For decades, 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**

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**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, Robbin 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 sero-clearance 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 sero-clearance (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 ≥10^6 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 10^6, 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’.\textsuperscript{24} 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.\textsuperscript{25}

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).\textsuperscript{26}

Likewise, the incontrovertible link between ongoing viral replication and HCC development from an intervention, rather than prevention perspective, was evident from the IHIIT studies in hepatitis C and the Cirrhosis Asian Lamivudine Multicenter Studies alluded to earlier.\textsuperscript{15} 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.\textsuperscript{27-30}

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 aetiological 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.\textsuperscript{31} It, however, 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.\textsuperscript{32} 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.\textsuperscript{33,34} 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.\textsuperscript{35} 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