Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries

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Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries

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Background	In many western countries an increase in incidence of adenocarcinoma of the oesophagus and/or gastric cardia have been reported. The aim of this study was to describe and compare trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in several areas of Europe, 1968–1995, using Eurocim (a database of cancer incidence and mortality data from 95 European cancer registries).
Methods	Time-trends in age-standardized incidence rates of adenocarcinomas of the oesophagus and gastric cardia are described in 11 population-based cancer registries from 10 countries in North, South, East, West and Central Europe, 1968–1995. The statistical significance of the time-trends in incidence was assessed using Poisson regression analysis.
Results	An increase in incidence of adenocarcinomas of the oesophagus and gastric cardia was observed in Northern Europe (Denmark), Southern Europe (Italy, Varese), Eastern Europe (Slovakia) and Western Europe (England and Wales, Scotland). In Central Europe (Switzerland, Basel) and in the cancer registries of Iceland (Northern Europe), France, Bas-Rhin and Calvados, Southern Ireland, and the Netherlands, Eindhoven (Western Europe) no rise in incidence was observed. The increase in incidence of adenocarcinomas of the oesophagus and gastric cardia was accompanied by a decrease in incidence of both adenocarcinomas and non-adenocarcinomas of the non-cardia part of the stomach in almost all of the 11 cancer registries studied. Increased histological verification of tumours of the oesophagus and stomach and improvement in precision of histological diagnosis may partly explain the increase in incidence of adenocarcinomas in some registries.
Conclusions	This study, using Eurocim data, supports the findings from other time-trend studies of population-based cancer registries in western countries.

Keywords	Adenocarcinoma, oesophagus, stomach, incidence, trends, Europe
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In the last decades, clinically based case series studies in American,[1] Canadian[2] and European centres[3] reported an increase in incidence of adenocarcinoma of the oesophagus and/or gastric cardia. These findings have been confirmed by many population-based studies in western countries like the US, Australia, New Zealand and several countries of Europe.[4–21] This increase began around the 1970s both in men and women,[9,12] but seemed to be most pronounced in (white) men.[6,14,16] This trend tends to affect all age groups. The highest rate of increase was nearly 10% per year and has been reported in the US.[10,22] However, in one small population-based study from the Swiss canton of Vaud no increase in incidence has been found for adenocarcinomas of the gastric cardia between 1976 and 1987.[23]

The increase in incidence of adenocarcinomas of the oesophagus and gastric cardia is different from trends observed in squamous cell carcinoma of the oesophagus and tumours in the non-cardia part of the stomach. The incidence of squamous

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cell carcinoma of the oesophagus is quite stable in western countries,[19,20] while the incidence of tumours in the non-cardia part of the stomach (mainly adenocarcinomas) is decreasing.[24]

There are also differences between adenocarcinomas of the oesophagus and gastric cardia, squamous cell carcinoma of the oesophagus and tumours in the non-cardia part of the stomach with respect to male-to-female-ratio (high M/F ratio for adenocarcinomas of the oesophagus and gastric cardia[25]), ethnicity (higher incidence among American whites compared to American blacks)[10] and geographical distribution.[16] This suggests that these three types of tumours are aetiologically distinct.[5] Recent epidemiological findings support this hypothesis.[26,27] In the same period in which the increase in incidence of adenocarcinomas of the oesophagus and gastric cardia has been reported, however, improvement in precision of histological diagnosis and improvement in diagnostic procedures for these tumours has been reported as well and may partly explain the increase in incidence.[10] Several explanations of this increase will be discussed later.

The aim of this study is to describe and compare trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in several areas of Europe, 1968–1995, using Eurocim data, a database of incidence and mortality data from 95 European cancer registries.[28]

Materials and Methods

Eurocim database

The Eurocim database is a computerized cancer incidence and mortality database developed by the European Network of Cancer Registries (ENCR). Cancer registries that are members of the ENCR are asked to make regular submissions of incidence, mortality and population data to a central Eurocim databank held at the International Agency for Research on Cancer in Lyon. The Eurocim database comprises detailed cancer data by topography and morphology from 95 European cancer registries over various years, 1960–1995. The Eurocim database also contains data-analysis software.[28]

Selection of cancer registries

We selected cancer registries based on the criteria 'period' using version 1.1 (1993) of the Eurocim database. At least 10 years of continuous registration of a cancer registry had to be available in the database in the overall study period 1968–1995. Furthermore, we aimed at 'geographical variation', i.e. at least one cancer registry had to be available in each of the following regions of Europe: North, South, East, West, and Central Europe. This first selection yielded 24 cancer registries of the 95. Because there were more potential cancer registries in some regions or countries, we used additional criteria. These criteria were: registries covering those populations that enlarged the contrast in incidence of oesophageal and stomach cancer between areas, registries covering a large population and registries with good data quality. The data quality of a cancer registry was measured with three indices of reliability (the percentage of cases histologically verified, the percentage of cases registered with a death certificate only and the ratio of mortality to incidence) as presented in *Cancer Incidence of Five Continents (Vols IV, V and VI)*.[29–31] The five regional cancer registries of Scotland were combined in the database to one cancer registry 'Scotland'. After this selection, 12 cancer registries were left. One cancer registry was excluded because no detailed data on morphology and topography were coded in the first 6 years of the available study period of this cancer registry. Finally, 11 cancer registries were included in the study (Table 1). After version 2.1 of the Eurocim database was released (in 1997) we continued working with the 11 selected cancer registries, but now more years of registration (minimal 12 years) of each cancer registry were available.

Table 1 Selected Eurocim cancer registries with 12 years of continuous registration or more in the Eurocim database (Eurocim version 2.1)

Eurocim cancer registry	Available period[a]	No. of AEC cases[b]	Population size (×1000) in 1990
Northern Europe			
Denmark	1978–1992	3064	5139.9
Iceland	1970–1995	184	254.8
Southern Europe			
Italy, Varese	1976–1992	311	793.0
Eastern Europe			
Slovakia	1968–1992	1300	5297.8
Western Europe			
England and Wales	1971–1990	32 952	50 718.8
France, Bas-Rhin	1975–1992	366	954.5
France, Calvados	1978–1992	242	617.6
Ireland, Southern	1981–1992	182	532.6
Netherlands, Eindhoven	1978–1992	433	935.7
Scotland[c]	1975–1995	6484	5102.2
Central Europe			
Switzerland, Basel	1981–1992	212	426.7

[a] Period in which all registries have data: 1981–1990.

[b] Adenocarcinomas of the oesophagus and gastric cardia.

[c] Combined data for five regional registries.

Selection of tumours

All primary tumours of the oesophagus and stomach (International Classification of Diseases for Oncology (ICD-O) codes 150 and 151, respectively) were included in the analyses. Oesophageal tumours were classified into the following morphology categories: squamous cell carcinoma, adenocarcinoma and all other morphology codes (Appendix). Stomach tumours were classified into the following combined topography and morphology categories: adenocarcinoma of the cardia, non-adenocarcinoma of the cardia, adenocarcinoma of the non-cardia part of the stomach and non-adenocarcinoma of the non-cardia part of the stomach (Appendix). For the analyses, we combined adenocarcinomas of the oesophagus and gastric cardia (AEC) (ICD-O codes 150 and 151.0 and 8140–8473, 8480–8490, 8500–8550).

Background information of cancer registries

We contacted each selected cancer registry with a written questionnaire to get more information on classification and coding practice of AEC during the study period. We asked whether the cancer registry had specific coding rules regarding AEC, whether there had been changes in coding practice, diagnostic criteria or procedures for AEC in the period in which the cancer registry provided data, whether the cancer registry coded adenocarcinomas of the (lower) oesophagus as cardia tumours, and if AEC was coded as 159.8 or 159.9 when it was difficult to distinguish tumours arising in the lower third of the oesophagus, the gastro-oesophageal junction and the gastric cardia. Seven of the 11 cancer registries responded.

Presentation of the data

In the Eurocim database cases are classified into 5-year age groups (0–4, 5–9, 10–14 etc..., and ≥85 years). For comparison, age-standardized incidence rates for all age groups together are calculated by the direct method using the standard European population and reported as number of incident cases per 100 000 person-years. Incidence rates of AEC and all oesophageal and stomach cancer together are calculated for each of the cancer registries by sex for the 5-year period 1986–1990 (in which all cancer registries provided data). Furthermore, incidence rates of AEC are calculated for each of the cancer registries by sex for 3-year periods (1969–1971, 1972–1974, etc., 1993–1995). To see whether an increase in incidence of one (morphology) type of tumour was accompanied by a decrease of another type of tumour of the oesophagus and/or stomach, we compared the trends in incidence of all types of tumours of the oesophagus and stomach simultaneously for each cancer registry. These rates are only graphically presented for two cancer registries with contrasting trends.

Statistical analysis

The statistical significance of the time trend in the age-standardized incidence rates for each cancer registry was assessed using Poisson regression. The model included the variables period (3-year periods entered as dummies variables), age (numerical variable) and sex (dummy variable). For each 3-year period relative risks (RR) of AEC were computed using 1981–1983 as reference period. Interaction between sex and period was tested for each cancer registry. If there was a significant interaction, RR of each 3-year period were presented for men and women separately, otherwise the RR were presented for men and women combined. The test for trend was based on a likelihood ratio test. In this case period was entered as a continuous variable in the model. The statistical package STATA was used for Poisson regression modelling.[32]

Results

Table 1 presents each of the 11 selected cancer registries with the available period, the number of AEC cases, and population size. The available period of the cancer registries ranged from 12 to 26 years in the overall period 1968–1995. During 1968–1995, all 11 registries together recorded a total of 45 730 incident cases of AEC (34 267 men, 11 463 women). For all cancers of the oesophagus and stomach these figures were 107 503 (63 259 men, 44 244 women) and 330 514 (197 833 men, 132 681 women), respectively.

Incidence in 1986–1990

Table 2 gives the age-standardized incidence rates for AEC, all cancers of the oesophagus and stomach for each cancer registry by sex, 1986–1990. The highest incidence rates of AEC were recorded in Scotland, both in men and women (9.7 and 2.9 per 100 000 person-years, respectively). The lowest incidence rate for men was recorded in Slovakia (3.5 per 100 000) and for women in France (Bas-Rhin) (0.4 per 100 000). The incidence of all cancers of the oesophagus was highest in France (Calvados) (34.2 per 100 000) and lowest in the Netherlands (Eindhoven) (4.8 per 100 000). For women, the oesophageal cancer rate was highest in Scotland (7.0 per 100 000) and lowest in Slovakia (0.7 per 100 000). The highest incidence rates of all cancers of the stomach for men and women were both recorded in Italy (Varese) (44.4 and 21.8 per 100 000 person-years, respectively) and the lowest rates were 15.8 (males, Denmark) and 7.6 (females, France, Calvados). The male-to-female sex ratio of AEC varied from 2.8:1 (Netherlands, Eindhoven) to 12.0:1 (France, Bas-Rhin). The sex ratio of all cancers of the oesophagus varied more than the sex ratio of AEC between the cancer registries (1.9–16.3), but the sex ratio for all cancers of the stomach was almost constant (about 2.0–2.5) across the countries.

Trends in incidence

Figure 1 (a,b,c and d) shows trends in incidence rates of AEC by sex in each of the 11 cancer registries. The corresponding age-standardized incidence rates of each cancer registry for men and women separately are shown in Tables 3a and 3b, respectively. In England and Wales, Scotland and Slovakia the incidence of AEC increased in both men and women. A slight increase in incidence was seen in Denmark in men but not in women. After a slight increase in incidence during 1975–1986 in Italy (Varese) among men and a rather stable incidence during 1978–1983 among women, the incidence rates doubled. In Iceland the incidence rate in men reached a peak in the mid 1980s and decreased again. The incidence rates seemed rather stable in France (Bas-Rhin) and the Netherlands (Eindhoven) among men and in Denmark among women. The incidence rates in the cancer registries of Iceland (women), France (Bas-Rhin, women), France (Calvados, men and women), the Netherlands (Eindhoven, women), Southern Ireland (men and

Table 2 Age-standardized incidence[a] in men and women and male-to-female sex ratios of adenocarcinomas of the oesophagus and gastric cardia, all cancers of the oesophagus and stomach in 11 cancer registries, 1986–1990

	AEC[b]			All cancers of the oesophagus			All cancers of the stomach		
Cancer registries	Men	Women	Sex ratio	Men	Women	Sex ratio	Men	Women	Sex ratio
Northern Europe									
Denmark	6.6	1.2	5.5	6.4	2.1	3.0	15.8	7.8	2.0
Iceland	7.7	0.8	9.6	7.0	2.7	2.6	34.6	15.3	2.3
Southern Europe									
Italy, Varese	5.0	1.1	4.5	11.3	1.3	8.7	44.4	21.8	2.0
Eastern Europe									
Slovakia	3.5	0.8	4.4	9.2	0.7	13.1	37.5	16.8	2.2
Western Europe									
England and Wales	7.1	1.5	4.7	11.2	5.4	2.1	25.3	10.3	2.5
France, Bas-Rhin	4.8	0.4	12.0	24.0	1.5	16.0	20.2	8.6	2.3
France, Calvados	4.7	1.0	4.7	34.2	2.1	16.3	22.1	7.6	2.9
Ireland, Southern	5.5	1.3	4.2	9.8	5.4	1.8	19.3	8.6	2.2
Netherlands, Eindhoven	5.9	2.1	2.8	4.8	1.5	3.2	26.9	12.3	2.2
Scotland	9.7	2.9	3.3	13.4	7.0	1.9	28.0	12.4	2.3
Central Europe									
Switzerland, Basel	6.2	1.1	5.6	7.0	2.2	3.2	20.7	9.3	2.2

[a] Using the standard European population, per 100 000 person-years.

[b] Adenocarcinomas of the oesophagus and gastric cardia.

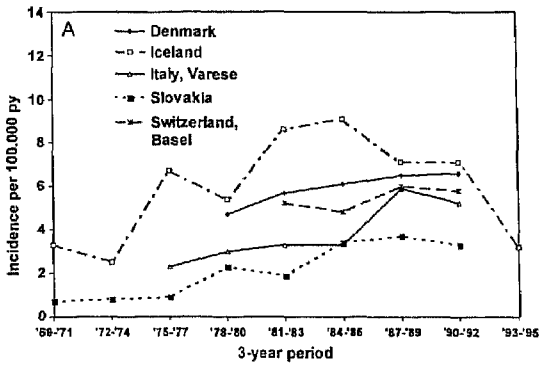

Figure 1A Age-standardized incidence rates of adenocarcinomas of the oesophagus and gastric cardia by 3-year period in cancer Registries of Northern, Southern, Eastern and Central Europe, men

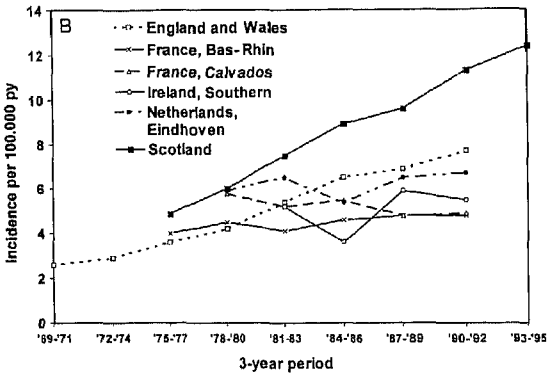

Figure 1B Western Europe, men

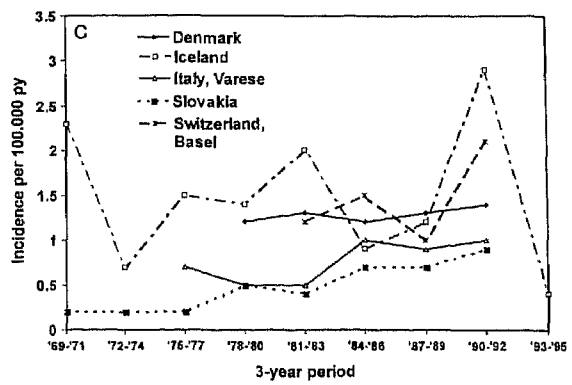

Figure 1C Northern, Southern, Eastern and Central Europe, women

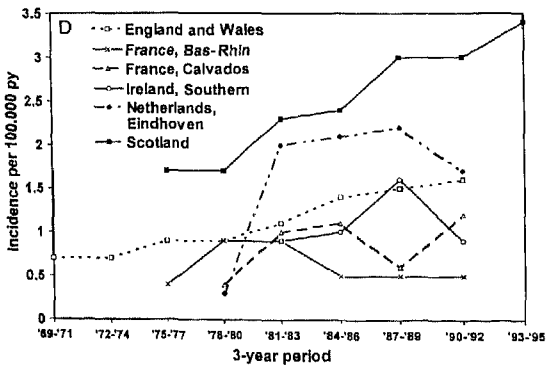

Figure 1D Western Europe, women

Table 3a Age-standardized incidence[a] (3-year averages) of adenocarcinomas of the oesophagus and gastric cardia in 11 cancer registries, 1969–1995, men

Cancer registries	1969–1971	1972–1974	1975–1977	1978–1980	1981–1983	1984–1986	1987–1989	1990–1992	1993–1995
Northern Europe									
Denmark	–	–	–	4.7	5.7	6.1	6.5	6.6	–
Iceland	3.3	2.5	6.7	5.4	8.6	9.1	7.1	7.1	3.2
Southern Europe									
Italy, Varese	–	–	2.3	3.0	3.3	3.3	5.9	5.2	–
Eastern Europe									
Slovakia	0.7	0.8	0.9	2.3	1.9	3.4	3.7	3.3	–
Western Europe									
England and Wales	2.6	2.9	3.6	4.2	5.4	6.5	6.9	7.7	–
France, Bas-Rhin	–	–	4.0	4.5	4.1	4.6	4.8	4.8	–
France, Calvados	–	–	–	5.8	5.2	5.5	4.8	4.9	–
Ireland, Southern	–	–	–	–	5.2	3.6	5.9	5.5	–
Netherlands, Eindhoven	–	–	–	5.9	6.5	5.4	6.5	6.7	–
Scotland	–	–	4.9	6.0	7.5	8.9	9.6	11.3	12.4
Central Europe									
Switzerland, Basel	–	–	–	–	5.2	4.8	6.0	5.8	–

[a] Using the standard European population, per 100 000 person-years.

Table 3b Age-standardized incidence[a] (3-year averages) of adenocarcinomas of the oesophagus and gastric cardia in 11 cancer registries, 1969–1995, women

Cancer registries	1969–1971	1972–1974	1975–1977	1978–1980	1981–1983	1984–1986	1987–1989	1990–1992	1993–1995
Northern Europe									
Denmark	–	–	–	1.2	1.3	1.2	1.3	1.4	–
Iceland	2.3	0.7	1.5	1.4	2.0	0.9	1.2	2.9	0.4
Southern Europe									
Italy, Varese	–	–	0.7	0.5	0.5	1.0	0.9	1.0	–
Eastern Europe									
Slovakia	0.2	0.2	0.2	0.5	0.4	0.7	0.7	0.9	–
Western Europe									
England and Wales	0.7	0.7	0.9	0.9	1.1	1.4	1.5	1.6	–
France, Bas-Rhin	–	–	0.4	0.9	0.9	0.5	0.5	0.5	–
France, Calvados	–	–	–	0.4	1.0	1.1	0.6	1.2	–
Ireland, Southern	–	–	–	–	0.9	1.0	1.6	0.9	–
Netherlands, Eindhoven	–	–	–	0.3	2.0	2.1	2.2	1.7	–
Scotland	–	–	1.7	1.7	2.3	2.4	3.0	3.0	3.4
Central Europe									
Switzerland, Basel	–	–	–	–	1.2	1.5	1.0	2.1	–

[a] Using the standard European population, per 100 000 person-years.

women) and Switzerland (Basel, men and women), fluctuated during the study period without an apparent trend. In these cancer registries relatively few incident cases were registered in each 3-year period.

Trends in subtypes of oesophageal and stomach cancer

The trends in incidence of all subtypes of oesophageal and stomach cancer are shown for Danish and Slovakian men (Figures 2a and b); two examples for the main trends in subtypes.

In Denmark, England and Wales, Scotland, Slovakia and Italy, Varese (men) the rise in incidence of AEC was accompanied by a decrease in incidence of non-adenocarcinomas of the non-cardia site of the stomach (including unspecified tumours and tumours with no morphology) and in Denmark and Scotland also by a decrease incidence of the adenocarcinomas of the non-cardia site of the stomach. The incidence rate of squamous cell carcinoma of the oesophagus increased in Denmark (men), Italy (Varese), Scotland and Slovakia or remained stable in England and Wales. For 'other cancers of the oesophagus', the incidence

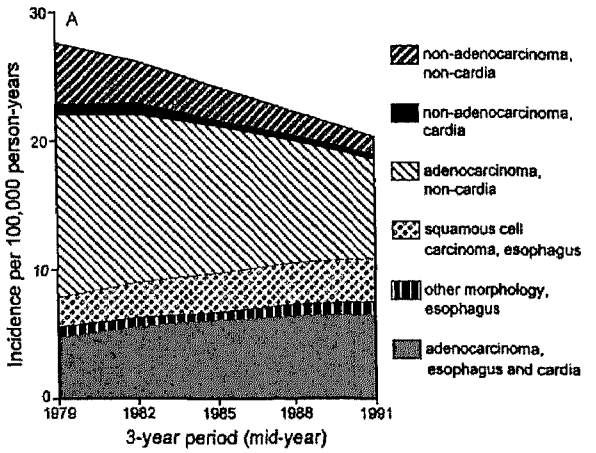

Figure 2A Age-standardized incidence of morphological subtypes of the oesophagus and stomach, Denmark, men

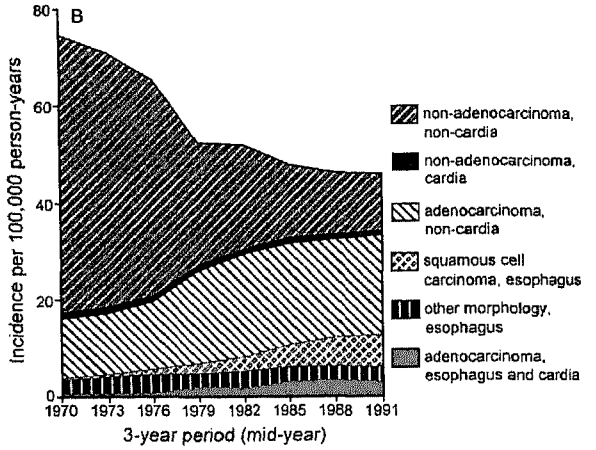

Figure 2B Slovakia, men

rate remained stable or decreased a little in these cancer registries. However, in some cancer registries the rise in incidence of the AEC was much smaller than the decrease in incidence of the other cancers of the oesophagus and stomach. In all cancer registries without a rise in incidence of AEC the incidence of the non-adenocarcinomas of the non-cardia site of the stomach decreased. In Iceland, France (Bas-Rhin and Calvados), the Netherlands (Eindhoven) and Switzerland (Basel) also a decrease in adenocarcinomas of the non-cardia site of the stomach was observed. The incidence of squamous cell carcinoma of the oesophagus and 'other cancers of the oesophagus' was rather stable in these cancer registries.

Poisson analysis

Results of the Poisson analysis are presented in Table 4. The model with age, sex and period gave a reasonably good fit to the data. In Denmark, England and Wales, Italy (Varese), Scotland and Slovakia the RR of developing AEC increased in the study period. In these countries the test for trend was also significant. In England and Wales, Italy (Varese), Scotland and Slovakia a relatively strong increase in risk (46–81%) was observed in the 12-year period 1981–1983 to 1990–1992 compared to the 15% increase in Denmark in the same period. The RR were slightly different in each 3-year period between men and women in England and Wales. In Italy (Varese), only the RR for 1987–1989 and 1990–1992 were significantly increased. In the Netherlands (Eindhoven, women), the RR for 1978–1980 was significantly different from one (RR = 0.13) compared to the reference period (1981–1983), resulting in a significant test for linear trend. The RR in the 3-year periods did not differ significantly from the RR of the reference period in France (Bas-Rhin), France (Calvados), Ireland (Southern), Netherlands (Eindhoven, males) and Switzerland (Basel). In Iceland, no clear linear trend was shown; the RR of 1972–1974 and 1993–1995 were significantly decreased.

Discussion

In this time-trend study of AEC using Eurocim data, we found an increase in incidence of AEC in Northern Europe (Denmark), Southern Europe (Italy, Varese), Eastern Europe (Slovakia), Western Europe (England and Wales, Scotland) during 1968–1995. A relatively strong increase in risk varying from 46% to 81% was observed in Italy (Varese), Slovakia, England and Wales and Scotland in the 12-year period 1981–1992. No particular trend was seen in Central Europe (Switzerland, Basel) and in the cancer registries of Iceland (Northern Europe), France, Bas-Rhin and Calvados, Southern Ireland, and the Netherlands, Eindhoven (Western Europe).

Our primary focus was to describe the overall direction of the trends in incidence of AEC for each region of Europe, not to separate effects of age, birth cohort and time period as determinants of the observed trend. Therefore, we used a relatively simple model with the variables period, age and sex.

This is one of the first studies that has used Eurocim data to investigate time trends in incidence rates, in this case, of AEC in ten European countries spread over five regions. The Eurocim database is very useful for all kinds of descriptive studies because detailed data are available from many European cancer registries. The data quality of the Eurocim database is dependent on the quality of the provided data of the contributing cancer registries. The contributing cancer registries make regular submissions of incidence, mortality and population data to the central Eurocim data bank. The data of each cancer registry are subjected to validity checks and, if needed, returned to the cancer registry for verification. However, the collection and coding of data by the cancer registries are not uniform, e.g. due to different coding rules, differences in coding precision between cancer registries, which hampers comparison of the data.

Several features of the data quality and coding practice of the cancer registries in our study are discussed which may be of importance in interpreting the observed trends in incidence. We used information of three indices of reliability for oesophageal and stomach cancer as presented in *Cancer Incidence in Five Continents (Vols IV, V and VI)*[29–31] as rough indicators of data quality. Regarding the percentage of histologically verified diagnoses (%HV) of tumours of the oesophagus and stomach, this percentage increased from 40% to 50% (1973–1977) to 70% to 85% (1983–1987) in the cancer registries of Italy (Varese) and Slovakia. This large increase in %HV may have affected the incidence rates of AEC and in particular the incidence of tumours with unspecified morphology. In our study, the

Table 4 Relative risks, adjusted for age and sex of adenocarcinomas of the oesophagus and gastric cardia by 3-year period in 11 cancer registries, 1969–1995, using Poisson analyses

Cancer registries	1969–1971	1972–1974	1975–1977	1978–1980	1981–1983[a]	1984–1986	1987–1989	1990–1992	1993–1995	*P*-trend
Northern Europe										
Denmark	–	–	–	0.85*	1.00	1.04	1.10	1.15*	–	0.00
Iceland	0.58	0.33*	0.77	0.65	1.00	0.95	0.78	0.98	0.36*	0.51
Southern Europe										
Italy, Varese	–	–	0.76	0.93	1.00	1.10	1.68*	1.53*	–	0.00
Eastern Europe										
Slovakia	0.43*	0.46*	0.49*	1.22	1.00	1.73*	1.91*	1.81*	–	0.00
Western Europe										
England and Wales (men)	0.49*	0.54*	0.66*	0.77*	1.00	1.21*	1.30*	1.46*	–	0.00
England and Wales (women)	0.58*	0.62*	0.75*	0.79*	1.00	1.23*	1.32*	1.49*	–	0.00
France, Bas-Rhin	–	–	0.82	1.08	1.00	0.97	1.00	1.00	–	0.57
France, Calvados	–	–	–	0.98	1.00	1.07	0.85	0.98	–	0.72
Ireland, Southern	–	–	–	–	1.00	0.80	1.31	1.16	–	0.16
Netherlands, Eindhoven (men)	–	–	–	0.89	1.00	0.83	0.99	1.02	–	0.49
Netherlands, Eindhoven (women)	–	–	–	0.13*	1.00	1.06	1.07	0.78	–	0.05
Scotland	–	–	0.67*	0.79*	1.00	1.16*	1.31*	1.47*	1.64*	0.00
Central Europe										
Switzerland, Basel	–	–	–	–	1.00	1.04	1.12	1.24	–	0.24

*95% confidence interval excludes one.

[a] Reference period.

increase in %HV in Italy (Varese) and Slovakia may partly account for the decrease in incidence of non-adenocarcinomas of the non-cardia part of the stomach. The %HV was high in the other cancer registries. However, we did not have information on histological verification rates of topographical subsites of oesophageal and stomach cancer. Furthermore, the proportion of 'cases known from a death certificate only' varied over time and varied between men and women in the cancer registries but was nearly always less than 15% which is considered to be acceptable.[33]

Improvement in precision of histological diagnosis and improvement in diagnostic procedures (such as increased use of endoscopy) may have affected the incidence rates of AEC as well.[7] In our study, the rise in incidence of AEC was accompanied by a much greater fall in rates of tumours with 'unspecified morphology' and 'no morphology'. It is unknown which proportion of tumours coded in early years of the study period as 'unspecified morphology' or 'no morphology' are being coded as AEC in later years of the study period.

In order to circumvent the potential problem of difficulties in distinguishing tumours arising in the lower third of the oesophagus, the gastro-oesophageal junction and the gastric cardia (Dr R Otter, personal communication) and changes in classification or coding practice regarding these tumours in the study period we decided to combine adenocarcinomas of the oesophagus and gastric cardia for analyses. We knew from the background information that certain cancer registries used to classify adenocarcinomas of the lower oesophagus as cardia tumours in the study period. Some cancer registries coded tumours to 151.0 in case of doubt about localization of an adenocarcinoma in the lower oesophagus or cardia.

Besides changes in histological verification of tumours of the oesophagus and stomach over time, improvement of precision of histological diagnosis and diagnostic improvements over time, the increase in incidence in adenocarcinomas of the oesophagus and cardia might be explained by the introduction of a 'new' environmental risk factor in the aetiologically relevant period. At present, little is known about risk factors of AEC, except for the link with Barrett's oesophagus, a condition associated with gastro-oesophageal reflux.[22]

Recently, obesity has been implicated as a risk factor of AEC.[26,27] Obesity is associated with increased intra-abdominal pressure which may promote gastro-oesophageal reflux and the development of Barrett's oesophagus. The prevalence of obesity is growing in a number of western countries.[34]

It has also been debated that long-term use of peptic ulcer drugs (e.g. cimetidine) could lead to an increased risk of AEC. The drug suppresses acid production and creates hypochlohydric conditions in the stomach. Reflux of the alkaline stomach juice causes irritation and oesophagitis, and may lead to development of Barrett's oesophagus which is believed to be a precursor of adenocarcinoma of the oesophagus.[35] However, these peptic ulcer drugs were introduced in the late 1970s, coinciding with the start of the increase in incidence of AEC. Given the latency period of AEC, the relation between peptic ulcer drugs and development of AEC is not likely.

This study using Eurocim data, in which an increasing trend of AEC was found in Denmark and England and Wales, confirms previous observations in other studies of population-based cancer registries in the same countries.[4,7–9,11,12] We could not reproduce the rise in incidence of adenocarcinomas of the oesophagus which was reported by Liabeuf *et al.*[20] in Burgundy, France in the two other French regions (Bas-Rhin and Calvados) that were investigated in this study. The rise in incidence of cardia tumours in women in the Netherlands (Eindhoven) reported by Van der Sanden *et al.*[15] was interpreted as a monotonic increase in our study, because the incidence rate of the first 3-year period 1978–1980 was low compared to the rates of the subsequent four 3-year periods. Another recent Dutch study reported stable gastric cardia cancer mortality rates between 1969 and 1994.[36] Nearly all other time-trend studies conducted in European countries (e.g.[9,19]), the US (e.g.[10,14]), Australia[18] and New Zealand[17] reported an increase in incidence, either in adenocarcinomas of the oesophagus or adenocarcinomas of the gastric cardia or a combination of two sites of the oesophagus and cardia. Exceptions were a study in Switzerland, Vaud[23] which reported a stable incidence of adenocarcinomas of the cardia during the period 1976–1987 in both men and women and a study in France (Côte d'Or and Calvados) which reported no significant change in incidence of adenocarcinomas of the oesophagus during the period 1978–1987.[37] In this study no increasing trend was found in another part of Switzerland (i.e. Basel) as well. Some studies reported an increase in incidence of adenocarcinomas of the oesophagus or cardia in males, but not in females.[6,11,19] In our study, only the cancer registries of Slovakia, England and Wales and Scotland showed a clear increase in women. To our knowledge no time-trend studies have been performed in non-western countries.

In conclusion, we could reproduce the rise in incidence of AEC using the Eurocim database in nearly all regions of Europe. We did not observe an increase in incidence in those cancer registries which covered smaller populations. Due to small number of cases probably unstable rates were calculated.

In the future, time trends of AEC should be monitored more closely to confirm the trend. In particular, small cancer registries may have more data for calculating stable rates. Furthermore, more attention should be paid to the bias that can occur in the diagnosis and coding of these tumours. In addition, analytical epidemiological studies are needed to investigate aetiological factors that are involved in the development of these specific tumours.

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