Original Article

Survival trends for primary liver cancer, 1995–2009: analysis of individual data for 578,740 patients from 187 population-based registries in 36 countries (CONCORD-2)

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Background: Primary liver cancer is the fifth most common cancer world-wide, and the second most common cause of death from cancer, with an estimated 841,100 new cases and 781,500 deaths each year. Hepatocellular carcinoma (HCC) accounts for 60–80% of cases, and cholangiocarcinoma 10–40%. We examined global trends in survival for both these sub-types of liver cancer, by country, age, sex and calendar period.

Methods: Data on 1,005,032 adults (aged 15–99 years) diagnosed with a primary, invasive malignant neoplasm of the liver or intrahepatic bile ducts between 1995 and 2009 were provided by 243 population-based cancer registries in 60 countries. Analysis was restricted to patients for whom the diagnosis of a primary malignancy had been confirmed by histological or cytological examination, or assignation of a specific morphology code, and to registries from which survival estimates were considered reliable. We estimated both five-year net survival and conditional five-year net survival, for patients who survived to the first anniversary of diagnosis. Funnel plots were used to examine international variation in survival and variation by age and morphology.

Results: Data on 578,740 patients from 187 registries in 36 countries were included after quality control. For patients diagnosed during 2004–2009, the pooled estimate of age-standardised five-year net survival for liver cancer was 14.8% (range, 4.4–23.7%), higher than for patients diagnosed during 1995–2000 (11.0%). Survival for patients diagnosed with HCC during 2004–2009 (pooled estimate 17.4%, range 7.7–25.5%) was higher than for those with cholangiocarcinoma (8.4%, range 3.7–16.0%). Survival for patients diagnosed

during 2004–2009 was higher in Canada, Italy, Japan, Taiwan and Korea (21.2–23.7%) than the pooled estimate for patients diagnosed some 10 years earlier (1995–2000; 11.0%). Conditional survival in 2004–2009 was also higher in New Zealand, Canada, Taiwan, Korea, and China (42.0–52.7%) than the pooled estimate for 1995–2000 (33.2%).

Conclusions: Survival from primary cancers of the liver has increased, but it remains poor in most countries we have examined. International variation in survival highlights the potential to improve outcomes, but prevention must also remain a priority. There is a need for continued and expanded surveillance of survival, especially in low- and middle-income countries, to assess the impact of interventions in policy and treatment. Greater consistency in registration practice and coding of liver cancer would reduce the variation in data quality and further improve the comparability of survival estimates.

Keywords: Survival; trends; liver cancer; hepatocellular carcinoma (HCC); cholangiocarcinoma; cancer registry; international

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Introduction

Primary liver cancer is the fifth most common cancer world-wide, and the second most common cause of cancer death, with an estimated 841,100 new cases and 781,500 deaths each year (1). More than 70% of cases and deaths arise in males. Hepatocellular carcinoma (HCC) accounts for 60–80% of invasive malignancies of the liver (2). It is estimated that 80% of HCC cases are secondary to chronic infection with hepatitis B or C (3). Aflatoxin contamination of cereals and peanuts is estimated to cause up to 28% of cases in sub-Saharan Africa, Southeast Asia, and China (4). In high-income countries, where incidence rates are lower, important risk factors are chronic hepatitis C infection, alcohol-induced cirrhosis (5), and increasingly, liver disease linked with diabetes and obesity (6).

Most other primary malignancies of the liver are cholangiocarcinomas [10–40% of cases (2)], arising in the intrahepatic bile ducts. In South-east Asia, particularly Thailand, infestation with the liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis* is an endemic risk factor (7). Risk factors in other countries include primary sclerosing cholangitis (8), cholelithiasis (9) and hepatitis C infection (10), but cholangiocarcinoma has also been associated with smoking (11) and obesity (12).

A large proportion of the global burden of liver cancer, therefore, is potentially preventable through reductions in exposure to risk, particularly chronic viral infection. However, over 80% of HCC occur in sub-Saharan Africa and Asia (3). Vaccination against hepatitis viruses for primary prevention can be difficult in low- and middle-income countries with limited infrastructure (13,14), although such a programme was successfully introduced in the Gambia (15). The global burden of incidence is thus likely to remain high for the foreseeable future. Global surveillance of survival is required, both to identify international variation in outcomes (16) and to identify modifiable prognostic factors in a given country, such as health-seeking behaviour, screening, access to services, early diagnosis and treatment, and health system organization (17).

Trends in population-based survival enable the overall effectiveness of the health system in each country to be monitored. Five-year net survival from liver cancer is very low (10–20%) in both developed and developing countries (18,19). Survival for patients whose cholangiocarcinoma is localised and who receive a transplant and chemoradiation can be as high as 68% at 5 years (20), while it can be as high as 75% for those with very early HCC (21); however, only a small proportion of patients are diagnosed sufficiently early for surgery and transplantation to be viable, even in developed countries. Patients with intra- or extra-hepatic metastases fare much less well, with five-year survival typically below 10% (21).

We present international comparisons of trends in population-based net survival up to five years after diagnosis of primary cancer of the liver among adults diagnosed during 1995–2009 in 36 countries that were included in the CONCORD-2 study (19).

Methods

Methods of data acquisition, quality control and analysis for the CONCORD-2 study, and ethical approval, have been described (19). Data were submitted by 243 population-based cancer registries in 60 countries on 1,005,032 adults (aged 15–99 years) diagnosed with their first, primary, invasive, malignant neoplasm of the liver or intrahepatic bile ducts [International Classification of Diseases for Oncology, third revision (ICD-O-3) (22), C22.0 and C22.1] between 1995 and 2009. After exclusion of 22,175 records during data quality control, 982,857 patients were eligible for inclusion in analyses.

The liver is a common site for metastatic spread from cancer in other organs, so we only included primary, invasive, malignant tumours of the liver (behaviour code /3) for which the registry provided evidence of histological or cytological confirmation of the diagnosis, or a specific morphology code (i.e., excluding ICD-O-3 8000–8005), irrespective of the basis of diagnosis. We also included patients whose cancer was diagnosed with the specific tumour marker alpha-fetoprotein (usually >200 ng/mL serum) and coded as HCC, not otherwise specified (ICD-O-3 morphology 8170), according to guidelines from the European Network of Cancer Registries (ENCR) (23). We excluded data from registries for which the liver cancer survival estimates had been flagged as less reliable in CONCORD-2 (19). We also excluded patients whose tumour was registered only from a death certificate (DCO), or solely at autopsy.

We defined two main morphological groups: HCC (ICD-O-3 8170–8175) and cholangiocarcinoma (ICD-O-3 8050, 8140–8141, 8160–8161, 8260, 8440, 8480–8500, 8570–8572) (24).

Five-year net survival was estimated with the non-parametric Pohar-Perme estimator (25) using the Stata (26) program *stns* (27). Net survival deploys life tables of all-cause mortality rates in the general population by age, sex and year, to correct for the effect of the wide international variations in non-cancer mortality. Life tables were constructed from death and population counts by single year of age or five-year age group, sex, race/ethnicity (where possible) and calendar year or period, for the territory of each participating registry or country (28). The classical cohort approach was used to estimate survival for patients diagnosed during 1995–2000 and 2001–2003, because at least five years of follow-up for vital status were available for all these patients by 31 December 2009. We estimated survival for patients diagnosed during 2004–2009 with the complete approach (29), because not all patients had been followed up for five years. We also estimated five-year survival conditional on survival to the end of the first year after diagnosis, as a surrogate for survival in patients with local or regional disease, since patients with advanced disease are unlikely to survive more than one year. The calendar periods were chosen to match the availability of data on stage from 2001, and changes in the data collection processes for coding SEER Summary Stage 2000 from 2004 (30).

We estimated net survival for each of five age groups, and used the International Cancer Survival Standard (ICSS) weights (15–44 years, 0.07; 45–54 years, 0.12; 55–64 years, 0.23; 65–74 years, 0.29; 75–99 years, 0.29) to produce age-standardised survival estimates for all ages combined (31). Age-specific survival was only estimated if data for at least 50 patients were available for analysis, and at least 10 deaths had been observed. If a survival estimate could not be obtained for a particular age group, the data for two adjacent groups were combined, and the analysis repeated. The pooled estimate was then used for both age groups in age-standardization.

Funnel plots (32) were adopted for graphical presentation, in preference to the conventional ranked bar charts, in order to identify countries with unexpectedly high or low survival, given the precision of the estimate. A random effects model (33), fitted by restricted maximum likelihood estimation, adjusted for the precision of each estimate, was used to estimate the mean and variance of the distribution of five-year survival estimates for all countries included in each analysis. The analysis was performed on the complementary log-log scale (34), with 5% 'winsorisation' (32) to reduce inflation of the variance. We use this pooled estimate as the target in the funnel plot, for purely descriptive purposes. The standard error of each estimate and the standard deviation between countries, derived from the random effects model, were used to construct the control limits of the funnel plot; estimates outside the 95.0% or 99.8% control limits are at least 1.96 and 3.09 standard deviations from the target, respectively (34).

Since none of the age-standardised survival estimates for 2004–2009 exceeded the upper 95% control limit in the funnel plot, we changed the 'target' or benchmark, to the pooled survival estimate for patients diagnosed during 1995–2000. This was done in order to help identify countries or registries in which the age-standardised 5-year net survival for patients diagnosed during 2004–2009 was

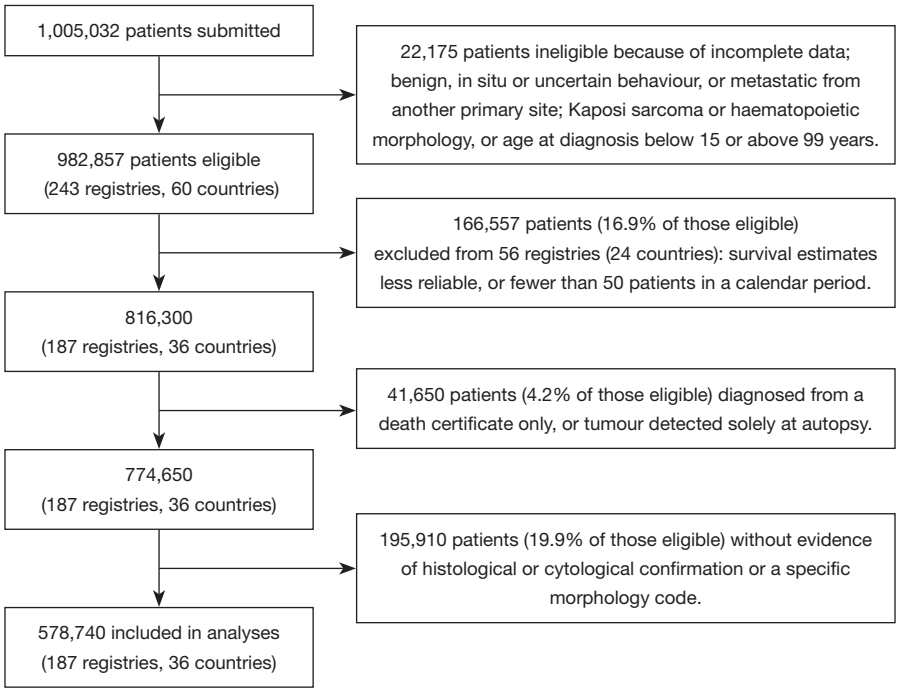

Figure 1 Patients diagnosed with liver cancer during 1995–2009: number submitted and excluded, and the final number included in the analyses.

higher than for patients diagnosed 10 years earlier. A similar approach was used to identify age-specific survival estimates for 2004–2009 that were higher than the corresponding pooled estimate for patients diagnosed during 1995–2000.

Results

Patients

Of the 982,857 patients eligible for inclusion in CONCORD-2, we excluded 166,557 (16.9%) patients from 56 registries in 24 countries for which the survival estimates were considered less reliable (19), or for which fewer than 50 patients were available for analysis in each calendar period, leaving 816,300 patients (*Figure 1*). We excluded a further 41,650 patients (4.2% of those eligible) whose tumour was registered from a death certificate only, or at post-mortem, or for other reasons (*Table 1*), and 195,910 patients (19.9% of those eligible) with no evidence of microscopic verification or a specific morphology code, including a code derived from the alpha-fetoprotein level (23). We included 578,740 patients (58.9% of eligible patients) from 187 registries in 36 countries in survival analyses. Age-standardised estimates of five-year net survival were available for 28 of the 36 countries (*Table 2*).

Data quality

The proportion of tumours registered as a DCO or without microscopic verification varied widely (*Table 1*). DCO registrations exceeded 10% in 12 of the 36 countries. In China, Indonesia, Mongolia, Thailand and Poland, more than 50% of patients were excluded for lack of microscopic verification or a specific morphology code (not shown). In Thailand, Denmark, Poland and Sweden, 20% or more of cholangiocarcinomas were coded as arising in the liver (C22.0), rather than the intrahepatic bile ducts, while in Malaysia, 14% of HCC were coded as arising in the intrahepatic bile ducts (C22.1; *Table S1*).

The number of patients with data on stage at diagnosis was too small to enable international comparison of age-standardised net survival by stage.

Age, sex and histological group

Patients in low- and middle-income countries were generally younger than in European countries and Japan

Table 1 Data quality indicators (%) and number of patients included in analysis: adults (15–99 years) diagnosed with primary liver cancer during 1995–2009

Country	Eligible patients	Exclusions (%)[†]		After exclusions	Data quality indicators (%)[††]				Patients included in analysis[†††]			
		DCO or PM	Other		MV	Non–specific morphology	Lost to follow-up	Censored	All periods (1995–2009)	1995–2000	2001–2003	2004–2009
America (Central and South)												
Colombia (Cali)	750	12.0	1.3	650	67.7	31.5	0.0	5.1	458	126	92	240
America (North)												
Canada*	22,479	4.7	1.3	21,124	53.1	0.0	0.0	0.0	11,902	3,774	2,247	5,881
US registries	197,772	5.9	3.0	180,218	74.6	0.0	0.0	<0.1	140,046	41,026	27,208	71,812
Asia												
Chinese registries	33,387	2.7	<0.1	32,482	25.6	71.2	1.4	<0.1	10,569	710	1,715	8,144
Indonesia (Jakarta)	305	1.3	0.0	301	21.6	71.8	0.0	0.0	85			85
Japanese registries	27,759	20.5	0.2	22,025	31.9	10.2	0.0	1.2	19,882	2,186	1,401	16,295
Korea*	184,632	<0.1	0.5	183,659	28.1	13.3	0.0	0.0	160,125	44,510	34,081	81,534
Malaysia (Penang)	986	10.3	0.7	877	65.3	9.0	0.0	0.0	814	214	126	474
Mongolia*	6,701	0.0	5.1	6,358	6.6	<0.1	15.5	0.0	422			422
Taiwan*	133,641	0.0	0.2	133,440	41.9	25.7	0.0	0.0	99,383	14,945	21,482	62,956
Thai registries	15,590	6.3	0.1	14,600	11.0	84.0	0.0	18.3	1,614	341	414	859
Turkey (Izmir)	1,399	6.2	1.6	1,290	57.1	0.8	0.0	21.2	736	183	147	406
Europe												
Austria*	10,088	0.3	6.8	9,368	88.6	3.7	0.0	0.0	9,184	3,198	2,053	3,933
Belgium*	3,079	<0.1	0.8	3,050	87.3	3.6	1.4	0.0	2,958			2,958
Denmark*	4,069	0.8	0.0	4,035	84.6	20.8	<0.1	0.0	3,519	1,288	734	1,497
Estonia*	1,016	13.7	<0.1	876	69.5	7.5	0.0	0.0	609	274	121	214
Finland*	4,817	14.2	<0.1	4,129	80.6	26.7	<0.1	0.0	3,434	1,122	611	1,701
French registries	9,025	<0.1	0.3	8,996	59.7	16.9	0.9	0.6	6,500	3,118	1,970	1,412
German registries	8,151	10.9	1.7	7,119	71.8	1.6	0.3	0.0	7,034	1,423	1,185	4,426
Ireland*	1,716	5.4	3.4	1,564	51.5	3.8	0.0	0.0	811	195	143	473
Italian registries	45,542	5.4	1.2	42,614	43.5	42.8	0.6	0.2	24,401	9,245	6,090	9,066
Malta*	82	13.4	6.1	66	100.0	25.8	0.0	0.0	66			66

Table 1 (*continued*)

Table 1 (*continued*)

Country	Eligible patients	Exclusions (%)[†]		After exclusions	Data quality indicators (%)[††]				Patients included in analysis[†††]			
		DCO or PM	Other		MV	Non–specific morphology	Lost to follow-up	Censored	All periods (1995–2009)	1995–2000	2001–2003	2004–2009
Netherlands*	4,940	2.9	0.7	4,764	74.1	25.8	0.5	0.0	3,557	1,215	711	1,631
Norway*	1,851	3.3	0.0	1,789	81.6	12.9	0.1	0.0	1,583	546	322	715
Polish registries	14,673	12.1	0.4	12,833	43.2	1.3	0.2	0.0	5,553	713	1,368	3,472
Portugal*	3,768	0.7	2.5	3,647	85.6	11.4	<0.1	0.3	3,285	542	891	1,852
Romania (Cluj)	362	55.2	0.3	161	82.0	0.6	0.0	0.0	142			142
Russia (Arkhangelsk)	245	11.4	4.1	210	56.2	4.3	1.0	0.0	119		51	68
Slovakia*	165	17.6	0.0	136	91.9	8.8	0.0	0.0	125	125		
Slovenia*	1,868	11.2	0.1	1,658	63.8	35.1	<0.1	0.0	1,086	388	228	470
Spanish registries	13,157	7.2	0.8	12,105	47.4	22.7	0.2	<0.1	7,811	2,864	1,765	3,182
Sweden*	7,543	0.0	0.0	7,543	92.9	10.8	0.2	0.0	7,044	2,961	1,419	2,664
Swiss registries	4,360	4.9	1.7	4,072	59.8	16.0	0.8	0.9	3,095	1,020	658	1,417
United Kingdom*	36,779	7.1	<0.1	34,152	46.0	5.7	<0.1	<0.1	29,912	8,751	5,843	15,318
Oceania												
Australian registries	11,150	4.0	1.1	10,583	56.5	16.7	0.0	1.0	8,845	2,804	2,002	4,039
New Zealand*	2,453	11.9	0.2	2,156	60.1	6.4	0.0	0.0	2,031	521	393	1,117
Total	816,300	–	–	774,650	–	–	–	–	578,740	150,328	117,471	310,941

*, data with 100% coverage of the national population; [†], DCO: patients registered from a death certificate only (DCO), or whose tumour was detected solely at autopsy. Other: vital status or sex unknown; invalid sequence of dates; inconsistency of sex-site, site-morphology, age-site, age-morphology, or age-site-morphology. [††], MV: microscopically verified. Non-specific morphology: ICD–O–3 morphology code in the range 8000–8005. Censored: for patients diagnosed during 1995–2004, alive with less than five years of follow-up. [†††], patients with microscopic verification as the basis of diagnosis, or with a specific morphology code (see 'Methods').

Table 2 Number of patients included in analysis, five-year net survival (NS, %) and 95% confidence interval (95% CI), patients diagnosed with primary liver cancer[†], 1995–2009, in 36 countries

Regional	1995–2000					2001–2003					2004–2009				
	No.	Age-standardized		Unstandardized		No.	Age-standardized		Unstandardized		No.	Age-standardized		Unstandardized	
		NS (%)	95% CI	NS (%)	95% CI		NS (%)	95% CI	NS (%)	95% CI		NS (%)	95% CI	NS (%)	95% CI
America (Central and South)															
Colombia (Cali)	126			3.9	0.0–7.9	92			7.4	1.2–13.7	240			3.4	0.0–7.2
America (North)															
Canada*	3,774	14.1	12.9–15.2	14.6	13.3–15.8	2,247	18.8	17.1–20.5	19.2	17.5–21.0	5,881	21.3	19.6–23.1	22.3	20.5–24.1
US registries	41,026	9.6	9.2–9.9	9.6	9.3–9.9	27,208	13.5	13.0–13.9	14.0	13.5–14.4	71,812	16.3	15.9–16.8	17.0	16.5–17.5
Asia															
Chinese registries	710	2.7	1.6–3.8	3.6	2.1–5.0	1,715	20.4	17.6–23.2	19.8	17.7–21.8	8,144	19.5	18.0–21.0	20.1	18.9–21.4
Indonesia (Jakarta)											85			1.9	0.0–5.8
Japanese registries	2,186	27.9	25.9–29.8	28.6	26.5–30.7	1,401	26.4	24.0–28.8	25.5	23.0–28.0	16,295	23.7	22.6–24.7	23.0	22.1–23.9
Korea*	44,510	12.3	11.9–12.8	14.5	14.1–14.8	34,081	16.4	15.8–16.9	19.4	19.0–19.9	81,534	21.2	20.6–21.7	24.4	24.0–24.9
Malaysia (Penang)	214			10.8	6.4–15.3	126			13.2	7.0–19.3	474	15.1	10.6–19.7	16.1	11.5–20.7
Mongolia*											422	8.5	3.1–13.9	11.3	2.0–20.7
Taiwan*	14,945	26.6	25.7–27.6	27.4	26.7–28.2	21,482	21.1	20.5–21.8	22.6	22.0–23.2	62,956	22.7	22.1–23.2	23.9	23.3–24.4
Thai registries	341	19.6	13.4–25.8	18.5	12.1–24.8	414	5.2	3.1–7.3	6.9	3.7–10.0	859	4.4	2.3–6.5	5.7	3.2–8.1
Turkey (Izmir)	183			19.1	9.9–28.4	147			27.8	18.6–37.0	406			21.5	15.7–27.2
Europe															
Austria*	3,198	8.5	7.4–9.6	7.6	6.6–8.6	2,053	12.0	10.4–13.6	11.3	9.8–12.8	3,933	12.8	11.2–14.4	11.9	10.4–13.4
Belgium*											2,958	20.5	17.8–23.1	20.3	17.6–23.1
Denmark*	1,288	2.7	1.8–3.5	2.5	1.6–3.4	734	3.8	2.5–5.1	3.6	2.2–5.1	1,497	6.7	4.8–8.6	6.2	3.9–8.4
Estonia*	274			5.0	2.2–7.8	121			8.4	3.2–13.6	214			7.5	2.8–12.1
Finland*	1,122	7.7	6.0–9.5	7.5	5.6–9.3	611			7.2	4.9–9.4	1,701	8.4	6.2–10.6	7.8	5.5–10.1
French registries	3,118	12.9	11.5–14.2	12.2	10. 9–13.5	1,970	14.9	13.1–16.6	14.3	12.6–16.0	1,412	18.6	16.2–21.0	18.4	15.9–21.0
German registries	1,423	7.4	6.0–8.8	6.6	5.2–8.1	1,185	8.5	6.9–10.1	8.2	6.4–9.9	4,426	14.7	12.9–16.5	13.5	11.8–15.2
Ireland*	195			9.0	4.7–13.3	143			17.9	11.1–24.7	473	17.0	12.9–21.1	16.1	11.0–21.2
Italian registries	9,245	15.1	14.2–15.9	14.5	13.7–15.3	6,090	19.3	18.1–20.5	18.2	17.1–19.3	9,066	21.7	20.4–23.0	19.9	18.6–21.1

Table 2 (*continued*)

Table 2 (*continued*)

Regional	1995–2000					2001–2003					2004–2009				
	No.	Age-standardized		Unstandardized		No.	Age-standardized		Unstandardized		No.	Age-standardized		Unstandardized	
		NS (%)	95% CI	NS (%)	95% CI		NS (%)	95% CI	NS (%)	95% CI		NS (%)	95% CI	NS (%)	95% CI
Malta*											66			2.2	0.0–5.6
Netherlands*	1,215	8.3	6.7–10.0	8.3	6.6–10.0	711	11.8	9.5–14.1	12.3	9.7–14.9	1,631	12.0	9.5–14.4	12.1	9.4–14.9
Norway*	546	6.1	4.2–8.1	5.2	3.2–7.2	322	7.2	4.6–9.8	6.7	3.9–9.6	715	11.0	7.9–14.1	10.3	6.9–13.6
Polish registries	713	8.3	5.7–10.9	8.1	5.9–10.4	1,368	10.3	8.4–12.1	10.2	8.5–12.0	3,472	9.3	7.6–11.0	9.6	8.0–11.3
Portugal*	542	10.4	7.9–12.9	10.1	7.4–12.8	891	13.0	10.6–15.4	13.3	10.8–15.7	1,852	16.3	13.8–18.8	15.8	13.4–18.2
Romania (Cluj)											142			2.4	0.0–5.8
Russia (Arkhangelsk)						51			2.2	0.0–5.5	68			8.3	0.9–15.6
Slovakia*	125			6.6	2.0–11.1										
Slovenia*	388	3.3	2.0–4.7	3.7	1.7–5.6	228			5.6	2.5–8.8	470	6.0	3.3–8.7	4.8	0.5–9.1
Spanish registries	2,864	12.5	11.1–13.8	11.8	10.5–13.1	1,765	15.6	13.8–17.5	14.6	12.8–16.4	3,182	18.0	16.1–20.0	17.4	15.4–19.4
Sweden*	2,961	5.6	4.6–6.6	4.4	3.6–5.2	1,419	5.8	4.6–7.1	5.1	3.8–6.4	2,664	12.9	11.0–14.7	10.8	9.0–12.6
Swiss registries	1,020	10.5	8.7–12.3	9.8	7.8–11.8	658	13.7	11.1–16.4	12.9	10.1–15.7	1,417	15.2	12.5–17.9	14.8	11.9–17.7
United Kingdom*	8,751	6.4	5.8–7.0	5.4	4.9–5.9	5,843	8.3	7.5–9.2	7.0	6.3–7.7	15,318	9.3	8.4–10.1	7.8	7.0–8.5
Oceania															
Australian registries	2,804	14.2	12.8–15.5	13.9	12.6–15.3	2,002	14.1	12.5–15.7	13.8	12.2–15.5	4,039	13.9	12.1–15.7	13.7	11.9–15.6
New Zealand*	521	12.2	9.2–15.1	13.5	10.3–16.7	393	12.4	9.5–15.4	14.5	10.8–18.2	1,117	16.5	13.2–19.9	17.0	13.5–20.5
Combined estimate††	150,328	11.0	8.4–13.5	10.4	8.1–12.7	117,471	13.3	10.9–15.7	12.6	10.4–14.9	310,941	14.8	12.8–16.8	13.2	11.0–15.5

*, data with 100% coverage of the national population; †, microscopically verified (see text); ††, estimated with a random effects model (see text).

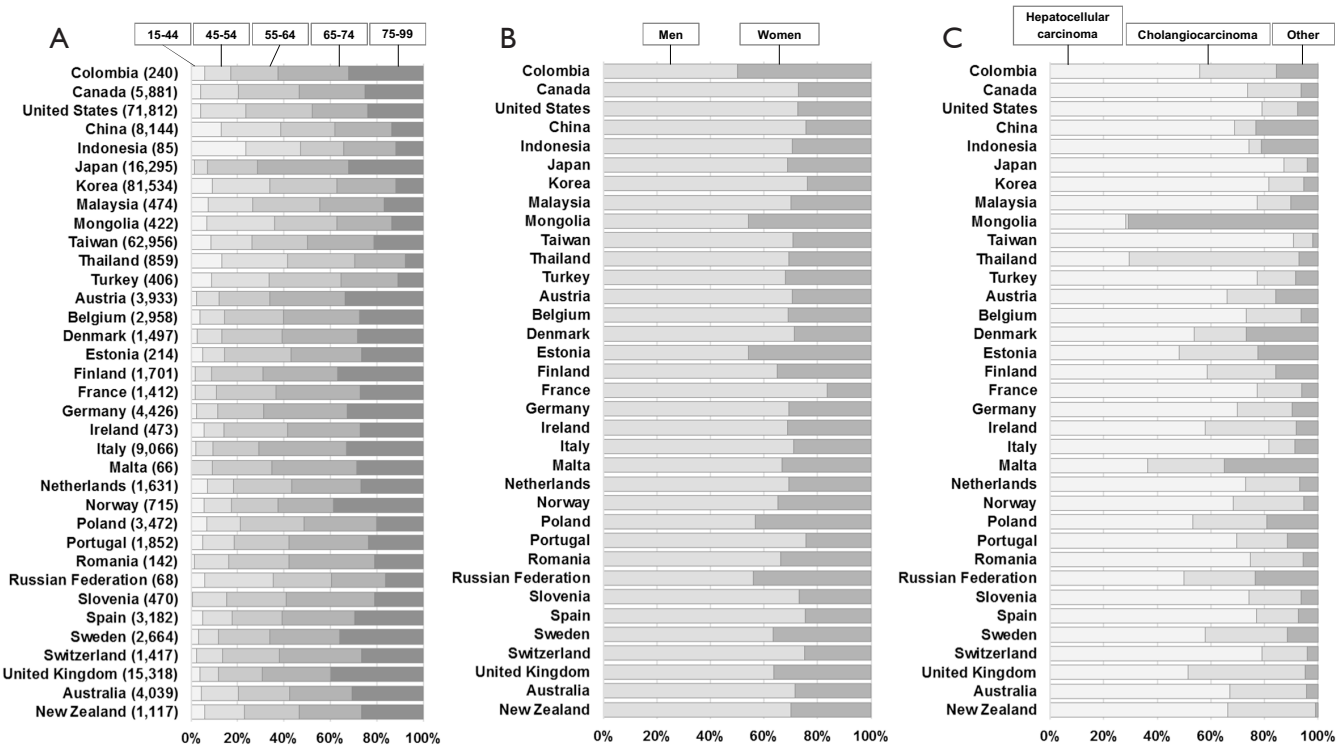

Figure 2 Distribution (%) of liver cancers diagnosed during 2004–2009 by (A) age, (B) sex and (C) morphology. Numbers of patients in parentheses. Only microscopically verified tumours (see 'Methods'). For definition of morphology groups, see text.

(*Figure 2A*). Most patients diagnosed during 2004–2009 were male (median proportion 69.4%, *Figure 2B*). HCC was more common than cholangiocarcinoma (median 70.4% and 19.4%, respectively; *Figure 2C*). HCC represented 84.0–89.7% of liver cancers in Taiwan, Japan, and Korea, while cholangiocarcinoma represented 67.4% of liver cancers in Thailand and 43.9% in the UK (*Table S1*).

Five-year net survival of patients diagnosed in 2004–2009

For all liver cancers combined, the pooled estimate of age-standardised five-year net survival in 28 countries for patients diagnosed during 2004–2009 was 14.8% (range 4.4–23.7%; *Table 2*). Survival was much lower than the pooled estimate for the same period in Denmark (6.7%), Slovenia (6.0%), and Thailand (4.4%; *Figure 3A*). None of the estimates exceeded the upper limit of the funnel plot.

Five-year survival for patients diagnosed during 2004–2009 in Canada, Italy, Japan, Taiwan, and Korea (21.2–23.7%) was higher than the upper 95% control limit around the 1995–2000 benchmark (11.0%) (*Figure 3B*).

Age-standardised five-year conditional survival for patients diagnosed during 2004–2009 who had survived for at least one year varied from 24.4% to 52.7% (*Table 3*). In New Zealand, China, Canada, Taiwan and Korea, conditional survival for 2004–2009 (42.0–52.7%) was above the upper 95% control limit around the 1995–2000 benchmark (33.2%; *Figure 3C*).

Hepatocellular carcinoma

The pooled estimate of age-standardised five-year net survival for patients diagnosed during 2004–2009 was 17.4% (range 7.7–25.5%; *Table 3*). Survival in Slovenia (7.7%) and Denmark was lower than the pooled estimate (8.1%; *Figure 4A*). None of the estimates exceeded the upper 95% control limit of the funnel plot.

Five-year survival for patients diagnosed during 2004–2009 was higher than the upper 95% control limit for 1995–2000 in Canada, Italy, Japan, Taiwan and Korea (24.0–25.5%; *Figure 4B*), suggesting progress from the levels ten years earlier.

Conditional survival for patients diagnosed during 2004–2009 was higher than the 95% control limits for 1995–2000

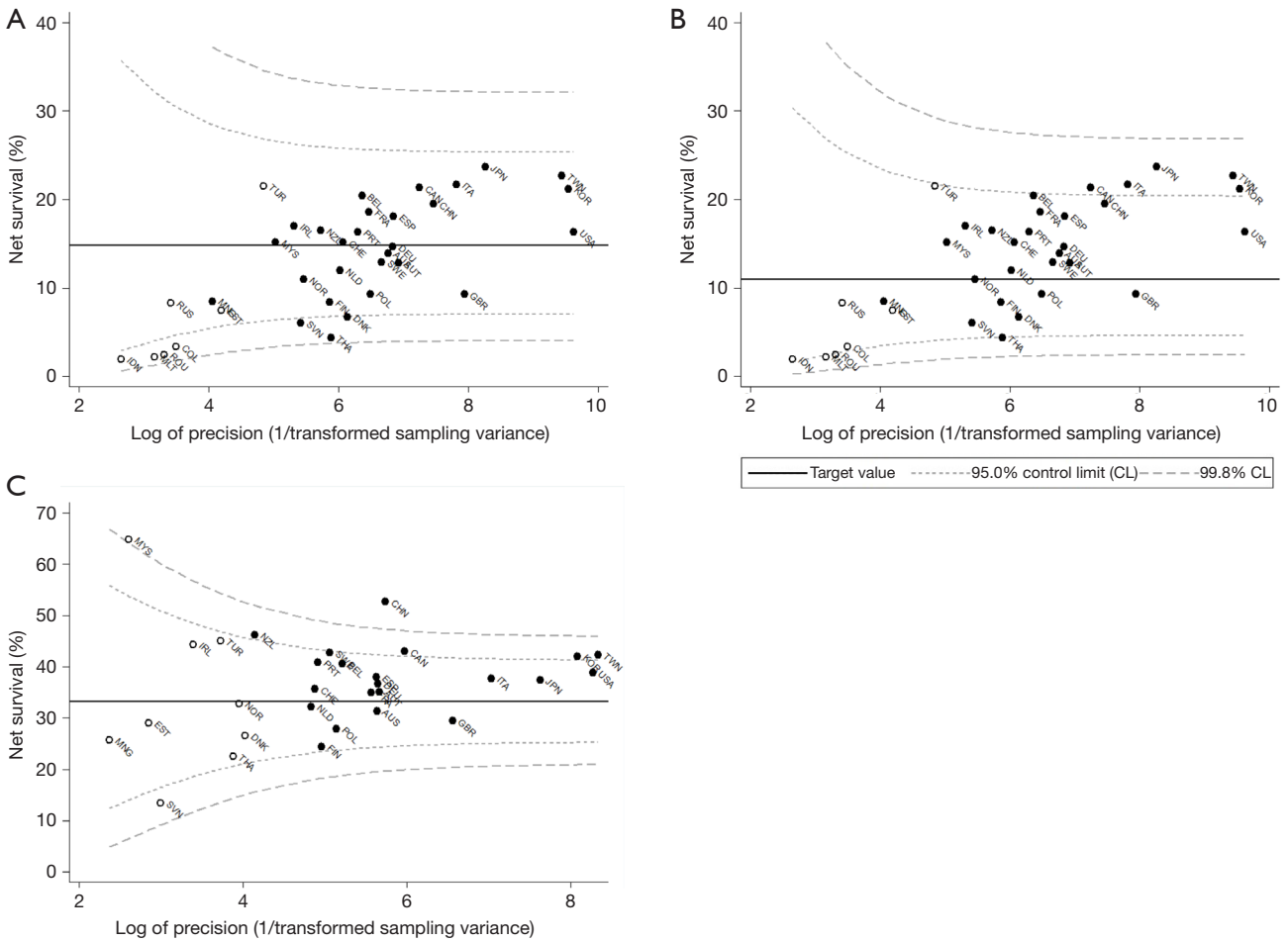

Figure 3 Age-standardised 5-year net survival for liver cancer patients diagnosed during 2004–2009: (A) the target value is the pooled estimate for the same period; (B) the target value is the pooled estimate for 1995–2000, 10 years earlier; (C) 5-year survival, conditional on survival to the end of the first year after diagnosis, for patients diagnosed during 2004–2009 with the pooled estimate for 1995–2000, 10 years earlier, as the target value. Hollow circles represent unstandardized survival estimates (*Table 2*). Only age-standardised estimates contributed to the construction of the funnel plot. UN country codes: AUS, Australian registries; AUT, Austria; BEL, Belgium; CAN, Canada; CHN, Chinese registries; COL, Colombian registries; DNK, Denmark; EST, Estonia; FIN, Finland; FRA, French registries; DEU, German registries; IDN, Indonesia (Jakarta); IRL, Ireland; ITA, Italian registries; JPN, Japanese registries; KOR, Korea; MYS, Malaysia (Penang); MLT, Malta; MNG, Mongolia; NLD, Netherlands; NZL, New Zealand; NOR, Norway; POL, Polish registries; PRT, Portugal; ROU, Romania (Cluj); RUS, Russia (Arkhangelsk); SVK, Slovakia; SVN, Slovenia; ESP, Spanish registries; SWE, Sweden; CHE, Swiss registries; TWN, Taiwan; THA, Thai registries; TUR, Turkey (Izmir); GBR, United Kingdom; USA, US registries.

in China, Sweden, Belgium, Canada, Korea and Taiwan (42.8–51.9%; *Figure 4C*), also suggesting progress in these countries.

Five-year net survival is generally lower in older patients. The pooled estimates of five-year net survival for patients diagnosed during 2004–2009 aged 15–44, 45–54, 55–64, 65–74 and 75–99 years were 30.6%, 24.6%, 21.4%, 15.8% and 10.2%, respectively (*Table 4*).

There is some evidence that age-standardised five-year survival tends to be slightly higher for women (21.8%) than men (17.5%; *Table 5*).

In every country except Poland, five-year net survival for younger patients (15–44 years) diagnosed during 2004–2009 was higher than the pooled estimate for patients diagnosed in that age group some 10 years earlier, 1995–2000 (20.2%; *Figure 5A*). In Korea, Taiwan and Italy, this increase was

Table 3 Age-standardised five-year net survival (NS, %) and conditional survival[†], with 95% confidence intervals (95% CI), patients diagnosed with hepatocellular carcinoma or cholangiocarcinoma[††] during 2004–2009, in 28 countries

Regional	All primary liver cancers				Hepatocellular carcinoma				Cholangiocarcinoma			
	5-year survival		Conditional survival		5-year survival		Conditional survival		5-year survival		Conditional survival	
	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI
America (North)												
Canada*	21.3	19.6–23.1	43.0	39.4–46.6	25.4	23.3–27.5	46.1	42.1–50.1	8.1	5.6–10.6	25.1	17.6–32.6
US registries	16.3	15.9–16.8	38.8	37.7–40.0	17.7	17.2–18.3	40.0	38.7–41.3	8.8	7.9–9.8	27.3	24.3–30.3
Asia												
Chinese registries	19.5	18.0–21.0	52.7	48.7–56.7	21.3	19.4–23.1	51.9	47.3–56.5	16.0	11.5–20.5		
Japanese registries	23.7	22.6–24.7	37.4	35.9–39.0	25.5	24.4–26.7	38.4	36.7–40.1	10.9	8.8–13.0		
Korea*	21.2	20.6–21.7	42.0	40.7–43.2	24.1	23.4–24.8	43.8	42.4–45.3	9.5	8.5–10.4	31.9	28.5–35.4
Malaysia (Penang)	15.1	10.6–19.7			10.6	6.9–14.3						
Mongolia*	8.5	3.1–13.9										
Taiwan*	22.7	22.1–23.2	42.3	41.2–43.4	24.0	23.4–24.7	42.8	41.7–44.0	8.3	7.1–9.6	31.9	27.2–36.5
Thai registries	4.4	2.3–6.5							3.7	1.9–5.6		
Europe												
Austria*	12.8	11.2–14.4	35.1	30.9–39.3	14.6	12.5–16.7	37.0	32.0–41.9	5.7	3.4–8.0		
Belgium*	20.5	17.8–23.1	40.6	35.3–45.9	23.0	19.8–26.2	44.4	38.4–50.4	14.4			
Denmark*	6.7	4.8–8.6			8.1	5.5–10.7						
Finland*	8.4	6.2–10.6	24.4	18.5–30.3	11.3	8.0–14.7			3.7	1.6–5.9		
French registries	18.6	16.2–21.0	34.9	30.5–39.3	20.5	17.6–23.4	35.9	31.0–40.8				
German registries	14.7	12.9–16.5	36.7	32.4–41.0	16.3	14.0–18.6	38.9	33.7–44.0	10.8	7.8–13.9		
Ireland*	17.0	12.9–21.1										
Italian registries	21.7	20.4–23.0	37.7	35.6–39.8	24.0	22.5–25.5	39.6	37.3–42.0	7.9	5.6–10.2		
Netherlands*	12.0	9.5–14.4	32.2	25.8–38.6	13.6	10.5–16.7	33.0	25.7–40.3	5.6	2.8–8.4		
Norway*	11.0	7.9–14.1			14.0	9.8–18.1						
Polish registries	9.3	7.6–11.0	27.8	22.4–33.2	9.4	7.0–11.9	25.2	18.7–31.6	8.8	6.4–11.3		
Portugal*	16.3	13.8–18.8	40.9	34.7–47.0	16.8	13.7–19.8	38.3	31.7–45.0	13.3	9.5–17.2		
Slovenia*	6.0	3.3–8.7			7.7	4.4–10.9						

Table 3 (*continued*)

Table 3 (*continued*)

Regional	All primary liver cancers				Hepatocellular carcinoma				Cholangiocarcinoma			
	5-year survival		Conditional survival		5-year survival		Conditional survival		5-year survival		Conditional survival	
	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI
Spanish registries	18.0	16.1–20.0	38.0	33.7–42.3	19.3	17.0–21.7	38.0	33.3–42.7	11.4	7.8–14.9		
Sweden*	12.9	11.0–14.7	42.7	37.0–48.3	17.3	14.9–19.7	46.5	40.0–52.9	5.4	3.4–7.5		
Swiss registries	15.2	12.5–17.9	35.6	29.4–41.9	18.2	15.1–21.4	40.2	33.4–47.0				
United Kingdom*	9.3	8.4–10.1	29.4	26.8–32.1	12.5	11.2–13.8	35.2	31.3–39.1	5.3	4.3–6.3	19.8	16.2–23.4
Oceania												
Australian registries	13.9	12.1–15.7	31.3	27.1–35.6	16.9	14.6–19.2	36.5	31.5–41.5	7.2	4.9–9.6	16.7	11.1–22.4
New Zealand*	16.5	13.2–19.9	46.1	37.3–54.9	20.3	15.9–24.7			8.7	5.0–12.4		
Combined estimate†††	14.8	12.8–16.8	37.6	34.9–40.4	17.4	15.2–19.5	39.7	37.2–42.3	8.4	7.0–9.9	25.6	20.6–30.6

*, data with 100% coverage of the national population; †, five-year survival conditional on survival to the end of the first year after diagnosis; ††, microscopically verified (see text); †††, estimated with a random effects model (see text).

seen in every age group (*Figure 5A,B,C,D,E*).

Cholangiocarcinoma

Age-standardised five-year net survival for patients diagnosed during 2004-2009 ranged from 3.7% in Thailand and Finland to 16.0% in China (*Table 3*; *Figure 6A*). The pooled estimate was 8.4%. Survival was similar for men (8.8%) and women (8.3%) (*Table 5*).

Five-year survival for patients diagnosed during 2004–2009 exceeded the upper 95% control limit for patients diagnosed during 1995–1999 in China (16.0%), Belgium (14.4%) and Portugal (13.3%) (pooled estimate 6.0%) (*Figure 6B*).

All the age-standardised five-year conditional survival estimates for 2004–2009 were within the control limits around the pooled estimate for patients diagnosed ten years earlier (22.0%), suggesting there had been little change in longer-term survival (*Figure 6C*).

Discussion

CONCORD-2 is the largest study to date of population-based survival from primary malignant neoplasms of the liver. The estimates of net survival up to five years after diagnosis presented here are based on data for 578,740 patients from 187 population-based registries in 36 countries over the 15-year period 1995–2009. All the estimates are corrected for international variation and trends in background mortality, and where possible they are age-standardised. For patients diagnosed during 2004–2009, age-standardised comparisons of net survival are now available for HCC in 25 countries and for cholangiocarcinoma in 20 countries.

The pooled estimate of age-standardised five-year net survival for primary liver cancer during 2004–2009 was 14.8% (range 4.4–23.7%). Survival was higher for patients diagnosed with HCC (17.4%, range 7.7–25.5%) than for those with cholangiocarcinoma (8.4%, range 3.7–16.0%).

Five-year net survival increased slightly between 1995–2000 (pooled estimate 11.0%) and 2004–2009 (14.8%), most noticeably in younger patients and for those with HCC. Given that survival is notably higher for HCC than for cholangiocarcinoma, and the wide international variation in the relative frequency of these two sub-types, international comparisons of liver cancer survival should probably be done separately for HCC and cholangiocarcinoma.

In Canada, Italy, Japan, Taiwan and Korea, five-year net

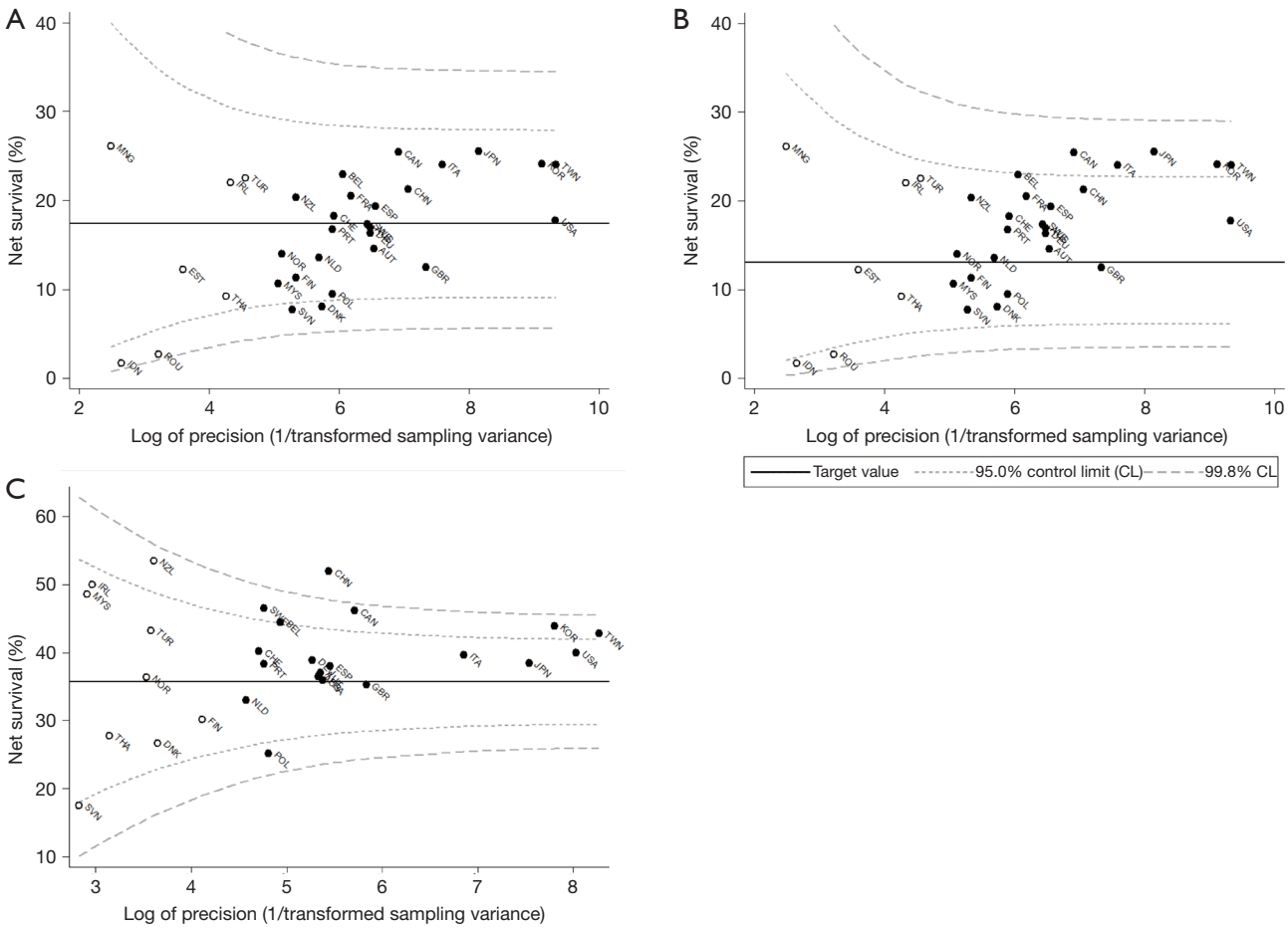

Figure 4 Hepatocellular carcinoma: age-standardised 5-year net survival for patients diagnosed during 2004–2009: (A) the target value is the pooled estimate for the same period; (B) the target value is the pooled estimate for patients diagnosed during 1995–2000, 10 years earlier; (C) 5-year survival, conditional on survival to the end of the first year after diagnosis, for patients diagnosed during 2004–2009 with the pooled estimate for 1995–2000, 10 years earlier, as the target value. Hollow circles represent unstandardized survival estimates. Only age-standardised estimates (*Table 3*) contributed to the construction of the funnel plot. Country codes: see *Figure 3*.

survival for HCC (21.2–23.7%) in 2004–2009 was higher than the pooled estimate for 1995–2000. Japan introduced a programme for early diagnosis with new imaging techniques from the 1980s, with advanced techniques in surgery and chemotherapy (35). The proportion of tumours larger than 10 cm fell from 65.0% to 6.0% during 1978–2005 (36). The proportion of patients diagnosed with localised disease in Japan (60%) (35) is higher than in Korea (44%) (37), the USA (41%) (38) or Taiwan (30%) (39). The evidence of reduced mortality from screening patients with chronic liver disease is weak (40), but a dose-dependent association was found in a national study in Taiwan between shorter intervals from ultrasonography examination to a confirmed diagnosis and subsequent mortality (41). The high proportion of DCO registrations in Japan (20.5%) and the low proportion of patients with histological confirmation of the diagnosis in Italy (43.5%) may have modified the stage distribution (data not shown), but we have not examined survival by stage.

Age-standardised 5-year net survival for HCC was slightly but systematically higher for women than for men. A similar result was seen in the US SEER programme from a study of 39,345 patients diagnosed between 1988 and 2010, in which the hazard ratio for all-cause survival was 17% lower in women than men (42). The role of sex hormones was invoked in that study, but earlier detection could also play a role.

Conditional survival (five-year net survival among

Table 4 Five-year net survival (NS, %) and 95% confidence interval (95% CI) of patients diagnosed with hepatocellular carcinoma during 2004–2009[†] by age at diagnosis, 28 countries

Regional	15–44 years			45–54 years			55–64 years			65–74 years			75–99 years		
	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
America (North)															
Canada*	177	42.8	33.4–52.2	746	38.9	34.0–43.8	1,145	35.4	31.3–39.6	1,206	21.7	17.5–26.0	1,055	11.3	7.3–15.4
US registries	2,273	31.6	29.2–34.1	11,720	22.9	21.8–24.0	17,104	21.6	20.5–22.6	13,152	16.2	15.1–17.3	12,507	10.8	9.6–11.9
Asia															
Chinese registries	707	23.8	20.0–27.7	1,538	25.7	22.9–28.4	1,313	23.2	20.0–26.3	1,336	19.0	15.8–22.2	721	19.6	14.7–24.5
Japanese registries	198	33.4	24.7–42.1	803	29.0	25.2–32.8	3,087	28.8	26.7–31.0	5,692	25.9	24.3–27.5	4,441	19.2	17.3–21.1
Korea*	6,646	30.3	28.8–31.8	18,418	31.1	30.1–32.1	19,688	30.1	29.0–31.1	15,510	23.2	22.0–24.4	6,289	15.8	13.9–17.7
Malaysia (Penang)				72	22.2	10.8–33.7	113	9.7	2.4–17.0	100	11.2	3.0–19.5	56	4.9	0.0–11.4
Taiwan*	5,078	30.3	28.7–31.9	10,154	28.0	26.7–29.3	13,817	29.1	27.9–30.3	16,304	25.6	24.5–26.8	11,787	15.2	13.8–16.6
Thai registries				83	12.6	4.2–21.0	72	14.2	3.0–25.4						
Turkey (Izmir)				80	24.4	11.9–37.0	105	31.4	19.7–43.1	69	12.7	1.9–23.4			
Europe															
Austria*	50	28.6	14.5–42.7	255	18.1	12.6–23.6	582	17.7	13.4–22.0	877	13.3	9.8–16.7	835	8.6	5.2–12.1
Belgium*	86	31.7	18.2–45.2	207	39.5	30.3–48.7	565	30.1	22.7–37.6	727	17.9	12.5–23.3	578	13.4	7.6–19.1
Denmark*				78	11.9	3.8–20.0	207	7.4	1.8–13.1	275	5.3	1.4–9.2	226	4.2	0.0–9.3
Finland*							210	10.5	3.1–17.9	340	15.7	10.1–21.4	388	7.3	2.3–12.4
French registries				94	25.8	15.0–36.7	275	27.4	21.0–33.7	400	18.3	13.6–23.0	306	14.4	8.9–19.8
German registries	61	39.9	25.6–54.1	266	22.4	15.4–29.4	608	19.9	14.8–25.1	1,165	13.5	10.4–16.7	992	8.0	4.2–11.8
Ireland*							74	37.2	21.3–53.1	84	10.2	0.1–20.3	75	9.5	0.0–19.0
Italian registries	143	43.7	34.0–53.3	519	32.7	27.5–37.9	1,462	29.5	26.3–32.7	2,783	20.6	18.4–22.9	2,498	14.7	12.3–17.1
Netherlands*	78	27.3	15.2–39.5	133	20.8	9.4–32.1	293	19.5	12.2–26.7	353	13.0	6.9–19.1	331	3.2	0.0–6.7
Norway*				58	20.4	8.1–32.8	91	16.8	6.4–27.1	119	15.3	6.2–24.4	196	5.8	0.9–10.7
Polish registries	144	18.5	10.6–26.4	256	15.8	8.9–22.6	499	8.7	4.2–13.1	598	5.8	2.4–9.3	352	8.9	3.1–14.7
Portugal*	62	25.7	13.5–37.8	183	25.3	17.3–33.3	317	19.1	13.6–24.5	454	11.6	6.8–16.4	273	14.4	7.2–21.6
Slovenia*				50	20.8	6.8–34.8	93	0.3	0.0–0.8	130	12.2	3.3–21.1	75	0.2	0.0–0.8
Spanish registries	115	36.8	26.6–47.0	325	23.7	17.5–30.0	536	27.0	21.7–32.3	786	16.4	12.5–20.3	693	10.2	5.8–14.6

Table 4 (*continued*)

Table 4 (*continued*)

Regional	15–44 years			45–54 years			55–64 years			65–74 years			75–99 years		
	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
Sweden*				141	32.0	23.2–40.8	330	20.7	14.6–26.8	457	11.0	6.7–15.3	577	7.4	4.1–10.7
Swiss registries				120	22.6	12.1–33.0	260	24.4	17.0–31.8	413	16.7	11.1–22.4	301	12.5	6.8–18.2
United Kingdom*	355	26.8	20.8–32.8	767	19.4	15.2–23.6	1,659	17.8	14.8–20.7	2,484	8.9	6.9–10.9	2,610	5.5	3.2–7.8
Oceania															
Australian registries	117	28.4	15.9–41.0	530	22.1	16.7–27.6	642	24.3	19.2–29.4	729	14.4	10.2–18.6	694	8.5	4.6–12.4
New Zealand*				151	21.7	9.4–34.1	194	24.3	15.2–33.4	184	22.6	13.6–31.7	164	14.0	5.5–22.6
Combined estimate[†††]	16,290	30.6	28.3–33.0	47,747	24.6	22.4–26.9	65,341	21.4	18.3–24.5	66,727	15.8	13.7–17.8	49,020	10.2	8.4–12.1

*, data with 100% coverage of the national population; [†], microscopically verified (see text); [††], estimated with a random effects model (see text).

Table 5 Age-standardised five-year net survival (NS, %), and 95% confidence interval (95% CI), patients diagnosed during 2004–2009 with hepatocellular carcinoma or cholangiocarcinoma, by sex, 22 countries

Regional	Hepatocellular carcinoma						Cholangiocarcinoma					
	Men			Women			Men			Women		
	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
America (North)												
Canada*	3,411	24.2	21.8–26.6	918	28.3	23.8–32.7	632	5.6	2.9–8.2	543	10.0	6.5–13.5
US registries	43,715	17.1	16.4–17.7	13,041	20.7	19.6–21.9	5,056	8.2	7.0–9.4	4,607	9.8	8.3–11.2
Asia												
Chinese registries	4,375	20.8	18.4–23.2	1,240	23.4	20.1–26.7	389	20.5	14.2–26.8	247	11.6	6.8–16.4
Japanese registries	9,864	25.1	23.8–26.5	4,357	28.2	26.1–30.2	876	11.4	8.7–14.2			
Korea*	52,577	23.8	22.9–24.7	13,974	26.7	25.5–27.9	6,708	9.4	8.2–10.6	4,006	9.3	7.9–10.8
Taiwan*	41,436	23.4	22.6–24.1	15,704	27.3	26.2–28.5	2,440	8.6	6.9–10.3	2,155	8.2	6.4–9.9
Europe												
Austria*	2,044	14.5	12.4–16.7	555	15.1	10.9–19.3	381	6.4	3.2–9.7			
Belgium*	1,604	21.9	18.3–25.5	559	26.1	20.4–31.9	330	12.3	7.7–16.9			
Denmark*	639	7.5	4.4–10.7									

Table 5 (*continued*)

Table 5 (*continued*)

Regional	Hepatocellular carcinoma						Cholangiocarcinoma					
	Men			Women			Men			Women		
	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
French registries	955	20.0	16.9–23.1									
German registries	2,334	15.2	12.8–17.6	758	15.8	11.7–19.8	483	12.9	8.7–17.2	419	9.1	5.2–13.0
Italian registries	5,430	24.0	22.3–25.8	1,975	24.1	21.4–26.9	493	7.5	4.8–10.2			
Netherlands*	894	11.4	8.0–14.9	294	18.6	13.5–23.8						
Norway*	351	11.7	7.5–16.0									
Polish registries	1,194	6.8	4.4–9.2	655	14.6	10.5–18.7	444	7.9	4.2–11.5	512	9.0	6.2–11.8
Portugal*	1,081	16.6	13.3–20.0									
Spanish registries	1,974	18.4	15.8–21.0									
Sweden*	1,112	16.5	13.8–19.2				412	5.1	2.8–7.5	404	6.1	3.2–9.1
Swiss registries	901	17.9	14.4–21.4									
United Kingdom*	6,176	12.0	10.5–13.5	1,699	14.3	11.8–16.8	3,170	4.9	3.6–6.2	3,530	5.7	4.3–7.1
Oceania												
Australian registries	2,172	15.9	13.4–18.5	540	20.5	16.0–24.9	622	8.3	5.2–11.4	528	6.5	3.6–9.3
New Zealand*	595	18.4	13.3–23.5									
Combined estimate[†]	184,834	17.5	15.3–19.7	56,269	21.8	19.0–24.6	22,436	8.8	6.9–10.7	16,951	8.3	7.2–9.5

*, data with 100% coverage of the national population; [†], estimated with a random effects model (see text).

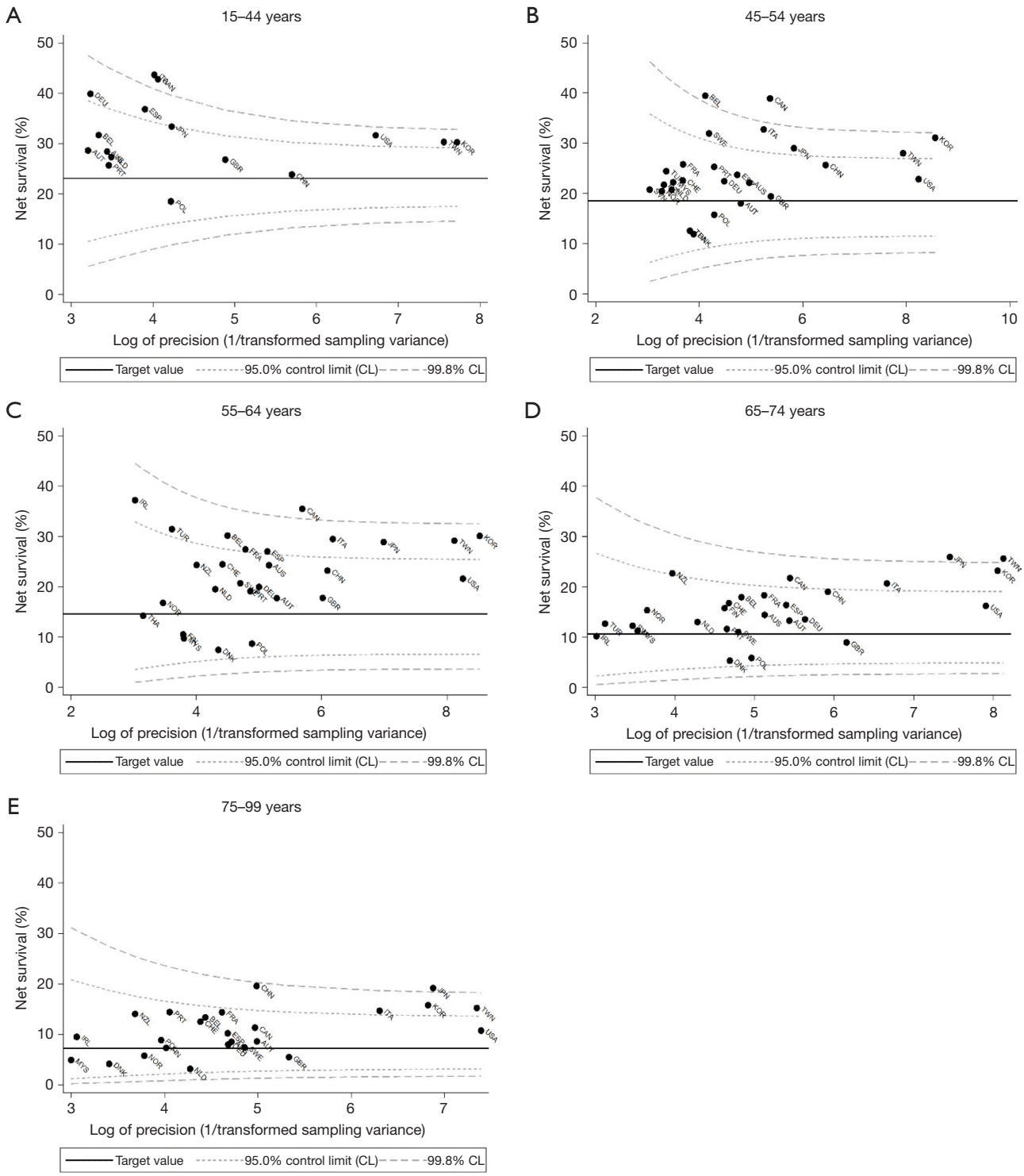

Figure 5 Hepatocellular carcinoma: 5-year net survival for patients diagnosed during 2004–2009, by age at diagnosis: (A) 15–44 years, (B) 45–54 years, (C) 55–64 years, (D) 65–74 years, and (E) 75–99 years. The target value in each funnel plot is the pooled estimate for that age group for patients diagnosed during 1995–2000, 10 years earlier. Country codes: see *Figure 3*.

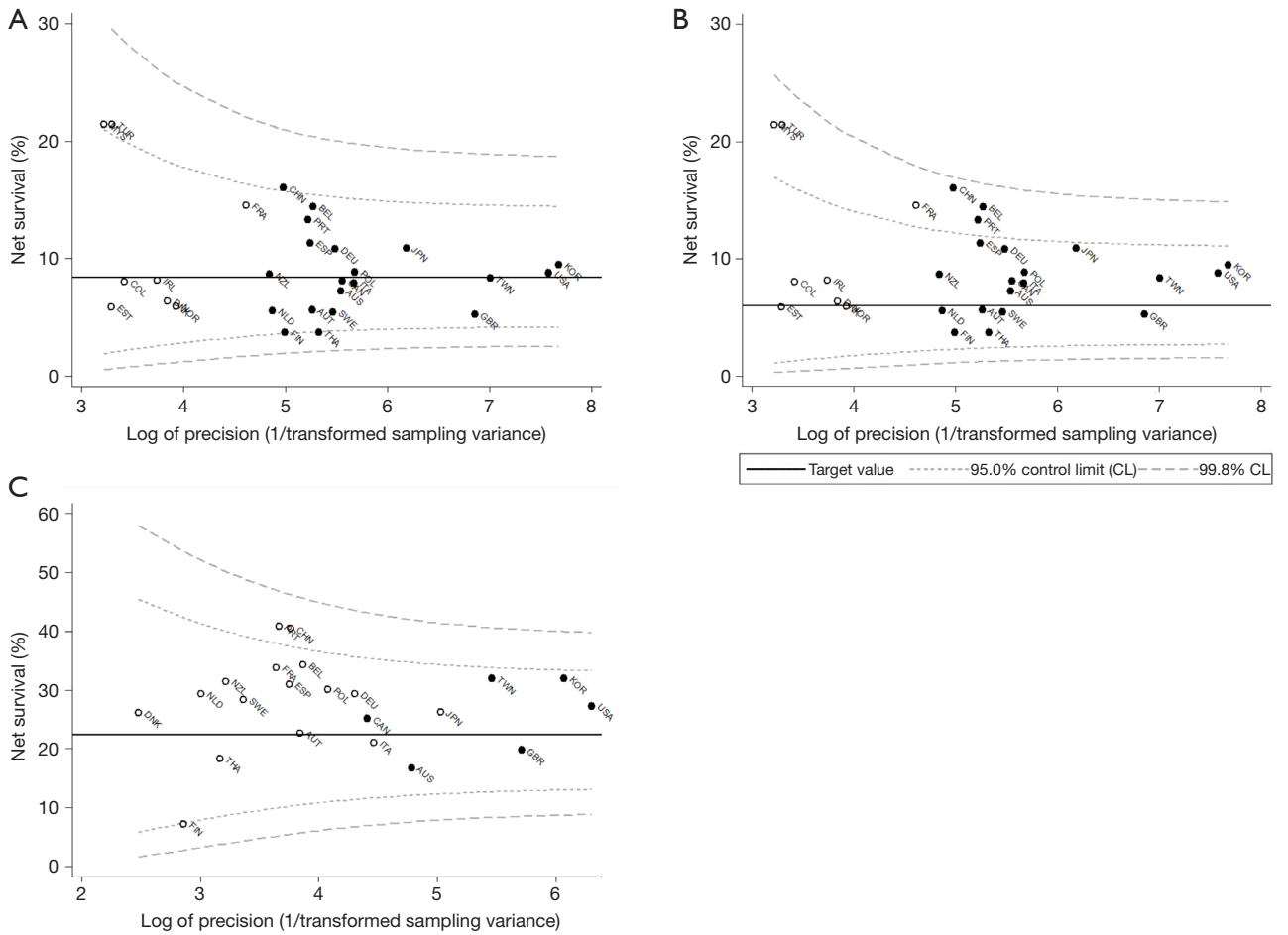

Figure 6 Cholangiocarcinoma: age-standardised 5-year net survival for patients diagnosed during 2004–2009: (A) the target value is the pooled estimate for the same period; (B) the target value is the pooled estimate for patients diagnosed during 1995–2000, 10 years earlier; (C) 5-year survival, conditional on survival to the end of the first year after diagnosis, for patients diagnosed during 2004–2009 with the pooled estimate for 1995–2000, 10 years earlier, as the target value. Hollow circles represent unstandardized survival estimates. Only age-standardised estimates (*Table 3*) contributed to the construction of the funnel plot. Country codes: see *Figure 3*.

patients who had survived to the first anniversary of diagnosis) in 2004–2009 was highest in New Zealand, Canada, Taiwan, Korea, and China (42.0–52.7%). International variation in conditional five-year survival from HCC is likely to reflect the impact of variation in treatment for earlier-stage disease better than variation in five-year survival estimates that include the first year, because many patients with advanced-stage disease will have died in the first year after diagnosis. It may also reflect variation in treatment for localised and early-stage disease, through wider access to surgery (38,43,44), including liver transplantation (45,46), better patient selection (47-49) and clinical experience (50-52). Almost all these studies were done in Taiwan or the US.

Five-year net survival for patients diagnosed with cholangiocarcinoma during 2004–2009 was extremely low world-wide (3.7–16.0%). Survival in China, Belgium and Portugal has improved since 1995–2000, but little improvement has been seen in most other countries. Improvements in survival have been reported from the SEER programme in the USA (53), but most patients still receive no liver-directed intervention (54), despite evidence of better outcomes from resection (17) and transplantation (55). Resection rates have not improved (17), and barriers to treatment, such as household income (56)

have been identified. Again, most of these are studies are from the US.

This study has highlighted the wide variation in data quality for liver cancer from population-based cancer registries. The problem arises partly because liver cancers are often diagnosed late, when invasive investigation is not warranted, survival is poor and the proportion of cases registered only from a death certificate (DCO) can be high. The liver is also a site of predilection for metastasis from other organs. These aspects of data quality can affect the comparability of survival estimates, both by exclusion of DCOs, for which the duration of survival is unknown but probably very short, and by the inability to determine accurately the morphologic type or the stage at diagnosis. Variability in data quality was also shown by the coding of cholangiocarcinoma to the liver parenchyma (20–30% of cases in four countries).

Misclassification of liver metastases as primary liver cancers will have been reduced by the exclusion of patients for whom the only basis of diagnosis was a death certificate. We also excluded patients for whom there was no evidence of microscopic verification. The European Network of Cancer Registries recommends assignation of a morphology code for HCC (ICD-O-3 M8170) if a liver tumour is diagnosed solely from high levels of alpha-fetoprotein, so some primary HCCs may have been excluded where this practice was not adopted. Survival estimates are more susceptible to bias when a large proportion of patients is excluded, such as in Romania, Thailand, Japan, Italy and China. Incomplete trace-back to find the date of diagnosis of cases first notified to the registry from a death certificate, resulting in a high proportion of DCO registrations, has been shown to bias survival estimates upwards, because such cases are often diagnosed shortly before death, leaving little time for routine cancer registration (57,58). By contrast, Denmark undertakes very intensive trace-back; the proportion of DCO cases for liver cancer is extremely low (0.8%), and this leads to inclusion in the analyses of many patients with very short survival.

Funnel plots are preferable to ranked bar charts for displaying survival estimates as higher or lower than a given benchmark, because they take due account of the precision of each estimate (34). Here, we devised a new method, using a random effects model to handle the wide international variation in both the survival estimates and the precision of those estimates, while maintaining control limits within the range 0 to 100%. The more objective comparison of survival estimates, presented alongside information on data quality, should motivate adoption of better registration practice, to improve both completeness and quality of the data. The collection of more complete data on tumour stage needs special emphasis, to enable evaluation of the contributions of early diagnosis and timely treatment to survival (59,60).

Unfortunately, many countries in Asia and Africa, where liver cancer incidence is usually high, could not be included in the analyses because of the lack of population-based cancer registry data. Survival in these countries is likely to be lower than in the high-income countries from which most of the data presented here were available (61).

Conclusions

Despite international variation and improvement over time, survival from liver cancer remains very low in most countries, particularly for cholangiocarcinoma. For hepatocellular carcinoma, prevention remains an urgent priority, through reduction in exposure to key risk factors such as aflatoxin (62), responsible for 5–28% of cases (4), and excessive alcohol consumption (63,64), as well as more widespread immunization against hepatitis B and C (14). Difficulties in implementing vaccination in low- and middle-income countries suggest that the incidence of hepatocellular carcinoma is likely to remain high (13).

Improving survival should therefore remain a high priority. Credible international comparisons of survival should stimulate policy to improve early diagnosis, and clinical trials of new approaches to treatment. Sustained effort is required to expand population-based cancer registration for surveillance of cancer incidence and survival worldwide. Global studies of cancer survival, such as CONCORD, contribute to this effort.

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Footnote

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Supplementary

Table S1 Adults (15–99 years) diagnosed with hepatocellular carcinoma or cholangiocarcinoma* during 1995–2009 in 36 countries: distribution (no., %) by subsite

Country	Total[§] No.	Morphology[†]				Topography[††]				Liver		Intrahepatic bile ducts[§]	
		Hepatocellular[§]		Cholangiocarcinoma[§]		Liver		Intrahepatic bile ducts[§]		HCC	CC	HCC	CC
		No.	%	No.	%	No.	%	No.	%	%	%	%	%
America (Central and South)													
Colombia (Cali)	458	241	52.6	156	34.1	319	69.7	139	30.3	75.5	9.7	0.0	89.9
America (North)													
Canada*	11,902	8,777	73.7	2,277	19.1	9,919	83.3	1,983	16.7	88.5	4.6	0.0	91.6
US registries	140,046	106,667	76.2	21,066	15.0	123,488	88.2	16,558	11.8	86.4	5.2	0.0	88.4
Asia													
Chinese registries	10,569	6,870	65.0	800	7.6	9,920	93.9	649	6.1	69.1	2.7	2.0	81.7
Indonesia (Jakarta)	85	63	74.1	<5	4.7	83	97.6	<5	2.4	75.9	2.4	0.0	100.0
Japanese registries	19,882	17,483	87.9	1,648	8.3	18,228	91.7	1,654	8.3	95.9	0.8	0.4	90.7
Korea*	160,125	134,561	84.0	18,036	11.3	138,431	86.5	21,694	13.5	97.2	1.0	0.0	76.9
Malaysia (Penang)	814	615	75.6	110	13.5	728	89.4	86	10.6	82.8	6.5	14.0	73.3
Mongolia*	422	119	28.2	<5	0.9	421	99.8	<5	0.2	28.3	0.7	0.0	100.0
Taiwan*	99,383	89,109	89.7	7,941	8.0	91,659	92.2	7,724	7.8	97.2	0.8	0.0	93.0
Thai registries	1,614	406	25.2	1,088	67.4	674	41.8	940	58.2	60.2	30.4	0.0	93.9
Turkey (Izmir)	736	588	79.9	90	12.2	625	84.9	111	15.1	94.1	0.2	0.0	80.2
Europe													
Austria*	9,184	6,162	67.1	1,656	18.0	7,309	79.6	1,875	20.4	84.3	3.8	0.0	73.5
Belgium*	2,958	2,163	73.1	607	20.5	2,341	79.1	617	20.9	92.4	1.2	0.0	94.0
Denmark*	3,519	1,838	52.2	945	26.9	3,157	89.7	362	10.3	58.1	20.7	1.4	80.1
Estonia*	609	277	45.5	154	25.3	433	71.1	176	28.9	64.0	3.9	0.0	77.8
Finland*	3,434	2,086	60.7	818	23.8	2,720	79.2	714	20.8	76.7	6.3	0.0	90.8
French registries	6,500	5,337	82.1	847	13.0	5,777	88.9	723	11.1	92.4	2.4	0.0	97.6
German registries	7,034	4,996	71.0	1,241	17.6	5,580	79.3	1,454	20.7	89.5	1.8	0.0	78.3
Ireland*	811	524	64.6	226	27.9	568	70.0	243	30.0	92.3	1.8	0.0	88.9
Italian registries	24,401	20,100	82.4	2,069	8.5	22,851	93.6	1,550	6.4	88.0	3.1	0.0	87.4
Malta*	66	24	36.4	19	28.8	45	68.2	21	31.8	53.3	4.4	0.0	81.0
Netherlands*	3,557	2,674	75.2	647	18.2	2,974	83.6	583	16.4	89.9	2.6	0.0	97.8
Norway*	1,583	1,099	69.4	376	23.8	1,194	75.4	389	24.6	92.0	0.0	0.0	96.7
Polish registries	5,553	2,749	49.5	1,607	28.9	4,926	88.7	627	11.3	55.6	22.0	1.3	83.1
Portugal*	3,285	2,337	71.1	580	17.7	2,827	86.1	458	13.9	82.7	7.2	0.0	82.1
Romania (Cluj)	142	106	74.6	28	19.7	112	78.9	30	21.1	94.6	2.7	0.0	83.3
Russia (Arkhangelsk)	119	55	46.2	29	24.4	98	82.4	21	17.6	56.1	11.2	0.0	85.7
Slovakia*	125	81	64.8	38	30.4	86	68.8	39	31.2	94.2	2.3	0.0	92.3
Slovenia*	1,086	758	69.8	218	20.1	877	80.8	209	19.2	86.4	5.7	0.0	80.4
Spanish registries	7,811	6,250	80.0	987	12.6	6,813	87.2	998	12.8	91.7	2.5	0.0	82.1
Sweden*	7,044	4,005	56.9	2,245	31.9	7,044	100.0	0	0.0	56.9	31.9		
Swiss registries	3,095	2,536	81.9	403	13.0	2,717	87.8	378	12.2	93.3	2.2	0.0	91.0
United Kingdom*	29,912	15,159	50.7	13,143	43.9	16,180	54.1	13,732	45.9	93.7	1.0	<0.1	94.5
Oceania													
Australian registries	8,845	6,316	71.4	2,145	24.3	6,625	74.9	2,220	25.1	95.3	0.6	0.0	94.8
New Zealand*	2,031	1,403	69.1	576	28.4	1,443	71.0	588	29.0	97.2	0.7	0.0	96.3

[§], microscopically confirmed (see text); *, data with 100% coverage of the national population; [†], hepatocellular carcinoma: ICD-O-3 morphology codes 8170–8175; cholangiocarcinoma: 8050, 8140–8141, 8160–8161, 8260, 8440, 8480–8500 and 8570–8572; [††], liver: ICD-O-3 topography code C22.0; intrahepatic bile ducts C22.1.