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## Prevention of hepatocellular carcinoma in chronic viral hepatitis B and C infection

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### Abstract

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, with the majority of cases associated with persistent infection from hepatitis B virus (HBV) or hepatitis C virus (HCV). Natural history studies have identified risk factors associated with HCC development among chronic HBV and HCV infection. High-risk infected individuals can now be identified by the usage of risk predictive scores. Vaccination plays a central role in the prevention of HBV-related HCC. Treatment of chronic HBV infection, especially by nucleoside analogue therapy, could also reduce the risk of HBV-related HCC. Concerning HCV infection, besides the advocacy of universal precautions to reduce the rate of infection, pegylated interferon and ribavirin could also reduce the risk of HCV-related HCC among those achieving a sustained virologic response. Recently there has been mounting evidence on the role of chemopreventive agents in reducing HBV- and HCV-related

HCC. The continued advances in the understanding of the molecular pathogenesis of HCC would hold promise in preventing this highly lethal cancer.

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**Key words:** Hepatitis B virus; Hepatitis C virus; Hepatocellular carcinoma; Vaccination; Prevention

**Core tip:** Hepatocellular carcinoma (HCC), with the majority of cases associated with infection from hepatitis B virus (HBV) or hepatitis C virus (HCV), is the most common primary liver tumor. We introduced risk factors and risk predictive scores associated with HCC development among chronic HBV and HCV infection for its early diagnose and prevention. Vaccination plays a central role in the prevention of HBV-related HCC. Treatment of chronic HBV infection, especially by nucleoside analogue therapy, could reduce the risk of HBV-related HCC. Pegylated interferon and ribavirin could reduce the risk of HCV-related HCC. Chemopreventive agents in reducing HBV- and HCV-related HCC were also discussed.

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### INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver tumor, and represents the third leading cause of cancer death worldwide. It is the fifth most common cancer in men and seventh in women, accounting for 7% of all cancers<sup>[1]</sup>. Hepatocarcinogenesis

is a multistep process mainly associated with persistent infection with hepatitis B virus (HBV) or hepatitis C virus (HCV)<sup>[2]</sup>, which affects more than 350 and 170 million individuals respectively worldwide. HCC is highly prevalent in regions endemic for chronic HBV and HCV infection<sup>[3]</sup>.

The incidence of HCC continues to increase worldwide, with a unique geographic, age, and sex distribution. The most important risk factor associated with HCC is liver cirrhosis, which is again predominantly caused by chronic HBV or HCV infection. Primary prevention in the form of HBV vaccination has led to a significant decrease in HBV-related HCC, and the antiviral therapy for chronic HBV and HCV infection also reduce the incidence of HBV- and HCV-related HCC<sup>[4]</sup>.

China has one of the highest carrier rates of HBV in the world, reaching nearly 10% of the general population. The disease burden of HBV infection and HCC is also believed to be among the world's largest, and that of HCV infection is likely to be substantial as well<sup>[5]</sup>.

## RISK PREDICTION

An important component of HCC prevention is the identification of high-risk HBV- and HCV-infected individuals, who will benefit from various chemopreventive therapies discussed below. Several natural history studies have identified important risk factors for HCC among patients with chronic hepatitis B (CHB) and chronic hepatitis C (CHC), with risk predictive scores also designed for practical usage.

### **Risk factors and prediction scores: CHB**

A study evaluating the relationship between serum HBV DNA level and risk of HCC demonstrated that the incidence of HCC among CHB patients increased with serum HBV DNA level. Elevated serum HBV DNA level ( $\geq 2000$  IU/mL) is a strong risk predictor of HCC independent of hepatitis B e antigen (HBeAg)-positivity, serum alanine aminotransferase levels, and liver cirrhosis<sup>[6]</sup>. Subsequent studies also showed patients with moderate levels of serum HBV DNA (60-2000 IU/mL), when compared to individuals not infected with HBV, still had a substantial increased risk of HCC and liver-related death<sup>[7]</sup>.

Besides serum HBV DNA levels, other host- and viral-related factors could also predispose to HCC. A meta-analysis found HBeAg-positive non-cirrhotic patients, when compared to HBeAg-positive cirrhotic patients, had a significantly reduced HCC risk after antiviral therapy<sup>[8]</sup>. HBV genotype also plays a role; HBV genotype C is closely associated with HCC especially in cirrhotic patients aged  $> 50$  years<sup>[9]</sup>. An observation study in Hong Kong also found genotype C HBV infection to be an independent risk factor for HCC development when compared with genotype B<sup>[10]</sup>.

Several clinical scoring systems have been developed for the prediction of HCC in CHB, as depicted in Table

1. These scoring systems are based on the longitudinal follow-up of treatment-naïve CHB patients for 5 years or more. Two common parameters used are age and serum HBV DNA levels. Other parameters used include gender, serum alanine aminotransferase levels, serum albumin, HBeAg status, presence of cirrhosis and presence of core promoter mutations<sup>[11-15]</sup>. Risk prediction is now also possible for CHB patients undergoing nucleoside analogue (NA) therapy. A recent study investigated the risk of HCC among a large population of CHB patients treated with entecavir. Older age and presence of cirrhosis were independently associated with HCC in the entire cohort; advanced age and hypoalbuminemia were associated with HCC in patients without cirrhosis. The risk scores accurately predict which patients with CHB treated with entecavir would have a higher chance of developing HCC<sup>[13]</sup>.

### **Risk factors: CHC**

When compared to CHB, fewer clinical scoring systems have been developed for the prediction of HCV-related HCC. These are as depicted in Table 1. The majority of HCV-related HCC develop in patients with established cirrhosis. In a study investigating prognostic risk factors for HCV-related HCC, among 913 patients followed up for at least 3 years, age, male sex, portal hypertension, hepatic inflammation, and iron storage were significant risk factors for HCV-related HCC<sup>[16]</sup>. In a meta-analysis involving HCV-infected persons, sustained virologic response (SVR) was associated with reduced risk for HCC<sup>[17]</sup>. Even transient virologic control among patients with subsequent relapse after treatment, was associated with a lower risk of the development of HCC<sup>[18]</sup>.

Prediction of HCV-related HCC may be enhanced by the development of related markers. Signal transducer and activator of transcription 1 and phosphatase and tensin homolog are associated with early growth response protein 1 signaling, which potentially promotes angiogenesis, fibrogenesis, and tumorigenesis in HCV-related HCC. This approach has potential for the early diagnosis and possible prevention of HCC. The corresponding serum markers found can help to predict high-risk groups for HCC<sup>[19]</sup>.

### **Host factors**

HCC is more common in HBV carriers with a family history of HCC. In a study of 5238 HBV carriers (553 with HCC and 4685 without HCC), the risk of HCC was significantly higher in those with a family history of HCC, with a multivariate-adjusted rate ratio for HCC of 2.41 compared with HBV carriers without a family history<sup>[20]</sup>. If the carriers had two or more affected family members, the risk was even higher with the ratio increased to 5.55. It is therefore recommended to begin surveillance in adults once a family history of HCC has been identified. A recently published study also included the presence of family history, besides traditional viral-related parameters as a component for risk prediction<sup>[15]</sup>.

**Table 1 Risk factors and prediction scores for hepatitis B virus- and hepatitis C virus-related hepatocellular carcinoma**

Risk factors	HBV-related HCC	HCV-related HCC
Increased age	√ <sup>[11-15]</sup>	√ <sup>[16]</sup>
Male gender	√ <sup>[11,12,15]</sup>	√ <sup>[16]</sup>
Increased serum HBV DNA levels	√ <sup>[11,12,14,15]</sup>	
Presence of cirrhosis	√ <sup>[12-14]</sup>	
Increased serum ALT concentration	√ <sup>[11,15]</sup>	
HBeAg positivity	√ <sup>[11,15]</sup>	
Presence of core promoter mutations	√ <sup>[12]</sup>	
Presence of virological remission after 24 mo	√ <sup>[13]</sup>	
Presence of hypoalbuminemia	√ <sup>[13]</sup>	
Decreased serum albumin	√ <sup>[14]</sup>	
Increased serum bilirubin	√ <sup>[14]</sup>	
HBV genotype C	√ <sup>[15]</sup>	
Presence of HBsAg	√ <sup>[15]</sup>	
Family history of HCC	√ <sup>[15]</sup>	
Presence of portal hypertension		√ <sup>[16]</sup>
Presence of hepatic inflammation		√ <sup>[16]</sup>
Increased iron storage levels		√ <sup>[16]</sup>
Presence of sustained virological response		√ <sup>[17]</sup>
Presence of complete viral suppression		√ <sup>[17]</sup>

HBV: Hepatitis B virus; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; HBsAg: Hepatitis B surface antigen; ALT: Alanine aminotransferase.

## PREVENTION OF HBV-RELATED HCC

HBV infection is the major cause of HCC. Vaccination against HBV is instrumental in the prevention of HCC, and is recommended for all newborns and individuals who are at increased risk for infection. Studies in Taiwan, where universal HBV vaccination was introduced in 1984, have documented a significant decrease in the incidence of HCC in both children and adolescents after the introduction of HBV vaccination as discussed below<sup>[21,22]</sup>.

In patients already chronically infected with HBV, antiviral treatment could prevent disease progression to cirrhosis or HCC. Additionally, periodic surveillance using ultrasonography and serum  $\alpha$ -fetoprotein every 3-6 mo for earlier detection of HCC is also important so that curative treatments (*e.g.*, hepatic resection) can be offered<sup>[23]</sup>.

The antiviral interventions and chemopreventive methods to prevent HBV-related HCC are summarized in Tables 2 and 3 respectively.

### Vaccination

Vaccination plays a central role in HBV prevention strategies worldwide, and a decline in the incidence and prevalence of HBV infection following the introduction of universal HBV vaccination programs has been observed in many countries<sup>[24]</sup>. Control and significant reduction in incidence of new HBV infections as well as HCC have been repeatedly reported in countries in East Asia and Africa<sup>[25]</sup>.

A study of the incidence of HCC in children in

**Table 2 Antiviral interventions for prevention of hepatitis B virus- and hepatitis C virus-related hepatocellular carcinoma**

Antiviral interventions	HBV-related HCC	HCV-related HCC
IFN: IFN- $\alpha$	+/- <sup>[28,29]</sup>	√ <sup>[46]</sup>
Pegylated IFN		√ <sup>[47]</sup>
NAs: Lamivudine	√ <sup>[36]</sup>	
Entecavir	√ <sup>[37,38]</sup>	
Ribavirin		√ <sup>[47]</sup>
Vaccination	√ <sup>[21,22]</sup>	
Screening of blood product	√ <sup>[27]</sup>	√ <sup>[27]</sup>

HBV: Hepatitis B virus; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; IFN: Interferon; NA: Nucleotide analogs.

**Table 3 Chemopreventive agents for hepatitis B virus- and hepatitis C virus-related hepatocellular carcinoma**

Chemopreventive agents	HBV-related HCC	HCV-related HCC
Statins	√ <sup>[42]</sup>	
Antidiabetic medications	√ <sup>[42]</sup>	√ <sup>[42]</sup>
Aspirin	√ <sup>[41,53]</sup>	√ <sup>[53]</sup>
Propranolol		√ <sup>[51]</sup>
FASN		√ <sup>[52]</sup>
Dietary agents: Coffee	√ <sup>[54]</sup>	√ <sup>[54]</sup>
Vitamin E	√ <sup>[54]</sup>	√ <sup>[54]</sup>
Vitamin D		√ <sup>[50]</sup>
Fish oil (n-3 PUFA)	√ <sup>[55-57]</sup>	√ <sup>[55-57]</sup>
Phytochemicals: Resveratrol	√ <sup>[43]</sup>	
EGb	√ <sup>[44]</sup>	

HBV: Hepatitis B virus; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; PUFA: Polyunsaturated fatty acid; FASN: Fatty acid synthase; EGb: Extract of ginkgo biloba leaf.

Taiwan from 1981 to 1994 showed that the average annual incidence of HCC in children 6-14 years of age declined from 0.70 per 100000 children (between 1981 and 1986), to 0.57 per 100000 (between 1986 and 1990), and to 0.36 per 100000 (between 1990 and 1994). The corresponding rates of mortality from HCC had also decreased. The incidence of HCC in children 6-9 years of age declined from 0.52 per 100000 (for those born between 1974 and 1984) to 0.13 per 100000 (for those born between 1984 and 1986). Since the institution of Taiwan's program of universal HBV vaccination from 1984, the incidence of HCC in children has declined dramatically<sup>[22]</sup>. The risk of developing HCC for vaccinated cohorts was statistically significantly associated with incomplete HBV vaccination. The prevention of HCC by HBV vaccination extends from childhood to early adulthood. Failure to prevent HCC results mostly from unsuccessful control of HBV infection by highly infectious mothers<sup>[21]</sup>.

### Antiviral therapy: Interferon and NAs

DNA integration of hepatitis viruses alters the function of critical genes, promoting malignant transformation of virus-infected liver cells<sup>[26]</sup>. Treatment of CHB infection aims to control viral replication and prevent the development of complications. There are currently seven

drugs available for the treatment of CHB, five NAs and two interferon (IFN)-based therapies. Long-term treatment with NA is often required, and the decision to treat is based on the clinical assessment including the phase of CHB infection and the presence and extent of liver damage<sup>[24]</sup>.

Concerning IFN therapy, a study involving 641 biopsy-proven CHB patients treated with IFN- $\alpha$ 2b were followed up for a median period of 113 months. Although HCC occurred less frequently in biochemical responders than in non-responders, virologic response is not associated with decrease in HCC development. Poor biochemical response, as well as older age and a higher serum AFP level remain independent predisposing factors of HCC development in CHB patients treated with IFN- $\alpha$ <sup>[27]</sup>. In addition, a study about the long-term effects of IFN- $\alpha$  in Chinese patients showed that IFN- $\alpha$  was of no long-term benefit in inducing HBeAg seroconversion or in the prevention of HCC and other cirrhosis-related complications<sup>[28]</sup>.

On the contrary, nearly all the studies showed that NA is able to reduce HCC<sup>[29]</sup>. Many randomized controlled trials showed that lamivudine, one of the earliest oral NAs for antiviral therapy in HBV infection, can reduce disease progression in HBV-related cirrhosis and HCC<sup>[29-34]</sup>. A recent study followed up 293 CHB patients without HCC who were treated with lamivudine for a mean duration of 67.6 mo. In cirrhotic patients, the attainment of maintained viral response (defined as HBV-DNA levels of  $< 4.0$  log copies/mL) during lamivudine treatment was revealed to reduce the risk of HCC development. No significant reduction was observed in the non-cirrhotic group<sup>[35]</sup>.

Entecavir is a potent NA with high genetic barrier to resistance, and prolonged treatment results in regression of fibrosis, hence is currently recommended as first-line antiviral therapy for CHB. In a study of CHB patients with liver cirrhosis, entecavir therapy reduces the risks of hepatic complications, HCC, liver-related and all-cause mortality of CHB patients with liver cirrhosis in 5 years, particularly among those who had sustained viral suppression<sup>[36]</sup>. In another multicentre cohort study, 372 entecavir-treated patients followed up for a mean duration of 114 mo were investigated. Clinical events were defined as development of HCC, hepatic decompensation or death. Virological response to entecavir (HBV DNA  $< 80$  IU/mL) was associated with a lower probability of disease progression in patients with cirrhosis, suggesting that complete viral suppression is essential for NA treatment, especially in patients with cirrhosis<sup>[37]</sup>.

A meta-analysis investigating the effects of IFN or NA on the risk of developing HCC in CHB patients shows that, the reduction in HCC is more significant among patients with early cirrhosis than among non-cirrhotic patients. Five studies ( $n = 2289$ ) compared patients treated by NA with control. The risk of HCC after treatment is reduced by 78%. HBeAg-positive patients have a more significant reduction in HCC risk with treatment.

Patients without cirrhosis benefit more from NA than those with cirrhosis, although resistance to NA blunts the benefit of treatment<sup>[8]</sup>.

In summary, while the evidence of the efficacy of IFN in preventing HBV-related HCC remains conflicting, there is a gradual accumulation of evidence supporting the positive effect of NA on reducing HBV-related HCC.

### Chemoprevention

The observation that anti-platelet therapy inhibits or delays immune-mediated hepatocarcinogenesis suggests that platelets may be one of the key players in the pathogenesis of HBV-associated liver cancer and that immune-mediated necroinflammatory reactions may be an important cause of malignant transformation during chronic hepatitis<sup>[38]</sup>. A prospective study on 300504 patients with chronic liver disease showed that aspirin users had statistically significant reduced risks of incidence of HCC and mortality due to chronic liver disease compared to those who did not use aspirin<sup>[39]</sup>. Further studies are needed to confirm this finding and clarify its underlying mechanism.

A study concerning the association between the use of statins in HBV-infected patients and the risk of HCC shows that statin use may reduce the risk for HCC in HBV-infected patients in a dose-dependent manner<sup>[40]</sup>. This may be related to the effect of statins in reducing fatty change in the liver, and requires future validation studies to confirm the findings.

There are also several investigational drugs which could have potential for chemoprevention against HBV-related HCC. Resveratrol is a natural polyphenol that has beneficial effects across various disease models. In an animal study investigating the efficacy of resveratrol against HBV-related HCC in HBV X protein (HBx) transgenic mice, resveratrol had a pleiotropic effect on HBx transgenic mice in terms of the down-regulation of lipogenesis, the promotion of transient liver regeneration, and the stimulation of antioxidant activity. Furthermore, at later precancerous stages, resveratrol delayed HBx-mediated hepatocarcinogenesis and reduced HCC incidence from 80% to 15%. The potential mechanisms for resveratrol on HCC prevention might be associated with its effects of stimulating the activity of Ampk and SirT1, and downregulating the expression of the lipogenic genes, Srebp1-c and peroxisome proliferator-activated receptor gamma. The decrease in Srebp1-c further downregulates the expression of its target genes, Acc and Fas<sup>[41]</sup>. Several other studies demonstrated resveratrol downregulates cyclin D1 as well as p38 MAP kinase, suppresses Akt and Pak1 expression and activity, and increases ERK activity, suggesting that growth inhibitory activity of resveratrol is associated with the downregulation of cell proliferation and survival pathways, and sensitization to apoptosis<sup>[42]</sup>. Resveratrol also acts as an inhibitor for sirtuins. Overexpression of SIRT1 in cancer tissue has been demonstrated to promote mitotic entry of liver cells, cell growth and proliferation, and inhibit apoptosis related to the PTEN/PI3K/AKT signaling pathway<sup>[43,44]</sup>.

A study in China suggested that extract of Ginkgo Biloba leaf (EGb) could reduce the incidence of the HCC with HBV transgenic mice. The reason may be that EGb could reduce liver HBx, p53, Bcl-2 protein expression in HBV transgenic mice<sup>[45]</sup>. These investigational products would need confirmation in human clinical trials in the future.

## PREVENTION OF HCC RELATED TO HCV

With the commencement of successful vaccination programs against HBV, CHC is now emerging as an important cause of chronic liver diseases. The drive of carcinogenesis during HCV infection is thought to result from the interactions of viral proteins with host cell proteins. Thus, the induction of liver mutation phenotypes through the expression of HCV proteins provides a key mechanism for the development of HCV-associated HCC. With the emerging importance of CHC, mechanisms of HCV-associated hepatocellular carcinogenesis should be clarified to provide insight into advanced therapeutic and preventive approaches to decrease the incidence and mortality of HCC<sup>[46]</sup>.

Strategies aimed at eliminating the virus may provide opportunities for effective prevention of the development of HCC. The first step is to encourage universal precautions to reduce infections transmitted *via* different modalities *e.g.*, iatrogenic routes, sharing of intravenous needles etc and further implementation of universal screening of donated blood products. Concerning therapy for HCV, pegylated IFN plus ribavirin therapy is effective at reducing the risk of HCC in patients with CHC who achieve SVR.

The effects of antiviral therapy and chemopreventive measures in preventing HCC are mentioned in Tables 2 and 3 respectively.

### Antiviral therapy: IFN and ribavirin

Current strategies to reduce HCC incidence in CHC patients include prevention of cirrhosis development by avoiding metabolic, pharmacological, or social factors associated with accelerated progression of liver disease, or through virus eradication by IFN-based treatments. Moreover, a successful antiviral treatment has positive impact on the rate of HCC development in patients who are already cirrhotic<sup>[1]</sup>.

Combination of pegylated IFN and ribavirin therapy is recommended for antiviral therapy worldwide, and is effective in reducing the rate of recurrence of HCV-associated HCC after curative resection or transplantation<sup>[47]</sup>. The pooling of data from the literature suggests a preventive effect of antiviral therapy on HCC development in patients with HCV-related cirrhosis, but the preventive effect is limited to those achieving SVR<sup>[48]</sup>. However, some HCV mutations, such as the amino acid substitution M91L, are associated with treatment failure and a poor prognosis<sup>[47]</sup>.

There is a recent study of the effect of pegylated IFN and ribavirin treatment of CHC on the incidence

of HCC. After a median observation period of 3.6 years, a significantly lower rate of HCC incidence was noted in patients achieving SVR when compared to non-virological responders. A similarly lower rate of HCC incidence was noted among cirrhotic patients achieving SVR (18.9%) when compared to cirrhotic non-virological responders (39.4%)<sup>[18]</sup>.

A meta-analysis study has been performed recently with the data sources from MEDLINE, EMBASE, CINAHL, the Cochrane Library, Web of Science, and the Database of Abstracts of Reviews and Effectiveness from inception through 2012, to systematically review observational studies to determine the association between response to HCV therapy and development of HCC among persons at any stage of fibrosis and those with advanced liver disease. Among HCV-infected persons, there is moderate-quality evidence demonstrating SVR to be associated with reduced risk for HCC; SVR after treatment among HCV-infected persons at any stage of fibrosis is associated with reduced HCC<sup>[17]</sup>.

### Chemoprevention

Vitamin D insufficiency has been associated with the occurrence of various types of cancer. A recent study aimed to determine the relationship between genetic determinants of vitamin D serum levels and the risk of developing HCV-related HCC. The data suggest a relatively weak but functionally relevant role for vitamin D in the prevention of HCV-related hepatocarcinogenesis<sup>[49]</sup>.

Propranolol has antioxidant, anti-inflammatory, anti-angiogenic properties and antitumoral effects and therefore is potentially active in the prevention of HCC. A retrospective long-term observational study suggests that propranolol treatment might decrease HCC occurrence in patients with HCV cirrhosis<sup>[50]</sup>. These findings also need to be verified by prospective clinical trials.

Understanding the interplay between the viral and cellular components of the HCV replication complex could provide new insight for prevention of the progression of HCV-associated HCC. Fatty acid synthase (FASN) is found to interact with NS5B. FASN may thereby serve as a target for the treatment of HCV infection and the prevention of HCV-associated HCC progression<sup>[51]</sup>. Thus, understanding the molecular mechanisms, which are implicated in the development of HCC during the course of HCV infection, may help to design a general therapeutic protocol for the treatment and for its prevention.

## PREVENTION OF HCC RELATED TO HBV AND HCV COINFECTION

HBV and HCV coinfection is not uncommon with an estimated 7-20 million infected individuals worldwide<sup>[52]</sup>. A community-based prospective cohort study evaluating HCC development in HBV and HCV co-infected subjects found the hazard ratios (HRs) of HBV monoinfection, HCV monoinfection, and HBV/HCV coinfection were 17.1, 10.4 and 115.0, respectively. Different geno-

types and multiplicative synergistic effect of HBV and HCV coinfection on HCC risk was observed. Infection with HCV genotype 1 (HR = 29.7) and mixed infection with genotype 1 and 2 (HR = 68.7) significantly elevated HCC risk, much higher than HBV infection. The effect of different HCV genotypes and the multiplicative synergistic effect of HBV/HCV coinfection on HCC risk underline the need for comprehensive identification of hepatitis infection status in order to prevent and control HCC<sup>[53]</sup>.

Pegylated interferon-alpha plus ribavirin should be recommended in patients with dominant HCV replication. However, HBV rebound may occur after elimination of HCV with anti-HBV treatment required. These therapeutic measures may contribute to the prevention of HCC this special group of patients<sup>[52]</sup>.

## OTHER POTENTIAL CHEMOPREVENTIVE METHODS

The use of aspirin, but not nonsteroidal anti-inflammatory drugs, is associated with a decreased risk of HCC and death from chronic liver disease in the National Institutes of Health-AARP Diet and Health Study of patients between the ages of 50 and 71 years<sup>[39]</sup>. However this study does not provide information on the HBV and HCV status of its participants, and would need confirmation by future studies specifically for the HBV- and HCV-infected population.

More recent data have suggested dietary factors, including increased intake of coffee<sup>[54]</sup>, unsaturated fatty acids and fish to be protective against HCC. Subjects with known HBV or HCV status, and subjects who were anti-HCV and/or hepatitis B surface antigen positive were analysed. Consumption of n-3 polyunsaturated fatty acid (PUFA)-rich fish or n-3 PUFAs, particularly eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid, appears to protect against the development of HCC, even among subjects with HBV and/or HCV infection<sup>[55]</sup>, probably through dampening the inflammation in the liver and decreasing formation of tumor necrosis factor (TNF)- $\alpha$ , and through simultaneously inhibition of COX-2 and beta-catenin<sup>[56,57]</sup>. The findings also point to a potential anticancer role for the n-3 PUFA-derived lipid mediators 18-HEPE and 17-HDHA, which can down-regulate the important proinflammatory and proliferative factor TNF- $\alpha$ .

## CONCLUSION

Clinical experts evaluated ten previously identified dimensions of HCC control: clinical education; risk assessment; HBV strategy; HCV strategy; life-style risk factors; national statistics; funding for screening; funding for treatment; political awareness; and public awareness. Of these strategies, the most significant needs in regional efforts to control HCC are political awareness, public awareness, and life-style risk factors<sup>[58]</sup>.

HCC is a challenging malignancy of global importance. As HCC is strongly associated with chronic viral hepatitis, prevention against the infection is crucial for prevention against HCC. Vaccination against HBV in the newborns and early childhood is highly effective to lower infection rates substantially. For HCV, universal precautions when dealing with human blood, education on high-risk behaviours and screening programs for blood donors can reduce infection rates. Although prevention and treatment of CHB and CHC have been improved within the last decades even in high-risk countries, further effective and sustainable reduction of these infections is still needed<sup>[26]</sup>.

Antiviral therapies for CHB and CHC, while important, can only reduce but not completely eliminate HCC. Improvement in identification of infected persons, accessibility of care and affordability of treatment are needed for antiviral therapy to have a major impact on the global incidence of HCC<sup>[59]</sup>. Further advances in our understanding of the molecular pathogenesis of HCC hold promise in improving the diagnosis and treatment of this highly lethal cancer<sup>[4]</sup>.

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