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Cancer incidence in people with hepatitis B or C infection: A large community-based linkage study

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Background/Aims: Risks of hepatocellular carcinoma (HCC) following hepatitis B and/or hepatitis C virus (HBV/HCV) infection are well known, those for other cancers are less well understood. The aim was to quantify the risk of cancers among persons diagnosed with HBV/HCV infections.

Methods: The data from a cohort of 39109 HBV, 75834 HCV, and 2604 HBV/HCV co-infected persons notified to the State health department, 1990–2002, were probabilistically linked to the Cancer Registry and standardised incidence ratios (SIRs) for cancer were calculated.

Results: The match rate for any cancer was 2.7%, 2.3% and 3.3% for HBV, HCV and HBV/HCV co-infected notifications. SIRs for HCC were 30.6 (95% CI 25.7–36.5), 22.7 (95% CI 19.1–26.5) and 30.3 (95% CI 13.6–67.5), respectively. Increased risk was detected for Burkitt's lymphoma and HBV (SIR 12.9, 95% CI 5.4–30.9) and immunoproliferative malignancies following HCV (SIR 5.6, 95% CI 1.8–17.5).

Conclusions: The risk of HCC in the infected cohort was 20–30 times greater than in the uninfected population with SIRs two to three times greater than those for the other HBV/HCV infection associated cancers. The modest though significant risk of immunoproliferative malignancies associated with HCV infection is consistent with recent findings.

Keywords: Hepatitis B; Hepatitis C; Hepatocellular carcinoma; Epidemiology; Linkage; Cancer

1. Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are primarily hepatropic. Chronic infection with these viruses causes progressive liver disease and hepatocellular carcinoma (HCC) [1–4], and HBV/HCV co-infection further increases the risk of HCC [5].

Also HBV and HCV have been shown more recently to be lymphotropic [6–8]. Some studies have examined the role of these infections in non-Hodgkin's lymphoma (NHL) but the findings were inconclusive [9,10]. HCV infection has been shown to be associated with other malignant diseases such as multiple myeloma and thyroid cancer [11].

There has been no single study that systematically examined the risk of all tumor types following HBV and/or HCV infection. In order to provide precise estimates of the risk of cancer following HBV and HCV infection, we investigated the incidence of malignant

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Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; NHL, non-Hodgkin's lymphoma; NSW, New South Wales; NDD, Notifiable Diseases Database; NDI, National Death Index.

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diseases in a large community-based cohort of people diagnosed with HBV and HCV infection in New South Wales (NSW), Australia. We hypothesised that risks would be elevated for (1) liver cancer in those with HCV or HBV infection, (2) lymphomas and haematopoietic diseases in those with HCV infection and that (3) there is no association between other cancer types and HBV or HCV infection.

2. Methods

We conducted a retrospective study, linking cases of HBV and HCV infection reported in the state of NSW, to the population-based NSW Central Cancer Registry and the National Death Index.

2.1. Data sources

Notification of newly diagnosed HBV and HCV infection to the NSW Health Department's Notifiable Diseases Database (NDD) has been mandatory for laboratories and medical practitioners (acute cases only) since 1991 [12]. HBV notification requires detection of HBV surface antigen (HBsAg) or HBV DNA. HCV notification requires detection of anti-HCV antibody or HCV RNA. Date of notification, sex, date of birth, last name, first name, date of diagnosis, postcode of residence and NDD registration number were extracted from the NDD for people notified with HBV or HCV infection between 1 January 1990 and 31 December 2002.

Notification of incident cancer to the NSW Central Cancer Registry (CCR) has been mandatory for hospitals, nursing homes, the Registrar of Births, Deaths and Marriages, radiotherapists and pathologists since 1972 [*Public Health Act NSW* 1991]. Notifications of all primary diagnoses are entered on the CCR; metastases and recurrences are not recorded. Year and month of diagnosis, sex, date of birth, last name, first name, date of diagnosis, postcode, ICD10 classification code [13] and sequence number were extracted for notifications received at the Cancer Registry by the end of 2002.

The National Death Index (NDI) database contains records of all deaths in Australia since 1980, based on reports from the Registrars of Births, Deaths and Marriages in each State and Territory. Last name, first name, date of birth (or estimated year of birth), age at death, sex, date of death, ICD10 classification code for underlying cause of death and NDI registration number were extracted for notifications received by the end of 2002.

2.2. Linkage procedure

Record linkage between the NDD cohort, CCR and NDI was carried out in three steps: (i) matching HBV and HCV notifications to identify co-infected cases, (ii) matching NDD notifications to cancer records in the CCR, (iii) matching NDD notifications to deaths in the NDI. Linkage was conducted probabilistically on the basis of name, date of birth, sex and place of residence data using AUTOMATCH [14,15]. Personal identifiers were removed from the data following steps one to three.

For the analysis of incident cancers the cohort was restricted to people diagnosed with HBV or HCV infection in whom the cancer of interest had not been reported prior to, or one year from, the date of HBV/HCV notification and for whom NDD information about sex and age at notification was available.

2.3. Statistical analysis

Cancer incidence was determined using person–time methodology. Person–time at risk was calculated for each person in the HBV/HCV cohort as time from date of NDD notification to either date of cancer or the first of date of death or 31 December 2002. For HBV/HCV co-infection, risk time commenced at the later of HBV or HCV notification.

For each type of cancer, incidence observed in the study cohort was compared to expected incidence derived from NSW population cancer rates by calculating standardised incidence ratios (SIRs) [16,17]. Expected numbers of cancers were calculated by five year age group, sex and calendar year. Confidence intervals (CIs) for SIRs were estimated assuming that the observed numbers of cancers followed a Poisson distribution. 95% confidence intervals do not take into account the number of evaluations. Cancer types were categorised according to the two digit ICD10 code. HCC, lymphomas and haematopoietic disease sub-groups were distinguished using the third digit of the ICD10 code. NHLs were analysed as a group (ICD10 codes C82–C85 and C96).

For HCC only (ICD 22.0), the sensitivity of SIRs for HBV/HCV co-infection was assessed using the date of first infection as the commencement of risk and including HCC subsequent to this time. For the three infection groups incidence rates were calculated using Kaplan–Meier methods, and stratified by sex.

2.3.1. Adjustment for HIV infection

There are strong associations between HIV infection, anal sex and Kaposi's sarcoma (KS), NHL and anal neoplasia [18,19], and a possible association between HIV and HBV or HCV infections. Therefore, SIRs were also calculated for these cancers after excluding HBV/HCV notifications from the 10 postcodes which account for 40% of HIV notifications [HIV surveillance data personal communication] but in which 3% of the NSW population reside. These are areas in which a high proportion of homosexual men reside [20].

2.3.2. Adjustment for date of HCV infection

For the majority of our cohort the date of HCV infection probably occurred many years prior to the date of notification [16]. A sub-analysis, based on estimated duration of HCV infection, was conducted for cancers significantly associated with HCV. The median age at HCV infection is estimated to be 25 years [16]. For notifications where the age of infection was greater than 25 years, the date of risk commencement was recalculated to correspond to 25 years of age. Associations with HBV infection were not assessed in this analysis as the risk factors for HBV infection are varied and age related [17].

Data linkage was conducted by NSW Health (NDD-CCR linkage) and the Australian Institute of Health and Welfare (AIHW) (NDD-NDI linkage). All personal identifiers were removed before the linked data were transferred to the National Centre in HIV Epidemiology and Clinical Research (NCHECR) for analysis. Ethics approval for the study was granted by NSW Health, The Cancer Council NSW, AIHW and the University of New South Wales.

3. Results

A total of 120815 HBV and HCV infections were notified to NDD from 1990 to 2002. The data linkage processes identified 664 duplicate records and 2604 persons with both HCV and HBV notifications to give a final study population of 117547 persons. From this population, three groups were defined based on HBV and HCV infection status (Table 1). The three groups were similar in their median year of NDD notification, and age at NDD notification; a larger proportion of the HBV/HCV co-infected group were male. Three and one percent of HBV and HCV notifications, respectively, were notified as acute infections.

Table 1
Characteristics and outcomes of data linkage among persons with HBV and/or HCV notified in NSW 1990–2002

	Viral hepatitis notification		
	HBV ($n = 39109$)	HCV ($n = 75834$)	HBV/HCV co-infected ($n = 2604$)
Year of viral hepatitis notification, median (IQR)	1997 (1994–2000)	1997 (1995–2000)	1999 (1996–2002)[a]
Age at viral hepatitis notification [years], median (IQR)	35 (27–44)	34 (28–41)	35 (29–42)[a]
Missing [n] (%)	1507 (4)[b]	789 (1)	13 (<1)
Males [n] (%)	20808 (53)	47903 (63)	1932 (74%)
Missing [n] (%)	772 (2)	555 (1)	14 (1)
Linked to cancer record [n] (%)	1052 (2.7)	1761 (2.3)	85 (3.3)
Linked to >1 cancer record (%)	47 (0.12)	103 (0.14)	0 (0)
Person years of follow up[c]	191496	356775	10388

IQR, interquartile range.
[a] At second infection.
[b] 84% received before 1993.
[c] To first incident cancer, see Section 2 for details.

3.1. Cancers

The median time at risk for first incident cancer for the HBV, HCV and HBV/HCV co-infected groups was 5.2, 4.6 and 3.8 years, respectively. The SIRs for cancers in these people are summarised in Table 2. Persons with HBV infection had increased rates of neoplasms of the nasopharynx (SIR = 3.1, 95% CI 1.3–7.3), and Kaposi's sarcoma (KS) (SIR = 3.4, 95% CI 1.6–7.1) (Table 2). Anal neoplasms were increased for co-infection and in men with HCV (observed cases (O) = 4, SIR = 3.5, 95% CI 1.3–9.3). Cancers of unknown primary site occurred at modestly elevated rates in both HCV infected (SIR = 1.5, 95% CI 1.1–2.0) and HBV/HCV co-infected (SIR = 4.4, 95% CI 1.4–13.7) groups.

Observed numbers were lower than expected in both the HBV and HCV mono-infected groups for: any cancer, melanoma, colorectal, breast (in women), and prostate neoplasms; in the HBV group for neoplasms of the brain and bladder; and for neoplasms of the ovary, testis and thyroid in those with HCV infection (SIR < 0.80, $p < 0.05$). No cancers occurred at significantly lower than expected rates in the HBV/HCV co-infected population.

3.2. HCC

The overall observed cases and SIRs for HCC (IDC10 C22.0) were two to three times greater than that for any other cancer (Tables 2 and 3). Only 3/127, 5/148 and 0/6 liver cancers were not HCC in the HBV, HCV and HBV/HCV co-infection groups, respectively. There were no observed HCCs linked to HBV or HCV in persons under the age of 15 years. The HCC SIR was similar for those with HBV alone (SIR = 30.6), and HBV/HCV co-infection (SIR = 30.3) and slightly lower for HCV infection (SIR = 22.5). Incidence of HCC was 6.5, 4.0 and 5.9 per 1000 for the HBV, HCV and HBV/HCV co-infected groups, respectively. Incidence for males was greater than for females in all the hepatitis groups. However, in the HCV and co-infected groups, females had higher SIRs than males, significantly so for the HCV group (SIR = 44.0, 95% CI 32.6–59.6 females, SIR = 18.7, 95% CI 15.4–22.7 males). In the alternative analysis of the co-infected cohort, where risk was taken to commence at first rather than second infection, the observed number of HCCs was 9 with SIR = 35.3 (95% CI 18.4–67.9).

3.3. Lymphoid, haematopoietic and related neoplasms

SIRs for lymphoid and haematopoietic related neoplasms were close to one in the three infection groups (Table 2). None of the major sub-groups of NHL were significantly elevated in persons with HBV infection, though the risk of sub-type Burkitt's lymphoma was significantly elevated (SIR = 11.8, 95% CI 4.9–28.4). In persons with HCV infection, risk was increased for immunoproliferative disease (SIR = 5.6, 95% CI 1.8–17.5) with two of the three cases identified as Waldenström's macroglobulinaemia (WM). There were single incident cases of T-cell lymphoma and other NHL in the HBV/HCV co-infected population.

3.4. Adjustment for HIV infection

Adjustment for possible HIV co-infection by exclusion of data from high prevalence postcodes of residence resulted in exclusion of 7% (2748/39109) of persons with HBV, 10% (7435/75834) with HCV and 8% (217/2604) with HBV/HCV co-infection. In this analysis, rates of KS (O = 4, SIR = 2.2, 95% CI 0.5–4.9) and anal neoplasms in men (O = 3, SIR = 2.8, 95% CI 0.9–8.8) were no longer associated with HBV infection. HBV infection remained associated with Burkitt's lymphoma (O = 5, SIR = 12.9, 95% CI 5.4–30.9). HCV infection remained associated with immunoproliferative diseases (O = 3, SIR = 6.1, 95% CI 2.0–19.0) and SIRs were elevated, though not significantly, for diffuse NHL (O = 17,

Table 2
Malignant neoplasms in persons with HBV, HCV or HBV/HCV infection, observed numbers of incident[a] cancers, SIRs and 95% confidence intervals in NSW 1990–2002

Cancer type		Viral hepatitis notification								
ICD10		HBV			HCV			HBV/HCV co-infected		
Code	Description	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
C	All	397	0.6	0.6–0.7	682	0.7	0.7–0.8	33	1.3	0.9–1.9
C00	Lip	1	0.2	0.0–1.1	12	1.0	0.6–1.7	0		
C01	Tongue	2	0.5	0.1–2.2	6	1.1	0.5–2.4	0		
C03–6	Mouth	0			7	1.5	0.7–3.2	0		
C09	Tonsil	0			6	2.1	1.0–4.8	0		
C11	Nasopharynx	5	3.1	1.3–7.3	1	0.3	0.0–2.3	0		
C15	Oesophagus	2	0.4	0.1–1.5	4	0.5	0.2–1.4	0		
C16	Stomach	11	1.0	0.6–1.8	23	1.4	0.9–2.1	0		
C18	Colon	15	0.4	0.2–0.6	37	0.6	0.5–0.9	0		
C19–20	Rectum	14	0.6	0.3–1.0	11	0.3	0.2–0.6	2	2.1	0.5–8.5
C21	Anus	4	2.0	0.7–5.2	4	1.2	0.5–3.2	1	11.1	1.6–78.6
C22	Liver	127	25.2	21.2–29.9	148	18.8	16.0–22.1	6	25.3	11.4–56.4
C23–24	Gallbladder	1	0.4	0.1–2.6	2	0.5	0.1–2.0	1	11.0	1.6–78.4
C25	Pancreas	6	0.7	0.3–1.6	17	1.4	0.8–2.2	1	3.3	0.5–23.7
C30–31	Nasal	1	1.0	0.1–6.9	1	0.6	0.1–4.0	0		
C32	Larynx	4	0.9	0.4–2.5	5	1.0	0.4–2.3	1	6.2	0.9–44.0
C33–34	Trachea	41	0.9	0.7–1.3	68	1.2	0.9–1.5	4	1.2	0.4–3.2
C43	Melanoma	10	0.1	0.1–0.2	53	0.4	0.3–0.5	0		
C45	Mesothelioma	0			3	0.8	0.3–2.6	0		
C46	Kaposi's sarcoma	7	3.4	1.6–7.1	7	1.4	0.7–3.0	1	6.5	0.9–45.9
C47–49	Connective and soft tissue	1	0.2	0.0–1.6	3	0.4	0.1–1.2	0		
C50	Breast	41	0.5	0.3–0.6	50	0.4	0.3–0.5	0		
C51	Vulva	0			1	0.5	0.1–3.9	0		
C53	Cervix uteri	3	0.3	0.1–1.1	16	1.1	0.7–1.9	1	4.0	0.6–28.1
C54	Corpus uteri	3	0.4	0.1–1.4	5	0.5	0.2–1.3	0		
C56	Ovary	2	0.3	0.1–1.1	3	0.3	0.1–0.9	0		
C61	Prostate	25	0.4	0.3–0.6	32	0.4	0.3–0.6	1	0.5	0.1–3.4
C62	Testis	4	0.4	0.2–1.1	15	0.6	0.4–1.0	1	1.1	0.2–7.9
C64	Kidney	7	0.5	0.2–1.1	18	0.9	0.6–1.4	2	3.4	0.8–13.5
C65	Renal	0			1	0.5	0.1–3.4	0		
C67	Bladder	4	0.4	0.1–0.9	11	0.7	0.4–1.2	1	2.5	0.4–18.0
C70–72	Brain and CNS	4	0.4	0.1–1.0	12	0.7	0.4–1.2	0		
C73	Thyroid	9	0.6	0.3–1.1	9	0.3	0.2–0.7	2	3.2	0.8–12.7
C75	Endocrine	0			0			1	38.9	5.5–276.1
C81	Hodgkin	4	0.8	0.3–2.1	4	0.4	0.2–1.1	0		
C82–85,96	NHL	27	1.2	0.8–1.7	33	0.9	0.6–1.2	2	0.8	0.2–3.0
C82	Follicular NHL	8	1.4	0.7–2.8	6	0.6	0.3–1.4	0		
C83	Diffuse NHL	10	1.0	0.5–1.8	19	1.1	0.7–1.7	0		
C84	T-cell lymphoma	2	1.8	0.4–7.1	2	1.1	0.3–4.2	1	17.3	2.4–122.6
C85	Other NHL	7	1.2	0.6–2.6	6	0.6	0.3–1.4	1	4.0	0.6–28.7
C88	Immunoproliferative diseases	0			3	5.6	1.8–17.5	0		
C90	Multiple myeloma	4	0.7	0.3–1.8	7	0.8	0.4–1.7	0		
C91	Lymphoid leukaemia	2	0.3	0.1–1.3	9	1.0	0.5–1.8	0		
C92–94	Other leukaemia	3	0.4	0.1–1.1	8	0.6	0.3–1.1	2	2.2	0.6–8.9
C95	Leukaemia unspecified	0			2	1.9	0.5–7.5	0		
C96	Other lymphoid	0			0			0		
C76–80, C25, C39	Unknown primary site	0			40	1.5	1.1–2.0	3	4.4	1.4–13.7

ICD, international classification of diseases; O, observed number of cases; SIR, standardised incidence ratio; CI, confidence interval, 95% confidence intervals do not take into account the number of evaluations; NHL, non-Hodgkin's lymphoma; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection.

[a] Excludes cancers prior to, or within one year subsequent from, hepatitis B and or C notification.

SIR = 1.1) and lymphoid leukaemia (O = 9, SIR = 1.1). In the HCV infected population, the exclusion of high HIV prevalence postcodes resulted in greater reduction of high-grade (3/19, 16%) than low-grade B-cell NHLs (1/23, 4%).

3.5. Adjusted age at HCV infection

In the cohort, 82% (62367/75834) of the HCV notifications and 86% (2239/2604) of the HBV/HCV notifications (at time of second infection) were more than 25

Table 3
Hepatocellular carcinoma (ICD10 C22.0) in persons with HBV, HCV or HBV/HCV infection, prevalent cancers, observed and expected numbers of incident cancers, rates, and SIRs and 95% confidence intervals by sex in NSW 1990–2002

Viral hepatitis notification	Prevalent cases[a]	Incident cases				
		Observed	Rate/10000 py	Expected	SIR	95% CI
HBV						
All	323	124	6.52	4.1	30.6	25.7–36.5
Male	267	105	10.41	3.4	30.6	25.3–37.1
Female	54	19	2.13	0.6	30.7	19.6–48.1
HCV						
All	268	143	4.04	6.4	22.5	19.1–26.5
Male	187	101	4.60	5.4	18.7	15.4–22.7
Female	78	42	3.13	1.0	44.0	32.6–59.6
HBV/HCV co-infected						
All	18	6	5.85	0.2	30.3	13.6–67.5
Male	16	5	6.52	0.2	27.5	11.4–65.9
Female	2	1	3.86	0.0	64.2	9.0–455.8

py, person years; SIR, standardised incidence ratio; CI, confidence interval, 95% confidence intervals do not take into account the number of evaluations; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection.
[a] Includes two persons with HBV and three with HCV of unknown sex.

years old. After adjustment of risk commencement the association between HCV infection and immunoproliferative disease (SIR 3.5, 95% CI 1.1–10.9) remained positive. The SIR for WM remained elevated though the association was no longer statistically significant (SIR 2.8, 95% CI 0.7–11.3). Results were similar after excluding HIV related postcodes. The associations for HCV and HBV/HCV co-infection and HCC were slightly lower than in primary analysis with SIRs of 12.7 (95% CI 10.8–14.9) and 14.9 (95% CI 6.7–33.2), respectively. The incidence rates of HCC in persons with HCV (1.2, 95% CI 1.1–1.5 per 10000 person years) and HBV/HCV co-infection (1.5, 95% CI 0.7–3.4 per 10000 person years) were significantly lower than in the primary analysis (4.0, 95% CI 3.4–4.8 per 10000 person years and 5.8, 95% CI 2.6–13.0 per 10000 person years, respectively).

4. Discussion

As far as we are aware this is the first community-based study to investigate the risk of any cancer following diagnosis of HBV/HCV. Further, it is the first study in which the risks of either mono-infection were compared to co-infection. In all infection groups the risk of HCC was 20–30 times that of the general population. Risk of HCC was also more than three times that of any other cancer within the cohort. Our data show a modest increased risk of immunoproliferative malignancies among people with HCV infection compared to the general population.

The major strengths of our study are the community-based cohort, the large study population and inclusion of HBV, HCV and HBV/HCV co-infected groups. It is estimated that 70–80% of HCV and 60% of HBV infections are reported to notification systems in Australia [21,22]. Therefore, we have a large cohort in which associations can be described with high precision and a study base that is largely representative of the infected populations (particularly HCV infections) in Australia.

While the risks of HCC associated with HBV and HCV infection have been frequently reported [23], there have been few population-based studies of HBV and HCC in countries of low endemicity, such as Australia [24]. Three studies investigating HCC mortality in HBsAg positive cohorts in the USA and UK reported standardised mortality ratios between 10 and 42 [23]. Our SIR of 31 is consistent with these studies. Case control studies report the synergism between HBV and HCV on HCC is between sub-additive, greater than in our study, and multiplicative [5,28].

Incidence rates of HCC in HCV infected cohorts range from 14 and 18 per 100000 in persons 65 years and older to 334 per 100000 in person 40 years and older [25,26]. Male sex is reported to confer a two- to fourfold increased risk of HCC among persons with HCV infection [27,26], higher than the SIR of 1.48 in this study. The higher SIR for HCC in females compared with males is unusual but may be explained by an uneven relative distribution of other risk factors for HCC, such as high alcohol consumption.

There has been recent suggestion of an association between HCV infection and lymphoma. Meta-analyses of case control studies investigating the association between HCV and NHL reported statistically significant odds ratios (ORs) of between 2.5 and 10.8, with the highest ORs reported from studies of B-cell type NHL, those using blood donor controls and those with an Italian study population [29,30]. In a Japanese hospital-based cohort study, four patients developed B-cell type NHL in 124000 person years of follow-up with an age, sex and calendar year adjusted SIR of 1.9

(95% CI 0.6–5.4) [31]. A Swedish population-based cohort study of 27150 people diagnosed with HCV infection found significantly increased risks for B-cell NHL and multiple myeloma in persons estimated to have been infected for more than 15 years (SIR = 1.89, 95% CI 1.10–3.03 and SIR = 2.54, 95% CI 1.11–5.69, respectively). However, after adjusting for HIV co-infection the risk of B-cell NHL was no longer statistically significant (SIR = 1.86, 95% CI 0.12–6.75) [32].

In our HCV infection group, a number of B-cell NHLs (diffuse NHL, immunoproliferative malignancies and chronic lymphocytic leukaemias) had SIRs greater than one, even after adjustment for possible HIV co-infection. Further, these low-grade NHLs are rarely associated with HIV infection [33]. In studies where NHL sub-types have been reported, HCV infection has been associated with all major sub-types [34–38], most frequently with lymphoplasmacytic lymphoma and immunocytoma [36,39,40], the underlying pathological diagnoses in WM [41,42]. Our study in conjunction with other epidemiological and biological studies [43] suggests an increased though low risk of B-cell lymphoma following HCV infection. Further investigations to confirm this association are warranted.

Our study is retrospective and based on population registries with only routinely collected information available. Thus, possible confounding by route of transmission, country of birth or other risk factors could not be directly assessed. An estimated 50% of Australia's chronic HBV infection is found in migrants from Asian countries. Other high risk groups include injecting drug users (IDUs), homosexual men and indigenous populations [24]. IDU is thought to account for approximately 80% of HCV acquisitions [44].

The association between HBV and nasopharyngeal cancer is probably confounded by country of birth. All five matched cases were in persons born in China and South East Asia and nasopharyngeal cancer is strongly associated with SE Asian country of birth [45–47]. Confounding by HIV co-infection (and also anal sex), particularly for association with KS and anal neoplasms in men, was reduced in this study by exclusion of areas of residence with a high prevalence of HIV infection. However, residual confounding may have contributed to the increased risk of Burkitt's lymphoma, a high-grade lymphoma commonly associated with HIV infection, in people with HBV infection.

Notification (or surveillance) bias, which may have resulted in an overestimation of risk, was accounted for by exclusion of cancers notified within 1 year of HBV or HCV notification. The cohort included those diagnosed with HBV and HCV who may have cleared the infection (either spontaneously or by treatment) and excludes those with undiagnosed infection. Further risk in this study pertains to risk from date of diagnosis and is likely to overestimate the risk of cancer from time of HBV/HCV infection. This hypothesis is corroborated by our adjusted analysis in which SIRs were lower than in the primary analysis. Further, for HCV the median age at infection is estimated to be 20–25 years whereas the median age at notification in the cohort was 34 years [44]. The median time from HCV infection to cirrhosis is estimated to be 30 years with more severe liver related outcomes taking longer to become evident [48,49]. Therefore, the results of this study describe relatively early outcomes.

In conclusion, this large scale community-based cohort study of incident cancers among persons with HBV and HCV infection shows that while it is possible that HCV may progress to immunoproliferative diseases, the relative risk is low. The relative risk of HCC is high in all infection groups. We are yet to see whether treatment uptake (especially for hepatitis C) can affect population rates of HCC and possibly NHL. Association between HBV infection and Burkitt's lymphoma has not been previously described and warrants further investigation in a well-characterised cohort study where risk factors can be accurately determined.

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