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Epidemiology of biliary tract cancers: an update

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Background: Biliary tract cancer (BTC) is a rare cancer in Europe and North America, characterized by wide geographic variation, with high incidence in some areas of Latin America and Asia.

Materials and methods: BTC mortality and incidence have been updated according to recent data, using joinpoint regression analysis.

Results: Since the 1980s, decreasing trends in BTC mortality rates (age-standardized, world standard population) were observed in the European Union as a whole, in Australia, Canada, Hong Kong, Israel, New Zealand, and the United States, and high-risk countries such as Japan and Venezuela. Joinpoint regression analysis indicates that decreasing trends were more favorable over recent calendar periods. High-mortality rates are, however, still evident in central and eastern Europe (4–5/100 000 women), Japan (4/100 000 women), and Chile (16.6/100 000 women). Incidence rates identified other high-risk areas in India (8.5/100 000 women), Korea (5.6/100 000 women), and Shanghai, China (5.2/100 000 women).

Conclusions: The decreasing BTC mortality trends essentially reflect more widespread and earlier adoption of cholecystectomy in several countries, since gallstones are the major risk factor for BTC. There are, however, high-risk areas, mainly from South America and India, where access to gall-bladder surgery remains inadequate.

Key words: biliary tract cancer, epidemiology, gall-bladder cancer, incidence, mortality, risk factors

introduction

Gall-bladder cancer (GC) is the most common biliary tract cancer (BTC) that also includes extrahepatic bile duct cancer (EBDC) and ampulla of Vater cancer (AVC) [1, 2]. Prognosis of GC is poor, with <10% survival at 5 years [3]. For this reason, GC mortality rates can be taken as a valid indicator of the incidence rates, where the latter are not available or difficult to obtain. GC incidence rates are characterized by a large worldwide variation, being low in several European countries and the United States, relatively high in selected central and eastern European countries, and very high in some countries of Latin America and Asia [4].

In most countries of the European Union (EU), age-standardized mortality rates of GC declined by ∼30% among women and by 10% among men in the 1990s, but mortality from GC was still high in central and eastern Europe [5]. Between the early 1980s and mid-1990s, falls in BTC mortality rates were also observed in the United States and Australia [6]. In contrast, Japan reported a rise of mortality rates for BTC [6]. GC is the first cause of death for cancer among women in Chile [7], and the very high mortality rates did not decline since the 1980s.

These patterns have been related to the prevalence of major risk factors for GC (mainly gallstones) and the implementation of treatments for gall-bladder diseases (mainly cholecystectomy) [4]. To provide an updated picture of this issue, we considered geographic and temporal variations in mortality and incidence rates of BTC in several countries worldwide.

materials and methods

We obtained age-adjusted incidence rates standardized on the basis of the world standard population from 'Cancer Incidence in Five Continents, Volume IX' [8]. Cancer registries were selected if they met the following criteria: (i) data available in Cancer Incidence in Five Continents, Volume IX and (ii) >70 female cases reported. In countries where several registries were available, the registries with the highest number of cases were used.

We obtained official death certification numbers for BTC from 45 countries worldwide for the period 1970–2004 from the World Health Organization (WHO) database [9]. We also obtained estimates of the resident populations, generally on the basis of official censuses, from the same WHO database [9]. We computed age-specific rates for each 5-year age group and calendar year from the matrices of certified deaths and resident populations. We further computed age-standardized rates per 100 000 women at all ages, and truncated 35–74 years using the direct method, on the basis of the world standard population [10]. We obtained mortality rates for the EU as defined since January 2007 (EU 27) by pooling together data from 27 member states when they were available from 1980 to

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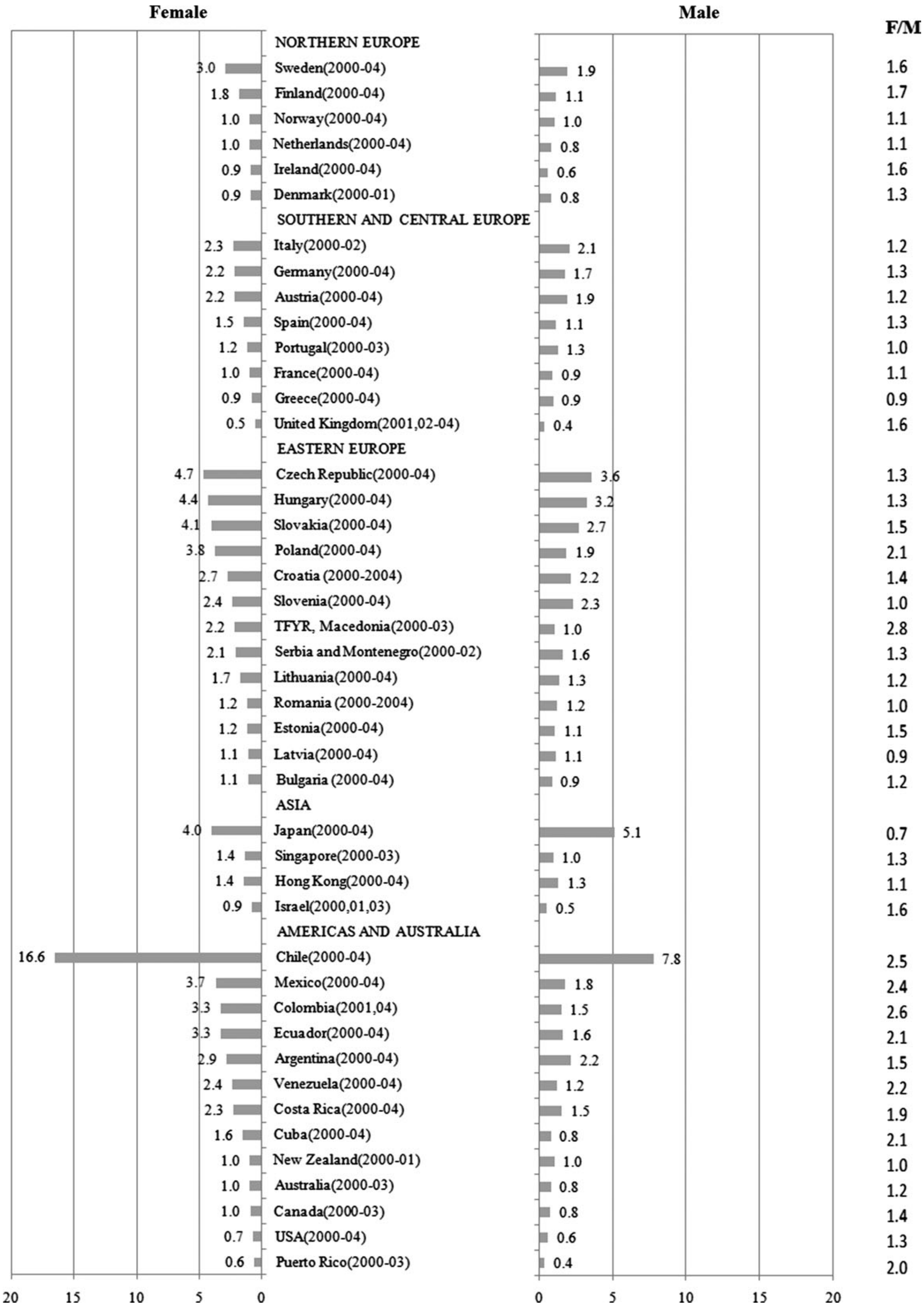

Figure 1. Age-standardized mortality rates per 100 000 (world standard population) and female-to-male ratio for biliary tract cancer in selected areas of the world for the last time period available.

2004, with the exception of Cyprus that presented no data. In the case of missing years in the 2000–2004 quinquennium, mortality and population data from the closest available year were duplicated over the missing data points (Denmark: 2003–2004, Italy: 2003–2004, Luxembourg: 2003, Portugal: 2003–2004, UK: 2000). Data for the EU as defined before May 2004 (EU 15) from 15 member states (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain, Sweden, and UK) were obtained in the same manner.

During the calendar period considered (1970–2004), three different Revisions of the International Classification of Diseases (ICD) were used [11–13]. Classification of cancer deaths was recoded, for all calendar periods and countries, according to the Ninth Revision of the ICD [12]; we considered all BTCs (ICD-9 = 156) including GC, EBDC, AVC, and unspecified cancers of the biliary tract.

We carried out joinpoint regression analysis on mortality data using the joinpoint software from the Surveillance Research Program of the US National Cancer Institute [14]. This analysis allowed us to identify points where a significant change in the linear slope of the trend occurred [15]. In joinpoint analysis, the best fitting points (the 'joinpoints') are chosen where the rate changes significantly. The analysis starts with the minimum number of joinpoints (e.g. zero joinpoints, which is a straight line), and tests whether one or more joinpoints (up to three) are significant and must be added to the model. In the final model, each joinpoint (if any) indicates a significant change in the slope. The estimated annual percent change (APC) is then computed for each of those trends by fitting a regression line to the natural logarithm of the rates using calendar year as a regressor variable [i.e. given $y = a + bx$, where $y = \ln$ (rate) and x = calendar year, the EAPC is estimated as: $100 \times (e^b - 1)$].

results

Figure 1 shows sex-specific, age-standardized death certification rates of BTC and female-to-male (F/M) ratios for the most recent time period available (generally 2000–2004) for selected countries worldwide. The highest mortality rate among women was observed in Chile (16.6/100 000), followed by selected countries in central Europe i.e. the Czech Republic, Hungary, and Slovakia (between 4.1 and 4.7/100 000) and by Japan (4.0/100 000). Among men, the highest rate was observed in Chile (7.8/100 000), followed by Japan (5.1/100 000) and some countries from central Europe (2–3.5/100 000). F/M ratio was higher in central and South America (~2) and around or below unity in Japan (0.8).

Table 1 gives overall and Table 2 truncated (35–74 years) age-standardized mortality rates from BTC in 29 European

Table 1. Overall ASR (world standard population) from biliary tract cancer per 100 000 men and women in selected European countries in 1980–1984, 1990–1994, and 2000–2004 (unless mentioned in parentheses) and the corresponding change in rates

Country	Women								Men							
	1980–1984		1990–1994		2000–2004		% change 1990–1994 versus 1980–1984	% change 2000–2004 versus 1990–1994	1980–1984		1990–1994		2000–2004		% change 1990–1994 versus 1980–1984	% change 2000–2004 versus 1990–1994
	ASR	*n*	ASR	*n*	ASR	*n*			ASR	*n*	ASR	*n*	ASR	*n*		
Austria	4.68	2334	3.41	1791	2.2	1245	−27.09	−35.63	3.07	855	2.36	693	1.9	678	−23.10	−19.39
Bulgaria (1980–1982, 1984)	1.33	388	1.17	482	1.07	506	−11.93	−8.74	0.69	171	0.71	245	0.89	317	3.63	25.00
Croatia	–	–	2.55	616	2.74	756	–	7.64	–	–	1.78	270	2.16	385	–	21.72
Czech Republic	–	–	6.17	3353	4.7	2891	–	−23.84	–	–	4.12	1407	3.57	1415	–	−13.33
Czech Republic and Slovakia (1980–1982)	5.38	6933	5.62	6849	4.51	3967	4.44	−19.65	3.42	3039	3.55	2802	3.30	1863	3.68	−6.94
Denmark (2000–2001)	2.19	752	1.31	486	0.9	119	−40.14	−31.34	1.28	315	0.97	254	0.83	84	−23.58	−15.36
Estonia (1994)	–	–	1.57	23	1.22	109	–	−22.53	–	–	0.73	6	1.06	51	–	46.42
Finland	2.82	880	2.73	802	1.8	639	−3.42	−33.88	1.62	293	1.61	287	1.14	261	−0.84	−29.03
France	1.74	5565	1.55	5842	1	4315	−10.76	−35.95	1.28	2667	1.35	3211	0.91	2651	5.66	−32.38
Germany	4.59	20 426	3.52	19 447	2.22	13 753	−12.18	−36.82	2.57	6484	2.29	7091	1.73	6699	1.63	−24.43
Greece	0.5	217	0.77	431	0.87	621	55.32	13.44	0.3	114	0.65	297	0.94	527	118.46	45.64
Hungary	8.14	4415	6.61	3914	4.36	2928	−18.88	−34.01	3.53	1324	3.61	1335	3.24	1302	2.26	−10.42
Ireland	1.45	174	1.22	185	0.92	161	−15.69	−24.73	1.22	132	0.79	98	0.6	80	−35.23	−24.45
Italy (2000–2002)	2.28	6460	2.72	9497	2.34	5915	19.44	−13.94	1.6	3270	2.04	5027	2.05	3675	27.71	0.79
Lithuania (1993–1994)	–	–	1.89	136	1.72	357	–	−9.05	–	–	1.25	52	1.32	149	–	5.64
The Netherlands	3.26	2243	1.88	1543	1	946	−42.20	−46.65	2.2	1048	1.39	761	0.84	541	−37.01	−39.06
Norway	1.01	309	1.08	274	1.03	288	7.79	−4.88	0.85	178	0.9	174	1	205	6.13	10.99
Portugal (1984, 2000–2003)	1.34	115	1.45	821	1.23	658	8.51	−15.34	1.32	84	1.38	521	1.25	487	4.61	−9.14
Slovakia (1992–1994)	–	–	4.38	604	4.1	1076	–	−6.45	–	–	2.61	247	2.68	448	–	2.54
Slovenia	–	–	3.59	363	2.4	308	–	−33.28	–	–	2.28	136	2.29	174	–	0.38
Spain	1.81	3092	2	4490	1.47	4340	10.43	−26.76	1.06	1307	1.27	1989	1.14	2359	20.31	−10.31
Sweden	3.63	2260	3.81	2108	2.96	1795	5.11	−22.29	2.09	1047	2.21	959	1.92	912	5.85	−13.16
Switzerland	2.23	1024	1.64	897	–	–	−26.34	–	1.52	438	1.03	406	–	–	−32.17	–
UK (2001–2004)	1.06	3455	0.76	2705	0.53	1600	−28.25	−29.95	0.94	2060	0.63	1552	0.36	842	−33.60	−41.86
EU 15	2.43	49 763	2.22	50 783	1.57	40 661	−8.71	−29.28	1.54	20 716	1.55	23 086	1.28	22 728	0.25	17.03
EU 27	2.63	56 894	2.41	59 213	1.86	57 747	−8.38	−22.98	1.62	23 236	1.63	26 274	1.41	30 052	0.62	−13.67

ASR, age-standardized mortality rates; *n*, number of deaths (average per year of the corresponding period).

Table 2. ASR (world standard population) from biliary tract cancer per 100 000 men and women aged 35–74 years in selected European countries in 1980–1984, 1990–1994, and 2000–2004 (unless mentioned in parentheses) and corresponding change in rates

Country	Women								Men							
	1980–1984		1990–1994		2000–2004		% change	% change	1980–1984		1990–1994		2000–2004		% change	% change
	ASR	*n*	ASR	*n*	ASR	N*n*	1990–1994 versus 2000–2004	1980–1984 versus 2000–2004	ASR	*n*	ASR	*n*	ASR	*n*	1990–1994 versus 2000–2004	1980–1984 versus 2000–2004
Austria	8.57	1064	6.19	755	4.02	486	−27.75	−35.11	5.64	467	4.4	389	3.35	352	−22.03	−23.87
Bulgaria (1980–1982, 1984)	3.01	285	2.74	369	2.26	315	−9.19	−17.26	1.51	128	1.55	183	1.87	213	2.81	20.71
Croatia	–	–	5.26	378	5.25	400	–	−0.20	–	–	3.64	185	3.82	231	–	5.05
Czech Republic	–	–	11.97	1782	8.8	1378	–	−26.53	–	–	8.28	946	6.69	845	–	−19.13
Czech Republic and Slovakia (1980–1982)	10.91	4116	11.09	3712	8.56	1965	1.68	−22.82	6.75	2049	7.23	1877	6.31	1141	7.18	−12.76
Denmark (2000–2001)	5.28	396	3.11	233	1.74	53	−41.07	−44.07	2.89	190	2.19	138	1.31	35	−24.12	−40.08
Estonia (1994)	–	–	4.04	20	2.55	64	–	−36.80	–	–	2.02	6	1.67	27	–	−17.40
Finland	6.47	460	5.32	398	3.28	266	−17.78	−38.26	3.48	176	2.9	164	1.94	135	−16.58	−32.99
France	3.29	2414	2.67	2185	1.67	1477	−18.98	−37.28	2.36	1421	2.42	1666	1.53	1176	2.76	−36.71
Germany	8.69	9966	6.49	8388	4.01	5594	−14.31	−38.31	4.8	3638	4.15	3940	3.2	3952	−1.94	−22.97
Greece	1.08	144	1.54	236	1.59	312	42.12	3.54	0.61	73	1.28	173	1.74	283	110.13	36.22
Hungary	16.63	2674	12.49	2073	8.2	1437	−24.93	−34.31	6.91	853	7.09	860	6.17	773	2.56	−12.87
Ireland	3.17	113	2.41	97	1.76	77	−23.86	−27.19	2.54	92	1.35	50	1.12	45	−46.63	−17.54
Italy (2000–2002)	4.72	3900	5.28	4663	4.38	2559	11.87	−17.03	3.3	2232	3.88	2869	3.78	1933	17.53	−2.65
Lithuania (1993–1994)	–	–	4.04	88	3.57	211	–	−11.58	–	–	2.75	39	2.86	108	–	4.13
The Netherlands	6.08	1094	3.5	702	1.84	401	−42.38	−47.43	4.23	630	2.62	448	1.68	336	−37.94	−36.02
Norway	2.27	138	2.19	133	1.98	113	−3.37	−9.52	1.95	105	1.67	90	1.85	98	−14.31	10.81
Portugal (1984, 2000–2003)	2.92	75	2.69	408	2.3	303	−7.96	−14.26	3.01	67	2.78	336	2.21	244	−7.70	−20.43
Slovakia (1992–1994)	–	–	9.04	382	8.07	587	–	−10.72	–	–	5.37	171	5.43	296	–	1.28
Slovenia	–	–	6.92	200	4.24	136	–	−38.75	–	–	4.1	82	4.1	107	–	−0.04
Spain	3.69	1831	3.71	2130	2.51	1639	0.66	−32.29	2.1	849	2.38	1151	1.98	1105	13.34	−16.89
Sweden	8.64	1125	7.65	971	5.88	773	−11.50	−23.11	4.71	560	4.19	497	3.68	456	−10.90	−12.17
Switzerland	5.24	488	3.96	385	–	–	−24.57	–	3.47	258	2.42	196	–	–	−30.26	–
UK (2001–2004)	2.12	1812	1.47	1186	1.03	699	−30.94	−30.01	1.9	1356	1.16	863	0.65	409	−38.59	−44.36
EU15	4.78	25 279	4.15	22 616	2.85	16 539	−13.03	−31.26	3.00	12 406	2.88	12 873	2.35	11 977	−4.08	−18.47
EU27	5.22	29 619	4.57	27 300	3.50	25 735	−12.45	−23.43	3.17	14 079	3.07	15 007	2.63	16 642	−2.94	−14.38

ASR, age-standardized mortality rates; *n*, number of deaths (average per year of the corresponding period).

countries and the EU overall in periods 1980–1984, 1990–1994, and 2000–2004.

From the early 1980s to the early 2000s in the EU as a whole, BTC mortality decreased by ∼30% for women and 13% for men; the decrease was stronger in the last decade. Almost all European countries presented decreasing trends among women in recent years, with the exception of Croatia and Greece. Most countries reporting high BTC mortality rates, including the Czech Republic, Hungary, and Slovakia, showed decreasing mortality trends. Among men, decreasing mortality trends were weaker, and almost half of the countries did not report decreasing trends. Major decreases were observed in France and The Netherlands, as well as in high-risk countries such as the Czech Republic, Hungary, and Slovakia. Truncated BTC mortality rates at ages 35–74 were much higher and reductions were greater than for all ages (Table 2), being >20% for women and >10% for men in at least half of the countries.

Tables 3 and 4 report BTC mortality rates in selected countries of the Americas and Australia for the periods 1980–1984, 1990–1994, and 2000–2004 for all ages and truncated at ages 35–74 respectively. Falls in BTC mortality were observed in Australia, Canada, New Zealand, the United States, Hong Kong, Israel, and Japan both in women and men. The only exception was Singapore where BTC mortality increased by ∼25% among women, but the mortality rate was low. Truncated mortality rates at ages 35–74 for the same countries were much higher, and decreasing trends were between 14% and 30% in the Americas and Australia and between 19% and 56% in Asia (Table 4).

Figure 2 for women (A) and men (B) and Table 5, give the results from joinpoint regression analyses in selected European countries. For women, almost all countries showed decreasing BTC mortality rates, with the exception of Greece that showed an increase, however, starting from low rates. The largest recent annual decreases were observed in Austria (−10.7% APC), and France (−6.5% APC). In the EU as a whole, BTC mortality rates decreased by 2.5% APC from 1987 to 2004, reaching 1.9/100 000 women. For men, BTC mortality rates decreased in

Table 3. Overall ASR (world standard population) from biliary tract cancer per 100 000 men and women in selected countries worldwide in 1980–1984, 1990–1994, and 2000–2004 (unless mentioned in parentheses) and the corresponding change in rates

Country	Women								Men							
	1980–1984		1990–1994		2000–2004		% change	% change	1980–1984		1990–1994		2000–2004		% change	% change
	ASR	*n*	ASR	*n*	ASR	*n*	1990–1994 versus 1980–1984	2000–2004 versus 1990–1994	ASR	*n*	ASR	*n*	ASR	*n*	1990–1994 versus 1980–1984	2000–2004 versus 1990–1994
Americas and Australia																
Australia (2000–2003)	1.6	922	1.34	1014	1	785	−16.28	−25.31	1.33	582	0.96	568	0.8	504	−28.08	−16.14
Canada (1970–2003)	1.74	1692	1.31	1666	0.96	1225	−25.08	−26.22	1.4	1017	1.05	1016	0.76	768	−25.33	−27.28
Chile (1983, 1997–2004)	14.01	720	–	–	16.57	6726	–	–	5.62	230	–	–	7.76	2437	–	–
New Zealand (2000–2001)	1.68	201	1.2	183	1.01	72	−28.89	−15.61	1.26	117	1.06	123	1	56	−15.65	−6.04
United States	1.28	13 907	0.96	12 328	0.74	10 895	−25.39	−23.06	1.04	7781	0.77	6962	0.6	6583	−25.77	−22.72
Venezuela	2.63	103	–	–	2.38	968	–	–	2.07	72	–	–	1.17	408	–	–
Asia																
Hong Kong SAR (1981, 1983–1984)	1.88	220	2.19	361	1.43	455	16.13	−34.43	3.09	277	2.46	331	1.30	339	−20.50	−47.03
Israel (2000–2001, 2003)	2.35	283	1.65	287	0.85	140	−29.64	−48.46	1.03	117	0.91	139	0.51	60	−11.26	−44.17
Japan	4.91	22 204	5.27	36 346	4.02	42 661	7.26	−23.76	4.70	15 939	5.77	27 807	5.10	36 026	22.82	−11.66
Singapore (1981–1984, 2000–2003)	1.00	38	1.10	77	1.37	111	10.00	24.82	0.99	33	1.02	63	0.96	67	2.75	−5.71

ASR, age-standardized mortality rates; *n*, number of deaths (average per year of the corresponding period).

Table 4. Age-adjusted (world standard population) mortality rates from biliary tract cancer per 100 000 men and women aged 35–74 in selected countries worldwide in 1980–1984, 1990–1994, and 2000–2004 (unless mentioned in parentheses) and corresponding change in rates

Country	Women								Men							
	1980–1984		1990–1994		2000–2004		% change	% change	1980–1984		1990–1994		2000–2004		% change	% change
	ASR	*n*	ASR	*n*	ASR	*n*	1990–1994 versus 1980–1984	2000–2004 versus 1990–1994	ASR	*n*	ASR	*n*	ASR	*n*	1990–1994 versus 1980–1984	2000–2004 versus 1990–1994
Americas and Australia																
Australia (2000–2003)	3.2	539	2.6	517	1.91	360	−18.66	−26.61	2.64	397	1.79	334	1.53	280	−32.17	−14.23
Canada (1970–2003)	3.23	874	2.5	827	1.87	576	−22.42	−25.45	2.68	635	1.9	566	1.34	390	−29.12	−29.70
Chile (1983, 1997–2004)	31.59	540	–	–	35.62	4540	–	–	11.59	168	–	–	14.48	1547	–	–
New Zealand (2000–2001)	3.35	115	2.24	89	1.93	32	−32.92	−14.02	2.47	78	1.95	70	2.03	35	−21.16	4.07
United States	2.43	7011	1.81	5626	1.42	4852	−25.73	−21.66	1.94	4587	1.42	3760	1.08	3277	−27.13	−23.52
Venezuela	5.85	81	–	–	4.74	658	–	–	4.14	53	–	–	2.13	270	–	–
Asia																
Hong Kong SAR (1981, 1983–1984)	3.86	144	3.96	187	2.28	175	2.79	−42.43	6.55	226	4.67	221	2.10	169	−28.76	−55.01
Israel (2000–2001, 2003)	5.07	202	3.29	160	1.45	57	−35.11	−55.81	1.94	71	1.56	66	0.93	30	−19.40	−40.23
Japan	9.97	14 199	9.39	17 335	6.17	14 150	−5.86	−34.30	9.32	10 682	10.43	15 946	8.45	17 512	11.92	−18.92
Singapore (1981–1984, 2000–2003)	2.01	26	2.48	57	2.68	68	23.76	7.79	2.36	29	1.89	40	2.03	50	−19.83	7.14

ASR, age-standardized mortality rates; *n*, number of deaths (average per year of the corresponding period).

most European countries, with the exception of Greece. In the EU as a whole, BTC mortality rates decreased annually by 1.4% APC from 1987 to 2004, reaching 1.4/100 000 men. Truncated mortality rates showed a similar pattern of trends, with higher values for both women and men.

Figure 3 for women (A) and men (B) and Table 6 give the joinpoint regression analysis for BTC mortality for selected countries from other areas of the world. For women, most of the countries from the Americas and Asia showed decreasing trends, with the exception of Singapore, where mortality rates increased annually by 1.4% APC. Truncated mortality rates were also increasing in Mexico by ∼1% APC. The largest annual decreases were observed in Israel (−5.4% APC), Canada (−3.1% APC), Australia, the United States and Japan (−2.7% APC). For men,

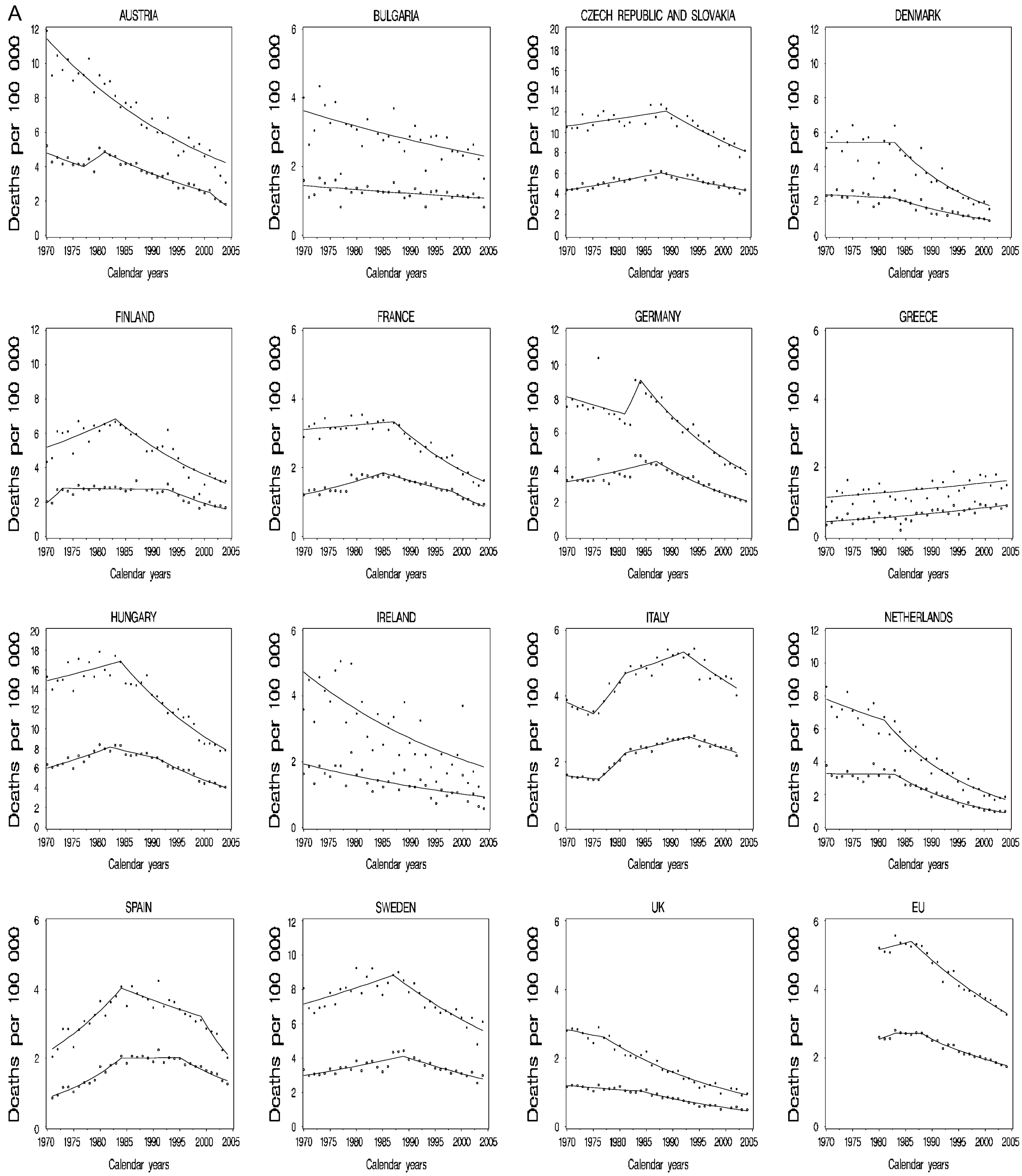

Figure 2. Joinpoint regression analysis for biliary tract cancer in women (A) and men (B) from 15 selected European countries and European Union as a whole, 1970–2004. All ages, empty circles; truncated at 35–74 years, X symbol.

decreasing BTC mortality rates were observed in almost all countries, except Mexico and Singapore where BTC mortality rates increased.

Figure 4 shows BTC incidence rates in 47 selected cancer registries worldwide by anatomical subsite and gender. In most countries, the incidence of BTC was below 10/100 000 for GC and 4/100 000 for EBDC. For women, the highest GC incidence rate was observed in Valdivia, Chile (25.3/100 000 women), followed by New Delhi, India (8/100 000 women), Trujillo, Peru (6.3/100 000 women), and Quito, Ecuador (4.9/100 000 women). High GC incidence rates were also reported in cancer registries of the Czech Republic and Slovakia in

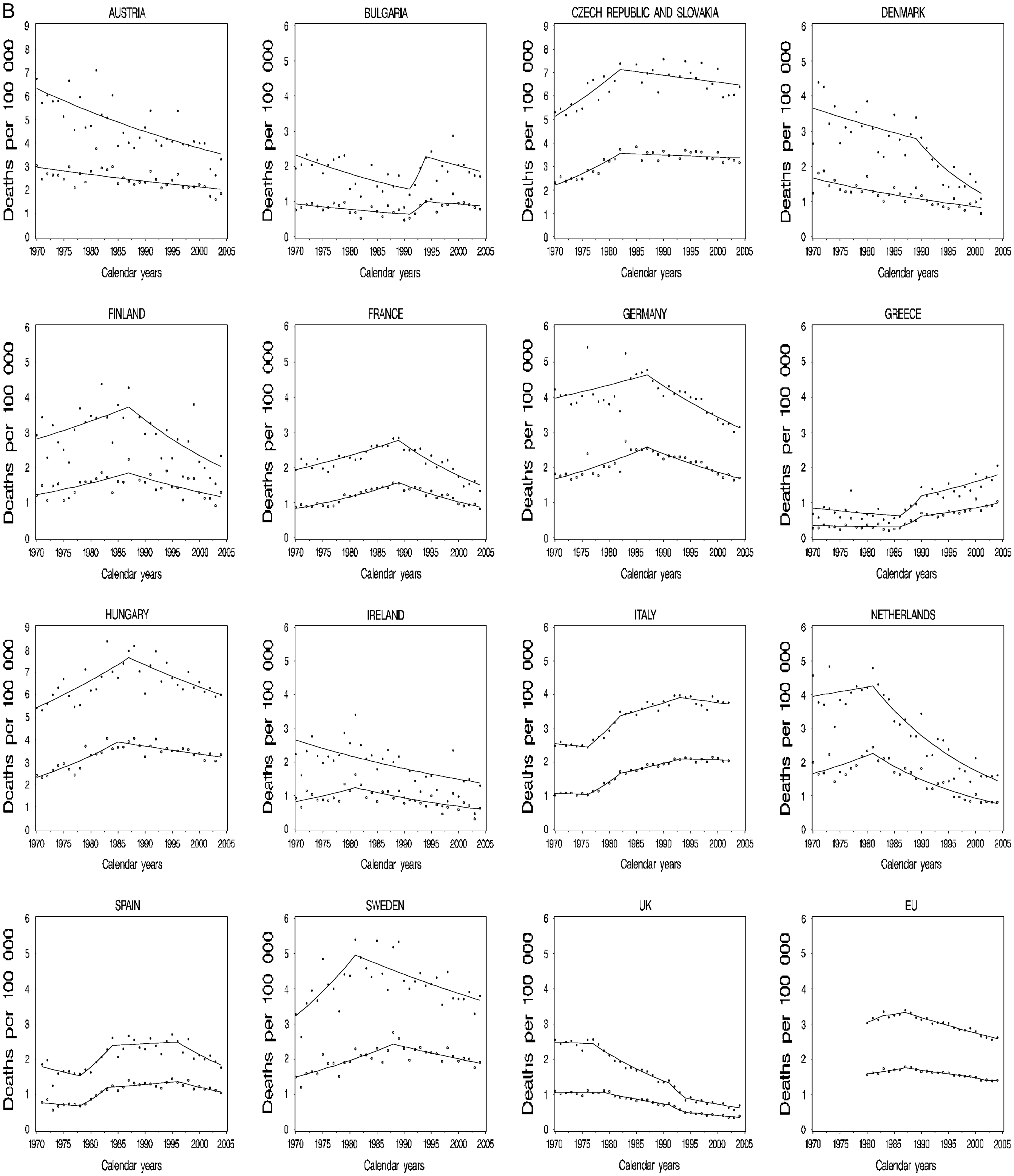

Figure 2. *Continued.*

central Europe (∼4/100 000 women). GC incidence rates among men were lower and characterized by less geographic variation, but the highest GC incidence rate was also observed in Valdivia, Chile (9.3/100 000 men). The F/M incidence ratio was generally above unity. EBDC incidence rates were very low, with the exception of some Asian countries (Japan and Korea) where incidence rates among men were ∼3/100 000. The F/M ratio was generally below unity. Incidence rates of the AVC were even lower (<1/100 000), with the exception of Valdivia, Chile, Quito, Ecuador, and Korea. Incidence rates

Table 5. Joinpoint regression analysis for biliary tract cancer mortality at all ages and truncated 35–74 years for selected European countries, 1970–2004

Country	Women								Men							
	Trend 1		Trend 2		Trend 3		Trend 4		Trend 1		Trend 2		Trend 3		Trend 4	
	Years	APC	Years	APC	Years	APC	Years	APC	Years	APC	Years	APC	Years	APC	Years	APC
All ages																
Austria	1970–1977	−2.5[a]	1977–1981	4.9	1981–2001	−3.2[a]	2001–2004	−10.7	1970–2004	−1.1[a]	–	–	–	–	–	–
Bulgaria	1970–2004	−0.8[a]	–	–	–	–	–	–	1970–1991	−1.8[a]	1991–1994	16.3	1994–2004	−1.2	–	–
Czech Republic	1986–2004	−2.5[a]	–	–	–	–	–	–	1986–2004	−0.9[a]	–	–	–	–	–	
Denmark	1970–1983	−0.6	1983–2001	−4.8[a]	–	–	–	–	1970–2001	−2.2[a]	–	–	–	–	–	–
Finland	1970–1973	12.9	1973–1993	−0.1	1993–2004	−4.8[a]	–	–	1970–1987	2.4[a]	1987–2004	−2.6[a]	–	–	–	–
France	1970–1985	2.8[a]	1985–1998	−2.6[a]	1998–2004	−6.5[a]	–	–	1970–1989	3.4[a]	1989–2004	−3.8[a]	–	–	–	–
Germany	1970–1987	1.9[a]	1987–2004	−4.2[a]	–	–	–	–	1970–1987	2.5[a]	1987–2004	−2.4[a]	–	–	–	–
Greece	1970–2004	2.2[a]	–	–	–	–	–	–	1970–1986	−0.7	1986–1990	19.0	1990–2004	3.3[a]	–	–
Hungary	1970–1982	2.5[a]	1982–1991	−1.6[a]	1991–2004	−4.1[a]	–	–	1970–1985	3.5[a]	1985–2004	−1.0[a]	–	–	–	–
Ireland	1970–2004	−2.1[a]	–	–	–	–	–	–	1970–1981	3.7	1981–2004	−3.1[a]	–	–	–	–
Italy	1970–1976	−1.1	1976–1981	9.1[a]	1981–1993	1.6[a]	1993–2002	−2.1[a]	1970–1976	−0.5	1976–1982	8.3[a]	1982–1993	2.1[a]	1993–2002	−0.2
The Netherlands	1970–1983	−0.0	1983–2004	−5.9[a]	–	–	–	–	1970–1981	2.8[a]	1981–2004	−4.6[a]	–	–	–	–
Norway	1970–2002	0.5	2002–2004	−29.6	–	–	–	–	1970–2002	1.4[a]	2002–2004	−21.9	–	–	–	–
Portugal	1984–2003	−1.1[a]	–	–	–	–	–	–	1984–2003	−0.1	–	–	–	–	–	–
Slovakia	1992–2004	−0.8	–	–	–	–	–	–	1992–2004	0.1	–	–	–	–	–	–
Slovenia	1985–2004	−2.9[a]	–	–	–	–	–	–	1985–2004	−0.3	–	–	–	–	–	–
Spain	1971–1984	6.4[a]	1984–1995	0.0	1995–2004	−4.4[a]	–	–	1971–1978	−1.6	1978–1983	12.3[a]	1983–1996	0.9	1996–2004	−2.9[a]
Sweden	1970–1989	1.7[a]	1989–2004	−2.5[a]	–	–	–	–	1970–1988	2.7[a]	1988–2004	−1.5[a]	–	–	–	–
Switzerland	1970–1994	−2.1[a]	–	–	–	–	–	–	1970–1982	1.3	1982–1994	−3.7[a]	–	–	–	–
UK	1970–1984	−1.0[a]	1984–2004	−3.8[a]	–	–	–	–	1970–1979	0.0	1979–1991	−3.3[a]	1991–1994	−11.2	1994–2004	−3.4[a]
EU	1980–1987	0.8	1987–2004	−2.5[a]	–	–	–	–	1980–1987	1.6[a]	1987–2004	−1.4[a]	–	–	–	–
Ages 35–74																
Austria	1970–2004	−2.1[a]	–	–	–	–	–	–	1970–2004	−1.1[a]	–	–	–	–	–	–
Bulgaria	1970–2004	−1.3[a]	–	–		–	–	–	1970–1991	−2.5[a]	1991–1994	19.1	1994–2004	−1.9	–	–
Czech Republic	1986–2004	−3.0[a]	–	–	–	–	–	–	1986–2004	−1.2[a]	–	–	–	–	–	–
Denmark	1970–1983	−0.0	1983–2001	−6.1[a]	–	–	–	–	1970–1989	−1.4[a]	1989–2001	−6.5[a]	–	–	–	–
Finland	1970–1983	2.1[a]	1983–2004	−3.7[a]	–	–	–	–	1970–1987	1.6	1987–2004	−3.5[a]	–	–	–	–
France	1970–1987	0.4	1987–2004	−4.2[a]	–	–	–	–	1970–1989	1.9[a]	1989–2004	−4.0[a]	–	–	–	–
Germany	1970–1981	−1.1	1981–1984	8.4	1984–2004	−4.2[a]	–	–	1970–1987	0.9[a]	1987–2004	−2.2[a]	–	–	–	–
Greece	1970–2004	1.0[a]	–	–	–	–	–	–	1970–1986	−1.9	1986–1990	17.9	1990–2004	2.9[a]	–	–
Hungary	1970–1984	0.8[a]	1984–2004	−3.7[a]	–	–	–	–	1970–1987	2.0[a]	1987–2004	−1.4[a]	–	–	–	–
Ireland	1970–2004	−2.7[a]	–	–	–	–	–	–	1970–2004	−1.9[a]	–	–	–	–	–	–
Italy	1970–1975	−1.8	1975–1981	5.1[a]	1981–1992	1.1[a]	1992–2002	−2.2[a]	1970–1976	−0.6	1976–1982	5.5[a]	1982–1993	1.3[a]	1993–2002	−0.5
The Netherlands	1970–1981	−1.6[a]	1981–2004	−5.6[a]	–	–	–	–	1970–1981	0.6	1981–2004	−4.6[a]	–	–	–	–
Norway	1970–2002	−0.1	2002–2004	−35.1	–	–	–	–	1970–2002	0.3	2002–2004	−20.8	–	–	–	–
Portugal	1984–2003	−1.4[a]	–	–	–	–	–	–	1984–2003	−0.9	–	–	–	–	–	–
Slovakia	1992–2004	−1.3	–	–	–	–	–	–	1992–2004	0.2	–	–	–	–	–	–
Slovenia	1985–2004	−3.6[a]	–	–	–	–	–	–	1985–2004	0.0	–	–	–	–	–	–
Spain	1971–1984	4.5[a]	1984–1999	−1.5[a]	1999–2004	−8.1[a]	–	–	1971–1978	−2.1	1978–1984	7.7[a]	1984–1996	0.3	1996–2004	−3.7[a]
Sweden	1970–1987	1.2[a]	1987–2004	−2.6[a]	–	–	–	–	1970–1981	3.9[a]	1981–2004	−1.3[a]	–	–	–	–
Switzerland	1970–1994	−1.8[a]	–	–	–	–	–	–	1970–1994	−1.3[a]	–	–	–	–	–	–
UK	1970–1977	−1.1	1977–2004	−3.7[a]	–	–	–	–	1970–1977	−0.2	1977–1991	−4.2[a]	1991–1994	−12.2	1994–2004	−3.6[a]
EU	1980–1986	0.7	1986–2004	−2.6[a]	–	–	–	–	1980–1987	1.0[a]	1987–2004	−1.5[a]	–	–	–	–

[a]Significantly different from 0 ($P < 0.05$).
APC, annual percent of change.

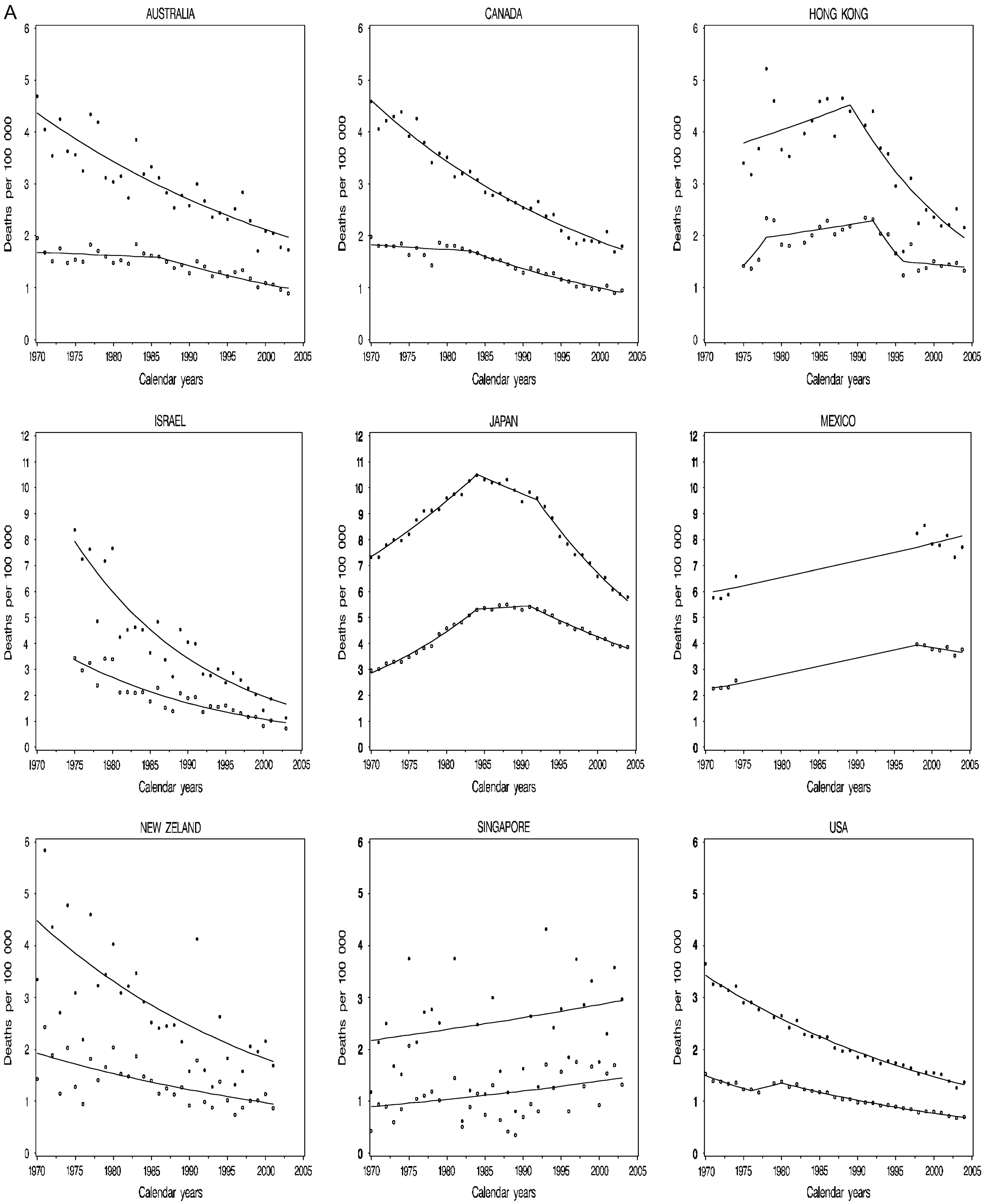

Figure 3. Joinpoint regression analysis for biliary tract cancer in women (A) and men (B) from nine selected countries worldwide, 1970–2004. All ages, empty circles; truncated at 35–74 years, X symbol.

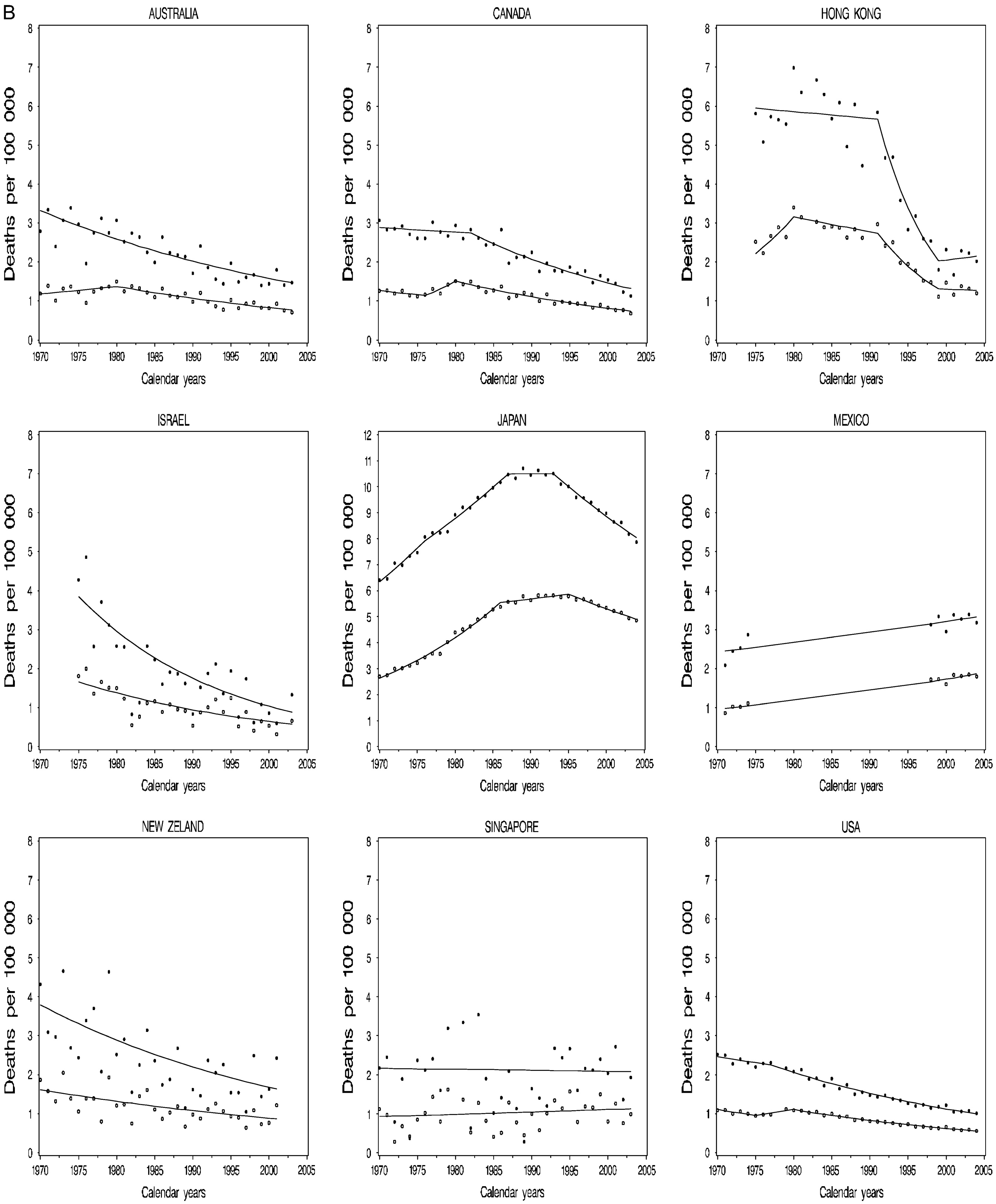

Figure 3. *Continued.*

Table 6. Joinpoint regression analysis for biliary tract cancer mortality at all ages and truncated 35–74 years for selected countries worldwide, 1970–2004

Country	Women								Men							
	Trend 1		Trend 2		Trend 3		Trend 4		Trend 1		Trend 2		Trend 3		Trend 4	
	Years	APC	Years	APC	Years	APC	Years	APC	Years	APC	Years	APC	Years	APC	Years	APC
All ages																
Australia	1970–1986	−0.3	1986–2003	−2.7[a]	–	–	–	–	1970–1980	1.5	1980–2003	−2.4[a]	–	–	–	–
Canada	1970–1983	−0.5	1983–2003	−3.1[a]	–	–	–	–	1970–1976	−1.7	1976–1980	7.1	1980–2003	−3.0[a]	–	–
Mexico	1971–1998	2.0	1998–2004	−1.2	–	–	–	–	1971–2004	1.9[a]	–	–	–	–	–	–
New Zealand	1970–2001	−2.2[a]	–	–	–	–	–	–	1970–2001	−1.9[a]	–	–	–	–	–	–
United States	1970–1976	−3.5[a]	1976–1980	2.8	1980–2004	−2.7[a]	–	–	1970–1975	−2.8[a]	1975–1980	2.9[a]	1980–2004	−2.8[a]	–	–
Venezuela	1970–2004	−1.0[a]	–	–	–	–	–	–	1970–2004	−1.6[a]	–	–	–	–	–	–
Hong Kong	1970–1978	11.0[a]	1978–1992	1.1	1992–1996	−9.9	1996–2004	−0.9	1970–1980	7.2[a]	1980–1991	−1.2	1991–1999	−8.8[a]	1999–2004	−0.5
Israel	1975–2003	−4.4[a]	–	–	–	–	–	–	1975–2003	−3.7[a]	–	–	–	–	–	–
Japan	1970–1984	4.5[a]	1984–1991	0.3	1991–2004	−2.7[a]	–	–	1970–1986	4.7[a]	1986–1995	0.6[a]	1995–2004	−1.9[a]	–	–
Singapore	1970–2003	1.4[a]	–	–	–	–	–	–	1970–2003	0.5	–	–	–	–	–	–
Ages 35−74																
Australia	1970–2003	−2.3[a]	–	–	–	–	–	–	1970–2003	−2.4[a]	–	–	–	–	–	–
Canada	1970–2003	−2.9[a]	–	–	–	–	–	–	1970–1982	−0.4	1982–2003	−3.4[a]	–	–	–	–
Mexico	1971–2004	0.9[a]	–	–	–	–	–	–	1971–2004	0.9[a]	–	–	–	–	–	–
New Zealand	1970–2001	−2.9[a]	–	–	–	–	–	–	1970–2001	−2.6[a]	–	–	–	–	–	–
United States	1970–2004	−2.7[a]	–	–	–	–	–	–	1970–1977	−1.2	1977–2004	−2.9[a]	–	–	–	–
Venezuela	1970–2004	−1.7[a]	–	–	–	–	–	–	1970–2004	−2.5[a]	–	–	–	–	–	–
Hong Kong	1970–1974	18.5	1974–1989	1.2	1989–2004	−5.4[a]	–	–	1970–1972	63.6	1972–1991	−0.3	1991–1999	−12.0[a]	1999–2004	1.1
Israel	1975–2003	−5.4[a]	–	–	–	–	–	–	1975–2003	−5.1[a]	–	–	–	–	–	–
Japan	1970–1984	2.6[a]	1984–1992	−1.2[a]	1992–2004	−4.2[a]	–	–	1970–1976	3.7[a]	1976–1987	2.5[a]	1987–1993	0.0	1993–2004	−2.3[a]
Singapore	1970–2003	0.9	–	–	–	–	–	–	1970–2003	−0.1	–	–	–	–	–	–

[a]Significantly different from 0 ($P < 0.05$).

APC, annual percent of change.

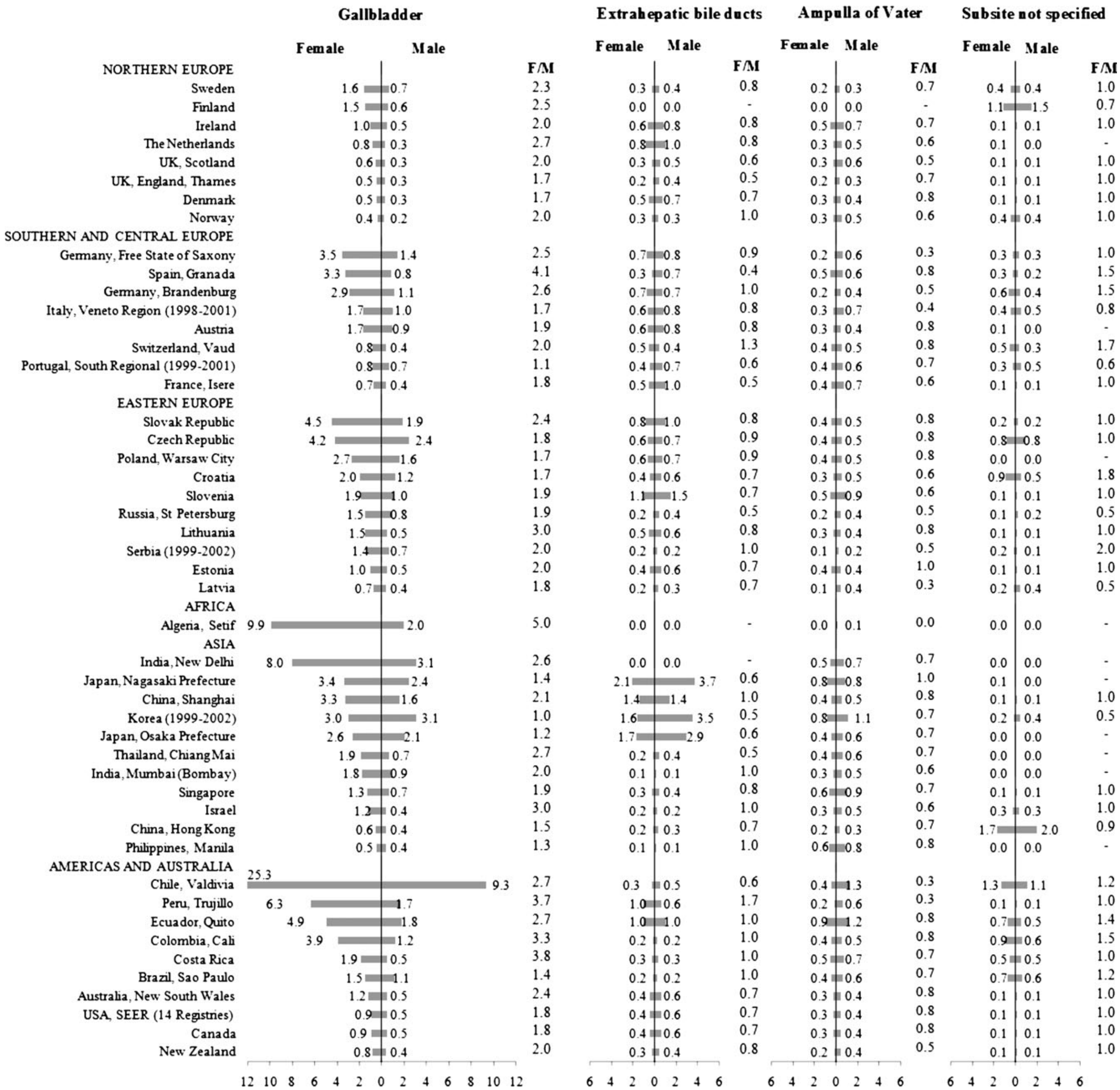

Figure 4. Age-standardized incidence rates per 100 000 (world standard population) and female-to-male ratio for biliary tract cancer by subsite and gender: gall-bladder cancer, extrahepatic bile duct cancer, ampulla of Vater, and 'subsite not specified' in selected areas of the world, 1998–2002.

for BTC classified as 'subsite not specified' were also very low (0.5/100 000 women and men) in most cancer registration areas.

discussion

The present comprehensive update shows a substantial decline in mortality rates for BTC in several areas of the world. Decreases were spread to wider areas and were generally stronger in the last decade. The decreases were more favorable in middle-aged women. Despite declining rates, a high mortality area is still evident in central and eastern Europe, including the Czech Republic, Hungary, and Slovakia. Outside the EU, decreasing trends in BTC mortality rates were observed in most countries. High mortality rates are still present in Japan, but falls were observed in the last decade. Countries from Latin America including Venezuela, Mexico, and Chile are still characterized by high or extremely high BTC mortality.

The decline of BTC mortality can be partly explained by changes in diagnosis and certification of the disease, following the introduction of more sophisticated diagnostic techniques such as ultrasound-computerized transaxial tomography, retrograde cholangiography, fine needle biopsy, and others [2, 5, 16].

Incidence of BTC showed a worldwide picture similar to that of mortality, with other high-risk areas in the north of India and in Algeria for GC and in Japan, China, and Korea for EBDC as well as GC. The high incidence rates observed in New

Delhi, India, and Shanghai, China, are of concern because of the increasing trends observed from the 1970s in some areas of these countries [17–19].

History of gallstones is the major risk factor for BTC and particularly for GC [3, 4, 20]. The association with gallstones is stronger for GC than for other subsites [21–24]. The etiology of cholesterol gallstones (that account for the majority of all gallstones) is thought to involve an interaction of genetic and other factors (age, female gender, obesity, multiple pregnancies, a family history of gallstones, and low levels of physical activity) that are similar to those associated with GC. High triglycerides and low high-density lipoprotein have been associated with gallstones, and a case-control study from China supported a role of serum lipids also in BTC, especially for EBDC and GC [25]. Consequently, there is a strong inverse association between GC incidence and mortality rates and the number of cholecystectomies in Chile [26], Great Britain [27, 28], Canada, and the United States [27]. The widespread adoption of cholecystectomy is likely to be the most relevant factor for the declining mortality in Europe [5]. A study on the US National Cancer Data Base reported no substantial differences in diagnosis, treatment, and survival of patients before (1989–1990) and after (1994–1995) the introduction of laparoscopic cholecystectomy in the United States [29] and a similar picture was observed in Taiwan [30]. These data support the introduction of laparoscopic cholecystectomy as a substitute for the conventional open cholecystectomy for gallstones. A study from Canada, reporting an increased rate of elective cholecystectomy after the introduction of laparoscopic technique in 1991, observed an overall reduction in the incidence of severe gallstone diseases that was attributable to a reduction in acute cholecystitis [31]. In Chile, peaks of mortality rates were observed in poorer areas with lower access to medical care and characterized by rural populations and the Mapuche ethnic mixture [7, 32]. Inadequate access to gall-bladder surgery may have affected the high GC mortality rates [7, 26, 32]. In India, prophylactic cholecystectomy has been suggested for young healthy women from high-risk regions whenever they are diagnosed with asymptomatic gallstones [19]. Criteria for cholecystectomy may include the type of stones, and genetic markers that determine the highest risk of developing GC [33].

Distinct etiologies have been hypothesized according to the different anatomic subsites of BTC [20, 23, 34]. Obesity and overweight are major risk factors for gallstones, and the association of BTC, and particularly of GC, with obesity is one of the strongest observed for any cancer site [35]. The association was stronger for women than for men [4, 36]. Overweight and obesity have become more common in most populations over recent decades. Still, assuming that gallstones are the major pathogenic link between obesity and BTC, it is not surprising that increases in obesity did not imply rises in BTC and GC rates. In a Japanese cohort study [22], the association between overweight, obesity, and BTC declined after allowance for cholelithiasis.

Chronic infection, inflammation, and irritation of the gall-bladder and bacterial degradation of bile may contribute to the carcinogenesis of gall-bladder. Most studies have shown associations with *Salmonella (S.) typhi* and *paratyphi*, and various *Helicobacter* species [4, 37]. An Indian study on 65 GC cases analyzed bile culture for the presence of Vi antibody for chronic typhoid carrier state and found that chronic bacterial infection of the bile leading to the production of carcinogenic precursors might be one of the etiological factors in the pathogenesis of GC and hence a target for its prevention [38].

Also hepatitis B and C viruses have been associated with EBDC in a case–control study from Shanghai, China [39], but no association was found for other subsites. Improving control of these infections may therefore account for at least part of the favorable trends observed.

Anomalous pancreatobiliary duct junction, a congenital malformation of the biliary tract more frequent in some Asian populations, such as Japan and possibly China, has been associated with GC in these areas [1], but possible associations have also been suggested in western populations from the United States [40].

Other risk factors, such as diet, alcohol and tobacco consumption, and hormonal and reproductive history for women, have been associated to BTC risk but the available information is limited, and any inference on their role on incidence and mortality rates is therefore difficult.

Patients with GC usually are in an advanced stage of disease at the time of diagnosis, except for a subset of patients who are diagnosed incidentally at the time of elective cholecystectomy for biliary colic and cholelithiasis [41]. Resection remains in fact the only cure for patients with GC [42]. The staging of GC at diagnosis is a critical component of the management of this neoplasm and is particularly related to survival of patients after GC diagnosis: >60% of GC patients present an advanced stage and are not suited for surgical resection [41].

GC survival varied greatly not only according to the stage of cancer at diagnosis but also depending on geographic area. According to data collected in the United States in the period 1989–1995, the 5-year survival rates were 60% for stage 0, 39% for stage I, 15% for stage II, 5% for stage III, and 1% for stage IV [29]. In a study from Japan on the basis of 4774 GC cases, conducted from 1988 to 1997, corresponding 5-year survival rates were 77% for stage I, 60% for stage II, 29% for stage III, 12% for stage IVA, and 3% for stage IVB [43]. A study from New Delhi, India, conducted over a 10-year period up to the early 2000s and on the basis of 634 GC cases reported that the majority of GC detected were advanced unresectable diseases (95% had stage III or IV) and 30-day mortality among operated patients was 10%, almost all diagnosed with stage IV GC [44].

Thus, detection of cholelithiasis and consequent gall-bladder removal represents the keystone to GC prevention in the majority of high-risk populations that often happen to be less economically advantaged. Public health policies geared toward the implementation of population screening for gall-bladder diseases and consequent appropriate therapies should be implemented in the most affected countries.

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