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Critical review

Liver Cancer

Hepatitis B-related hepatocellular carcinoma

SY Wong[1], HW Hann[1,2]*

Abstract

Introduction

Hepatocellular carcinoma is one of the most deadly cancers in the world and has been found to be prevalent in hepatitis B virus endemic regions. The association of hepatitis B virus as a major factor in the development of hepatocellular carcinoma has been observed in the past. However, the mechanisms of hepatocarcinogenesis are not fully understood. Multiple studies have shown that treatment of hepatitis B with anti-viral therapy has led to the decreased incidence of hepatocellular carcinoma. More emerging data suggest that anti-viral therapy may also have a role in preventing the recurrence of hepatocellular carcinoma. The aim of this critical review was to discuss hepatitis B-related hepatocellular carcinoma.

Conclusion

The incidence of hepatitis B virus worldwide has overall decreased due to these preventive measures. However, hepatocellular carcinoma continues to be very prevalent and deadly. With further developments in more effective anti-viral therapy and worldwide implementation of vaccination programmes, it may be possible that hepatitis B virus and its associated hepatocellular carcinoma will be eradicated in the near future.

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Introduction

Liver cancer is the sixth most common malignant neoplasm in the world and the second leading cause of cancer death worldwide with an estimated 782,000 new liver cancer cases and 746,000 death during 2012[1]. Seventy to eighty-five per cent of the total liver cancer cases is hepatocellular carcinoma (HCC)[2]. Current data indicate that hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most significant hepatocarcinogens and these two viruses account for 78% (HBV 53%; HCV 25%) of the total liver cancer deaths in the world[2]. Although HCC is less common in the United States, it is perhaps the most prevalent cancer in Asia and West Africa where the prevalence of HBV infection is high. International variation in liver cancer rates is reflected by the different distribution of HBV and HCV infections. The vast majority of deaths from HCC occur in East Asia and Sub-Saharan Africa where HBV is prevalent, with China alone accounting for more than 50% of the total cases[1]. This paper discusses hepatitis B-related HCC.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

History of the hepatitis B virus

The discovery of HBV was made by Blumberg during his search for human polymorphisms. Blumberg's[3] work began with testing the sera of patients who had received a large number of blood transfusions for the development of antibodies to the proteins of the blood donors. In 1965, Blumberg discovered a new antigen in the blood of an Australian Aborigine and named it Australia antigen. This unknown antigen reacted with a possible antibody in the sera of haemophiliac patients. Blumberg's subsequent work linked this antigen to post-transfusion hepatitis[3,4]. Prince[5] independently identified the serum hepatitis antigen in patients with post-transfusion hepatitis and found that it was identical to the Australia antigen. Both of these represented the hepatitis B surface antigen (HBsAg). In 1970, Dane and his colleagues[1,6] identified the whole virus particle, termed the Dane particle, by electron microscopy. The HBsAg was found to be the envelope (surface) protein of the virus particle. The genome of the virus was sequenced by the work of Galibert et al.[7]. Using the HBsAg alone, Millman and Blumberg initiated the development of the hepatitis B vaccine, which was a plasma vaccine[3]. The vaccine was highly efficacious and reduced the incidence of infection by 92%[8]. In 1983, the vaccine became available and was designated as 'the first cancer vaccine' by the World Health Organisation (Figures 1 and 2). Later a recombinant vaccine replaced the plasma vaccine.

Pathogenesis of hepatitis B

The pathogenesis of HBV is mainly immune-mediated, not cytopathic, in that the host response to the virus and not the replication of the virus itself is responsible for hepatocellular injury[9]. Cytotoxic T-lymphocytes, in particular CD8 T cells,

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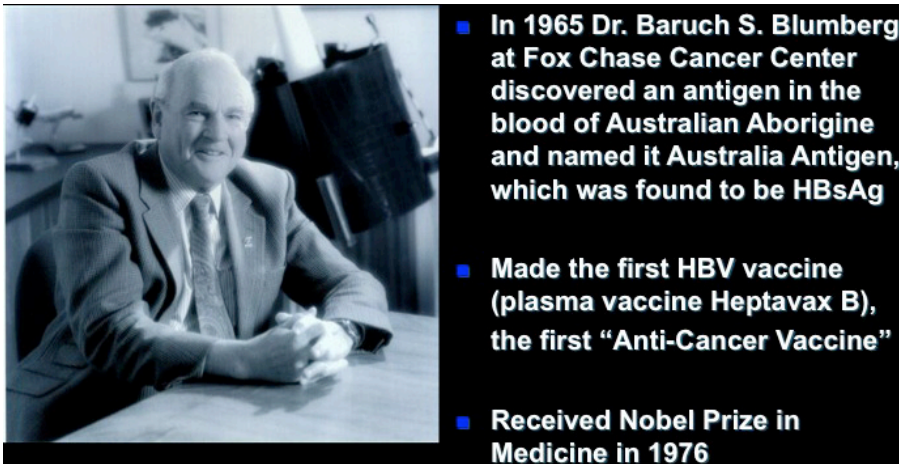

Figure 1: Discovery of hepatitis B virus(Philadelphia). HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

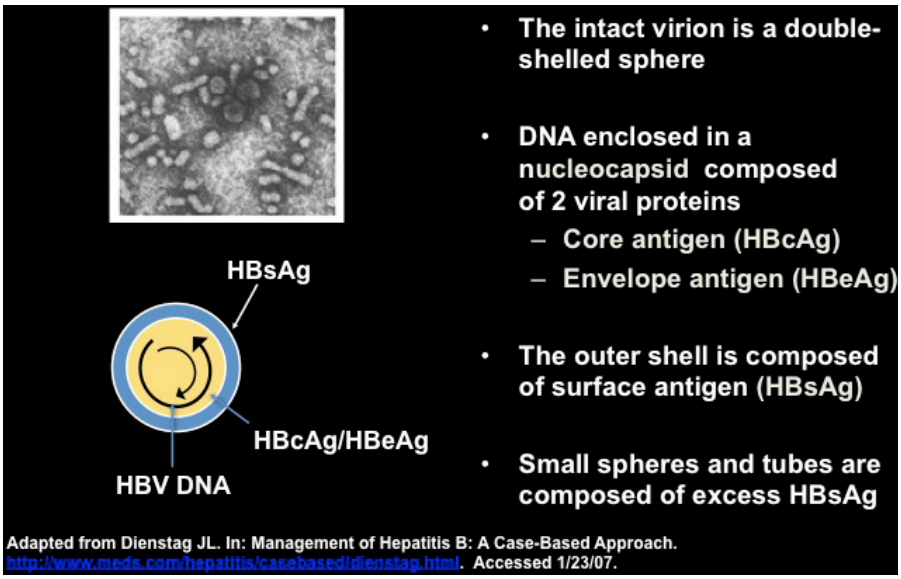

Figure 2: Electron microscopy of hepatitis B virus reveals multiple layers. DNA, deoxyribonucleic acid; HBcAg, hepatitis B core antigen; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

are thought to play the central role. Studies have shown that in acute, self-limiting HBV infection, the CD8 T cell response is strong compared with chronic hepatitis B where the response is weak[10]. Viral clearance from cytotoxic T-lymphocytes is thought to occur through direct lysis of infected hepatocytes but mainly by indirect injury with secretion of interferon gamma and tumour necrosis factor that inhibits HBV gene expression and replication in the remaining hepatocytes[9,10].

This immune response determines the clinical outcome of HBV infection. The majority of infections are self-limiting with 5% of patients developing chronic infection and 20% of those developing cirrhosis. The persistence of HBV is not completely understood and appears to be due to several factors affecting an inadequate immune response. Mutations of B and T cells, hepatitis B envelope antigen, HBsAg and HBV X protein may have a role in suppressing immune response[10]. An adequate early CD4 T cell response has also been found to be necessary to induce the appropriate CD8 T cell response for viral clearance[9]. Other studies have suggested that certain haplotypes of cytotoxic T-lymphocyte antigen 4, a gene responsible for inhibition of T cell responses, has been associated with virus persistence[11].

Hepatitis B and hepatocarcinogenesis

The link between HBV and HCC has been supported by multiple studies. Early studies from the 1950s showed a high prevalence of HCC in Africa that was associated with cirrhosis and an increased activity of the cirrhosis that was thought to be due to a viral hepatitis[12]. Beasley[13] in a long-term prospective study of 22,000 men in Taiwan found an increased incidence of HCC in carriers of HBsAg with a relative risk of 98. This observation suggested that HBV has a primary role in the aetiology of HCC. Progression of HBV infection is shown in Figure 3, although rarely patients can progress from chronic HBV to HCC without developing cirrhosis.

The serum HBV DNA levels itself is an important risk factor in the progression of chronic hepatitis B. A 12-year longitudinal prospective study by Chen et al.[14] indicated that serum HBV DNA level is associated with HCC development in a dose-dependent manner. An elevated serum HBV DNA level (≥10,000 copies/mL) was a strong independent predictor of HCC (Figure 4). Patients with HCC and high levels of HBV DNA also have a higher risk of recurrence and mortality compared with those with lower levels[15]. These findings suggest that HBV replication, with subsequent immune-mediated liver injuries, is the primary driving force for liver disease progression and development of HCC.

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Although the association of HBV and HCC is clear, the mechanism of hepatocarcinogenesis is not completely understood. Multiple factors such as HBV DNA integration and viral proteins may induce genetic alterations at different stages (Figure 5). Several studies have suggested that the integration of HBV DNA into the host DNA can lead to rearrangement of chromosome, deregulation and instability of gene expression contributing to oncogenesis[16–18]. The virus itself may also play a direct role via viral proteins. The HBx protein, a viral regulator gene, has been implicated to alter host gene expression[19]. The HBx protein has multiple pathways affecting cellular growth including the ability to inhibit p53-mediated apoptosis and cause hypermethylation of DNA leading to malignancy[10,16,20].

Chronic hepatocyte injury with inflammation, cytokine release and fibrosis may also play a role in carcinogenesis. In 1987, Popper et al.[21] showed that in animal liver histology infected with woodchuck hepatitis virus, there was a gradual progression from normal to neoplastic nodules to HCC. Another study with transgenic mice with chronic hepatitis B with T cell response and no evidence of liver disease developed HCC after several months[22]. It is thought that this immune-mediated hepatocellular injury is an oncogenic factor in HBV similar to other chronic liver disease states such as HCV, alcoholism and haemochromatosis that are also risk factors for HCC[10].

Occult hepatitis B virus and hepatocellular carcinoma

Occult hepatitis B (OHB) has been well described in the literature to be associated with HCC[23,24]. It is defined as the presence of HBV DNA in liver tissue and/or serum with a negative HBsAg. Although these patients have spontaneous seroclearance, they are still at risk for HCC[25]. Interestingly, several studies have shown a higher

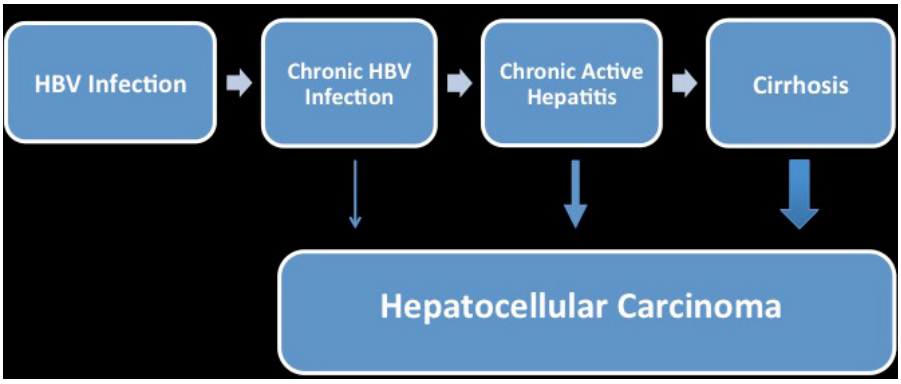

Figure 3: Progression of HBV infection. HBV, hepatitis B virus.

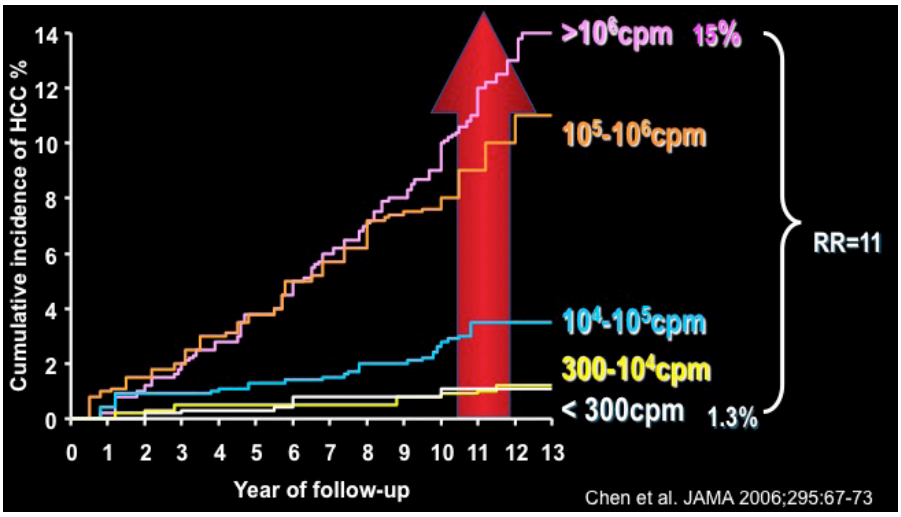

Figure 4: Progression of HBV infection to HCC related to baseline HBV DNA level. HBV, hepatitis B virus; HCC, hepatocellular carcinoma; DNA, deoxyribonucleic acid.

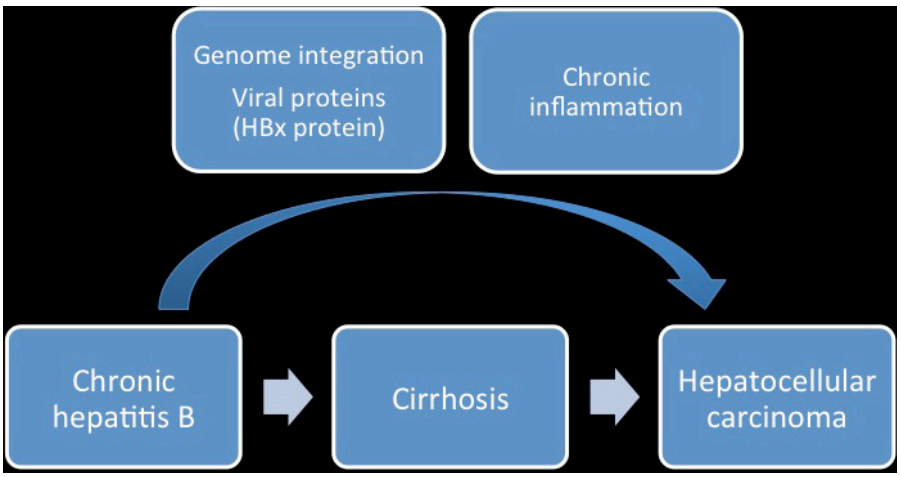

Figure 5: HBV-induced hepatocarcinogenesis. HBV, hepatitis B virus.

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prevalence of OHB in HCC patients with HCV infection when compared with patients with only HCV infection. Thus, OHB may be an important risk factor for HCC in patients with chronic hepatitis C and suggests the synergistic interaction between OHB and HCV infection leading to liver damage and promoting the development of HCC[26–30].

As awareness of the association with OHB and HCC is increasing, the diagnosis of OHB still presents to be a challenge. A high clinical suspicion and a sensitive HBV DNA detection method are both important for the diagnosis and surveillance of HCC[31].

Prevention of hepatitis B virus and hepatocellular carcinoma

Primary prevention of HBV-related HCC is HBV vaccination for uninfected individuals. Vaccination has proven to be efficacious and safe[8]. A prime example is the nationwide vaccination programme in Taiwan that began in 1984. They have shown that primary prevention is not only effective but important by significantly decreasing the annual incidence of HCC and rate of mortality[32]. As of 2006, according to World Health Organisation recommendations to prevent and control global scale HBV infection and its sequelae, 168 countries have implemented universal vaccination programmes[33].

Secondary prevention of hepatocellular carcinoma and its recurrence: role of anti-viral therapy

Secondary prevention of HBV-related HCC is anti-viral therapy for those already infected with HBV. The current mainstay of treatment for HBV is anti-viral therapy that targets the viral reverse transcriptase (Figure 6). Several anti-HBV drugs, mostly nucleos(t)ide analogues that exert inhibitory effect on reverse transcriptase and suppress viral replication, have become available: lamivudine (LAM) appeared first in 1998 followed by adefovir (2002), entecavir (2005), telbivudine (2006) and tenofovir (2008). Injection forms including interferon and pegylated interferon are also available but less commonly used due to side effects (Figure 7).

LAM has been the most studied anti-viral drug for its efficacy in preventing HCC. The largest and most significant study exploring whether or not suppression of viral replication might decrease the incidence of HCC was a randomised, controlled study of LAM versus placebo in patients with advanced chronic HBV and high serum levels of HBV DNA[34]. The primary outcome of the study was progression

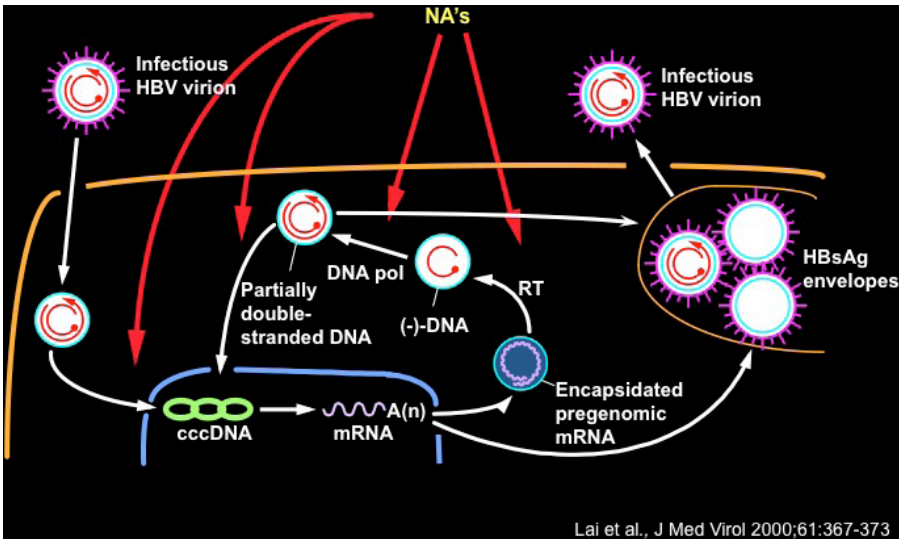

Figure 6: HBV replication: inhibition by nucleoside analogue. HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; mRNA, messenger ribonucleic acid; RT, reverse transcriptase; DNA, deoxyribonucleic acid.

Generic Name	Trade Name	Date Approved for Hepatitis B
Interferons		
Interferon alfa-2b, recombinant	INTRON® A	1992
Peginterferon alfa-2a	PEGASYS®	2005
Nucleosides/Nucleotides		
Lamivudine	EPIVIR-HBV®	1998
Adefovir dipivoxil	HEPSERA®	2002
Entecavir	BARACLUDE®	2005
Telbivudine	TYZEKA®	2006
Tenofovir DF	VIREAD®	2008

Figure 7: FDA approved therapies for chronic HBV. HBV, hepatitis B virus.

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of liver disease and the development of HCC. The study was halted early because there was a distinct benefit for the group on LAM treatment compared with the placebo group. A United States multicentre trial of patients with chronic HBV with decompensated cirrhosis also showed significant improvement of cirrhosis with LAM treatment[35]. A number of other studies have had similar results and a meta-analysis of those studies showed that LAM therapy had a significant reduction in the incidence of HCC among chronic HBV patients compared with no treatment[36–38].

Less is currently known about the new anti-viral drugs but more data will emerge as they are more commonly used. As LAM has had success with preventing HBV-related HCC, the new anti-viral drugs are likely as effective. One retrospective study has shown that patients treated with entecavir had a significant lower rate of incidence of HCC at 5 years compared with control groups at 3.7% versus 13.7%, respectively ($P < 0.001$)[39].

Prevention of hepatocellular carcinoma recurrence

With the advent of anti-viral therapy, it is now possible to reduce inflammation, regress cirrhosis and reduce the incidence of HCC in patients with chronic hepatitis B. Treatment with nucleos(t)ide analogues may prevent *de novo* primary tumours and further progression of liver disease. The carcinogenic process by sustained viraemia with active viral replication has long been considered to be the result of the viral DNA insertion in or near proto-oncogenes, tumour suppressor genes or regulatory element of cellular DNA or the integration of viral DNA that leads to the production of the transactivator protein HBxAg and binding to P53 tumour suppressor genes. It appears that continuous viral replication is the key risk factor for recurrence and/or progression of hepatocarcinogenesis. Therefore, successful control of HBV replication is of utmost importance in prevention of tumour recurrence and improvement of survival.

Recent data have supported this role for anti-viral therapy in preventing HBV-related HCC recurrence. Retrospective studies have shown improvement of liver function in patients who have received concomitant anti-viral therapy after curative liver resection and local tumour ablation[40,41]. Several studies further support the benefit of anti-viral therapy in this group of patients by showing a reduction in HCC recurrence[42–46]. A meta-analysis of these studies showed a decrease in risk of HCC recurrence by 41% in the anti-viral treatment group as well as lower liver-related and overall mortality[47]. The longest survivors of those who benefit from anti-viral therapy following initial tumour ablation have reached over 12 years of tumour-free survival[48].

This novel treatment strategy may offer a significant alternative to relieve the current graft shortage. Due to the availability of effective and potent treatment options for HBV infection, there has been a decrease in the proportion of annual liver transplant performed for this indication[49].

Conclusion

Since the discovery of HBV in 1965, there have been major developments in the management of HBV. Beginning from the identification of the virus, followed by elucidation of its association with HCC, there is now successful primary and secondary prevention of HCC with HBV vaccination and anti-viral therapy. Anti-viral therapy may also have an emerging role not only in preventing HCC but also in preventing HCC recurrence following initial tumour ablation. The incidence of HBV worldwide has overall decreased due to these preventive measures. However, HCC continues to be very prevalent and deadly. With further developments in more effective anti-viral therapy and worldwide implementation of vaccination programmes, it may be possible that HBV and its associated HCC will be eradicated in the near future.

Conflict of Interest

Hie-Won Hann receives research grants from Bristol Myers-Squibb and Gilead Sciences.

Abbreviations list

HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LAM, lamivudine; OHB, occult hepatitis B.

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