For decades, to physicians in developed nations, hepatocellular cancer (HCC) was an infrequent clinical concern. The disease presented in people in their 6th and 7th decades and at an advanced stage, when little except supportive care was provided, so HCC was a pre-terminal event for most. In precious few, resection was offered if advanced liver disease did not preclude surgery. This approach and ‘acceptance’ contrasted markedly with global epidemiological data that indicated HCC was a major cause of cancer-related death.

This fatalistic approach to HCC has changed markedly over the last two decades in both developed countries and most importantly, in the developing economies of the Far East, in which a large proportion of at-risk individuals reside. In the developed world, the elimination of the cognitive dissonance by clinicians and scientists coincided with the rising incidence and prevalence of HCC, a consequence both of the epidemic of chronic hepatitis C and global migration trends. The latter saw individuals from countries in which chronic viral hepatitis (particularly hepatitis B) was a common occurrence migrate to more affluent nations.

In parallel with these developments, developing economies have expended more effort on public health initiatives, such as vaccination, surveillance and medical therapies, to deal with what is clearly a major public health issue. Many of these treatments, including transarterial chemoembolisation and radiofrequency ablation, may in the future seem like sledgehammer therapy, compared to the molecular therapies now being developed. However, it is clear that the overall management of HCC, from risk factor detection and risk factor control to early HCC detection and therapy, has exponentially improved over the last two decades. We are now at the start of a bright, or at least a brighter future in our approach to HCC. This issue of Cancer Forum serves to put HCC in perspective: where we have been, where we are now and where we are heading. It is a story of hope for those affected by cancer and particularly for those with hepatocellular cancer.

**OVERVIEW: HEPATOCELLULAR CARCINOMA – THE FUTURE STARTS NOW**

**Abstract**

While hepatocellular cancer remains relatively uncommon in Australia, incidence rates have been progressively rising over the last few decades. Hepatocellular cancer has well-defined risk factors, some of them amenable to modulation or eradication. Currently, chronic hepatitis B or C infection accounts for approximately 80% of all primary liver cancers, but as hepatitis B vaccination will lead to fewer hepatitis B-related cancers, more cases will be due to hepatitis C or non-alcoholic fatty liver disease. Cancer control strategies are contingent upon the ability to prevent liver disease progression to cirrhosis and the eradication or suppression of viral replication; the extent to which screening improves disease-specific or all-cause mortality remains unclear. Our understanding of hepatocellular cancer biology and of viral hepatitis has dramatically increased in recent years, as a result of cross-disciplinary collaborations between clinicians, epidemiologists, public health practitioners and basic scientists. Hepatocellular cancer responds poorly to conventional chemotherapy, but the advent of new and more effective therapies – particularly biological agents that specifically target the molecular basis of neoplastic growth and metastasis – is expected to make a significant impact in coming years. We hope that this issue of Cancer Forum will convince the reader that we are now at the threshold of a better future for this previously untreatable malignancy.
Liver cancer is relatively uncommon in Australia, where it ranks fifteenth in males and twentieth in females. However, over the last three decades, HCC incidence rates have been rising in Australia, both from cases attributed to hepatitis C and from hepatitis B – the latter related to migration from high prevalence countries. Data from the NSW Cancer Registry indicate that age-standardised primary liver cancer incidence rates have increased from 2.0 and 0.5 per 100,000 in males and females respectively in 1972, to 7.4 and 2.9 per 100,000 in 2004. The annual changes in incidence and mortality of cancers in both genders between 1987 and 1997 was highest for liver cancer (~8% annual increase in males and ~7% in females for incidence and ~8% annual increase in males and ~6% in females for mortality), compared to all other internal malignancies. Finally, data from Cancer Council NSW indicates that the standardised incidence ratios for liver cancer in NSW males between 1991 and 2001, compared to that of males born in Australia was 11.66 (99% CI 8.68-15.31) for persons born in Vietnam and 6.18 (CI 4.82-7.80) for those born in China. Males born in Hong Kong and Macau had 9.3 times the incidence of HCC, those from Korea 8.6 times that rate and those from Indonesia 6.4 times the rate of males born in Australia; similar findings were noted in females. This unique ethnic-specific distribution of HCC reflects the HCC risk profiles in the countries of origin of these migrants, one that is principally driven by hepatitis B virus (HBV) infection acquired early in life. The epidemiology of liver cancer in Australia is described in the article by Alam, Robotin and Baker.

Unlike many malignancies, HCC has well-defined risk factors that include chronic viral hepatitis, aflatoxin exposure, alcohol-associated liver disease and non-alcoholic fatty liver disease. Some of these risk factors are amenable to modulation or eradication. For example, the consumption of foods contaminated with fungi that produce aflatoxin is a significant health hazard in sub-Saharan Africa and South-East Asian countries, greatly increasing the risk of liver cancer in these countries. Changes in individual and community practices around the storage of grains and pulses has been associated with significant reductions in HCC incidence in West Africa and in the QiDong province in China.

In chronic hepatitis C, HCC virtually only occurs in the setting of liver cirrhosis, while in chronic hepatitis B, some 80% of HCCs occur in cirrhotic livers. In both these diseases, risk factor eradication or modulation can favourably influence HCC risk as outlined in this Forum by Thein and Dore with regard to Australian trends in chronic viral hepatitis, treatment uptake and their respective effects on local liver cancer incidence and trends.

Currently, chronic infection with hepatitis B and C accounts for more than three quarters of all primary liver cancers, but the relative proportions of HCC attributable to various etiologies are likely to change significantly over the next few decades and between countries. Incident cases of hepatitis B-related HCC will markedly diminish among individuals born in countries with effective and universal infant hepatitis B vaccination programs, such as Taiwan, Singapore, European countries and Australia. The total hepatitis B-related HCC burden from currently infected persons however, is likely to persist for decades. Likewise, migration patterns will influence the burden of HCC in countries which have an active immigration policy. This contrasts with the increasing non-hepatitis B-related HCC incidence in parts of Europe, the US and Australia, thought to be related to increased rates of hepatitis C infection in certain sub-populations. In the US, hepatitis C accounts for most of the cases of liver cancer, with a 3-fold increase in age-adjusted rates of primary liver cancer due to hepatitis C in recent years. The rising burden of non-alcoholic fatty liver disease over the last few decades and its observed association with HCC has led to the recognition that in coming years, up to a third of future HCC burden will be ‘metabolic’ in origin.

In patients with chronic viral hepatitis, a recent population-based study of 23,820 Taiwanese residents aged over 14 years has shown that obesity increases the risk of HCC in Hepatitis C virus (HCV) infection 4-fold, while the presence of diabetes increases HCC risk in HBV (2.27-fold) and HCV infection (3.52-fold). However, the presence of both diabetes and obesity independently increases HCC risk 265-fold (in the case of HBV) and 135-fold (in the case of HCV), indicating the critical synergistic effects of metabolic factors and viral hepatitis. The theme of the complex interplay between risk factors in ascribing population attributable risk is highlighted in the paper by Kane and Macdonald.

Sustained viral eradication: a new paradigm in cancer control

Overall, data clearly indicate that cancer control strategies in relation to hepatitis B and C are intricately linked to preventing liver disease progression to cirrhosis and eradicating (hepatitis C), or suppressing viral replication (hepatitis B). In people infected with hepatitis C, sustained viral eradication (SVR) is associated with reductions in HCC. This has been best documented in Japan by the Inhibition of Hepatocarcinogenesis by Interferon Therapy (IHIT) study, a retrospective multicenter large scale cohort study supported by the Japan Ministry of Health and Welfare, as one of the 10-year Strategy for Cancer Control Projects. The second IHIT study examined the development of liver cancer in 2890 patients with chronic hepatitis C, of whom 2400 received interferon and 490 were untreated. Among untreated subjects, the annual incidence of HCC increased with the extent of hepatic fibrosis from 0.5% among those with mild fibrosis (F0/1) to 7.9% in those with cirrhosis. Following antiviral therapy, those achieving SVR had significant reductions in the annual incidence of HCC. Incidence was reduced 10.9-fold among patients with cirrhosis and an SVR, compared to those with cirrhosis and a non-sustained virological response; in those with advanced (F3) fibrosis, the cancer incidence was ~50% among those achieving an SVR.
compared to those with a non-sustained virological response. The incidence of HCC in those with milder stages of fibrosis (F0-1) was no different between those achieving a virological response and those failing to achieve such a response. Importantly, this reflects the fact that HCC development in hepatitis C predominantly occurs in the setting of ongoing viral replication in a liver with advanced hepatic fibrosis. Virological responses to hepatitis C can be achieved with current therapies in ~80% of those infected with genotypes 2 and 3 and ~50% of those infected with the other genotypes. These figures are likely to be superseded in the next decade, with the advent of novel therapies including protease and polymerase inhibitors. Until an effective vaccine against HCV is available, anti-viral therapy for those infected remains the best hope for preventing liver cancer in this population.

While the relationship between hepatitis B viral suppression and HCC remains a matter of debate, at least one study suggests that HCC risk can be halved by effective viral suppression in patients with advanced fibrosis or cirrhosis. A recent study by Yuen et al in 2008 suggests that the age at which HBsAg seroconversion occurs is an important determinant of HCC risk: HBsAg seroclearance before the age of 50 was associated with both a lower risk of HCC development and a lower risk of significant fibrosis, compared to later HBsAg seroclearance (in ages >50 years). In this context, it is tempting to speculate that similar results in terms of HCC prevention may be achieved with earlier viral suppression, before viral integration events and advanced fibrosis have intervened.

In a landmark study, the Taiwan-based REVEAL study group reported on the long-term outcomes of a prospective study of 3582 untreated subjects with chronic hepatitis B. During a mean follow up of 11 years and in excess of 40,000 person years, the incidence of cirrhosis rose across a biological gradient of HBV DNA level, from 4.5% with a viral load <300 copies/ml to 36.2% at loads of ≥10⁸ copies/ml. Using Cox proportional hazards modelling and adjusting for HBeAg status and serum alanine aminotransferase (ALT), viral load was the strongest predictor of progression to cirrhosis. A similar gradient of risk for HCC development in relation to HBV DNA levels was also published by the same investigators. The latter study examined for HCC outcomes in a cohort of 3653 HBsAg positive Taiwanese subjects aged 30-65. During a mean follow up of 11.4 years, 164 incident cases of HCC were reported and cancer incidence increased with serum HBV DNA levels in a dose-response manner, from 108 per 100,000 person-years for HBV DNA levels <300 copies/ml to 1152 per 100,000 person years for levels of greater than 10⁶. With corresponding cumulative incidence rates of HCC being 1.3% and 14.9% respectively. This relationship with viral replication remained significant (p<0.01) after adjusting for age, gender, cigarette smoking, alcohol consumption, e-antigen status, ALT and the presence or absence of cirrhosis at study entry. The article by Warner, Locarnini and Nguyen discusses in more detail the role of anti-viral medications in preventing liver cancer, making the point that without effective treatment, progression to liver failure and liver cancer can be expected for a significant proportion of those infected.

Role of HCC screening in cancer control

Epidemiological risk factors for HCC, the slow progression of liver disease to cirrhosis and the development of the majority of cancers in a cirrhotic liver, suggests that this malignancy may be amenable to early detection through regular surveillance, as discussed in the paper by Gane. The population at risk (people with cirrhosis or those with hepatitis B as per the American Association for the Study of Liver Disease guidelines) is well characterised, suitable diagnostic tests are available for screening and potentially curative options are available, suggesting that HCC outcomes may be influenced by screening. Furthermore, we have randomised trial evidence of a reduction of mortality in the screened population. One large randomised control trial in China (enrolling over 18,000 people with chronic hepatitis B) demonstrated a 37% reduction in mortality for people screened, compared to controls. Study limitations, such as poor follow-up and the fact that liver transplantation was not part of the treatment protocol, makes these results difficult to extrapolate to other settings. However, the extent to which screening improves disease-specific or all-cause mortality for HCC remains unresolved to date. As screening increases the proportion of cancers amenable to liver resection or liver transplantation, and the benefit is maintained after correction for lead-time bias of up to four years, surveillance is gradually becoming accepted as the standard of care in at-risk groups, with both US and European guidelines now stating that patients with cirrhosis or those with chronic viral hepatitis B should have regular monitoring with ultrasound every 6-12 months. This aspect is further developed by Tipper and Penman, who describe a population-based model of disease control and prevention that is currently being piloted in NSW - the B positive project.

New understanding of HCC biology and HCC outcomes

As this review highlights – and as will be emphasised throughout this issue – our understanding of HCC biology and of viral hepatitis has increased tremendously over the last four decades (reviewed in this Forum by Tirnitz-Parker and Olynyk). This has critically depended on cross-disciplinary collaborations between clinicians, epidemiologists, public health practitioners and basic scientists. The pace of these developments in improving our understanding of HCC natural history, biology and therapy when viewed in hindsight, has truly been astounding. Research in one area has fed on leads for developments in others – and many of these developments have occurred simultaneously and often not in the expected chronological sequence.
Our understanding of HCC natural history, causation, biology and treatment has progressed often in quanta, rather than by increments. Within six years of the Australia antigen being described (in 1963), Smith and Blumberg postulated a causal association between it and hepatocellular cancer, later termed ‘geographical parallelism’. Twelve years later, this hypothesis was to be confirmed through Beasley’s definitive prospective study of over 22,000 Taiwanese men, showing that the relative risk of developing liver cancer was 98.4-fold higher in HBsAg+ve participants, compared to people who were uninfected.

To many physicians, human papilloma virus vaccination is the “anti-cancer vaccine,” protecting women against cervical cancer, yet it must be remembered that HBV vaccination was truly the first anti-cancer vaccine. In a great success for public health, within a decade of instituting mass hepatitis B vaccination, the incidence of HCC in children aged 6-9 fell from 0.52 per 100,000 for those born between 1974 and 1984 to 0.13 for those born between 1984 and 1986 (P<0.001).

Likewise, the incontrovertible link between ongoing viral replication and HCC development from an intervention, rather than prevention perspective, was evident from the IHI study in hepatitis C and the Cirrhosis Asian Lamivudine Multicenter Studies alluded to earlier. The role of different viral factors, including HBV genotype, viral co-infection and the significance of polymorphisms in genes encoding glutathione S-transferases or basal core promoter mutations in the development of liver cancer remain the subject of intense research.

In contrast to these ‘success stories’, curbing the HCC risk related to non-alcoholic fatty liver disease is likely to be a formidable challenge that will require concerted and coordinated action to tackle its aetiologic causes – excess caloric intake, poor diet quality and physical inactivity.

**Recent advances in HCC treatment**

The first liver transplantation for HCC was performed in 1967 and still remains the “gold standard” for the curative treatment for people with cirrhosis and localised tumours, as it not only removes the tumour, but also cures the underlying liver disease. It took nearly 30 years for Mazzaferro et al to define selection criteria that have become known as the Milan criteria, which have delivered five-year survival rates in excess of 50% and low recurrence rates. The article by Lam describes the role played by liver resection and transplantation in liver cancer management.

A significant impediment to the establishment of standardised treatment practices for HCC and for their comparison across centres has been the lack of appropriate staging systems that recognise the unique nature of HCCs, not captured by the usual TNM classification systems. Therapy, outcomes and prognosis in HCC are intimately linked to both tumour characteristics and organ (liver) function. The Barcelona Clinic Liver Cancer staging system recognises both these aspects, has been endorsed by several organisations and is increasingly used for patient selection into clinical trials. This comprehensive system classifies the patient according to the severity of liver disease and the degree of portal hypertension (Child-Turcotte Pugh score), tumour status and physical status, and allows recommendations for appropriate management and for comparison between centres.

Hepatocellular carcinoma shares with other solid tumours a lack of response to conventional chemotherapy, however the field is beginning to change, with the advent of biological agents that specifically target the molecular basis of cancer cell proliferation, growth and metastases. These discoveries have depended on our improved understanding at the cellular level of cancer cell biology and are discussed in the article by Strasser. The Phase III SHARP trial demonstrated that in patients with advanced hepatocellular carcinoma, the administration of sorafenib (a multikinase inhibitor with potent anti-angiogenic and anti-proliferative effects) was associated with a nearly three month longer median survival compared to placebo. In some patients that respond, anecdotal evidence suggests that this can be sustained long-term and is accompanied by significant improvements in quality of life. While the overall survival advantage with sorafenib remains modest, research in the next few years will determine if combining potent molecular targeted therapies with existing therapies (including local therapies such as radiofrequency ablation and trans-arterial chemo-embolisation), will lead to improvements in survival. Likewise, the role of adjuvant molecular targeted therapies after ‘curative’ resection is an unexplored area, which in the short-term is limited by drug toxicity and cost. However, it should be remembered that newer therapies that inhibit different pathways of the cancer cell life cycle (eg. bevacizumab and erlotinib) are in development and hold promise. In the longer term, therapies that target the cancer stem cell alone, or in combination with other forms of therapy, remain the ‘holy grail’ for research and development.

**What will the future bring?**

While HCC is a feared complication of liver disease, there is much hope at all levels for dealing with this scourge. Risk factor identification and targeted therapies can significantly reduce HCC risk. This is already being achieved for significant numbers of patients with chronic viral hepatitis B and C. Newer and more effective therapies, with fewer side-effects and less anti-viral resistance, are certainly likely to be developed in the coming few years. For those with established HCC, in whom curative surgical therapies are not possible because of tumour or liver function characteristics, cost or organ availability, targeted biological therapies offer the hope of significant improvements in outcomes. For those in whom advanced liver disease is diagnosed, or in whom risk factor reduction/elimination is not possible, HCC surveillance is an effective tool to detect tumours.
and to treat them more effectively. In this regard, novel markers for early HCC detection, that are more sensitive and specific than serum alpha fetoprotein, remains a goal that must await further research.

The major roadblocks to screening at present are at government and public health level – influencing policy to implement surveillance in high-risk groups and raising public and professional awareness. This is discussed by Wallace in his paper on community engagement and its implications for health policy.

The diagnosis of HCC will remain a devastating event for those affected. However, we are clearly at the threshold of a better and brighter future for this previously untreatable malignancy. The future has already started.

References

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.\(^3\)

**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.

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**Figure 1. Age standardised¹ incidence of liver cancer in selected regions by sex, all ages, 2002 (per 100,000)**

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<th>Region</th>
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Source: GLOBOCAN 2002\(^2\)

¹ Standardised to world population.
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). The early age of infection with HBV in Asian patients accounts for significant differences in the clinical course of disease compared to Caucasians, 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. 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). Similar to incidence, mortality rates are generally higher in less developed countries, compared with more developed countries.

**Primary liver cancer in Australia**

Overall, Australia has comparable rates of incidence and mortality from liver cancer to those recorded for similar developed countries. 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. 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).

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.

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.

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. 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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{5,23} contribute to the increasing prevalence of PLC in Australia.\textsuperscript{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.\textsuperscript{24} Indigenous Australians represented only 2.4% of the Australian population in the 2001 census, but accounted for 16% of estimated CHB infections.\textsuperscript{25} One study found that among Aboriginal people diagnosed with PLC in Australia, more than 60% were HBsAg positive,\textsuperscript{24} suggesting that CHB infection is the major cause of HCC in this population.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{1} while recent declines in PLC have been attributed to the effects of hepatitis B vaccination programs.\textsuperscript{1,22}

The high level of migration to Australia from countries of high hepatitis B prevalence has been associated with increasing prevalence of CHB infection.\textsuperscript{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.\textsuperscript{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,\textsuperscript{24} 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.\textsuperscript{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.\textsuperscript{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%.\textsuperscript{1} People with chronic HBV or HCV infection are at 20 to 200-fold greater risk of developing HCC than those uninfected.\textsuperscript{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.\textsuperscript{26}
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.52,43

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.47,48 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,52 coupled with public health strategies addressing the significant burden of disease related to liver cancer in at risk populations.

**References**


Hepatic tissue renewal

Compared to intestine and skin, where tissue is renewed within days or weeks respectively, the healthy liver has a very slow cell turnover rate and hepatocytes are considered to be in the quiescent, non-proliferative G0 phase of the cell cycle. It has been estimated that only one in 20,000 to 40,000 cells divides at any time with an average hepatocyte life span of 200 to 300 days.1 However, in response to injury, the liver has a remarkable potential to regenerate itself. Replication of the remaining healthy hepatocytes is the most efficient way to restore liver mass during normal tissue renewal and repair. If this process is impaired due to chronic liver injury, such as occurs in most chronic liver diseases, the liver relies on restoration of cellular mass through the activation, expansion and differentiation of stem-like cells termed liver progenitor cells (LPCs).2-5

Liver progenitor cells

Early animal studies identified small ovoid cells, which appeared periportally and proliferated readily following chronic or carcinogenic injury.6 Many experimental models involving toxins and carcinogens, alone or in combination with other surgical or dietary regimes,7-10 have since facilitated the study of these cells, which are now widely accepted to represent adult liver progenitor cells, the progeny of hepatic stem cells.11 Evidence from experiments showing that LPCs always emerge from periportal liver zones and the fact that selective perportal damage inhibits the LPC response, has led to the conclusion that the precursor cell likely resides somewhere in the vicinity of the canal of Hering.12 The canal of Hering is a channel partly lined by hepatocytes and partly by cholangiocytes. It represents the anatomic and physiological link between the intralobular canalicular system and the biliary tree.13,14 Undetectable in healthy tissue, LPCs are detected periportally following chronic insult. They proliferate and migrate into the parenchyma and eventually differentiate into cholangiocytes and hepatocytes to restore liver mass, morphology and function (figure 1). The LPC response is most evident in

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**Abstract**

Hepatocellular carcinoma occurs most commonly in the setting of cirrhosis, where the annual rate of cancer development approximates 3-7%. Most cases arise in the setting of impaired liver regeneration combined with chronic inflammation and fibrosis. Liver progenitor cells play an important role in cell renewal processes in the liver in the setting of chronic injury and have recently emerged as potential candidates in the carcinogenic pathway. There are two main hypotheses which have been proposed to explain hepatocellular carcinogenesis, namely the de-differentiation and the maturation arrest hypotheses. Understanding the carcinogenic pathways and the role of liver progenitor cells will provide greater understanding and novel approaches to preventative strategies.

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**Figure 1. Liver progenitor cell (LPC) ontogeny and potential role in carcinogenesis**

During liver development, hepatoblasts differentiate into cholangiocytes and hepatocytes and may be incorporated into the canals of Hering to serve as an immature precursor or stem cell compartment during chronic liver injury. Activated LPCs that proliferate after appropriate stimuli are capable of self-renewal and later commit towards either the cholangiocytic or hepatocytic lineage to regenerate the liver. If kept in a proliferative state, LPCs are likely candidates for transformation and subsequent hepatic tumour formation.

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chronic liver diseases which predispose to hepatocellular carcinoma and their high proliferative potential makes them possible targets for transformation, associations that overshadow their restorative capability. These features mandate that we continue to investigate factors that govern their activation, proliferation and differentiation into mature, functional cells, so that in the future we can direct LPCs towards regeneration as opposed to carcinogenesis.

Liver progenitor cells in human pathologies

It is now generally accepted that LPCs exist in human liver and are activated like their rodent counterparts to regenerate chronically injured liver. Like the so-called ‘oval cells’ in rodents, human LPCs are usually associated with hepatocellular necrosis. Their proliferation is frequently seen in patients with hereditary haemochromatosis, alcoholic liver disease and chronic hepatitis B or C infection. They also proliferate in non-alcoholic fatty liver disease when hepatocytes are injured by oxidative stress. The number of LPCs induced in these pathologies is directly proportional to the severity of the underlying liver fibrosis. Furthermore, inhibition of the LPC response in chronically injured liver results in reduced formation of cancerous lesions, strongly supporting the association between LPCs and hepatocarcinogenesis. Therapy of human chronic liver disease, which reduces the risk of hepatocellular carcinoma, has been shown to also reduce the number of LPCs and promote their differentiation, again supporting a role for these cells in carcinogenesis.

Liver progenitor cell involvement in multistep hepatocarcinogenesis

LPC activation and proliferation during chronic liver injury is associated with an inflammatory response that involves activation of resident as well as recruited immune cells. These inflammatory cells initiate tissue regeneration by promoting the removal of cellular debris and by directly stimulating LPCs to proliferate through release of inflammatory cytokines and growth factors. This stimulation leads to the differentiation of LPCs into mature, functional cells that can participate in the repair and regeneration of damaged liver tissue. Ultimately, however, this process can also lead to the transformation of LPCs into malignant cells, contributing to the development of hepatocellular carcinoma.

Figures 2a, 2b, 2c. Haematoxylin and Eosin staining of healthy and three week chronically injured liver.

Adult mice on a control diet display normal liver architecture with cords of hepatocytes and sinusoidal structures in between the plates (A). On day 21 of feeding a choline-deficient, ethionine-supplemented diet that induces chronic liver damage, the liver architecture is highly disrupted by steatosis and scattered aggregates of liver progenitor cells and infiltrating inflammatory cells (B). Immunohistochemistry of LPCs (blue, CK19 antibody) and activated hepatic stellate cells (red, alpha smooth muscle actin antibody) in chronic liver injury. LPCs co-localise with hepatic stellate cells during chronic liver injury.

Figure 3 Histological section demonstrating human hepatocellular carcinoma staining positively with antibody to the LPC marker M-pyruvate kinase (brown). Note that the non-cancerous surrounding liver tissue does not stain for the LPC marker.
of mitogenic growth factors and cytokines. \(^{11,20,28}\) For periportally induced LPCs to regenerate the liver in pericentral areas, they need to migrate through the liver parenchyma. It is not surprising that LPCs are usually seen in close spatial organisation with hepatic stellate cells (HSCs) that become activated into myofibroblasts to release tissue-degrading matrix metalloproteinases and secrete tissue-remodelling extracellular matrix components (figure 2). HSCs are key mediators of the fibrotic process that accompanies the wound healing process. Fibrosis is characterised by accumulation of proteins such as collagen types I and II, proteoglycans, fibronectin and lamin, providing the scaffold for migrating cells. \(^{29}\) Recent work even suggests that HSCs are a type of LPC that can transition through an LPC intermediary into hepatocytes. \(^{30}\) LPCs and HSCs have been reported to influence each other’s behaviour through paracrine signalling. \(^{31}\) LPCs produce a range of cytokines, including lymphotxin-\(\beta\) (LT-\(\beta\)), LT-\(\beta\) signals via the LT-\(\beta\) receptor on HSCs to activate the NF-\(\kappa\)B pathway, which results in production of intercellular adhesion molecule 1 and secreted (RANTES). These act as chemotactic agents for LPCs and inflammatory cells, which are involved in the wound healing response to liver injury. \(^{31}\) Abrogation of the LT-\(\beta\) pathway inhibits the LPC response to injury and prevents liver fibrosis in animal models. \(^{22,23,27}\)

**Hepatocellular carcinoma**

**De-differentiation or maturation arrest?**

Most cases of hepatocellular carcinoma arise in the setting of impaired liver regeneration combined with chronic inflammation and cirrhosis. Cancer is typically caused by accumulated mutations in genes critical for cell cycle control, self-renewal, cell proliferation and differentiation and it has been postulated that three to six of these genetic aberrant alterations are necessary to transform a normal cell into a cancerous cell. \(^{32,33}\) This makes rapidly replicating cells, such as the progeny of stem cells and LPCs, obvious targets for transformation events. \(^{34}\) In vitro studies confirm that LPCs are easily transformed in culture into malignant cells \(^{35,36}\) and tissue-based studies demonstrate that hepatocellular carcinomas often express LPC immunochemical markers, supporting the role of LPCs as targets for malignant transformation in chronic liver injury (figure 3). \(^{37,38}\) This concept has recently been confirmed for various tissue-specific stem cells, including those shown to be involved in the formation of breast cancer. \(^{39,40}\) In the context of the liver, it remains controversial as not one cell type, but several cell populations, in addition to hepatic stem cells, are capable of responding to the demand for cell proliferation (and in the case of LPCs, differentiation) to restore dysfunctional liver mass. In general, two main hypotheses have been commonly proposed to explain the cellular origin of hepatocellular carcinoma, and derive from the fact that carcinogenesis always involves proliferation of immature, less differentiated cells – the de-differentiation and the maturation-arrest hypotheses.

**De-differentiation hypothesis**

Exposure to some hepatocarcinogens leads to the development of pre-malignant foci that arise by clonal proliferation of hepatocytes. \(^{41-43}\) These “enzyme-altered” lesions are believed to sequentially give rise to larger nodules that displace normal hepatic tissue and ultimately evolve into liver tumours. \(^{44}\) The progressive morphological and enzymatic changes from foci to nodules and the formation of cancer have led to the hypothesis that mature, “initiated” hepatocytes de-differentiate to an immature phenotype to obtain a high proliferate capacity. It is possible that the observations supported by this hypothesis can also be explained by LPC proliferation during the early stages of hepatocarcinogenesis, when the designated preneoplastic changes occur. \(^{11}\)

**Maturation arrest hypothesis**

A more accepted hypothesis of tumour formation was first proposed by Potter and has been referred to as the maturation arrest or blocked ontogeny hypothesis. \(^{45}\) It postulates that tumours arise when tissue-specific or determined stem cells are blocked from terminally differentiating without undergoing apoptosis. Thereby, a cell mass accumulates with maturation-arrested cells displaying an immature phenotype, which may acquire genetic alterations resulting in carcinogenesis.

Numerous studies provide evidence in support of this hypothesis. Not only are LPCs seen during the early stages of hepatocarcinogenesis, it has also been demonstrated that LPCs are cellular sources of hepatocellular carcinoma in animal models. \(^{2,24-26}\) Additionally, it has been shown that a proportion of precursor lesions and hepatocellular carcinomas express markers that are not present in mature hepatocytes. About half of the small cell dysplastic foci, the earliest pre-malignant lesions in human hepatocellular carcinoma, have been shown to be LPC-derived as judged by expression of markers such as CK7, C19 and OV-6. \(^{47}\) Furthermore, inactivation of the MYC oncogene in a murine model of hepatocellular carcinoma triggered their differentiation into normal hepatic lineages, including hepatocytes and biliary cells. Reactivation of the MYC oncogene resulted in hepatocytes and LPC transforming back to hepatocellular carcinoma cells, revealing their pluripotency and supporting the concept that hepatocellular carcinoma may originate from the maturation arrest of LPCs. \(^{48}\) Zender and co-workers recently strengthened the hypothesised relationship between tissue-specific stem or progenitor cells and hepatocellular carcinoma by demonstrating that LPCs, which had been genetically manipulated ex vivo by retroviral gene transfer of oncogenes, rapidly produced liver tumours upon transplantation into conditioned recipient mice, which histopathologically resembled human hepatocellular carcinoma. \(^{49}\) While it has been very difficult to determine the exact origin of any specific hepatocellular carcinoma, there is likely more than one potential target cell for transformation and hepatocarcinogenesis. The available data suggest that poorly differentiated hepatocellular carcinomas most likely originate from LPCs and have a poorer, more aggressive progression than well-differentiated cancers, which might be derived from...
mature hepatocytes.\textsuperscript{50,51} Furthermore, a side population of cells in human hepatocellular carcinoma cell lines, which show both biliary and hepatocytic characteristics, was highly proliferative and found to give rise to persistently aggressive tumours on serial transplantation into immunodeficient non-obese diabetic/severe combined immunodeficient mice.\textsuperscript{52}

**Conclusion**

Much evidence has been gathered demonstrating that hepatocellular carcinoma can arise from dysregulated LPC maturation and proliferation during chronic liver injury in humans and in animal models of liver disease and carcinogenesis. The carcinogenic and fibrogenic processes are amenable to manipulation by agents which interfere with LPC proliferation and differentiation. These approaches may be useful for future therapeutic approaches for the prevention of hepatocellular carcinoma.

**References**

8. Knight B, Matthews VB, Olynyk JK, Yeap BB, Olynyk JK. Inhibition of adult liver progenitor (oval) cell growth and viability by an agonist of the peroxisome proliferator activated receptor (PPAR) family member gamma, but not alpha or delta. Cancerogenesis. 2005;26:1782-1792.
12. Jonsson JR. Fibrosis correlates with a ductular reaction in hepatitis C: Fate-mapping evidence that hepatic stellate cells are epithelial progenitors in adult mouse livers. Stem Cells. 2006;24:2104-2113.
TRENDS IN CHRONIC VIRAL HEPATITIS: NOTIFICATIONS, TREATMENT UPTAKE AND ADVANCED DISEASE BURDEN

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Abstract
Since the introduction of mandatory notification in the early 1990s, around 110,000 and 260,000 cases of hepatitis B and hepatitis C respectively, have been reported through public health surveillance mechanisms in Australia. The number of hepatitis B notifications is likely to be a considerable underestimation of the number of people living with chronic hepatitis B. Over the period 1998-2008, a small decrease in hepatitis B notifications (around 10%) and a more marked decrease in hepatitis C notifications (around 40%) has occurred, with the latter related to reductions in heroin supply. Rates of antiviral therapy remain low for both chronic hepatitis B (<3%) and chronic hepatitis C (<2%). Incidence of hepatocellular carcinoma has increased over the period 1990-2002, largely due to increasing contributions of hepatitis B virus and hepatitis C virus related hepatocellular carcinoma. Further increases in hepatocellular carcinoma incidence are projected, particularly if antiviral therapy uptake remains low. A combination of enhanced access to treatment programs and increased hepatocellular carcinoma screening among high risk people with chronic hepatitis B and chronic hepatitis C is required to limit the emerging epidemic of chronic viral hepatitis related hepatocellular carcinoma.

Globally, the major causation of hepatocellular carcinoma (HCC) is chronic hepatitis related to infection with hepatitis B virus (HBV) and hepatitis C virus (HCV). More than 300 million people are estimated to be living with chronic HBV infection while 150 million are living with chronic HCV infection. Despite the availability of a highly effective HBV vaccine for two decades, global chronic HBV prevalence will remain high for many years related to the late introduction of vaccine programs in many highly endemic countries and improved life expectancy. The long latency of HBV infection to advanced liver disease including HCC and low global HBV treatment uptake means that HCC incidence reduction will be even more protracted, possibly taking decades. The limited advances in HCV vaccine development, low HCV treatment uptake on a global level, and long latency from HCV infection to advanced liver disease mean that HCV related HCC will similarly be a major public health challenge for decades to come.

High level immigration from HBV endemic countries, particularly China and Vietnam, have increased HBV prevalence in Australia, with resultant increasing HBV related HCC incidence and projections of further increases over the next two decades. Escalating prevalence of injecting drug use in Australia from the 1980s has driven the expanding HCV epidemic, with increases in HCV related HCC and further increases projected, similar to the situation with HBV.

This review will cover available epidemiological data on HBV and HCV in Australia, including public health notifications, antiviral therapy uptake, and trends in HBV and HCV related HCC.

Unspecified/prevalent hepatitis B notifications
The low rate of progression to chronic HBV infection following incident infection among adolescents and adults, the major component of new transmission in Australia, means that incident infections make a limited contribution to the overall burden of HBV disease. The number and trends in unspecified or prevalent HBV notifications are therefore more informative of disease burden. A diagnosis of hepatitis B has required mandatory notification in most Australian states and territories since the early 1990s. A total of 109,749 unspecified/prevalent hepatitis B infections were notified to the National Notifiable Diseases Surveillance System from 1990 to 2008 (table 1). Of note, there were no notifications from the Northern Territories during this period.
Territory (NT) from 1990 until 2003. Notifications were also incomplete for other states and territories such as the Australian Capital Territory (ACT), South Australia (SA), and Victoria (VIC) until 1997. Thus, we report the data from 1998 to 2008.

Over the period 1998 to 2008, the highest number of hepatitis B notifications was from New South Wales (NSW, 47%), followed by VIC (26%), Queensland (QLD, 12%), Western Australia (WA, 7%), and SA (5%) (table 1 and figure 1). Hepatitis B notifications from the ACT and Tasmania (TAS) represent 1% or less each of the total notifications over the period.

Over the period 1998-2008, the number of hepatitis B notifications has fluctuated between 5000 and 8000 notifications per annum, with peaks in 2001 (7931) and 2008 (6948) (table 1). Over the last decade, there was a net 10% increase in the number of hepatitis B notifications. Hepatitis B notifications were relatively stable for most states and territories, apart from NSW, which reflects the fluctuating national pattern.

Notifications for males were consistently higher than females, with a male to female ratio of approximately 1.1:1 to 1.3:1 (figure 2). The net increase in the number of notifications over the period was mainly attributable to the increase in the notifications for females; a 17% increase in notifications for females compared to only a 3% increase for males. The number of hepatitis B notifications was highest among people aged 30 to 39 years, followed by those aged 20 to 29 years and 40 to 49 years (figure 3). An increasing trend from 2006 to 2008 was seen among people aged 30 to 39 years, 50 to 59 years and those aged 60 and above.

Figure 1. National notifications of unspecified/prevalent hepatitis B by state and territory and year

Figure 2. National notifications of unspecified/prevalent hepatitis B by gender and year
Table 1. Notifications of unspecified/prevalent hepatitis B by state and territory and year

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NN, no notifications

Note: i) notifications for some state and territories such as ACT, SA, and VIC may be incomplete up to 1997.
ii) no notifications for NT until 2004.
iii) notifications for 2008 may be incomplete for all states and territories at the time of preparation of this manuscript.

Figure 3. Hepatitis B notifications (unspecified/prevalent) by age group and year

Unspecified/prevalent hepatitis C notifications

The generally asymptomatic nature of incident HCV infection and lack of enhanced hepatitis C surveillance in most states and territories means that notified incident infections make a limited contribution to the overall burden of HCV disease. The number and trends in unspecified or prevalent HCV notifications are therefore more informative of disease burden.

A diagnosis of hepatitis C has required mandatory notification in most Australian states and territories since the early 1990s. A total of 259,861 unspecified/prevalent hepatitis C infections were notified to the National Notifiable Diseases Surveillance System from 1990 to 2008 (table 2). Notifications were incomplete for some states and territories such as the ACT and SA until 1994, and NT and WA until 1992. For consistency, we report the data from 1998 to 2008.

Similar to hepatitis B notifications, the highest hepatitis C notifications over the period 1998 to 2008 were from NSW (41%), followed by VIC (25%), QLD (19%), WA (7%), and SA (4%) (table 2 and figure 4). Hepatitis C notifications from TAS and the NT represent 2% each and the ACT represents 1% of the total notifications over the period.

In contrast to the fluctuating pattern of hepatitis B, hepatitis C notifications peaked in 1999 (20,061) and have demonstrated a considerable decline since (table 2 and figure 4), although they have been relatively stable at just below 12,000 since 2005. There was a 30% decrease in the number of hepatitis C notifications from 1998 to 2008. Hepatitis C notifications declined in NSW, VIC and SA, but have been relatively stable in other states and territories.
Table 2. Notifications of unspecified/prevalent hepatitis C by state and territory and year

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Note: notifications for 2008 may be incomplete.

Figure 4. National notifications of unspecified/prevalent hepatitis C by state and territory and year

Figure 5. National notifications of unspecified/prevalent hepatitis C by gender and year
Similar to hepatitis B, hepatitis C notifications for males were consistently higher than females, with a male to female ratio of approximately 1.7:1 (figure 5). The number of hepatitis C notifications was highest among people aged 20 to 29 years, 30 to 39 years and 40 to 49 years (figure 6). The number of hepatitis C notifications declined from 1998 to 2008 for all age groups except those aged 50 to 59 years. The largest decline (57-72%) was seen in people aged less than 20 years. The number of notifications for people aged 20 to 39 were almost halved (40-44%) over the period.

Age distributions of both hepatitis B and C notifications were similar over the period 1998 to 2008 (figure 7), peaking in those aged 25-34 years and 25-39 years respectively.

**Figure 6.** Hepatitis C notifications (unspecified/prevalent) by age group and year

**Figure 7.** Age distribution of unspecified/prevalent hepatitis B and hepatitis C notifications, 1998-2008

**Trends in treatment uptake for hepatitis B**

Antiviral therapy for chronic hepatitis B in Australia is provided largely through the Australian Government’s Highly Specialised Drug S100 scheme, which provides highly subsidised treatment by approved specialist practitioners. The pattern of antiviral therapy uptake for chronic hepatitis B in Australia is shown in figure 8. The total number of prescriptions for chronic hepatitis B tripled from around 1000 at the beginning of 1999 to around 3000 at the end of 2007. Lamivudine was licensed in 1999 in many countries for treating selected patients with chronic hepatitis B. In Australia, lamivudine was the only agent available through the S100 scheme until 2004. The number of lamivudine prescriptions...
through the S100 scheme increased from around 1000 at the beginning of 2003 to around 1400 at the end of 2007. Adefovir was included in the S100 scheme from the last quarter of 2004. The number of prescriptions for adefovir has doubled (from ~360 to ~720) since and contributed about a quarter of the total prescriptions in 2007. Entacavir was included in the S100 scheme from the last quarter of 2006, and its number of prescriptions has tripled from around 280 in 2006 to around 850 in 2007. Prior to 2008, these antiviral therapy agents were only approved as monotherapy for chronic hepatitis B. In 2008, approval was gained for combination lamivudine and adefovir therapy in the setting of lamivudine resistance. Pegylated interferon alfa-2a was also approved for chronic hepatitis B therapy in 2008.

Figure 8. Antiviral therapy for chronic hepatitis B, 2003 – 2007

Number of people dispensed drugs for hepatitis B infection through the Highly Specialised Drugs (S100) scheme, by year.
Lamivudine: Number of person years of treatment with lamivudine 100mg estimated from the HSD Program Public Hospital Dispensed National Pack Number Report.
Adefovir included in S100 scheme from October 2004.
Entacavir included in S100 scheme from October 2006.

Source: Highly Specialised Drugs (S100) scheme; National Centre in HIV Epidemiology and Clinical Research (NCHECR) Annual Surveillance Report 2008.7

Figure 9. Interferon-based treatment for chronic hepatitis C, 2003 – 2007

Number of people dispensed drugs for hepatitis C infection through the Highly Specialised Drugs (S100) scheme. An estimated 1142, 1831, 1847, 2847 and 3539 people were receiving treatment throughout 2003 to 2007, respectively. From 1 April 2006, biopsy proven liver damage was no longer a requirement for treatment of hepatitis C infection. Pegylated interferon and ribavirin were included in the S100 scheme from 1 November 2003.

Source: Highly Specialised Drugs (S100) scheme; National Centre in HIV Epidemiology and Clinical Research (NCHECR) Annual Surveillance Report 2008.7
Trends in treatment uptake for hepatitis C

Antiviral therapy for chronic hepatitis C in Australia is also provided largely through the Australian Government’s Highly Specialised Drug S100 scheme. The recent pattern of antiviral therapy for chronic hepatitis C is shown in figure 9.7 Hepatitis C treatment has improved in recent years with a substantial shift in the treatment from the standard interferon and ribavirin therapy prior to 2004 to pegylated interferon and ribavirin combination therapy in 2004. The number of prescriptions for hepatitis C through the S100 scheme has tripled from around 1000 in 2003 to around 3500 in 2007. The increase in the number of prescriptions for treatment of chronic hepatitis C started between the first and second quarters of 2006 coincided with the removal in April 2006 of the requirement for biopsy proven liver damage prior to treatment.

Trends in hepatitis B and hepatitis C related hepatocellular carcinoma in NSW

From 1990 through 2002, a total of 2727 primary liver cancer notifications were received by the NSW Central Cancer Registry.3 Of these, the majority (2072, 76%) were for HCC. The number of HCC notifications from 1990 to 2002 is shown in figure 10. Overall, 16% and 13% of HCC notifications were attributed to hepatitis B and C infections respectively, with higher proportions in more recent years. The majority (71%) of HCC notifications were unlinked. The number of hepatitis B related HCC notifications per annum increased by 48% from 27 in 1998 to 40 in 2002. The number of hepatitis C related HCC notifications per annum increased to a lesser extent (by 28%) from 29 to 37, over the same period.

Age distribution of hepatitis B and C related HCC in NSW is shown in figure 11. Median age at HCC diagnosis was 58, 67, and 69 years for HBV and HCV linked and unlinked groups, respectively.3 Age distributions at HCC diagnosis for the HBV and HCV linked groups were bimodal, peaking in those aged 40-49 and 50-59 years and 45-49 and 70-74 years, respectively. In contrast, the age distribution of the unlinked HCC notifications was unimodal, with a peak in those aged 70-74 years.

Implications

Expanding epidemics of chronic hepatitis B and chronic hepatitis C in Australia are contributing to escalating rates of HCC. Total notifications of around 110,000 and 260,000 for hepatitis B and hepatitis C respectively, indicate the large burden of chronic viral hepatitis related liver disease. Low antiviral therapy uptake for both chronic hepatitis B and chronic hepatitis C suggest that therapeutic intervention is having a limited impact on HBV and HCV related HCC incidence.

Total notifications for unspecified/prevalent hepatitis B are the minimum estimate of chronic hepatitis B prevalence in Australia. Limited national reporting of hepatitis B diagnoses from some jurisdictions prior to 1997, in particular Victoria, would indicate that total diagnoses are considerably higher than the 110,000 notifications. The proportion of people with chronic hepatitis B in Australia who have undergone screening is difficult to

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Figure 10. Distribution of hepatocellular carcinoma notifications by hepatitis linkage status over time, 1990-2002.3
estimate accurately, but is likely to be less than 75%. A more realistic estimate of the number of people living with chronic hepatitis B in Australia would be closer to 200,000. The major burden of chronic hepatitis B in Australia is among people born in the Asia-Pacific region, with estimates ranging from 50–70% and the two major sub-groups being those born in China and Vietnam. Other Australian population groups with relatively high prevalence of chronic hepatitis B are people born in sub-Saharan Africa and the Southern Mediterranean region, Indigenous Australians, men who have sex with men, and injecting drug users (IDU). There has been a small overall decline in hepatitis B notifications over the past decade, however the fluctuating levels of notifications is probably related to immigration flows from HBV endemic countries rather than a reflection of HBV transmission within Australia.

Hepatitis B notifications are based on detection of HBsAg which generally indicates evidence of chronic hepatitis B. In contrast, hepatitis C notifications are based on detection of anti-HCV antibody which does not indicate chronic hepatitis C. An estimated 25% of people with HCV infection will undergo spontaneous HCV clearance and not progress to chronic hepatitis C. Further, when screening is undertaken in low risk populations, false positive anti-HCV antibody results are common. Thus, total notifications of unspecified/prevalent hepatitis C of around 260,000 are likely to reflect chronic hepatitis C cases of closer to 200,000. A proportion of people with chronic hepatitis C in Australia, possibly 25%, will not have been screened, therefore the estimate of people living with chronic hepatitis C in Australia may be around 250,000. The major population groups in Australia with chronic hepatitis C are IDU (former and current) and people born in high prevalence countries such as Egypt, Italy and South-East Asia. The considerable decline in hepatitis C notifications since 2000 has been attributed to reductions in heroin supply, the so-called ‘heroin drought’, from the same period. The marked decline in notifications among younger age groups indicates this trend is likely to reflect true declines in HCV transmission. In contrast, the increasing number of notifications in the 50-59 year age group may reflect increased screening of both former IDU and people from high prevalence countries.

Data from the NSW linkage study clearly indicates the increasing contribution of hepatitis B and hepatitis C to HCC incidence. The bimodal age distribution of both HBV and HCV related HCC is particularly interesting. In the case of HCV related HCC, it is likely to reflect two distinct hepatitis C epidemics: a large epidemic among former and current IDU, with many now infected for more than 20 years and therefore at risk of having progressed to advanced liver disease, and; a smaller epidemic among people born in high prevalence countries, but with many of this group being infected for more than 30 years and the longer duration of infection contributing to a relatively greater burden of HCC. Previously published data from the NSW linkage study indicates that a large proportion of the older HCV related HCC cases are among people born overseas. Given the continued rising incidence of
HCC since the end of the linkage study period in 2002, it is highly likely that numbers of HBV and HCV related HCC are continuing to increase. Recent modelling of hepatitis B among people born in Asia-Pacific countries and the hepatitis C estimates and projections working group report support this upward trend. Of greater concern are the further increases in HBV and HCV related HCC over the next two decades that are projected, particularly if therapeutic uptake remains low.

The number of people currently on antiviral therapy for chronic hepatitis B through the S100 scheme is around 3000. Although additional prescriptions are provided through private hospitals and practitioners and through clinical trial protocols, the total number of people receiving therapy is likely to be less than 5000. This would represent less than 3% of the estimated number of people with chronic hepatitis B in Australia. Although a large proportion of people with chronic hepatitis B do not require antiviral therapy, particularly younger people in the immunotolerant phase of infection, the rate of treatment uptake is extremely low and unlikely to be having a major impact on HCC incidence. Two major strategies are required to limit the projected increase in HBV related HCC over coming years: increased antiviral therapy uptake, particularly for those older than 40 years with high HBV viral load, and; HCC screening for those with established or suspected cirrhosis.

Rates of antiviral therapy uptake for chronic hepatitis C are similarly low, at around 3500 per year and again representing a small proportion (less than 2%) of the estimated number of people with chronic hepatitis C in Australia. This level of therapeutic intervention is likely to have a limited impact on HCC incidence. Although antiviral therapy uptake through the S100 scheme has increased from around 2000 per year since the removal of mandatory pre-treatment liver biopsy staging, the simultaneous broadening of treatment criteria (previously evidence of significant liver damage was required) means that many people with early liver disease are likely to be receiving therapy. The limited risk of advanced liver disease over the next one to two decades in this group means that recent therapy uptake increases may have a relatively limited impact on HCC incidence. Similar to chronic hepatitis B, a combination of further increases in antiviral therapy uptake, particularly among people with significant liver fibrosis, and HCC screening among people with proven or suspected cirrhosis is required to limit projected increases in HCC incidence.

In conclusion, expanding epidemics of chronic hepatitis B and chronic hepatitis C in Australia are contributing to the rapidly escalating incidence of HCC. Considerable investment in expanded treatment and care programs, along with more widespread implementation of HCC screening, is required to reduce the anticipated further increases in HCC incidence.

Acknowledgements

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References

Hepatocellular carcinoma (HCC) is a complication of chronic viral hepatitis and is associated with significant morbidity and mortality. Hepatitis B, C and D (HBV, HCV and HDV) are the viral hepatitides associated with chronic infection and HCC. The worldwide burden of chronic viral hepatitis is significant – approximately 400 million people (7%) with chronic HBV (CHB) and 170 million (3%) with chronic HCV (CHC). In Australia, an estimated 91,500 to 163,500 people (0.5% to 0.9%) have CHB and 210,000 (1.1%) CHC. These two infections are the most important diseases associated with the development of HCC. Worldwide, more than 50% of registered cases of HCC are associated with CHB and 25% with CHC. In developed countries, up to 70% of HCC is attributable to HCV, whereas in Asia and Africa, HBV is mainly responsible.

While the viral hepatitides are a major cause of HCC worldwide, determining the risk associated with being infected with these viruses is not straightforward. Other recognised risk factors for HCC include the presence of cirrhosis, viral co-infection, age, sex, alcohol exposure, obesity and diabetes mellitus. Genetic factors also appear to play a role, as well as environmental agents. The interactions between these factors and HCC are complex. In its simplest form, the viral agents: may be directly oncogenic; may contribute to HCC risk by causing chronic liver damage that results in cirrhosis; or may be associated with other risk factors such as diabetes.

Role of cirrhosis

In general, the presence of cirrhosis in both HBV and HCV is the most important risk factor for HCC. In developed countries, 85% of HCC in CHB arises in cirrhotic livers, with the remainder occurring in non-cirrhotic livers. In CHC, HCC is uncommon in the absence of cirrhosis, at least in western countries. Risk factors for progression to cirrhosis and the development of HCC in viral hepatitis are well described. In CHB, these include young age at the time of infection, longer duration of infection, elevated serum alanine aminotransferase (ALT) levels, male gender, alcohol excess and viral co-infection with HCV, HDV and/or HIV. Serum HBV DNA concentration is a key predictor of the development of cirrhosis and HCC. The importance of other HBV viral factors remains incompletely understood. In HCV, in addition to co-infection with HBV and/or HIV, progression of liver disease is adversely affected by alcohol, smoking, hepatic steatosis and insulin resistance.

Other risk factors for HCC

Men are more likely to develop HCC than women. This is most evident in high prevalence regions, where men are affected 2.1 to 5.7 times more frequently than women (mean 3.7:1). The ratio is lower (mean of 2.4:1) in intermediate prevalence areas, and is lower again in low prevalence regions. The differences in gender distribution may reflect variations in hepatitis carrier states, exposure to environmental toxins, and the trophic effect of androgens. Age >50 year increases risk for HCC 4-fold compared with younger individuals. The effect may be due to age per se, or be a consequence of longer duration of infection. Alcohol appears to synergistically increase the risk of developing HCC. The risk in HBsAg positive populations is doubled in those who drink more than 60g/day of alcohol compared to non-drinkers. Smoking is associated with a 1.5-2.0 fold increase in the risk of HCC compared to non-smokers. Obesity is another risk factor.
factor for HCC in CHB, especially in combination with alcohol, tobacco and diabetes. Environmental factors also play a role, with the dietary mycotoxin, aflatoxin B1 found on mouldy food, being a major contributor to HCC risk in regions with a high prevalence of HCC such as sub-Saharan Africa. While this is not a significant problem in Australia, it is relevant for immigrants from these regions.

**Risk of HCC in viral hepatitis compared to other liver diseases**

Although there are relatively few studies directly comparing the incidence of HCC in different liver diseases, there appears to be significant variation. Fattovich et al compared the five-year cumulative incidence of HCC in patients with cirrhosis from different aetiologies. In CHC with cirrhosis in western countries this was 17%, and up to 30% in Japan, while for CHB these figures were 10% in the west and 15% in highly endemic regions. This compared with 21% for hereditary haemochromatosis, 8% in alcoholic cirrhosis and 4% in advanced biliary cirrhosis. There is limited data on HCC risk in cirrhosis of other causes. It is tempting to ascribe this to the underlying liver disease, but it may also reflect the disease specific processes that contribute to the development of cirrhosis. For example, cirrhosis from haemochromatosis is more likely to occur in older males, the group at highest risk of developing HCC, while biliary cirrhosis is more likely to occur in younger women, a lower risk group. In an old study of the prevalence of HCC at autopsy in patients with cirrhosis, the proportion of patients in each disease group with HCC was closely related to the proportion that were male. Thus, the variation in HCC risk between different chronic liver diseases does not necessarily reflect direct oncogenic effects of the underlying disease.

**Risk of HCC in chronic hepatitis B infection**

HBV is a DNA hepadnavirus. It is transmitted by perinatal, parenteral and sexual exposure. In highly endemic areas such as Eastern Asia, China and Africa, approximately 70% of HBV infections are acquired either perinatally or in early childhood. Perinatal exposure leads to chronic infection in 90-95% of cases, while childhood exposure leads to CHB in 50% of cases. The lifetime risk of cirrhosis is 20-30% in perinatal and childhood infections. In low prevalence areas such as Australia, North America and Western Europe, infection mostly occurs in adulthood through sexual contact or injecting drug use. Ninety five per cent of adults acutely infected will clear HBV and become immune. HCC develops in 0.5%-0.8% per annum in patients with CHB compared with 1.4-2.5% in those with cirrhosis secondary to CHB.

Epidemiological data strongly supports a causal relationship between CHB and HCC. The regional variation in the incidence of HCC worldwide mirrors the prevalence of CHB in the local population. In highly endemic countries such as Taiwan with successful immunisation programs, there has been a decline in both the prevalence of CHB and in the incidence of HCC. Experimental data using animal hepadnavirus provides additional support for this relationship. Newborn woodchucks inoculated with woodchuck hepatitis virus (a hepadnavirus used as a model of human HBV infection) develop chronic viral hepatitis and HCC within three years.

**Mechanisms of carcinogenesis in chronic hepatitis B infection**

As stated above, in CHB, HCC usually occurs in cirrhotic patients. However, in 20% of cases in the developed world and 40% in sub-Saharan Africa and China, HCC occurs in non-cirrhotic livers. The contribution of hepatocellular injury and fibrosis in non-cirrhotic patients with CHB and HCC is difficult to quantify, but there is evidence that HBV is directly oncogenic. HBV DNA integrates into the host genome leading to alterations in cellular signalling and growth control. Chromosomal alterations are significantly increased in HBV-related tumours compared with tumours associated with other liver diseases. Additionally, HBV proteins may enhance genomic instability. The HBV encoded X antigen (HBxAg) produced in chronically infected cells facilitates malignant transformation through several mechanisms. HBxAg has a direct stimulatory effect on cell growth. It binds and inactivates the key tumour suppressor p53 protein and may interfere with DNA repair mechanisms, allowing genomic damage to accumulate. The usual site of viral integration into the host DNA is adjacent to the HBx gene, facilitating expression of the associated protein. It is likely that the cellular immune response against infected hepatocytes, combined with long-term toxic effects of viral gene products, trigger chronic necroinflammation with subsequent fibrosis and hepatocyte proliferation, increasing the likelihood of malignant transformation.

**Hepatitis B viral factors which modify risk of HCC**

Serum HBV DNA levels across a biological gradient appear strongly predictive of the risk of disease progression and the development of HCC, independently of HBeAg status, serum ALT and liver cirrhosis. In a community based survey, Taiwanese patients developed HCC at a 10 times greater rate if HBV DNA was persistently >20,000 IU/mL than in those with HBV DNA <2,000 IU/mL. However, even with a serum HBV DNA titre of 2000 IU/mL, an increased risk for HCC existed.

The importance of HBV e antigen (HBeAg) sero-status, pre-core or core promoter mutants and HBV genotype in relation to HCC risk remains incompletely understood. Several case control studies suggest that HBeAg positivity may be a predictive marker for HCC. HBeAg prevalence is higher among patients with HCC than among matched HBsAg carriers. A large cohort study found that the relative risk of HCC was increased by six-fold among patients who were HBeAg and HBsAg positive, compared with those positive for HBsAg alone.

HBV genotype appears to play a role in Asian studies of genotype B and C HBV. Genotype C has been shown to have a more aggressive disease course than genotype B in HBeAg positive patients and is an independent risk factor for HCC, with an adjusted relative risk of 2.8. The relative risk associated with cirrhosis was 10.2. In Western Europe and North America, genotype D is
The prevalence of the T1762/A1764 mutation in the basal core promoter region increases with the progression of liver disease and this mutation is significantly associated with the development of HCC, in both genotypes B and C. The T1762/A1764 mutation can be detected in plasma up to eight years prior to HCC diagnosis and may be a strong predictive biomarker of HCC.

Mechanisms of carcinogenesis in chronic hepatitis C infection

HCV does not integrate into the host genome as reverse transcription of viral RNA to DNA does not occur. In CHC, HCC almost always arises in the setting of cirrhosis. The likely mechanism of hepatocarcinogenesis is chronic necroinflammation, cellular regeneration and fibrosis which predispose to genomic damage. HCC in patients with CHC who are not cirrhotic has been reported. However, there is limited evidence supporting a direct carcinogenic role for HCV. Animal models provide support for a direct oncogenic effect of HCV. Transgenic mice expressing the complete HCV core gene at similar levels to that found in human infection develop hepatic steatosis after three months, adenomas after 12 months and eventually HCCs within the adenomas. This was in the absence of significant inflammation or fibrosis. HCC did not develop in mice expressing HCV envelope proteins, suggesting that the oncogenic potential is specific for the HCV core protein.

In vitro studies have also shown that HCV core peptide can bind to and influence proteins involved in the regulation of apoptosis and hepatocyte proliferation, including p53, tumour necrosis factor receptor 1, the Fas system, nuclear factor-kappa and the cell cycle regulator, p21WAF1. These interactions may contribute to the development of HCC.

Factors which modify risk of HCC in chronic hepatitis C infection

The risk for patients with CHC developing HCC varies by country of report, length of follow-up and presence of cirrhosis. As occurs in other liver diseases, males are at increased risk of HCC. Other risk factors in CHC are longer duration of infection and age greater than 60 years. Among patients with HCV cirrhosis the risk of HCC is significantly increased in current smokers and former heavy drinkers, but is not significantly increased in current heavy drinkers. This suggests that alcohol is an important risk factor for progression to cirrhosis, but once cirrhotic, alcohol does not confer any additional risk for HCC than that attributable to cirrhosis alone. Cigarette smoking may have a role in the development of HCC from liver cirrhosis.

Steatosis and insulin resistance are frequently observed in CHC. Steatosis is associated with an increased rate of progression of hepatic fibrosis. In a local study, hepatic steatosis was not associated with increased risk of HCC. Among blacks, Hispanic and non-Hispanic whites in Los Angeles with CHC and/or CHB, diabetes was shown to be an independent risk factor for HCC. Synergistic effects on HCC risk of HBV/HCV co-infection, hazardous alcohol consumption and diabetes were demonstrated in this study population.

The role of HCV genotype is undefined. Some reports indicate increased association of HCC with genotype 1b, while others have not found this association. Treatment with interferon reduces the incidence of HCC in some studies, but not in others.

Risk of hepatocellular carcinoma in viral co-infection

HBV and HCV co-infection is prevalent, occurring in more than 10% of CHB patients worldwide. Patients with co-infection have more severe liver disease and are more likely to develop cirrhosis with decompensation. In addition, they have a higher risk of developing HCC than individuals with HCV or HBV alone. After five years of co-infection with CHB and CHC, the cumulative risk of developing HCC is 23%, compared with 10% for CHB and 21% for CHC. By 10 years the risk of HCC in co-infection is as high as 45%, compared with 16% and 28% for CHB and CHC respectively. The risk of HCC in HBV/HCV co-infection has been analysed in a meta-analysis. This found a more than additive effect of co-infection with HBV and HCV on the risk of developing HCC. The odds ratio for HCC compared to the non-infected population for HBsAg positive, anti-HCV/HCV RNA negative subjects was 20.4. In HBsAg negative, anti-HCV/HCV RNA positive subjects it was 23.6 and in subjects positive for both markers it was 135.

HDV super-infection in CHB is associated with more severe liver disease and accelerated progression to cirrhosis. The effect of HDV infection on HCC risk was evaluated in the EUROHEP retrospective cohort study of 200 HBsAg positive compensated cirrhotic patients, followed for a mean of 6.6 years. HDV co-infection was present in 20% of the population and was associated with a 3-fold increased risk of HCC.

In the context of prolonged survival of HIV patients on highly active antiretroviral therapy, HCV/HIV co-infection results in the accelerated development of cirrhosis, liver failure and HCC. Likewise, HBV/HIV co-infection leads to increased liver fibrosis, cirrhosis, HCC and liver-related mortality. Schistosomiasis is a major health problem in Africa, particularly in Egypt, and is relevant to migrants from these areas.
appears to worsen portal hypertension with accelerated progression to fibrosis and HCC.\textsuperscript{82,83}

In summary, in CHB and CHC, host and environmental factors modulate the risk of developing HCC. For both viruses, the presence of cirrhosis is a major contributor to HCC risk. This may be mediated through necrosis and inflammation related to viral infection, resulting in genotoxicity and enhanced hepatocyte proliferation. There is evidence supporting a direct carcinogenic effect for both viruses, although the evidence in support of this appears stronger for HBV. Viral factors may impact upon HCC risk. The role of viral genotype requires further study, as do other viral factors. Longer duration of infection, age of acquisition, serum ALT, viral co-infection, male gender, alcohol excess, cigarette smoking and hepatosteatosis all appear to increase the risk of HCC in patients with chronic hepatitis B or C.

References

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Chronic hepatitis B (CHB) represents a significant public health issue in Australia. Despite a low overall prevalence of <2%, high risk population groups exist within the community. A national sero-survey in 1996-1999 estimated a CHB prevalence in Australia of up to 160,000. This figure is likely to be much higher now with ongoing active migration of individuals from high CHB prevalence countries into Australia.

The natural history of CHB can be divided into four phases of variable duration – immune tolerance, immune clearance, immune control (non-low replicative) and high-replicative immune escape (Hepatitis B e antigen [HBeAg] negative disease). These phases are determined by both host and viral factors, including HBeAg serostatus, HBV DNA level, serum alanine aminotransferase (ALT) and immunological status. The risk of progressive liver disease is highest during the immune clearance and immune escape phases, during which host immunological attack of hepatitis B infected hepatocytes is actively occurring. Without effective treatment, the natural history of CHB is that it can progress to liver failure and hepatocellular carcinoma (HCC). HCC is the fifth most common cancer and the third most common cause of cancer related mortality worldwide. Approximately 80% of HCC cases have been attributed to infection with either hepatitis B virus (HBV) or hepatitis C virus (HCV) and approximately half the total number of HCC cases can be attributed to chronic hepatitis B (CHB). The relative risk of HCC in patients with CHB is 100 fold compared to that in uninfected individuals.

The initial therapeutic endpoint in patients with HBeAg positive CHB is HBeAg seroconversion, as it is usually associated with suppression of viral replication and an improved prognosis. The HBeAg seroconversion rate following 48 weeks of therapy is approximately 20% with oral NA, and 32% with Peg-IFN. HBeAg seroconversion rates can increase with ongoing oral NA use, and the beneficial effects of Peg-IFN can persist after treatment. In HBeAg negative disease however, therapeutic endpoints are less predictive due to the high rate of relapse following drug cessation. Consequently, long-term oral NA is recommended to effectively suppress HBV viral replication, a strategy which increases the risk of antiviral resistance over time. While Peg-IFN therapy results in a 63% undetectable HBV rate at end of therapy, only 19% of patients continue to have adequate suppression of viral replication six months after treatment cessation.

Anti-viral medication to prevent HCC development: where are we now?

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Abstract

Hepatitis B virus was the first human virus unequivocally associated with malignancy. Long-term persistent infection with hepatitis B virus can result in the development of chronic liver disease, cirrhosis and hepatocellular carcinoma. Not surprising then, the main goal of antiviral therapy for chronic hepatitis B is to prevent the development of these life-threatening complications. The clinical trial treatment data now indicates that these goals are beginning to be achieved. Unfortunately, treatment failure due to the emergence of drug-resistant hepatitis B viruses compromises the success of antiviral therapy. Furthermore, the majority of drug-resistant hepatitis B viruses have an altered envelope which may even serve to accelerate the progression to hepatocellular carcinoma. The treating physician needs to ensure that current treatment regimens for chronic hepatitis B prevent active replication, interrupt the progression of liver disease and prevent the emergence of drug resistance.
In CHB, HBsAg seroconversion is the preferred endpoint of therapy because it is believed to represent successful immunological control of the hepatitis B virus. In acute infection, HBsAg is cleared during recovery and following vaccination, an anti-HBs immune response is generally protective against possible subsequent infection. Although HBsAg seroconversion is associated with a favourable prognosis in CHB, a recent longitudinal study evaluating the clinical outcome of HBsAg seroclearance has identified the age of the patient at which HBsAg seroclearance occurs as an important factor. This study followed 238 patients and demonstrated that HBsAg seroclearance before the age of 50 was associated with both a lower risk of HCC development and a lower risk of significant fibrosis on transient elastography in comparison to later HBsAg seroclearance (>50 years). This will certainly impact on current treatment guidelines for CHB, especially in the Asia Pacific region.

The annual rate of spontaneous HBsAg seroclearance is 1-2%. Treatment with standard interferon (IFN)-α or Peg-IFN results in HBsAg loss at a rate of 7.8% and 3% following 10-24 weeks and 48 weeks of therapy respectively. Furthermore, in long-term virologic responders to interferon, HBsAg loss can still occur after cessation of therapy, highlighting the ongoing immune-modulating effects of interferon. HBsAg loss has also been reported with potent oral antiviral agents such as tenofovir and entecavir. The rate of HBsAg loss following 96 weeks of tenofovir in HBsAg positive patients has been recently shown to be 6%; similarly, 48 weeks of therapy with entecavir in HBeAg-positive patients results in a HBsAg loss of 5% at 120 weeks follow-up.

A critical issue in treating patients with CHB is the evaluation of predictive markers of response to therapy. This is currently difficult with traditional serological and virological assays. The HBV genotype may influence HBeAg seroconversion and response to Peg-IFN therapy, testing is not routinely performed. Recent clinical studies have shown that evaluating dynamic on-therapy changes in quantitative serum HBeAg and HBsAg titres may have promise as a biomarker in predicting responses to therapy. In HBeAg positive patients treated with Peg-IFN, a critical baseline HBeAg level of ≥31 PE IU/ml has been associated with an increased likelihood of HBeAg seroconversion. Furthermore, in this study, the negative predictive value of an HBeAg titre of >100 PE IU/ml at week 24 was greater than that of serum HBV DNA (96% compared to 86%). In HBeAg-negative patients also treated with Peg-IFN, an early reduction in HBsAg titre was shown to have a high predictive rate of sustained suppression of viral replication, and increased HBsAg seroclearance at four years post treatment. Ongoing research is required to validate these assays and to determine their feasibility for use in everyday clinical practice.

HBV and hepatocellular carcinoma

The development of HCC in chronic HBV infection is a multistep process proposed to be a consequence of the combination of at least three mechanisms: ongoing inflammation, liver damage, and regeneration; chromosomal instability due to integration of HBV DNA; and a direct effect of the virus or viral proteins.

High levels of replicating HBV have been significantly associated with ongoing liver damage, inflammation, fibrosis and progression to HCC, particularly during the immune clearance and immune escape phases of CHB. Genotype C HBV has been reported to replicate to higher levels than other HBV genotypes and can cause more rapid progression to HCC. Infection with HBeAg negative strains of HBV has also been associated with more rapid progression to HCC. The host immune response to this higher level of replication may also contribute to HCC development.

In addition, most HBV-associated HCCs harbour integrated HBV DNA, which can cause chromosomal instability, however integrated HBV DNA can also be found in non-tumourous tissue from patients with CHB. Integration of viral DNA into the host chromosome is not necessary for HBV replication, but does occur and may allow persistence of the viral genome. Integration can lead to the development of HCC due to deletion of cellular genes at the integration site, or transposition of viral and cellular genes. HBV DNA can integrate directly into, and modify, genes that regulate cell signalling, proliferation and viability. The protein products of some integrated HBV genes, notably Hbx, one of the accessory proteins of HBV, and truncated L and M surface proteins, have also been implicated in the progression to HCC.

HBV proteins expressed from either the HBV genome or integrated DNA may be involved in the development of HCC, and mediate their HCC-promoting effects via activation of pathways involved in cellular transformation either through direct transcriptional transactivation, or via other cellular responses including endoplasmic reticulum (ER) stress. These proteins include the widely studied HBx protein, the HBV splice protein, and C-terminally truncated HBV surface proteins which have been isolated from HCC samples and shown to have transcriptional transactivation activity due to their altered topology. Importantly, these truncated surface proteins are selected in the HBV genome during NA therapy (see below).

Antiviral drug resistance and chronic hepatitis B

The introduction of nucleotide analogue (NA) therapy has also witnessed the emergence of antiviral drug resistance, which has become the main factor limiting the long-term treatment of patients with CHB. Several major NA-resistance pathways for HBV (rtM204V/I, rtN236T and rtA181T/V) have now been characterised. The first pathway, rtM204V/I, is responsible for resistance to the L-nucleosides such as lamivudine and telbivudine, and also entecavir which is also used as rescue therapy in lamivudine-experienced patients. This pathway is associated with clusters of secondary mutations (rtT184G, rtS202I) that can affect subsequent treatment with NAs such as entecavir. The second pathway, rtN236T, accounts for adeovir and tenofovir resistance. The third pathway, rtA181T/V, is associated with resistance to lamivudine and adeovir and is a potential multi-drug pathway.
resistance pathway that will probably impact on tenofovir sensitivity, either alone or with the rtN236T. In naïve patients treated with entecavir, a fourth pathway has been described where at least three mutations need to be selected out at the same time – rtL80M+rtM204V plus either one of rtT184 or rtS202 or rtM250 codon changes. Finally, in highly experienced NA treated patients, other multi-drug resistance pathways are being increasingly recognised such as rtA181T+rtN236T+rtM250L. Sequential monotherapy treatment with NAs promotes the selection of multi-drug resistant HBV.

Antiviral drug resistance in CHB is not surprising when the viral life-cycle of HBV is taken into consideration. Viral genome replication revolves around two key processes: generation of HBV covalently closed circular DNA from genomic relaxed circular DNA and its subsequent processing by host enzymes to produce viral RNA; and reverse transcription of the pregenomic RNA within the viral nucleocapsid to form relaxed circular DNA. Active replication of HBV is marked by a high frequency of mutational events resulting from an enormous viral turnover rate combined with the error prone reverse transcriptase/polymerase. In the patient, this produces a large quasispecies pool of HBV at any one point in time.

A link between anti-viral drug therapy and HCC development?

As shown in figure 1, the viral surface gene overlaps completely with the reverse transcriptase gene, hence nucleotide mutations encoding NA resistance in the reverse transcriptase can result in changes in the surface proteins. Other viruses that are treated with NAs, including HIV and HSV, do not have the added complexity of poor proof-reading ability and overlapping reading frames in their polymerase regions, hence treatment with NA for those viruses is straightforward and directly affects only the polymerase. In contrast, NA treatment for HBV has more far-reaching consequences. The reverse transcriptase-surface gene overlap in HBV is important since it has been shown that common LMV resistant HBVs such as rtV173L+rtL180M+rtM204V have important and significant changes in HBsAg (sE164D+sI195M) which significantly reduce anti-HBs (vaccine-associated) binding in vitro.41

Recent studies have shown that these NA selected S mutants may also enhance the progression to HCC. In particular, the mutation encoding the multi-drug resistant rtA181T change also results in a stop codon in the overlapping surface gene at position s172 (sW172*). The C-terminally truncated surface proteins expressed from this variant are very similar to those isolated from patients with HCC and have been shown to be transactivators.38-40 Studies from our group and others have shown that the surface proteins expressed by this variant accumulate within the cell,42 transactivate cellular promoters, and cause tumours when injected into nude mice, whereas the wt full-length surface proteins do not.42,44 Several other C-terminally truncated S variants have been selected in patients who developed HCC during NA-therapy.44

Figure 1
Treatment with nucleoside/nucleotide analogues can result in the selection of a mutation encoding the A181T mutation in the polymerase (light grey box). The DNA that encodes the polymerase protein also encodes the surface proteins from another reading frame (dark grey box), and the point mutation that encodes A181T in the polymerase also encodes W172* in the surface proteins. This results in truncation of the hepatitis B virus large (L), middle (M) and small (S) surface proteins and loss of the C-terminal hydrophobic region from amino acid 172 (shown as dashed region). Mutations in the overlapping reverse transcriptase and surface genes, and the corresponding changes to the surface proteins are represented by x. Truncated L and M proteins have transactivational activity and have been implicated in the development of hepatocellular carcinoma (HCC). Endoplasmic reticulum (ER).
of algorithms to minimise antiviral resistance. However, there remains a need for the development of additional antiviral therapies which target different steps in the hepatitis B viral replication cycle or the host immune response. The key goals for these future novel classes of antiviral agents should be to alter the natural history of CHB, and in particular, to improve HBsAg and HBeAg serocconversion rates, ensure total suppression of active replication and adopt strategies that prevent the emergence of resistance.

References

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer death worldwide. More than half the estimated 800,000 cases per annum occur within the Asia-Pacific region, reflecting the prevalence of the major risk factors – chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection and aflatoxin exposure. Although universal neonatal HBV vaccination is already reducing HBV related cases, the incidence of HCC is expected to treble by 2050 because of the increasing numbers of cases related to the current epidemics of chronic hepatitis C and non-alcoholic fatty liver disease.

HCC is one of the few diseases where annual mortality exceeds incidence. This abysmal prognosis reflects the delayed diagnosis of this condition in most patients. In the absence of regular surveillance, diagnosis follows the presentation with symptoms which reflect advanced disease, either from a large tumour burden (cachexia, bone pain from distant metastases), liver failure from massive liver replacement (jaundice, encephalopathy, ascites, capsular pain) or direct vascular invasion and thrombosis of the hepatic veins, portal vein, vena cava and right atrium (variceal haemorrhage, ascites, lower limb oedema). The only possible therapeutic interventions in such cases are sorafenib or palliative measures. In most series, the median survival in patients with symptomatic HCC is less than three months, with five-year survival at <20%.

In contrast, the natural history of small hepatocellular carcinomas (≤1-3cm) is vastly different, with five-year survival exceeding 50%. This reflects the suitability of small HCCs for curative therapies, namely surgical resection, liver transplantation, or radiofrequency ablation. However, early-stage HCC is always asymptomatic and can only be detected by imaging. This is the basis on which the argument for routine surveillance for HCC in at-risk populations has grown.

When assessing the benefit of any surveillance program, it is useful to determine whether this would meet all internationally accepted criteria for screening, as outlined by Wilson and Junger in 1968.1,2

1. There should be a high burden of disease in the population.
2. The population at risk for this disease, who would be targeted by the screening program, should be easily identifiable.
3. There should be a readily available screening method, which is associated with low morbidity, but which has a high accuracy for the identification of the screened disease.
4. The natural history of the disease is well understood and includes a preclinical period, during which screening can identify the disease at an early, potentially curable stage.
5. There is available a standardised recall procedure, which is acceptable to the targeted population.
6. There is evidence that earlier diagnosis by screening improves survival in those patients who develop the disease and also in the entire “at-risk” population.
7. There is evidence that screening meets the cost-effectiveness threshold in that population (realising that this figure may depend on many factors, including direct medical costs, local reimbursement and finally the economic wealth of that country).

In this review, each of these aspects will be discussed to ascertain whether the argument for routine surveillance for HCC in at-risk populations can be recommended.
High burden of disease in the at-risk population

The incidence of HCC is determined by the prevalence of risk factors in the population. The two major risk factors are chronic hepatitis B infection and cirrhosis. HBV is one of the most important carcinogens in the world today, second only to tobacco as a cause of cancer deaths in males. It is directly responsible for almost 500,000 cases of HCC each year, chiefly in the Asia-Pacific and sub-Saharan Africa. The risk of HCC is not the same among all patients with chronic HBV infection, but is influenced by other factors such as gender, age, smoking, aflatoxin exposure, viral co-infections (HIV, HCV or HDV), family history and stage of liver disease.

A cost-effectiveness analysis has demonstrated that screening with six monthly alpha fetoprotein (AFP) and ultrasound is justified in any patient with chronic HBV infection, with an estimated annual incidence of HCC greater than 0.2%. This would include all HBeAg+ males and females, HBeAg negative males over the age of 40, HBeAg negative females over the age of 50, cirrhcotics and anyone with a single first degree or at least two second degree relatives who have had a confirmed diagnosis of HCC. Recent sub-analyses of the REVEAL study (a prospective cohort study of 3653 Taiwanese patients with chronic HBV infection), would suggest that these baseline predictors may be replaced by quantitative serum HBV DNA measurements, since there is a direct correlation between HBV DNA titre and HCC risk. The risk exceeds 1% per annum for all patients with baseline HBV DNA >10^4 copies/ml. Other studies have suggested that maintained virologic suppression with long-term antiviral therapy may reduce HCC risk. Finally, it is generally accepted that baseline and serial HBV DNA levels are the best predictors of risk for HCC, but affordable, reproducible HBV DNA assays are not widely available for screening those populations in the Asia-Pacific and Africa with endemic HBV infection. Epidemiologic studies have also observed an increased risk of HCC in Asian patients infected with HBV genotype C compared to B.

In HBsAg negative patients, surveillance for HCC is justified for those with an annual risk of HCC exceeding 1.5%. In this regard, established cirrhosis is a risk factor for HCC, although the link between fibrogenesis, regeneration and hepatocarcinogenesis in non-HBV cirrhosis remains poorly understood. The risk is highest in those patients with cirrhosis secondary to HCV, alcohol, non-alcoholic fatty liver disease and haemochromatosis. Although HCV core protein may have direct oncogenic effects, the few anecdotal reports of HCC developing in non-cirrhotic patients probably represent under-staging of liver fibrosis because of the sampling error of liver biopsy. The incidence of HCC has doubled in the west since 1983, despite a falling prevalence of HBV infection in these countries, reflecting the impact of the recent HCV epidemic. The incidence of HCV related HCCs is projected to treble in western countries during the next 20 years.

The incidence of HCC is moderate (1-1.5%) in patients with autoimmune cirrhosis. In contrast, the incidence is low (<1%) in patients with alpha-1-antitrypsin deficiency, primary sclerosing cholangitis and primary biliary cirrhosis and the benefit of HCC surveillance in these patients is uncertain.

One group at particularly high risk of developing hepatocellular carcinoma are those awaiting liver transplantation for decompensated cirrhosis.

At-risk population is easily identifiable

Patients with chronic hepatitis B infection or non-HBV cirrhosis are at highest risk for developing HCC and therefore should be considered for HCC surveillance. Chronic HBV infection is asymptomatic in the early stages and can only be detected through screening programs. Although national screening programs could be justified in countries with endemic HBV infection, especially those in the Asia-Pacific region, these are rare because of the considerable resources required, not only to screen, but then to provide long-term follow-up of all identified carriers. Instead, opportunistic testing is encouraged through public awareness and primary care campaigns targeting those from high-risk ethnic groups. Successful HBV screening programs exist in New Zealand, Shanghai, Taiwan and Alaska. HCC surveillance in patients with non-HCV cirrhosis is facilitated by the fact that most identified cirrhotics are already under regular secondary care follow-up at least six-monthly.

Available, acceptable screening methods with low morbidity and high accuracy

Optimal surveillance tests are serum AFP measurements and abdominal ultrasound examinations. Both are safe, non-invasive and reasonably inexpensive. Unfortunately, serum AFP is troubled by a lack of sensitivity (ranging between 39 and 61%). Almost one third of HCCs are not associated with elevated serum AFP or tissue expression of AFP, reflecting dedifferentiation of the tumour. Serum AFP also lacks specificity (ranging between 75 and 91%). Extrahepatic production of AFP may also occur in placenta or embryonic tumours and in population screening; the most common source of elevated AFP is pregnancy. In addition, AFP may be produced within the liver in the presence of active liver regeneration and is actually a useful prognostic marker in patients with acute hepatic failure.

The accuracy of AFP for the detection of HCC is influenced by the value of AFP adopted as the cut-off for normality. In a case-control study of 170 patients with HCC and 170 matched patients without HCC, an AFP cut-off of 20g/L had a sensitivity of 69% and a specificity of 89%. A cut-off of 100g/L increased specificity to 99%, but reduced sensitivity to only 31%. A cut-off of 400g/L did not increase specificity any further, but reduced sensitivity to 17%. In this particular study, the accuracy of AFP for the detection of HCC was lower in patients with chronic hepatitis B infection than in those with HCV-cirrhosis. The overall specificity of AFP for HCC is lower in the HBV population than in non-HBV cirrhotics because of the higher incidence of acute hepatitis flares in chronic hepatitis B. For these reasons, the recently updated American Association Study of Liver Diseases guidelines have
dropped serum AFP measurements as recommended screening for HCC.\textsuperscript{27} Several new serum markers have been advocated in an attempt to improve the accuracy of non-invasive screening for HCC (Lectin-bound AFP (AFP-L3; DES-\(\gamma\)-carboxy prothrombin); Protein-induced Vit K Antagonist-Il (PIVKA-II); P53 antibodies; Glypican-3; serum Osteopontin; Golgi Protein 73; \(\alpha\)-1-fucidase).\textsuperscript{24} Unfortunately, while many of these are more specific than AFP, this is at the expense of sensitivity. As a result, the accuracy of these serum markers is poor and none have yet been adopted into clinical practice.

Compared to AFP, ultrasonography is more sensitive (78%) but less specific (71%) for the detection of HCC.\textsuperscript{26} Although one study has suggested that six monthly AFP testing alone may be effective for the detection of early HCC,\textsuperscript{26} more recent studies suggest that a combination of serum AFP levels and abdominal ultrasound is a more accurate means of screening.\textsuperscript{27,28} Although CT is more sensitive and specific than ultrasonography and is the investigation of choice for the diagnosis of suspected HCC, repeated abdominal scans are associated with a significant cumulative radiation exposure (three abdominal CT scans have the radiation exposure of 60 milliGrays, equivalent to that of an atomic bomb survivor).\textsuperscript{29} Six monthly surveillance CT scans would be associated with a real increase in lifetime cancer risk. Repeated MRI is not associated with cumulative radiation exposure and is therefore not associated with this risk. However, it is expensive and not widely available for mass screening.\textsuperscript{30}

Although the recently updated American Association Study of Liver Diseases guidelines\textsuperscript{23} have stated that surveillance for HCC should be with six-monthly ultrasonography and that AFP should only be used when ultrasound is not readily available. However, the accuracy of AFP as a screening test for HCC is higher in populations with a high proportion of non-cirrhotic cases (related to the prevalent HBV genotype). For this reason and reasons of cost and availability, most screening programs in countries with endemic HBV infection still utilise serum AFP in addition to ultrasound examinations.\textsuperscript{31,32}

### Natural history of the disease is understood and identifies a long preclinical latent period allowing for early diagnosis

For HCC, cure is highest when the tumour is detected at an early stage prior to vascular invasion and extrahepatic spread. Cross-sectional studies have demonstrated a direct correlation between size of tumour and risk of vascular invasion. In a histopathologic study of more than 1000 explants following transplantation for HCC, vascular invasion could be demonstrated in more than 40% of tumours larger than 3cm, more than 50% in those larger than 5cm and more than 60% of those larger than 6.5cm.\textsuperscript{33} Radiofrequency ablation, resection or liver transplantation will achieve greater than 50% five-year survival in patients diagnosed with early-stage HCC (as defined by the Barcelona Clinic Liver Cancer classification ie. single tumour or up to three tumours <3cm).\textsuperscript{34} Studies of serial imaging of small untreated HCCs demonstrate that the median doubling time is six months.

The estimated time interval for the HCC to grow from 1-3cm is 18 months.\textsuperscript{35,36} From these data, a screening interval of six months would seem optimal. When compared to tumours detected in a group of patients screened with annual surveillance, HCCs detected in patients undergoing six monthly ultrasound were more likely to be <3cm (76% v 42%) and within Milan criteria for transplantation (68% v 60%).\textsuperscript{37} However, a subsequent study in haemophiliacs with HCV found no difference.\textsuperscript{38} It should be noted that this study was flawed in that all HCV infected patients were included, not just patients with established cirrhosis. Hence the incidence of HCC in both groups was extremely low (<1% over 6 years), resulting in a type 2 error.

### Standardised recall procedures

Most cirrhotic patients who are undergoing surveillance for HCC have the initial diagnosis of cirrhosis made during secondary care assessment. As a consequence of this diagnosis, most are receiving six monthly clinic visits, which include HCC surveillance, according to regional guidelines: European Association of the Study of the Liver, Asia-Pacfic Association of the Study of Liver Diseases and American Association Study of Liver Diseases. In contrast, in countries with endemic HBV infection, less than 10% of patients will ever meet criteria for referral to secondary care. Even in those with a diagnosis of chronic HBV infection, local economic factors, lack of reimbursement and access to medical care prevent take-up of HCC surveillance. The only successful HCC surveillance programs in populations with endemic HBV are those funded and co-ordinated by the state.\textsuperscript{26,32,39}

### Screening improves survival

Multiple studies have demonstrated that surveillance for HCC in high-risk populations results in the detection of smaller tumours at an earlier, potentially curable stage, and subsequently an increased likelihood of suitability for curative surgical therapies, either radio-frequency ablation, resection or liver transplantation.\textsuperscript{26,40,41,42} These studies also demonstrate increased survival from the time of diagnosis of HCC, in patients with screen-detected HCC compared to patients with non-screen-detected HCC. The survival benefit is maximised when liver transplantation is available. This benefit is maintained after correction for lead-time bias of up to four years.

To answer the question as to whether screening for HCC will reduce HCC mortality in the overall target population, there needs to be a study comparing screening versus not screening for HCC in this population. The only randomised control study of screening for HCC was conducted in 19,000 HBV carriers in Shanghai. Screening reduced HCC mortality by 40% (from 132/100,000 per annum to 83/100,000 per annum). This was despite lack of availability of transplantation and poor access to resection.\textsuperscript{32} Attempts to reproduce this study in a western population have failed due to subject refusal to be randomised to an unscreened group.\textsuperscript{43} Of note, the 2003 European Association of the Study of the Liver HCC consensus noted a lack of randomised control studies of screening versus not screening, but concluded that such
studies were now unethical given that effective therapy for small HCC tumours is available.

Screening is cost-effective

Cost-effectiveness has remained the most controversial issue concerning screening for HCC because cost-effectiveness is dependent on a number of factors: prevalence of HCC in the screened population; direct costs of screening and medical intervention; and local cost-effectiveness threshold – what is accepted as cost-effective in one country may not be considered so in another.

In countries with a high prevalence of HCC where the primary treatment modality is resection, the cost for detection of each treatable HCC is $12,000 and $26,000 for each year of life saved (all costs in US dollars).6,27 In western countries where the prevalence of HCC is low, the cost is between $18,000 per treatable HCC identified and between $25,000 and $50,000 per year of life saved.44,48 These figures are comparable to those for cervical cancer screening ($38,000), breast cancer ($30,000) and colonic cancer ($25,000). The availability of liver transplantation increases the survival benefit (from 0.5 QALY to 0.9 QALY), but significantly reduces the cost-effectiveness (from $30,000 per QALY to $60,000 per QALY). The widening gap between deceased donor supply and demand has resulted in increasing waiting times for liver transplantation and increased waiting list drop-off of patients with HCC (as high as 30% at 12 months).49,50 Despite initiatives such as the introduction of tumour Model of End-Stage Liver Disease (MELD) prioritisation for deceased donor organ allocation and the growth of live-donor liver transplantation, it is likely that transplantation will become a less available therapeutic option for screen detected HCC.

Conclusion

HCC surveillance with six monthly combination serum AFP measurement and abdominal ultrasound examinations is widely recommended in patients with cirrhosis and those with chronic HBV infection. HCC surveillance in these at-risk populations results in earlier detection of smaller HCC, increases the possibility of curative therapy, reduces mortality, reduces overall HCC related mortality in the screened population and meets the cost-effectiveness threshold. There is an ethical obligation to provide effective screening and treatment for HCC in patients at high risk for this complication. It is hoped that in the future, better screening methods and more widespread availability of liver transplantation and adjuvant anti-tumour therapies, which prevent recurrent HCC following resection or radiofrequency ablation, will further improve survival. The cost-effectiveness ratios of screening however, are likely to remain high.

References


NON-SURGICAL TREATMENT OF PRIMARY LIVER CANCER

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Abstract
The majority of patients diagnosed with hepatocellular carcinoma are not able to undergo surgical resection either because of the severity of their underlying liver disease, or because the size and number of tumours precludes such an approach. Liver transplantation is also inappropriate for many patients with hepatocellular carcinoma either because of the extent of disease or limitations in access. A range of effective non-surgical treatments is available for patients of hepatocellular carcinoma, so that now an effective therapy is potentially available to all but those with terminal disease. Commonly used local ablative treatments for patients with smaller tumours include radiofrequency ablation and percutaneous alcohol injection. Transarterial chemoembolisation is most suitable for patients with intermediate stage disease, multifocal tumours without vascular invasion and those with large solitary lesions (≥3cm diameter). Recently, targeted systemic therapy with an oral multikinase inhibitor, sorafenib, has shown significant benefit in prolonging survival in patients with advanced hepatocellular carcinoma. Many other targeted drug therapies are in clinical trial development. Combination approaches with radiofrequency ablation and transarterial chemoembolisation, and with radiofrequency ablation or transarterial chemoembolisation with sorafenib or other targeted therapies, are under evaluation. It is critical that patients are staged at presentation with regard to the severity of liver disease, tumour stage and performance status, and that management is undertaken within a multidisciplinary setting to ensure the best outcomes.

The majority of patients who are diagnosed with hepatocellular carcinoma (HCC) are unsuitable for surgical resection or liver transplantation. However, there are effective treatments for these patients that while not being ‘curative’, have been shown to prolong survival. It is therefore imperative that every patient is considered by a multidisciplinary team to decide an overall management approach both initially and repeatedly over time.1

Non-surgical treatments include so-called ablative techniques such as percutaneous alcohol injection or radiofrequency ablation and trans-arterial treatments such as transarterial chemoembolisation. Systemic chemotherapy, hormonal therapies and external beam radiation have been shown to be ineffective in the treatment of HCC. Recently however, a large multicentre study has demonstrated the benefit of an oral multikinase inhibitor, sorafenib, in delaying tumour progression and improving overall survival in patients with advanced HCC.

The choice of which treatment or combinations of treatment to use in any individual case is complex and related to the size, number and location of the tumours, whether vascular invasion or extrahepatic disease is present, the status of the underlying liver disease and the performance status of the patient.

Staging systems
Both prognosis and the choice of therapy are determined by the stage of the patient at presentation. Multiple staging systems have been reported and validated in patients with HCC, including systems from Spain, France, Italy, Japan and China. Increasingly, the Barcelona Clinic Liver Cancer staging system (figure 1) is forming the basis for patient selection into clinical trials and treatment algorithms and has been endorsed by several international associations.2,3 This system has the advantage of classifying the patient according to the severity of liver disease and the degree of portal hypertension (Child-Turcotte Pugh score), tumour status and physical status, allowing recommendations for appropriate management. With this system, patients are classified as stage 0 (very early), stage A (early), stage B (intermediate), stage C (advanced) and stage D (terminal). Recommendations for evidence-based appropriate treatment are made for each stage, except stage D (terminal) where only supportive care is appropriate. Non-surgical treatments are appropriate for patients with stage A and stage B disease, although some of these patients may also be appropriate for liver transplantation, with loco-regional therapies being used to control disease while on the transplant waiting list.

The American Joint Committee on Cancer has developed and recently modified, a TNM (tumour, node, metastases) staging system for HCC.4 However, this system is really only applicable for patients undergoing surgical resection or liver transplantation and has less relevance for patients with non-surgical disease. It is a pathologic staging system incorporating histologic grading, extent of local disease, regional lymph nodes and distant metastases, but it does not include the features of liver disease (synthetic function and portal hypertension), nor the patient’s performance status.

Most major treatment centres have developed local management algorithms that take into account stage of liver disease and tumour stage, as well as local resources and facilities.5
**Ablative techniques**

**Percutaneous ethanol injection**

Percutaneous ethanol injection (PEI) of small HCCs was first described in 1983 and until recently, has been the most widely used local ablative therapy. Its advantages relate to it being inexpensive, widely available and well tolerated, and the fact that it can be administered in an outpatient setting. The procedure involves instillation of 95-100% ethanol through a fine needle directly into the tumour nodule under ultrasound or CT guidance, with the aim of inducing complete tumour necrosis. The risk of needle track seeding of tumour is minimal (case reports only). In general, effective use of PEI is limited to tumours less than 3cm in diameter, with superior outcomes in patients with solitary rather than multiple lesions. In patients with three or fewer lesions, all under 3cm, PEI is associated with one, three and five-year survival rates of approximately 94%, 70% and 27% respectively, and tumour recurrence rates by five years of 74%-98%.6,8

Several recent meta-analyses of randomised trials comparing PEI with a newer ablative technique, radiofrequency ablation (RFA), identified inferior overall, one, two and three-year survival rates, and inferior local tumour responses for PEI.9-11 Hence, because of high tumour recurrence rates and poor long-term outcomes, PEI can no longer be recommended as primary therapy in patients for whom other techniques such as RFA or transarterial chemoembolisation (TACE) can be performed.

**Radiofrequency ablation**

Radiofrequency ablation has become the primary ablative modality for the treatment of HCC in most institutions and is accepted as the most appropriate therapy for the treatment of small lesions in patients who are unsuitable for surgical resection or liver transplantation.12 It can also be used to control small tumours in patients awaiting liver transplantation.

In most cases, RFA is performed percutaneously under intravenous sedation or general anaesthetic, with imaging guidance provided by real-time ultrasound, CT or MRI, according to the preference of the radiologist. Not all lesions are suitable for RFA because of a higher risk of complications. In particular, lesions approximating the liver capsule, lesions located high in the liver, and those occurring adjacent to other organs such as gallbladder or bowel, pose particular risks for RFA and are usually avoided except by the most experienced interventional radiologists.13 Laparoscopy or cushioning techniques, such as injection of dextrose, may be of use in these difficult circumstances to reduce the risk of complications.

Proximity of tumours to large vessels also poses a

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**Figure 1. Barcelona Clinic Liver Cancer staging classification and treatment schedule**

![Barcelona Clinic Liver Cancer staging and treatment approach](https://www.thelancet.com)

problem with RFA, as the vessels act as a heat sink and reduce the effectiveness of the procedure in attaining complete tumour necrosis.

A number of commercial RF devices (comprising radiofrequency generator and needle electrode) are approved for use. One device comprises a needle with multiple hook-shaped expandable electrodes that are deployed within a tumour, and others, a single or cluster cooled-tip needle electrode that is inserted directly into the tumour. Variable rates of needle tract seeding have been reported following RFA, with increased risk seemingly related to prior biopsy, subcapsular location, poor tumour differentiation, high serum AFP levels and the use of cooled-tip needles. The overall rate of needle tract seeding seems to be around 0.1-1.4%.

In the management of small HCC (<3cm), outcomes following RFA have been evaluated in randomised control trials against other ablative therapies. One, two and three-year survival rates of 90-97%, 82-91% and 63-81% respectively are reported with RFA. This excellent survival relates to high initial tumour control rates of 93-100%. Apart from improved survival and local disease control, RFA requires fewer treatment sessions and shorter hospitalisation than PEI. These excellent results have led some commentators to suggest that RFA, not surgical resection, should be the standard of care for patients with solitary lesions <2cm diameter.

**Other ablative techniques**

A range of other ablative techniques are used with variable enthusiasm in the management of HCC. In general, they have limited applicability and are less supported by clinical trial evidence of efficacy than PEI and RFA. These techniques include cryoaablation, microwave ablation, laser interstitial thermal therapy and extracorporeal high intensity focused ultrasound which is largely practiced in China.

**Non-ablative therapies**

**Transarterial chemoembolisation (TACE)**

TACE is particularly suitable for patients with intermediate-stage (stage B) disease, multifocal tumours without vascular invasion and for patients with larger solitary lesions (>3cm diameter).

TACE involves femoral artery catheterisation with an angiographic micro-catheter, passage to the hepatic artery, and preferably, super-selective catheterisation of the feeding vessel to the target tumour. Currently there is no standardisation of technique, or of treatment schedules, with significant variability between publications and centres. Most protocols involve injection of an emulsion of lipiodol mixed with a chemotherapeutic agent such as cisplatin, doxorubicin or mitomycin. Following this injection, further embolisation may be performed, for instance with gelatine sponge particles or polyvinyl alcohol. Treatments may be repeated according to a strict treatment schedule (usually every 3-4 months), or based on evidence of ongoing tumour activity by dynamic imaging.

Recently, TACE with doxorubicin-loaded drug-eluting beads has been developed for treatment of patients with HCC, and compared with conventional TACE in a randomised-control trial. This technique enhances drug delivery to the tumour and reduces systemic exposure to the chemotherapeutic drug, avoiding high peak levels that are usually seen within 10 minutes of a conventional TACE procedure. Particularly in patients with more advanced liver disease, the use of drug-eluting beads seems to result in less direct liver toxicity and side-effects than conventional TACE.

TACE is of particular benefit in patients with intermediate-stage (stage B) HCC. These patients have preserved liver function (CTP A), and multinodular tumour without vascular invasion. The benefits of TACE compared to conservative treatment have been demonstrated in randomised-control trials, and confirmed in a meta-analysis of seven trials involving more than 500 subjects. Meta-analysis showed that TACE led to a significant improvement in two-year survival (OR, 0.53; 95% CI, 0.32-0.89; p=0.017). Ultimately however, the majority of patients treated with TACE will eventually die of tumour progression.

TACE has been regarded as being contraindicated in the presence of portal vein thrombosis (PVT), as there is concern that interruption to both portal venous and hepatic arterial flow would result in a large segment of hepatic necrosis. However, there are reports of successful TACE in the presence of PVT, even in quite large tumours. While half the patients in one report developed post-embolisation syndrome (abdominal pain, fever and nausea/vomiting), none required prolonged hospitalisation or additional treatment. No randomised control trial has been performed in patients with PVT and it is therefore unclear whether a survival benefit is obtained.

**Combined therapies**

Combined locoregional therapies are increasingly being utilised in the management of HCC, and several combinations have been evaluated in controlled clinical trials. Combined percutaneous alcohol injection and RFA has been evaluated in the treatment of HCC. In this procedure both a Chiba needle and an RFA electrode are placed inside the tumour, 100% alcohol is instilled, the Chiba needle withdrawn and RFA performed after approximately one minute. In a randomised controlled trial, the combined procedure showed significantly superior survival in patients with tumours of 3.1 to 5cm diameter (but not in those less than 3cm), and reduced local recurrence. The injection of alcohol prior to RFA appears to extend the ablation zone, and also delineates the tumour making the RFA procedure somewhat easier.

A number of retrospective studies report good outcomes following combined TACE and RFA and in early-stage disease, combination therapy achieves overall (one, three and five year survival rates of 98, 94 and 75%) and disease-free survival (one, three and five year rates of 92%, 64%, and 27%), rates similar to those achieved with hepatectomy. Recently, TACE with doxorubicin-loaded drug-eluting beads combined with RFA (DEB-enhanced...
RF ablation) was shown to be safe and effective in a pilot study of 20 patients who had incomplete responses to standard RFA.28

**Systemic therapies**

Until recently, systemic chemotherapy for HCC was associated with no clear benefit, but significant toxicity, and no chemotherapy regimen could be recommended.29 Management of patients with advanced disease (stage C) was limited to supportive care, or enrolment in clinical trial protocols. In 2008 and 2009, the publication of positive results of two large randomised placebo-controlled Phase III trials of Sorafenib has dramatically changed the recommendations for patients with advanced HCC. This agent is now considered to be the standard of care in this patient group.30,31

Sorafenib is an orally active, multikinase inhibitor that inhibits cell surface tyrosine kinase receptors and downstream intracellular serine/threonine kinases, thereby inhibiting tumour cell proliferation and tumour angiogenesis.32 Monotherapy with oral sorafenib 400mg was investigated in patients with well-compensated liver disease, but advanced HCC in 602 randomised subjects (sorafenib n=299; placebo n= 303) in the SHARP trial and the Asia-Pacific trial (sorafenib n=150; placebo n=76).30,31 Despite differences in the study populations with subjects in the Asia-Pacific trial having more advanced disease, the findings were similar. Sorafenib led to significantly prolonged overall survival (SHARP trial: median survival 10.7 months v 7.9 months; Hazard Ratio (HR) 0.69 (0.55,0.87)) (Asia-Pacific trial: median survival 6.5 months v 4.2 months; HR 0.68 (0.50,0.93)) and delayed time to radiologic progression. Significantly more patients achieved disease control with sorafenib, defined as partial response or stable disease, although no patient achieved a complete response.

In the Phase III trials in advanced HCC, sorafenib was generally well tolerated. The main toxicities seen included diarrhoea, hand-foot skin reactions and weight loss. Most toxicities respond to dose reduction or brief periods of dose interruption. Hand-foot skin reactions seem to be more common in Asian than Caucasian patients.

Sorafenib is now approved for use in advanced HCC in many countries and is available on PBS-authority in Australia for this indication. Clinical trials are underway to assess the benefits of sorafenib in patients with intermediate stage (stage B) disease treated with TACE, and as adjuvant therapy in patients undergoing hepatic resection or RFA (stage A disease).

Other molecular targeted therapies currently under clinical investigation as monotherapy or combination therapy in HCC include sunitinib, brivanib, bevacizumab, erlotinib, everolimus and sirolimus.

**Assessment of response to non-surgical treatment**

Traditionally in oncology practice, response to therapy has been determined by application of the RECIST (Response Evaluation Criteria In Solid Tumours) criteria35 which relies on changes in measurements of the greatest dimension of all target lesions. This approach has been shown to be unreliable in a number of tumour types, including HCC,34 as commonly no change in the size of treated lesions is observed despite attainment of complete necrosis (with loco-regional therapies) or with tumour stasis (with cytostatic drugs). Currently, tumour response following treatment of HCC is determined by loss of arterial enhancement using dynamic techniques.35

Dynamic CT or MRI performed at regular intervals is therefore used to monitor response to loco-regional therapies. Persistent hypovascularity on both arterial and portal phases of the scan in all treated lesions is required to determine a complete tumour response.10 Contrast-enhanced ultrasound is also very useful for monitoring the response of target lesions.36 Long-term follow-up requires assessment for local tumour recurrence, the development of new intrahepatic lesions and for the development of extrahepatic disease.

Serum tumour markers such as AFP and PIVKA-II (predominantly in Japan) are also useful in monitoring new tumours or assessing tumour recurrence following treatment of HCC, and are usually performed every 2-3 months.10,37 The identification of new response markers is an area of active investigation.

**Conclusion**

Ultimately, the prevention of HCC by eradication of chronic viral hepatitis will have the biggest impact on mortality from this malignancy. The introduction of screening programs in high-risk individuals will also lead to the identification of early stage disease and to a greater number of patients who are amenable to surgery, transplantation or ablative therapies. Currently however, the majority of patients present with non-resectable disease. Even for these patients, an increasing array of effective locoregional and systemic therapies are now available. Only patients with terminal disease, poor liver function or extensive HCC, have no effective treatment options. It is becoming increasingly important that all patients with HCC are evaluated in centres with multidisciplinary expertise, so that the most appropriate and effective therapies can be offered.

**References**


SURGICAL MANAGEMENT OF HEPATOCELLULAR CARCINOMA

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Abstract

Hepatocellular carcinoma (HCC) is among the three most common causes of cancer death worldwide. Liver resection and liver transplantation are regarded as the standard curative treatments for hepatocellular carcinoma. Although liver transplantation for early stage hepatocellular carcinoma has been shown to have excellent long-term survival outcomes and low recurrence rates, the shortage of donor liver grafts limits its wide application. Liver resection can be safely performed in patients with early stage hepatocellular carcinoma and preserved liver function. Although postoperative recurrence after liver resection of hepatocellular carcinoma is almost universal, the reported five-year overall survival rates are around 50%. Recently, the concept of primary liver resection and salvage liver transplantation has been proposed in patients with early stage hepatocellular carcinoma and preserved liver function. Universal adoption of either liver resection or liver transplantation for hepatocellular carcinoma is unwarranted and overly simplistic. The use of different therapeutic approaches that incorporate liver resection or liver transplantation, depends not only on the availability of donor liver grafts and waiting time, but also on the expertise of individual centres.

Hepatocellular carcinoma (HCC) is a major health problem worldwide with an estimated incidence of 500,000 new cases every year. It is among the three most common causes of cancer death worldwide, accounting for about 315,000 deaths annually. Although it is predominantly a cancer found in the east, its incidence in the west has recently doubled and is predicted to double again over the next 20 years. This phenomenon is largely explained by the emerging burden of hepatitis B and C viral infection. Liver resection and liver transplantation are regarded as the standard curative treatments for HCC. It is now well established that liver transplantation is the treatment of choice for unresectable early stage HCC in patients with decompensated cirrhosis. The best treatment strategy for early stage HCC in patients with preserved liver function remains controversial.

Liver resection

With the increased understanding of liver segmental anatomy and the improvements in surgical techniques and peri-operative care, there has been a dramatic reduction in peri-operative mortality and an improvement in survival outcomes after liver resection for HCC in the past two decades. In recent series from the east and the west, a peri-operative mortality rate of less than 5% and a five-year overall survival rate of 40%-50% has been reported. However, a high incidence of post-operative recurrence is universal and continues to be the major cause of late deaths. The cumulative five-year recurrence rate is in the range of 75% to 100%. Recurrence occurs in the liver remnant in 78%-96% of cases as a result of either intrahepatic metastasis from the primary tumour or multicentric occurrence.

Most patients with HCC have underlying cirrhosis. Liver resection for HCC in the presence of cirrhosis is associated with a significant risk of morbidity and mortality. Careful patient selection for liver resection is therefore paramount to avoid post-operative liver failure and death. This involves an adequate assessment of the tumour extent, the severity of the underlying liver disease and the functional liver reserve. Only 10-37% of patients with HCC are amenable to liver resection at the time of diagnosis. A recent study from Australia showed that liver resection and liver transplantation were the primary treatment in only 17% and 16% of the total cohort of 235 patients with HCC respectively. In general, large tumour size with insufficient liver remnant after liver resection, extensive and multifocal bilobar tumours, extrahepatic metastases and tumours with main portal vein thrombosis or hepatic vein/inferior vena cava involvement, are all considered a contraindication to liver resection.

Preoperative assessment of liver function

Because HCC is associated with varying degrees of liver disease, inadequate functional liver reserve after liver resection is always a concern. Determination of the amount of liver that can be safely resected is multi-factorial and depends on the extent of cirrhosis, the functional liver remnant/reserve and the regenerative response following liver resection. In general, a normal liver can tolerate the resection of up to 75% of functional liver parenchyma. On the other hand, the risk of postoperative liver failure and subsequent death are high after major liver resection in patients with cirrhosis. Pre-operative assessment of liver function and prediction of post-operative functional liver remnant/reserve are of paramount importance to minimise the risk of post-operative liver failure. Measurement of the volume of liver remnant by CT volumetry has been shown to be helpful in selecting patients for major liver resection. Vauthey et al demonstrated that small liver remnant volume was associated with worse post-operative liver function and
On the other hand, Child-Pugh classification (table 1) is the most simple, widely used and reproducible method to identify the patient at risk of liver failure after liver resection. In general, Child-Pugh class A patients can be considered for resection of up to 50% of the liver parenchyma, whereas Child-Pugh class B patients tolerate resections up to 25%. Patients with Child-Pugh class C cirrhosis are considered as an absolute contraindication for liver resection. Numerous quantitative liver function tests have also been developed and evaluated. However, none of these tests on its own can take into account the complexities of liver failure, nor has been demonstrated to be clearly superior to another in predicting postoperative outcome after liver resection for HCC. In the east, indocyanine green clearance at 15 minutes (ICG15) is the most commonly used quantitative assessment of liver function. The value of ICG15 >20% precludes major liver resection. In the west, selection of candidates for liver resection is often based on the presence of portal hypertension in addition to the Child-Pugh classification. Clinically relevant portal hypertension is defined as the presence of a hepatic vein pressure gradient (HVPG) ≥10mmHg, the presence of oesophageal varices or splenomegaly with a platelet count less than 100x10^9/L. Bruijx et al demonstrated that HVPG ≥10mmHg was associated with postoperative liver failure in patients with HCC and Child-Pugh class A cirrhosis. Recently, the model for end-stage liver disease (MELD) score has been shown to be an accurate predictor of postoperative liver failure and death after liver resection. Patients with a MELD score <9 had a reported zero perioperative mortality after liver resection for HCC.

### Table 1. Child-Pugh Classification of the severity of liver disease

<table>
<thead>
<tr>
<th>Parameter</th>
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<tr>
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<tr>
<td>Bilirubin (mmol/L)</td>
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<tr>
<td>Albumin (g/L)</td>
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<tr>
<td>Ascites</td>
<td>Absent</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
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### Figure 1. Right portal vein embolisation

(a) CT image of a 5cm hepatocellular carcinoma occupying segments 5 to 8; the tumour was very close to the middle hepatic vein. Segments 2 and 3 were free of tumour. Curative resection would require a right hepatectomy with inclusion of the middle hepatic vein.

(b) On CT volumetry, the left liver volume was 24% of the total estimated liver volume before right portal vein embolisation (PVE).

(c) Percutaneous transhepatic ipsilateral right PVE with Gelfoam particles was performed.

(d) On CT volumetry, the left liver volume was increased to 40% of the total estimated liver volume four weeks after right PVE.
Liver resection. Pre-operative portal vein embolisation (PVE) induces atrophy of the embolised segments and compensatory hypertrophy of the unembolised segments of the liver (figure 1). PVE can be performed using an open transileocolic approach, percutaneous transhepatic contralateral approach or percutaneous transhepatic ipsilateral approach. These approaches are chosen on the basis of the type of resection planned, the location of the tumour and the available surgical and radiological expertise. In general, PVE is indicated in patients with a predicted functional liver remnant of <25% in non-cirrhotic patients, or <40% in patients with cirrhosis. A recent meta-analysis has shown that PVE is safe and effective in inducing liver hypertrophy to prevent liver failure after liver resection due to insufficient functional liver remnant. PVE has also been shown to increase the resectability of HCC with comparable long-term survival outcomes.

Liver resection for large or multinodular HCC

Several prognostic staging models have been developed to predict survival and to assess the survival outcomes of HCC treatment. The Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely used in the west and stratifies patients with HCC into four categories – early, intermediate, advanced and terminal. It has been recently integrated into the American Association for the Study of Liver Diseases and the European Association for the Study of Liver guidelines on the management of HCC. The BCLC staging system recommends different treatment options for each stage of the disease. Liver resection is indicated only in patients with early stage HCC, as defined by, within the Milan criteria: a single HCC ≤5cm in diameter or up to 3 HCCs ≤3cm in diameter, normal clinical performance status; and preserved liver function (absence of clinical portal hypertension and Child-Pugh class A status). There is no doubt that patients with early stage HCC have excellent prognosis after liver resection. Although large tumour size (>5cm) and multiple tumour nodules have been shown to be less favourable prognostic factors for patients with HCC, liver resection remains the only hope of cure in patients with large or multinodular HCC outside the Milan criteria. Previous studies have shown that up to 50% of patients with HCC who underwent liver resection had disease classified as being intermediate or advanced stage according to the BCLC algorithm. In a multi-institutional study, Ng et al demonstrated that liver resection could be safely performed in patients with large or multinodular HCC, providing the functional liver reserve is acceptable. A five-year overall survival of 39% and a five-year disease free survival rate of 26% could be achieved.

Liver transplantation

The first successful liver transplant for HCC was performed on a 19-month-old girl by Starzl and his team in July 1967. In theory, liver transplantation is a better treatment option than liver resection as it simultaneously removes the tumour, the underlying cirrhosis and cures the portal hypertension. Early experience with liver transplantation for HCC was, however, associated with a high tumour recurrence rate and poor long-term survival. These poor results were presumably due to the broad selection criteria used, with inclusion of extensive and bulky tumours two decades ago. In 1996, Mazzaferro et al published a landmark paper in which they validated the tumour characteristics associated with superior survival outcome following liver transplantation. The four-year overall and disease-free survival rates were 85% and 92% respectively with a tumour recurrence rate of 8.3%. These constitute the Milan criteria – a single HCC ≤5cm in diameter or up to three HCCs ≤3cm in diameter. These results are comparable with those of non-cancer liver transplant recipients. To push the boundary further, the University of California San Francisco (UCSF) group demonstrated that size criteria could be expanded without compromising the survival outcome. The UCSF criteria consist of single HCC ≤5cm or up to three HCCs with the largest tumour ≤4.5cm and total tumour diameter ≤8 cm, without gross vascular invasion. One-year and five-year overall survival rates of 90% and 75.2%, with tumour recurrence rates of 11.4% were reported. Chen et al analysed and validated these excellent survival outcomes of liver transplantation for HCC in Australia and New Zealand. One-year and five-year overall survival rates were 88% and 74% respectively in patients within the Milan criteria, and 87% and 73% respectively in patients within the UCSF criteria. In patients outside the USCF criteria, the survival outcomes were poor, with one-year and five-year survival rates of 71% and 36% respectively.

Although tumour recurrence is much less a problem after liver transplantation for HCC within the Milan or UCSF criteria, there are other complications specific to transplantation that compromise long-term survival, such as graft rejection, opportunistic infections and the development of other malignancies as a result of immunosuppression. In addition, the major drawback of liver transplantation for the treatment of HCC is the scarcity of deceased organ donors. Many patients with HCC either die before the organ becomes available or drop out from the transplant waiting list because of tumour progression. The dropout rate can be as high as 25% to 37.8% in 12 months. It has also been shown that the results of liver transplantation were adversely affected by increasing waiting times with a two-year intention-to-treat survival falling from 84% for 62 days of waiting time, to 54% for 162 days of waiting time. The survival benefit of liver transplantation over liver resection has been shown to disappear once the waiting time for a donor liver graft exceeds six months.

A variety of bridging therapies, such as transarterial chemoembolisation and radiofrequency ablation, have been advocated as a means to address the prolonged waiting time. In theory, these therapies slow down tumour progression, decrease tumour cell dissemination during recipient total hepatectomy and lower the risk of post-operative recurrence. While some studies demonstrated favourable results of bridging therapies in decreasing the drop-out rate, others reported similar drop-out rates of 15% at six months and 25% at 12 months, but longer
waiting times for liver transplantation.\textsuperscript{46,51,52} Although most transplant physicians and surgeons would agree that bridging therapy is useful, there is currently no evidence to support its use. Future studies are required to confirm the efficacy of bridging therapies before liver transplantation for HCC. The questions of which therapy and when to commence the therapy, also require further evaluation.\textsuperscript{50}

**Live donor liver transplantation**

As a consequence of deceased donor shortage, live donor liver transplantation (LDLT) for adults has developed as an alternative over the past decade.\textsuperscript{53} The shortage of deceased donor liver grafts is particularly severe in the east. The deceased donor rates are fewer than five donors per million in the east, compared with those of 10 to 35 donors per million population in the west.\textsuperscript{54} With HCC being the most common cancer and the most frequent indication for liver transplantation in the east, the enthusiasm for LDLT therefore continues to surge. In theory, LDLT can provide an unlimited source of donor liver grafts and eliminate the uncertainty of prolonged waiting times and the risk of dropout due to tumour progression.\textsuperscript{55} Using a decision analytical model taking into account the risk of dropout while waiting (4% per month), the expected survival of the recipient (70% at five years) and the risk for the donor (0.3% to 0.5% mortality), Sarasin et al demonstrated that patients with HCC waiting more than seven months for a deceased donor liver would benefit from LDLT.\textsuperscript{56} Previous studies on LDLT for HCC also demonstrated favourable long-term survival outcomes.\textsuperscript{57,58} However, the question of whether the outcome after LDLT for HCC is comparable with that of deceased donor liver transplantation remains unclear.\textsuperscript{53}

More importantly, LDLT poses an ethical dilemma to all transplant physicians and surgeons – “First do no harm”.\textsuperscript{59} Donor hepatectomy is a surgical procedure that subjects a healthy volunteer to a major operation with 20% morbidity and 0.5% mortality, without direct therapeutic benefits.\textsuperscript{60} Currently, LDLT remains a novel treatment for HCC with unresolved issues regarding indications and results.

**Liver resection v liver transplantation**

The superiority of liver transplantation over liver resection remains a topic of debate. In specific clinical circumstances, it is clear that liver transplantation may be the only option, namely for patients with early stage HCC that clearly do not have sufficient functional liver reserve to tolerate liver resection. On the other hand, liver resection may be the only curative option in patients with large HCC without cirrhosis. The controversy remains over the management of patients with early stage HCC and well compensated cirrhosis that would tolerate liver resection or transplantation.\textsuperscript{61} There are no randomised control trials that directly compare the two modalities.

Using the best available evidence, patients with early stage HCC who are eligible for either liver resection or transplantation, have a better survival with liver transplantation than resection. The tumour recurrence rates are also significantly lower in the liver transplantation group.\textsuperscript{5,62,63} Therefore, in an ideal world with unlimited organs, liver transplantation would offer improved oncologic outcomes over liver resection. However, because of the growing shortage of donor liver grafts throughout the world, the superior outcomes of liver transplantation may be significantly compromised by patients dropping out of the transplant waiting list, largely from tumour progression. Recently, the concept of primary liver resection and salvage liver transplantation has been proposed in patients with early stage HCC and preserved liver function. It has been shown to be a feasible strategy, as up to 80% of patients with tumour recurrence after liver resection may still be amenable to liver transplantation.\textsuperscript{6,63} Salvage liver transplantation has also been shown to be as safe and efficacious as primary liver transplantation, with no difference in morbidity and perioperative mortality. In addition, the long-term survival outcomes are comparable.\textsuperscript{64}

In summary, universal adoption of either liver resection or liver transplantation for HCC is unwarranted and overly simplistic. The use of different therapeutic approaches that incorporate liver resection or transplantation should be dictated by the clinical and local situation. Factors will include not only medical and surgical expertise, donor graft availability and anticipated waiting times, but also patient and tumour specific factors.

**References**

In New South Wales (NSW), liver cancer accounts for over 400 new cancer cases and nearly 300 deaths per year and its incidence is rising faster than any other internal cancer in NSW.\(^1\)

The ‘B Positive’ Project has been developed based upon the following premises:

- In NSW, hepatocellular cancer (HCC) incidence and mortality have increased ~5-fold since 1972 and, at the current rate, may double again by 2020.\(^1\)

- In NSW, people born in countries of high prevalence of chronic hepatitis B infection (CHB) are 6-12 times more likely to be diagnosed with HCC than Australian-born individuals (figure 1).\(^2\)

- Antiviral treatment is likely to significantly reduce CHB progression to cirrhosis and HCC.\(^3\)

The project will address the significant challenge of reducing the disease burden for a cancer with poor prognosis and limited options for curative treatment, which affects some of the least well-served populations in NSW.

**Figure 1. SIRs for HCC diagnosed in NSW (1991-2001) by place of birth:**

\(^1\) (SIR % compared to the Australian-born population)
An overarching project evaluation process has been planned with collection of relevant key indicator measures and outcomes. Currently the project is in implementation phase and too immature for formal project evaluation; this paper provides the descriptive findings and statistical results to date.

Figure 2. Standardised Incidence Ratio of primary liver cancer per 100,000 NSW population (Figure for male only shown, data 1998-2002)

Methodology for project development

An analysis of data from the NSW cancer registry, national census and reviews of relevant literature about hepatitis B infection and liver cancer provided the evidence-base underpinning the planning, development of resources and implementation of the project.

Cancer Council NSW has responsibility for the overall governance of the project and key responsibilities for developing communication strategies with primary care practitioners and at-risk communities.

Project activities are supported by culturally appropriate community advertising, education and media liaison. Community and patient engagement is mediated by local GPs and community-based organisations serving the needs of specific migrant groups. The collaboration of high-profile professionals, clinicians and community organisational representatives with links to the relevant target populations is a key component of the development and implementation of the project.

The project has five main focus areas, detailed below:

1. Development of a hepatitis B screening and HCC surveillance protocol using input from experts on the project steering committee, including a comprehensive review of world literature, clinical decision support algorithm and recruitment process. These components had development feedback from peer GPs.

2. Development of a register of people with chronic hepatitis B infection (CHB) – data collection forms and participant information and consent forms were developed in English, Vietnamese and Chinese, with community input. Engagement with pathology service providers, supported by project and clinical experts was initiated early in 2008 to develop the pathology test data capture and database download processes. The patient enrolment and follow-up data collection process was designed by Cancer Council NSW project staff in collaboration with an academic with clinical and information systems knowledge. A contracted database developer was engaged to build the register and with Cancer Council NSW the data custodian.

3. Development of an economic model, to estimate the cost-effectiveness of different screening and surveillance strategies, was managed through a working party process. This working party included Cancer Council NSW project staff and clinical investigators from the project steering committee, and received expert input from consultants. Critical review of the model was undertaken by health economist academics from the University of Sydney and a modelling expert from the National Centre for HIV Epidemiology and Clinical Research. This component of the pilot project included modelling the cost effectiveness for a targeted program of hepatitis B and liver cancer detection through screening on a geographical basis. Four scenarios were investigated, based in the pilot project area (Fairfield-Liverpool), a Greater Sydney, NSW-wide and national scenario, each targeting populations with high hepatitis B seroprevalence.

4. Development of educational resources for primary care providers in collaboration with the local GP Division, the Royal Australian College of General practitioners (RACGP), the Australian Society for HIV Medicine and other interest groups. A range of resources were developed, including a hepatitis B monograph, a ‘B Positive’ Project GP Kit of decision support and related patient information resources. The knowledge and skill needs of GPs in the target geographical region were assessed in 2008. An RACGP accredited educational program was developed encompassing the prevention, diagnosis and management of hepatitis B infection and liver cancer.

5. Development and implementation of effective communication strategies about hepatitis B infection and HCC management for at-risk community populations. In collaboration with local medical practitioners and prominent community leaders,
Cancer Council NSW engaged with community associations/societies in the pilot project area in south western Sydney. Two part-time Community Liaison Officers (Chinese & Vietnamese) with advanced language skills were appointed, and targeted activities in two phases – a community education campaign aimed at awareness raising in 2008, followed by a patient recruitment phase, which commenced in the first half of 2009.

The distribution of consumer resources was supported by a media strategy, using ethnic and local media (newspapers, radio, community magazines). A detailed marketing plan was implemented with various information posters and pamphlets. All were pilot tested with community group feedback.

The communications plan included briefings of Members of Parliament and local government representatives (Fairfield and Liverpool city councils elected officials and staff) throughout the project.

**Results**

**Screening and surveillance protocol**

A protocol to support individualised treatment planning has been developed, with treatment decisions based on liver function and viral load. This included a key ‘B Positive’ Project decision-support resource (algorithm schematic figure 3), with a matching GP process flowchart for patient enrolment and follow-up produced as a laminated two-sided sheet. The GP kit includes both GP resources and patient information packs in relevant languages for use in recruitment and follow-up consultations. The protocol and related materials have been approved by both the RACGP National Research and Evaluation Ethics Committee and National Ethics Application Form processes.

**Prototype register**

The register of patients enrolling in the ‘B Positive’ Project is currently in final-phase testing by Cancer Council NSW, in collaboration with clinicians at Liverpool and Westmead Hospitals. Since the initiation of the patient-recruitment phase in February 2009, recruitment has been incremental, however the number of GPs participating in education (see below) and visited to date by project staff, indicates the target of 250 enrolments by June 2009 and 1000 by December 2009 is achievable.

Successful collaborations were developed among staff and researchers from three NSW tertiary hospitals (Westmead, Liverpool and Royal Prince Alfred) with Cancer Council NSW project staff in the pilot project.

**Economic model**

The outputs of the model can be summarised as:

A program of CHB screening, follow-up and treatment could significantly reduce the proportion of people progressing to cirrhosis (by 52%), HCC (by 47%) and HBV-related deaths (by 56%).

The current management practice of limited hepatocellular carcinoma screening and treatment would cost about AU$26 million over 50 years. In comparison a CHB screening, follow-up and treatment program would cost

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**Figure 3: Hepatitis B screening and liver cancer surveillance protocol**

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about AUS$146 million, for an additional 9279 Quality Adjusted Life Years (QALYs) gained. The incremental cost effectiveness (discounted) was calculated to be AUS$12,913 per QALY gained. For the four scenarios investigated, the model found that a comprehensive screening and treatment program of high-risk populations across NSW was both feasible and cost-effective, compared to current clinical practice. The cost, based on liver function tests and viral load, is comparable to that of existing population-based cancer screening programs in Australia (breast, cervical and colorectal cancer). The results have recently been reported in a peer-reviewed international journal article with an accompanying editorial. Cancer Council’s economic model estimated the costs incurred by different participants and funding bodies in this program. By far the largest expenses were associated with disease staging (hepatitis B viral load testing) and drug treatment (entecavir and interferon), borne by the Federal Government through the Pharmaceutical Benefits Scheme. According to the model, the Federal Government would bear at least 70% of the program cost in the first year, rising to 90% by the fifth year.

**Educational resources**

A Hepatitis B monograph, *B Positive - all you wanted to know about hepatitis B*, was developed specifically for GPs by the Australasian Society for HIV Medicine, in collaboration with clinicians and Cancer Council NSW. The publication was distributed nationally, with state/territory government funding, and formally launched in October 2008 at the 6th Australasian Viral Hepatitis Conference. Cancer Council NSW has developed and delivered a series of educational workshops (November 2007 - November 2008) in the Fairfield - Liverpool area for GPs participating in the ‘B Positive’ Project. All 329 GPs in the local divisions were invited to participate, with 57 in 2008 attending at least one evening seminar. Early results were presented at the World Organisation of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians and RACGP combined conference in November 2008.

The first GP education seminar in March 2009 attracted 30 new GPs into the accredited education program, supported by the monograph and a comprehensive GP resource kit. This included language-specific patient information packs about the project and other Cancer Council NSW information for patients and carers. The GP Kit resources have recently been made accessible on-line from a new Cancer Council NSW micro-site at www.cancercouncil.com.au/bpositive.

Cancer Council NSW has become an RACGP Accredited Provider Organisation, with management-level staff completing accredited training. This enables the design, delivery and administrative support needed for the GP education component of the ‘B Positive’ Project consistent with implementation of the broader Cancer Council NSW GP Engagement Strategy.

**Effective communication strategies**

To November 2008, 23 presentations to raise community awareness and ensure program support have been made to over 1000 people from the targeted communities. The ‘B Positive’ Project was officially launched on 31 October 2008, with approximately 500 participants, mainly from the target Vietnamese and Chinese communities. A parallel activity stream in the pilot project area has provided information about the project and access to its written resources through many migrant resource centres, libraries and similar facilities.

Consumer information about hepatitis B infection (creation of a new pamphlet, slides in relevant languages) and information provided to the target populations at community presentations are accessible on-line, from www.cancercouncil.com.au/bpositive.

To the end of March 2009, more than 60 reports on the ‘B Positive’ Project have appeared in local newspapers, on ethnic radio or TV and in community publications (society newsletters etc).

**Conclusions**

Chronic hepatitis B is an important cause of liver cancer, particularly in some overseas-born Australians, so devising cost-effective programs to reduce the burden of disease is a key component of disease management planning. The disease control challenge in migrant populations is fundamentally different from the vaccine-driven strategies targeted at the Australian born non-Indigenous population. The ‘B Positive’ Project contributes important field research in accordance with the National Cancer Control Initiative, focused on the educational needs of GPs and patients in responding to the needs of local communities.

Further roll-out from the south western Sydney pilot project to other metropolitan NSW communities has been proposed to the NSW Government. The development of a ‘National Hepatitis B Strategy’ would be a significant next step in hepatitis B prevention and control. By systematically engaging affected communities, improving disease detection and opportunities for treatment, enhancing collaborations among clinical and advocacy groups, and prioritising research and surveillance activities, we aim to address the needs of all at-risk communities on a national basis.

**References**

Antiviral therapy for hepatitis B-related liver cancer prevention is more


7. Cancer Council NSW. Improving outcomes, sparing pain – A new
economy for cancer control in NSW. Budget Initiatives for Cancer Control

about hepatitis B: a guide for primary care providers. Australasian Society
ashm.org.au/B-positive/.

9. Tipper S, Robotin M, George J, Zwar N. The GP as an innovative cancer
control professional: the “B Positive” Project. World Organization of
National Colleges, Academies and Academic Associations of General
Practitioners/Family Physicians WONCA 2008 Asia Pacific Regional

and Ageing on Phases I and II of the Primary Care Perspective on Cancer
ENGAGING COMMUNITIES AFFECTED BY HEPATITIS B

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Abstract
The impact of chronic hepatitis B infection on the health care system is increasing. To effectively reduce this burden, the health care system needs to understand how people and the communities most affected respond. Through talking with people with chronic hepatitis B and health workers, the National Hepatitis B Needs Assessment highlights significant gaps in the health care system response to chronic hepatitis B. This article highlights some of these gaps, including poor diagnostic processes, lack of information available about chronic hepatitis B for people who are infected, the need for workforce development (particularly for health and community workers involved with communities most at risk) and issues relating to access to treatment for chronic hepatitis B. The Australian health care system needs to develop effective coordinated responses to chronic hepatitis B before its burden can be reduced.

The following assumptions were made about chronic hepatitis B in the report:

■ The burden of liver disease on the health care system is increasing.
■ Hepatitis B is a chronic disease, with chronicity mostly discussed using clinical language and concepts.
■ Populations most affected by chronic hepatitis B do not have the same understanding of the body, the blood or the liver as those used in the western health system.
■ People with knowledge and understanding about their infection are more likely to engage in health promoting activity.
■ Barriers to access the health system exist for the populations most affected by chronic hepatitis B.

Community beliefs and understanding of hepatitis B
The majority of people with chronic hepatitis B come from culturally and linguistically diverse communities, whose understanding of the body is based on their own cultural experience and framed by a different understanding of the body from that used in western medicine.

Hepatitis B is a complex virus. Providing often technical and complex information about hepatitis B into languages and concepts understood by people from culturally and linguistically diverse backgrounds is challenging. One study done among a Cambodian community in the United States highlights these challenges.° Hepatitis B pamphlets targeting the Cambodian community and written in Khmer, the principal Cambodian language, used the term “liver disease” (rauk tlaam), or “swollen liver disease” (rauk hoem tlaam) for “hepatitis B.” Rauk tlaam was chosen by translators as the more appropriate Khmer term for hepatitis, as this phrase was thought to best capture the organ damage expressed by the word “hepatitis,” as derived from the Greek. The distinction “B” was routinely
dropped and considered unnecessarily confusing. When the understanding of Cambodian people's comprehension of these terms was measured, the authors found that rauk tlaam was meaningless to 82% of respondents and Cambodian refugees often associate liver disease with heavy alcohol use, rather than the hepatitis B virus.

Both language difficulties and certain health beliefs and practices significantly influence health literacy, including access to health services. While many people in the broader community do not understand what the liver is or what it does, there are common understandings of basic western medical concepts, which provide a common language from which to start a dialogue about health. This is often not the case of people with chronic hepatitis B. One clinician reported to the needs assessment that people with hepatitis B "really have very little understanding of their disease...partly because their background concept of health and liver, and what it does, is minimal."

**Diagnosing chronic hepatitis B**

A person with hepatitis B finds out that they are infected after receiving a blood test, primarily from a general practitioner. The health sector has learned from responses to other blood borne viruses that a pre and post-test discussion fundamentally influences how people respond to receiving a positive diagnosis. A supportive diagnostic experience can mean that an individual can incorporate chronic hepatitis B infection into their lives and respond in effective ways. These effective ways can mean making dietary changes, reducing alcohol intake or having their infection monitored by a general practitioner or specialist, thereby reducing the impact of the infection.

There were several people with hepatitis B who reported not providing formal consent to be tested for hepatitis B: "I didn’t ask for (the test), just through a normal blood test".

Several people with chronic hepatitis B said they were provided with limited or no information at the point of a chronic hepatitis B diagnosis and several described the event as shocking. This shock of finding out that they have chronic hepatitis B can be significant and may not allow people to comprehend any additional information beyond the diagnosis if this had been provided: "Nothing that I remember – if there was (information provided) it didn’t stick". One person with hepatitis B assumed that their positive diagnosis equalled cancer: "I think it was like a cancer or something".

Refugee workers reported people newly arrived in Australia receiving correspondence from the immigration department notifying that they had been diagnosed with chronic hepatitis B: “A standard letter which they pop in the mail…no treatment.”

The National Hepatitis C Testing Policy released in 2007, describes the purpose of a pre-test discussion being to “prepare individuals for hepatitis C testing and to sufficiently equip the person requesting the test such that she/he can give informed consent”. The policy notes that test results should be delivered to the patient as soon as possible after results are received from the lab. It is strongly recommended that test results be given in person. These processes recognise the psychological and social impact that infection with a blood borne virus can have, and that the diagnostic event provides an opportunity to give information to people that effectively minimises the impact of infection, and reduces the risk of further transmission.

Given the lack of systemic testing protocols for hepatitis B, there was a wide variation in responses to being diagnosed with chronic hepatitis B. As noted previously, this included one person assuming they had cancer; while another person reported that they “didn’t know that hepatitis B could be problematic … I don’t think that was explained to me”.

The majority of people with chronic hepatitis B come from culturally and linguistically diverse backgrounds and many have little or no knowledge of the Australian medical system or of the language used within the system. Good English language skills were seen by one person with chronic hepatitis B as important in accessing basic and reliable information: “If you don’t speak English, nobody tells you nothing”.

**Seeking information about hepatitis B infection**

In the context of a lack of information provided to people with hepatitis B at the point of diagnosis, and a paucity of accessible and relevant information about living with chronic hepatitis B generally, several people with chronic hepatitis B reflected a poor understanding of their condition and/or had a fatalistic view of their options:

- “Only one thing I know is that there is no medicine.”
- “I had hep B not much just a little bit, just carrier and no treatment.”
- “I’ve got it … there’s nothing much I can do, it’s up to the virus.”

In responding to the lack of information being provided at the point of diagnosis, people with hepatitis B reported seeking guidance from a range of sources – “I had to ask a couple of people, because the people that I did ask didn’t have all the information … the doctors, they didn’t have enough time to go through the specific questions”. Identifying information which is accurate and credible is important if people are using it to base decisions about their health.

Being infected with chronic hepatitis B occurs within the broader context of a person’s life. Several people interviewed for the needs assessment came from significantly disrupted backgrounds and were engaged in a process of establishing their lives in a new country. Responding to chronic hepatitis B was not a clear priority for some. One community worker noted that for refugees – “Hepatitis B is not the dominant thing on their mind, it’s creating a life here is far, far, far more important”.

Hepatitis B is a global issue and while vaccination programs are not effectively implemented in other countries, chronic hepatitis B will remain a key issue.
Organisations funded to provide services to populations most at risk of chronic hepatitis B have unique challenges, including an increasing number of clients coming from a broader range of cultural backgrounds. One community worker reported the increasing breadth of cultural diversity within their client group: “The service I coordinate have currently over 50 different countries of origin in our client group”. The implications of this cultural diversity for delivering information about chronic hepatitis B to people with differing understandings of the body, blood and the liver are significant.

### Knowledge of hepatitis B among health workers

While the lack of information for people with hepatitis B is self-evident, another factor highlighted in the needs assessment was community based health workers reporting an increased number of requests for information from clients about chronic hepatitis B.

There were significant gaps in the level of knowledge about hepatitis B by people with hepatitis B, and this extended to people working with communities with higher prevalence of chronic hepatitis B. One community worker noted their significant lack of knowledge about chronic hepatitis B and the available options related to treatment: “Even the natural history - I’m not clear about it, and to be honest, I don’t even know if treatment is available”.

Several workers noted that responding to these requests required professional skill development so they could effectively explain to their clients issues related to what is a complex virus: “Hepatitis B is so bloody complicated”. Another public policy professional noted that even with their prior nursing experience, understanding and providing information about hepatitis B was challenging: “I’ve done hepatitis B 101 three times and every time that I think I’ve got it, I try to explain it to someone else and I realise that I haven’t got it”.

Several health professionals noted the need for increased workforce development to improve their skills. The complexity of hepatitis B and its sequelae, and differing understandings of some aspects of hepatitis B among clinicians and other health workers further complicates communicating about hepatitis B to people from culturally and linguistically diverse backgrounds. As one community worker noted: “If you think about the number of hepatitis B specialists who argue about the natural history of hepatitis B [and] can not agree amongst themselves; and then you try to tell this person about these nuances through an interpreter”.

### Access to hepatitis B treatment

An essential group of clinicians that need to be engaged to reduce the impact of hepatitis B infection are general practitioners. The role of general practitioners in reducing the burden of chronic hepatitis B was identified by a public policy professional as “diagnosing the unrecognised pool (of hepatitis B),” which a clinician suggested could be done through “screening for hepatitis B (as) part of the routine health care check of populations who are high risk”.

Access to treatment services by Indigenous people, who make up about 16% of people infected with chronic hepatitis B, was noted as lacking. One clinician working in a region with a significant Indigenous population noted that Indigenous people made up “less than 1% of their patients, while another reported absolutely no contact with Indigenous populations”. One of the few clinicians interviewed for the needs assessment who was in contact with Indigenous people described “people dying early from end-stage liver disease and that’s complicated by alcohol use”. This clinician noted that hepatitis B “is actually a killer and a lot of people aren’t being referred in”.

While general practitioners were identified as having a role in screening for chronic hepatitis B, it was also noted that specialists, particularly those providing treatments which suppress the immune system, needed to be more proactive in checking their patients’ hepatitis B status before instituting treatment. One clinician noted that “there are high risk areas of medical therapy that impact on hepatitis B and there’s very little awareness among clinicians involved in delivering those therapies … I have been told by a medical oncologist and a haematologist … ‘we can’t screen everyone for hepatitis B’ … and I just asked ‘why not?’”

### Treating people with hepatitis B

Several clinicians talked of the challenges in treating and managing people from culturally and linguistically diverse communities with chronic hepatitis B. One challenge related to the power dynamics that occur between clinicians and patients. Having patients understand how treatment works, and what to expect from treatment is important and leads to clinicians engaging with patients in meaningful ways. As one clinician noted: “You’re much more likely to get people who want to be treated and stick to their therapy if they understand what they are doing and they think it’s good for them”.

One perception from clinicians was that people with hepatitis B were compliant and followed what the specialists told them, but there was also an awareness that this may not always be the case: “They are sitting there nodding saying ‘yes, yes, yes, thank you very much’ but they don’t understand, they won’t say ‘what does that mean?’”

The impact of patients with chronic hepatitis B coming from highly disrupted backgrounds can challenge the health care system, and one clinician reported the impact of “huge social disruption and post traumatic stress … psychological problems that clearly we don’t address very effectively in our clinic setting”.

### Conclusion

The health care system in Australia has a history of responding effectively to blood borne viral infections. Our national responses to the transmission of the human immunodeficiency virus, and of hepatitis C, showed the capacity to engage and develop partnerships effectively with marginalised communities and reduce the burden of infection of these viruses on the broader community.
There are significant gaps in the health care system response to chronic hepatitis B throughout the trajectory from diagnosis to treatment. Current diagnostic testing protocols for hepatitis B are inadequate. Diagnostic testing needs to be provided in meaningful ways so that when a person is diagnosed with chronic hepatitis B, they understand what the diagnosis means and have the knowledge, skills and willingness to effectively respond.

The unaddressed needs of people with chronic hepatitis B highlight the requirement for workforce development within the health care system. This education needs to range from improving the capacity of community workers to provide fundamental information, through raising the awareness of hepatitis B among communities most at risk, through to improving the capacity of specialists to work effectively with patients from a broad range of cultures and experiences.

There are significant gaps in access to treatment services, particularly for people from Indigenous communities. Indigenous people are estimated to make up 16% of people with chronic hepatitis B infection and yet only two of 30 clinicians reported seeing patients who were Indigenous. The public hospital system is learning to effectively engage with people from culturally and linguistically diverse backgrounds, but more needs to be done.

Health care systems need to be resourced to engage and develop relationships with communities most at risk of chronic hepatitis B. These relationships are necessary to develop effective and efficient interventions that reduce the burden of infection on individuals infected with chronic hepatitis B, communities most at risk of infection and the broader community.

References

Tackling tobacco in socially disadvantaged populations

Disadvantaged groups are an important target for smoking cessation intervention. Smoking rates are markedly higher among severely socially disadvantaged groups such as Aboriginal and Torres Strait Islander people, the homeless, and people with mental illness or drug and alcohol problems, than in the general population. Community social service agencies provide an ideal setting for delivering smoking cessation care; accessing a high proportion of the groups with high smoking rates, they are a trusted source of support and open to providing cessation support. Cancer Council NSW has been working with NSW based community services at establishing partnerships for tackling tobacco among their clients.

As part of the Tackling Tobacco Initiative, CheRP will conduct two linked action research projects. In the first study, CheRP is conducting a series of focus groups with staff and clients of six community social service organisations, including Salvation Army, Benevolent Society, Uniting Care, Anglicare, Ted Noffs Foundation and Samaritans, regarding barriers and facilitators to providing smoking cessation care in this setting. The results of this phase will help inform the development of an appropriate intervention. The second study will be a pilot project in two community services to test the acceptability and feasibility of a smoking cessation intervention and examine the validity of smoking self-reporting among clients.

It is intended that this research will inform the development of suitable strategies for addressing the high smoking rates prevalent among socially disadvantaged clients of community social service agencies.

Qualitative exploration of dietary supplement use by recent cancer survivors

Food supplements and vitamins are widely used by cancer survivors as an adjunct to conventional treatment. A systematic review of the efficacy of nutritional interventions in cancer patients concluded that their impact was unknowable because of the limited number and poor quality of trials. Currently, no evidence indicates that dietary modification by cancer patients improves survival and benefits disease prognosis. Nutritional interventions may not be benign; beta-carotene supplementation yields unexpected adverse effects on lung cancer recurrence in smokers.

Lacking evidence of effectiveness (and showing evidence of harm), cancer patients nevertheless use dietary supplements. Diet is a clear area where they may feel they have some control. Better understanding their patterns of consumption and reasons for using supplements would improve communication about the use of supplements during cancer treatment.

CheRP conducted qualitative research investigating the use of dietary supplements among survivors. Twenty survivors who had indicated they used dietary supplements were recruited from the longitudinal Cancer Survival Study. Participants took part in 20 minute semi-structured telephone interviews. Verbatim interview transcripts were analysed thematically. Theoretical saturation of relevant themes was reached after 18 interviews.

Preliminary analyses identified three strong themes in the areas of supplement and vitamin use: 1) assessing efficacy and confirmation of legitimacy; 2) the health professional-patient dynamic; and 3) access/use being mediated by socioeconomic status. In addition, the discussions helped to identify how and what patients want in terms of resources and access to advice from health professionals.

Behavioural Research and Evaluation Unit (BREU), South Australia

Program evaluations

Behavioural Research and Evaluation (BREU) conducts ongoing evaluations to inform the future directions of programs and services offered by Cancer Council SA. The extended hours of the Cancer Council Helpline, a workshop offered to general practitioners on prostate testing and accommodation facilities offered to rural people who require treatment or care in Adelaide in relation to cancer diagnosis, have recently been evaluated.

National sun protection in early childhood services

BREU recently completed a national survey evaluating the sun protection policies and practices of 1017 early childhood services. Reports were prepared for individual states and territories, and together with the national report they will provide Cancer Councils across Australia with a baseline for future monitoring. The national report found that while most early childhood services across Australia have written policies that include multiple sun protection strategies (in line with Cancer Council recommendations), sun protection could still be improved. The report also found that Cancer Council’s SunSmart Early Childhood Program has had a positive impact on services’ sun protection and provides an important reason for services to become SunSmart. The national report recommends that the program should continue to be promoted, with particular emphasis on the benefits of joining the program and what is involved in becoming a SunSmart service.
Community support for legislation restricting tobacco advertising at point of sale

In 2008, a telephone survey was conducted of 1876 adults aged 18+, from randomly selected households in South Australia, investigating community awareness of tobacco point of sale laws introduced in the previous year. Respondents were asked whether they approved, disapproved, or were indifferent to the new laws restricting the size and placement of cigarette pack displays, which includes the requirement for larger shops such as supermarkets to remove tobacco products from sight if their tobacco kiosks are visible from outdoors or from a mall. The findings revealed that awareness of the legislation among the community, particularly among smokers was high. Support for the legislation was high among the community overall and particularly non-smokers. Many respondents (unprompted) believed that tobacco product displays or advertising should not be allowed (31.3%) and 21.9% believed that displays encourage young people to start or continue smoking. The vast majority of current smokers reported that the tobacco product display legislation would have no impact on their cigarette consumption, while 11.3% reported that they may be more likely to smoke less cigarettes.

BREU has also secured a contract for three years with SA Government to continue providing Tobacco Control Research and Evaluation services. This funding allows Cancer Council SA to monitor progress and inform strategic directions for tobacco control in South Australia.

Centre for Behavioural Research in Cancer (CBRC) Victoria

Mass media campaign improves cervical screening across all socio-economic groups

Low socio-economic status (SES) has been associated with lower cervical screening rates. Mass media is one known strategy that can increase cervical screening participation. This study sought to determine whether a mass media campaign conducted in Victoria, Australia in 2005, was effective in encouraging women across all SES groups to screen. Data were obtained from the Victorian Cervical Cytology Registry for each Pap test registered during 2005 and categorised into SES quintiles using the Index of Socio-Economic Advantage/Disadvantage. Negative binomial regression was used to determine the impact of the campaign on the weekly number of Pap tests, and whether the media campaign had a differential effect by SES, after adjusting for the number of workdays per week, age group and time since previous test. Cervical screening increased 27% during the campaign period, and was equally effective in encouraging screening across all SES groups, including low SES women. Mass media campaigns can prompt increased rates of cervical screening among all women, not just those from more advantaged areas. Combining media with additional strategies targeted at low SES women may help lessen the underlying differences in screening rates across SES. *Health Education Research* (In press).

Web-based intervention to reduce distress and improve quality of life among younger women with breast cancer: randomised control trial

Younger women with breast cancer experience greater psychological distress and greater physical symptoms than older women with this disease. A new research grant has been awarded to CBRC and partners from beyondblue: the national depression initiative, Cancer Australia and National Breast Cancer Foundation. A randomised control trial will test the effectiveness of a web-based intervention addressing unmet information and supportive care needs in improving quality of life of younger breast cancer survivors. The web-based intervention will use expert system technology. We aim to recruit 342 women under 50 diagnosed with early stage breast cancer. Women will be randomised to the intervention or control condition. Women in the intervention condition will be directed to the website and will work through a four-step process comprising: (1) an assessment of unmet needs; (2) nomination of needs they would like to address; (3) nomination of preferences for receiving advice on how to access professional help, information about the issue, and information about self management strategies; and (4) provision of tailored strategies addressing the need. Women will be encouraged to use the program as often as needed over the nine month study period and will receive formal invitation to do so at two, four and six months. All participants will complete baseline and follow-up surveys at three and nine months post-study entry. If effective, the model is transferable to other cancer types and could be readily implemented to make delivery of information to address unmet needs of cancer survivors highly plausible.

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to understand how men make decisions about their preventive health behaviours. The study commenced in April 2008, with over 300 men with a family history of prostate cancer aged between 40-70 years currently participating. Information from this study will inform the development of supportive care programs and educational resources aimed at addressing the specific needs of men with a family history of prostate cancer.

**Sun Exposure, Vitamin D and Outcome of Prostate Cancer Study**

This study is being conducted in collaboration with Cancer Council NSW and the University of Sydney to investigate the relationship between sun exposure, vitamin D and the recurrence or progression of prostate cancer. Men in ProsCan are invited to participate in this project, with over 300 men taking part since May 2008.

**ProsCan Partners Study**

At present we have limited information on the long-term quality of life experiences of partners of men with prostate cancer. The Partners Study will address this issue by examining the experiences of the partners of men in the ProsCan project. Results will help us to understand how we can better support partners through the prostate cancer experience and allow Cancer Council Queensland to develop new support programs and services targeted to the needs of this group. Recruitment for the Partners Study began in February 2009.

**ProsCan for Couples**

A significant proportion of men experience erectile problems after prostate cancer treatment. The ProsCan for Couples study will investigate the effectiveness of a new support program to help couples adjust to changes in sexual functioning resulting from radical prostatectomy. This telephone based intervention is designed to be delivered by trained nurses or peer support volunteers (men who have themselves undergone radical prostatectomy). Study recruitment commenced in March 2009.
Breast Cancer 2nd Edition

KK Hunt, GL Robb, RA Strom and NT Ueno
Springer 2008
ISBN: 9780387349503
561 pages
RRP: $US99.95

MD Anderson Cancer Care Series has seven volumes, with this being the 2nd edition of the Breast Cancer volume. All of the chapters have been updated from the 1st edition and incorporate important developments in the management and treatment options for breast cancer. There are 19 chapters going from prevention, through treatment modalities, to rehabilitation and survivorship issues. Each chapter is written by experts in their individual field of practice.

Early on in this book, the recurring theme emerges around the focus on the multidisciplinary approach to breast cancer management. A similar emphasis in Australia over recent years has been seen as a more holistic approach to patient care.

I found that most of the chapters in this book, although comprehensive descriptions of treatment protocols, were written with a technical focus. Each chapter provides details and suggestions based around current practice at MD Anderson Cancer Centre. The chapters towards the end of the volume on rehabilitation and survivorship issues are very informative. Coming to the end of up to a year’s worth of varying treatment modalities, these patients report feelings of isolation and fear at the prospect of ‘going it alone’ and issues of whether they can ever feel ‘normal’ again. The book addresses some of these issues and suggests proven strategies which can be put in place prior to the end of treatment, with interventions continuing after active treatment has been completed. Individualising coping measures are discussed, all designed to help patients reintegrate into what they regard as a normal routine. High emphasis is put on a holistic approach in assessing patient needs, in order to avoid divorcing emotional care from physical care.

This book is primarily aimed at physicians specialising in care of the patient with breast cancer. It would serve well as a resource for trainee medical oncologists and nurses and would be a good addition to any oncology reference library.

Gaynor Stevenson, Department of Radiation Oncology, Capital Region Cancer Stream, The Canberra Hospital, Australian Capital Territory.
Contemporary Issues in Women's Cancers

Suzanne Lockwood
Jones and Bartlett Publishers (2009)
349 pages
RRP: $115.00

Contemporary Issues in Women's Cancers is a comprehensive text edited by the leader of the Society of Gynaecologic Nurse Oncologists (SGNO), with each chapter authored by a member of SGNO. The SGNO is an international organisation of nurses and other health professionals, with over 600 members, whose aim is to advance patient care, education and research in the specialised fields of gynaecological oncology and women's health care. Although SGNO is an international society, all authors are American, which is reflected in the text, but does not detract from the content.

This text has a different focus to the society’s previous text, entitled Women and Cancer: a Gynaecologic Oncology Nursing Perspective, with the aim of the new book being to enhance clinical practice, and address new concerns by placing a greater emphasis on the role that patients play in clinical practice.

This book explores contemporary issues, drawing on the expertise and clinical experience of the authors, to assist readers in providing optimal care to their patients amidst the changing ways in which women’s cancers are diagnosed and treated.

The book contains 17 chapters, commencing with an overview and epidemiology chapter to set the scene, before continuing on to cover specific diseases in greater detail. Breast cancer, endometrial cancer, epithelial ovarian cancer, non-epithelial ovarian malignancies, pre-invasive cervical cancer, invasive cervical cancer, vulval and vaginal cancers and gynaecologic sarcomas are all covered in suitable detail. Nursing issues/implications are addressed in each chapter and highlight the invaluable role that nurses play in all aspects of the patient’s journey.

There is a chapter exploring cancer genetics and then several chapters dedicated to issues pertinent to women with gynaecological cancer. Sexuality, infertility issues, menopause and the sequelae of cancer and its treatment are all covered and the author of each chapter focuses on the major implications for the patient and interventions aimed at improving the quality of life of the woman.

The final chapters are centred around psychosocial aspects of care, addressing issues such as the impact of gynaecological cancer on the family and living with recurrent cancer.

This hard-copy text is logically sequenced and provides relevant tables, flow-charts and diagrams to assist readers in their comprehension.

Overall, I found this to be a useful, well-referenced text, suitable for nurses interested in women's cancers, who have a basic understanding of current issues and who would like to update and complement their existing knowledge.

Shannon Philp, Sydney Gynaecologic Oncology Group, Sydney Cancer Centre, Sydney, New South Wales.
Dx/Rx: Cervical cancer – Diagnosis and treatment of pre-cancerous lesions (CIN) and cervical cancer

DS Dizon & K Robison
Jones and Bartlett Publishers (2008)
76 pages
RRP: $65.00

The authors have designed this text as a “comprehensive handbook for the treatments of pre-invasive and invasive cervical pathology”. They have succeeded in creating a good basic introduction to cervical neoplasia and cancer incorporating current treatment recommendations.

The book is compact in size. It contains six chapters which are brief and the information is presented in bulleted format. The chapters flow in a logical sequence, beginning with epidemiology, risk factors and co-factors, cervical anatomy, histology and histopathology, through to diagnosis and staging, treatment of pre-invasive lesions and invasive cervical cancer and prevention and screening. The authors include statistical information, unfortunately the majority of which is from the American perspective. However, they do include a brief overview of worldwide demographics and the bulk of the text matches treatment recommendations in Australia.

Each chapter is well referenced, which is useful for the reader if they wish to undertake further investigation of the topic. They have utilised simple tables throughout the text covering topics such as Human Papillomavirus (HPV) subtypes, common colposcopic findings, the natural history of cervical intraepithelial lesions, types and complications of hysterectomies, radiation, prognostic factors and comparison of HPV vaccines. There is also a summary of numerous randomised trials comparing concurrent chemo-radiation versus radiation therapy alone in cervical cancer.

The information on cytology is categorised under the Bethesda System, the terminology of which has minor differences to the modified Bethesda system that has been used in Australia since 2004, but the categorisations are virtually the same. They have also included the International Federation of Gynaecology and Obstetrics staging, plus a description of Tumour, Nodal and Distant Metastasis staging for cervical carcinoma.

While this text would not be viewed as a comprehensive manual, I found it to be a good introductory text and it would certainly be a helpful beginning guide and source of reference to those seeking information on the diagnosis and treatment of pre-cancerous lesions and cervical cancer.

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Manual of Clinical Oncology
6th Edition

DA Casciato
Lippincott Williams & Wilkins (2008)
ISBN: 9780781768849
794 pages
RRP: $US49.95

The sixth edition of the Manual of Clinical Oncology is in essence, a concise textbook of oncology.

The information is presented in a consistent format, with the chapters grouped into four parts. Part one presents the general aspects of cancer management, such as the principles of diagnosis and treatment, definitions and statistics, treatment modalities, supportive care and communication strategies. Parts two and three address specific disease groups, covering epidemiology and aetiology, pathology and natural history, clinical presentation, diagnostic methods, staging and prognostic factors, prevention and early detection, management and follow-up. Part four presents complications according to end organ involvement, whether by local invasion, metastasis, paraneoplasia or therapy. The chapters themselves are organised into a series of bold type headings and sub-headings, which flow logically and are quick and easy to locate.

At the end of the book there is a series of appendices with detailed tables presenting the glossary of cytogenetic nomenclature, toxicity of chemotherapy, tumour identifiers and chemotherapy regimens for lymphomas.

This is a useful reference book to clarify questions that arise in day-to-day practice and gets referred to frequently, rather than some of the larger, bulkier textbooks. It is packed with information suitable for clinicians with varied knowledge and experience. The section on cell reproduction and cancer growth has proven very useful to assist newer staff to understand the underlying principles of cytotoxic chemotherapy, along with the subsequent chapter on the different classes of drugs used. The section on complications is well written and particularly relevant for nursing staff, both for prevention and problem solving, as is the section on supportive care, which offers some useful management strategies for various symptoms of the disease and/or treatments.

As with a large percentage of oncology texts, it is written for a North American audience, so occasionally the drugs discussed will not apply in an Australian context. However, it was interesting to read about the newer targeted agents such as the Tyrosine Kinase Inhibitors and some of the more recently developed monoclonal antibodies that we may see in future clinical use.

In summary, this is a handy little desk reference that provides clear concise information in a very accessible format. Perhaps what I liked most, is that it reminds us that a person's experience of cancer does not follow a clinical course of a predictable statistical model. Its main purpose is to guide the oncology clinician in their therapeutic decision making, in order to tailor the intervention to the individual using a sound synthesis of good science, personal experience and common sense.

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The Molecular Basis of Cancer
3rd Edition

J Mendelsohn, PM Howley, MA Israel, JW Gray, CB Thompson
Saunders Elsevier (2008)
757 pages
RRP: $230.00

I am sure many of us have attended a talk where a molecular biologist puts up what looks like the wiring diagram of the flight deck of a jumbo, but in fact a cartoon of the various intracellular signaling pathways of a cancer cell. This is often done to portray the dazzling complexity of all the possible ways in which cell growth is regulated, how it can go wrong, as well as which pathways are or may be targets for new therapeutics. But it also provides a slightly unsettling moment when we realise that the more we learn, the less we seem to know. It is also often met with the uneasy smile we also use when confronted with complex mathematical formulae, one inspired by gratitude that we don’t have to know or understand the details to get on with our lives.

However, it is going to become increasingly difficult to be engaged in modern oncology practice without the rudiments of a molecular viewpoint of cancer cell behaviour. So it is a relief that a book like *The molecular basis of cancer* exists that allows us to delve in an accessible manner into the intricacies of the cell and how it may go wrong.

The book, now in its 3rd edition, is presented as 59 chapters within five sections that cover the breadth of our molecular understanding of cancer and how this may be applied in clinical practice. Since cancer is understood to be a genetic disorder, it is no surprise that the very first chapter sets the scene through an excellent summary written by the eminent Robert Weinberg. The subsequent chapters of section 1 further explore the way in which pathways are or may be targets for new therapeutics. But it also provides a slightly unsettling moment when we realise that the more we learn, the less we seem to know.

The chapters in this book do not attempt to be exhaustive about the topic they address, however instead provide sufficient information that fulfils the stated intent of the editors “…to describe the scientific underpinnings that will enable clinicians and other professionals who manage cancer patients to better understand the disease and its therapy”. Unfortunately, there are a few exceptions, such as the chapter on “Regulation of the cell cycle”, which is written in such a technically challenging manner that it is hard to reconcile that it fits the editors’ intent. But on the whole one may pick up this book and turn to any chapter at random and not find oneself hopelessly lost in jargon.

I would thoroughly recommend this book as a starting point for anyone interested in the molecular basis of cancer (a particularly apt title) and suggest it ought to be on the shelves of any person or organisation engaged in the treatment of cancer.

Nikolajs Zeps, St John of God Pathology, Wembley, Western Australia.
Churchill Livingstone Pocket Radiography and Medical Imaging Directory

C Gunn
Churchill Livingstone (2007)
424 pages
RRP: $75.00

The *Pocket Radiography and Medical Imaging Dictionary* would be a welcome addition for any person working in a medical imaging department. It is a user friendly book and contains a plethora of terms used by medical, nursing and therapy professionals and even has business and quality assurances terminology.

The dictionary gives a clear and concise understanding of terms that may be unfamiliar to the novice. These include ultrasound, photography, anatomy and physiology, dental imaging, osteology, magnetic resonance imaging and radionuclide imaging. It also provides other common use of terms in italics such as otitis media, which is also known as *glue ear*.

Illustrations and diagrams that assist in the understanding of terms are also included in the dictionary. The only criticism would be that ideally the author could have provided more diagnostic imaging examples of the norm and the abnormal to help facilitate the learning process for students. However, at the back of the dictionary there are two useful appendices, one of radionuclide applications and one of the most common medical abbreviations.

Overall, the dictionary is to be recommended to students and staff working in the imaging field as a quick reference guide.

*Carolyn Hook, Department of Radiation Oncology, Prince of Wales Hospital, Randwick, New South Wales.*
Supportive Care Framework: A Foundation for Person-Centred Care

MI Fitch, HB Porter & BD Page (Editors)
Pappin Communications Ontario (2008)
ISBN: 9780973807325
143 pages
RRP: $39.00

From the very beginning of this book the supportive care framework for cancer care is described as a useful tool in a range of settings, including service planning, education and research. A ‘something for everyone’ type claim, which in this case holds true. In essence, this well written and highly relevant book demonstrates how theory can be translated and used in practice. It consists of eight chapters (143 pages) written by 12 authors. The only non-Canadian author is Professor Sanchia Aranda from the Peter MacCallum Cancer Centre and University of Melbourne.

So now you are thinking, what is in this book for me? For those who have heard the term ‘supportive care’, but do not fully understand its meaning, the first chapter by Dr Fitch provides a concise definition and describes how the concept of a supportive care framework was developed. Some of its appeal and usefulness has to be attributed to its development by a range of health professionals involved in cancer care and its validation with patients and survivors. In simple terms supportive care “is an overarching concept to describe all the help cancer patients and their families may need beyond their medical, surgical or radiation interventions”.

Those involved in nursing education will be particularly interested in chapter two, which outlines how the supportive care framework was used to guide the development, delivery and evaluation of undergraduate nursing courses.

For readers with an interest in research there are several chapters that will appeal. Chapter three describes in some detail how the seven domains of the supportive care framework can be successfully measured in samples of patients with lung and gynaecological cancers and those receiving rapid response radiotherapy for palliation. This was achieved using an adapted version of the Supportive Care Needs Survey originally developed in Australia by Sanson-Fisher and colleagues (2000). Chapter four describes how the supportive care framework was used as the guiding framework to investigate the supportive care needs of parents of children with cancer and chapter six describes the usefulness of the framework when used to evaluate the effectiveness of community based oncology nurse-led supportive care programs.

For those in the more strategic positions in health care, chapters five, seven and eight are particularly relevant. Chapter five describes the highs and lows of an Australian cancer centre’s attempt to use the supportive care framework to improve supportive care service delivery. Chapter seven takes the supportive care framework outside cancer and discusses its applicability and relevance to patients who have had a stroke and their caregivers. The final chapter describes how the framework has informed policy in local, regional, provincial and national jurisdictions within Canada.

For those providing clinical care there is something relevant to practice in most of the chapters. But for me there is also an important reminder that patients cope with their situation in a variety of ways. Therefore, we must remember to discuss with patients and their family the different options for interventions, their desire for assistance and then determine together how best to provide the required assistance. While seemingly obvious to most of us, I believe this fact can easily be forgotten in the everyday business of providing care to patients with cancer.

While the text is dense, and in my view somewhat crowded, the content is useful and informative for a wide range of health professionals. I trust my grouping together of chapters according to specific interests is seen as it was meant: a guide for the ‘time short reader’ rather than a constraint.

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The Cancer Clock

S Missailidis (Editor)
John Wiley & Sons (2007)
ISBN: 9780470061527
300 pages
RRP: £27.50

The Cancer Clock is described in the preface as a reflection of the cancer experience. Cancer begins prior to abnormality being detected. As time progresses, cancer too progresses. Abnormalities become evident, leading to diagnosis. The proceeding path is similar to a ticking clock. Time moves on as the patient undergoes tests, biopsies, a number of treatments and further tests. Just as a clock continues to tick, cancer continues to progress onwards whether through treatments, ongoing follow-up or withdrawal from treatment.

Like the 12 numerals on a clock, this book has 12 chapters focusing on different aspects of cancer. It begins by looking at the socioeconomic and molecular contributors to cancer such as diet, alcohol and tobacco. Then the book moves on to metal ions and cancer, as well as genetics and cancer, followed by inflammation and cancer.

From here there is discussion on diagnosing cancer and various imaging technologies available. Next, information is provided on the various cancer treatments such as surgery and anti-cancer therapeutics and finally palliative care.

The book then changes focus and discusses physiotherapy and to a lesser extent, the contributions of other allied health professionals to cancer care. It concludes with a chapter on the emotional effects of cancer and psychosocial oncology.

A variety of experts have contributed to this book. They predominately work in the United Kingdom, Greece and Brazil, with two others from the United States and Germany.

An easy to follow index provides a quick reference to topics covered in each chapter. Occasionally a diagram may be too small to read the details, but the text usually provides these. Each chapter generally presents some history, current practice and research, as well as future developments.

The editor was aiming to capture a range of audiences. He believes books like this are often targeted at professionals in specific disciplines, only covering a specific aspect or treatment of cancer. He hopes this overview of cancer and treatment will be useful to students and health professionals who are undecided about the field in which to specialise. The editor also intends it to be useful to the general public wanting to know more about cancer, whether they themselves have cancer or are carers of people with cancer. However, the language used may be too technical for the lay person to understand. He also hopes it will be useful to health professionals specialising in specific fields of cancer treatment, wanting to increase their understanding of other cancer specialties.

This book does not claim to be an exhaustive reference of information, but a general overview of cancer. It does provide at the end of each chapter useful self assessment questions, an extensive list of references and suggested resources for more comprehensive information.

The Cancer Clock provides a good overview of cancer diagnosis and treatment, being a suitable starting point for those wishing to expand their knowledge in areas of cancer treatment with which they may not yet be familiar.

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