

EPIDEMIOLOGY OF PRIMARY LIVER CANCER

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Abstract

Cancer of the liver is a significant cause of morbidity and mortality worldwide. Globally, 625,000 cases of liver cancer were reported in 2002. The worldwide distribution of liver cancer is characterised by a great geographic variability, with age-standardised incidence rates ranging from more than 30 cases per 100,000 population in eastern Asia and parts of Africa, to fewer than five per 100,000 in the Americas and in Northern Europe. Much of this variability in the distribution of the disease is related to the global distribution and the natural history of infection with hepatitis B and C viruses. In Australia, both the incidence of and mortality from liver cancer have been progressively rising since the mid-1980s. The age standardised incidence rates for liver cancer are highest in some overseas-born Australians, especially among those born in hepatitis B and C endemic countries. The incidence of primary liver cancer in Australia is projected to continue to rise over the next two decades, as a result of a large reservoir of asymptomatic infections with chronic viral hepatitis, immigration from countries of high hepatitis B virus prevalence and the slow disease progression from chronic hepatitis B virus infection to liver cancer. Public health strategies for targeted interventions for the prevention, treatment and control of chronic viral hepatitis infection may effectively reduce the burden of liver cancer globally, as well as in Australia.

Cancer of the liver is the sixth most common type of cancer worldwide, with 625,000 cases recorded in 2002. Globally, liver cancer accounts for 5.6% of all cancers in humans - with more cases diagnosed in males (where it accounts for 7.5% of all cancers) than females (3.5% of all cancers).¹

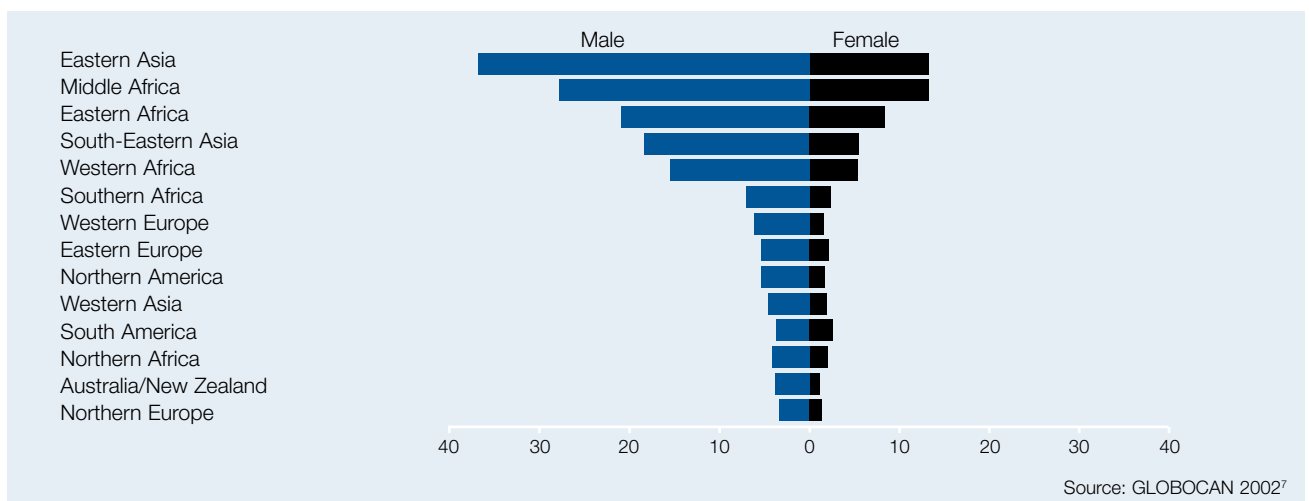
The most common malignant primary liver cancer (PLC) is hepatocellular carcinoma (HCC), which represents 75–90% of liver cancers worldwide. Less common types of primary liver cancer include cholangiocarcinoma, tumours of mesenchymal tissue, sarcomas and hepatoblastoma.² Cancer of the liver and intrahepatic biliary ducts are grouped together in the International Agency for Research on Cancer publications and as specific statistics for the rarer forms of cancer are not generally available, we

used the term 'primary liver cancer' (PLC) throughout this report. Here we propose to define the magnitude of primary liver cancer incidence and mortality globally and in Australia, with particular focus in New South Wales.

International patterns of liver cancer incidence and mortality

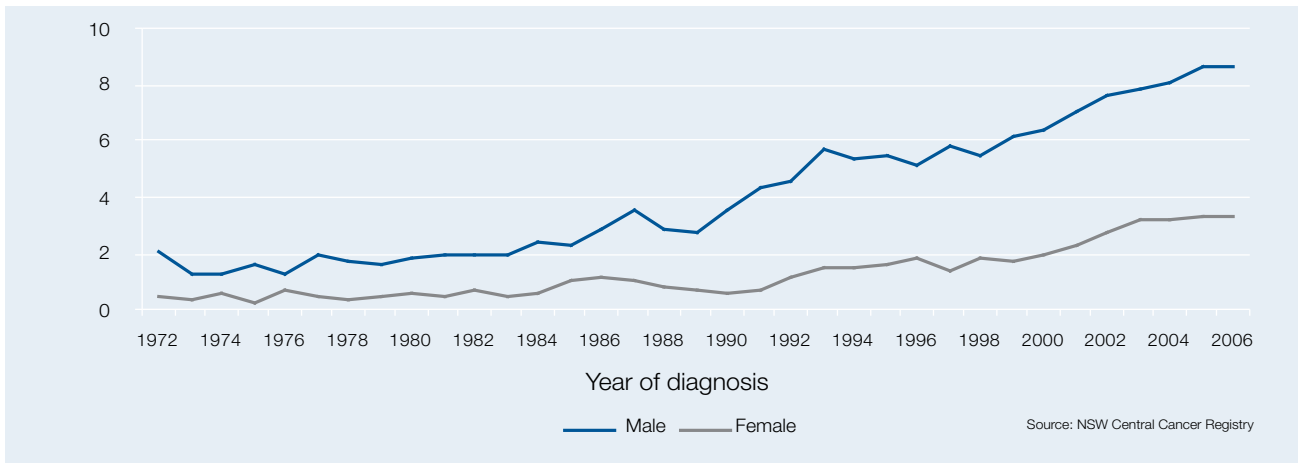
There are substantial variations in the distribution of liver cancer incidence and mortality across geographical locations, with PLC more common in regions of Africa and Asia than in Western countries and more common in middle and low income countries than in developed nations. Approximately half of all primary liver cancers occur in China.³

Figure 1. Age standardised^a incidence of liver cancer in selected regions by sex, all ages, 2002 (per 100,000)



^a Standardised to world population.

Figure 2. Trends in liver cancer: age-standardised incidence rate per 100,000 population by sex, all ages, NSW 1972-2006



Liver cancer incidence and mortality rates vary considerably across different geographical areas, with much of this variability related to the global distribution and natural history of infection with hepatitis B virus (HBV) and hepatitis C virus (HCV).⁴ The early age of infection with HBV in Asian patients accounts for significant differences in the clinical course of disease compared to Caucasians,⁵ placing them at a higher risk of liver cancer than other populations who acquire the infection in adolescence or adulthood.

In 2000, PLC was most prevalent in eastern Asia, middle Africa and some countries of western Africa, with an estimated age-adjusted incidence rate (AAIR) per 100,000 men approximately 10 times higher in eastern Asia, compared to Australia and New Zealand.⁶ AAIRs in 2002 were highest in eastern Asia (36.9 per 100,000 males) and in middle Africa (13.4 per 100,000 females) and lowest in northern Europe (3.4 per 100,000 males and 1.7 per 100,000 females). Overall, Australia and New Zealand had some of the lowest AAIRs of 1.3 per 100,000 population (figure 1).

Significant PLC variations can exist among different populations from the same countries, depending on their ethnic origins. For example, during 1992-1996, the overall AAIRs for liver cancer in the US were 3.1 per 100,000 people, but significant differences existed along racial lines. The lowest rates were documented in Caucasians (8.6 for males and 2.7 for females) and the highest in Asian and Pacific islanders (20.9 in males and 7.9 in females).^{8,9} In the US and the Netherlands, primary liver cancer affected migrants from Asia and the Pacific Islands disproportionately, compared to the locally-born populations.⁹⁻¹¹ Similarly in New Zealand, significant discrepancies were noted between the rates of PLC in Pacific Islanders, (in whom the annual incidence was 5.8 per 100,000 per year), the native Maori population (2.8/100,000/year) and those of European descent (0.6/100,000/year).¹² Excess mortality rates are most marked in the first generation migrants, compared to subsequent generations.^{1,13}

Compared with females, males have substantially higher age-standardised incidence rates for PLC, with male to female age adjusted incidence ratios worldwide ranging from 1.3 to 3.6. In eastern Asia, primary liver cancer is the

most common cause of cancer-related death.^{7,14} Similar to incidence, mortality rates are generally higher in less developed countries, compared with more developed countries.^{7,15,16}

Primary liver cancer in Australia

Overall, Australia has comparable rates of incidence and mortality from liver cancer to those recorded for similar developed countries.^{15,17} Primary liver cancer is relatively uncommon, ranking fifteenth in males and twentieth in females, but its incidence has been progressively rising over the last three decades. Age-standardised incidence rates in males increased from 2.06 per 100,000 in 1983-1985 to 3.97 during 1995-1997, and from 0.57 to 0.99 in females in the same time periods.¹⁸ In Australia, males are 2.5 times more likely to be diagnosed and to die of liver cancer than females. An Australian male's risk of developing liver cancer is one in 198 to age 75 and one in 113 to age 85, which is comparable to the risk of developing brain cancer (which is one in 164 by age 75 and one in 111 by age 85).¹⁹

During 1999-2003, the age-standardised incidence rates of PLC in all states and territories in Australia ranged from a high of 11.8 new cases per 100,000 for males in the Northern Territory to a low of 1.4 cases per 100,000 females in Tasmania. It was estimated that, between 2002 and 2011, the rates will continue to increase by 27% in females and 43% in males.²⁰

During 2001-2005, the mortality rate for liver cancer in males ranged from a high of 11.1 in the Northern Territory to a low of 1.8 deaths per 100,000 in Western Australian females. The Northern Territory statistics may be attributable to higher incidence rates for HBV and HCV infection.²¹

In 2006, in New South Wales (NSW), PLC ranked 13th in males and 20th in females in terms of incidence, and 11th in males and 13th in females in terms of cancer mortality.¹⁷ From 1972 to 2006 in NSW, age-standardised incidence rates in males increased over 4-fold; from 2.0 new cases per 100,000 to 8.4 per 100,000. In the same period, a similar increase occurred for females, with rates increasing from 0.5 new cases to 3.2 per 100,000 (figure 2).

Age standardised incidence rates for liver cancer in Australia are highest in some overseas-born populations, with this discrepancy unlikely to be caused by increased liver cancer screening, or increased alcohol consumption in specific groups, but most likely due to chronic infection with hepatitis B or C.¹⁸

Although people born in China and Vietnam represent only about 5% of the Australian population, half of all cases of chronic hepatitis B (CHB) infection in Australia occur in these populations.²² The significant numbers of undiagnosed CHB infections in these populations, coupled with the natural history of CHB infection in populations where the infection is acquired early in life,^{5,23} contribute to the increasing prevalence of PLC in Australia.¹⁸

Another population group at increased risk of PLC in Australia are Indigenous people, in whom PLC incidence rates are 5-10 times greater than in non-Indigenous Australians.²⁴ Indigenous Australians represented only 2.4% of the Australian population in the 2001 census, but accounted for 16% of estimated CHB infections.²⁵ One study found that among Aboriginal people diagnosed with PLC in Australia, more than 60% were HBsAg positive,²⁴ suggesting that CHB infection is the major cause of HCC in this population.²⁶

During 1991–2000, the Indigenous populations in the Northern Territory had substantially higher death rates from liver and gallbladder cancer, compared with the total Australian population (RR 5.7, 95% CI: 4.2–7.6).²⁷ Similarly, from 2000 to 2004 in NSW, liver cancer represented 2.1% of all cancers in Aboriginal males, as compared to 1.3% in non-Aboriginal Australian males.²⁸

In NSW, PLC incidence rates have been rising faster than any other cancer, with an average annual increase recorded between 1997 and 2006 of 5.3% for males and 8.8% for females, surpassing cancers of the prostate, thyroid, skin (melanoma) and oesophagus.^{17,29} Approximately half of all PLCs occurred in overseas-born people in NSW, with males born in Vietnam, Hong Kong, Macau, Korea, Indonesia and China, and females born in Vietnam and China, 6-12 times more likely to develop PLC than Australian-born individuals.³⁰

PLC exhibits a striking pattern of geographic clustering in NSW, with the highest rates occurring in South Western Sydney where, in 2005, the incidence of PLC (7.7 per 100,000, 95% CI: 7.0-8.4) far exceeded the NSW state average (5.2 per 100,000, 95% CI: 5.0-5.5).¹⁵ A hospital-based case series of patients presenting to the two teaching hospitals in this region found a 36% increase of incidence of HCC from 1993 to 2003.³¹ Almost half (46%) of these patients were Asian-born, with 42% having evidence of CHB infection and 75% presenting at a symptomatic stage, explaining a poor median survival of 5.1 months.³¹

In NSW, the median age at diagnosis for liver cancer in 2005 was 64 years for males and 76.5 years for females. In 2005, 46.4% of all new cases of liver cancer in NSW

were localised, 9.1% had regional spread, approximately 30% were disseminated; in 15% of cases the degree of spread was unknown. In 2006, liver cancer accounted for 3% of all male cancer deaths and 1.9% of all female cancer deaths in NSW. The trend of mortality rates mirror the trend of incidence mainly due to poor survival.¹⁷

Projected trends in liver cancer incidence and mortality

Future projections of liver cancer incidence suggest a continuing upward trend in developed countries for some decades to come, as a result of past infection with hepatitis B and C viruses,¹ while recent declines in PLC have been attributed to the effects of hepatitis B vaccination programs.^{1,32}

The high level of migration to Australia from countries of high hepatitis B prevalence has been associated with increasing prevalence of CHB infection.^{29,33} As national vaccination programs in Vietnam and China have only commenced during the last decade, it is unlikely that any substantial reductions in the burden of chronic hepatitis B and liver cancer among people born in these countries will occur over the next two decades.²⁹ If the current trend in population migration to Australia from the CHB prevalent countries continues, the incidence of PLC will continue to rise, with one study suggesting that among Australians born in China, the number of CHB-related HCC cases will double over the period 2005-2025,³⁴ unless pharmacological treatments of hepatitis B infection can reverse this trend.

In NSW, if the historical trends in the incidence of liver cancer continue, the age-standardised incidence rates for liver cancer are expected to increase by 11.3-16.4% for males and 24.8% for females over the next five years (2007–2011), with the trends in mortality expected to follow incidence patterns.¹⁵

Risk factors for primary liver cancer

Chronic infection with HBV and HCV, aflatoxin ingestion and excessive alcohol consumption contribute to significant inter-country variations of HCC incidence around the world. Although other factors, such as genetic/family history, diet and tobacco smoking, have been implicated in disease development, their contribution to disease causation remains uncertain.^{2,16}

Overall, it is estimated that 75-80% of cases of PLC are attributable to chronic HBV or HCV infections, with HBV responsible for 50-55% cases overall and HCV for approximately 25-30%.¹ People with chronic HBV or HCV infection are at 20 to 200-fold greater risk of developing HCC than those uninfected.³⁵⁻³⁷ According to a World Health Organisation report published in 2004, an estimated two billion people worldwide were infected with HBV (with approximately 350 million chronically infected) and 170 million people were infected with HCV. Some 500,000 – 1.2 million deaths each year are caused by HBV infection, with 320,000 deaths due to liver cancer.³⁸

As almost a third of all people with HBV infection in the world live in China, its burden of HBV related disease is considerable, with 300,000 deaths annually from HBV related conditions, including 180,000 deaths from HCC.³⁹ The strong positive correlation between the incidence of HCC and the prevalence of HBV surface antigen in a population, termed “geographic parallelism”, was first described in 1969,⁴⁰ explaining, for example, the high rates of PLC in Taiwan, where 80% of cases are associated with chronic HBV infection.⁴¹

In Africa and Asia the largest attributable fractions for PLC (approximately 60%) relate to CHB infection, with HCV infection accounting for another 20%. In Europe and the United States the figures are reversed, with 60% attributable to HCV infection, 22% to HBV and 45% due to alcohol ingestion (allowing for the joint effects of several risk factors in some cases).¹ A synergistic effect of co-infection with HBV and HCV on HCC development has been documented.^{42,43}

Approximately 30% of chronic viral hepatitis cases are complicated by cirrhosis, with the annual incidence of liver cancer in people with cirrhosis ranging from 2-3% in Western countries to 6-11% in Asian populations.⁴⁴ Approximately 80% of PLCs develop in cirrhotic livers,¹⁴ but liver cancer can also develop in livers with minimal histological changes. This phenomenon is more common in southern Africa (where approximately 40% of liver cancer cases have minimal liver damage) than in Asia, America and Europe (where more than 90% are associated with liver cirrhosis).⁴⁵

Ample evidence exists that chronic alcohol consumption is a cause of liver cirrhosis, which predisposes to liver cancer, but the exact mechanism that explains this process remains unclear. A systematic review of 133 studies found that alcoholics with HCV infection are at increased risk of developing liver diseases, compared with non-alcoholics, with or without HCV infection.⁴⁶ Alcoholics with HCV also have more rapid and frequent occurrence of cirrhosis, compared with non-alcoholics.⁴⁷⁻⁴⁹ While liver cancer was not considered a tobacco-related cancer in a recent review by the International Agency for Research on Cancer,⁵⁰ some studies found an association between smoking and liver cirrhosis,⁵¹⁻⁵³ particularly among drinkers (relative risk (RR)=9.3, 95% CI:1.1–78.8), compared to non-drinkers (RR=1.85, 95% CI: 0.98-3.51).⁵³

Being diabetic also increases the risk of liver cancer, with a large cohort study finding standardised incidence ratios of 4.1 (95% CI: 3.8–4.5) in diabetics compared to non-diabetics.⁵⁴ Retrospective studies also found a positive association between type-2 diabetes mellitus and the risk of HCC.⁵⁵⁻⁵⁷

Several studies have found an association between increased body fat and primary liver cancer.^{58,59} A cohort study of over 350,000 Swedish men found that obesity significantly increased the risk of liver cancer for men (RR 3.6, 95% CI: 2.6–5.0).⁶⁰

Conclusion

The incidence of primary liver cancer in Australia is likely to continue to rise over the next two decades, as a result of a large reservoir of asymptomatic chronic viral hepatitis, immigration from countries of high HBV prevalence and the slow disease progression from chronic HBV infection to liver cancer.^{18,22,61} Without targeted interventions for the prevention, treatment and control of chronic viral hepatitis, 25% of these people are likely to die from the consequences of liver disease, which include liver cancer, as well as end-stage liver disease.⁶¹ While the impact of hepatitis B vaccination is likely to provide significant long-term dividends for disease prevention, vaccination will not have a significant impact for those already infected and asymptomatic. Increasing the accuracy and reliability of predictors of malignant transformation in individual patients with established risk factors is needed to improve disease outcomes,⁶² coupled with public health strategies addressing the significant burden of disease related to liver cancer in at risk populations.

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