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Epidemiology of cholangiocarcinoma

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Abstract

Aim: We aimed to analyze temporal trends in mortality from intrahepatic (ICC) and extrahepatic (ECC) cholangiocarcinoma in selected countries worldwide.

Methods: Official death certification data for ICC and ECC and populations estimates for 29 countries worldwide (17 from Europe, 8 from the Americas, and 4 from Australasia) and for Hong Kong Special Administrative Region of the People's Republic of China (SAR), from 1995 to 2018, were extracted from the World Health Organization and the Pan American Health Organization databases. Age-standardized mortality rates were computed. A joinpoint regression analysis was performed.

Results: In both sexes, ICC mortality rates increased in most countries considered, including the USA, the UK, and Australia; in some countries, including Italy and France, the increasing trends leveled off over the most recent years. In men, around 2016, the highest rates (1.7-2.3/100,000) were observed in Hong Kong SAR, Portugal, France, Spain, Australia, Austria, the UK, and Canada; Latin American countries and some eastern European countries had the lowest rates (0.2-0.8/100,000). A similar pattern was observed in women, but with lower rates (from 1.7/100,000 in Hong Kong SAR to 0.14/100,000 in Argentina). ECC mortality declined in most European and Australasian countries, but it tended to increase in Americas. In both sexes, rates were below 1/100,000 around 2016, with the only exceptions being Japan (2.6/100,000 men and 1.2/100,000 women) and Hungary (1.5/100,000 men and 1.1/100,000 women).

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Conclusion: ICC mortality increased in most areas of the world, likely due to increased prevalence of risk factors and improved cancer recognition and classification. ECC mortality fell in most countries, largely due to the widespread use of cholecystectomy.

Keywords: Cholangiocarcinoma, mortality, epidemiology, temporal trends, intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma

INTRODUCTION

Cholangiocarcinoma is a heterogeneous group of aggressive neoplasms of the biliary duct system, accounting for approximately 3%-5% of all gastrointestinal cancers[1]. The incidence of cholangiocarcinoma is relatively low in most high-income countries (0.3-2 cases per 100,000 people) but much higher (even 40-fold greater) in some regions of Thailand and China[2], where infection with liver flukes - a key determinant of cholangiocarcinoma - is endemic. While surgery and liver transplantation are therapeutic options for a small fraction of patients, the prognosis of cholangiocarcinoma is dramatically poor, with 95% of patients dying within five years[3]; therefore, mortality parallels incidence rates.

Risk factors for the disease include infection with hepatitis C (especially in Western countries, where it is more prevalent) and B (particularly in Asian countries, where it is endemic) viruses, gallstones (cholelithiasis), heavy alcohol use, cirrhosis and alcohol-related diseases, inflammatory bowel disease, diabetes, obesity, smoking, and selected genetic polymorphisms[4,5]; non-alcoholic fatty liver disease (NAFLD) also increases the risk[6]. Aspirin use has been suggested as a protective factor for the disease[7]. Other established risk factors for cholangiocarcinoma are infection with liver flukes (*Opisthorchis viverrini* and *Clonorchis sinensis*), hepatolithiasis, biliary duct cysts (e.g., Caroli's disease), primary sclerosing cholangitis (PSC), and the banned carcinogen agent Thorotrast[4,5]. Hepatolithiasis and, especially, infection with liver flukes account for a large proportion of cases in Southeast Asia, where these conditions are common; PSC is a strong, although rare, predisposing factor in the West[4].

Anatomically, cholangiocarcinoma is classified as intrahepatic cholangiocarcinoma (ICC) when arising from epithelial cells above the hilar junction of bile ducts or extrahepatic cholangiocarcinoma (ECC) when arising below the hilum. Cholangiocarcinomas arising at the liver hilum (i.e., hilar cholangiocarcinoma or Klatskin tumor) are a subset of ECC[8]. ICC represents 10%-15% of all primary liver tumors and is the second primary hepatic malignancy after hepatocellular carcinoma[9]. ICC appears to be the most common biliary tract cancer[10] and accounts for over two-thirds of all cholangiocarcinomas[11]; however, the literature on the topic is ambiguous, with some studies indicating that ECC, including hilar cholangiocarcinoma, accounts for the large majority of all cholangiocarcinoma cases[5].

Although both ICC and ECC are associated with selected biliary tract conditions, hepatitis B and C, and NAFLD, these associations are quantitatively different, which suggests that the two cancers have distinct epidemiology and biology[12].

ICC and ECC have rarely been studied comparatively due to difficulties in diagnosis, registration, and certification. In particular, changes in *International Classification of Disease for Oncology* (ICD-O) coding rules over time have resulted in the misclassification of Klatskin tumors as ICC[13]. However, improvements in diagnosis and death certification validity for these neoplasms have occurred over recent years.

Various studies indicated that the incidence of ICC has increased over the last decades in most countries[14-17]. By contrast, reported trends for ECC have been inconsistent, with some studies showing a decrease or stabilization[15,16] and others an increase[14], possibly at a slower rate compared to ICC[17,18].

As for mortality, a study based on official death certification data showed a global increase in ICC mortality and a decrease or stabilization in ECC mortality over the 1995-2016 period, with wide variations in rates across geographic regions[19]. Recently, a mortality trends study based on American data from 2009 to 2018 showed an increase in ICC mortality over the whole period, but a stable trend for ECC mortality until 2013, followed by an increase thereafter[16].

In the present study, we updated temporal trends in mortality from ICC and ECC in countries worldwide with reliable data from the World Health Organization (WHO) database.

METHODS

We extracted official death certification data from ICC and ECC, separately, from the WHO mortality database[20], from 1995 to 2018 or the last available year 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).

We selected countries according to population size and data coverage, i.e., all countries considered had over two million inhabitants and more than 85% death certification coverage[21]. Thus, we analyzed data from 29 countries worldwide, including 17 countries from Europe [13 of which belonging to the European Union (EU)], 8 countries from the Americas, and 4 from Australasia. We also analyzed data from Hong Kong as a Special Administrative Region of the People's Republic of China (SAR).

We extracted estimates of the resident populations, based on official censuses, from the same WHO database[20]. 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[22].

From the matrices of certified deaths and resident populations, we computed age-specific rates for each five-year age group (from 0-4 to ≥ 85 years and from 0-4 to ≥ 80 years for American countries), country, 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 based on the 1960 world standard population[23].

For nine major countries with a population greater than 40 million (plus Australia), we performed a joinpoint regression analysis of ICC and ECC mortality trends over the period 1995-2018[24]. 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 zero up to a maximum of three inflection points (called "joinpoints")[25]. 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 covariate. We also estimated the average APC over the entire study period.

RESULTS

Table 1 gives the age-standardized mortality rates from ICC and ECC per 100,000 person-years, in 2010-2014 (around 2012) and 2015-2018 (around 2016), the annual average deaths in the last period, and the percent change in rates, according to country and sex.

Table 1. Age-standardized (world population) mortality rates per 100,000 person-years from intrahepatic and extrahepatic cholangiocarcinoma (ICC and ECC) at all ages in selected countries worldwide during 2010-2014 (around 2012) and 2015-2018 (around 2016) (according to data availability), annual average deaths of the latest period, and the corresponding percent change in rates

	Men								Women							
	ICC				ECC				ICC				ECC			
	2012	2016	Average deaths	% change (2016/12)	2012	2016	Average deaths	% change (2016/12)	2012	2016	Average deaths	% change (2016/12)	2012	2016	Average deaths	% change (2016/12)
European Union																
Austria	1.75	1.73	160	-1.1	0.66	0.76	79	15.2	1.16	0.98	114	-15.5	0.47	0.54	77	14.9
Belgium	1.35	1.63	190	20.7	0.12	0.12	16	0.0	1.05	1.03	165	-1.9	0.07	0.05	10	-28.6
Croatia	1.02	1.09	46	6.9	0.63	0.58	28	-7.9	0.72	0.72	47	0.0	0.38	0.40	33	5.3
Czech Republic	0.60	0.67	69	11.7	0.52	0.48	54	-7.7	0.42	0.50	69	19.0	0.34	0.33	49	-2.9
Denmark	0.78	1.01	61	29.5	0.13	0.10	8	-23.1	0.76	0.95	70	25.0	0.20	0.13	10	-35.0
France	1.78	1.89	1336	6.2	0.07	0.05	48	-28.6	1.04	1.14	1156	9.6	0.05	0.04	58	-20.0
Germany	1.15	1.27	1264	10.4	0.70	0.92	1008	31.4	0.82	0.92	1145	12.2	0.53	0.63	968	18.9
Hungary	0.48	0.53	48	10.4	0.69	1.48	133	114.5	0.30	0.37	48	23.3	0.56	1.06	153	89.3
Italy	1.00	1.11	837	11.0	0.21	0.19	173	-9.5	0.67	0.72	700	7.5	0.13	0.11	156	-15.4
Netherlands	0.91	1.24	232	36.3	0.40	0.33	64	-17.5	0.68	1.04	216	52.9	0.33	0.30	71	-9.1
Portugal	1.40	2.12	252	51.4	0.36	0.14	18	-61.1	0.75	0.99	170	32.0	0.25	0.07	13	-72.0
Spain	1.69	1.86	967	10.1	0.09	0.17	100	88.9	0.98	1.09	789	11.2	0.04	0.09	77	125.0
Sweden	0.68	0.81	86	19.1	0.54	0.69	82	27.8	0.66	0.61	83	-7.6	0.61	0.71	102	16.4
Other European countries																
Belarus	.	0.58	39	.	.	0.44	28	.	.	0.36	39	.	.	0.22	25	.
Norway	1.06	1.36	68	28.3	0.07	0.11	5	57.1	1.00	1.01	58	1.0	0.05	0.08	5	60.0
Switzerland	1.23	1.39	125	13.0	0.32	0.36	35	12.5	1.00	0.96	103	-4.0	0.30	0.22	31	-26.7
UK	1.55	1.71	1232	10.3	0.05	0.06	44	20.0	1.46	1.64	1477	12.3	0.04	0.04	37	0.0
American countries																
Argentina	0.23	0.19	53	-17.4	0.04	0.09	24	125.0	0.16	0.14	49	-12.5	0.02	0.07	26	250.0
Brazil	0.35	0.42	470	20.0	0.34	0.30	333	-11.8	0.36	0.40	564	11.1	0.42	0.36	521	-14.3
Canada	1.40	1.69	632	20.7	0.07	0.07	30	0.0	1.22	1.37	615	12.3	0.07	0.06	30	-14.3
Chile	0.50	0.83	107	66.0	0.09	0.12	15	33.3	0.45	0.70	113	55.6	0.09	0.06	11	-33.3
Colombia	0.55	0.58	140	5.5	0.09	0.13	32	44.4	0.69	0.71	215	2.9	0.09	0.13	39	44.4
Mexico	0.44	0.49	286	11.4	0.05	0.06	40	20.0	0.61	0.64	433	4.9	0.07	0.08	56	14.3

Puerto Rico	0.74	0.71	21	-4.1	0.06	0.10	3	66.7	0.48	0.41	19	-14.6	0.07	0.04	2	-42.9
USA	1.04	1.16	3342	11.5	0.11	0.13	390	18.2	0.82	0.98	3311	19.5	0.08	0.10	382	25.0
Australasian countries/regions																
Hong Kong SAR	2.50	2.33	192	-6.8	0.10	0.07	6	-30.0	1.71	1.68	171	-1.8	0.05	0.04	3	-20.0
Israel	0.97	0.87	55	-10.3	0.04	0.08	5	100.0	0.86	0.79	59	-8.1	0.05	0.07	6	40.0
Japan	1.10	1.15	2186	4.5	2.81	2.57	5932	-8.5	0.57	0.58	1579	1.8	1.37	1.19	4698	-13.1
Australia	1.52	1.75	421	15.1	0.08	0.05	13	-37.5	1.23	1.47	406	19.5	0.05	0.02	9	-60.0
New Zealand	1.06	1.30	54	22.6	0.24	0.21	9	-12.5	1.02	0.81	39	-20.6	0.14	0.16	8	14.3

SAR: Special Administrative Region of the People's Republic of China. [a]Years 2015-2016 for Belgium, France, the UK, and New Zealand; Years 2015-2017 for Croatia, Italy, Spain, Canada, Colombia, Mexico, Puerto Rico, the USA, and Hong Kong SAR; and Year 2018 for Belarus.

During 2010-2014, European male mortality rates from ICC ranged between 0.48/100,000 in Hungary and 1.78/100,000 in France. The American rates ranged between 0.23/100,000 men in Argentina and 1.40/100,000 men in Canada. Among the Australasian countries, ICC mortality rates were around 1 death per 100,000 men in Israel, Japan, and New Zealand, with the highest rate observed in Hong Kong SAR at 2.5/100,000 men. Between 2012 and 2016, rates increased in most countries, with the exceptions of Austria, Argentina, Puerto Rico, Hong Kong SAR, and Israel. The greatest rises were observed in Portugal (+51.4%) and the Netherlands (+36.3) among European countries, Chile (+66%), Brazil, and Canada (about +20%) among American countries, and New Zealand (+22.6%). Increases of about 10-11% were observed in Germany, Italy, Spain, the UK, and the USA. In the most recent considered period, the highest rates exceeded 2 deaths per 100,000 men in Hong Kong SAR (2.3) and Portugal (2.1), followed by France, Spain, Austria, and the UK among European countries, where rates were around 1.7-1.9/100,000 men [Figure 1]. The lowest rates were registered in Latin American countries and some eastern European countries (rates of 0.19-0.83/100,000). Rates of around 1 death per 100,000 men were observed in several countries including Germany (1.27), the USA (1.16), Japan (1.15), and Italy (1.11). In men, as well as in women, the differential between the highest and the lowest rates was over 10-fold, possibly attributable to certification bias.

Corresponding female mortality rates from ICC had similar patterns, but with lower values than those of males. Apart from a few exceptions, rates increased from 2010-2014 to 2015-2018 in most countries. The greatest percent changes were observed in the Netherlands (+53%) and Portugal (+32%) among European countries and Chile (+56%). Among countries showing a drop in rates, the largest percent changes were in Austria (-15.5%), Argentina (-12.5%), and Puerto Rico (-14.6%). During 2015-2018, as in men, in women the highest rates were observed in Hong Kong SAR, with a rate of 1.68/100,000, followed by some major European countries, including the UK, France, Spain, the Netherlands, Belgium, and Norway, but also Australia and Canada [Figure 1]. ICC rates reached 0.98/100,000 women in the USA, 0.92 in Germany, and 0.72 in Italy. The lowest rate was registered in Argentina, with 0.14/100,000 women, followed by other Latin American countries as well as some eastern European ones.

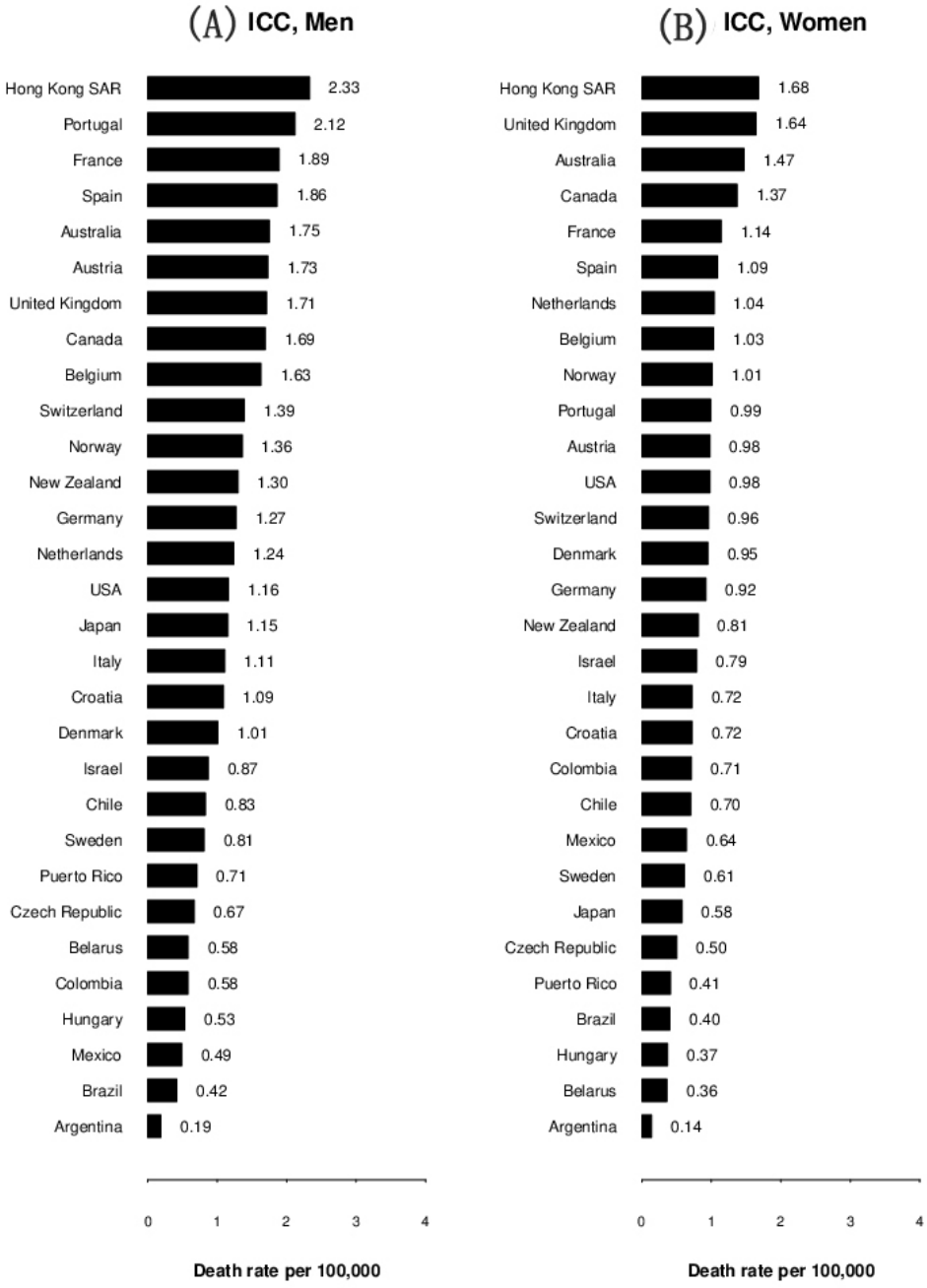

Figure 1. Bar plot for the age-standardized (world population) death rates of intrahepatic cholangiocarcinoma (ICC) around 2016, ordered from the highest to the lowest rate, in men (A) and women (B).

Around 2012, ECC male mortality rates among countries of the EU varied: 0.07/100,000 in France and 0.09/100,000 in Spain, 0.21/100,000 in Italy, 0.54/100,000 in Sweden, and 0.70/100,000 in Germany. Among American countries, Brazil registered the highest rate (0.34/100,000), followed by the USA (0.11). Japan had the highest rate, with 2.8 deaths per 100,000 men. Over the studied period, ECC mortality rates decreased in most European and Australasian countries. In contrast, rates tended to increase in most American countries, except in Brazil. Around 2016, ECC mortality rates were below 1/100,000 men in all countries, with the exception of Japan and Hungary (2.57/100,000 and 1.48/100,000 men, respectively) [Figure 2].

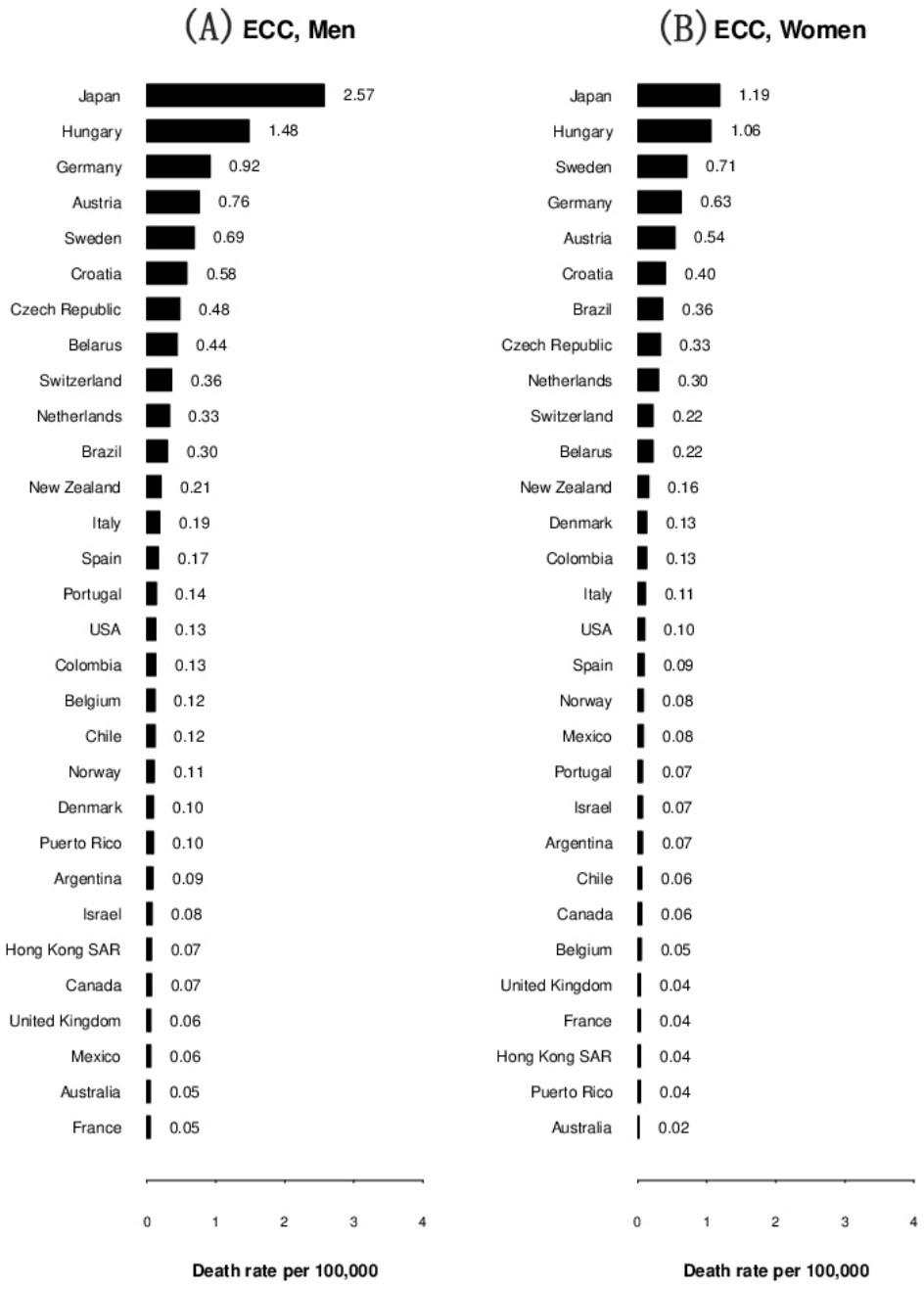

Figure 2. Bar plot for the age-standardized (world population) death rates of extrahepatic cholangiocarcinoma (ECC) around 2016, ordered from the highest to the lowest rate, in men (A) and women (B).

Geographic variations in ECC mortality patterns were observed for women. The most recent highest rates were registered in Japan and Hungary, as for men, although with lower values (1.19/100,000 and 1.06, respectively) [Figure 2].

Table 2 gives the age-standardized mortality rates at ages 45-64 years. Over the two considered periods, ICC mortality rates increased in most countries in both sexes. Around 2016, male rates from about 1.1/100,000

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Table 2. Age-standardized (world population) mortality rates per 100,000 person-years from intrahepatic and extrahepatic cholangiocarcinoma (ICC and ECC) in the age group 45-64 in selected countries worldwide during 2010-2014 (around 2012) and 2015-2018 (around 2016) (according to data availability), annual average deaths of the latest period, and the corresponding percent change in rates.

	Men								Women							
	ICC				ECC				ICC				ECC			
	2012	2016	Average deaths	% change (2016/12)	2012	2016	Average deaths	% change (2016/12)	2012	2016	Average deaths	% change (2016/12)	2012	2016	Average deaths	% change (2016/12)
European Union																
Austria	3.30	3.15	39	-4.5	0.92	1.03	13	12.0	2.19	1.88	24	-14.2	0.74	0.80	10	8.1
Belgium	2.36	2.86	46	21.2	0.15	0.18	3	20.0	2.05	1.82	29	-11.2	0.09	0.03	1	-66.7
Croatia	1.56	2.06	13	32.1	0.91	0.41	3	-54.9	1.50	1.25	8	-16.7	0.57	0.42	3	-26.3
Czech Republic	1.18	1.37	21	16.1	0.83	0.62	10	-25.3	0.80	0.81	13	1.3	0.53	0.58	9	9.4
Denmark	1.36	1.77	15	30.1	0.17	0.19	2	11.8	1.34	1.83	15	36.6	0.37	0.16	1	-56.8
France	3.25	3.41	306	4.9	0.08	0.03	3	-62.5	1.93	1.85	178	-4.1	0.05	0.05	5	0.0
Germany	2.16	2.35	302	8.8	1.01	1.40	179	38.6	1.58	1.81	237	14.6	0.89	0.97	126	9.0
Hungary	1.28	1.14	16	-10.9	1.36	3.08	43	126.5	0.66	0.88	14	33.3	1.04	2.12	34	103.8
Italy	1.95	1.97	171	1.0	0.22	0.23	21	4.5	1.19	1.36	126	14.3	0.10	0.12	12	20.0
Netherlands	1.56	2.22	57	42.3	0.74	0.56	15	-24.3	1.30	2.18	55	67.7	0.60	0.55	14	-8.3
Portugal	2.53	3.93	57	55.3	0.52	0.18	3	-65.4	1.26	1.83	30	45.2	0.41	0.11	2	-73.2
Spain	2.93	3.25	209	10.9	0.13	0.24	15	84.6	1.53	1.94	129	26.8	0.04	0.11	8	175.0
Sweden	1.20	1.43	19	19.2	0.86	0.97	12	12.8	1.19	1.01	13	-15.1	0.81	1.04	14	28.4
Other European countries																
Belarus	.	1.01	13	.	.	0.54	7	.	.	0.65	10	.	.	0.41	6	.
Norway	2.22	2.92	21	31.5	0.19	0.15	1	-21.1	1.87	2.02	14	8.0	0.07	0.07	1	0.0
Switzerland	2.29	2.20	27	-3.9	0.42	0.50	6	19.0	1.77	1.79	22	1.1	0.54	0.22	3	-59.3
UK	2.49	2.84	242	14.1	0.07	0.06	5	-14.3	2.46	2.67	236	8.5	0.06	0.04	4	-33.3
American countries																
Argentina	0.51	0.41	17	-19.6	0.05	0.14	6	180.0	0.36	0.32	15	-11.1	0.04	0.16	8	300.0
Brazil	0.70	0.77	163	10.0	0.59	0.51	109	-13.6	0.71	0.86	205	21.1	0.78	0.67	160	-14.1
Canada	2.30	2.86	154	24.3	0.09	0.10	5	11.1	2.19	2.46	134	12.3	0.07	0.08	5	14.3
Chile	0.81	1.30	28	60.5	0.17	0.11	3	-35.3	0.89	1.39	33	56.2	0.14	0.13	3	-7.1
Colombia	0.88	0.92	44	4.5	0.11	0.21	10	90.9	1.01	1.24	66	22.8	0.15	0.26	14	73.3
Mexico	0.79	0.94	99	19.0	0.09	0.08	8	-11.1	1.26	1.30	149	3.2	0.13	0.14	16	7.7

Puerto Rico	1.29	1.14	5	-11.6	0.12	0.23	1	91.7	0.85	0.34	2	-60.0	0.20	0.00	0	-100.0
USA	2.08	2.31	1040	11.1	0.18	0.21	94	16.7	1.69	2.06	958	21.9	0.13	0.17	81	30.8
Australasian countries/regions																
Hong Kong SAR	3.72	3.31	41	-11.0	0.10	0.14	2	40.0	2.49	2.55	33	2.4	0.04	0.06	1	50.0
Israel	1.67	1.31	11	-21.6	0.05	0.09	1	80.0	1.63	1.51	13	-7.4	0.02	0.14	1	600.0
Japan	1.91	1.91	335	0.0	3.12	2.66	477	-14.7	0.96	0.93	163	-3.1	1.38	1.01	180	-26.8
Australia	2.49	2.79	87	12.0	0.08	0.03	1	-62.5	2.00	2.68	86	34.0	0.06	0.01	0	-83.3
New Zealand	1.98	2.42	15	22.2	0.50	0.32	2	-36.0	1.54	1.77	11	14.9	0.13	0.14	1	7.7

SAR: Special Administrative Region of the People's Republic of China.

in Hungary to 3.9/100,000 in Portugal were found in Europe, from 0.4/100,000 in Argentina to 2.9/100,000 in Canada in Americas, and from 1.9/100,000 in Japan to 3.3/100,000 in Hong Kong SAS in Australasia. Similar rates were observed in women, but with lower values than those in men. Variable patterns emerged for ECC mortality rates, with rates below 1/100,000 for most countries. Among those, Hungary had the worst pattern in both sexes, with the highest rate and the largest increase, from about 1.4/100,000 to 3.1/100,000 men and from about 1/100,000 to 2.1/100,000 women.

Figure 3 gives results from the joinpoint trends in major countries considered; joinpoint indices for separate calendar periods are given in Table 3. Considering the nine major countries worldwide [Figure 3], we observed steady increases in the USA, the UK, and Australia over the entire studied period (APCs of 3.6%, 4.8%, and 4.3% in men and 4%, 5.5% and 4.8% in women, respectively). Japan showed stable trends since the early 2000s in both sexes. In contrast, increasing trends have been slowing down over recent years in the other considered countries, i.e., Brazil, France, Germany, Italy, and Spain.

More favorable patterns emerged for ECC mortality in most countries as compared to those observed for ICC. Of note, we observed a leveling-off trend in the USA in the most recent years (APC: +5.9% during 2013-2017 for men and +4.3% during 2010-2017 for women). Germany presented a decline in rates from 1998 to 2009 (APC: -3%) followed by a rapid but short increase during 2009-2013 (APC: +14.8%), which arrested thereafter.

DISCUSSION

The present global analysis, based on countries with acceptably reliable data, showed rising trends of ICC mortality for both sexes in most of the countries considered, with some decelerations over the most recent years in selected countries; in the USA, the UK, and Australia, ICC mortality trends steadily increased over the whole period. ECC mortality declined in most European and Australasian countries, while it tended to increase in American countries, with the exception of Brazil.

Table 3. Joinpoint analysis for intrahepatic and extrahepatic cholangiocarcinoma (ICC and ECC), from 1995 to 2018 (according to data availability), by country and sex

	Period 1	APC 1	Period 2	APC 2	Period 3	APC 3	AAPC	Period 1	APC 1	Period 2	APC 2	Period 3	APC 3	AAPC
ICC														
Brazil	1996-2011	8.1*	2011-2018	3.2*			6.5*	1996-2006	10.1*	2006-2016	4.7*	2016-2018	-6.1	6.1*
USA	1999-2017	3.6*					3.6*	1999-2017	4*					4*
Japan	1995-2001	5.9*	2001-2017	0.3			1.8*	1995-2000	5.7*	2000-2017	-0.1			1.2*
France	2000-2013	5.6*	2013-2016	-0.2			4.5*	2000-2008	7.5*	2008-2016	3*			5.2*
Germany	1998-2006	14*	2006-2018	1.8*			6.5*	1998-2000	32.3	2000-2008	9.3*	2008-2018	1.8*	7.5*
Italy	2003-2007	11.5*	2007-2017	3.6*			5.8*	2003-2012	6.6*	2012-2017	0.6			4.4*
Spain	1999-2011	6.3*	2011-2017	2.1*			4.9*	1999-2010	5.5*	2010-2017	2.5*			4.4*
UK	2000-2016	4.8*					4.8*	2000-2016	5.5*					5.5*
Australia	1998-2018	4.3*					4.3*	1998-2018	4.8*					4.8*
s														
Brazil	1996-2001	11.1*	2001-2018	-2.3*			0.6	1996-2000	8.7*	2000-2008	-0.8	2008-2018	-4*	-0.6
USA	1999-2008	-5.4*	2008-2013	-1.1	2013-2017	5.9*	-1.8*	1999-2010	-4.6*	2010-2017	4.3*			-1.2*
Japan	1995-2012	-1*	2012-2017	-2.4*			-1.3*	1995-1999	-0.2	1999-2013	-2.1*	2013-2017	-4.1*	-2.1*
France	2000-2016	-3.4*					-3.4*	2000-2016	-2.6*					-2.6*
Germany	1998-2009	-3*	2009-2013	14.8*	2013-2018	3.9	2.1	1998-2009	-5.6*	2009-2012	19.5	2012-2018	2.2	0.2
Italy	2003-2017	-3.5*					-3.5*	2003-2017	-4.7*					-4.7*
Spain	1999-2011	-4.5*	2011-2014	58.7	2014-2017	-0.4	4.6	1999-2011	-5.3*	2011-2015	38.3*	2015-2017	-4.7	3.1
UK	2000-2016	-2.6					-2.6	2000-2016	-4.3*					-4.3*
Australia	1998-2018	-9.3*					-9.3*	1998-2018	-10.6*					-10.6*

APC: Annual percent change; AAPC: average annual percent change; *significantly different from 0 ($P < 0.05$).

We documented a wide variation in ICC mortality rates among the studied countries-from 0.19/100,000 men and 0.14/100,000 women in Argentina to 2.3/100,000 men and 1.7/100,000 women in Hong Kong SAR around 2016. As for ECC, mortality rates were below 0.5/100,000 in most countries in both sexes, with the highest rates observed in Japan (2.6/100,000 men and 1.2/100,000 women). Rates were higher for men compared to women. Most of the variation in the mortality of these cancers worldwide can be accounted for by differences in the geographical distribution of risk factors and, for ECC, the differing prevalence of the use of cholecystectomy. Particularly for ICC, the low rates observed in some countries may be explained by under-certification of these cancers.

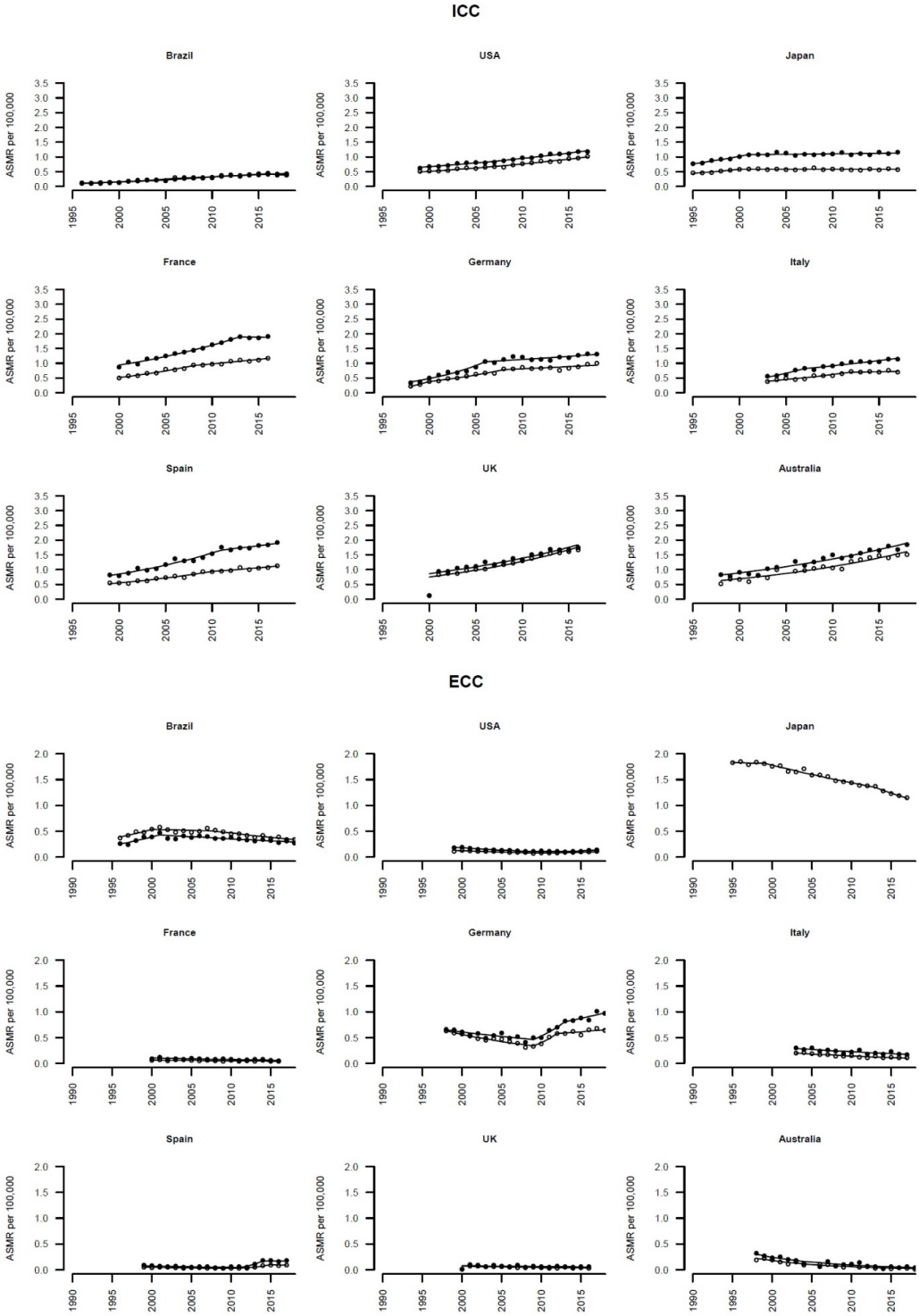

Figure 3. Joinpoint analysis of trends in age-standardized (world population) mortality rates from intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC) for men (filled circles) and women (open circles) at all ages. Data for nine selected major countries, from 1995 to 2018 (according to data availability), are shown.

Differences in mortality trends for ICC and ECC indicate quantitatively different etiologies. Indeed, while

the two tumors actually share most of the risk factors, differences in the magnitude of associations have been observed. Although the evidence is not fully consistent, and only a few investigations directly compared the risk factors of the two tumors within the same study[7,26-28], cirrhosis, chronic hepatitis B and C, heavy alcohol use, diabetes, obesity, and NAFLD and its aggressive phenotype nonalcoholic steatohepatitis (NASH) are more strongly associated with ICC, suggestive of common pathogenesis of ICC and hepatocellular carcinoma; bile duct conditions, including gallstones, tend to be more strongly related to ECC[6,7,29-35]. In particular, in an American study based on 2000-2011 data from the Surveillance, Epidemiology and End Results -Medicare databases, similar risk factors for ICC and ECC were identified, but cirrhosis, HCV infection, alcohol-related disorders, and obesity were more strongly associated with ICC than ECC, while bile duct conditions, chronic pancreatitis, and smoking were more associated with ECC[27]. As for HBV infection, the association was stronger for ICC than ECC. In a meta-analysis published in 2020 and based on case-control studies, biliary duct cysts were the strongest risk factors for both ICC and ECC, increasing the risks, respectively, by 27- and 35-fold[35]. The pooled odds ratios (OR) for the other biliary tract conditions considered were higher for ECC than ICC, being, respectively, 18.6 and 10.1 for choledocholithiasis, 5.9 and 3.4 for cholelithiasis, and 2.9 and 1.8 for cholecystolithiasis. As for the other factors analyzed, the pooled OR were 15.3 for ICC and 3.8 for ECC for cirrhosis, 4.6 for ICC and 2.1 for ECC for HBV infection, 4.3 for ICC and 2.0 for ECC for HCV infection, 3.2 for ICC and 1.8 for ECC for alcohol, and 1.7 for ICC and 1.5 for ECC for diabetes.

The increase in mortality from ICC observed in some Western countries may be, at least in part, the result of a true increase in the incidence of the tumor, in turn explained by the rising prevalence of HCV in selected generations, alcohol drinking, and NAFLD. Indeed, in the USA-as well as in most European and American countries-the prevalence of obesity[36], alcohol use, diabetes, the metabolic syndrome and its hepatic manifestation NAFLD/NASH[37] are all rising. In addition, acute and chronic infections with HCV have dramatically increased over recent calendar periods in the USA[38,39], consistently with the nation's opioid crisis.

Conversely, the decrease in heavy alcohol use documented in the last decades in France and Italy, with the consequent decreasing rates of cirrhosis and alcohol-related chronic liver diseases[40], may explain the leveling off ICC trends observed over the most recent years.

The increase in mortality from ICC could also be due, at least in part, to a diagnostic drift favored by the increased recognition of cholangiocarcinoma subtypes and an enhanced ability to recognize the tumor from liver cancer due to improved diagnostic techniques. In addition, in the past, ICC was frequently misdiagnosed as a metastatic disease from another primary site including breast, lung, pancreas, and gastrointestinal tract[15]. More recently, new tests and criteria have been developed to differentiate ICC from hepatocellular or other metastatic carcinomas[41]. In any case, differentiating intrahepatic and extrahepatic locations may be challenging when the cancer is diagnosed at advanced stages.

In addition, hilar tumors were classified as ICC instead of ECC under prior versions of the ICD-O coding systems. This caused an overestimation of ICC and an underestimation of ECC. However, the ICD-O-3 version, published in 2000 but adopted by different countries at different times, partially rectified the coding allowing the classification of Klatskin tumors as both ICC and ECC. Klatskin tumors are relatively rare and such misclassification should not have a major impact on our findings, especially in consideration that our analysis focused on more recent data. Some studies reported increasing mortality from ICC in recent calendar periods after correctly classifying hilar cholangiocarcinomas as ECC[13,42]. In any case, a certain role of coding misclassification in the observed rates cannot be ruled out.

ICC mortality rates somewhat reflect the trends observed for hepatocellular carcinoma, with steady increases in the USA, the UK, Australia, and Germany[43]. However, hepatocellular carcinoma mortality rates have been declining in France, Italy, and Spain over the last two decades[43], but these are not reflected in ICC death rates. This may reflect the quantitatively different role of major risk factors, in particular HBV and HCV, on hepatocellular carcinoma versus ICC, or improved diagnosis of ICC over recent years.

The favorable trends observed for ECC mortality in several countries worldwide are likely the result of increasing rates of cholecystectomy, with the use of safer procedures such as laparoscopic cholecystectomy for gallstone disease, a major risk factor for biliary tract cancers including ECC and gallbladder cancers[44,45]. Advances in the management of PSC, strongly related to cholangiocarcinoma, especially ECC, in the West may also account for some of the favorable mortality trends.

Among the limitations of the present analysis, misclassification with hepatocellular carcinomas, other liver cancers, gallbladder cancers, and between ICC and ECC may affect the validity of death certification. Notably, hilar tumors ("Klatskin" tumors) tend to invade the liver and are possibly misclassified as ICC, even though they account for a small proportion of ECC[46]. In our analysis, however, we only considered countries with reasonably valid data in terms of coverage of deaths and population size. However, in cirrhotic patients without biopsy, ICC and hepatocellular carcinoma can be misclassified. In addition, problems in tumor registry reporting still make it difficult to accurately estimate the true incidence and mortality of these tumors.

In conclusion, the present analysis confirmed a global increase in ICC mortality and showed more favorable trends for ECC, with, however, some differences across countries. How much of the observed increased mortality from ICC is attributable to a real increase in incidence, rather than improved cancer recognition, and better classification by recent coding systems needs clarification. The widespread fall in ECC mortality largely reflects the wider adoption of (laparoscopic) cholecystectomy for the treatment of gallstones and related bile duct conditions.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and interpretation: La Vecchia C, Negri E

Performed data analysis and made contributions to interpretation: Bertuccio P

Drafted the manuscript and made contributions to interpretation: Turati F

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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