Trends in hepatocellular carcinoma incidence and survival among people with hepatitis C: an international comparison

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Title: Trends in hepatocellular carcinoma incidence and survival among people with hepatitis C: an international comparison

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Abstract (250 words)

Background: This study evaluates trends in hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC) incidence and survival in three settings, prior to introduction of direct-acting antiviral (DAA) therapies. **Methods:** HCV notifications from British Columbia (BC), Canada, New South Wales (NSW), Australia, and Scotland (1995-2011/2012/2013, respectively) were linked to HCC diagnosis data via hospital admissions (2001-2012/2013/2014, respectively), and mortality (1995-2013/2014/2015, respectively). Age-standardised HCC incidence rates were evaluated, associated factors were assessed using Cox regression, and median survival time after HCC diagnosis was calculated. **Results:** Among 58,487, 84,529, and 31,924 people with HCV in BC, NSW, and Scotland, 734 (1.3%), 1,045 (1.2%), and 345 (1.1%) had an HCC diagnosis. Since mid-2000s, HCC diagnosis numbers increased in all jurisdictions. Age-standardised HCC incidence rates remained stable in BC and Scotland, and increased in NSW. The strongest predictor of HCC diagnosis was older age [birth <1945, aHR in BC 5.74, 95% CI 4.84, 6.82; NSW 9.26, 95% CI 7.93, 10.82; Scotland 12.55, 95% CI 9.19, 17.15]. Median survival after HCC diagnosis remained stable in BC (0.8 years in 2001-2006 and 2007-2011) and NSW (0.9 years in 2001-2006 and 2007-2013), and improved in Scotland (0.7 years in 2001-2006 to 1.5 years in 2007-2014). **Conclusions:** Across the settings, HCC burden increased, individual-level risk of HCC remained stable or increased, and HCC survival remained extremely low. These findings highlight the minimal impact of HCC prevention and management strategies during the interferon-based HCV treatment era, and form the basis for evaluating the impact of DAA therapy in the coming years.

Keywords: HCV; liver disease; primary liver cancer; population-based; data linkage

Globally, in 2012, primary liver cancer was the fifth most common cancer in men, and the ninth in women (1). The alarmingly poor prognosis enhances the burden of primary liver cancer; the second leading cause of cancer mortality in 2012 (1). In high-income countries, an increasing proportion of the most common type of primary liver cancer, hepatocellular carcinoma (HCC), is attributed to hepatitis C virus (HCV) infection (1). Opportunities to increase the uptake of antiviral therapy offer promise for reducing the current and future HCC burden (2-4). However, evaluating the success of treatment programs depends on having solid baseline data and the ability to monitor population-level HCC diagnosis trends, risk factors, and prognosis in different settings over time.

The rising burden of HCV-related HCC can be explained by the natural history of HCV infection, the contribution of risk factors for liver disease progression such alcohol-use disorder, and negligible population-level impact of interferon-based treatments on HCV-related liver disease (5). Given the advent of interferon-free direct-acting antiviral (DAA) therapies, many future cases of HCV-related HCC diagnosis could be prevented if greater numbers of people undergo treatment (6). Several barriers remain to increase access to HCV treatment programs, including the high cost of new regimens and treatment capacity in most settings (7). Further, potential impact of improved therapies on the risk of HCC recurrence and HCC survival are not well understood (8, 9). As a result, the projected burden of HCC in the DAA era remains unclear, highlighting the need for ongoing international surveillance of HCC to inform and improve public health policy and clinical practice over the next decade.

Globally, British Columbia (BC), Canada, New South Wales (NSW), Australia, and Scotland are among the few settings with established population-based surveillance systems that enable monitoring people with HCV infection by linkage between HCV diagnosis databases

and hospitalisation records. The aim of this study was to assess trends in population-level HCC diagnosis rates, contribution of risk factors to HCC diagnosis, and survival after HCC diagnosis among people with HCV infection.

Materials and methods

Data sources and record linkages

British Columbia, Canada

The British Columbia Hepatitis Testers Cohort (BC-HTC) holds records of all individuals tested for HCV, HBV, and HIV at the BC Centre for Disease Control Public Health Laboratory, since 1992, or reported as a confirmed case of HCV, HBV, and HIV/AIDS, since 1990 (10). At the end of each episode of admission, all BC hospitals submit their hospitalisation records (including demographic, administrative, and diagnosis information) directly to the Canadian Institute of Health information for inclusion in the Discharge Abstracts Database, since 1985 (11). All hospitalisation records are coded using the 10th revision of the Classification of Diseases and Related Health Problems (ICD-10), since 2001. Information on all deaths registered in BC are held by the BC Vital Statistics Agency, since 1985 (12). Using personal health numbers assigned to each individual in BC, BC-HTC records were deterministically linked to hospitalisation and mortality datasets. Record linkages were carried out by the BC Centre for Disease Control and BC Ministry of Health (10).

New South Wales, Australia

The NSW Notifiable Conditions Information Management System (NCIMS) holds records of all individual with positive HCV and HBV serology tests, notified of diagnoses via mandatory notification procedures, since 1991 (13). National HIV Registry holds records of all notifications of HIV infection, since 1985 (14). NSW Admitted Patient Data Collection covers all inpatient admissions from all hospitals in NSW, since 2001 (13). Each hospitalisation record includes demographic, administrative and diagnosis information coded at discharge according to ICD-10 (13). Information on all deaths registered in NSW is held

by the Registry of Births, Deaths and Marriages, since 1993 (13). Using demographic details (including full name, gender, date of birth, and address), probabilistic linkages of records between the NCIMS, hospitalisation, and mortality datasets were undertaken by the NSW Centre for Health Record Linkage (13).

Scotland

Health Protection Scotland holds records of all individual with positive HCV and HBV serology tests since 1991 (15). Notifications of HIV diagnosis have been recorded since 1981 (15). Hospital admission data are available from the Scottish Morbidity Records, comprising all Scottish hospitalisations since 1981, including demographic, administrative and diagnosis information coded at separation (according to ICD-10 since 1996) (15). Information on all deaths registered in Scotland is held by the National Records of Scotland, since 1980 (16). Using unique identifiers and demographic details (including forename initial, surname Soundex, gender, date of birth, and postcode district of residence), a combination of deterministic and probabilistic linkages of records between the HCV notifications, hospitalisation, and mortality datasets were undertaken by Information Services Division Scotland (15).

Study period

HCV notifications were extracted for the study period between 1 January 1995 and 31 December 2011 (BC), 2012 (NSW), and 2013 (Scotland) and linked hospitalisation records were extracted for the study period between 1 January 2001 and 31 December 2012 (BC), 2013 (NSW), and 2014 (Scotland). In each setting, linked mortality records were extracted for the study period between 1 January 1995 and six months after the latest hospitalisation record.

Study outcome

The primary outcome of interest was first-time hospitalisation due to HCC. A hospital discharge diagnosis code was used to define HCC diagnosis; coded in either the principal or secondary diagnosis fields of a linked inpatient hospital record (ICD-10 code C22.0). Hereafter, a first-time HCC hospital admission is referred to as HCC diagnosis.

Exclusion criteria

Exclusion criteria were applied as follows: records where date of birth was missing, and records where the date of HCV notification occurred more than three months after date of death (post-mortem notification), or prior to January 1, 1995.

Statistical analysis

Among people with an HCV notification in each setting, trends in HCC diagnosis numbers were evaluated. Age-standardised HCC incidence rates [per 100 person-years (PY)], and corresponding 95% CIs were calculated using the Poisson distribution. The European Standard Population 2013 was used for standardisation. The strength of association between risk factors and HCC diagnosis was assessed using unadjusted and adjusted Cox proportional hazard regression analyses; covariates included birth cohort, gender, year of HCV notification, HBV and HIV co-infection, and alcohol-use disorder. Among people with an HCC diagnosis, median survival time after HCC diagnosis was evaluated.

Alcohol-use disorder is a standard term used to define continued drinking despite adverse mental and physical consequences (17). Liver-related consequences of alcohol use are not

included in the definition of alcohol-use disorder (17). Hospital discharge diagnosis codes (ICD-10) were used to define alcohol-use disorder; coded in either the principal or a secondary diagnosis field of a linked inpatient hospital record. The set of relevant codes included: alcohol-induced Pseudo-Cushing's syndrome (E24.4), mental and behavioural disorders due to use of alcohol (F10), degeneration of nervous system due to alcohol (G31.2), alcoholic polyneuropathy (G62.1), alcoholic cardiomyopathy (I42.6), alcoholic myopathy (G72.1), alcohol rehabilitation (Z50.2), and alcohol abuse counselling and surveillance (Z71.4). Hereafter, having a history of at least one alcohol-use disorder-related hospital admission is referred to as alcohol-use disorder. Alcohol-use disorder was not included as a time-dependent variable in Cox proportional regression analyses, given that it is considered to be an indicator of a long-standing condition. To calculate age-standardised HCC incidence rates and assess factors associated with HCC diagnosis, person-time at risk was defined to start six months post the date of HCV notification (but was left-censored to 1 January 2001 if HCV notification was before this date), and to end at whichever occurred first; death, or end of follow-up, assigned by year. To calculate median survival time, observation time was defined to start on the date of HCC diagnosis, and to end at whichever occurred first; death, or end of follow-up. Statistical analyses were carried out in STATA versions 12 and 13 or SAS version 9.4.

Results

Study participants

There were 58,487 people with an HCV notification in BC, 84,529 in NSW, and 31,924 in Scotland (total n=174,940). A higher proportion of people from BC (61%) were born during 1945-64 compared to NSW (41%) and Scotland (24%) (Table 1). Across the three settings, 63-65% were male, 29-49% had an HCV notification during 1995-2000, and 18-27% had alcohol-use disorder (Table 1). The proportion of people with an HCV notification who developed HCC was very similar across the three settings: 1.3% (n=734) in BC, 1.2% (n=1,045) in NSW and 1.1% (n=345) in Scotland. Across the three settings, those with an HCC diagnosis were more likely to be born during 1945-1964, and male. Among people with an HCC diagnosis, the proportion of individuals with alcohol-use disorder ranged from 17% in BC, to 23% in NSW and 27% in Scotland (Table 1).

Age at HCC diagnosis

The age distribution at HCC diagnosis varied across settings. In BC, NSW, and Scotland, those aged 50 years or older at the time of HCC diagnosis comprised 89%, 66%, and 77% of the population with an HCC diagnosis in the mid-2000s, respectively. In early 2010s, people in the same age group comprised 95%, 84%, and 87% of the population with an HCC diagnosis in BC, NSW and Scotland, respectively (Figure 1).

HCC diagnosis numbers and rates

Compared to 2004, HCC diagnosis numbers increased in all jurisdictions [38 to 92 in 2011 in BC (P<0.001), 47 to 167 in 2012 in NSW (P<0.001), and 12 to 52 in 2013 in Scotland (P<0.001)] (Figure 2). Since 2004, age-standardised HCC incidence rates remained stable in BC (0.02 to 0.02 per 100 PY in 2011, P=0.774) and Scotland (0.10 to 0.11 per 100 PY in

2013, *P*=0.995). However, in NSW, age-standardised HCC incidence rates increased from 0.10 in 2004 to 0.15 per 100 PY in 2012, *P*=0.005 (Figure 2).

Factors associated with HCC diagnosis

In unadjusted analyses across the three settings, HCC diagnosis was associated with older age, male gender, and HCV notification year ≥2007. In unadjusted analyses, HBV co-infection was associated with HCC diagnosis in NSW and HIV co-infection was associated with reduced likelihood of HCC diagnosis in BC (Supplementary Table 1). In adjusted analysis, older age (birth before 1945) was the strongest predictor of HCC diagnosis [adjusted hazard ratio (aHR) in BC 5.74, 95% CI 4.84, 6.82; in NSW 9.26, 95% CI 7.93, 10.82; and in Scotland 12.55, 95% CI 9.19, 17.15], followed by male gender in BC (aHR 2.70, 95% CI 2.21, 3.31), and HCV notification year ≥2007 in NSW (aHR 3.71, 95% CI 2.88, 4.78), and Scotland (aHR 3.00, 95% CI 1.97, 4.55) (Table 2). The association between HCC diagnosis and more recent HCV notification years was driven by older age (Supplementary Table 2).

Survival after HCC diagnosis

Median survival time after HCC diagnosis remained stable during the study period in BC (0.8 years in 2001-2006 and 2007-2011) and NSW (0.9 years in 2001-2006 and 2007-2013). However, median survival after HCC diagnosis improved in Scotland, from 0.7 years in 2001-2006 to 1.5 years in 2007-2014. Across the three settings, median survival after HCC diagnosis was highest in Scotland (1.3 years, 95% CI 0.99, 1.97) (Table 3).

Discussion

The burden of HCV-related HCC continued to increase in BC, Canada; NSW, Australia; and Scotland, despite availability of curative interferon-based treatment that had limited uptake and effectiveness. Since 2004, HCC diagnosis numbers increased significantly in all settings, while age-standardised HCC incidence rates remained relatively stable in BC and Scotland, and increased in NSW. While linkage to HCV treatment data was not possible in all settings, these findings suggest interferon-based antiviral treatment programs have had no impact on the population-level burden and individual-level risk of HCC. During the study period, interferon-based HCV treatment uptake and outcomes remained suboptimal across the settings, particularly among people with advanced liver disease (2-4). Access to highly effective interferon-free DAA regimens is now provided in the three countries and expected to prevent end stage liver disease including HCC. However, there is a need to monitor population level impact of treatment scale up on end stage liver disease. The availability of data on mandatory HCV notifications and the capacity for regular linkage to other administrative databases provides the opportunity for ongoing evaluation and comparison of HCV public health strategies in the DAA era between BC, NSW, and Scotland.

Survival following HCC diagnosis remained extremely poor across the three settings; however, median survival increased in recent years in Scotland. The apparent improvement is consistent with data from the Scottish Cancer Registry and may result from enhanced HCC screening practices and receipt of curative HCC procedures, or may reflect lead time bias (18). Nevertheless, in the mid-2000s, the 3-year and 5-year HCC survival were only 11.8% and 4.4% among Scottish men, respectively (18). HCC outcomes among people with HCV infection are influenced by contributing factors including antiviral treatment uptake. A systematic review and meta-analysis of interferon-based studies demonstrated a 77%

reduction in HCC risk among patients with cirrhosis who achieved sustained virological response (SVR) (19). However, SVR rates were sub-optimal in patients with compensated cirrhosis and interferon-based therapy was not utilised in those with decompensated cirrhosis. DAA regimens have been shown to be highly effective among people with compensated and decompensated cirrhosis, leading to remarkable short-term liver function improvements and even delisting for liver transplantation (20). Yet, contrasting reports of HCC occurrence and reoccurrence risk after DAA-induced viral clearance add to current uncertainties on impact of DAA treatments on HCC risk (8, 9). Older age is a key risk factor for HCC risk among people with cirrhosis, even following SVR, therefore the apparent higher risk of HCC following SVR in the DAA era is likely due to confounding by older age, and also shorter follow-up in DAA era studies (21-24). Further evaluation of the issue of HCC risk post-SVR in the DAA era should be possible in the near future in BC, NSW, and Scotland, as access to government funded DAA treatments improve uptake and availability of integrated surveillance datasets to monitor HCC trends.

Other factors influencing HCC outcomes include appropriate HCC screening and timely HCC treatment initiation. The last decade has witnessed developments in the clinical management of HCC (25); however, these advances have not been translated into major improvements in HCC outcomes at the population-level. HCC screening and diagnosis among people with cirrhosis remain underutilised, given barriers at the patient-, provider- and system-levels, and lack of high-quality evidence in favour of screening (26, 27). In the absence of data from randomised trials, however, observational studies provide evidence linking HCC screening with improved outcomes (28, 29). Given the rising burden of HCC, this evidence should be used to enhance the patient and provider knowledge of HCC risk

factors, screening and treatment options, and improve provision of care through multidisciplinary teams (30).

Across the three settings, older age was the strongest predictor of HCC diagnosis. Other factors associated with HCC diagnosis included alcohol-use disorder, male gender, and HBV/HCV/HIV co-infection. These well-documented risk factors for liver disease progression and tumour development could characterise high-risk populations who might benefit from enhanced prevention strategies (23, 24). Our findings also highlight the implications of the multifactorial etiology of HCC. Due to its complex nature and association with advanced liver disease, HCC prevention and management requires close collaboration among a multidisciplinary team of healthcare professionals (25, 31-33). Given availability of curative procedures, timely diagnosis, selection of a therapeutic intervention, and referral to the appropriate specialist are critical steps for delivery of optimal HCC care.

This study has several limitations. First, to improve the accuracy of trends in HCC diagnosis numbers and age-standardised rates across the settings, these data were displayed and analysed since 2004. In Scotland, the pre-2004 HCC trends were overestimated, given low HCV diagnosis rates during the early-mid 2000s (62% undiagnosed in 2006) (34). Second, two factors might have contributed to lower age-standardised HCC rates in BC, including older age distribution in this setting (compared to the European standard population), and residual confounding. Third, the lack of clinical details on HCC screening, HCC stage of diagnosis, and HCC clinical management strategies is a clear limitation. Therefore, analysis of HCC survival time could not be adequately adjusted for lead-time bias. Fourth, using administrative data for defining alcohol-use disorder has clear limitations. The current study has potential under-ascertainment of alcohol-use disorder, with potential overestimation of the impact on HCC risk if more severe forms of alcohol-use disorder were more likely to be

classified (35, 36). Fifth, HCV diagnosis for surveillance reporting is generally based on anti-HCV antibody detection and does not require HCV RNA confirmation. Thus, an estimated 25% of HCV notifications would have undergone spontaneous HCV clearance. These limitations should, however, not have a major impact on the study findings, given the surveillance definition and systems in the three settings have been stable throughout the study period.

In conclusion, this international comparison of population-level data provides evidence for the rising burden of HCV-related advanced liver disease in BC, NSW, and Scotland, highlighting the combined impact of ageing, suboptimal HCV treatment efficacy and uptake, and low levels of HCC screening and early diagnosis. Over the coming years, the population-level-burden and individual-level risk of HCC would be expected to decline, given the potential impact of well tolerated and effective DAA treatments. In addition, enhanced HCC screening could enable early diagnosis and better management options. Use of administrative databases for surveillance, particularly with the addition of individual-level antiviral treatment data will be a valuable tool for evaluation and monitoring trends of HCV and HCC burden in relation to public health intervention strategies across the three settings.

Conflict of interest statements

J Grebely has received research support and personal fees from Gilead Sciences and Merck. J Grebely has received research support from Abbvie, Bristol-Myers Squibb, and Cepheid. HI has received personal fees from Gilead Sciences. PCH has received research support and personal fees from Roche. PCH has received personal fees from MSD, Gilead Sciences, Abbvie, Janssen, Bristol-Myers Squibb, Pfizer, and Novartis. MK has received research support (via his institution) from Roche, Boehringer Ingelheim, Merck, Siemens Healthcare Diagnostics, and Hologic Inc. MGL has received research support from Boehringer Ingelheim, Merck, Bristol-Myers Squibb, Janssen, and ViiV HealthCare. MGL has received research support and personal fees from Gilead Sciences. MGL has received personal fees from Sirtex Pty Ltd. J George has received personal fees from MSD, Gilead Sciences, Bristol-Myers Squibb, Abbvie, and Pharmaxis. DJG has received personal fees from Gilead Sciences, Merck, and Abbvie. GJD has received research and travel support, and personal fees from Abbvie, Merck, Bristol-Myers Squibb, and Roche. GJD has received research support and personal fees from Janssen. GJD has received personal fees and travel support from Gilead Sciences. GJD has received personal fees from GlaxoSmithKline and Abbott Diagnostics. Other authors have no commercial relationships that might pose a conflict of interest in connection with this manuscript.

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Ethics statement

This publication involved information already collected by population-based health administration registries; therefore, people have not been 'recruited' for the purposes of this research. A waiver of consent has been approved for each component of this work, by the relevant ethics committees in BC and NSW, and the Scottish Government. The BC component of this work has received ethics approval from the Behavioural Research Ethics Board, Office of Research Services, University of British Columbia (reference number H14-01649). The NSW component of this work has received ethics approval from NSW Population & Health Services Research Ethics Committee, Cancer Institute NSW (reference number HREC/13/CIPHS/63). The Scottish component of this work has utilised information within the surveillance framework of National Services Scotland. Approval for updating the linkage was granted by the National Services Scotland Public Benefit Privacy Panel.

Author contributions

MA, NZJ, and GJD contributed to study conception and design, data acquisition and analysis, interpretation of findings, and drafting of the manuscript; MC, J Grebely, EJA, HI, HMV, BH, and JA contributed to data acquisition and analysis and interpretation of findings, and; PCH, MK, MGL, J George, DJG, and SJH contributed to study conception and design, data acquisition and analysis, and interpretation of findings.

Disclaimer

All inferences, opinions, and conclusions drawn in this publication are those of the author(s), and do not necessarily reflect the opinions or policies of the British Columbia Ministry of Health, Australian Government Department of Health, or the Scottish Government.

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Table 1. Demographic characteristics among people with an HCV notification in BC, NSW, and Scotland, since 1995

	BC, Canada HCV notifications 1995-2011				NSW, Australia HCV notifications 1995-2012				Scotland HCV notifications 1995-2013			
	All		HCC[α]		All		HCC[α]		All		HCC[α]	
Characteristics, n %	**n=58,487**	**%**	**n=734**	**%**	**n=84,529**	**%**	**n=1,045**	**%**	**n=31,924**	**%**	**n=345**	**%**
Birth cohort												
≥1965	17,397	30	11	2	45,298	54	50	5	22,889	72	16	5
1945-1964	35,616	61	504	69	34,518	41	732	70	8,051	25	264	77
<1945	5,474	9	219	30	4,713	6	263	25	984	3	65	19
Male[β]	38,212	65	600	82	53,146	63	826	79	21,369	65	278	81
Year of HCV notification												
1995-2000	28,517	49	367	50	39,043	46	490	45	9,141	29	96	28
2001-2006	18,339	31	257	35	26,754	32	345	33	9,645	30	120	35
≥2007	11,631	20	110	15	18,732	22	210	20	13,138	41	129	37
Co-infection status												
None	51,381	88	661	90	80, 112	95	971	93	30,653	96	329	95
HBV	3,255	6	52	7	3,467	4	68	7	587	2	10	3
HIV	2,910	5	11	2	888	1	5	<1	645	2	5	1
HBV/HIV	941	2	10	1	62	<1	1	<1	39	<1	1	<1
Alcohol-use disorder[γ]	11,078	19	122	17	14,797	18	240	23	8,737	27	93	27

[α]HCC diagnosis during 2001-2012 in BC, 2001-2013 in NSW, and 2001-2014 in Scotland, [β]among people with available information, [γ]among people with an HCC diagnosis, alcohol-use disorder was included if occurred prior to HCC diagnosis

Table 2. Adjusted analysis of factors associated with HCC diagnosis among people with an HCV notification in BC, NSW, and Scotland, since 1995

Characteristics, n %	BC, Canada HCV notification, 1995-2011 n=56,640				NSW, Australia HCV notification, 1995-2011 n=83,061				Scotland HCV notification, 1995-2013 n=31,132			
	HCC[α] n=646	aHR[β]	95% CI	*P*	HCC[α] n=908	aHR[β]	95% CI	*P*	HCC[α] n=275	aHR[β]	95% CI	*P*
Birth cohort												
≥1945	459	1.00	-	-	678	1.00	-	-	223	1.00	-	-
<1945	187	5.74	4.84, 6.82	<0.001	230	9.26	7.93, 10.82	<0.001	52	12.55	9.19, 17.15	<0.001
Gender												
Female	116	1.00	-	-	183	1.00	-	-	62	1.00	-	-
Male	530	2.70	2.21, 3.31	<0.001	725	2.59	2.20, 3.05	<0.001	213	1.91	1.44, 2.55	<0.001
Year of HCV notification												
1995-2000	366	1.00	-	-	453	1.00	-	-	86	1.00	-	-
2001-2006	219	1.48	1.24, 1.76	<0.001	315	1.70	1.44, 2.02	<0.001	101	1.69	1.20, 2.28	0.003
≥2007	61	2.21	1.64, 2.98	<0.001	140	3.71	2.88, 4.78	<0.001	88	3.00	1.97, 4.55	<0.001
Co-infection status[δ]												
None	577	1.00	-	-	848	1.00	_	_	262	-	-	-
HBV	48	1.30	0.96, 1.74	0.085	54	1.46	1.11, 1.92	0.007	7	-	-	-
HIV	11	0.42	0.23, 0.77	0.005	5	0.62	0.26, 1.49	0.283	5	-	-	-
HBV/HIV	10	1.24	0.66, 2.33	0.501	1	1.81	0.25, 12.84	0.555	1	-	-	-
Alcohol-use disorder[ε]												
No	532	1.00	-	-	683	1.00	-	-	195	1.00	-	-
Yes	114	1.02	0.83, 1.25	0.829	225	2.05	1.75, 2.39	<0.001	80	1.40	1.08, 1.83	0.013

[α]HCC diagnosis during 2001-2012 in BC, 2001-2013 in NSW, and 2001-2014 in Scotland, [β]adjusted hazard ratio, [γ]birth cohort categories ≥1965 and 1945-1964 were combined, given small numbers of HCC diagnosis among those born in or after 1965, [δ] not included in all adjusted models, given small numbers with an HCC diagnosis and/or *P* value >0.2 in unadjusted analyses, [ε]among people with an HCC diagnosis, alcohol-use disorder was included if occurred prior to HCC diagnosis

Table 3. Median survival after HCC diagnosis among people with an HCV notification in BC, NSW, and Scotland, since 1995

	BC, Canada HCC diagnosis, 2001-2012 n=646			NSW, Australia HCC diagnosis, 2001-2013 n=908			Scotland HCC diagnosis, 2001-2014 n=275		
Study period	**Subjects, n**	**Median survival, years**	**95% CI**	**Subjects, n**	**Median survival, years**	**95% CI**	**Subjects, n**	**Median survival, years**	**95% CI**
2001-2006	191	0.8	0.57, 1.06	225	0.9	0.57, 1.33	52	0.7	0.32, 1.25
≥2007	372	0.8	0.66, 1.00	765	0.9	0.73, 1.14	245	1.5	1.04, 2.41
Total	563	0.8	0.68, 0.98	908	0.9	0.75, 1.10	275	1.3	0.99, 1.97

Figure 1. Age at HCC diagnosis among people with an HCV notification in BC, NSW, and Scotland, since 1995

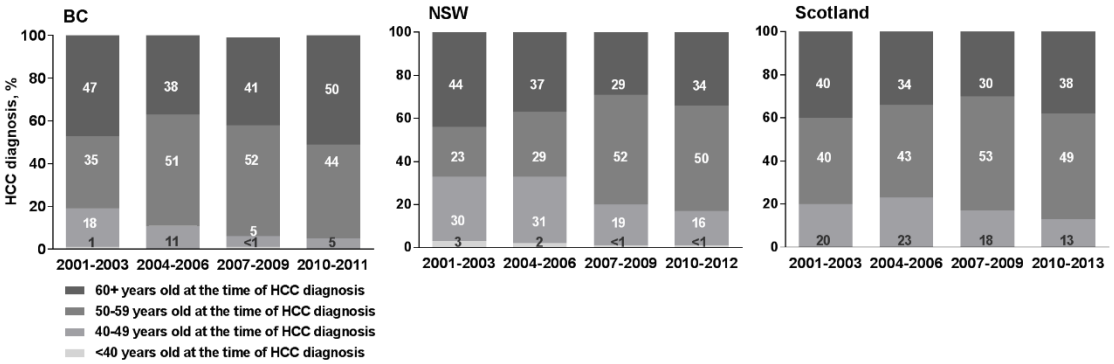
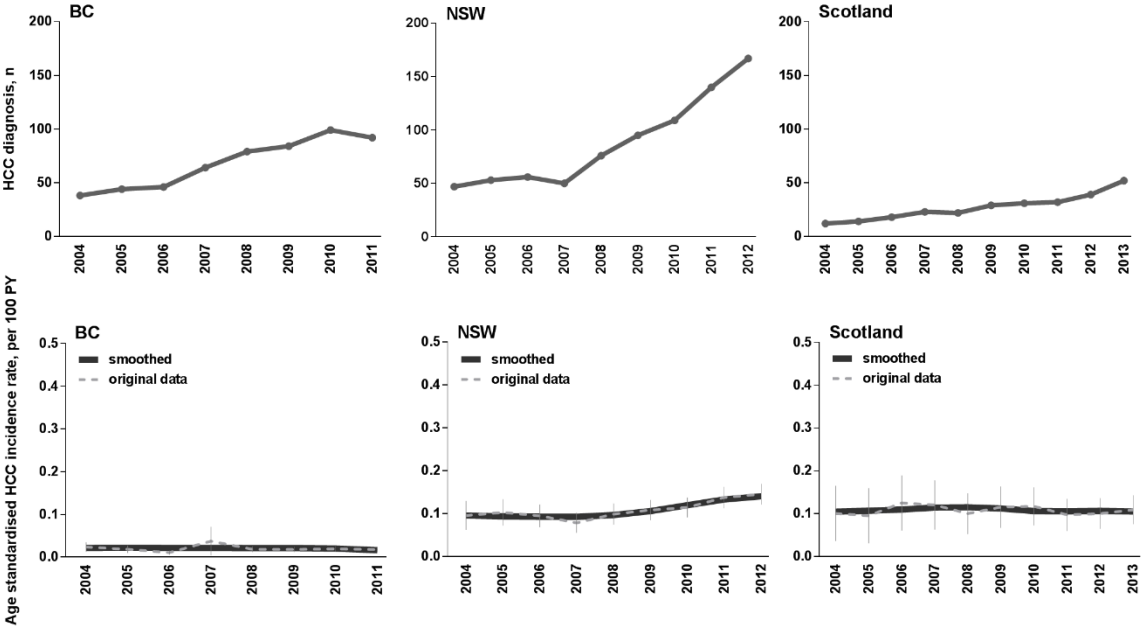


Figure 2. Temporal trends in HCC diagnosis numbers and age standardised incidence rates among people with an HCV notification in BC, NSW, and Scotland, since 1995



Supplementary material

Table 1. Unadjusted analysis of factors associated with DC diagnosis among people with an HCV notification in BC, NSW, and Scotland, since 1995

	BC, Canada HCV notification, 1995-2011 n=56,640				NSW, Australia HCV notification, 1995-2011 n=83,061				Scotland HCV notification, 1995-2013 n=31,132			
Characteristics, n %	**HCC[α] n=646**	**HR[β]**	**95% CI**	***P***	**HCC[α] n=908**	**HR[β]**	**95% CI**	***P***	**HCC[α] n=275**	**HR[β]**	**95% CI**	***P***
Birth cohort												
≥1945	459	1.00	-	-	678	1.00	-	-	223	1.00	-	-
<1945	187	5.27	4.45, 6.25	<0.001	230	6.86	5.90, 7.96	<0.001	52	9.86	7.31, 13.38	<0.001
Gender												
Female	116	1.00	-	-	183	1.00	-	-	62	1.00	-	-
Male	530	2.50	2.05, 3.06	<0.001	725	2.39	2.04, 2.82	<0.001	213	1.72	1.30, 2.28	<0.001
Year of HCV notification												
1995-2000	366	1.00	-	-	453	1.00	-	-	86	1.00	-	-
2001-2006	219	1.38	1.16, 1.64	<0.001	315	1.59	1.34, 1.88	<0.001	101	1.57	1.11, 2.21	0.010
≥2007	61	1.94	1.44, 2.61	<0.001	140	3.26	2.53, 4.19	<0.001	88	2.62	1.73, 3.98	<0.001
Co-infection status												
None	577	1.00	-	-	848	1.00	-	-	262	1.00	-	-
HBV	48	1.21	0.90, 1.62	0.209	54	1.58	1.20, 2.08	0.001	7	1.38	0.65, 2.93	0.396
HIV	11	0.35	0.19, 0.64	0.001	5	0.67	0.28, 1.60	0.363	5	1.05	0.43, 2.54	0.919
HBV/HIV	10	0.98	0.55, 1.82	0.938	1	2.48	0.35, 17.63	0.364	1	3.99	0.56, 28.44	0.167
Alcohol-use disorder [δ]												
No	532	1.00	-	-	683	1.00	-	-	195	1.00	-	-
Yes	114	0.93	0.76, 1.14	0.103	225	1.76	1.51, 2.04	<0.001	80	1.19	0.92, 1.54	0.193

[α]HCC diagnosis during 2001-2012 in BC, 2001-2013 in NSW, and 2001-2014 in Scotland, [β]hazard ratio, [γ]birth cohort categories ≥1965 and 1945-1964 were combined, given small numbers of HCC diagnosis among those born in or after 1965, [δ] among people with an HCC diagnosis, alcohol-use disorder was included if occurred prior to HCC diagnosis

Supplementary material

Table 2. Adjusted analysis of factors associated with HCC diagnosis among people with an HCV notification in BC, NSW, and Scotland, since 1995

Characteristics, n %	BC, Canada HCV notification, 1995-2011 n=56,640				NSW, Australia HCV notification, 1995-2011 n=83,061				Scotland HCV notification, 1995-2013 n=31,132			
	HCC[α] n=646	aHR[β, γ]	95% CI	*P*	HCC[α] n=908	aHR[β, γ]	95% CI	*P*	HCC[α] n=275	aHR[β, γ]	95% CI	*P*
Interaction between birth cohort and calendar period of HCV notification												
Born ≥1945, HCV notified 1995-2000	250	1.00	-	-	308	1.00	-	-	62	1.00	-	-
Born ≥1945, HCV notified 2001-2006	158	1.45	1.18, 1.79	<0.001	246	1.85	1.53, 2.24	<0.001	84	1.82	1.25, 2.65	0.002
Born ≥1945, HCV notified ≥2007	51	2.45	1.77, 3.41	<0.001	124	4.56	3.47, 5.99	<0.001	77	3.23	2.07, 5.04	<0.001
Born <1945, HCV notified 1995-2000	116	5.83	4.68, 7.28	<0.001	145	10.36	8.53, 12.57	<0.001	24	15.66	9.66, 25.08	<0.001
Born <1945, HCV notified 2001-2006	61	9.07	6.81, 12.09	<0.001	69	15.97	11.92, 21.41	<0.001	17	20.33	11.43, 36.18	<0.001
Born <1945, HCV notified ≥2007	10	8.62	4.52, 16.43	<0.001	16	22.55	14.80, 44.10	<0.001	11	34.04	16.73, 69.26	<0.001

[α]HCC diagnosis during 2001-2012 in BC, 2001-2013 in NSW, and 2001-2014 in Scotland, [β]adjusted hazard ratio, [γ] in each setting adjusted for factors associated with HCC diagnosis in multivariable analysis, including gender and alcohol-use disorder (in BC, NSW, and Scotland), and HBV/HIV co-infection (in BC and NSW)