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A comparison of trends in mortality from primary liver cancer and intrahepatic cholangiocarcinoma in Europe

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Background: To update and compare mortality from primary liver cancer (PLC) and intrahepatic cholangiocarcinoma (ICC) in Europe in 1990–2010.

Materials and methods: We used data from the World Health Organization (WHO) to compute age-standardized (world population) mortality rates, and used joinpoint analysis to identify substantial changes.

Results: Between 2002 and 2007, PLC rates in the European Union (EU) declined from 3.9 to 3.6/100 000 men. Around 2007, the highest male rates were in France (6.2/100 000), Spain (4.9), and Italy (4.0), while the lowest ones were in Sweden (1.1), the Netherlands (1.2), and the UK (1.8). In women, mortality was lower (0.8/100 000 in 2007 in the EU), and showed more favourable trends, with a decline of over 2% per year over the last two decades as compared with 0.4% in men, in the EU. In contrast, the EU mortality from ICC increased by around 9% in both sexes from 1990 to 2008, reaching rates of 1.1/100 000 men and 0.75/100 000 women. The highest rates were in UK, Germany, and France (1.2–1.5/100 000 men, 0.8–1.1/100 000 women).

Conclusions: PLC mortality has become more uniform across Europe over recent years, with an overall decline; in contrast, ICC mortality has substantially increased in most Europe.

Key words: cancer, cholangiocarcinoma, hepatocellular carcinoma, intrahepatic, liver, mortality

introduction

Over the last few decades, rates and trends in mortality from liver cancer have been considerably different across Europe [1, 2]. In the 1980s, mortality was about fivefold higher in France and Italy when compared with most of northern Europe, but over the last two decades trends have been downwards in these countries, while they have been upwards in the UK, Germany and most other central European countries. Substantial increases in liver cancer incidence over recent years took place in Northern Europe and North America [3, 4].

Part of this variation may be due to a different proportion and variable time trends of primary liver cancer (PLC, defined as including hepatocellular carcinoma (HCC) and other rarer liver cancers, such as hepatoblastoma or angiosarcoma), versus intrahepatic cholangiocarcinoma (ICC). These two neoplasms have different sex ratios, with a much greater male preponderance for HCC than for ICC [5]. The incidence of ICC has also increased in the United States [6], though this may be due—at least in part—to improved diagnosis and pathological confirmation.

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The risk factors of HCC and ICC are—at least in part—different: diabetes, heavy alcohol drinking and cirrhosis are associated with both HCC and ICC, but the association with hepatitis C virus (HCV) infection is much stronger for HCC than for ICC [7–10], while history of gallstones is associated with the risk of ICC, but not of HCC [11].

To provide updated information on trends in mortality from PLC and ICC, and for comparative purpose, extrahepatic bile ducts cancer (extrahepatic cholangiocarcinoma, ECC), we considered data from major European countries up to 2010.

materials and methods

We extracted official death certification data for PLC, ICC and ECC over the period 1990–2010 from the World Health Organization (WHO) database as available on electronic support [12]. We analysed data for 12 major selected European countries, i.e. those countries for which it was possible to compute separate rates for PLC and ICC, and with more stable data: Austria, the Czech Republic, Denmark, Finland, France, Germany, Italy, the Netherlands, Portugal, Spain, Sweden, and the UK. To compute rates for the European Union (EU) as a whole, we included data from the same 12 countries plus Ireland, for a total of 379 out of 493 million inhabitants (80%). We also analysed data for the United States, Japan, and Australia for comparative purpose. For ICC, data were available since 1996 for Finland. For both PLC and ICC, data were available since 1994 up to

2006 for Denmark, and up to 2006 for Australia, up to 2007 for the United States, up to 2008 for France, Italy, and Spain, and up to 2009 for the Czech Republic, Finland, Portugal, the UK, and Japan. In a few countries, data were missing for one or more calendar years. No extrapolation was made for missing years.

During the calendar period considered two different Revisions of the International Classification of Diseases (ICD) were used [13, 14]. Thus, we considered ICD-9 code 155.0 and ICD-10 codes C22.0, C22.2–C22.4 and C22.7 for PLC, and ICD-9 code 155.1 and ICD-10 code C22.1 for ICC. Classification of cancer deaths was re-coded, for all calendar periods and countries, according to the 10th Revision of the ICD. For ECC, only data with ICD-10 code C24.0 were used. For Sweden, only data since the 1997 were considered, because of substantial changes between the 9th and 10th Revision of the ICD.

The estimates of the resident populations were obtained from the same WHO database [12]. From the matrices of certified deaths and resident populations, we computed age-specific rates for each 5-year age group (from 0, 1–4, 5–9 to 80–84 and ≥85 years) and calendar year, separately for men and women. We also computed age-standardized rates per 100 000 persons at all ages and truncated at age 45–64 years using the direct method, on the basis of the world standard population [15].

To identify substantial changes in trends, we carried out joinpoint regression analysis using the 'Joinpoint' software from the Surveillance Research Program of the US National Cancer Institute [16]. This analysis allows to identify the years where a substantial change in the linear slope of the trend (on a log-scale) is detected over the study period [17]. The estimated annual percentage change (APC) was then computed for each of the identified trends by fitting a regression line to the natural logarithm of the rates using the calendar year as a regressor variable. Finally, to simplify trend comparisons between sexes and countries, we also calculated the average APC (AAPC) over the entire period 1990–2010 (when available), based on an underlying joinpoint model. This was estimated as the geometric weighted average of the APC, with the weights equal to the length of each time interval segment [18].

results

Table 1 gives the overall age-standardized mortality rates per 100 000 men and women from PLC and ICC separately, in 12 selected European countries and in the EU, plus the United States, Japan, and Australia, around 2002 (2000–2004) and 2007 (2005–2009), and the corresponding percentage changes in rates. In the EU, the overall mortality rates from PLC decreased from 3.9 to 3.6/100 000 men and from 0.93 to 0.77/100 000 women between 2002 and 2007. Male mortality decreased in Italy, the Czech Republic, Spain, and France, but increased in all other European countries considered, except Austria, where mortality remained stable. Within Europe, in 2007, the highest male mortality rates from PLC were in France (6.2/100 000), Spain (4.9), Austria (4.3), and Italy (4.0), while the lowest ones were in Sweden (1.1), the Netherlands (1.2), the UK (1.8), and Denmark (1.9). Between 2002 and 2007, female mortality decreased particularly in Italy, Spain, Denmark, and the Czech Republic, while increased in Sweden, the Netherlands, and the UK. The mortality rates remained almost stable in Austria, Finland, Germany, and Portugal. In 2007, the highest female mortality rates were around 1/100 000 in Spain and Italy, while the lowest ones were in Denmark (0.32), Sweden, and the UK (0.41). In the United States, male PLC mortality rates increased from 2.3 to 2.5/100 000 men; in Japan, rates were appreciably higher, but decreased from 17.6 to 13.7/100 000 men; while in Australia they were almost stable around 2.3/100 000 men. In women, rates were almost stable in the United States (around 0.6) and in Australia (around 0.5), and decreased from 5.1 to 4.1/100 000 women in Japan.

Male mortality rates from ICC increased from 0.79 to 1.1/100 000 in the EU overall. Mortality rates rose in all European countries considered, with the largest increases in Austria, Denmark, France, Germany, Italy, and Spain. Within Europe, in 2007, the highest male mortality rates from ICC were in Austria, France, Spain, the UK, Finland, and Germany (between 1.5 and 1.1/100 000 men), while the lowest ones were in the Czech Republic, Sweden, the Netherlands, Denmark, Italy, and Portugal (between 0.5 and 0.9/100 000 men). In women, the EU rates increased from 0.55 in 2002 to 0.75/100 000 women in 2007, and the patterns were similar to those in men. From 2002 to 2007, the rates were stable in Japan (around 1.1/100 000 men and around 0.6/100 000 women), while the rates increased in the United States (from 0.73 to 0.82/100 000 men and from 0.56 to 0.64/100 000 women) and Australia (from 0.94 to 1.2/100 000 men and from 0.76 to 0.91/100 000 women).

Table 2 gives the corresponding mortality rates for men and women aged 45–64 years. For PLC, the mortality rates decreased from 7.4 in 2002 to 7.0/100 000 men in 2007, and from 1.4 to 1.1/100 000 women in the EU. In 2007, the highest male mortality rates were reported in France (12.7/100 000) and Spain (10.2), while the lowest ones were in the Netherlands and Sweden (2.5). In women, the mortality rates varied from 0.7/100 000 women in the UK and in the Netherlands to 1.5/100 000 women in France. Some increases in PLC mortality were observed in the United States and Australia, with rates, respectively, of 7.3 and 5.2/100 000 men and 1.1–1.2/100 000 women in 2007, whereas substantial declines were registered in Japan, though with exceedingly high rates (25.1/100 000 men and 4.1/100 000 women in 2007). For ICC, truncated 45–64 years mortality rates increased from 1.5 in 2002 to 2.0/100 000 in men in 2007, and from 1 to 1.3 in women in the EU. In 2007, the highest male ICC mortality rates were 3.0/100 000 men in Austria, and the lowest one was 1.0/100 000 men in Sweden. In women, the mortality rates varied from 0.7/100 000 women in the Czech Republic and Sweden to 2.0/100 000 women in Austria. Some increases in mortality from ICC were observed in the United States and Australia too, while some declines were registered in Japan.

Table 3 considers, for comparative purposes, trends in ECC mortality. In the EU, the United States, and Australia, the mortality rates were downwards, and three to five times lower than those of ICC, i.e. between 0.06 and 0.27/100 000. In Japan, ECC rates were much higher (around 3/100 000 men and 1.5/100 000 women), and only moderately declined over recent calendar periods.

The findings from the joinpoint regression analysis in men and women at all ages, over the period 1990–2010, are given in Figure 1 (and Supplementary Table S1, available at *Annals of Oncology* online) for PLC, and in Figure 2 (and Supplementary Table S2, available at *Annals of Oncology* online) for ICC. In all European countries considered, mortality trends for PLC were more frequently falling or levelling off in women than in men

Table 1. Overall age-standardized (world population) mortality rates from primary liver cancer (PLC) and intrahepatic cholangiocarcinoma (ICC) per 100 000 men and women in selected European countries, the European Union (EU), the United States, Japan, and Australia, around 2002 (2000–2004) and 2007 (2005–2009), and the corresponding percentage changes in rates

	Men				Women			
	2002	2007	No. of deaths[a]	% Change 2007/2002	2002	2007	No. of deaths[a]	% Change 2007/2002
PLC								
Austria	4.27	4.31	343	0.8	0.92	0.89	101	−3.5
Czech Republic	2.76	2.32	180	−15.9	0.99	0.76	78	−23.1
Denmark (2005–2006)	1.46	1.89	90	29.6	0.42	0.32	16	−25.1
Finland	2.68	2.97	163	10.7	0.91	0.89	74	−2.3
France (2005–2008)	6.73	6.21	3340	−7.8	0.95	0.85	735	−10.8
Germany	2.89	3.05	2727	5.4	0.75	0.76	954	1.9
Italy (2000–2003/2006–2008)	6.08	4.02	2462	−33.9	1.72	1.01	989	−41.5
The Netherlands	1.05	1.18	212	12.3	0.33	0.39	79	17.3
Portugal (2000, 2002–2003/2007–2009)	2.71	3.66	379	34.8	0.68	0.66	108	−2.1
Spain (2005–2008)	5.66	4.89	1927	−13.7	1.53	1.10	675	−28.1
Sweden	0.76	1.13	120	49.0	0.30	0.41	42	35.6
UK	1.40	1.83	1102	30.6	0.35	0.41	321	16.0
EU (2005–2008)[b]	3.88	3.56	12 696	−8.3	0.93	0.77	4114	−17.2
United States (2005–2007)	2.30	2.52	5428	9.6	0.58	0.59	1629	1.7
Japan	17.55	13.65	19 696	−22.3	5.05	4.06	9646	−19.6
Australia (2006)	2.34	2.26	349	−3.6	0.51	0.46	85	−10.7
ICC								
Austria	1.02	1.50	118	46.8	0.71	1.07	128	50.6
Czech Republic	0.43	0.49	42	12.7	0.27	0.36	48	30.8
Denmark (2005–2006)	0.41	0.76	35	87.8	0.31	0.67	39	120.1
Finland	1.13	1.22	75	8.0	0.96	1.03	86	7.3
France (2005–2008)	1.04	1.35	835	30.0	0.59	0.84	781	40.7
Germany	0.64	1.06	1078	64.8	0.46	0.72	999	54.7
Italy (2000–2003/2006–2008)	0.48	0.79	495	65.6	0.31	0.50	499	62.8
Netherlands	0.58	0.63	119	9.4	0.43	0.46	112	7.8
Portugal (2000, 2002–2003/2007–2009)	0.79	0.94	99	19.3	0.39	0.50	75	29.4
Spain (2005–2008)	0.95	1.29	569	35.7	0.60	0.77	558	27.4
Sweden	0.42	0.49	55	15.9	0.38	0.39	60	5.0
UK	1.00	1.24	859	23.6	0.87	1.12	996	27.6
EU (2005–2008)[b]	0.79	1.07	4109	36.5	0.55	0.75	4244	36.2
United States (2005–2007)	0.73	0.82	1916	11.2	0.56	0.64	1939	13.8
Japan	1.08	1.09	1757	0.4	0.58	0.58	1304	−0.3
Australia (2006)	0.94	1.22	214	30.2	0.76	0.91	184	19.5

[a]Number of deaths of the latest year available.

[b]Including data from 13 countries (Austria, Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Portugal, Spain, Sweden, and the UK).

(Figure 1 and Supplementary Table S1, available at *Annals of Oncology* online). The major change in PLC mortality was the steady and substantial fall in Italy, with an AAPC of −4% per year in men, and −5% in women. Other appreciable declines were observed in the Czech Republic, France (after the mid-1990s) and Spain (after 2000). In the EU, mortality from PLC, after an increase in the early 1990s (APC = 5.1% in men and 2.7% in women), started to decline since 1994 (APC = −1.9% in men, and −3.4% in women). In contrast, recent trends were upwards in Germany, the UK, a few other northern European countries, and Portugal, particularly in men. PLC trends were upwards in US men (but not in women), appreciably downwards in Japanese of both sexes after 1996–1997 (by ~4% per year), though Japanese rates for PLC remain exceedingly high, while they were almost stable in Australia in both sexes.

ICC mortality steadily increased throughout Europe, for both sexes (Figure 2 and Supplementary Table S2, available at *Annals of Oncology* online). The major rises were in Austria, France, Germany, and Italy, with AAPCs for the entire period around 13%–15% per year. EU mortality from ICC increased by over 10% between 1990 and 2004–2005 in both sexes, followed by smaller rises (APC = 2.2% in men, and 4.5% in women) over most recent years. Trends were also upwards in the United States, Japan, and Australia. In the United States, the rates increased by ~9% per year in men and women until 1993–1994, and by around 3.5% from 1993–1994 to 2007. In Australia, a steady increase in ICC mortality was observed over the entire period (APC ~5% in men and 6% in women). In Japan, trends steeply increased until the second mid of the 1990s (APC 30.4% per year in men and 26.7% in women), to rise by only about 1% per year in both sexes, thereafter.

Table 2. Age-standardized (world population) mortality rates from primary liver cancer (PLC) and intrahepatic cholangiocarcinoma (ICC) per 100 000 men and women truncated at age 45–64 years, in selected European countries, the European Union (EU), the United States, Japan, and Australia, around 2002 (2000–2004) and 2007 (2005–2009), and the corresponding percentage changes in rates

	Men				Women			
	2002	2007	No. of deaths[a]	% Change 2007/2002	2002	2007	No. of deaths[a]	% Change 2007/2002
PLC								
Austria	8.57	9.00	80	5.0	1.46	1.31	14	−9.7
Czech Republic	6.41	4.65	65	−27.5	1.88	1.40	21	−25.2
Denmark (2005–2006)	3.39	4.34	38	28.3	0.87	0.40	1	−54.7
Finland	4.05	4.44	40	9.7	1.13	1.27	10	12.2
France (2005–2008)	13.35	12.65	1046	−5.3	1.59	1.47	125	−7.7
Germany	5.53	5.85	667	5.8	1.28	1.30	150	0.9
Italy (2000–2003/2006–2008)	11.50	7.25	545	−37.0	2.30	1.15	85	−49.9
The Netherlands	2.20	2.50	72	14.0	0.63	0.71	20	12.2
Portugal (2000, 2002–2003/2007–2009)	6.41	8.69	126	35.4	1.16	1.00	15	−13.3
Spain (2005–2008)	10.92	10.19	556	−6.7	1.93	1.17	62	−39.5
Sweden	1.64	2.50	42	52.1	0.44	0.77	9	75.0
UK	2.77	3.77	328	35.8	0.62	0.69	64	10.1
EU (2005–2008)[b]	7.42	7.03	3551	−5.2	1.39	1.12	536	−19.0
United States (2005–2007)	6.15	7.26	2850	18.2	1.11	1.22	485	10.4
Japan	33.72	25.06	4289	−25.7	6.02	4.06	678	−32.5
Australia (2006)	4.85	5.20	127	7.3	0.95	1.12	28	18.6
ICC								
Austria	1.88	3.02	33	60.8	1.41	2.01	29	42.3
Czech Republic	0.92	1.31	20	43.1	0.53	0.68	14	28.7
Denmark (2005–2006)	0.91	1.71	13	87.6	0.45	1.23	7	171.5
Finland	2.43	2.61	21	7.4	1.88	1.91	21	1.2
France (2005–2008)	2.27	2.56	231	13.1	1.00	1.60	156	59.8
Germany	1.30	2.01	255	53.9	0.82	1.28	164	55.8
Italy (2000–2003/2006–2008)	1.07	1.64	126	53.0	0.65	0.93	94	43.6
The Netherlands	1.03	1.10	30	6.9	0.79	0.76	22	−3.5
Portugal (2000, 2002–2003/2007–2009)	1.54	1.87	23	21.0	0.77	0.77	15	1.0
Spain (2005–2008)	1.55	2.23	121	43.4	0.83	1.15	72	38.5
Sweden	1.01	1.00	19	−1.1	0.85	0.70	13	−17.5
UK	1.73	1.94	165	12.0	1.57	1.94	167	23.6
EU (2005–2008)[b]	1.52	1.99	1031	30.9	0.97	1.33	768	37.6
United States (2005–2007)	1.43	1.61	584	12.9	1.13	1.28	527	13.4
Japan	1.99	1.95	385	−1.9	1.02	0.99	190	−3.2
Australia (2006)	1.56	1.85	47	18.6	1.43	1.46	36	1.9

[a]Number of deaths of the latest year available.

[b]Including data from 13 countries (Austria, Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, the Netherlands, Portugal, Spain, Sweden, and the UK).

Table 3. Overall age-standardized (world population) mortality rates from extrahepatic bile ducts cancer per 100 000 men and women in the European Union (EU), the United States, Japan, and Australia, around 2002 (2000–2004) and 2007 (2005–2009), and the corresponding percentage changes in rates

	Men				Women			
	2002	2007	No. of deaths[a]	% Change 2007/2002	2002	2007	No. of deaths[a]	% Change 2007/2002
EU (2005–2008)[b]	0.29	0.27	965	−6.2	0.25	0.21	1082	−17.0
United States (2005–2007)	0.16	0.13	302	−19.8	0.11	0.09	315	−17.0
Japan	3.15	2.99	5410	−4.9	1.71	1.53	4412	−10.3
Australia (2006)	0.20	0.06	12	−69.3	0.14	0.10	25	−28.0

[a]Number of deaths for the latest year available.

[b]Including data from 13 countries (Austria, Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, the Netherlands, Portugal, Spain, Sweden, and the UK).

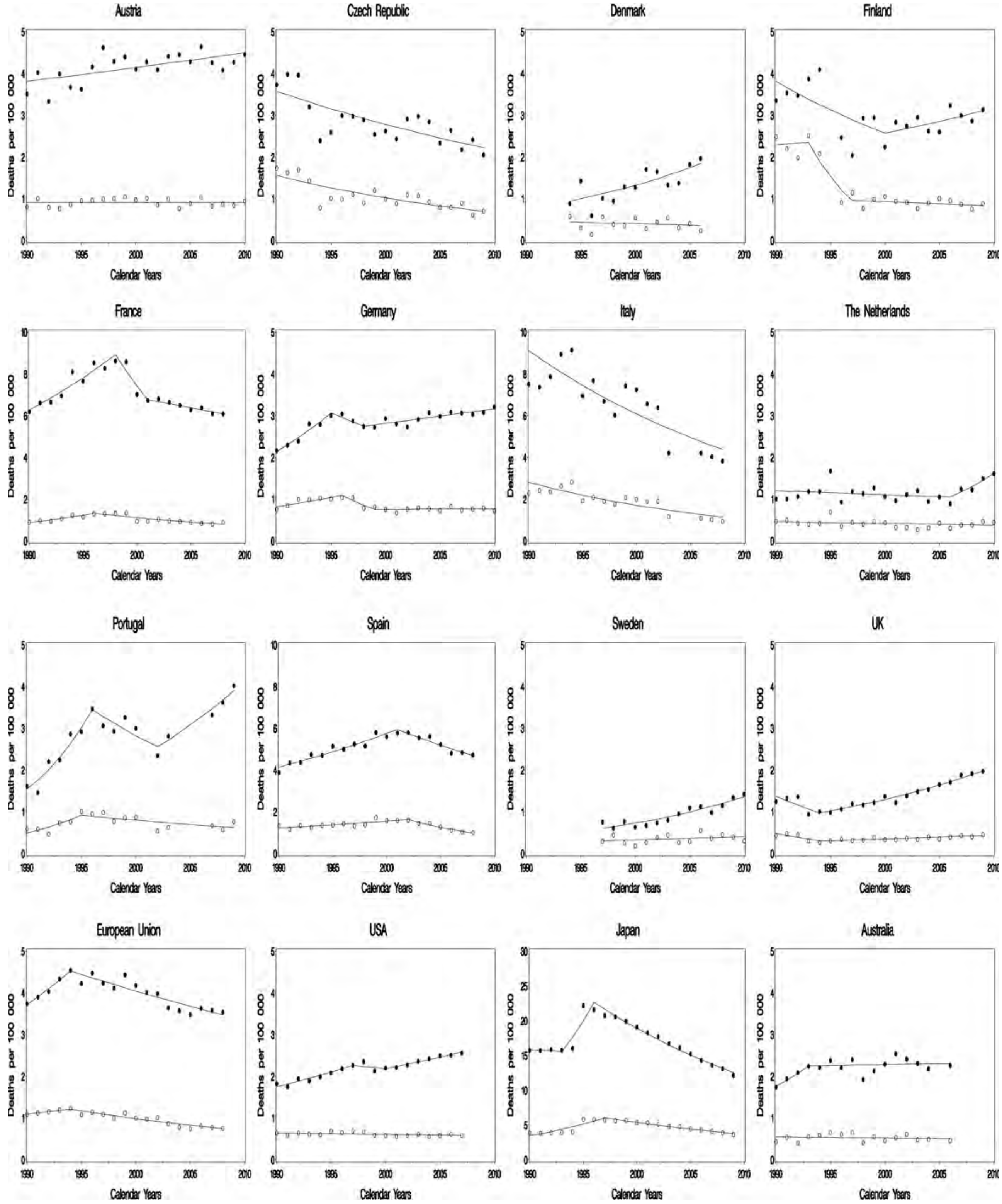

Figure 1. Joinpoint analysis for age-standardized (world population) death certification rates from primary liver cancer (PLC) in 12 selected European countries, the European Union (EU), the United States, Japan, and Australia, 1990–2010. Men, ●——●; women ○——○.

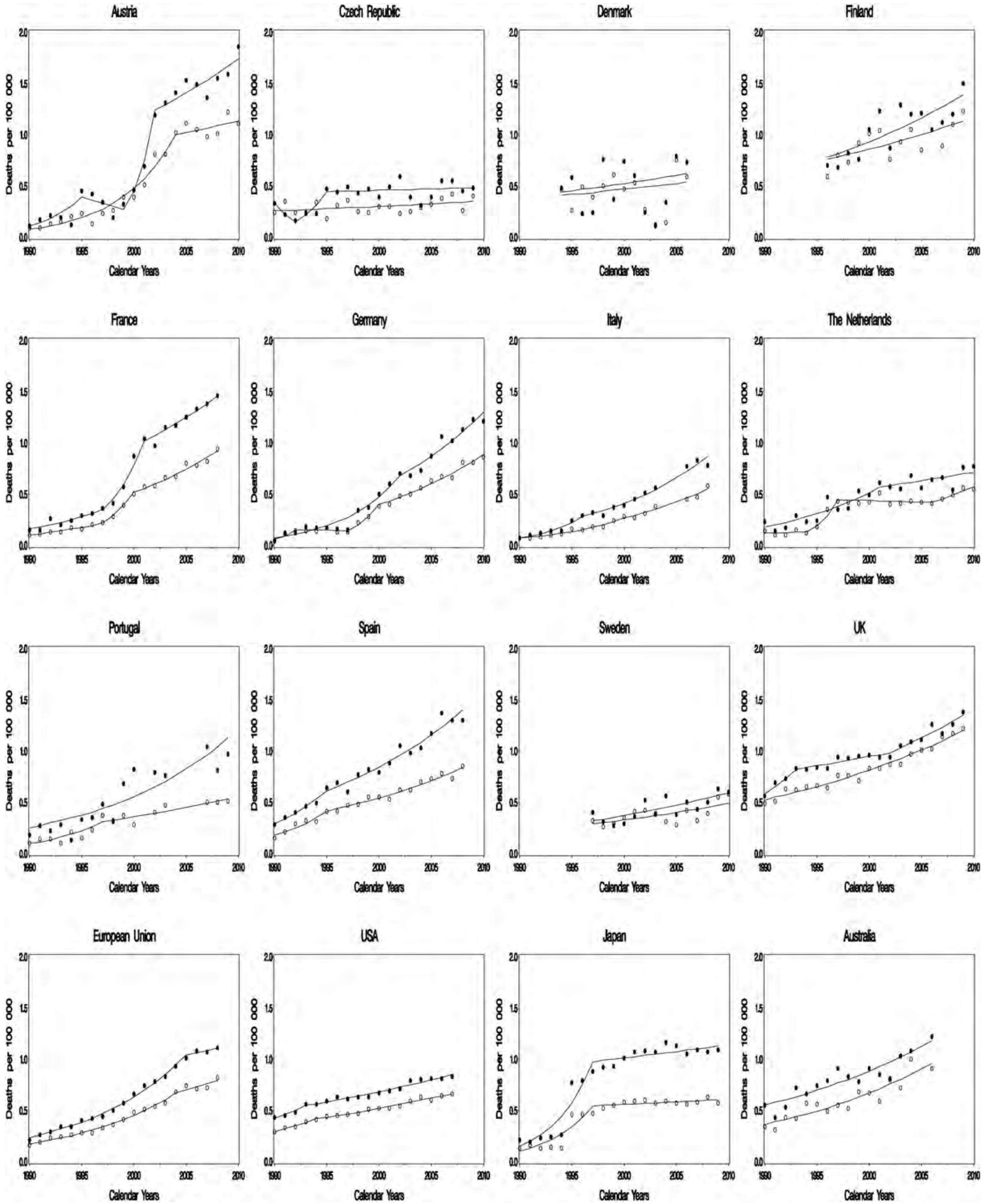

Figure 2. Joinpoint analysis for age-standardized (world population) death certification rates from intrahepatic cholangiocarcinoma (ICC) in 12 major selected European countries, the European Union (EU), the United States, Japan, and Australia, 1990–2010. Men, ●—●; women ○—○.

discussion

There are several important messages from this updated analysis of trends of liver cancer mortality in Europe. PLC (essentially HCC) has decreased over the last decade in traditionally high mortality areas from southern European countries, such as Italy and France, and recently Spain, but has increased in former low mortality areas of central and northern Europe, and in Portugal. Consequently, the mortality rates of PLC have become more uniform across Europe over recent years, being 3.6/100 000 men and 0.8/100 000 women in the EU as a whole over the last period considered (2005–2008). In most European countries, mortality trends from PLC in women were more favourable than in men. In contrast, mortality from ICC has increased in all EU countries considered, and over recent years ICC accounted for over a fourth of all liver cancer deaths in men and ∼50% in women. Trends in PLC mortality in the United States and Australia were similar to those observed in central and northern European countries, showing upward trends particularly in people aged 45–64 years, but more favourable trends in women. The rates in Japan remain extremely high, even if marked falls were observed since the mid-1990s. Upward trends in ICC mortality were observed in the United States, Japan, and Australia, too.

In the interpretation of trends in liver cancer mortality, great caution is required, given the substantial problems of validity of death certification data, mainly due to the difficulty in distinguishing primary and secondary liver neoplasms [2, 19]. For this reason, we have considered only a few selected countries for which death certification data appeared consistent and valid. Still, even in Sweden, the majority of liver cancer deaths are classified as liver unspecified [20].

Some of the observed trends may, therefore, be due to changes in the classification of the diseases. An additional problem of classification is posed by the particular case of hilar tumours (also called 'Klatskin' tumours), since they are often misclassified as ICC instead of ECC, due to their tendency to quickly invade the liver [21, 22]. In parallel, in England and Wales as well as in the United States, coding misclassification of hilar tumours from ECC to ICC before 2000 may have contributed to earlier rises in ICC rates [23]. However, a previous study on the impact of such misclassification showed that the incidence of ICC significantly increased over time, even after excluding deaths from hilar cancers [24]. Since the change in classification occurred in the early 2000s, this cannot explain the recent rises in ICC and falls in ECC. Further, given the much lower rates of ECC than ICC in Europe, any change in classification between ICC and ECC cancers is unlikely to have had any strong impact on ICC rates. Some misclassification is also possible between HCC and ICC, but this is difficult to quantify.

In any case, the consistency of mortality trends at all ages and in middle-age populations, and the differences observed between sexes, weigh against the possibility that problems in diagnosis and classification explain the observed trends.

Trends in PLC, mainly HCC, across Europe can be largely related to changes in hepatitis B virus (HBV) and HCV prevalence in subsequent generations in various countries [2, 3, 25], since HBV and HCV are more strongly related to HCC than to ICC. In southern Europe, the decreased prevalence of HBV and HCV in younger generations, after the adoption of HBV vaccination programs [26], and the reduction in alcohol drinking over the last few decades likely explain the favourable HCC trends in those countries. Conversely, whereas the increasing prevalence of HCV (and HBV) infection and alcohol consumption in central and northern European countries accounts for the unfavourable trends in those areas of the continent. The decline in the prevalence of tobacco smoking—another recognized risk factor for HCC [27]—in men from Western European countries may also have favourably influenced HCC mortality trends.

Some of the risk factors shared by HCC and ICC, including diabetes and cirrhosis [8, 9, 28–31], have shown unfavourable patterns over recent years in central and eastern Europe [32, 33], this may at least in part explain the recent rises in HCC and ICC, at least in these areas of Europe. Furthermore, improvements in survival from cirrhosis have increased the development and the identification not only of PLC but also of ICC [34].

It is more difficult to explain the diverging trends in ICC and ECC, since most risk factors are common to both sites [6, 8, 9, 35], though HCV and heavy alcohol drinking appear to be more strongly related to ICC than ECC [9]. Likewise, gallstones are related to both ICC and ECC, but they appear to have a stronger association with ECC [11, 36]. Diagnosis of gallstones and removal of gallbladder are considered the main reason for the recent declines in gallbladder cancer mortality in Europe [37] and other areas of the world [38, 39], and may also, at least in part, explain the recent favourable trends in ECC.

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disclosure

The authors have declared no conflicts of interest.

references

1. La Vecchia C, Lucchini F, Franceschi S et al. Trends in mortality from primary liver cancer in Europe. Eur J Cancer 2000; 36: 909–915.
2. Bosetti C, Levi F, Boffetta P et al. Trends in mortality from hepatocellular carcinoma in Europe, 1980–2004. Hepatology 2008; 48: 137–145.
3. Center MM, Jemal A. International trends in liver cancer incidence rates. Cancer Epidemiol Biomarkers Prev 2011; 20: 2362–2368.
4. McGlynn KA, London WT. The global epidemiology of hepatocellular carcinoma: present and future. Clin Liver Dis 2011; 15: 223–243.
5. von Hahn T, Ciesek S, Wegener G et al. Epidemiological trends in incidence and mortality of hepatobiliary cancers in Germany. Scand J Gastroenterol 2011; 46: 1092–1098.

6. Shaib YH, Davila JA, McGlynn K et al. Rising incidence of intrahepatic cholangiocarcinoma in the United States: a true increase? J Hepatol 2004; 40: 472–477.
7. El-Serag HB, Engels EA, Landgren O et al. Risk of hepatobiliary and pancreatic cancers after hepatitis C virus infection: a population-based study of U.S. veterans. Hepatology 2009; 49: 116–123.
8. Shaib YH, El-Serag HB, Davila JA et al. Risk factors of intrahepatic cholangiocarcinoma in the United States: a case–control study. Gastroenterology 2005; 128: 620–626.
9. Shaib YH, El-Serag HB, Nooka AK et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: a hospital-based case–control study. Am J Gastroenterol 2007; 102: 1016–1021.
10. Welzel TM, Graubard BI, El-Serag HB et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case–control study. Clin Gastroenterol Hepatol 2007; 5: 1221–1228.
11. Nordenstedt H, Mattsson F, El-Serag H et al. Gallstones and cholecystectomy in relation to risk of intra- and extrahepatic cholangiocarcinoma. Br J Cancer 2012; 106: 1011–1015.
12. World Health Organization Statistical Information System. WHO mortality database http://www.who.int/whosis/mort/download/en/index.html (November 2011, last accessed).
13. World Health Organization. International Classification of Disease: 9th Revision. Geneva: World Health Organization 1977.
14. World Health Organization. International Statistical Classification of Disease and related Health Problems: 10th revision. Geneva: World Health Organization 1992.
15. Doll R, Smith PG. Comparison between registries: age-standardized rates. Vol. IV. IARC Sci Publ No. 42. In Waterhouse JAH, Muir CS, Shanmugaratnam K et al. (eds), Cancer Incidence in Five Continents. Lyon: IARC 1982; 671–675.
16. National Cancer Institute. Joinpoint Regression Program, version 3.5.2. http://srab.cancer.gov/joinpoint/ (October 2011, Last accessed).
17. Kim HJ, Fay MP, Feuer EJ et al. Permutation tests for joinpoint regression with applications to cancer rates. (Erratum in: Stat Med 2001;20: 655). Stat Med 2000; 19: 335–351.
18. Clegg LX, Hankey BF, Tiwari R et al. Estimating average annual per cent change in trend analysis. Stat Med 2009; 28: 3670–3682.
19. Percy C, Ries LG, Van Holten VD. The accuracy of liver cancer as the underlying cause of death on death certificates. Public Health Rep 1990; 105: 361–367.
20. Duberg AS, Hultcrantz R. Misleading figures on trends in mortality from hepatocellular carcinoma in Europe. Hepatology 2009; 49: 336; author reply 336–337.
21. Okuda K, Nakanuma Y, Miyazaki M. Cholangiocarcinoma: recent progress. Part 1: epidemiology and etiology. J Gastroenterol Hepatol 2002; 17: 1049–1055.
22. de Martel C, Plummer M, Franceschi S. Cholangiocarcinoma: descriptive epidemiology and risk factors. Gastroenterol Clin Biol 2010; 34: 173–180.
23. Khan SA, Emadossadaty S, Ladep NG et al. Rising trends in cholangiocarcinoma: is the ICD classification system misleading us?. J Hepatol 2012; 56: 848–854.
24. Welzel TM, McGlynn KA, Hsing AW et al. Impact of classification of hilar cholangiocarcinomas (Klatskin tumors) on the incidence of intra- and extrahepatic cholangiocarcinoma in the United States. J Natl Cancer Inst 2006; 98: 873–875.
25. Nordenstedt H, White DL, El-Serag HB. The changing pattern of epidemiology in hepatocellular carcinoma. Dig Liver Dis 2010; 42(Suppl 3): S206–S214.
26. Raza SA, Clifford GM, Franceschi S. Worldwide variation in the relative importance of hepatitis B and hepatitis C viruses in hepatocellular carcinoma: a systematic review. Br J Cancer 2007; 96: 1127–1134.
27. Trichopoulos D, Bamia C, Lagiou P et al. Hepatocellular carcinoma risk factors and disease burden in a European cohort: a nested case-control study. J Natl Cancer Inst 2011; 103: 1686–1695.
28. Randi G, Altieri A, Gallus S et al. History of cirrhosis and risk of digestive tract neoplasms. Ann Oncol 2005; 16: 1551–1555.
29. La Vecchia C, Negri E, Cavalieri d'Oro L et al. Liver cirrhosis and the risk of primary liver cancer. Eur J Cancer Prev 1998; 7: 315–320.
30. La Vecchia C, Negri E, Decarli A et al. Diabetes mellitus and the risk of primary liver cancer. Int J Cancer 1997; 73: 204–207.
31. Bosetti C, Rosato V, Polesel J et al. Diabetes mellitus and cancer risk in a network of case-control studies. Nutr Cancer 2012; 64: 643–651.
32. Bosetti C, Levi F, Lucchini F et al. Worldwide mortality from cirrhosis: an update to 2002. J Hepatol 2007; 46: 827–839.
33. Zatonski WA, Sulkowska U, Manczuk M et al. Liver cirrhosis mortality in Europe, with special attention to Central and Eastern Europe. Eur Addict Res 2010; 16: 193–201.
34. Chuang SC, La Vecchia C, Boffetta P. Liver cancer: descriptive epidemiology and risk factors other than HBV and HCV infection. Cancer Lett 2009; 286: 9–14.
35. El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011; 365: 1118–1127.
36. Chow WH, McLaughlin JK, Menck HR et al. Risk factors for extrahepatic bile duct cancers: Los Angeles County, California (USA). Cancer Causes Control 1994; 5: 267–272.
37. Levi F, Lucchini F, Negri E et al. The recent decline in gallbladder cancer mortality in Europe. Eur J Cancer Prev 2003; 12: 265–267.
38. Randi G, Malvezzi M, Levi F et al. Epidemiology of biliary tract cancers: an update. Ann Oncol 2009; 20: 146–159.
39. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. Int J Cancer 2006; 118: 1591–1602.