



# Trends in mortality from primary liver cancer in Europe

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## Abstract

Upward trends in incidence and mortality from primary liver cancer have been reported from Japan, the USA and a few European countries. Thus, we systematically reviewed trends in age-standardised death certification rates from primary liver cancer between 1970 and 1996 in 20 European countries providing data for the World Health Organisation database. Overall age-standardised (world population) mortality rates were approximately stable or showed no consistent trends in seven countries, including Bulgaria and Hungary (with exceedingly high rates), Finland, The Netherlands and the UK. Moderate rises were observed in Austria, Germany and Switzerland, and much larger upward trends in France and Italy, particularly for males. Downward trends were observed in both sexes in Belgium, Spain, Ireland, Greece and several Scandinavian countries. The per cent change in rates per year ranged, for males, from  $-7.4\%$  for Ireland and  $-5.1\%$  for Spain to  $+4.4\%$  for Italy and  $+8.6\%$  for France. Trends were more favourable in women, with 15 out of 20 countries showing downward trends in rates, and moderately more favourable in middle age (45–64 years) and, in major European countries, in young adults (20–44 years of age). In conclusion, trends in liver cancer mortality in Europe are heterogeneous. The fall in mortality in countries like Spain may be largely explained by improvements in the distinction between primary and secondary liver neoplasms, whereas upward trends in Central Europe and Italy are likely to be, at least in part, real. Increases in infection with the hepatitis C virus, and improved and increased searches for liver cancer in cirrhotic patients are two of the likeliest explanations for these observations. © 2000 Elsevier Science Ltd. All rights reserved.

**Keywords:** Liver neoplasms; Trends; Mortality rates; Descriptive epidemiology; Europe

## 1. Introduction

Upward trends in incidence and mortality from hepatocellular carcinoma over the last two decades have been reported from Japan [1], the UK [2,3], France [4] and the USA [5]. These rises were observed in men and women, in blacks and whites in the USA, in younger and elderly populations, suggesting that they cannot be accounted for totally by increased diagnosis and certification of the disease. It has also been suggested that the increased prevalence of hepatitis C viruses (HCV) may, at least in part, explain these upward trends [6,7].

Liver cancer incidence and, even more, mortality rates have to be interpreted with the utmost caution, due to

the substantial problems of reliability and validity of certification data for liver cancer [8–10], most notably the difficulty of distinguishing accurately primary from secondary liver cancers.

With these cautions in mind, we have systematically reviewed the data from death certificates for primary liver cancer between 1970 and 1996 in 20 major European countries providing data for the World Health Organisation (WHO) database.

## 2. Patients and methods

The numbers of deaths certified from primary liver cancer over the period 1970–1996 were abstracted for 20 European countries from the WHO database. All classifications used were re-coded according to the Ninth Revision of the International Classification of Diseases

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(ICD-9 code 155.0; [11]). Estimates of the resident populations, based on official censuses, were obtained from the same WHO database. In order to assess the extent to which different practices of death certification over time may have influenced trends in liver cancer mortality, liver neoplasms not specified as primary or secondary (ICD-9: 155.2; [11]) were considered for males in four selected countries over the period 1980–1994 (i.e. the period where such distinction was possible).

From the matrices of certified deaths and resident populations, age-specific rates for each 5-year age group and for the individual years and calendar periods considered were computed. Age-standardised rates were based on the world standard population. When a single year was missing within a period, numerators and denominators were interpolated linearly from the previous and subsequent calendar year. The per cent annual change in rates was derived from a log-linear model (based on single calendar year rates).

### 3. Results

Fig. 1 gives the trends in age-standardised (at all ages and truncated from 35 to 64 years; world standard population) mortality rates from primary liver cancer in

20 major European countries from 1970 to 1996, using three different scales (5, 10 and 20/100 000). Rates were approximately stable or showed no consistent trend in seven countries, including Bulgaria and Hungary, Finland, The Netherlands and the UK. Moderate rises, particularly in more recent calendar periods, were observed in Austria, Germany and Switzerland, and much larger upward trends in France and Italy particularly for males. Downward trends were observed for both sexes in Belgium, several Nordic countries, Ireland, Greece and Spain. In 1990–1996, rates in males exceeded 6/100 000 in Bulgaria, Hungary, France and Italy.

Corresponding values in tabular form for overall liver cancer mortality are given in Table 1, together with the corresponding per cent change in rates per year. These ranged, for males, from –7.4% in Ireland, –5.1% in Spain, –4.5% in Greece and –2.9% in Belgium, to +4.4% in Italy and +8.6% in France. Trends were more favourable in women, with 15 out of 20 countries showing declines in rates. Moderate upward trends were observed in France, Germany and Italy for females, too.

The pattern was similar when only deaths in middle age (45–64 years, Table 2) were considered, with substantial declines in Belgium, Greece, Ireland, Norway and Spain, and appreciable increases in France, Germany and Italy for males. For middle aged females,

Table 1  
Trends in overall liver cancer mortality<sup>a</sup> in selected European countries: 1970–1996

	Death rate/100 000 males				Death rate/100 000 females			
	1970–1974	1980–1984	1990–1996	Per cent change/year <sup>b</sup> 1970–1996	1970–1974	1980–1984	1990–1996	Per cent change/year <sup>b</sup> 1970–1996
Austria	2.73	3.53	3.76	1.4 <sup>c</sup>	0.91	1.30	0.88	–0.3
Belgium (1990–1992) <sup>d</sup>	3.67	3.12	2.35	–2.9 <sup>c</sup>	2.54	1.69	1.11	–5.3 <sup>c</sup>
Bulgaria (1990)	10.40	8.49	8.03	–1.6 <sup>c</sup>	6.90	5.35	4.49	–2.4 <sup>c</sup>
Denmark (1990–1993)	2.46	2.28	1.97	–1.2 <sup>c</sup>	1.58	1.53	1.24	–1.8 <sup>c</sup>
Finland (1990–1994)	2.77	3.95	3.67	0.9	1.41	2.16	2.24	1.4
France (1990–1994)	1.33	3.57	6.91	8.6 <sup>c</sup>	0.57	0.69	1.02	3.1 <sup>c</sup>
Germany <sup>c</sup>	1.31	1.34	2.66	3.6 <sup>c</sup>	0.76	0.51	0.95	1.2
Greece	1.98	1.30	0.86	–4.5 <sup>c</sup>	0.98	0.52	0.19	–8.9 <sup>c</sup>
Hungary (1990–1995)	7.58	7.79	8.26	0.3 <sup>c</sup>	5.27	3.80	3.83	–1.5 <sup>c</sup>
Ireland (1990–1994)	2.48	0.71	0.63	–7.4 <sup>c</sup>	1.88	0.22	0.13	–13.3 <sup>c</sup>
Italy (1990–1994)	3.28	5.61	8.14	4.4 <sup>c</sup>	1.87	2.49	2.49	1.0 <sup>c</sup>
The Netherlands (1990–1995)	1.17	1.22	1.19	0.2	0.65	0.52	0.48	–1.6 <sup>c</sup>
Norway (1990–1995)	1.35	1.47	0.75	–2.8 <sup>c</sup>	0.70	0.36	0.36	–2.8 <sup>c</sup>
Poland	7.63	7.68	5.86	–1.5 <sup>c</sup>	8.85	6.83	4.24	–3.6 <sup>c</sup>
Spain (1990–1995)	10.21	6.98	4.54	–5.1 <sup>c</sup>	9.22	4.12	1.30	–11.2 <sup>c</sup>
Sweden (1990–1995)	2.98	3.32	2.35	–1.8 <sup>c</sup>	1.90	1.86	1.30	–2.6 <sup>c</sup>
Switzerland (1990–1994)	4.10	4.58	5.60	1.8 <sup>c</sup>	1.43	1.12	1.50	0.1
UK, England and Wales (1990–1995)	0.98	1.14	1.10	0.5	0.43	0.49	0.36	–1.0 <sup>c</sup>
UK, Northern Ireland (1990–1995)	0.46	0.54	0.52	–0.9	0.23	0.32	0.20	–1.7
UK, Scotland (1990–1995)	1.66	1.66	1.68	0.5	0.66	0.49	0.52	–1.3

<sup>a</sup> Age-standardised rates on the world population.

<sup>b</sup> From a log-linear model based on single calendar year rates.

<sup>c</sup>  $P < 0.05$ .

<sup>d</sup> Whenever incomplete, available years for the last calendar period are given in parentheses.

<sup>e</sup> Before 1973, rates refer to Federal Republic of Germany only.

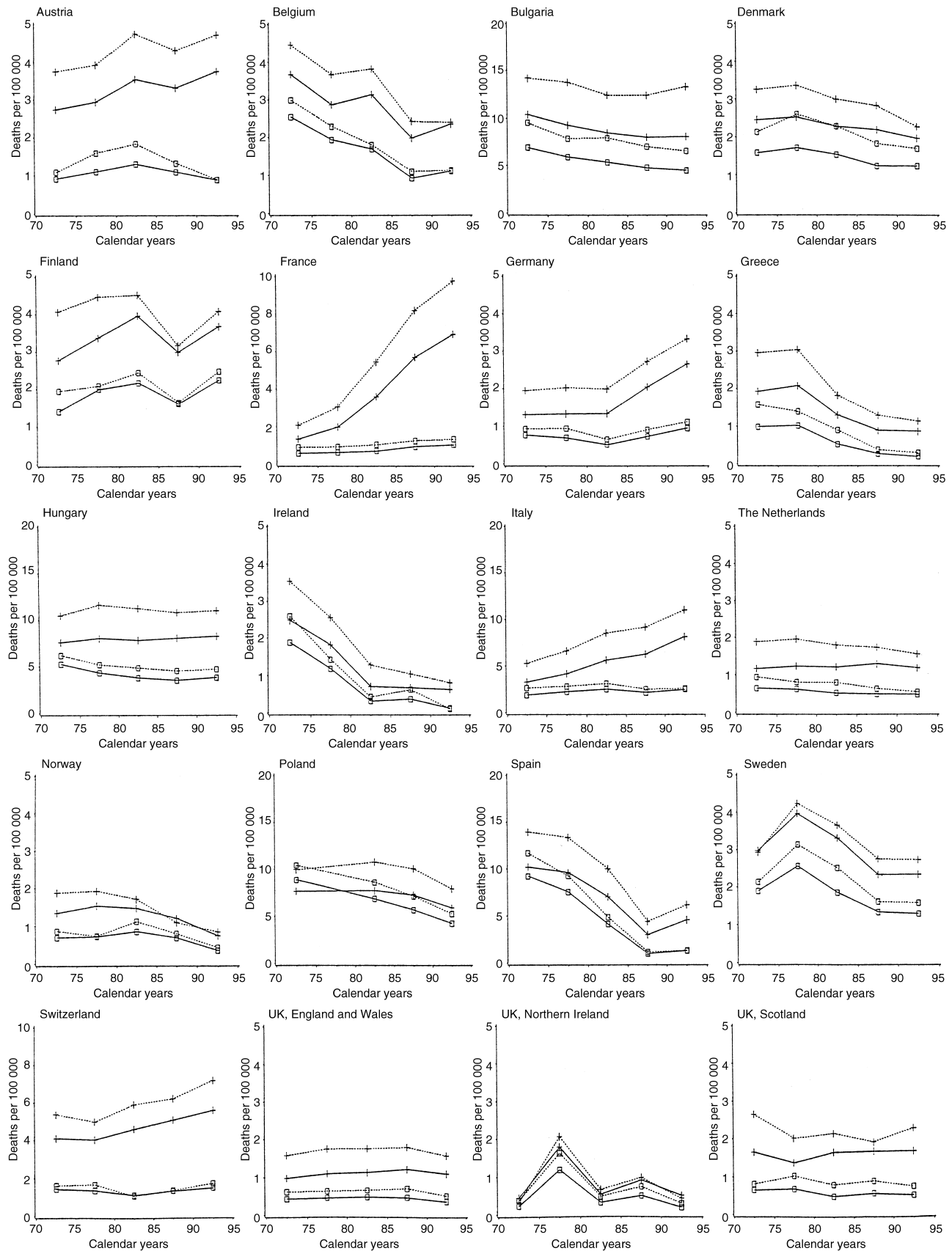


Fig. 1. Trends in overall and truncated (35–64 years) age-standardised (world population) death certification rates (per 100 000) from liver cancer in 20 European countries, 1970–1994 (males, all ages +—+; males, 35–64 years +---+; females, all ages □—□; females, 35–64 years □---□).

Table 2

Trends in mortality<sup>a</sup> from liver cancer at age 45–64 years in selected European countries: 1970–1996

	Death rate/100 000 males				Death rate/100 000 females			
	1970–1974	1980–1984	1990–1996	Per cent change/year <sup>b</sup> 1970–1996	1970–1974	1980–1984	1990–1996	Per cent change/year <sup>b</sup> 1970–1996
Austria	5.78	7.33	7.31	1.0	1.62	2.59	1.32	–1.2
Belgium (1990–1992) <sup>d</sup>	6.78	5.71	3.61	–3.5 <sup>c</sup>	4.48	2.63	1.64	–5.7 <sup>c</sup>
Bulgaria (1990)	21.80	18.64	19.34	–0.9 <sup>c</sup>	14.13	11.82	10.03	–1.8 <sup>c</sup>
Denmark (1990–1993)	4.86	4.62	3.45	–1.6 <sup>c</sup>	3.20	3.32	2.38	–1.8 <sup>c</sup>
Finland (1990–1994)	6.36	6.97	5.99	0.9	3.03	3.74	3.65	–0.1
France (1990–1994)	3.06	8.29	15.25	8.3 <sup>c</sup>	1.29	1.48	1.95	2.4 <sup>c</sup>
Germany <sup>c</sup>	2.96	3.06	5.13	2.7 <sup>c</sup>	1.36	0.96	1.64	0.9
Greece	4.57	2.82	1.72	–5.3 <sup>c</sup>	2.24	1.29	0.40	–9.3 <sup>c</sup>
Hungary (1990–1995)	16.47	13.32	16.02	–0.2	9.32	7.35	6.66	–1.4 <sup>c</sup>
Ireland (1990–1994)	5.09	2.09	1.22	–8.6 <sup>c</sup>	3.64	0.56	0.13	–10.2 <sup>c</sup>
Italy (1990–1994)	7.84	13.15	17.36	3.8 <sup>c</sup>	3.92	4.70	3.97	–0.1
The Netherlands (1990–1995)	2.74	2.71	2.36	–0.6	1.33	0.98	0.73	–2.6 <sup>c</sup>
Norway (1990–1995)	2.82	2.47	1.26	–4.6 <sup>c</sup>	1.30	1.57	0.67	–2.9 <sup>c</sup>
Poland	15.01	16.30	12.07	–1.5 <sup>c</sup>	16.00	13.05	7.91	–3.5 <sup>c</sup>
Spain (1990–1995)	20.93	15.29	9.54	–4.9 <sup>c</sup>	17.38	7.31	2.02	–12.2 <sup>c</sup>
Sweden (1990–1995)	4.57	5.49	4.21	–1.2	3.08	3.68	2.37	–2.0 <sup>c</sup>
Switzerland (1990–1994)	8.20	9.30	11.21	1.7 <sup>c</sup>	2.47	1.63	2.56	–0.3
UK, England and Wales (1990–1995)	2.36	2.61	2.35	0.0	0.87	0.92	0.75	–0.5
UK, Northern Ireland (1990–1995)	0.38	1.09	0.71	–3.1	0.47	0.80	0.40	–2.0
UK, Scotland (1990–1995)	3.91	3.31	3.44	–0.3	1.30	1.19	0.97	–1.3

<sup>a</sup> Age-standardised rates on the world population.<sup>b</sup> From a log-linear model based on single calendar year rates.<sup>c</sup>  $P < 0.05$ .<sup>d</sup> Whenever incomplete, available years for the last calendar period are given in parentheses.<sup>e</sup> Before 1973, rates refer to Federal Republic of Germany only.

liver cancer death rates increased only in France and Germany, and the trends were downwards in the other 18 countries.

Liver cancer mortality rates in the five major European countries (France, Germany, Italy, Spain, and the UK, England and Wales) were also considered in young adults (20–44 years, Table 3), where absolute numbers are small, but death certification reliability is more satisfactory. Significant rises were observed in France for males, and in Germany for both sexes, and significant declines in Italy for females, and in Spain for both sexes.

Male trends between 1980 and 1994 in mortality rates from primary liver cancer, liver neoplasms not specified as primary or secondary and the combination of the two are shown in Fig. 2. Four large European countries, which showed different trends in males, were chosen for this purpose. In France and Italy, rates for primary liver cancer and unspecified ones were similar in 1980, but steady rises in primary liver cancer were observed thereafter. These were accompanied by approximately stable rates for the unspecified cases. In Spain, unspecified liver neoplasms were very rarely certified in the early 1980s. Curves of primary liver

Table 3

Trends in mortality<sup>a</sup> from liver cancer at age 20–44 years in major European countries: 1970–1996

	Death rate/100 000 males				Death rate/100 000 females			
	1970–1974	1980–1984	1990–1996	Per cent change/year <sup>b</sup> 1970–1996	1970–1974	1980–1984	1990–1996	Per cent change/year <sup>b</sup> 1970–1996
France (1990–1994) <sup>d</sup>	0.28	0.45	0.49	2.7 <sup>c</sup>	0.13	0.16	0.14	0.4
Germany <sup>c</sup>	0.17	0.18	0.23	1.6 <sup>c</sup>	0.11	0.09	0.15	1.9 <sup>c</sup>
Italy (1990–1994)	0.52	0.54	0.41	–0.8	0.30	0.29	0.21	–2.3 <sup>c</sup>
Spain (1990–1995)	1.39	0.90	0.35	–7.9 <sup>c</sup>	1.29	0.48	0.13	–12.5 <sup>c</sup>
UK, England and Wales (1990–1995)	0.21	0.23	0.20	–0.7	0.12	0.17	0.11	–0.9

<sup>a</sup> Age-standardised rates on the world population.<sup>b</sup> From a log-linear model based on single calendar year rates.<sup>c</sup>  $P < 0.05$ .<sup>d</sup> Whenever incomplete, available years for the last calendar period are given in parentheses.<sup>e</sup> Before 1973, rates refer to Federal Republic of Germany only.

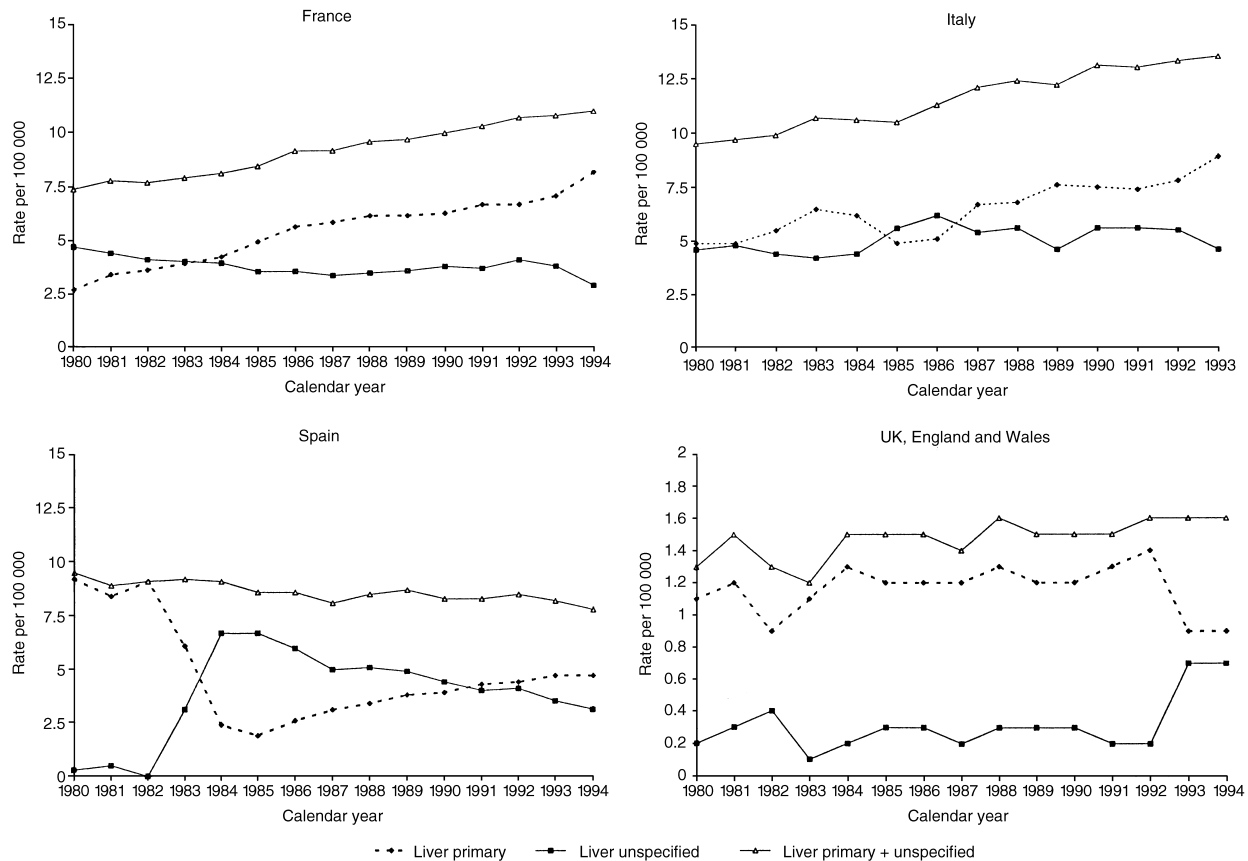


Fig. 2. Trend in age-standardised (world population) death certification rates (per 100 000) from primary and unspecified liver cancer in four large European countries, 1980–1994.

cancer and unspecified cases were virtually specular, with a sudden decrease of primary liver cancer between 1982 and 1985. If combined, no change was observed in the combination of primary and unspecified liver neoplasms in Spain. The UK showed between 1980 and 1992 stable, albeit somewhat fluctuating, low mortality rates for primary liver cancer. Certifications for unspecified liver neoplasms were few over the whole observed period and in the early 1990s a fall in primary liver cancer seemed to be reflected in a concurrent increase in mortality from unspecified liver cancer.

#### 4. Discussion

The present analysis confirms the existence of substantial variations in mortality rates from primary liver cancer across Europe (from below 1 in Norway and Ireland to above 6 per 100 000 males in Bulgaria, Hungary, Italy and France [12]). Inconsistent patterns also emerged for mortality trends. The pattern of trends was also diverging in the two sexes, since liver cancer mortality tended to increase in males, but to decline in females in most countries of the European Union.

With respect to southern Europe, substantial rises were observed, except in Spain or Greece. Trends were upwards, mostly in males, in central Europe (France, Germany, Austria, Switzerland), but approximately stable in low-risk countries of northern Europe (e.g. in the UK and in Nordic countries).

Rises in liver cancer mortality [2,4] and/or incidence [3,5,13,14] in the last two decades were reported for various European countries and the US. The consistency in mortality trends from primary liver cancer at all ages and in young and middle age, but the marked difference between the two sexes weigh against the possibility that death certification improvements account completely for the present findings, particularly for the increases in several intermediate-high-risk countries. However, combined assessment of rates for liver neoplasms not specified as either primary or secondary suggests that changes in coding practice may explain liver cancer declines reported, for instance, in Spain. For comparison purposes, it is worth noting that between 1980 and 1994 no change in mortality rates for unspecified liver neoplasms was seen in the US, aside from a steady increase in primary liver cancer [5].

Probably of greater importance are the substantial improvements in the detection of liver cancer in cirrhotic

patients since the early 1980s, through ultrasonography and the measurement of alpha-fetoprotein. Mortality from cirrhosis is in several European countries many-fold greater than liver cancer mortality, and shift of death certification from cirrhosis to liver cancer in even a small proportion of cases might have been important, particularly amongst males and in countries like France, Germany, Italy or Hungary, where mortality from cirrhosis is relatively common [15]. Thus, in the early 1990s, mortality from liver cirrhosis was 57.5/100 000 males in Hungary, 27.8/100 000 in Italy, 20.3/100 000 in Germany and 18.8/100 000 in France. In western (but not eastern) Europe, trends in liver cirrhosis mortality have been declining from the mid-1990s onwards [15]. Increased surveillance of cirrhotic patients is going to affect the incidence trends of liver cancer to an equal, if not greater extent, than the mortality trends.

It has also been suggested that age-standardised mortality methods do not fully account for population ageing in age-dependent diseases like primary liver cancer [16]. In men from Italy and Central European countries increases in mortality rates were clearly seen in the 35–64 year age group and the standardisation on the world standard population gives a relatively low weight to the oldest age groups.

Possible causes of real increases in at least some European countries should be searched for in the two most important groups of risk factors for liver cancer in developed countries: hepatitis B (HBV) and HCV viruses and high alcohol consumption and/or their combination [17,18]. Other risk factors such as aflatoxin, low intake of vegetables and fruit or oral contraceptive use in females probably play a small [7,19], or minimal role [20] in liver cancer trends in western Europe.

In a meta-analysis of 32 studies, the odds ratio of liver cancer was 20.4 for HBV serum markers, 23.6 for HCV serum markers and 132 for both [21]. At least 80% of liver cancer cases worldwide is attributable to infection with HBV and/or HCV [22]. It has been estimated that liver cancer develops in approximately 20% of male life-long carriers [23]. Cumulative rates of liver cancer are still undefined for HCV carriers, who have been identifiable only during the last ten years. However, in intermediate-high-risk developed countries, falling HBV infection rates amongst the general population have been documented [5,24], as well as an increase in HCV-related liver cancers (approximately 70% of all liver cancers [25]). An increased prevalence of HCV infection has been hypothesised after World War II, chiefly through transfusion of unscreened blood and blood products and, lately, by needle sharing amongst intravenous drug users [3,5]. Prevalence of antibody to HCV has been estimated to be approximately 0.5% in the UK [6], 1.8% in the USA [26], and may approach 3% in Greece [27] and 5% in Italy [28], although

representative population-based estimates for various countries are unavailable.

With respect to alcohol, per capita consumption declined in the last decades in high-risk Western European countries [29]. Mortality from cirrhosis had fallen since the late 1970s in France, Italy, Germany, Japan and the USA, i.e. in those countries where liver cancer increases occurred, whereas it has increased in eastern Europe [15,30]. Alcohol intake in certain populations may have contributed to liver disease progression in individuals infected by HCV [27,31].

In conclusion, trends in liver cancer mortality in Europe are heterogeneous. The fall in mortality in countries like Spain may be largely explained by improvements in the distinction between primary and secondary liver neoplasms, whereas upward trends in Central Europe and Italy are likely to be, at least in part, real. Increases of HCV infection incidence in the last decades are difficult to document, but are a possible explanation for at least part of the upward trends observed. Increased surveillance of cirrhotic patients must also have contributed to the rise of liver cancer mortality, particularly amongst men and in countries where hepatitis and alcoholic cirrhosis are most common. A more uniform and standardised system of liver cancer diagnosis and certification throughout Europe may help to promote better understanding and interpretation of future trends in liver cancer mortality.

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