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Title:
Hepatocellular carcinoma over three decades in Victoria, Australia: epidemiology, diagnosis and trends, 1984–2013

Date:
2018-07-01

Citation:
Carville, K. S., MacLachlan, J. H., Thursfield, V. & Cowie, B. C. (2018). Hepatocellular carcinoma over three decades in Victoria, Australia: epidemiology, diagnosis and trends, 1984–2013. Internal Medicine Journal, 48 (7), pp.835-844. https://doi.org/10.1111/imj.13823.

Persistent Link:
https://hdl.handle.net/11343/284130

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Title: Hepatocellular carcinoma over three decades in Victoria, Australia: epidemiology, diagnosis, and trends, 1984–2013

Running head: HCC epidemiology and trends

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/imj.13823

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Acknowledgements:

The authors would like to thank the Victorian Cancer Registry for the provision of the data used. We would like to acknowledge the Australian Bureau of Statistics for the publication of essential population statistics in the public domain.

Manuscript: 2,988
Abstract word count: 249
Tables: 4

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Figures: 3

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List of abbreviations

HCC	Hepatocellular carcinoma
HBV	Hepatitis B virus
HCV	Hepatitis C virus
VCR	Victorian Cancer Registry
ABS	Australian Bureau of Statistics
SACC	Standard Australian Classification of Countries
LGA	Local Government Area

Conflict of interest disclosures:

None of the authors have any conflict of interest to disclose.

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Abstract:

Background

Liver cancer continues to be a health priority in Australia, with the majority attributable to preventable causes, and certain populations at higher risk.

Aims

Epidemiological assessment of incidence, trends, and distribution to inform prevention, and reassessment of data in light of recent changes to registry case definitions.

Methods

Reported cases of hepatocellular carcinoma in Victoria, Australia, 1984-2013 were obtained from the Victorian Cancer Registry. Demographic characteristics were examined, incidence and survival assessed using Poisson and Cox regression, and geographic distribution mapped. Incidence was compared before and after inclusion of non-histologically confirmed cases in Registry data, to assess impacts on incidence trends.

Results

Incidence of hepatocellular carcinoma rose substantially between 1984 and 2013, increasing six-fold from 0.9 to 5.9 per 100,000. The rate of increase per year accelerated from 5.3% between

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1984-2003 to 9.5% between 2004-2013. Cases were disproportionately male (80%), median age at diagnosis was 66 years, and half (53%) were born overseas. Even during 2004-2013, 5-year survival was only 16%, although higher among younger people, metropolitan residents, and people born overseas. Incidence showed strong geographic clustering. The proportion of cases diagnosed clinically increased from 1% during 1984-2004 to 43% in 2009-2013. The revised case definition added 993 cases (27.3% of total).

Conclusions

Hepatocellular carcinoma incidence is increasing more rapidly than previously believed, highlighting the impact of case definitions in the context of changing diagnostic approaches. The rising burden, disproportionate population distribution, and low survival emphasize the importance of prevention and early detection as a public health imperative.

Keywords: Epidemiology, viral hepatitis, Prevention, Liver cancer, Diagnosis, Screening

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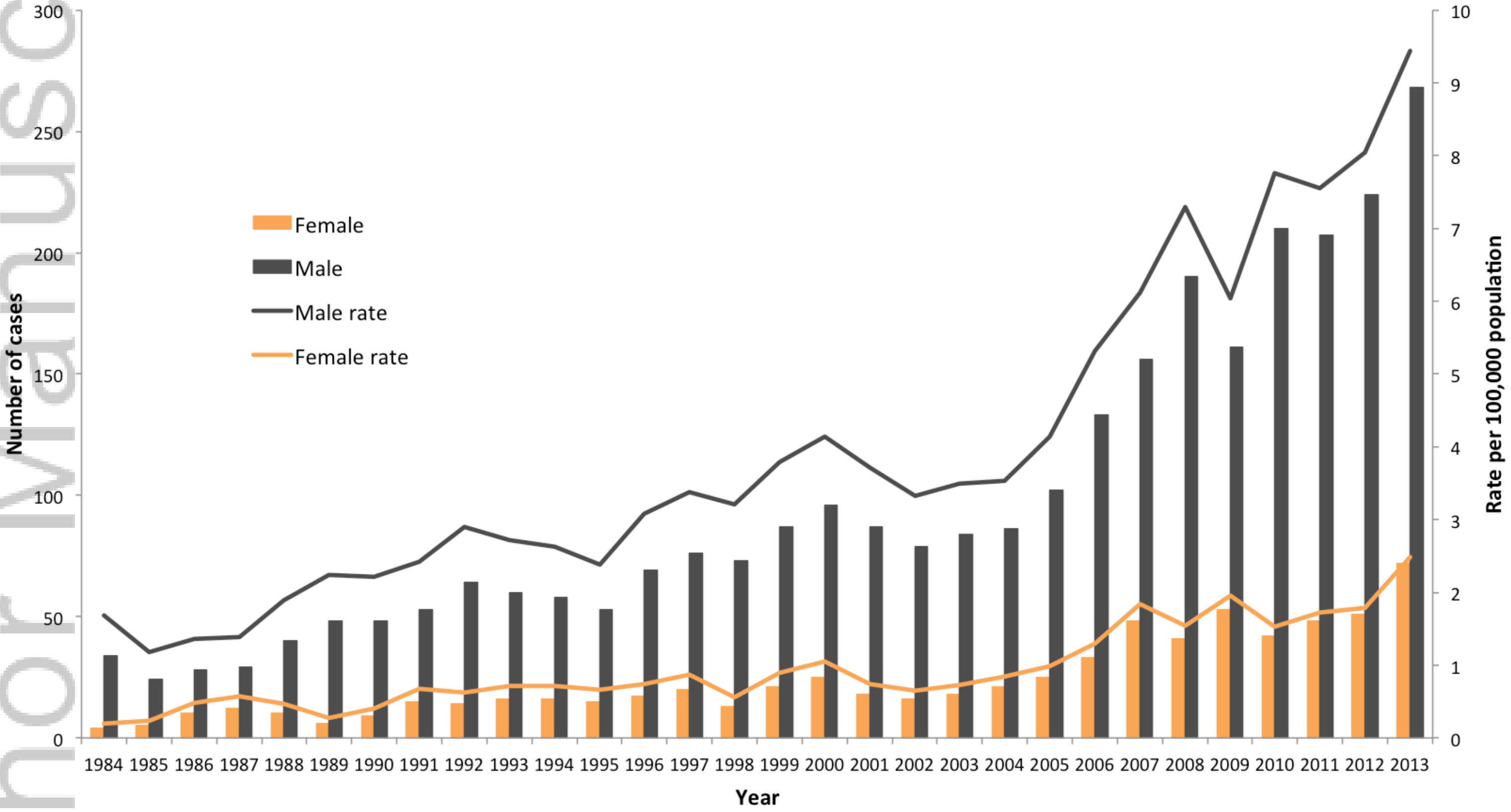

Figure 1a.tiff

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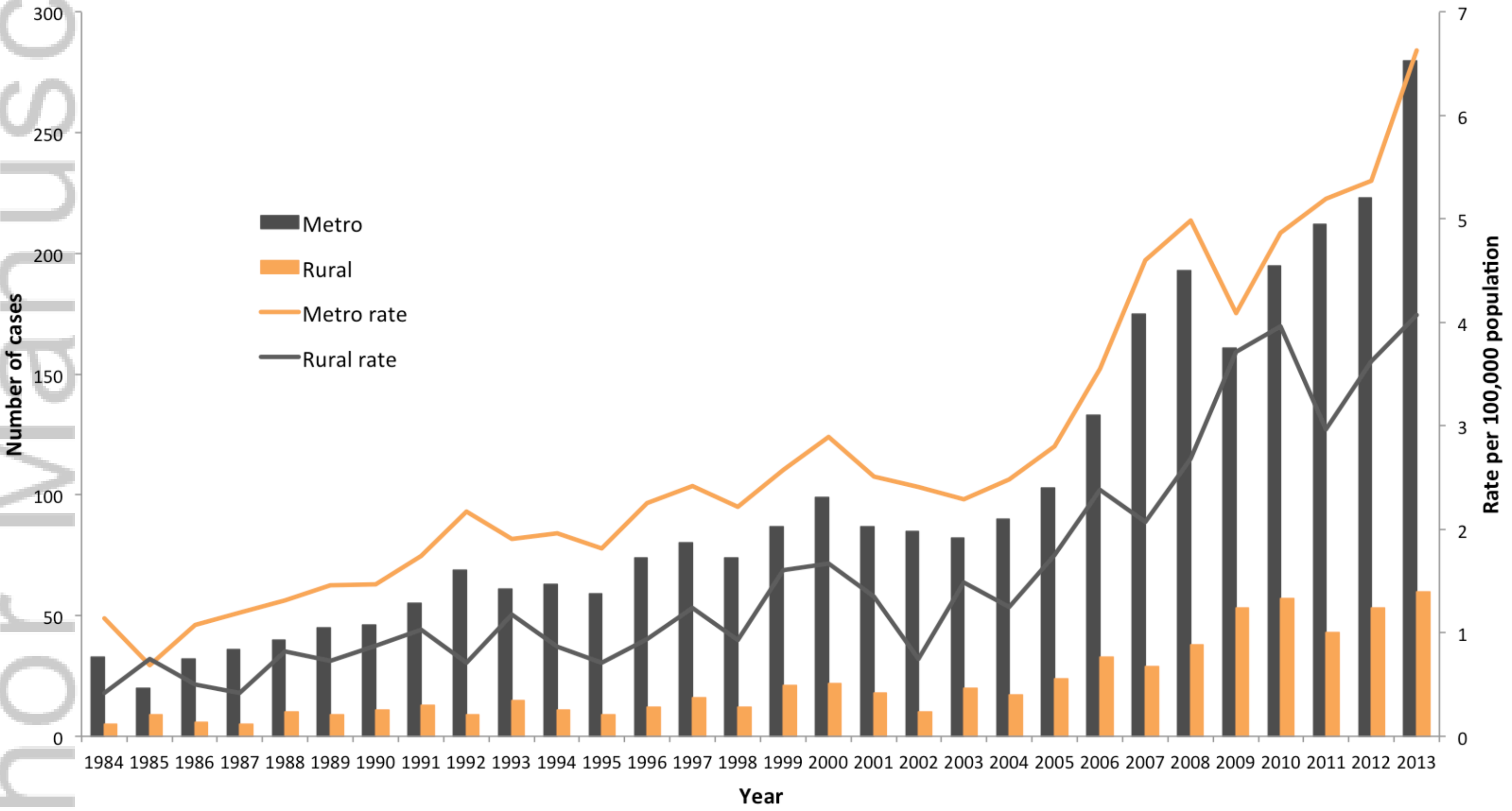

Figure 1b.tiff

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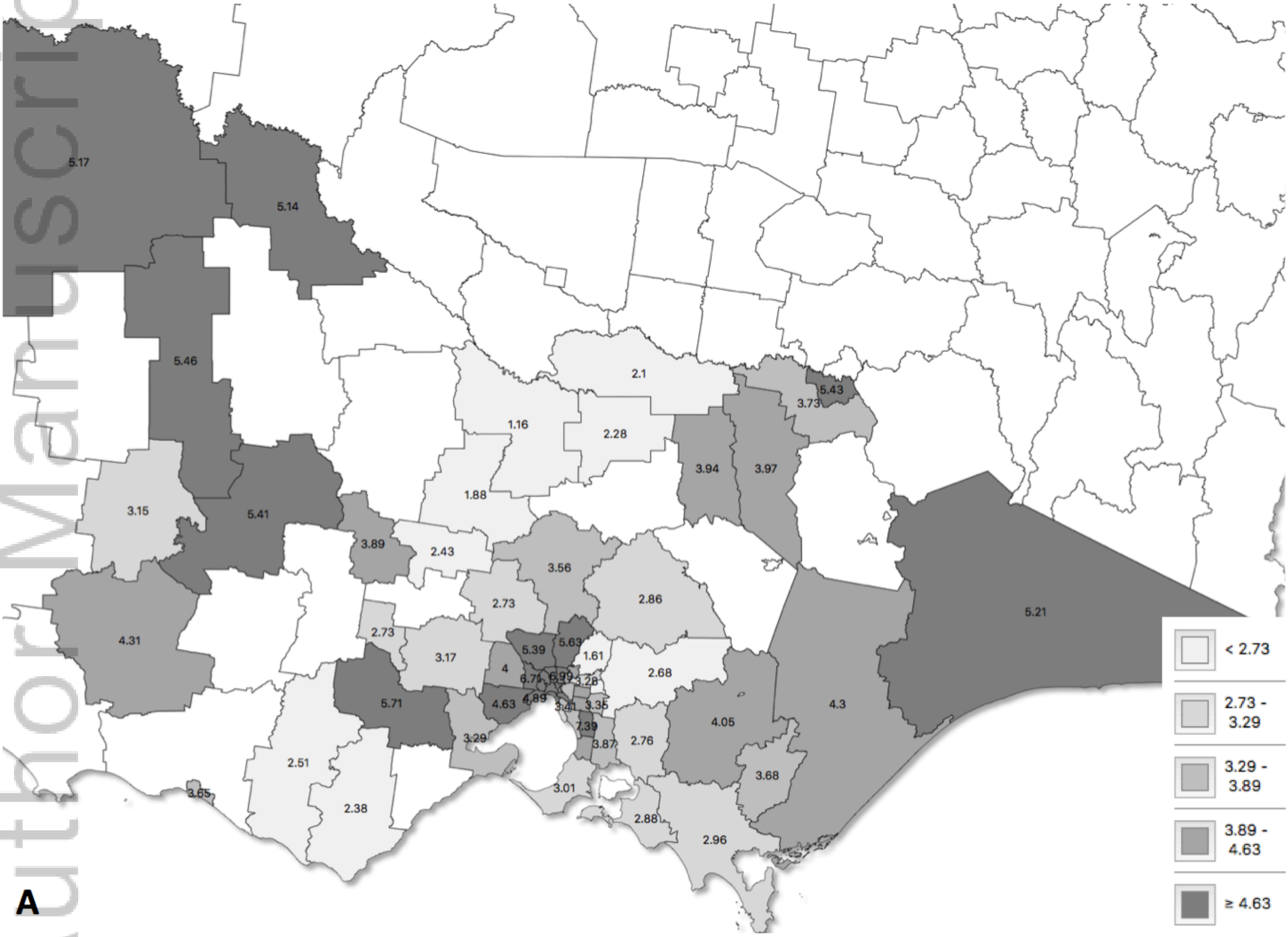

Figure 2a.tiff

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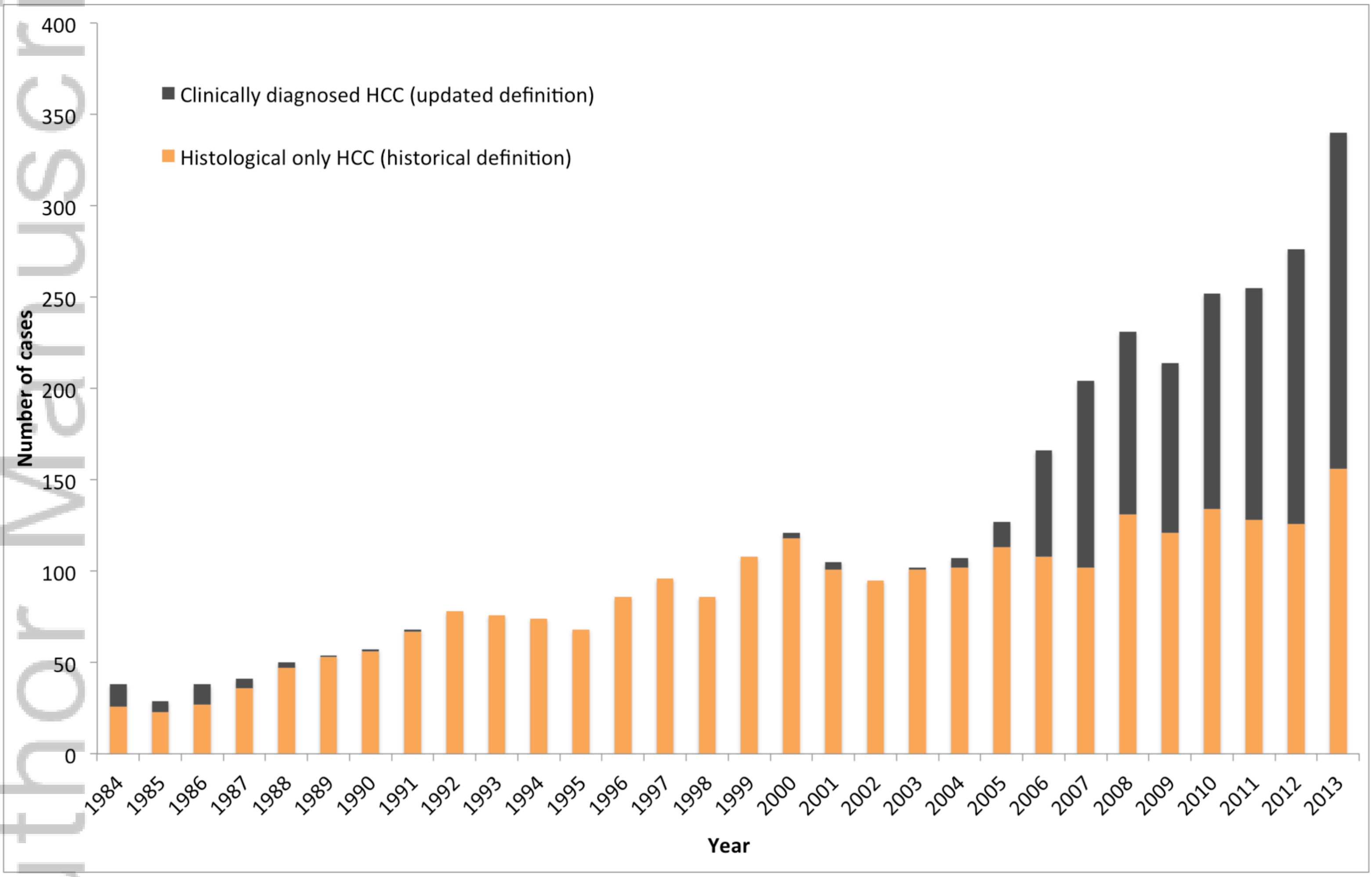

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Reported cases of hepatocellular carcinoma in Victoria, Australia, 1984-2013 were obtained from the Victorian Cancer Registry. Demographic characteristics were examined, incidence and survival assessed using Poisson and Cox regression, and geographic distribution mapped. Incidence was compared before and after inclusion of non-histologically confirmed cases in Registry data, to assess impacts on incidence trends.

Results

Diagnoses of hepatocellular carcinoma rose substantially between 1984 and 2013, increasing six-fold from 0.9 to 5.9 per 100,000. The rate of increase per year accelerated from 5.3% between 1984-2003 to 9.5% between 2004-2013. Cases were disproportionately male (80%), median age at diagnosis was 66 years, and 53% were born overseas. Even during 2004-2013, 5-year survival was only 16%, although higher among younger people, metropolitan residents, and people born

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overseas. Incidence showed strong geographic clustering. The proportion of cases diagnosed clinically increased from 1% during 1984-2004 to 43% in 2009-2013. The revised case definition added 993 cases (27.3% of total).

Conclusions

Cases of hepatocellular carcinoma are becoming increasingly common, and revised incidence estimates highlight the impact of case definitions in the context of changing diagnostic approaches. The ongoing burden, disproportionate population distribution, and low survival emphasize the importance of prevention and early detection as a public health imperative.

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Text

Introduction

Liver cancer, which is predominately hepatocellular carcinoma (HCC), is an increasingly important health problem globally. Liver cancer is the 4th most common cause of cancer mortality, leading to ~800,000 deaths each year, which disproportionately occur in low and middle income countries.(1) In Australia, liver cancer is the fastest increasing cause of cancer death, and five-year survival remains poor, at 16%(2).

The majority of HCC is preventable, linked to hepatitis B (HBV) and/or C virus (HCV) infection, alcohol use, and other factors such as metabolic diseases.(3, 4) Epidemiological analysis to identify priority populations, determinants of incidence, and geographic variability is essential for assessment of burden and targeting of interventions. Previous Australian research has demonstrated the disparate impact on Aboriginal and Torres Strait Islander people, those born overseas, and rural and remote residents.(2, 5, 6),(7) Prevention interventions, including diagnosis and treatment of chronic HBV and HCV infection, mitigation of metabolic and behavioral factors, and early detection of tumours through surveillance, can reduce mortality and be highly cost effective.(8, 9) These initiatives depend on community and practitioner awareness of risk factors and populations most at risk.

Legislation requires that all diagnoses of cancer in Victoria be reported to the Victorian Cancer Registry (VCR) of the Cancer Council Victoria. Previously, reported liver cancer diagnoses were

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only classified as HCC if the case was histologically confirmed, and were otherwise recorded as unspecified primary liver cancer. However, a recent study which compared hospital records with registry recorded cases determined that HCC diagnoses were underestimated by 50% by the VCR.(10) In response, the VCR retrospectively reassessed all liver cancer diagnoses from 1982 onwards, and reclassified those liver cancers with a clinical diagnosis of HCC as HCC in the registry. This reflects current diagnostic and management guidelines, which no longer require biopsy for diagnosis,(11-13) and means that underreporting of HCC in Registry data is no longer occurring and previous under-reporting has been rectified, incorporation of historical clinically diagnosed cases. This study represents the first analysis of HCC epidemiology using this complete dataset, which includes all true cases of HCC since 1982, including those diagnosed using clinical methods. We aimed to examine demographic, temporal and geographic patterns in HCC in order identify changes over time, to assess the impact of diagnostic criteria on epidemiological measures, and help target interventions to the areas where they will be most effective.

Materials and methods

Data source

De-identified data for HCC diagnoses (coded as C22.0 for primary site and/or with morphology in ICDO-3 range 8170/3 to 8180/3, which includes all HCC variants) in Victorian residents from 1st January 1984 to 31st December 2013 were obtained from the VCR. Historical data, analysed and extracted in 2014 according to the same parameters (for the period 1982-2012), but which included only histologically confirmed cases as HCC, were also analysed, to assess the impact of

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changing case definitions during the period. Only the first instance of diagnosed HCC in a given individual is included the Victorian Cancer Registry as a case, in accordance with the recommendations of the International Agency for Research on Cancer(14). Cell counts with fewer than 5 cases were suppressed to prevent any possibility of identification (indicated in tables as “<5”), in accordance with data access agreements.

Statistical analysis was performed using Stata 14, with graphs produced using Microsoft Excel. Maps were produced in MagicMaps 1.4.16.

Descriptive analyses

For most analyses data were grouped into three time periods (1984-1993, 1994-2003, and 2004-2013). Demographic characteristics including sex, age, place of residence, and country of birth were assessed for each time period. Country of birth was categorized into regions using the Australian Bureau of Statistics (ABS) Standard Australian Classification of Countries (SACC), and into a dichotomous Australian-born/overseas-born variable, which was used in regression for model stability given small numbers. Place of residence was grouped using postcode into metropolitan and non-metropolitan categories according to the Australian Statistical Geography Standard for Remoteness Structure.

Population denominator data were obtained from the ABS by age, sex, and geographic area.(15) Crude and age-adjusted incidence of HCC per 100,000 persons was calculated by sex for each year of diagnosis, and for each Victorian Local Government Area (LGA). Due to low numbers and changing statistical boundaries over time, geographic analysis was restricted to the period 2004-2013. Incidence according to geographic area was mapped.

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Significance of differences in proportions were evaluated using two-sample tests of proportions and the Ç^2 test for variables with more than two categories. The Wilcoxon rank-sum test was used to test the equality of distributions of continuous variables. P-values less than 0.05 were considered significant.

Trends and survival

Poisson analysis was used to assess trends in crude incidence over time, by sex and by place of residence. This was done for 1984-2013 and also separately for 1984-2003 and 2004-2013. The change in age-standardized incidence for males and females was calculated from 2004-2013. Multivariate Poisson regression was conducted using sex, age group, and place of residence to determine association with HCC incidence over 2004-2013. Place of birth was not included in this analysis as population denominator data were not available according to these parameters.

Life tables were generated, and the log-rank test was used to compare median survival between subgroups. Cox regression was used to assess survival after diagnosis according to demographic factors. Those with date of death equal to date of diagnosis were excluded from survival analysis (135 cases, 3.8%). Variables included in the model were place of birth (Australia/overseas), place of residence (metropolitan/non-metropolitan), age group, and sex, if subgroups were significantly different at $p<0.20$ by the log-rank test. As the year variable violated the proportional hazards model, and because survival has changed over the three decades under study, three separate models were created to explore the impact of demographic characteristics within each decade. Plausible two-way interactions were tested for inclusion in the model at a

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$p<0.10$ significance level. Final model fit was assessed using Cox-Snell residuals. Results are presented as hazard ratios (HR) with 95% confidence intervals.

Diagnostic changes

We assessed the number of cases diagnosed using histological compared to clinical methods as a proportion of the total over time, with histological diagnoses including histology of primary tumour, histology of metastasis, and cytology, according to the VCR case definition. We compared age, sex, metropolitan area of residence, and the proportion of cases still alive after five years according to diagnosis method during the period 2006 onwards, when clinical diagnoses became a notable proportion of all cases. Differences in these variables were assessed using the two-sample test of proportions and Wilcoxon rank-sum test.

Results

Characteristics of cases

From 1 January 1984 to 31 December 2013, 3,642 cases of HCC were diagnosed in Victoria. Cases were predominately male (n= 2,927, 80.4%) with no change in sex distribution over time (Table 1, $p=0.992$). Median age at diagnosis was 66 years, higher among women than men (70 compared to 65 years, $p<0.001$). Although median age was relatively stable over time, age group distribution shifted, with the proportion of diagnoses increasing in those aged over 80 (5% to 13%, $p<0.001$) and decreasing in those aged 60-69 (38% to 26%, $p<0.001$, Table 1).

Median age was similar in metropolitan and non-metropolitan residents (66 and 67 years, $p=0.100$). However, a higher proportion of metropolitan residents were aged <50 years (11.5%

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compared to 7.7%, p=0.005) and >80 years (11.7% compared to 8.6%, p=0.023) and correspondingly smaller proportions aged 60-79 years.

Data were largely complete for most demographic fields (>95% for age, sex, country of birth and area of residence), however Indigenous status was only available for 81% of cases during the time period. Completeness improved substantially from 47% during 1984-1993 to 90% during 2004-2013. Of the 18 cases identified as being in Aboriginal and/or Torres Strait Islander people, 16 were during the latest decade. These represented 0.8% of all cases during this time period, during which with Aboriginal and Torres Strait Islander people constituting 0.7% of the Victorian population.(15)

Just over half of those diagnosed with HCC were born overseas (Table 1), most commonly in Southern and Eastern Europe (40% of those born overseas; predominantly Italy and Greece), South East Asia (19%; predominantly Vietnam) and North-West Europe (16%; predominantly England). The proportion overseas-born was more than twice as high in metropolitan residents (61.2%) than non-metropolitan residents (23.8%), and more than double the average population proportion during the time period(16). Those with European backgrounds predominated in both metropolitan (54.1%) and non-metropolitan (83.6%) regions, however the proportion born in Asia was considerably higher in the metropolitan region (33.8%) than in non-metropolitan (7.2%).

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Temporal trends in incidence

Incidence of HCC in Victoria increased substantially over time, with crude rates increasing more than sixfold from 0.9 per 100,000 in 1984 to 5.9 per 100,000 in 2013. This increase occurred among both men (1.7 to 9.5) and women (0.2 to 2.5, Figure 1). Age-standardised rates were similar, increasing among men from 2.0 to 8.3 per 100,000 and among women from 0.2 to 2.0 per 100,000 between 1984 and 2013.

Crude rates among men and women increased twice as fast in 2004-2013 than in the previous two decades (male 9.5% (95%CI 7.1%-11.9%) per year compared with 5.3% (95%CI 7.1%-11.9%); female 8.6% (95%CI 4.2%-6.4%) per year compared with 4.9% (95%CI 2.7%-7.1%)). Age-standardised rates for 2004 to 2013 increased 8.6% per year (95%CI 6.3%-10.9%) in men and 8.3% per year (95%CI 4.7%-11.9%) in women.

Geographic distribution

Age-standardised incidence of HCC varied considerably within Victoria (Figure 2A), however was concentrated within the metropolitan area of Melbourne. Incidence by LGA during the period 2004-2013 ranged from 1.2 to 12.4 per 100,000 per year, triple the average for Victoria (4.1 per 100,000). Eight of the 10 LGAs with the highest incidence were located in metropolitan Melbourne (Figure 2B). The top 10 LGAs accounted for 28.9% of cases, while representing 19.0% of the Victorian population. Age standardization increased the gap between highest and lowest rates (crude range, 1.3-9.8 per 100,000). Age standardised rates were generally higher than crude rates in metropolitan areas, while being lower in the non-metropolitan areas.

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HCC diagnosis and stage

The majority of HCC cases were diagnosed by histology of the primary tumour (65%), however the proportion diagnosed by clinical investigation increased from 1.5% of diagnosis prior 2004 to 28% in 2004–2013 (Table 1). Data on histologic tumour grade were only available for 25% (n=893) of diagnoses. Most were well differentiated (40% of those with data, n=358) or moderately differentiated (39%, n=352).

Comparison between current and historical data for the period of crossover available (1984-2012) demonstrated that when Registry data only included histologically confirmed HCC, there were 2,493 cases; inclusion of new cases under the changed definition increases the total to 3,302, an additional 809 cases. There were a further 340 cases diagnosed during 2013, of which 184 would not have been classified as HCC based on the historical definition, resulting in the overall addition of 993 cases of HCC during the period 1984-2013, an increase of 37.6%. The vast majority of these non-clinical diagnoses occurred during 2006-2013 (950 of the 993 cases, 95.7%, Figure 3). Due to this increasing frequency of non-histological diagnoses in later years, the number of HCC cases during 2006-2013 almost doubled, from 1,016 to 1,938 cases (94.4% increase).

Demographic characteristics of cases were very similar between those diagnosed using histological and non-histological methods, with no significant differences in the proportion of males (79.7% compared to 80.2%, p=0.775), metropolitan residents (81.2% compared to 81.0%, p=0.906), or in median age (65 compared to 66, p=0.6489). Five-year survival however was

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lower among those diagnosed using non-histological methods (13.6% compared to 19.7%, p=0.022).

Factors associated with incidence

Men were 4.5 times more likely than women to be diagnosed with HCC during 2004 to 2013 (Table 2). After controlling for year, sex, and age, people living in metropolitan areas were 54% more likely to be diagnosed than rural counterparts. Diagnoses increased with age, with people aged 70-79 years 36 times more likely to be diagnosed than those aged <50 years. Incidence increased by 9% per year when controlling for sex, age, and place of residence.

Survival following diagnosis

Crude five-year survival was 14% (95%CI 13%–15%), increasing over time from 5% (95%CI 4%–8%) during 1984-1993 to 16% (95%CI 14%–18%) in 2004-2013. Median survival increased from 2.7 months in 1984-1993 to 12.6 months in 2004-2013 (Table 3), decreased with age, and was higher for metropolitan residents. No difference in survival was seen according to sex. Overall, survival was longer for those born overseas than for those born in Australia, however within those born overseas, survival was longer for people born in South-East and North-East Asia than in Southern and Eastern and North-West Europe.

The hazard ratio (HR) of death increased with age at diagnosis (Table 4), with the greatest magnitude of effect in 1984-1993 and in those aged over 80 years compared to other age groups. HR of death was 10-15% lower metropolitan compared to non-metropolitan residents, however this only reached statistical significance in the most recent decade (Table 4). The HR of death for

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Australian-born people was 17% higher compared with those born overseas in 1994-2003, and 30% higher in 2004-2013. The associations observed were similar for age, place of residence and place of birth across the time periods, but the latter two factors did not always meet statistical significance, potentially as a result of smaller sample sizes in earlier decades (particularly in non-metropolitan areas).

Discussion

This is the first comprehensive study of HCC incidence and survival in Victoria, over a period of three decades, and represents the first assessment of the impact of considerable changes to the case definition. HCC is clearly a growing public health concern, with a disproportionate impact in particular groups.

Nearly two-thirds of all cases during the past thirty years occurred in the most recent decade, and those diagnosed were disproportionately older and male, with an uneven geographic distribution and an increasing burden among people born overseas. The prognosis for Victorians diagnosed with HCC has improved, however even recently, 80% of people died within five years of diagnosis. Survival was longer for people diagnosed at younger ages, metropolitan residents, and those born overseas, particularly Asia.

Inclusion of clinical diagnoses in the VCR HCC case definition profoundly increased the number of cases recorded in recent years, allowing for more complete assessment of incidence and

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trends, and suggesting that the burden in Victoria had been previously under-appreciated. This strongly supports the use of clinical classifications for HCC in cancer registries, and accords with findings in other settings such as the United States, where during 1998-2008 nearly a third of HCC were diagnosed using non-histological methods.(17) In Victoria, this change reclassified nearly 1,000 liver cancer cases to HCC in Registry and changed the observed incidence trend from a plateau to a strong increase. These changes have considerable impact when considering HCC incidence in the context of other cancers; with these clinically diagnosed cases included, the rank of HCC incidence relative to all cancers increases from 21st to equal 12th among men and from 36th to 26th among women.(18)

Although increasing the number of cases, demographics indicate that this definitional change has not shifted the distribution of sex, age, and geography. Lower survival in those diagnosed clinically likely reflects the higher likelihood of histological diagnosis in those who receive curative treatment, which often involves resection of the tumour and biopsy-based testing. Previous findings indicate those diagnosed clinically were more likely to have advanced disease at the time of diagnosis.(10)

The changes in diagnostic practices do highlight the potential limitation of assessing incidence of cancer over time, as increasingly accurate and more widely-used methods of detection may identify cases which in earlier years would have not been found and make rate changes appear more rapid than is the case. It is likely that the marked increase in HCC rates in Victoria during the period assessed in part relates to increased diagnosis. If this is the case, it indicates that HCC has historically been underdiagnosed and underestimated as a cause of death. The increase in

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rates, however, is still seen during the period 1984-2005, when the majority of diagnoses were still made using histological methods, suggesting diagnostic methods are not entirely the cause of the pattern seen.

Other improvements in registry completeness over time include in Indigenous status recording, allowing for accurate estimation of the burden of HCC in this group. The incidence of HCC in Aboriginal and Torres Strait Islander Victorians was proportional to population size, which contrasts with findings from other states demonstrating disproportionately high burden.(5, 6) This may represent differing epidemiology of viral hepatitis or other risk factors in the Victorian Aboriginal and Torres Strait Islander population, however there is also potential for underdiagnosis and misidentification of Indigenous status.

Notification of cancer diagnosis is a legal requirement and registry data represent a near-complete collection of all cancer diagnoses in Victoria,(18) however previous research has identified that in a minority of cases, HCC diagnoses have not been reported to the registry by diagnosing hospitals(10), which would lead to an under-estimation of the true incidence. Registry data also do not include aetiology of HCC, thus we cannot draw conclusions regarding attributable causes. However, a recent study outlined aetiology in HCC cases diagnosed in metropolitan Victoria in 2012-2013, indicating that the vast majority of cases had at least one identifiable risk factor for chronic liver disease, most commonly HCV (41%), alcoholic liver disease (39%), HBV (22%), and/or fatty liver disease (14%). Lifestyle interventions and work to improve low rates of HBV and HCV treatment(19) could play a significant role in alleviating the future burden of HCC.(3, 20, 21) The geographic clustering of HCC incidence likely relates to

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the distribution of these risk factors, and high regional variability within Victoria of chronic HBV in particular have previously been demonstrated.(22) Further research into the drivers of incidence in these high burden areas, and preventative efforts focused on those most at risk of HCC, should have substantial impact on rates of HCC in Victoria.

Decreasing survival with increasing age likely reflects general health status or diagnosis later in the course of illness with more severe disease. Without data on the specific cause of cancer we are unable to attribute differences in survival amongst this cohort, however our findings reflect other evidence that survival from HCC is higher in those with a higher HBV prevalence country of origin.(5) As people born in these countries are more likely to live in metropolitan areas,(23, 24) difference in survival according to aetiology could explain the longer survival in those born outside Australia and those living in metropolitan areas. The accessibility of treatment and care services may also be a factor, particularly in the disparity between rural and metropolitan residents.

Further information about the aetiology and clinical characteristics of HCC diagnoses would assist in identifying underlying causes of these disparities. Data linkage approaches between registry and hospital data have already helped establish the new clinical case definition which has substantially improved our understanding of the true burden of HCC in the population,(10) and a record linkage project incorporating additional datasets to estimate access to diagnosis and treatment for viral hepatitis is currently being conducted in Victoria, with results expected in 2018.

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The disproportionate impact of HCC on particular populations, and the reality that many of these cancers are readily preventable, highlights the urgent need to expand effective interventions for those most at risk to halt the continued rapid increase in morbidity and mortality.

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Figure legends

Figure 1. HCC diagnoses according to year, by sex (A) and place of residence (B), 1984-2013. Counts are represented by bars are counts and rates by lines. Note different scales on secondary vertical axes.

Figure 2. Age-standardised HCC incidence per 100,000 per year by Local Government Area in Victoria (a) and in Metropolitan Melbourne only (b), Victoria, 2004-2013. Incidence grouped in quintiles; blank areas had <5 cases during the period.

Figure 3: Number of HCC cases, according to year of diagnosis and diagnostic classification, 1984-2013

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Tables

Table 1. Demographic and diagnostic characteristics of people diagnosed with HCC in Victoria, 1984-2013.

	1984-1993	**1994-2003**	**2004-2013**	**Total**
Total cases	529	941	2171	3641
Sex				
Male	428 (81%)	762 (81%)	1737 (80%)	2927 (80%)
Female	101 (19%)	179 (19%)	434 (20%)	714 (20%)
Median age (IQR)	64 (57-71)	67 (58-74)	66 (56-75)	66 (56-74)
Age group				
< 50	60 (11%)	119 (13%)	214 (10%)	393 (11%)
50 - 59	98 (19%)	147 (16%)	524 (24%)	769 (21%)
60-69	202 (38%)	272 (29%)	555 (26%)	1029 (28%)
70-79	138 (26%)	304 (32%)	601 (28%)	1043 (29%)
80+	31 (6%)	99 (11%)	277 (13%)	407 (11%)
Place of residence				
Metropolitan	437 (83%)	790 (84%)	1765 (81%)	2992 (82%)
Rural	92 (17%)	151 (16%)	407 (19%)	650 (18%)
Region of birth				
Australia	283 (54%)	406 (44%)	932 (44%)	1621 (45%)
Southern & Eastern Europe	107(21%)	219 (24%)	454 (21%)	780 (22%)
North-West Europe	49 (9%)	72 (8%)	195 (9%)	316 (9%)
South-East Asia	36 (7%)	105 (11%)	224 (11%)	365 (10%)
North-East Asia	22 (4%)	60 (6%)	106 (5%)	188 (5%)
North Africa and Middle East	12 (2%)	22 (2%)	66 (3%)	100 (3%)
Southern and Central Asia	7 (1)	10 (1%)	46 (2%)	63 (2%)

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Sub-Saharan Africa	*<5*	9 (1%)	32 (2%)	41 (1%)
Oceania (not Australia)	*<5*	12 (1%)	42 (2%)	54 (2%)
Americas	*<5*	8 (1%)	22 (1%)	30 (5%)
Best basis of diagnosis*				
Histology of primary tumour	397 (75%)	844 (90%)	1136 (52%)	2377 (65%)
Clinical investigation	14 (3%)	*<5*	615 (28%)	631 (17%)
Clinical only	*<5*	5 (1%)	167 (8%)	173 (5%)
Cytology or Haematology	78 (15%)	71 (8%)	33 (2%)	182 (5%)
Death certificate only	15 (3%)	*<5*	*39 (2%)*	54 (1%)
Other	14 (3%)	18 (2%)	57 (3%)	89 (2%)
Unknown	10 (2%)	*<5*	125 (6%)	136 (4%)

*'Clinical investigation' diagnoses include imaging and exploratory surgery. 'Other' includes histology of metastasis and specific tumour markers. 'Clinical only' refers to patients in whom investigation type is not clear. Missing data: sex, n=1; age, n=1; place of residence, n=0; country of birth, n=79. Cells with <5 suppressed, totals do not include <5 cells.

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Table 2. Demographic factors associated with incidence of HCC, multivariate Poisson regression, Victoria, 2004 to 2013.

	Incidence Rate Ratio	**95% Confidence Interval**
Sex		
Female	1	
Male	4.52	4.02 – 5.09
Age (years)		
< 50	1	
50 - 59	13.55	11.27 – 16.31
60-69	20.49	17.07 – 24.59
70-79	35.99	30.02 – 43.15
80+	27.48	22.48 – 33.58
Place of residence		
Non-metropolitan	1	
Metropolitan	1.54	1.37 – 1.74
Year	1.085	1.066 – 1.105

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Table 3: Median survival after HCC diagnosis according to demographic characteristics, Victoria, 1984-2013

	N	Median survival (95% CI, months)	p-value
Sex			0.315
Male	2,815	9.0 (8.2, 9.6)	
Female	691	9.8 (8.0, 11.6)	
Age (years)			<0.001
< 50	386	14.8 (10.7, 18.1)	
50 - 59	748	12.7 (9.9, 15.4)	
60-69	984	9.5 (8.1, 10.7)	
70-79	1,003	8.1 (6.8, 9.5)	
80+	385	4.9 (4.0, 6.3)	
Place of residence			<0.001
Non-metropolitan	627	6.8 (4.9, 7.9)	
Metropolitan	2,880	9.6 (9.0, 10.4)	
Place of birth			<0.001
Overseas	1,885	10.0 (9.2, 11.3)	
Australia	1,546	7.0 (5.9, 7.9)	
Region of overseas births			<0.001
Southern and Eastern Europe	755	9.1 (7.7, 10.6)	

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North West Europe	301	8.5 (6.0, 7.9)	
South East Asia	360	13.9 (10.0, 19.5)	
North East Asia	185	18.8 (9.9, 24.5)	
Southern and Central Asia	61	9.5 (4.2, 12.2)	
North Africa and Middle East	94	18.1 (8.0, 31.9)	
Sub-Saharan Africa	42	10.3 (7.0, 15.7)	
Americas	32	17.8 (3.2, 32.7)	
Oceania (not Australia)	55	6.7 (4.3, 11.3)	
Period of diagnosis			<0.001
1984-1993	474	2.7 (2.3, 3.4)	
1994-2003	903	6.9 (6.0, 8.2)	
2004-2013	2,130	12.6 (11.3, 13.5)	

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Table 4: Hazard ratio of death from HCC according to demographic characteristics, Victoria, 1984-2013

	1984-1993		**1994-2003**		**2004-2013**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age (years)		<0.001		<0.001		<0.001
< 50	1		1		1	
50 - 59	2.17 (1.52, 3.11)		1.29 (0.99, 1.70)		1.15 (0.94, 1.41)	
60-69	2.41 (1.74, 3.35)		1.62 (1.27, 2.07)		1.27 (1.04, 1.54)	
70-79	2.27 (1.62, 3.20)		1.65 (1.30, 2.10)		1.75 (1.44, 2.12)	
80+	3.50 (2.16, 5.71)		2.19 (1.63, 2.96)		2.66 (2.15, 3.30)	
Place of residence		0.368		0.107		0.016
Rural	1		1		1	
Metropolitan	0.89 (0.70, 1.14)		0.85 (0.70, 1.03)		0.85 (0.75, 0.97)	
Place of birth		0.169		0.032		<0.001
Overseas	1		1		1	
Australia	1.15 (0.94, 1.40)		1.17 (1.01, 1.36)		1.32 (1.19, 1.46)	

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Acknowledgements:

The authors would like to thank the Victorian Cancer Registry for the provision of the data used. We would like to acknowledge the Australian Bureau of Statistics for the publication of essential population statistics in the public domain.

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