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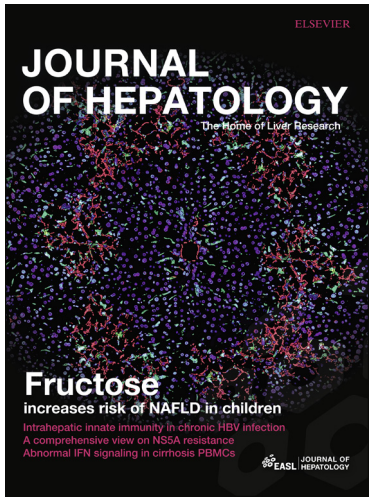

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Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma

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Abstract (255 words)

Background and Aims. Intrahepatic (ICC) and extrahepatic cholangiocarcinoma (ECC) have been rarely studied distinctively, probably due to difficulties in their diagnosis and certification. Mortality trends from these two neoplasms have been inconsistent over the last decades. The aim of this study is to analyze trends in mortality from ICC and ECC in selected countries worldwide.

Methods. We extracted death certification data from ICC and ECC and population estimates from the World Health Organization and Pan American Health Organization databases for 32 selected countries from Europe, the Americas, and Australasia over the 1995-2016 period. We computed age-standardized (world population) mortality rates from ICC and ECC, and performed joinpoint regression analysis.

Results. Mortality rates from ICC increased in all countries considered, with a levelling off over recent years in Germany (women), Italy (men), Argentina (men), the USA (men), Hong Kong (men), and Japan (both sexes). The highest rates in 2010-2014 (1.5-2.5/100,000 in men and 1.2-1.7/100,000 in women) were registered in Hong Kong, France, Austria, Spain, the UK, and Australia. The lowest rates (0.2 to 0.6/100,000 in both sexes) were registered in Latin America and eastern European countries. Mortality from ECC decreased in most of the countries considered, with rates being below 1/100,000 in both sexes, with the only exception of Japan (2.8/100,000 in men and 1.4/100,000 in women).

Conclusions. Increasing mortality from ICC was observed globally, possibly due in part to better disease classification, but also to trends in risk factors. Mortality from ECC levelled off or decreased, most likely following the increased use of laparoscopic cholecystectomy.

Lay summary: Biliary tract cancers include intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC), whose determinants differ at least in quantitative terms; consequently, the distinction between ICC and ECC is important. Over the last few decades, mortality from ICC tended to rise in several areas of the world, following the increased prevalence

of its major risk factors, i.e. HBV and HCV, alcohol, and NAFLD. In contrast, mortality from ECC tended to decrease in most countries, following the increased use of laparoscopic cholecystectomy.

Introduction

Cholangiocarcinoma is the second most common primary liver neoplasm after hepatocellular carcinoma [1, 2]. These neoplasms arise from the epithelial cells of the biliary tree, commonly classified as intrahepatic cholangiocarcinoma (ICC) if they arise above the hilar junction of bile ducts or extrahepatic cholangiocarcinoma (ECC) if they arise within or below the hilum.

These two types of cancer have some recognized differences in risk factors and clinical presentation [3-6]. However, ICC and ECC have rarely been studied comparatively, possibly due to difficulties in their diagnosis, registration and certification [7-9]. Death certification validity from these neoplasms, however, has improved in recent years [8, 9].

Still, mortality trends from ICC and ECC have been inconsistent over the last decades [10-12]. This work, therefore, aims to analyze recent mortality trends from ICC and ECC in countries with valid data.

Material and Methods

We extracted official death certification data from ICC and ECC, from the World Health Organization (WHO) database, as available on electronic support [13], over the 1995–2016 period, when the Tenth Revision of the International Classification of Diseases (ICD-10) was used (ICD-10 code C22.1 for ICC, and C24.0 for ECC) [14]. Gallbladder cancer (ICD-10 code C23) was not included. Histological codes were not available.

We analyzed data for 18 European countries, 16 of which belonging to the European Union, 9 countries from the Americas, and 5 countries from Australasia. We selected these countries because they reported consistent and valid data, according to the WHO guidelines [15, 16], i.e. all countries considered had over 2 million inhabitants and death certification coverage was above 85%.

We extracted estimates of the resident population, based on official censuses, from the same WHO database [13]. For American countries, since data were unavailable in the WHO database for

several years, we extracted the populations from the Pan American Health Organization database [17].

From the matrices of certified deaths and resident populations, we computed age-specific rates for each 5-year age group (from 0-4 to 85+ years, and from 0-4 to 80+ years for American countries), sex, and calendar year. We then computed age-standardized mortality rates per 100,000 person-years at all ages and for the age group 45-64 years, using the direct method of standardization based on the 1960 world standard population [18].

For 24 countries with a population greater than 10 million or annual average number of deaths greater than 200 in the last quinquennium, we performed a joinpoint regression analysis, over the 1995-2016 period, for ICC mortality. We thus identified the years when a significant change in the linear slope of the temporal trend (on a log scale) occurred, by testing from a zero up to a maximum of three inflection points (called "joinpoints") [19, 20]. 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 calendar year as a regressor variable.

Results

Table 1 shows age-standardized mortality rates from ICC and ECC per 100,000 person-years, at all ages, around 2002 (2000-2004), 2007 (2005-2009), and 2012 (2010-2014), the annual average number of deaths of the more recent period, and the corresponding percentage change in rates, according to sex and country.

Mortality rates from ICC were consistently below 1/100,000 among men in the early 2000s' in most countries. Between 2002 and 2012, mortality increased in all countries except in Finland. The highest incremental changes were observed in Norway, Croatia, Denmark, the UK, Germany, and Portugal among European countries, in Argentina, Chile, and Brazil among American countries, and in Australia. As a result, in the 2010-2014 period, mortality rates from ICC in men were between 1-2/100,000 person-years in most countries (**Figure 1**). The highest mortality rates were in

Hong Kong (2.5/100,000 in men), and in France, Austria, Spain, the UK, and Australia (between 1.5 and 1.8/100,000 in men). The lowest rates (0.2 and 0.5/100,000) were registered in the Latin American countries considered. ICC rates were 1.04/100,000 for men in the USA, and 1.1/100,000 in Japan. The differences in rates across countries were highly significant.

Women had similar patterns although with lower rates than men. Mortality rates from ICC increased in all countries, except in Finland (-15%) and Japan (-1.7%). The highest percentage changes were observed in Croatia, Norway, Lithuania, Denmark, the UK, Argentina, and Chile. The highest mortality rates over 1/100,000 women were registered in Hong Kong (1.7), the UK (1.5), Australia, Canada, and Austria (around 1.2), Belgium, France, Switzerland, and Norway (about 1). The lowest rates (below 0.5/100,000 women) were observed in Argentina (0.2), Hungary (0.3), Brazil, Venezuela, and the Czech Republic (around 0.4), Chile and Puerto Rico (almost 0.5). ICC rates in the USA were 0.8/100,000 women, and 0.6/100,000 in Japan (**Figure 1**).

With reference to ECC, rates of 0.5-0.9/100,000 in the early 2000s' were observed in Lithuania (about 0.5/100,000 men), Croatia, Germany, Sweden (about 0.6), Austria and Hungary (almost 0.9). Japan had a mortality rate of 3.2/100,000 men around 2002. Over the last decade, ECC rates decreased in most countries. In 2010-2014, mortality from ECC showed rates below 1/100,000 men in all countries, with the only exception of Japan (2.8/100,000 men, **Figure 2**). The lowest rates below 0.1/100,000 men were observed in some central and northern European countries, in Canada and most Latin American countries, Israel, and in Australia.

Mortality rates from ECC decreased in women, too, in most countries. The highest rates in 2010-2014 were registered in Japan (1.4/100,000), followed by Austria, Germany, and other central European countries (**Figure 2**).

Table 2 shows the age-standardized mortality rates at age 45-64 years. For ICC, male mortality rates showed substantial increases over the last decade with rates that varied between 2 and 3/100,000 men. In 2010-2014, the highest mortality rates were observed in Hong Kong (3.7/100,000), and in Austria, France and Spain (around 3/100,000). The lowest rates were

registered in Latin American countries. For ECC, mortality rates were below 1/100,000, with the exceptions of Japan (3.1/100,000 men), Hungary (1.4) and Germany (1.0). Also in middle-aged women, upward trends were observed for ICC. In 2010-2014, ICC rates varied around 1-2/100,000 person-years. In contrast, mortality from ECC in women 45 to 64 declined in most countries, with rates below 0.4/100,000, and only a few countries showing rates between 0.5-1.0/100,000.

Figure 3 and **Table 3** report the joinpoint regression analysis results on mortality trends from ICC. Upward trends were observed in most countries. The annual percent changes in Europe varied between 2% in the Czech Republic and 7.6% in Portugal for the whole period. There were substantial early increases in Germany and Italy, followed by a levelling off thereafter. In the Americas the highest increases were in Chile and Argentina. Rising mortality trends until 2013 in the USA slowed down in the recent years. Hong Kong showed stable rates followed by a marked decrease in most recent years, whereas in Japan they were upward until the early 2000's and stable thereafter.

Discussion

This work showed global increases in mortality from ICC, and declines from ECC for both sexes, in most countries providing acceptable data reliability. It also shows substantial variations, with the highest rates in East Asia and northern and central Europe.

The reliability and validity of death certification for correctly ascertaining ICC and ECC is affected by the possibility of diagnostic misclassification between hepatocellular cancers, other liver neoplasms, gallbladder cancers, and between ICC and ECC [8]. Thus, in our analysis we selected countries with acceptably valid data, according to death certification coverage and population size. Still, a misclassification between ICC and hepatocellular carcinoma (HCC) is possible, particularly in cirrhotic patients to whom a biopsy was not performed. While we recognize that using the more granular anatomic classification of intrahepatic, perihilar or distal may have additional clinical implications [21], we were limited to the classification system used by most countries.

Mortality trends from ICC and ECC may have been influenced by changes in classification of these neoplasms. Before the 2000s, cases of hilar cholangiocarcinoma, called "Klatskin" cancer, were often classified as ICC instead of ECC. However, "Klatskin" tumours are relatively uncommon (e.g 7% of cholangiocarcinoma in the US) and mortality from ICC progressively increased over recent calendar periods, even after correctly classifying hilar cholangiocarcinoma as ECC [8, 9, 22].

More in general, improvements in diagnostic techniques could partly explain the rises in ICC, i.e. better classification of different forms of intrahepatic neoplasms [9]. With reference to incidence, an analysis of data from the North American Association of Central Cancer Registries over the 1999-2013 period reported a rise in ICC across sexes and racial/ethnic groups, and a smaller one in ECC [23]. Despite the recent advancement in the surgical management of this neoplasm, the prognosis remains dramatic [3, 24, 25].

The divergent mortality trends observed for ICC and ECC suggest that they have at least partially different etiologies [23]. Only a few studies have investigated the epidemiology of ICC and ECC separately. Available data indicate that these neoplasms may share several risk factors albeit with quantitative differences [4-6]. A US record-linkage study based on the Surveillance, Epidemiology, and End Results (SEER)-Medicare dataset [5] found a positive association with HBV and HCV mostly for ICC. An association between HCV infection and increased risk of ICC but not ECC was also reported in a large cohort study from the USA [26]. Likewise, tobacco smoking, alcohol consumption and non-alcoholic fatty liver diseases (NAFLD) were more strongly associated with ICC, whereas most bile duct conditions tended to be more strongly related with ECC [4, 5].

Knowledge of risk factors helps to explain ICC trends, which showed a levelling off over recent years in France and Italy, i.e. countries that experienced a decrease in alcohol-related chronic liver disease and cirrhosis in the recent past. In contrast, ICC rates remain upwards in other countries, including most European and American ones, which over recent calendar periods showed increases in the prevalence of HCV infection, heavy alcohol consumption, overweight and obesity, and NAFLD [27, 28]. Liver flukes (i.e., *Opisthorchis viverrini* and *Clonorchis sinensis*) are a known cause of ICC and

ECC in South East Asia [29]. They may have somewhat influenced rates in Hong Kong, but are unlikely to be important causes of these diseases in the other countries examined in this study.

On the basis of death certification, no information was available on cirrhosis, which is a strong determinant and pathogenic link to liver cancer [30].

A plausible explanation for the generalized decrease in ECC mortality is the increasing use of cholecystectomy, facilitated by laparoscopic techniques over the last decades [31] given the known strong association between gallstones and the risk of ECC including gallbladder. Given the low ECC rates, they may be more susceptible to misclassification of Klatskin and gallbladder tumors than ICC. A previous study showed that in the US, after correcting for misclassification of Klatskin, ECC may be stable or slightly increasing [8]. The less strong association of ECC than ICC with major liver diseases and cancer risk factors, such as HBV and HCV infections, alcohol, and NAFLD is also compatible with more favourable incidence and mortality trends of ECC. Still, primary sclerosing cholangitis (PSC) is also a relevant risk factor, particularly for ECC in the USA and northern Europe [32]. Thus, at least part of the fall in ECC mortality in those countries may reflect improved management of PSC.

In conclusion, our study provided strong confirmatory evidence on a global increase in mortality from ICC, whose determinants need to be better understood by conducting targeted investigations. Such studies should consider ICC separately from ECC.

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Figure legends

Figure 1. Age-standardized (world population) mortality rates from intrahepatic cholangiocarcinoma (ICC) in men and women in 32 countries worldwide in the 2010-2014 quinquennium (when available).

Figure 2. Age-standardized (world population) mortality rates from extrahepatic cholangiocarcinoma (ECC) in men and women in 32 countries worldwide in the 2010-2014 quinquennium (when available).

Figure 3. Joinpoint analysis of trends in age-standardized (world population) mortality rates from intrahepatic cholangiocarcinoma (ICC) in 24 major countries worldwide, over the period 1995-2016, in men (solid circle) and women (empty circle).

Table 1. Age-standardized (world population) mortality rates per 100,000 person-years from intrahepatic (ICC) and extrahepatic cholangiocarcinoma (ECC) at all ages around 2002 (2000-2004), 2007 (2005-2009) and 2012 (2010-2014) (unless indicated in parentheses), average deaths of the latest period and the corresponding change in rates, according to sex and selected countries worldwide.

	ICC					ECC				
	2002	2007	2012	Average deaths	% change (2012/02)	2002	2007	2012	Average deaths	% change (2012/02)
Men										
European Union countries										
Austria (2002-2004)	1.31	1.51	1.75	146	33.6	0.85	0.68	0.66	59	-22.4
Belgium	0.85	1.07	1.35	154	58.8	0.07	0.08	0.12	16	71.4
Croatia	0.47	0.70	1.02	42	117.0	0.57	0.56	0.63	28	10.5
Czech Republic	0.43	0.49	0.60	57	39.5	0.39	0.42	0.52	51	33.3
Denmark	0.41	0.54	0.78	43	90.2	0.28	0.18	0.13	8	-53.6
Finland	1.13	1.22	1.04	58	-8.0	0.32	0.36	0.30	18	-6.3
France	1.04	1.39	1.78	1143	71.2	0.09	0.09	0.07	55	-22.2
Germany	0.64	1.06	1.15	1062	79.7	0.56	0.50	0.70	702	25.0
Hungary	0.28	0.27	0.48	38	71.4	0.87	0.36	0.69	61	-20.7
Italy (2003-2004)	0.57	0.78	1.00	689	75.4	0.29	0.25	0.21	172	-27.6
Lithuania (2001-2004)	0.36	0.41	0.62	16	72.2	0.52	0.35	0.28	8	-46.2
Netherlands	0.58	0.63	0.91	149	56.9	0.43	0.42	0.41	65	-4.7
Portugal (2002-2003/2007-2009)	0.78	0.94	1.40	156	79.5	0.49	0.57	0.36	43	-26.5
Spain	0.95	1.31	1.69	818	77.9	0.06	0.05	0.09	48	50.0
Sweden	0.42	0.49	0.68	68	61.9	0.62	0.59	0.54	58	-12.9
UK	0.84	1.24	1.55	1029	84.5	0.07	0.07	0.05	38	-28.6
UK, England and Wales (2001-2004)	0.98	1.22	1.55	914	58.2	0.08	0.06	0.05	33	-37.5
UK, Northern Ireland (2001-2004)	1.35	1.38	1.61	26	19.3	0.30	0.15	0.10	2	-66.7
UK, Scotland	1.26	1.41	1.59	89	26.2	0.10	0.07	0.06	4	-40.0
Other European countries										
Norway	0.36	0.73	1.06	46	194.4	0.20	0.10	0.07	3	-65.0
Switzerland	0.83	1.19	1.23	98	48.2	0.32	0.24	0.32	28	0.0
American countries										
Argentina	0.08	0.09	0.23	55	187.5	0.09	0.07	0.04	11	-55.6
Brazil	0.19	0.26	0.35	334	84.2	0.40	0.38	0.34	324	-15.0
Canada (2010-2013)	0.80	1.03	1.38	449	72.5	0.18	0.11	0.07	26	-61.1
Chile	0.22	0.38	0.50	54	127.3	0.15	0.13	0.09	10	-40.0
Colombia	0.32	0.49	0.55	112	71.9	0.12	0.11	0.09	18	-25.0
Mexico	0.36	0.38	0.44	226	22.2	0.09	0.08	0.05	26	-44.4
Puerto Rico	0.57	0.53	0.74	21	29.8	0.10	0.08	0.06	2	-40.0
USA	0.73	0.84	1.04	2693	42.5	0.16	0.12	0.11	307	-31.3
Venezuela (2010-2013)	0.27	0.30	0.35	42	29.6	0.09	0.05	0.05	7	-44.4
Australasian countries										
Hong Kong SAR (2001-2004)	2.40	2.49	2.50	180	4.2	0.18	0.10	0.10	7	-44.4
Israel	0.76	0.90	0.97	50	27.6	0.07	0.05	0.04	3	-42.9
Japan	1.08	1.09	1.10	1916	1.9	3.15	2.99	2.81	5694	-10.8
Australia (2006-2009)	0.94	1.27	1.52	315	61.7	0.20	0.10	0.08	19	-60.0
New Zealand (2010-2013)	0.70	1.26	1.08	42	54.3	0.32	0.22	0.22	9	-31.3
Women										
European Union countries										
Austria (2002-2004)	0.88	1.07	1.16	138	31.8	0.64	0.53	0.47	58	-26.6
Belgium	0.75	0.87	1.05	157	40.0	0.07	0.04	0.07	15	0.0
Croatia	0.20	0.43	0.72	43	260.0	0.37	0.32	0.38	27	2.7
Czech Republic	0.27	0.36	0.42	53	55.6	0.43	0.38	0.34	51	-20.9
Denmark	0.31	0.55	0.76	52	145.2	0.19	0.22	0.20	14	5.3
Finland	0.96	1.03	0.82	66	-14.6	0.24	0.26	0.26	23	8.3
France	0.59	0.86	1.04	953	76.3	0.06	0.05	0.05	61	-16.7
Germany	0.46	0.72	0.82	1010	78.3	0.50	0.38	0.53	764	6.0
Hungary	0.21	0.19	0.30	39	42.9	0.62	0.30	0.56	79	-9.7
Italy (2003-2004)	0.41	0.52	0.67	625	63.4	0.21	0.16	0.13	171	-38.1
Lithuania (2001-2004)	0.23	0.30	0.61	27	165.2	0.36	0.26	0.20	10	-44.4
Netherlands	0.43	0.46	0.68	138	58.1	0.34	0.32	0.33	71	-2.9
Portugal (2002-2003/2007-2009)	0.43	0.49	0.75	119	74.4	0.43	0.32	0.25	43	-41.9
Spain	0.60	0.80	0.98	701	63.3	0.04	0.03	0.04	39	0.0
Sweden	0.38	0.39	0.66	78	73.7	0.66	0.75	0.61	84	-7.6

	ICC					ECC				
	2002	2007	2012	Average deaths	% change (2012/02)	2002	2007	2012	Average deaths	% change (2012/02)
UK	0.73	1.12	1.46	1236	100.0	0.06	0.05	0.04	39	-33.3
UK, England and Wales (2001-2004)	0.84	1.11	1.45	1090	72.6	0.07	0.05	0.04	36	-42.9
UK, Northern Ireland (2001-2004)	1.21	1.29	1.36	29	12.4	0.11	0.07	0.07	2	-36.4
UK, Scotland	1.26	1.17	1.57	117	24.6	0.11	0.07	0.03	2	-72.7
Other European countries										
Norway	0.35	0.76	1.00	54	185.7	0.18	0.05	0.05	3	-72.2
Switzerland	0.73	0.90	1.00	103	37.0	0.31	0.25	0.30	34	-3.2
American countries										
Argentina	0.06	0.07	0.16	52	166.7	0.09	0.09	0.02	10	-77.8
Brazil	0.19	0.28	0.36	432	89.5	0.53	0.51	0.42	527	-20.8
Canada (2010-2013)	0.60	0.83	1.19	465	98.3	0.13	0.08	0.07	35	-46.2
Chile	0.22	0.33	0.45	64	104.5	0.15	0.12	0.09	13	-40.0
Colombia	0.46	0.69	0.69	177	50.0	0.20	0.14	0.09	23	-55.0
Mexico	0.46	0.57	0.61	351	32.6	0.14	0.11	0.07	44	-50.0
Puerto Rico	0.35	0.33	0.48	19	37.1	0.09	0.06	0.07	3	-22.2
USA	0.56	0.66	0.82	2615	46.4	0.11	0.09	0.08	297	-27.3
Venezuela (2010-2013)	0.34	0.33	0.37	51	8.8	0.15	0.07	0.06	8	-60.0
Australasian countries										
Hong Kong SAR (2001-2004)	1.62	1.66	1.71	148	5.6	0.13	0.06	0.05	4	-61.5
Israel	0.46	0.77	0.86	58	87.0	0.07	0.04	0.05	4	-28.6
Japan	0.58	0.58	0.57	1398	-1.7	1.71	1.53	1.37	4682	-19.9
Australia (2006-2009)	0.76	1.02	1.23	305	61.8	0.14	0.08	0.05	15	-64.3
New Zealand (2010-2013)	0.62	0.96	0.98	46	58.1	0.25	0.15	0.15	8	-40.0

Table 2. Age-standardized (world population) mortality rates per 100,000 person-years from intrahepatic (ICC) and extrahepatic cholangiocarcinoma (ECC) at age 45-64 years around 2002 (2000-2004), 2007 (2005-2009) and 2012 (2010-2014) (unless indicated in parentheses), average deaths of the latest period and the corresponding change in rates, according to sex and selected countries worldwide.

	ICC					ECC				
	2002	2007	2012	Average deaths	% change (2012/02)	2002	2007	2012	Average deaths	% change (2012/02)
Men										
European Union countries										
Austria (2002-2004)	2.57	3.03	3.30	38	28.4	1.03	0.95	0.92	10	-10.7
Belgium	1.42	2.21	2.36	36	66.2	0.08	0.14	0.15	2	87.5
Croatia	0.91	1.42	1.56	10	71.4	0.65	0.60	0.91	6	40.0
Czech Republic	0.92	1.31	1.18	19	28.3	0.64	0.66	0.83	13	29.7
Denmark	0.91	1.12	1.36	11	49.5	0.40	0.32	0.17	1	-57.5
Finland	2.43	2.61	1.85	16	-23.9	0.43	0.52	0.36	3	-16.3
France	2.27	2.58	3.25	285	43.2	0.11	0.14	0.08	7	-27.3
Germany	1.30	2.01	2.16	260	66.2	0.91	0.80	1.01	122	11.0
Hungary	0.69	0.60	1.28	17	85.5	1.49	0.66	1.36	19	-8.7
Italy (2003-2004)	1.22	1.57	1.95	163	59.8	0.36	0.29	0.22	18	-38.9
Lithuania (2001-2004)	1.18	0.91	1.36	5	15.3	1.32	0.72	0.28	1	-78.8
Netherlands	1.03	1.10	1.56	39	51.5	0.89	0.67	0.74	18	-16.9
Portugal (2002-2003/2007-2009)	1.61	1.87	2.53	36	57.1	0.47	1.16	0.52	7	10.6
Spain	1.55	2.33	2.93	175	89.0	0.13	0.06	0.13	8	0.0
Sweden	1.01	1.00	1.20	16	18.8	1.09	0.93	0.86	11	-21.1
UK	1.47	1.94	2.49	206	69.4	0.07	0.13	0.07	6	0.0
UK, England and Wales (2001-2004)	1.73	1.92	2.51	184	45.1	0.08	0.12	0.08	6	0.0
UK, Northern Ireland (2001-2004)	1.89	2.68	2.64	6	39.7	0.42	0.19	0.00	0	-100.0
UK, Scotland	2.25	1.85	2.19	16	-2.7	0.07	0.17	0.05	0	-28.6
Other European countries										
Norway	0.82	1.29	2.22	15	170.7	0.31	0.10	0.19	1	-38.7
Switzerland	1.58	2.57	2.29	26	44.9	0.51	0.48	0.42	5	-17.6
American countries										
Argentina	0.16	0.14	0.51	20	218.8	0.16	0.08	0.05	2	-68.8
Brazil	0.35	0.48	0.70	128	100.0	0.60	0.63	0.59	109	-1.7
Canada (2010-2013)	1.33	1.68	2.24	113	68.4	0.25	0.15	0.10	5	-60.0
Chile	0.40	0.68	0.81	15	102.5	0.29	0.21	0.17	3	-41.4
Colombia	0.55	0.82	0.88	37	60.0	0.24	0.18	0.11	4	-54.2
Mexico	0.62	0.66	0.79	72	27.4	0.15	0.11	0.09	8	-40.0
Puerto Rico	1.21	0.93	1.29	5	6.6	0.12	0.00	0.12	1	0.0
USA	1.42	1.65	2.08	885	46.5	0.22	0.19	0.18	79	-18.2
Venezuela (2010-2013)	0.42	0.61	0.77	18	83.3	0.10	0.08	0.05	1	-50.0
Australasian countries										
Hong Kong SAR (2001-2004)	3.20	3.66	3.72	40	16.3	0.27	0.07	0.10	1	-63.0
Israel	1.20	1.45	1.67	13	39.2	0.14	0.03	0.05	0	-64.3
Japan	1.99	1.95	1.91	374	-4.0	3.97	3.49	3.12	630	-21.4
Australia (2006-2009)	1.56	2.04	2.48	73	59.0	0.27	0.16	0.08	2	-70.4
New Zealand (2010-2013)	1.02	2.16	2.22	13	117.6	0.44	0.34	0.44	3	0.0
Women										
European Union countries										
Austria (2002-2004)	1.84	2.01	2.19	26	19.0	1.15	0.75	0.74	9	-35.7
Belgium	1.12	1.50	2.05	32	83.0	0.05	0.01	0.09	1	80.0
Croatia	0.35	0.72	1.50	10	328.6	0.76	0.33	0.57	4	-25.0
Czech Republic	0.53	0.68	0.80	13	50.9	0.78	0.51	0.53	9	-32.1
Denmark	0.45	1.26	1.34	11	197.8	0.39	0.31	0.37	3	-5.1
Finland	1.88	1.91	1.38	12	-26.6	0.21	0.35	0.45	4	114.3
France	1.00	1.65	1.93	179	93.0	0.06	0.06	0.05	5	-16.7
Germany	0.82	1.28	1.58	193	92.7	0.73	0.57	0.89	109	21.9
Hungary	0.41	0.45	0.66	11	61.0	1.03	0.59	1.04	16	1.0
Italy (2003-2004)	0.84	0.98	1.19	106	41.7	0.30	0.22	0.10	9	-66.7
Lithuania (2001-2004)	0.53	0.58	1.26	6	137.7	0.71	0.44	0.25	1	-64.8
Netherlands	0.79	0.76	1.30	32	64.6	0.49	0.47	0.60	15	22.4
Portugal (2002-2003/2007-2009)	0.92	0.77	1.26	20	37.0	0.72	0.33	0.41	6	-43.1
Spain	0.83	1.22	1.53	96	84.3	0.04	0.04	0.04	2	0.0
Sweden	0.85	0.70	1.19	15	40.0	1.29	1.37	0.81	11	-37.2

	ICC					ECC				
	2002	2007	2012	Average deaths	% change (2012/02)	2002	2007	2012	Average deaths	% change (2012/02)
UK	1.32	1.94	2.46	212	86.4	0.08	0.08	0.06	5	-25.0
UK, England and Wales (2001-2004)	1.50	1.91	2.48	188	65.3	0.08	0.08	0.06	4	-25.0
UK, Northern Ireland (2001-2004)	1.97	2.51	2.06	5	4.6	0.11	0.00	0.15	0	36.4
UK, Scotland	2.30	2.03	2.45	19	6.5	0.22	0.08	0.03	0	-86.4
Other European countries										
Norway	0.53	1.33	1.87	12	252.8	0.36	0.03	0.07	0	-80.6
Switzerland	1.09	1.54	1.77	20	62.4	0.50	0.48	0.54	6	8.0
American countries										
Argentina	0.15	0.16	0.36	15	140.0	0.21	0.20	0.04	2	-81.0
Brazil	0.34	0.54	0.71	148	108.8	0.95	0.91	0.78	162	-17.9
Canada (2010-2013)	1.18	1.48	2.13	108	80.5	0.20	0.08	0.08	4	-60.0
Chile	0.52	0.74	0.89	18	71.2	0.24	0.15	0.14	3	-41.7
Colombia	0.87	1.22	1.01	48	16.1	0.30	0.20	0.15	7	-50.0
Mexico	1.00	1.26	1.26	123	26.0	0.31	0.22	0.13	13	-58.1
Puerto Rico	0.75	0.55	0.85	4	13.3	0.11	0.08	0.20	1	81.8
USA	1.13	1.31	1.69	751	49.6	0.16	0.12	0.13	58	-18.8
Venezuela (2010-2013)	0.68	0.65	0.82	20	20.6	0.22	0.12	0.12	3	-45.5
Australasian countries										
Hong Kong SAR (2001-2004)	2.35	2.37	2.49	28	6.0	0.11	0.08	0.04	0	-63.6
Israel	0.63	1.20	1.63	14	158.7	0.11	0.07	0.02	0	-81.8
Japan	1.02	0.99	0.96	190	-5.9	1.91	1.59	1.38	281	-27.7
Australia (2006-2009)	1.43	1.82	2.00	60	39.9	0.20	0.10	0.06	2	-70.0
New Zealand (2010-2013)	1.10	1.80	1.55	9	40.9	0.18	0.38	0.16	1	-11.1

Table 3. Joinpoint analysis for intrahepatic bile ducts at all ages, from 1995 to 2016 (according to data availability), by country and sex

	Men								Women							
	Period 1	**APC 1**	**Period 2**	**APC 2**	**Period 3**	**APC 3**	**Period 4**	**APC 4**	**Period 1**	**APC 1**	**Period 2**	**APC 2**	**Period 3**	**APC 3**	**Period 4**	**APC 4**
Europe																
Austria	2002-2016	2.4[1]							2002-2016	1.4						
Belgium	2000-2015	4.7[1]							2000-2015	3.3[1]						
Czech Republic	1995-2016	2[1]							1995-2016	2.9[1]						
France	2000-2014	5.4[1]							2000-2008	7.5[1]	2008-2014	3.1[1]				
Germany	1998-2007	12.9[1]	2007-2015	0.5					1998-2000	34.1[1]	2000-2009	9.1[1]	2009-2015	-0.8		
Hungary	1996-2016	4.4[1]							1996-2005	-4.3	2005-2016	8.7[1]				
Italy	2003-2012	7[1]	2012-2015	-0.5					2003-2015	5.3[1]						
Netherlands	1996-2016	5.9[1]							1996-2007	0.6	2007-2016	9.9[1]				
Portugal	2002-2014	7.6[1]							2002-2014	7.7[1]						
Spain	1999-2015	5.3[1]							1999-2015	4.6[1]						
Sweden	1997-2016	5.2[1]							1997-2016	5.5[1]						
Switzerland	1995-2015	3.9[1]							1995-2015	3.8[1]						
UK	2000-2015	5[1]							2000-2015	5.8[1]						
The Americas																
Argentina	1997-2007	1.8	2007-2013	22.1[1]	2013-2015	-10.4			1997-2015	9[1]						
Brazil	1996-2015	7.1[1]							1996-2006	10.5[1]	2006-2015	4.6[1]				
Canada	2000-2013	5.8[1]							2000-2013	7.5[1]						
Chile	1997-2015	10.4[1]							1997-2015	9.7[1]						
Colombia	1997-2015	4.8[1]							1997-2005	5.9[1]	2005-2008	16	2008-2011	-9.3	2011-2015	5.8[1]
Mexico	1998-2015	2.5[1]							1998-2015	2.8[1]						
USA	1999-2004	5.1[1]	2004-2007	0.9	2007-2013	4.9[1]	2013-2015	0.7	1999-2015	3.9[1]						
Venezuela	1996-2013	2.9[1]							1996-2013	2.4[1]						
Australasia																
Hong Kong	2001-2013	0.6	2013-2015	-9.3					2001-2015	0.5						
Japan	1995-2001	5.9[1]	2001-2015	0.2					1995-2001	4.8[1]	2001-2015	-0.3				
Australia	1998-2015	4.6[1]							1998-2015	5.4[1]						

APC: annual percent change.

[1]Significantly different from zero ($P < 0.05$).

Figure 1

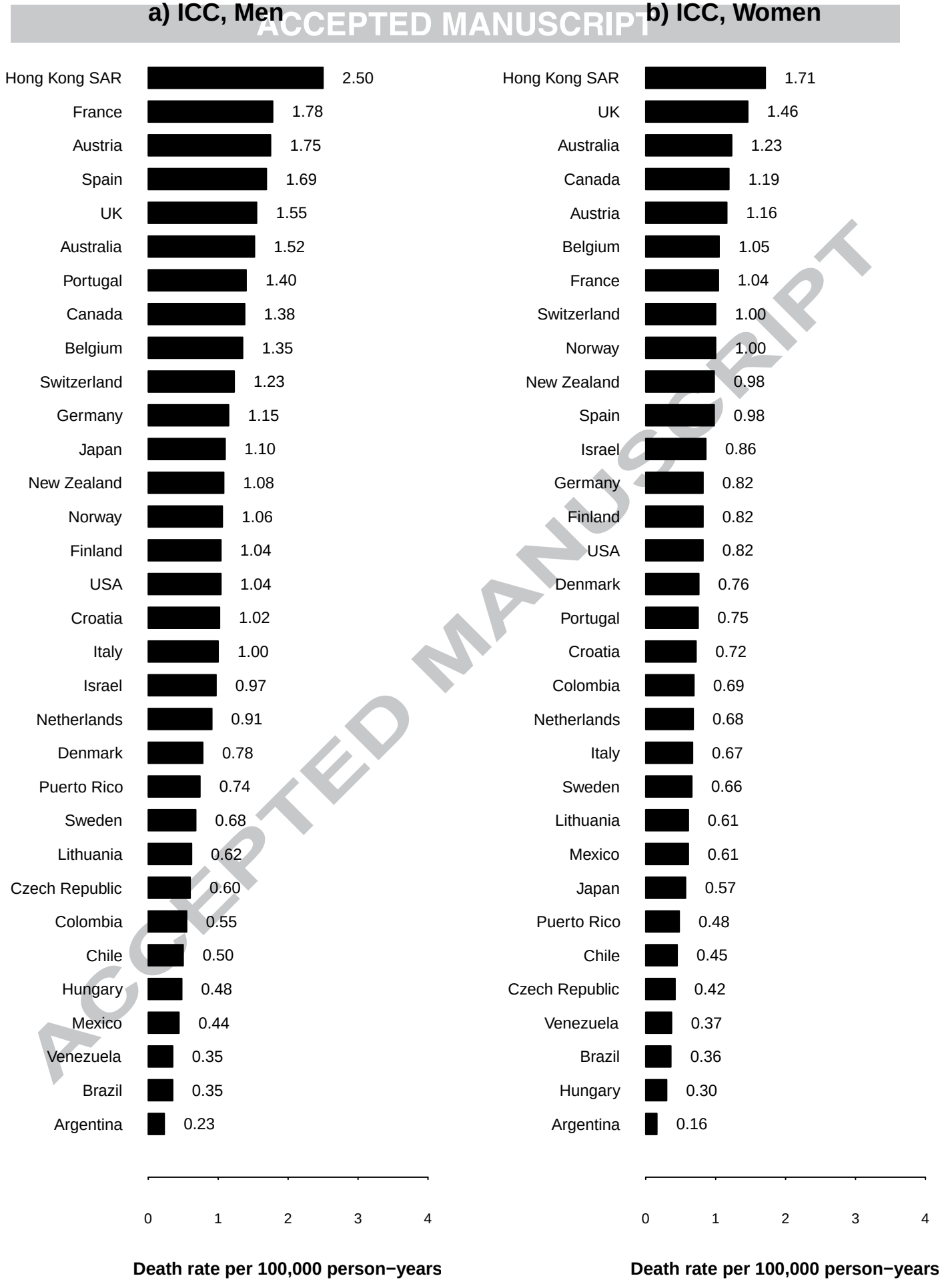


Figure 2

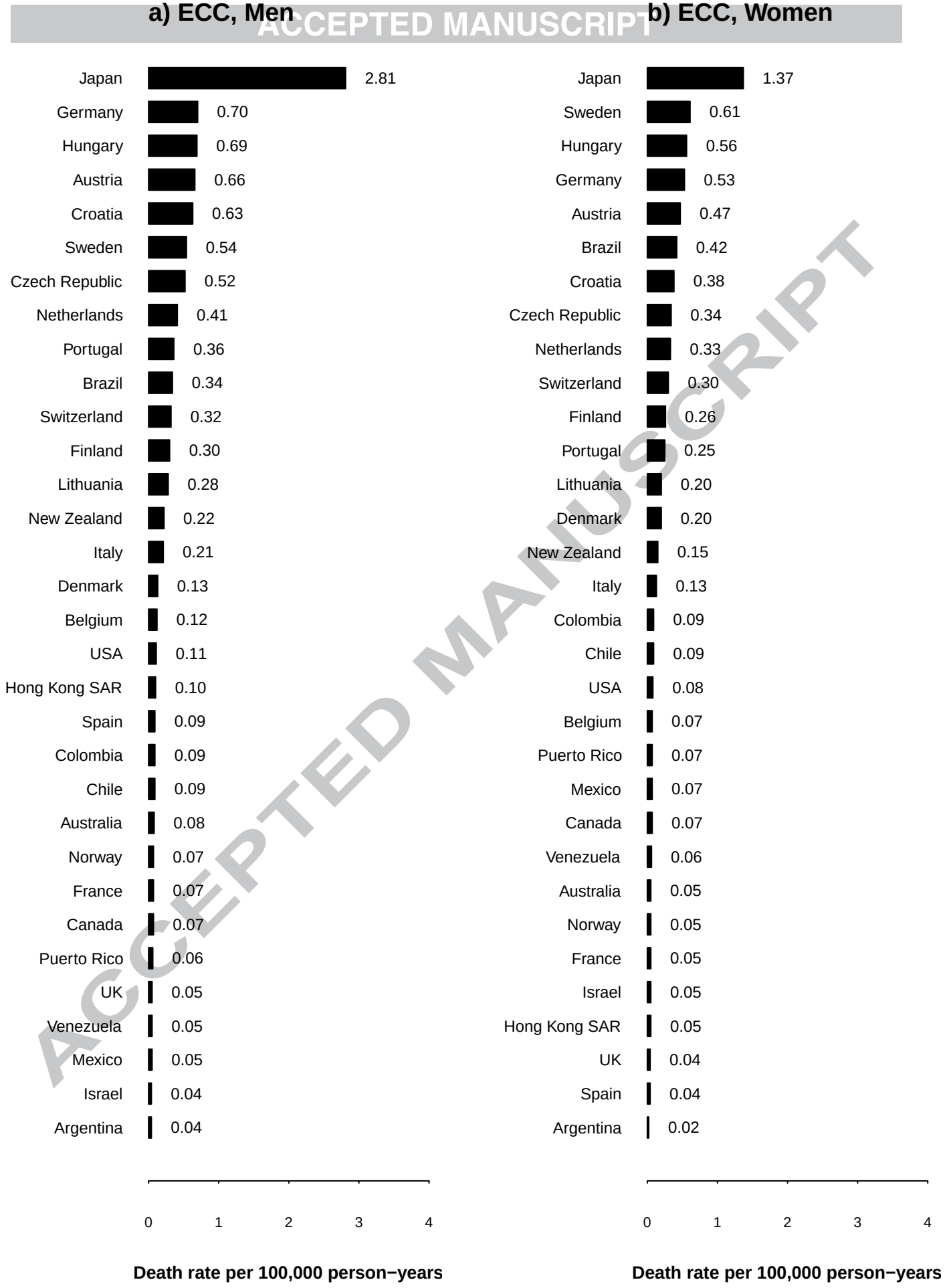
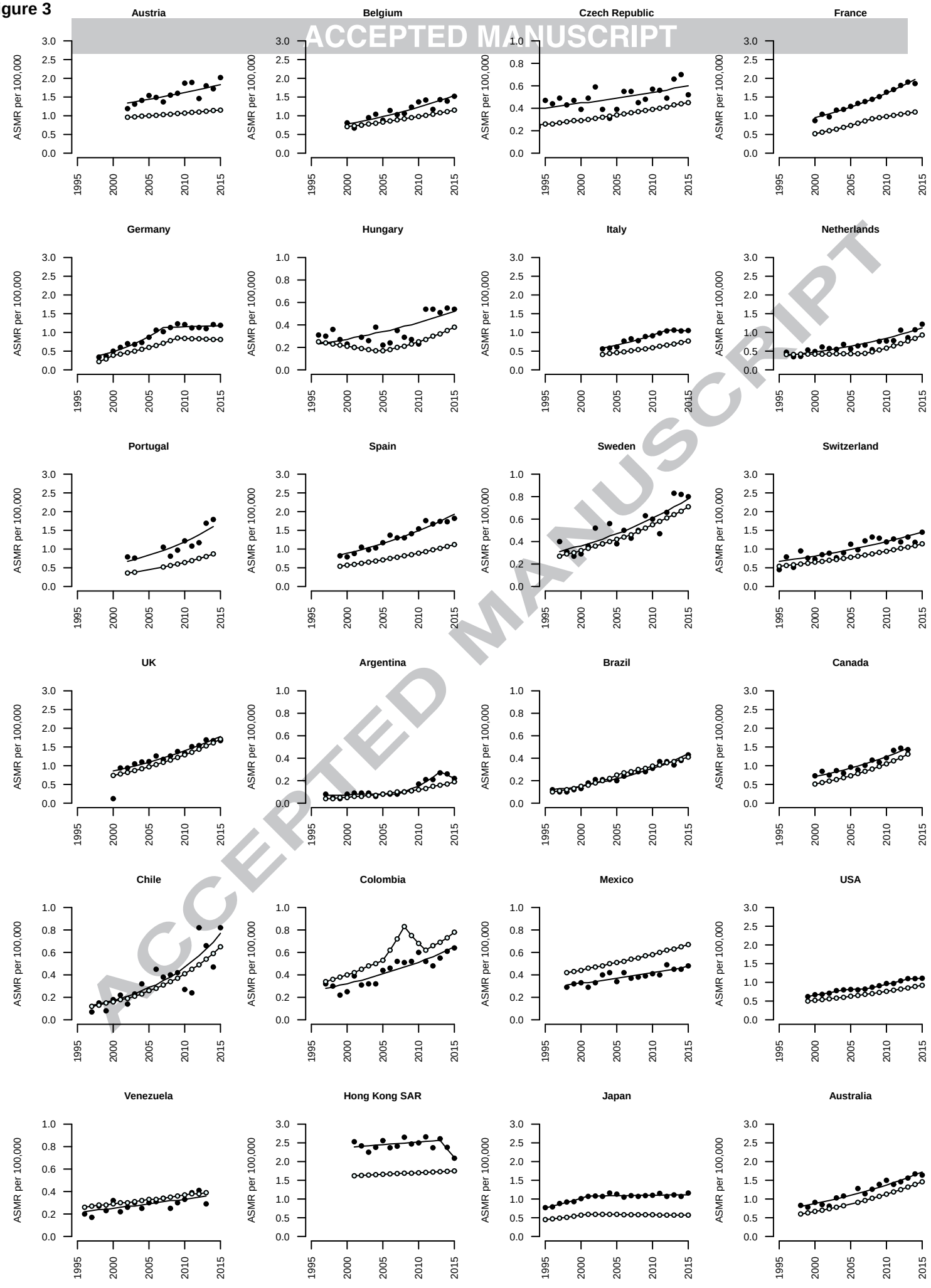


Figure 3



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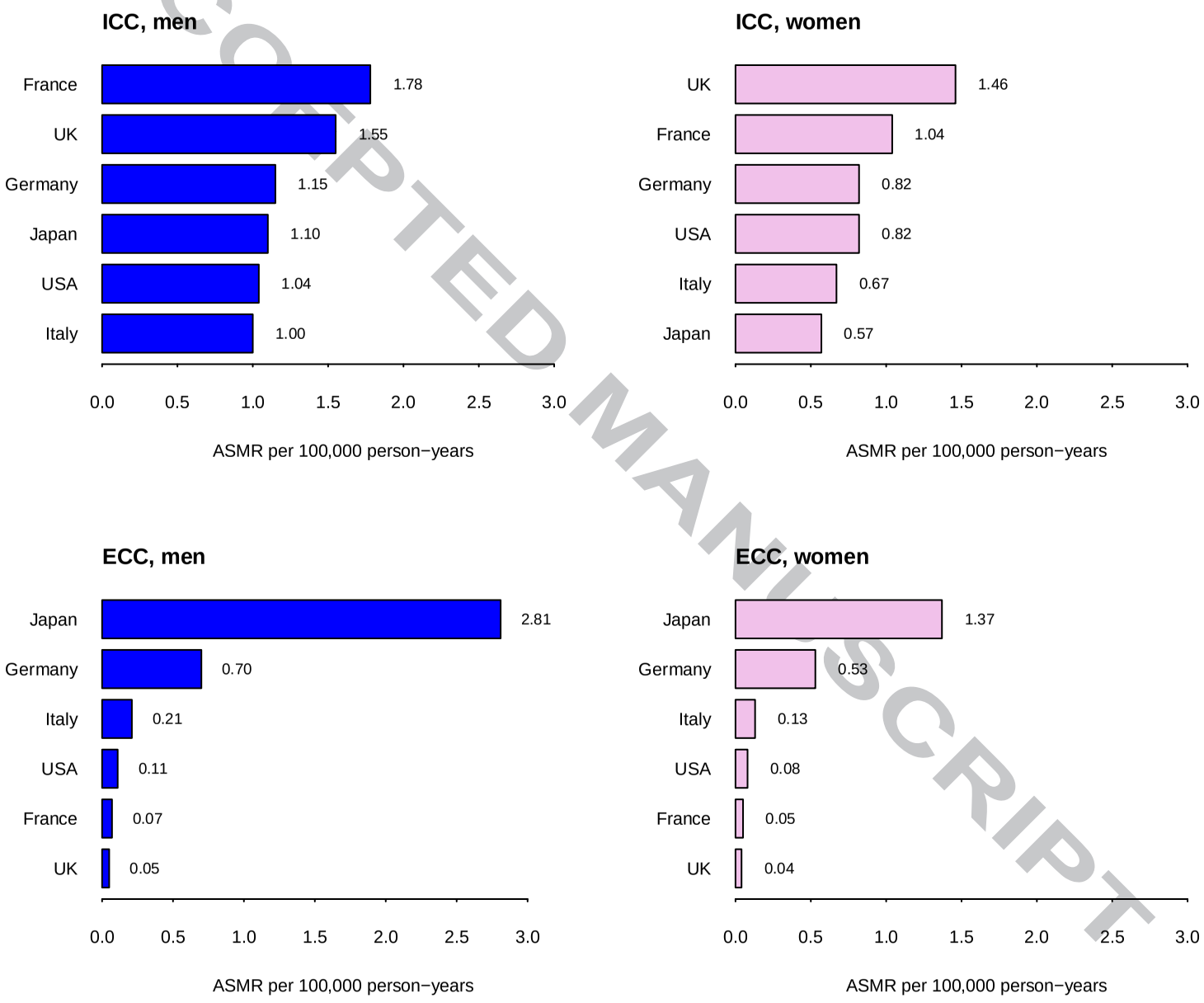
Age−standardized mortality rates (ASMRs) per 100,000 men and women from intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC) in selected major countries, 2015



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Highlights

- Mortality from intrahepatic cholangiocarcinoma (ICC) tended to rise globally
- Mortality from extrahepatic cholangiocarcinoma (ECC) decreased in most countries
- Rates were around 1-2/100,000 for ICC, below 1/100,000 for ECC in most countries
- The rise in ICC mortality is due to increased incidence
- The fall in ECC mortality is due to laparoscopic cholecystectomy

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