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Review article

Epidemiology and risk factors for oesophageal adenocarcinoma

Côme Lepage[a,b,c,*], Antoine Drouillard[a,b,c], Jean-Louis Jouve[a,b,c], Jean Faivre[a,b,c]

[a] Burgundy Digestive Cancer Registry, INSERM U866, 21079 Dijon Cedex, France
[b] University of Burgundy, France
[c] University Hospital of Dijon, 2 Bd de Lattre de Tassigny, Dijon, France

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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

* Corresponding author at: Burgundy Digestive Cancer Registry, INSERM U866, 21079 Dijon Cedex, France. Tel.: +33 380381314.
E-mail address: come.lepage@u-bourgogne.fr (C. Lepage).

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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%).

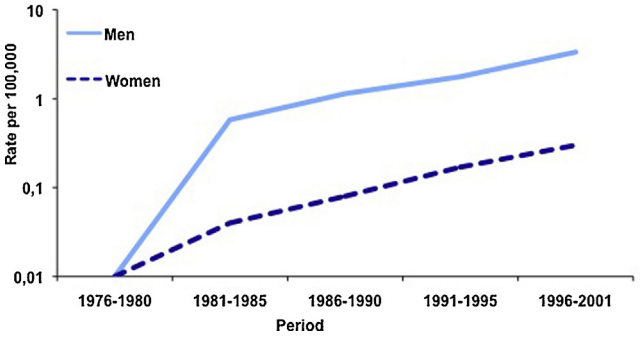

Fig. 1. Evolution of age-standardized incidence rates for adenocarcinoma of the oesophagus in Burgundy [8] (logarithmic scale).

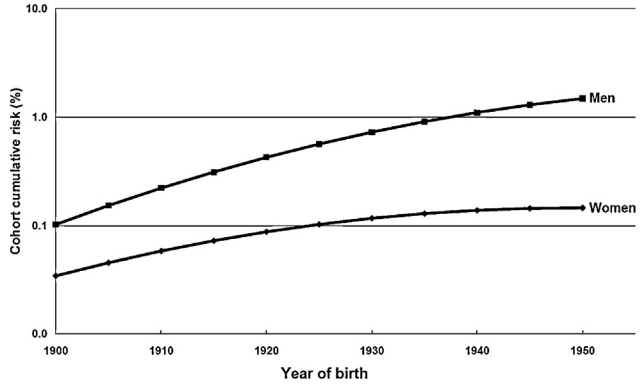

Fig. 2. Cumulated risk of developing adenocarcinoma of the oesophagus by birth cohort between 15 and 74 years [9].

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.

Increasing BMI has also been associated with oesophageal adenocarcinoma [30]. A recent analysis of 10 case–control studies and two cohort studies including nearly 2000 cases of oesophageal adenocarcinoma and 12,000 controls indicated that the risk of oesophageal adenocarcinoma increased with greater BMI. Compared with a BMI <25, a BMI ≥40 was associated with an odds ratio of 4.8 [3.0–7.7] [31]. Three case–control studies showed an increased risk of Barrett's oesophagus that was probably mediated predominantly by intra-abdominal adipose tissue [32–35]. The association between abdominal obesity and Barrett's oesophagus was found in males, but not in females [34] and this association was minimally attenuated by gastro-oesophageal reflux. Differences in adipose tissue distribution between men and women may explain, at least in part, the much higher incidence of oesophageal adenocarcinoma in men. Abdominal obesity may increase intra-abdominal pressure, which subsequently relaxes the lower oesophageal sphincter increasing the risk of gastro-oesophageal reflux. However, it could also be suggested that hormonal and systemic changes associated with abdominal obesity in men may explain the higher risk of oesophageal adenocarcinoma. Abdominal obesity is associated with changes in the physiological function of adipose tissues leading to insulin resistance, chronic inflammation, and altered secretion of adipokines. BMI is associated with oesophageal adenocarcinoma also in the absence of gastro-oesophageal reflux, suggesting that it is an independent risk factor for oesophageal adenocarcinoma [31]. Research on the identification of the mechanisms underlying the metabolic effect has been undertaken only recently and the results will be extremely important.

4.3. Barrett's oesophagus and risk of oesophageal adenocarcinoma

Barrett's oesophagus is a well-established precancerous condition for the development of oesophageal adenocarcinoma. Relatively abundant literature exists concerning this risk. Data have mostly been provided by hospital units or tertiary care centres and as such cannot be used as a reference because of unavoidable selection bias. This situation explains the wide-ranging variations in the reported risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus. Population-based series are needed to determine the risk of oesophageal adenocarcinoma in everyday life. Such studies are rare because they require pathological and clinical data to be available at a population level, the existence of a good-quality cancer registry and a complete follow-up of the Barrett's oesophagus cohort. The three large population-based studies published to date [36–38] included 8500–42,000 subjects with Barrett's oesophagus, and thus provide a more precise evaluation of the risk of oesophageal cancer. This is the reason why we limited this review to population-based studies [36–40].

In large nationwide cohorts of unselected patients with histologically confirmed Barrett's oesophagus, the annual risk of oesophageal adenocarcinoma was remarkably similar ranging between 0.12% and 0.14% [36–38] (Table 2). These annual risks were several times lower than those reported in published systematic reviews of hospital-based series [41–44]. Results on oesophageal adenocarcinoma incidence are also consistent (Table 2), as it was calculated to be between 1.2 and 1.4 person-years at risk. In one study [37] the analysis was also conducted among patients with endoscopic surveillance. The annual risk was found to be 0.43% indicating that these patients might have been a selected partly symptomatic population.

Although the diagnosis of dysplasia depends on the number and the site of biopsies and of the pathologist's interpretation, it remains the best indicator of cancer-risk. In population-based series the incidence of oesophageal adenocarcinoma was 4–7 times higher in patients with low-grade dysplasia than in patients without dysplasia (Table 2). Male sex is also an independent predictor of malignant transformation. The incidence in men was 2–3 times higher than in women. This can be explained by higher tobacco consumption in men and by abdominal obesity. Although there are some differences, the incidence of oesophageal adenocarcinoma in patients with Barrett's oesophagus generally increases with age. There is still debate concerning the relationship between the length of Barrett's oesophagus and the risk of oesophageal adenocarcinoma. The data available in population-based studies are insufficient to provide firm conclusions.

In population-based studies, the risk of developing oesophageal adenocarcinoma in patients with Barrett's oesophagus is ten times that in the population at large (Table 2). However, because of the rarity of this type of cancer only a minority of Barrett's oesophagus patients will develop an oesophageal adenocarcinoma. The 10-year cumulative risk of oesophageal adenocarcinoma varied between 3% and 6% in the absence of dysplasia, and between 7% and 13% in the case of low-grade dysplasia at baseline. Indeed, subjects with Barrett's oesophagus have the same life expectancy as the general population and less than 5% of them will die from oesophageal adenocarcinoma [45]. A few studies have explored the cost effectiveness of Barrett's oesophagus surveillance. A US study suggested that with an annual risk of oesophageal adenocarcinoma of 0.4%, surveillance every 5 years was the only strategy that improved quality of life [46]. A study in the UK, which has

Table 2
Incidence of oesophageal adenocarcinoma among patients with Barrett's oesophagus in large population-based studies [36–38].

	Hvid-Jensen et al. [36]	Bhat et al. [38]	de Jonge et al. [37]
Place of the study	Denmark	Northern Ireland	The Netherlands
Barrett's oesophagus	11.028	8522	42,207
Follow-up period	1992–2009	1993–2005	1991–2006
Person-years at risk	67.105	59.784	234.821
Median follow-up time (years)	5.2	7.0	–
% low grade dysplasia	6%	4%	10%
Annual oesophageal adenocarcinoma risk	0.12%	0.13%	0.14%
Oesophageal adenocarcinoma Incidence rate for 1000 person-years			
Overall	1.2	1.3	1.4
No dysplasia	1.0	1.0	1.2
Low-grade dysplasia	5.1	9.2	3.6
Men	1.5	1.7	1.9
Women	0.5	0.8	0.8
Standardizes incidence rate	11.3	–	10.0
10-years oesophageal cancer cumulative risk			
No dysplasia	3%	2.6%[a]	6%
Low-grade dysplasia	7%		13%

[a] No dysplasia and low-grade dysplasia.

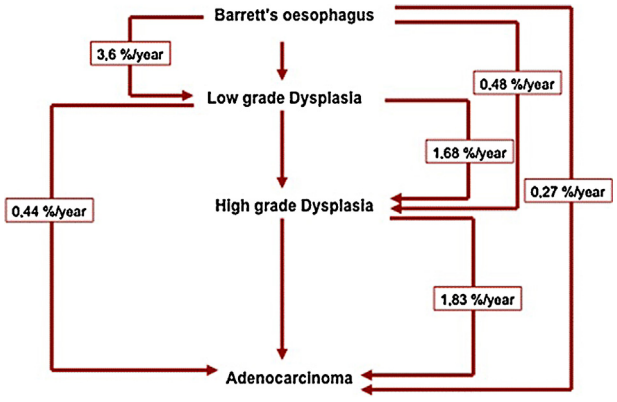

Fig. 3.

an annual oesophageal adenocarcinoma rate of 0.5%, concluded that any surveillance conferred less benefit and more costs than no surveillance at all [47]. New quality of life studies targeting patients with at least a 1% for year risk of oesophageal adenocarcinoma, i.e. patients with at least low-grade dysplasia, must be conducted.

Endoscopic eradication therapy for Barrett's oesophagus is possible. However, we do not have any efficacy data demonstrating a reduction in the risk of oesophageal adenocarcinoma. Recently, the American Gastroenterology Association recommended endoscopic eradication therapy only for the treatment of patients with high grade dysplasia [48].

Several hypotheses to determine the risk of progression of Barrett's oesophagus to oesophageal adenocarcinoma using accurate biological tools have been tested. Different potential biomarkers have been identified. These include the surface expression of cyclin A [49], DNA abnormalities [50], inactivation of tumour-suppressor p 53 [51], sialyl Le^a and Le^x expression [52], wheat-germ agglutinin and the decreased binding of Aspergillus oryzae lectine [53]. Of particular interest is the case–control study conducted in the population-based cohort that included all cases of Barrett's oesophagus diagnosed in Northern Ireland [38]. It compared cases that progressed rapidly to severe dysplasia or oesophageal adenocarcinoma with cases that did not progress. The authors identified a panel model of three markers, low grade dysplasia, DNA abnormalities and Aspergillus oryzae lectine binding that discriminated between cases and controls. The last two biomarkers could help to identify more objectively patients with low-grade dysplasia who are at a high risk of progression. However, more data are necessary to apply available results in everyday practice. The proportion of progressors according to biomarker abnormalities has not yet been adequately determined.

It must be underlined that most cases of Barrett's oesophagus remain undiagnosed. In a population- based cohort of 120,000 subjects aged 55–69 years in the Netherlands followed between 1986 and 2003, Barrett's oesophagus was diagnosed in only a few subjects (0.005%) [40]. In Denmark, 197 oesophageal cancers were diagnosed in patients with known Barrett's oesophagus, and these cases accounted for 7.6% of all oesophageal adenocarcinoma diagnosed in the country [36].

Figures on the prevalence of Barrett's oesophagus vary considerably. In an autopsy study in Olmsted County (USA), the prevalence was found to be 0.4% [54]. Its prevalence was established in a population-based endoscopic study in Sweden [55]. Barrett's oesophagus was present in 1.6% of the subjects. Among these, 40% reported reflux symptoms. The prevalence of Barrett's oesophagus in those with gastro-oesophageal reflux was 2.3% and in those without reflux symptoms was 1.2%. The identification of asymptomatic Barrett's oesophagus is a major challenge (Fig. 3).

5. Aspirin, non-steroidal anti-inflammatory drugs and statins

A systematic review of seven case–control studies and two cohort studies supported a significantly lower risk of oesophageal adenocarcinoma among those who frequently used non-steroidal anti-inflammatory drugs or aspirin than in never users [56]. Four observational studies have also suggested that the regular use of aspirin and other non-steroidal anti-inflammatory drugs is associated with a reduction of about 50% in risk of oesophageal adenocarcinoma [57–60]. These findings persisted after adjustment for major risk factors. A study that aimed to assess the role of non-steroidal anti-inflammatory drugs in people with high-grade dysplasia who reported current use showed that such people had a lower risk of progression to oesophageal adenocarcinoma than those who reported former use or never use of non-steroidal anti-inflammatory drugs [59]. Such drugs might be effective even in late stages of neoplastic progression. Two studies that aimed to evaluate the relationship between non-steroidal anti-inflammatory drugs and the risk of Barrett's oesophagus [61,62], reported diverging results. One of the studies [62] found evidence of an inverse association between the use of aspirin and non-steroidal anti-inflammatory drugs and the risk of Barrett's oesophagus, the other [61] did not. The question of whether or not non-steroidal anti-inflammatory drugs prevent the onset of Barrett's oesophagus remains open.

Recent observational studies suggest that statins may have a protective effect on the development of cancers [63]. Experimental data suggests that statins might have potential chemo-preventive effect against the development of oesophageal adenocarcinoma. However, human studies on Barrett's oesophagus are lacking.

6. Conclusion

Adenocarcinoma of the oesophagus will soon cease to be a rare form of cancer. The risk of developing oesophageal adenocarcinoma has multiplied tenfold in men and fivefold in women over just one generation. Intervention to reduce the prevalence of obesity and eradicate smoking habits, two independent risk factors for oesophageal adenocarcinoma, represent a good start to prevent oesophageal adenocarcinomas. Barrett's oesophagus is a precancerous lesion, but its risk of deterioration has long been overestimated. Population-based studies provide solid evidence that oesophageal adenocarcinoma will develop in few patients with Barrett's oesophagus. Dysplasia is the most clearly identified indicator of cancer risk. In the absence of dysplasia, routine surveillance is of questionable value, particularly in women and in subjects under 50 years. On the basis of the recent population-based data, current surveillance guidelines should be revised.

Conflict of interest statement
None declared.

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