Recognising the Role of Infection: Preventing Liver Cancer in Special Populations

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Abstract

Hepatitis B virus is the second most important known human carcinogen after tobacco. Increasing prevalence of chronic viral hepatitis in Australia has resulted in rapidly rising liver cancer incidence. Prevalence of Hepatitis B virus, and consequently incidence of liver cancer, is highest in migrants born in Hepatitis B virus endemic areas, and in Aboriginal and Torres Strait Islander people. Often Hepatitis B virus is acquired at birth or in early childhood, when the likelihood of developing chronic infection is high. Globally the best preventative strategy for Hepatitis B virus associated liver cancer is universal infant vaccination, but vaccination in Australia will prevent a very small proportion of future liver cancer. Approximately 170,000 Australians live with chronic Hepatitis B virus infection. A comprehensive program of Hepatitis B virus management, including liver cancer surveillance and appropriate antiviral therapy, is very likely to be cost-effective as a cancer prevention program. Under-treatment of chronic Hepatitis B virus infection in Australia partly relates to the high proportion of affected people who are from culturally and linguistically diverse backgrounds, or are Aboriginal or Torres Strait Islander people. Health inequities and reduced access to appropriate diagnosis, treatment and care must be addressed as a matter of priority to address one of the fastest increasing causes of cancer death in Australians.

A number of chronic infections contribute to the burden of cancer in humans. Viruses including human papilloma virus (cervical cancer), Epstein Barr virus (nasopharyngeal carcinoma and some lymphomas), and bacteria including Helicobacter pylori (gastric cancer) cause human malignancy through a variety of mechanisms. It is estimated that approximately 8% of all cancers in Australia are caused by chronic infections.1

However, the hepatitis B (HBV) and hepatitis C (HCV) viruses, which cause chronic viral hepatitis, are responsible for more human cancer deaths than any other infectious disease. Primary liver cancer is the third most common cause of cancer death globally, with chronic viral hepatitis responsible for more than three quarters of these cancers.2,3 Chronic HBV infection alone has been estimated by the World Health Organisation (WHO) to be the tenth leading cause of death globally,4 and HBV as the second most important known human carcinogen, after tobacco.5

HCV causes liver cancer through chronic liver damage leading to progressive scarring and ultimately cirrhosis. However, HBV infection can cause liver cancer in a number of ways in addition to causing cirrhotic liver disease.6 HBV can be integrated into the host genome and lead to genetic instability; viral proteins such as HBx have been implicated in carcinogenesis; and some viral mutations have been associated with development of liver cancer.6,7 Finally, chronic HBV infection acts synergistically with exposure to dietary aflatoxin (a fungal toxin produced by aspergillus species, particularly in grains stored in warm humid conditions) to significantly increase the risk of liver cancer.7,8 Approximately 25% of people living with chronic HBV infection will develop cirrhosis and/or liver cancer.4

Australian context

Although primary liver cancer remains relatively uncommon in Australia, the increasing prevalence of chronic viral hepatitis in Australia over the last four decades has resulted in a rapidly rising incidence of liver cancer.4 There are now estimated to be 170,000 Australians living with chronic HBV infection, and 221,000 with chronic HCV infection,9 for a combined prevalence of approximately 2% of the population. As a consequence, liver cancer demonstrates the fastest increasing incidence, and (with melanoma) joint fastest increasing mortality of any cancer reported to Australian cancer registries.1 The increasing mortality is also related to the very low relative survival of people diagnosed with liver cancer,10 and to a significant problem with late diagnosis of chronic viral hepatitis, often only being made once the patient presents with decompensated cirrhosis or liver cancer, with limited ability for therapeutic intervention.11

The prevalence of chronic HBV infection in Australia is highly variable, with much higher prevalence noted in migrants born overseas in endemic areas (particularly in the Asia-Pacific and Sub-Saharan Africa), and also in Aboriginal and Torres Strait Islander people.12,13 These two groups constitute the majority of Australians living with chronic hepatitis B.14 This increased prevalence of HBV
infection translates into far higher liver cancer incidence and mortality in people born overseas in high prevalence regions, and in Aboriginal and Torres Strait Islander people, when compared to the rest of the Australian population.\textsuperscript{15,16}

As a result, both prevalence of chronic HBV,\textsuperscript{13,17} and incidence of liver cancer,\textsuperscript{9,10,18} demonstrate significant geographic clustering, related to the proportion of the population either born in high prevalence countries, or who are Aboriginal or Torres Strait Islander people (with a greater burden among rural and remote Indigenous people relative to those living in urban environments).\textsuperscript{12}

**Prevention of HBV-associated liver cancer related mortality**

**Vaccination against HBV**

Most people living with chronic HBV infection worldwide were infected at the time of birth through mother to child transmission, or through transmission from other close contacts with chronic HBV infection in the first years of life. This is because the risk of developing chronic infection is related to age at infection, ranging from 90\% among newborn infants to approximately 5\% among adolescents and adults.\textsuperscript{19} From a global perspective, the most effective method of preventing chronic HBV infection, and resultant liver cancer, is to vaccinate all infants against HBV infection, including the provision of a birth dose of vaccine (which is key to preventing transmission from mother to child at birth).\textsuperscript{20,21} This has been WHO policy since 2009,\textsuperscript{20} and although substantial progress has been made in improving coverage of infant hepatitis B vaccination in the last decade, the proportion of infants receiving timely birth dose vaccination remains suboptimal. The Western Pacific Region of the World Health Organisation, within which approximately half of all global HBV related deaths occur, adopted a regional target of reducing the prevalence of chronic HBV infection among 5 year-old children to less than 2\% by 2012.\textsuperscript{22} Twenty-seven countries, representing 87\% of the population of the region, are estimated to have achieved this target.\textsuperscript{22}

The time lag between infant vaccination and impact on liver cancer incidence will take decades to be fully realised, but early indications are available.\textsuperscript{21} The best example is Taiwan, previously a high HBV prevalence country. Universal infant vaccination commenced in Taiwan in July 1984, with significant reductions in liver cancer incidence in vaccinated age groups reported since. Up to June 2004, there was a three-fold drop in liver cancer risk in vaccine-eligible age groups, and where liver cancer was diagnosed in those born after universal vaccination was implemented, incomplete vaccination was associated with a 4.3-fold increase in risk of liver cancer.\textsuperscript{23} Similar direct evidence for the prevention of liver cancer through infant vaccination is expected from large field trials conducted in Qidong Province, China and in The Gambia in the next few years.\textsuperscript{21}

In low HBV prevalence countries like Australia, universal infant vaccination remains not only cost-effective, but cost saving to society.\textsuperscript{4,24} However, it must be recognised that more than 90\% of new cases of chronic HBV infection entering the population do so through migration, and not through incident infections acquired here progressing to chronicity.\textsuperscript{25} Thus universal infant hepatitis B infection in Australia will have minimal impact on future HCC incidence, with the exception of Aboriginal and Torres Strait Islander people, given the higher prevalence of chronic HBV infection contributing to high liver cancer mortality.\textsuperscript{16} Even though universal infant vaccination against HBV is cost saving in Australia, it may be even more cost-effective for Australia to support vaccination programs in high HBV prevalence countries contributing significant migrant flows into the population.\textsuperscript{25}

**Liver cancer surveillance for people living with chronic HBV infection**

Regular surveillance for liver cancer with six monthly ultrasound +/- serum alpha-foetoprotein measurement is another proven method for preventing liver cancer mortality in people living with chronic hepatitis B. The rationale for this surveillance is the early detection of liver cancer when intervention (such as surgical resection or liver transplant) may result in cure. International guidelines have established criteria for such surveillance among people living with HBV, based on cost-effectiveness considerations and risk of liver cancer.\textsuperscript{26} The indications for surveillance in these guidelines are shown in box 1.

**Box 1: Recommendations for liver cancer surveillance in people living with chronic hepatitis B infection (adapted from reference 26).**

- All patients with cirrhosis
- Asian males over 40 years age
- Asian females over 50 years age
- Africans over 20 years age
- Patients with a first degree family history of liver cancer

The survival benefit of liver cancer surveillance has been demonstrated in observational studies,\textsuperscript{27} and in a large Chinese randomised trial.\textsuperscript{28} However, this survival benefit comes at significant cost, and a recent Australian cost-effectiveness analysis suggested that liver cancer surveillance in isolation was not a cost-effective cancer prevention strategy.\textsuperscript{29}

**Antiviral treatment for chronic hepatitis B**

Another approach to preventing liver cancer in people living with chronic HBV infection is through treatment of HBV infection with specific antiviral agents. The central importance of HBV viral load in determining risk of progressive liver disease and incidence of liver cancer was demonstrated in the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL–HBV) study from Taiwan,\textsuperscript{30} with more recent analysis of this cohort demonstrating that reduction in viral loads over time led to reduced cancer incidence.\textsuperscript{31} However the REVEAL study was a natural history study, and extrapolation of the natural history of HBV infection
was not able to directly answer the question of whether treatment-induced reductions in HBV viral replication would lead to the same reduction in risk of liver cancer.

More direct evidence of the impact of HBV antiviral therapy on liver cancer incidence has recently become available. There is increasing evidence for the ability of treatment for chronic HBV infection to prevent liver cancer, with the most compelling evidence to date published in 2010.22 This systematic review of 21 studies demonstrated that, over a median four year follow-up, the risk of liver cancer in patients treated with antiviral therapy was less than half that of untreated patients (2.8% vs 6.4%, p=0.005). Furthermore, these results were achieved with less potent, more resistance prone antivirals than those which are standard of care currently.

The cost effectiveness of antiviral therapy for HBV as a cancer prevention intervention was assessed in the Australian context in the study mentioned previously.29 This study found that a comprehensive program of HBV management, including liver cancer surveillance where indicated, but also incorporating appropriate antiviral therapy for eligible patients, was very likely to be cost-effective in Australia. The estimated incremental cost-effectiveness ratio per quality adjusted life year was comparable with other, established pillars of cancer prevention policy in this country, such as breast, colon and cervical cancer screening. This reflects similar international evidence of the cost effectiveness of HBV screening alone, and screening with appropriate antiviral treatment.33-36

Given this evidence of clinical and public health effectiveness of cancer prevention through treatment and care of people living with HBV infection, what is the current uptake of this population health intervention?

Uptake of antiviral therapy

Of the estimated 170,000 Australians living with chronic HBV infection, less than 3% are estimated to be receiving antiviral therapy.14 Although it is difficult to establish the proportion of all those with chronic infection who are eligible for antiviral therapy and who could benefit, it is likely that approximately five times the number currently receiving treatment could benefit.37,38 Part of the reason for the marked under-treatment of people living with chronic HBV infection relates to the high proportion of these people who are migrants from culturally and linguistically diverse backgrounds, or Aboriginal or Torres Strait Islander people, both groups being subject to broader health inequities and reduced access to appropriate diagnosis, treatment and care.39

Clearly, strategies are needed to enhance access to comprehensive and appropriate health care for people living with HBV infection in Australia. A strategic approach to this question was outlined in 2010, in the National Hepatitis B Strategy 2010-2013.40 This strategy, endorsed by the Commonwealth and State/Territory health ministers, contains priorities for action and specific indicators to assess progress in addressing a primary determinant of the joint fastest increasing cause of cancer deaths among Australians.1 The five priority action areas outlined in the strategy are: building partnerships and strengthening community action; preventing hepatitis B transmission; optimising diagnosis and screening; clinical management of people with chronic hepatitis B; and developing health maintenance, care and support for people with hepatitis B.14

Without substantial involvement in education of, and partnership with affected communities, including Australians born overseas in HBV endemic areas, and Aboriginal and Torres Strait Islander people, together with clinical workforce development to address access to testing and antiviral treatment, the steadily rising burden of liver cancer mortality attributable to HBV infection will continue.14

Acknowledgements

BCC is supported by a Victor Hurley Medical Research Grant, Royal Melbourne Hospital.

References