As outlined in the assessment of risk factors for cancer of the esophagus, primary prevention must be directed chiefly at reducing the consumption of tobacco and alcoholic beverages. In developing countries, diet supplementation studies are being carried out, in order to identify specific beneficial micronutrients, with, however, no clear evidence of benefit [39, 40]. Primary prevention deserves, however, the greatest efforts, since cancer of the esophagus offers still little opportunities with respect to secondary prevention and treatment.

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