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Title

Novel population-based study finding higher than reported hepatocellular carcinoma incidence suggests an updated approach is needed

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List of Abbreviations

HCC	Hepatocellular carcinoma
VCR	Victorian Cancer Registry
PLC	Primary liver cancer
ICC	Intrahepatic cholangiocarcinoma
ABS	Australian Bureau of Statistics
MSD	Melbourne Statistical Division
ICD	International classification of diseases
BCLC	Barcelona Clinic Liver Cancer
AASLD	American Association for the Study of Liver Diseases

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Abstract

Novel population-based study finding higher than reported hepatocellular carcinoma incidence suggests an updated approach is needed

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Background Hepatocellular carcinoma (HCC) incidence is rising rapidly in many developed countries. Primary epidemiological data has invariably been derived from cancer registries that are heterogeneous in data quality and registration methodology; many registries have not adopted current clinical diagnostic criteria for HCC and still rely on histology for classification. We performed the first population-based study in Australia using current diagnostic criteria, hypothesizing that HCC incidence may be higher than reported.

Method Incident cases of HCC (defined by AASLD diagnostic criteria or histology) were prospectively identified over a 12-month period (2012-2013) from the population of Melbourne, Australia. Cases were captured from multiple sources: admissions to any of Melbourne's seven tertiary hospitals, attendances at outpatients, radiology, pathology and pharmacy services. Our cohort was compared to the Victorian Cancer Registry (VCR) cohort (mandatory notified cases) for the same population and period, and incidence rates were compared for both cohorts.

Results There were 272 incident cases (79% male, median age 65 years) identified. Cirrhosis was present in 83% of patients, with HCV infection (41%), alcohol (39%), and HBV infection (22%) the commonest aetiologies present. Age-standardized HCC incidence (per 100,000, Australian Standard Population) was 10.3 (95%CI: 9.0 to 11.7) for males and 2.3 (95%CI: 1.8 to 3.0) for females. The VCR reported significantly lower rates of HCC: 5.3 (95%CI: 4.4 to 6.4) and 1.0 (95%CI: 0.7 to 1.5) per 100,000 males and females respectively, $p<0.0001$.

Conclusion HCC incidence in Melbourne is two-fold higher than reported by cancer registry data due to underreporting of clinical diagnoses. Adoption of current diagnostic criteria and additional capture sources will improve registry completeness. Chronic viral hepatitis and alcohol remain leading causes of cirrhosis and HCC.

HEP-15-0704

Primary liver cancer (PLC) has become the second leading cause of cancer mortality worldwide and is also the fifth most common cancer(1). Hepatocellular carcinoma (HCC), the predominant type of primary liver cancer, mostly arise in the setting of cirrhosis, with the most common aetiologies being chronic viral hepatitis B and C, alcohol and non-alcoholic fatty liver disease.

The incidence of HCC has been widely reported to be increasing in regions with historically low incidence(2,3). In Australia, liver cancer is the fastest rising cause of cancer death (4). Multiple factors may contribute to this phenomenon, including increased migration from regions with high HCC and viral hepatitis prevalence, an increasing burden of cirrhosis as patients are surviving longer with better medical treatments, and the obesity epidemic causing rising prevalence of non-alcoholic steatohepatitis related cirrhosis (5).

The HCC epidemiology literature has been reliant upon cancer registries as the primary source of incidence data(6), and hence is subject to the limitations of cancer registry data capture methodology. Cancer registries vary in a number of important features. Mandatory reporting laws that help improve registration completeness are not universal and where laws exist, not all potential sources of case identification are utilised. For example, in Victoria, Australia, cancers identified from hospital admissions and pathology services are registered but diagnoses made in outpatient settings and radiology services are not reportable, possibly leading to incomplete registration.

Differences also occur in the criteria for HCC classification. The traditional approach used by the Victorian Cancer Registry (VCR, Victoria, Australia) and many other registries across the world (eg. China, Italy(7) (8)) relies upon histological verification for HCC classification; all clinically diagnosed PLC without histology are classified as Liver Cancer Unspecified. However, in current clinical practice, HCC is predominantly diagnosed using clinico-radiological criteria in subjects with cirrhosis rather than histology, as approved by current guidelines from Learned Societies(9,10). Hence, some registries (United States, some European countries) now accept clinical diagnosis as a basis for HCC classification(7).

In this context, many studies have therefore reported HCC incidence using total PLC rates as a surrogate marker (11,12). However, this is misleading as a significant proportion of primary liver cancers are intrahepatic cholangiocarcinomas (ICC), forming up to 45% of PLC figures as reported by some cancer registries(8) (Figure 1). Compared to ICC, HCC has entirely different biologic, prognostic and management implications and hence epidemiological research needs to be HCC specific. Accurate and current epidemiology informs policy decisions by government concerning health resource utilization, identifies risk factors for HCC, and provides targets for prevention.

In Victoria, Australia, we hypothesised that HCC incidence rates may be higher than currently reported by the cancer registry, due to incorrect classification of clinically diagnosed cases, and incomplete capture from non-reported sources. Therefore, our aim was to determine the incidence rate of HCC in an independent population-based study using current clinical diagnostic criteria. We then compared results with data from the VCR for the same period and population.

Methods

The Study Population

We performed a population-based study of HCC incidence in Melbourne, Australia, within the geographical region defined by the Australian Bureau of Statistics (ABS) as the Melbourne Statistical Division (MSD). This area has an estimated population of 4,300,207 (ABS Census 2011, projected for the 2012/2013 incident period), suitable for epidemiological study. The population is ethnically diverse with 35% born outside Australia(13) including those from countries with high HCC incidence.

This region contains seven tertiary referral public health services all of which were participating study sites. Each health service consists of a tertiary university teaching hospital, with associated secondary hospitals, radiology and pathology services. There were no tertiary hospitals in Victoria outside the MSD. The VCR is the population-based registry responsible for the MSD. Patients residing outside the MSD (defined by residential postcodes) were excluded.

Case Ascertainment

From 1 July 2012 to 30 June 2013, potential cases were screened from multiple concurrent and overlapping sources. These included patients attending HCC outpatient clinics or discussed at multidisciplinary meetings as well as those found on database searches of the radiology, pathology, pharmacy and medical coding services of the hospitals involved. In addition, the tertiary hospital hepatology units kept prospective databases of patients diagnosed with HCC and these were also queried. Private physicians and surgeons managing HCC in the community were also invited and contributed to case finding.

Search parameters included radiological procedures (transarterial chemoembolisation, radio frequency, microwave or ethanol ablation), histological diagnoses of HCC (ICD-0-3 C22.0 M8170/3), sorafenib dispensing and medical admissions coding of International Classification of Diseases ICD-10 C22.0 Hepatocellular carcinoma, and C22.9 Liver Cancer Unspecified. American Association for the Study of Liver Disease (AASLD) clinico-radiological diagnostic

criteria (9) and/or histology were used to define HCC cases. Cases of HCC recurrence or diagnosis dates outside the designated study period were excluded. Readmissions or attendance of a case at another site was only counted for the first instance.

Data collected included demographics, underlying aetiology of chronic liver disease, hepatic synthetic liver function, the presence of cirrhosis, Child-Pugh scores, mode of diagnosis, involvement in surveillance programs and tumour staging according to Barcelona Clinic Liver Cancer (BCLC) staging (10). The aetiology of chronic liver disease was defined by the consulting physician with verification from pathology or radiology results if it was not documented. Data were de-identified and recorded on a secure study database.

Independent human research ethics committees governing each of the associated tertiary health networks granted ethics approval.

Victorian Cancer Registry Correlation

Current Australian legislation mandates notification of cancers from hospital admissions and pathology, but not outpatient attendances such as clinics or radiology. The VCR provided de-identified data for incident cases of all primary liver cancer subtypes (ICD-10 C22.0 to C22.9) notified during the study incident period. We excluded cases with residential postcodes outside the MSD. In 2012-2013, the VCR methodology required histological verification to code a liver cancer as HCC (C22.0). Clinically diagnosed HCC reported to the VCR without histology were coded as Liver Cancer Unspecified (C22.9). The de-identified information provided by the VCR included patient initials, dates of birth, residential postcode, diagnostic coding and source of registration (public hospital, private hospital, pathology, death certificate). Records were matched to our cohort using these parameters.

Statistical Analysis

Age-standardised incidence rates were calculated using the direct-method for age-standardisation with 18 groups of 5 year age groups (0-, 5-, 10-,…, 85+) for each sex separately. The population data for each age group was derived from ABS Australian Census 2011, with the same figure used as denominator for both MSD and VCR rate calculations. Incidence rates were

standardised to the Australian Standard Population, using the Australian Census 30 June 2001 standard population as recommended by the ABS(14). Incidence rates were reported with 95% confidence intervals (CIs), assuming a Poisson distribution. Categorical variables were compared using Chi-square test or Fisher's exact test, while continuous variables were compared using Mann Whitney test with statistical significance assessed at the 0.05 level. Calculations were performed using StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP.

Results

There were 327 new diagnoses of HCC captured across the study sites of which 272 cases fulfilled inclusion criteria for the study; 55 patients living outside the study region were excluded. Hospital HCC multi-disciplinary meetings and clinics were the source of most cases captured, with 82% (224 of 272) patients having attended or been referred for discussion. Searches of hospital admission coding captured 68% of patients while the combination of multidisciplinary meetings and coding search captured 97% (263 of 272) of cases. The remaining cases (3%) not captured by either of these means were sourced by radiology, pathology or pharmacy searches and private physician referrals.

The baseline characteristics of the cohort are reported in Table 1. The majority of HCC patients were male (79%). Patients had a median age of 65 years at diagnosis with men significantly younger than women (median age 64 (range 28-93) and 74 (range 39-91) respectively, p=0.0001).

Incidence rates

The age-standardised incidence rates of HCC in the MSD were 10.3 (95%CI: 9.0 to 11.7) and 2.3 (95%CI: 1.8 to 3.0) per 100,000 males and females, respectively.

In comparison, for the same period and population, the VCR recorded 138 cases of HCC (112 males, 26 females) equating to incidence rates of 5.3 (95%CI: 4.4 to 6.4) and 1.0 (95%CI: 0.7 to 1.5) per 100,000 males and females, respectively. This was significantly lower than the clinically diagnosed HCC incidence rates from our study ($p<0.0001$ and $p=0.0014$ respectively, Figure 2).

Adjusted VCR cohort

At the time of study (2012/3), only cases with histology were classified as HCC (ICD-10 C22.0) by the VCR (138 cases). For the same period, a further 162 cases (118 males, 44 females) without histology were registered by the VCR and coded as Liver Cancer Unspecified (ICD-10 C22.9). Prompted by this study, the VCR reviewed these 162 Liver Cancer Unspecified cases and reclassified them using clinical (non-histological) information supplied at the time of initial cancer registration, resulting in 123 reclassified as HCC, 24 as ICC, 1 as other, and 14 remained

Liver Cancer Unspecified. Therefore, for the 12 month period of comparison (2012-2013), it was possible to define an adjusted total of 261 cases of HCC recorded by the VCR, consisting of 123 newly reclassified HCC and the original 138 histologically coded HCC.

We cross-referenced the new adjusted VCR cohort (n=261) with our study cohort (n=272) and matched 205 cases of incident HCC common to both cohorts (see Figure 3). Of the 56 VCR cases that were not identified in our study, there were 5 verifiable HCC incidence cases missed by our capture method, equating to 1.8% of our cohort size. There were 25 non-incident HCC cases with clinical diagnosis dates outside our study inclusion period (i.e. clinical diagnosis prior to 1 July 2012 but delayed registration in the VCR or diagnosed after 30 July 2013 and yet still incorrectly included in the VCR incidence cohort) and three cases of incorrect diagnoses (not HCC). The remaining 23 cases were notified to the VCR by sources beyond our study sites including private hospitals (12 cases), other public hospitals not associated with our study (8 cases), pathology laboratories (2 cases) and death certificate only notifications (1 case). We were not able to verify these diagnoses as our ethics approvals were site-specific and did not allow case-identification at non-study sites.

Adjusted VCR rates

If we were to presume that all of the 23 unverified cases of the VCR cohort would have met inclusion criteria, then the composite VCR group of likely incident HCC cases would be 233 cases (including the 205 matched cases and 5 cases we missed). For this composite group, the HCC incidence rates are 8.8 (95%CI: 7.6 to 10.2) and 1.9 (95%CI: 1.4 to 2.5) per 100,000 males and females, respectively. These rates remain lower than our rates, but not significantly so ($p=0.0981$ for males, and $p=0.3729$ for females).

Cases missed by VCR registration

Our study captured 67 HCC cases (25% of cohort) that were not registered by the VCR. There were 37 patients who were admitted and coded as HCC but not reported to the VCR by hospitals. Another 16 patients were admitted for HCC treatment (liver transplantation 2, resection 1, transarterial chemoembolization 8, radiofrequency ablation 5) but not did not receive the correct HCC coding on discharge to trigger notification. There were also 14 outpatients receiving

palliative treatments (sorafenib or best supported care) who would not have been reportable under current mandatory reporting methods.

To account for cases that may have been notified subsequent to our study period and registered with incorrect diagnosis dates (date of admission rather than date of initial diagnosis), we matched these 67 cases with VCR registrations to 4 March 2015. There were 26 cases registered incorrectly, only 2 cases of late registration and 39 cases remained unaccounted for.

Differences between histology defined and clinically diagnosed HCC in the VCR cohort

We examined the 205 matched VCR cases for which we had clinical information from our independent data collection, and compared the 100 cases defined by histology with the 105 cases diagnosed clinically (see supplementary Table 1a). The clinically diagnosed cases were significantly different in racial background (higher proportion of Caucasian (p=0.0315), lower Asian (p=0.0387) and more likely to have advanced disease (presence of cirrhosis (p=0.0004), higher Child-Pugh scores (p=0.0021), and later BCLC staging (p=0.0001)). They were also less likely to be undergoing surveillance despite fulfilling indications for screening (p=0.0254).

Discussion

The management of HCC is complex and costly, requiring involvement of tertiary health care and the use of advance diagnostic modalities and therapeutics, including liver transplantation. Accurate representation of HCC epidemiology is required to adequately address the increasing burden of disease on the health system. This is the first study in Australia to independently define the problem at the population-based level using current clinico-radiological diagnostic criteria, thus addressing the shortcomings of current epidemiologic literature that is primarily dependent upon cancer registries.

We have shown that HCC incidence rates in Melbourne are two-fold higher than those reported by the Victorian Cancer Registry using histology as a basis for classification. The data demonstrate the importance of using current diagnostic criteria for registry classification of HCC in cancer registries. HCC is no longer diagnosed histologically but based on clinic-radiological criteria. These criteria have been validated and accepted by international liver societies; histology is reserved for indeterminate cases.

As a direct result of our study, the VCR have adopted new methodology to classify HCC by both histological and/or clinico-radiological criteria as of 1 January 2014. Indeed, cancer registries across the world are starting to recognise the need for a change in classification of HCC to a broader diagnostic criteria consisting of both clinical and radiological bases of diagnosis. Comparing reports from the International Association of Cancer Registries in Cancer Incidence in Five Continents Vol IX (2007) (7) and Vol X (2014) (15) many registries from China, South East Asia, Italy and other regions are gradually implementing clinical criteria, resulting in lower rates for unspecified primary liver cancer and higher rates for HCCs. As with Victoria from 2014 onwards, incidence rates for HCC will be higher than previously reported.

We then tested whether a population-based incidence study, using multiple capture methods to diagnose cases identified through comprehensive clinical case collection, would identify a greater number of incident HCCs compared to our local cancer registry. For the comparator we used the adjusted VCR incident data for the matching time period, after reclassification of cases that were originally classified as Liver Cancer Unspecified, but which on review, had been given

a clinical diagnosis of HCC at the point of notification. We still identified higher incidence rates than the adjusted registry incidence rates for clinically diagnosed HCC. This difference did not meet statistical significance, possibly owing to our conservative approach in presuming that all 23 cases notified to the VCR from non-study sources were indeed HCC.

Nevertheless, the fact remains that a quarter of the total HCC cases identified in our study were not notified to the VCR (including those notified incorrectly and thus not included in published incidence figures). In contrast, using this capture method, our missed rate was less than 2%. This highlights both the importance of identifying appropriate sources of case capture to optimise cancer registration completeness, as well as the need to be familiar with the methodology of the local registry, especially in light of newer clinical diagnostic criteria. Best practice management of HCC should involve multi-disciplinary case review meetings involving hepatologists, radiologists, surgeons and oncologists. On the basis of our findings, we propose that mandatory notification from multi-disciplinary meetings to cancer registries should be required and supported.

In addition to correctly classifying HCC using current diagnostic criteria, it is also important for researchers to differentiate HCC epidemiology from that of ICC. Many studies (11,12,16,17) have used HCC and PLC interchangeably, quoting total PLC rates from cancer registries for incidence and mortality when, in fact, the discussion relates to HCC. Greater emphasis needs to be made of the significant contribution ICC rates make to PLC figures in different populations. For example, ICC make up between 5% and 25% of total PLC rates across United States registries, and up to 45% in UK registries (IACR)(7). ICC incidence and mortality rates have also risen in recent times(18-20), suggesting that trends in PLC incidence need to account for changes in both HCC and ICC rates independently, particularly since the biological behavior, clinical management, prognosis and survival rates differ significantly between HCC and ICC. Hence, more accurate representation will assist planning of education and preventative screening practices as well as allow appropriate utilization of healthcare resources.

While tertiary referral bias may be a concern in terms of adequate population representation, the unique nature of HCC management reduces this limitation. HCC is a complex disease with a

poor prognosis, mostly referred to specialists and generally requiring a tertiary hospital service for diagnosis or treatment at some point. In addition, as a cancer, HCC is mandatorily reportable in Australia; patients, including those with terminal disease and palliative needs, who present elsewhere (eg private hospitals, nursing homes, death certificate only notifications) are captured by the population-based VCR. Our favourable comparison with the VCR data suggests that tertiary referral bias has not negatively influenced our reported incidence rates. Instead, the cases missed by the VCR did in fact present to a tertiary hospital as hypothesized and were captured by our methods. Moreover, any residual failure of capture on our part would serve to further strengthen our suggestion that incidence is currently underreported.

We recognize that the two-fold discrepancy between our HCC incidence and the local registry rates examined over a one year period in Melbourne may not be generalizable to other populations. Incidence rates in any population will depend upon the prevailing risk factors present; in the case of developed countries with historically low incidence, migrants from countries with high HCC incidence play an important role. Our data shows that people born overseas are overrepresented in HCC cases in Melbourne. We suggest that our methodology could be validated in other cities, such as those in Australia, the United States, Canada and Europe, which have similarly high proportions of overseas-born residents. Further, the degree of discrepancy between rates from an independent, population-based study such as this and that of the local registry will also depend upon individual cancer registry practices as well as local epidemiology. Particularly important would be populations where the local registry is yet to adopt clinical criteria in cancer registrations and is still reporting disproportionally high rates of unspecified primary liver cancers (Figure 1). While our results based on a capture period of only one year may not reflect longer term trends, and may not be reproducible in all populations, our methodology may nevertheless help other regions improve case ascertainment to better inform health policies.

Conclusion

This study is the first Australian study to describe HCC incidence at a population-based level using current accepted clinico-radiologic and pathologic criteria, independent of cancer registry data. Our HCC incidence rates are two-fold higher than that reported by the cancer registry, suggesting that the revision of cancer registration methodology in line with current diagnostic criteria was required. Furthermore, the inclusion of additional clinical sources of cases may improve data capture and estimates. Finally, we reiterate the importance of using HCC specific data in publications and discussion of epidemiologic data, which requires having a full understanding of registration methodologies of the local reporting cancer registry. Accurate epidemiological data will assist policymakers to implement public health interventions such as education, screening for viral hepatitis and cancer, and allow effective resource allocation.

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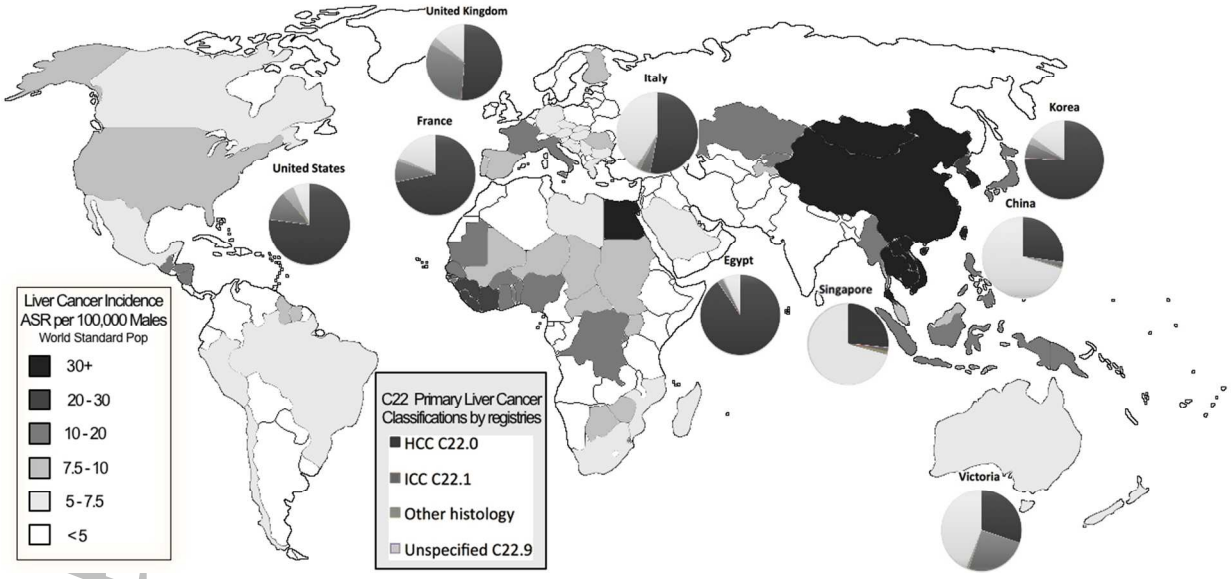

Figure 1: Disproportionate contributions of different types of Primary Liver Cancer, as classified by various national cancer registries, with heterogeneous distribution of liver cancer incidence in males worldwide. Original analysis of data from Globocan 2012 (21), Cancer in Five Continents Vol X 2014(8), and Victorian Cancer Registry, 2012. HCC Hepatocellular Carcinoma, ICC Intrahepatic Cholangiocarcinoma, ASR Age-Standardised Rate

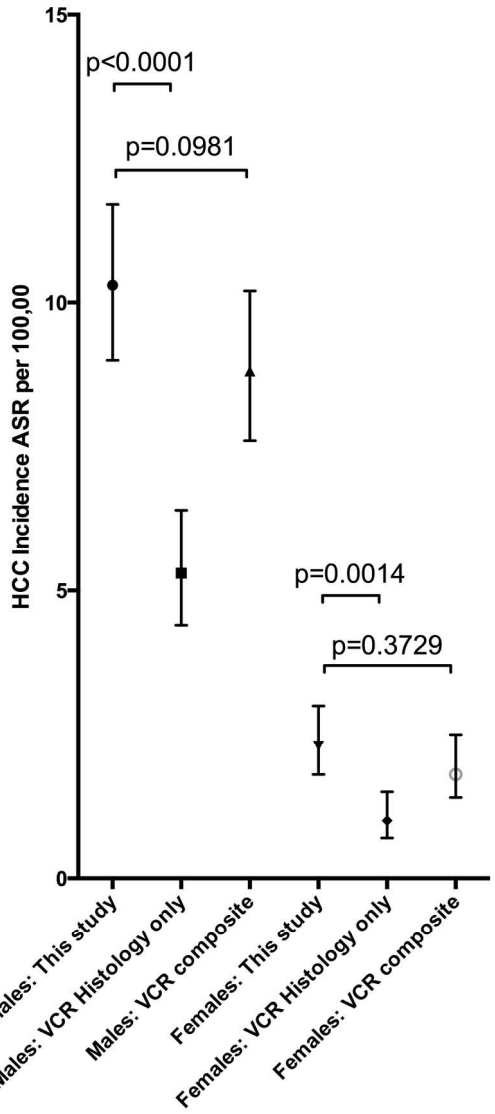

Figure 2: Comparison of HCC incidence rates between this study and VCR groups according to histology and composite (clinical and histology) classifications. Age-standardised incidence rate per 100,000 (Australian Standard Population) with 95% confidence intervals.

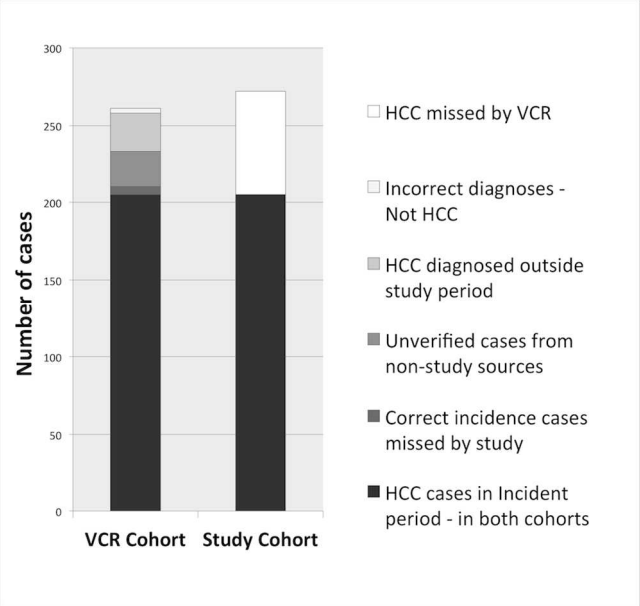

Figure 3: Case-matching the study cohort (n=272) with the VCR cohort (n=261)

Table 1: Baseline Characteristics

Total cohort, n	272
Sex: males, n (%)	216 (79%)
Age: median, years (range)	65 (28 - 93)
Males	64 (28 - 93)
Females	74 (39 - 91)
Race: n (%), median age (range)	
Caucasian	201 (74%), 66 (39 -93)
Asian	59 (22%), 63 (33 - 91)
African	10 (4%), 56 (28 - 76)
Unknown	1%
Place of birth, %	
Australia	39%
Overseas	57%
Unknown	4%
Overseas born in Melbourne population(13)	35%
Risk factors for chronic liver disease present	
Chronic hepatitis C	112 (41%)
Alcoholic liver disease	107 (39%)
Chronic hepatitis B	60 (22%)
Fatty liver disease	39 (14%)
Haemochromatosis	6 (2%)
Primary biliary cirrhosis	5 (2%)
Autoimmune hepatitis	3 (1%)

Other / Unknown	17 (6%)
More than one risk factor	73 (27%)
Mode of presentation	
Surveillance program (6-12 monthly US)	110 (40%)
Known cirrhotic but not screened	53 (19%)
First presentation of cirrhosis or incidental	105 (39%)
Unknown	4 (2%)
Liver functional status	
Cirrhosis present	225 (83%)
Child Pugh A	125 (56%)
Child Pugh B	67 (30%)
Child Pugh C	33 (15%)
Barcelona Clinic Liver Clinic Staging	
BCLC-A	70 (26%)
BCLC-B	59 (22%)
BCLC-C	98 (36%)
BCLC-D	41 (15%)

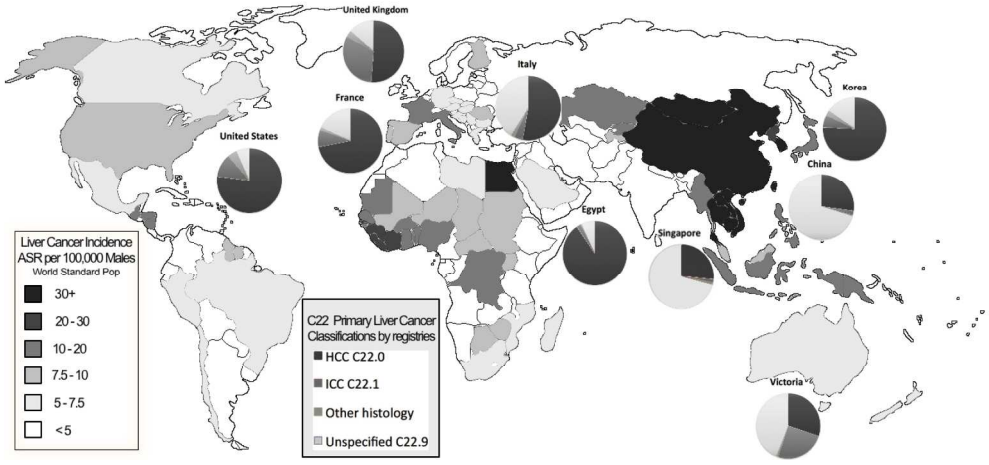

Figure 1: Disproportionate contributions of different types of Primary Liver Cancer, as classified by various national cancer registries, with heterogeneous distribution of liver cancer incidence in males worldwide. Original analysis of data from Globocan 2012 (21), Cancer in Five Continents Vol X 2014(8), and Victorian Cancer Registry, 2012. HCC Hepatocellular Carcinoma, ICC Intrahepatic Cholangiocarcinoma, ASR Age-Standardised Rate
241x111mm (300 x 300 DPI)

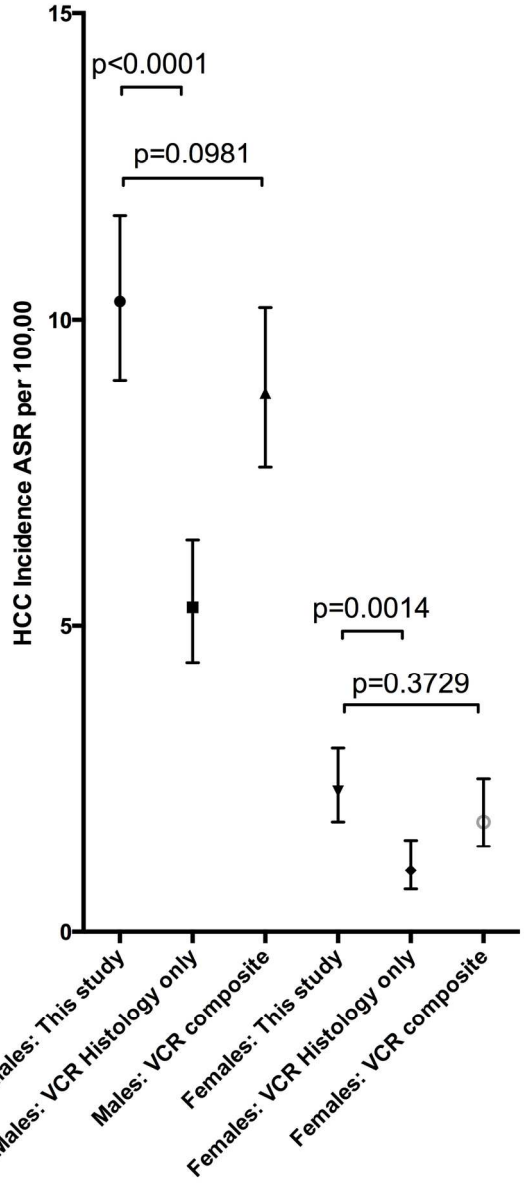

Figure 2: Comparison of HCC incidence rates between this study and VCR groups according to histology and composite (clinical and histology) classifications. Age-standardised incidence rate per 100,000 (Australian Standard Population) with 95% confidence intervals.
97x209mm (300 x 300 DPI)

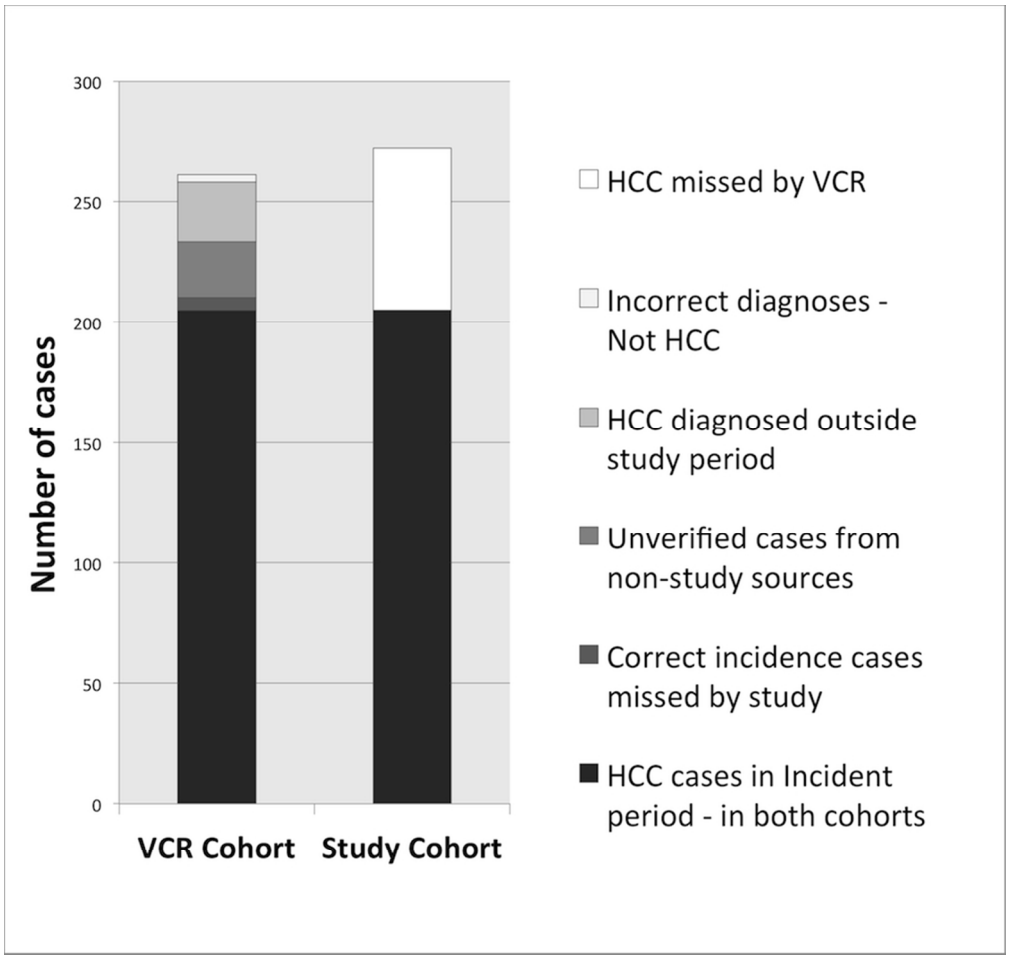

Figure 3: Case-matching the study cohort (n=272) with the VCR cohort (n=261)
84x80mm (300 x 300 DPI)

Table 1a: Baseline Characteristics of VCR HCC cases defined by histology or clinical diagnosis.

	VCR HCC cases (histology)	VCR Unspecified cancer (clinical only)	p-value
Number of cases	100	105	NS
Sex: males, n (%)	83 (83%)	83 (79%)	NS
Age: median, years (range)	64 (28 - 91)	65 (40 - 91)	NS
Males	63 (28 - 87)	63 (44 - 91)	NS
Females	68 (39 - 91)	77 (40 – 89)	NS
Race: n (%), median (years): age (range)			
Caucasian	69 (69%), 66 (39 - 87)	86 (82%), 65 (40 - 89)	0.0315
Asian	27 (27%), 56 (33 - 91)	16 (15%), 75 (44 – 90)	0.0387
African	3 (3%), 52 (28 - 74)	2 (2%), 63 (52 - 76)	NS
Other (Unknown)	1 (1%)	1 (1%)	
Place of birth, %			
Australia	36%	43%	NS
Overseas	57%	54%	NS
Unknown	7%	3%	NS
Risk factors for chronic liver disease present			
Chronic hepatitis C	33 (33%)	48 (46%)	0.0627
Alcoholic liver disease	34 (34%)	48 (46%)	0.0870
Chronic hepatitis B	27 (27%)	18 (17%)	0.0883
Fatty liver disease	16 (16%)	15 (14%)	NS
Haemochromatosis	2 (2%)	4 (4%)	NS
Primary biliary cirrhosis	2 (%)	2 (2%)	NS
Autoimmune hepatitis	0	0	NS

Other / Unknown	6 (6%)	5 (5%)	NS
More than one risk factor	23 (23%)	34 (32%)	NS
Mode of presentation			
Surveillance program (6-12 monthly US)	40 (40%)	39 (37%)	NS
Known cirrhotic but not screened	15 (15%)	29 (28%)	0.0254
First presentation of cirrhosis or incidental	43 (43%)	36 (34%)	NS
Unknown	2 (2%)	1 (1%)	NS
Liver functional status			
Cirrhosis present	71 (71%)	95 (90%)	0.0004
Child Pugh A	50 (70%)	41 (43%)	0.0005
Child Pugh B	17 (24%)	32 (34%)	NS
Child Pugh C	4 (6%)	22 (23%)	0.0021
Barcelona Clinic Liver Clinic Staging			
BCLC-A	34 (34%)	14 (13%)	0.0005
BCLC-B	24 (24%)	22 (21%)	NS
BCLC-C	33 (33%)	44 (42%)	NS
BCLC-D	5 (5%)	25 (24%)	0.0001