Novel Population-Based Study Finding Higher Than Reported Hepatocellular Carcinoma Incidence Suggests an Updated Approach Is Needed

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Hepatocellular carcinoma (HCC) incidence is rising rapidly in many developed countries. Primary epidemiological data have 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. Incident cases of HCC (defined by American Association for the Study of Liver Diseases 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; and 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. There were 272 incident cases (79% male; median age: 65 years) identified. Cirrhosis was present in 83% of patients, with hepatitis C virus infection (41%), alcohol (39%), and hepatitis B virus infection (22%) the commonest etiologies present. Age-standardized HCC incidence (per 100,000, Australian Standard Population) was 10.3 (95% confidence interval [CI]: 9.0-11.7) 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). Conclusions: HCC incidence in Melbourne is 2-fold higher than reported by cancer registry data owing to under-reporting 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. (HEPATOLOGY 2016;63:1205-1212)

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 arises in the setting of cirrhosis, with the most common etiologies being chronic viral hepatitis B and C, alcohol, and nonalcoholic fatty liver disease.

Abbreviations: ABS, Australian Bureau of Statistics; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; ICD, International Classification of Diseases; MSD, Melbourne Statistical Division; PLC, primary liver cancer; VCR, Victorian Cancer Registry.

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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 nonalcoholic 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 utilized. 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 (e.g., China and 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 clinicoradiological criteria in subjects with cirrhosis rather than histology, as approved by current guidelines from Learned Societies.\(^9,10\) Hence, some registries (United States and some European countries) now accept clinical diagnosis as a basis for HCC classification.\(^7\)

Therefore, in this context, many studies have reported HCC incidence using total PLC rates as a surrogate marker.\(^11,12\) However, this is misleading given that a significant proportion of primary liver cancers are intrahepatic cholangiocarcinomas (ICCs), forming up to 45% of PLC figures as reported by some cancer registries\(^8\) (Fig. 1). Compared to ICC, HCC has entirely different biological, 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 hypothesized that HCC incidence rates may be higher than currently reported by the cancer registry, owing to incorrect classification of clinically diagnosed cases, and incomplete capture from nonreported 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.

**Materials and 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, 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, as well as 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 July 1, 2012 to June 30, 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 (International Classification of Diseases [ICD]-0-3 C22.0 M8170/3), sorafenib dispensing and medical admissions coding of ICD-10 C22.0 Hepatocellular carcinoma, and C22.9 Liver Cancer Unspecified. American Association for the Study of Liver Diseases (AASLD) clinicoradiological diagnostic criteria 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 etiology of chronic liver disease, hepatic synthetic liver function, presence of cirrhosis, Child-Pugh scores, mode of diagnosis, involvement in surveillance programs, and tumor staging according to Barcelona Clinic Liver Cancer (BCLC) staging. The etiology of chronic liver disease was defined by the consulting physician with verification from pathology or radiology results if it was not documented. Data were deidentified 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 deidentified 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 deidentified information provided by the VCR included patient initials, dates of birth, residential postcode, diagnostic coding, and source of registration (public hospital, private hospital, pathology, or death certificate). Records were matched to our cohort using these parameters.

STATISTICAL ANALYSIS

Age-standardized incidence rates were calculated using the direct method for age standardization with 18 groups of 5-year age groups (0-, 5-, 10-, ..., 85+) for each sex separately. The population data for each age group were derived from ABS Australian Census 2011, with the same figure used as denominator for both MSD and VCR rate calculations. Incidence rates were standardized to the Australian Standard Population, using the Australian Census June 30, 2001 standard population as recommended by the ABS. 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, whereas continuous variables were compared using Mann-Whitney’s test with statistical significance assessed at the 0.05 level. Calculations were performed using StataCorp software (2011; Stata Statistical Software: Release 12; StataCorp LP, College Station, TX).

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 multidisciplinary meetings and clinics were the source of most cases captured, with 82% (224 of 272) of patients having attended or been referred for discussion. Searches of hospital admission coding captured 68% of patients whereas 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-standardized incidence rates of HCC in the MSD were 10.3 (95% CI: 9.0–11.7) and 2.3 (95% CI: 1.8–3.0) 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: 4.4–6.4) and 1.0 (95% CI: 0.7–1.5) 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, Fig. 2).

ADJUSTED VCR COHORT

At the time of study (2012-2013), 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 (nonhistological) 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 Fig. 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 nonincident HCC cases with clinical diagnosis dates outside our study inclusion period (i.e., clinical diagnosis before July 1, 2012, but delayed registration in the VCR or diagnosed after July 30, 2013 and yet still incorrectly included in the VCR incidence cohort) and 3 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 because our ethics approvals were site specific and did not allow case identification at nonstudy 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, and 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 March 4, 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 Supporting Table 1). 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 clinicoradiological diagnostic criteria, thus addressing the shortcomings of current epidemiological literature that is primarily dependent upon cancer registries.

We have shown that HCC incidence rates in Melbourne are 2-fold higher than those reported by the VCR 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 a new methodology to classify HCC by both histological and/or clinicoradiological criteria as of January 1, 2014. Indeed, cancer registries across the world are starting to recognize 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 PLC and higher rates for HCCs. As with Victoria from 2014 onward, 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 nonstudy sources were indeed HCC.

Nevertheless, the fact remains that one 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 optimize 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 multidisciplinary case review meetings involving hepatologists, radiologists, surgeons, and oncologists. On the basis of our findings, we propose that mandatory notification from multidisciplinary 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, ICCs make up between 5% and 25% of total PLC rates across United States registries and up to 45% in UK registries (International Association of Cancer Registries).\(^7\) 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 given that 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 health care resources.

Although 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 (e.g., private hospitals, nursing homes, and death-certificate-only notifications) are captured by the population-based VCR. Our favorable 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 under-reported.

We recognize that the 2-fold discrepancy between our HCC incidence and the local registry rates examined over a 1-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 show that people born overseas are over-represented 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. Furthermore, 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 disproportionately high rates of unspecified PLCs (Fig. 1). Although our results based on a capture period of only 1 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.

This study is the first Australian study to describe HCC incidence at a population-based level using current accepted clinicoradiologic and pathological criteria, independent of cancer registry data. Our HCC incidence rates are 2-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 epidemiological data, which requires having a full understanding of registration methodologies of the local reporting cancer registry. Accurate epidemiological data will assist policy makers to implement public health interventions such as education, screening for viral hepatitis and cancer, and allow effective resource allocation.

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Supporting Information

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