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Review article

Epidemiology and risk factors for oesophageal adenocarcinoma

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ABSTRACT

Oesophageal adenocarcinoma will soon cease to be a rare form of cancer for people born after 1940. In many Western countries, its incidence has increased more rapidly than other digestive cancers. Incidence started increasing in the Seventies in England and USA, 15 years later in Western Europe and Australia. The cumulative risk between the ages of 15 and 74 is particularly striking in the UK, with a tenfold increase in men and fivefold increase in women in little more than a single generation. Prognosis is poor with a 5-year relative survival rate of less than 10%. The main known risk factors are gastro-oesophageal reflux, obesity (predominantly mediated by intra-abdominal adipose tissues) and smoking. Barrett's oesophagus is a precancerous lesion, however, the risk of degeneration has been overestimated. In population-based studies the annual risk of adenocarcinoma varied between 0.12% and 0.14% and its incidence between 1.2 and 1.4 per 1000 person-years. Only 5% of subjects with Barrett's oesophagus die of oesophageal adenocarcinoma. On the basis of recent epidemiological data, new surveillance strategies should be developed. The purpose of this review is to focus on the epidemiology and risk factors of oesophageal adenocarcinoma.

1. Introduction

The incidence of oesophageal cancers varies markedly from one country to another [1]. The epidemiology of oesophageal adenocarcinoma has evolved considerably over the last 30 years. In many countries it has become the predominant histological type [2]. In most Western countries the incidence of adenocarcinoma of the oesophagus has increased more rapidly than that of other digestive cancers. Elsewhere, the incidence has hardly changed. Certain studies have combined adenocarcinoma of the oesophagus with that of the cardia and of the proximal stomach [3–5], for which the epidemiological characteristics and risk factors are different [6]. This review will be limited to oesophageal adenocarcinoma. It is a malignant tumour that develops in the oesophagus from glandular epithelium. In most cases, this cancer develops from Barrett's oesophagus. The latter is a type I lesion according to the Siewert classification [7], that is to say the distance between the centre of the tumour and the Z line is between −5 and −1 cm in the endoscopic position.

2. Incidence of oesophageal adenocarcinoma

Because of the rapidly increasing incidence of oesophageal adenocarcinoma, incidence rates must be compared over a similar period of time. In Europe, from 1978 to 1995, the highest incidence rates were reported in Scotland with an incidence of 3.9 in men and 1.1/100,000 in women (Table 1). In other countries, the mean incidence rates ranged from 0.6 in the Netherlands to 1.8/100,000 in Iceland in men. France appears to be a medium-risk country, since adenocarcinoma of the oesophagus is a rare disease accounting for 1% of all digestive cancers versus 5% in England [2,8,9] (Table 1). In France, it accounts for 25% of oesophageal cancers in men and 64% in women.

Besides differences in incidence according to the area of the world, trends in incidence are striking. An increase in incidence starting in the 1970s was first reported in both UK and US [10,11]. For the period 1996–2001 age standardised incidence rates in England and Wales were 4.5/100,000 in men and 0.9/100,000 in women, an almost fivefold increase compared with the 1971–1975 period [9]. The cumulative risk of developing oesophageal adenocarcinoma in the age range 15–74 years has increased strikingly in successive birth cohorts in England and Wales with a 10-fold rise in men and a 5-fold rise in women for those born in 1940 compared with those born in 1900 (Fig. 2). In France [8], Holland [12] and Australia [13], the increase in incidence began some 15 years later than in the UK or US [10,11]. During the period 1996–2001, the incidence rate in France [8] was 3.3/100,000 for men, and

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Table 1
Age standardised[a] incidence rates for oesophageal adenocarcinoma in selected countries according to Vizcaino et al. [2].

	Period	Men	Women
North America			
USA			
White	1973–1995	1.5	0.3
Black	1973–1995	0.4	0.1
Canada	1981–1993	1.3	0.2
Europe			
Scotland	1981–1995	3.9	1.1
Denmark	1978–1996	1.5	0.3
Iceland	1978–1996	1.8	0.3
Finland	1982–1997	0.8	0.5
Sweden	1977–1996	0.6	0.1
Norway	1978–1996	0.6	0.1
The Netherlands	1978–1992	0.6	0.2
Switzerland	1978–1996	1.1	0.4
France	1978–1995	1	0.1
Australia	1979–1993	1.4	0.2

[a] Direct standardisation using the world standard population.

0.3/100,000 for women. The sex ratio was 10 in France and 5 in England. The reasons for the reported trends are not well understood. The incidence of oesophageal adenocarcinoma in France has grown faster than that of any other digestive cancer over the past 30 years, with a mean 5-year variation of +68.1% in men and +97.4% in women (Fig. 1). Incidence rates, which, initially, were similar in the different socio-professional categories, have increased in every social class, but faster, since 1995, in the higher social categories [9,14]. This reflects changes in the prevalence of risk factors.

3. Prognosis of oesophageal adenocarcinoma

The prognosis for oesophageal adenocarcinoma is dismal. In France the relative survival rate (adjusted for age of patients at diagnosis) at 1, 3, and 5 years is 34.7%, 14.4% and 9.2%, respectively [8]. The five-year survival rate for epidermoid carcinoma was similar over the same period (9.2%). The survival rates reported by other registries around the world are comparable [8–10]. Stage at diagnosis is the major prognosis factor. The 5-year relative survival rate reported in Burgundy was 38.4% for T1-3 N0 M0 oesophageal adenocarcinoma, 19.8% for N + M0, and 1.8% for more advanced stages [8]. In multivariate analysis the risk of death was increased by a factor of 1.8 in case of lymph node involvement and by a factor of 4.3 in the presence of distant metastases, compared with cancers limited to the oesophageal wall. At the present, the proportion of cancers diagnosed at a local stage (T1-2 N0 M0) is low (11.2%).

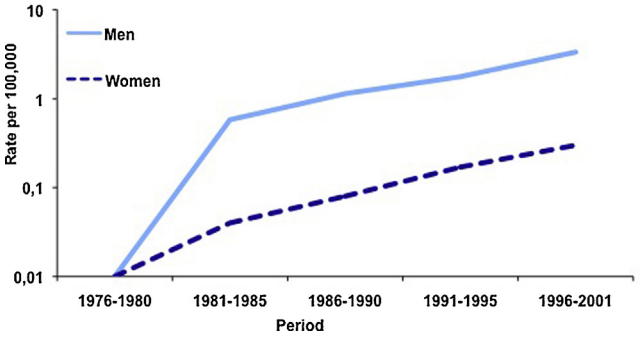

Fig. 1. Evolution of age-standardized incidence rates for adenocarcinoma of the oesophagus in Burgundy [8] (logarithmic scale).

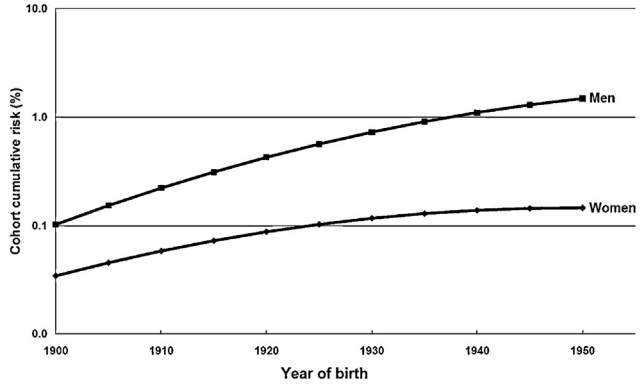

Fig. 2. Cumulated risk of developing adenocarcinoma of the oesophagus by birth cohort between 15 and 74 years [9].

4. Risk factors for oesophageal adenocarcinoma

4.1. General factors: lifestyle and dietary factors

A very high sex-ratio (around 10 in France [8], is characteristic of cancers closely linked to smoking and/or alcohol consumption. One of the principal known risk factors of adenocarcinoma of the oesophagus is smoking [1]. In smokers, the risk of progression from non-dysplastic Barrett's oesophagus to high-grade dysplasia or oesophageal adenocarcinoma is two to four times that in patients who have never smoked [15–19]. Smoking should be discouraged in patients with Barrett's oesophagus to decrease the risk of oesophageal adenocarcinoma. In contrast, in case–control studies investigating the association between alcohol intake, Barrett's oesophagus and oesophageal adenocarcinoma, alcohol consumption does not appear to confer an increased risk [20–22]. Tobacco smoking, however, does not explain the increase in incidence reported in European countries, the United States and Australia [8–11,23,12]. The reasons for this increase are still unknown although various hypotheses have been put forward. In France, Holland, and Australia the increase in incidence began some 15 years later than in the UK or the US. The evolution in incidence is quite similar to that observed for adenocarcinoma of the lung in terms of timing and geography. The progressive increase in the use of filter cigarettes may thus be the cause [24]. On the other hand, high consumption of fruit and vegetables has a protective effect as with many other digestive cancers [25]. However, changes in the consumption of fruit and vegetables and the apparently protective effect of Helicobacter pylori infection [26,27], do not seem to be plausible explanations for the trend in incidence rates.

Finally, a history of mediastinal radiation (breast cancer before 1980, lymphoma, thymoma, etc.) increases the risk of developing adenocarcinoma of the oesophagus (to the same degree as epidermoid carcinoma) by a factor of 10, ten years after exposure [28].

4.2. Gastro-oesophageal reflux and overweight

Gastro-oesophageal reflux is a documented risk factor for the occurrence of oesophageal adenocarcinoma. Among published papers, a population-based case–control study in Sweden is particularly interesting [29]. The odds ratio for oesophageal adenocarcinoma was 7.7 for persons with recurrent symptoms of gastro-oesophageal reflux compared with persons without such symptoms. This effect was independent of other studied variables (sex, age, body mass index (BMI), smoking status and alcohol use). For subjects with long-standing and severe symptoms the odds ratio was 43.5. However, the authors calculated that if endoscopic surveillance was implemented for Swedish men older than 40 who had symptoms of reflux severe enough to entail a risk 20 times higher than normal, a Swedish gastroenterologist would need to follow more than 1400 patients for one year to find one case of oesophageal adenocarcinoma.