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Review article: the prevention of hepatitis B-related hepatocellular carcinoma

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Summary

Background: Ample evidence indicates an aetiological association of persistent hepatitis B virus (HBV) infection with hepatocellular carcinoma (HCC). Several viral, host and external risk factors for the development of HBV-related HCC have been documented.

Aims: To summarise and discuss the risk stratification and the preventive strategies of HBV-related HCC.

Methods: Recent published studies identified from PubMed were comprehensively reviewed. The key words included chronic hepatitis B, HBV, hepatocellular carcinoma, prevention and antiviral therapy.

Results: The incidence of HCC is extremely high in HBV hyperendemic areas. For HBV patients left untreated, significant risk factors for HCC include male gender, aging, advanced hepatic fibrosis, persistent serum transaminase elevation, specific HBV entry receptor (NTCP) genotype, PM2.5 exposure, HBeAg positivity, HBV genotype C/D/F, high proportion of core promoter mutation, pre-S deletion, high serum levels of HBV DNA and HBsAg as well as co-infection with HCV, HDV and HIV. Primary prevention of HBV-related HCC can be achieved through universal HBV vaccination and anti-viral prophylaxis for high viraemic mothers. The goal of secondary prevention has been reached by effective anti-viral therapy to reduce the risk of HCC development in chronic hepatitis B patients. However, whether HCC is prevented or delayed deserves further examination. Finally, several studies confirmed the tertiary preventive effect of anti-viral therapy in reducing risk of HCC recurrence after curative therapies.

Conclusions: Through the strategies of three-level prevention, the global burden of HBV-related HCC should decline over time and even be eliminated in conjunction with HBV cure.

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1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common tumour worldwide and the second most common cause of cancer-related death in the world.[1] The incidence rates of HCC widely vary in different geographic areas, from the low endemicity area, such as Northern Europe and United States, to the high endemicity area, such as Far East and Southeast Asia.[2-4] The aetiologies of HCC include hepatitis B virus (HBV) or hepatitis C virus infection, the presence of cirrhosis, haemochromatosis, alpha-1 antitrypsin deficiency, aflatoxin B1 exposure, non-alcoholic fatty liver disease and alcohol liver disease.[5-9] Among these causes, persistent HBV infection is one of the most important causative agents, especially in Asia and Africa.[10,11] Previous epidemiologic studies revealed that HBsAg carriers had a higher risk of HCC compared to HBsAg-negative controls.[10,11] These findings indicated an aetiological association of persistent HBV infection with HCC development. In addition, observations concerning the natural history of chronic HBV infection showed that patients with chronic HBV infection have a high cumulative lifetime risk of adverse outcomes, including cirrhosis, end-stage liver disease, hepatic decompensation and HCC.[10]

Considering HBV infection as an aetiology of HCC, identification of risk factors for the development of HCC in HBV carriers is important for the prevention of liver cancer. In this review article, the risk stratification of HBV-related HCC and the preventive strategies of HBV-related HCC will be summarised and discussed.

2 | AETIOLOGICAL ASSOCIATION AND RISK STRATIFICATION OF HBV-RELATED HCC

Epidemiologically, the incidence of HCC is extremely high in HBV hyperendemic areas.[4] Since early 1980s, several studies revealed that the relative risk of HCC is higher in HBsAg carriers compared to HBsAg seronegative populations.[11-13] Molecular studies also showed the integration of HBV DNA into the host genome to cause genomic instability, which may lead to hepatocarcinogenesis.[14-16] In addition, persistent hepatic inflammation through the interactions between HBV and immune cells may also alter the expression of host genes and then induce HCC.[17] Therefore, the causal relationship between chronic HBV infection and HCC has been firmly established.

Several population-based cohort studies reported the viral biomarkers associated with the risk of HCC development in patients with chronic HBV infection left untreated. In an early long-term follow-up study of adult patients with chronic HBV infection, positivity of HBeAg was strongly associated with increasing risk of HCC. The relative risk of HCC was 60 as compared with HBsAg-negative population.[13] A recent study focusing on molecular mechanisms revealed that HBeAg positivity may contribute to HCC development by reducing the transcriptional activity of p53.[18] Among virus-derived quantitative markers, serum HBV DNA level was associated with increasing the risk of HCC in a dose-response relationship. The relative risk increased at the cut-off value of 2000 IU/mL [hazard ratio (HR): 2.3; $P = 0.02$].[19] Similar to HBV DNA level, levels of serum HBsAg were also associated with HCC development, especially in patients with low viral load (HBV DNA level <2000 IU/mL). Of particular note is the HCC risk significantly increased with the HBsAg level over 1000 IU/mL in HBeAg-negative patients with low viraemia.[20]

Growing evidence suggests that HBV genotypes and genome mutations correlate with an increased HCC risk in untreated HBV patients. Among 10 genotypes of HBV, genotypes C, D and F was associated with an increased risk of HCC than other genotypes.[20-28] With regard to the role of naturally occurring HBV genome mutations in the carcinogenesis, both qualitative and quantitative core promoter mutations are confirmed to be associated with an increased risk of HCC.[27-29] The pre-S deletion mutations also play a critical role in hepatocarcinogenesis. These deletion mutations may induce defective immunity against HBV.[30] The accumulation of in-frame pre-S2 mutant large surface protein inhibits hepatocyte DNA double-strand break repair and is associated with HCC tumourigenesis.[31,32] On the other hand, the presence of truncated pre-S/S protein has the function of transcriptional transactivator.[33,34] Such truncated pre-S/S protein may increase ER stress response as well as apoptosis, follow by the increase in hepatocyte proliferation and turnover, and the decrease in tumour suppressor gene expression. These results suggested that truncated pre-S/S mutation could contribute to the hepatocarcinogenesis.[35,36]

In the clinical practice, several risk stratification models which incorporate host and viral factors can help clinicians predict the risk of HCC development in patients with chronic HBV infection (Table 1).[37-41] In patients with multiple risk factors for HBV-related HCC, including male gender, ageing, advanced hepatic fibrosis, persistent serum transaminase elevation, specific HBV entry receptor (NTCP) genotype, PM2.5 exposure, positivity of HBeAg, HBV genotype C/D/F, high proportion of core promoter mutation, pre-S deletion mutation, high serum levels of HBV DNA and HBsAg as well as co-infection with HCV, HDV and HIV, a close follow-up for HCC surveillance is required. Among patients with a low HCC risk, such as female, younger age, negativity of HBeAg, HBV genotype A/B, low serum levels of HBV DNA and HBsAg, a follow-up with regular interval is still advised.[42] However, all of the patients with chronic HBV infection should receive the evaluation for the indications of anti-HBV treatment. Anti-viral therapy of individual patients should be based on the recommendations of the international therapeutic guidelines.[43-45]

The global prevalence of non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH)/metabolic syndrome-associated end-stage liver disease and HCC has been growing in recent years.[46] The superimposed NAFLD in HBV carriers is an important issue in HBV endemic area. In a recent long-term follow-up study of Taiwanese with chronic HBV infection, metabolic risk factors were associated with an increased risk of HCC. HBV carriers with multiple metabolic risk factors had significantly higher risk of

TABLE 1 Summary of current predicting models of hepatitis B virus-related hepatocellular carcinoma development

	CU-HCC[37]	GAG-HCC[38]	REACH-B[39]	LSM-HCC[40]	PAGE-B[41]
Authors	Wong et al	Yuen et al	Yang et al	Wong et al	Papatheodoridis et al
Developed area	Hong Kong	Hong Kong	Taiwan	Hong Kong	Europe
Number of patients	1005	820	3584	1035	1325
Including cirrhosis	Yes	Yes	No	Yes	Yes
Components of model	Age	Age	Age	Age	Age
	Albumin	Male	Male	Albumin	Male
	Bilirubin	BCP mutation	ALT	HBV DNA	Platelet
	Cirrhosis	Cirrhosis	HBeAg-positive	LS value	
	HBV DNA	HBV DNA	HBV DNA		
Risk score					
Low	<5	<100	≤5	<11	≤9
Medium	5-20		6-11		10-17
High	>20	≥100	≥12	≥11	≥18
Accuracy for prediction of hepatocellular carcinoma	5-year AUROC: 0.76	5-year AUROC: 0.88	5-year AUROC: 0.796	3-year AUROC: 0.83	5-year cumulative probability of HCC
	10-year AUROC: 0.78	10-year AUROC: 0.89	10-year AUROC: 0.769	5-year AUROC: 0.83	Low risk: 0% Medium risk: 3% High risk: 17%

ALT, alanine aminotransferase; AUROC, area under receiver operating characteristic; BCP, basal core promoter; LS, liver stiffness.

HCC than those without metabolic risk factors (adjusted hazard ratio: 5.06; 95% CI: 2.23-11.47).[47] Accordingly, NAFLD/NASH/metabolic syndrome-related HCC will be a distinct disease entity in HBV endemic area in the future.

3 | PREVENTION OF HBV-RELATED HCC

Preventive strategies of HBV-related HCC can be divided into primary, secondary and tertiary prevention. The goal of primary prevention is preventing susceptible individuals from acute HBV infection. Secondary prevention will focus on providing effective treatment to control precancerous or cancerous processes in patients with chronic HBV infection. Tertiary prevention is to provide effective treatment to reduce HCC recurrence in HBV patients who received curative HCC therapy (Figure 1).

4 | PRIMARY PREVENTION

Hepatitis B vaccination is the most cost-effective measure of primary prevention of HBV-related HCC. For HBV, maternal or vertical transmission during the perinatal period and horizontal transmission in early life are the major transmission routes.[10] In Taiwan, a country hyperendemic for HBV infection, 40% of HBV patients were born to HBsAg-positive mothers and 85%-95% of newborns with HBV exposure became persistent HBV infection.[48] In 2015, universal infant HBV vaccination has been implemented in 180 countries worldwide.[49] Among these countries, Taiwan is the first one to launch a nationwide universal hepatitis B vaccination programme since 1984.[50] In Taiwan, hepatitis B vaccines are administered in 3 doses to all infants. The schedules are first dose at birth with the second dose given 1 month after the first dose. Finally, the third dose was given 6 months after the first dose. For infants born to HBeAg-positive carrier mothers, additional hepatitis B immunoglobulin (HBIG) will be administered within 24 hours of birth.[51] With successful implementation, a coverage rate of hepatitis B vaccination as high as 97% was reached in 2004. The HBV infection rate (anti-HBc positivity) decreased from 38% to 4.6% in children.[52] The HBsAg seropositive rate in infants and children remarkably declined up to 90% in 2012.[51] Similarly, the reduction in HBsAg positivity in children was also observed in other countries after the implementation of universal hepatitis B immunisation.[53] In addition to prevent HBV infection of infants, hepatitis B vaccination also reduced liver cancer in children, teenagers and young adults.[54,55] After the implementation of HBV vaccination programme in Taiwan, the incidence of HCC in children decreased from 0.92 per 100 000 in the unvaccinated cohort to 0.23 per 100 000 in the vaccinated birth cohorts.[55] A population-based analysis from Taiwan Cancer Registry revealed that the changes in incidence rates and trends of HCC stratified by age group were obvious during 2003-2011. A slight increasing annual incidence (1.3%) was observed for elderly people, in contrast to annual incidence decreasing (16.6%) for children. Of particular note, the incidence rate of HCC in children decreased to zero since 2011.[56]

These encouraging data from Taiwan and other countries provide the convincing evidence that universal HBV vaccination notably reduces HBsAg prevalence and HCC incidence in vaccinated subjects (Figure 2). Furthermore, HBV-related HCC can be primarily

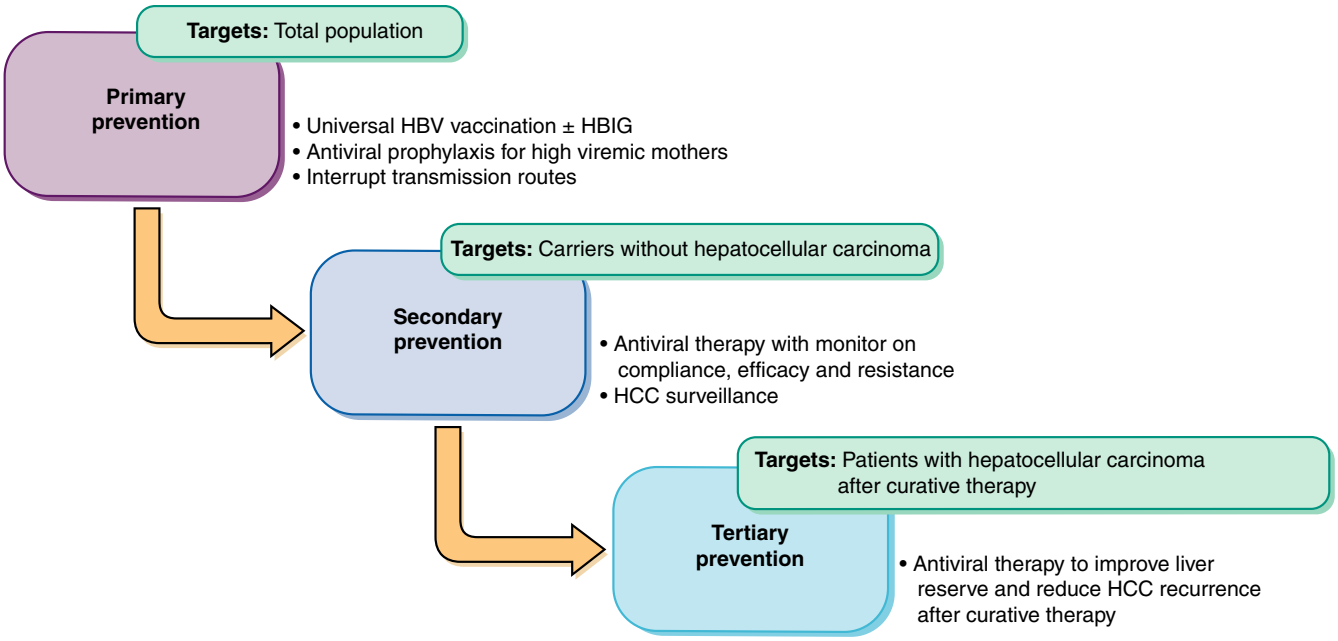

FIGURE 1 Preventive strategies of hepatitis B-related hepatocellular carcinoma

prevented by HBV vaccination and hepatitis B vaccine is indeed the first cancer preventive vaccine in the human history.[53]

In addition to vertical transmission, it is essential to prevent horizontal transmission for persons at risk of acquiring HBV infection. Appropriate information about safe sex, provision of means for prevention and HBV vaccination are effective measures to reduce the risk of HBV infection in people who inject drugs (PWID), homosexual men, HIV carriers and sex workers.[49]

Despite effective HBV vaccination could reduce HCC incidence in vaccinated individuals, HBV-related HCC still occurs sporadically. A long-term follow-up study for 3.8 million vaccinated children in Taiwan showed that among vaccinees, the risk predictors of residual HCC included maternal HBsAg seropositive only, both maternal HBsAg and HBeAg seropositivity and incomplete immunisation with HBIG or vaccine.[57] Taken together, maternal HBeAg positivity with incomplete hepatitis B immunisation may increase the risk of mother-to-child transmission (MTCT) of HBV. It is known that administration of HBIG is important for newborns of HBeAg-positive mothers. However, the challenge of current immunisation programme is the timing of HBIG administration. An analysis of in US HBIG/vaccine trial revealed that there was a trend towards a higher incidence with a longer interval of HBIG given after birth.[48] It is thus advised that HBIG should be given as soon as possible after birth, ideally within 12 hours after birth for infants born to HBeAg-positive carrier mothers. Another challenge is the immunoprophylaxis failure due to HBeAg-positive mothers with a high viral load. There were striking differences between maternal low and high levels of HBV DNA in predicting the rates of MTCT (0.9% in maternal HBV DNA levels of 5 $\log_{10}$ copies per mL vs 27.7% in maternal HBV DNA levels of 9 $\log_{10}$ copies per mL).[58] To enhance the blocking rate of

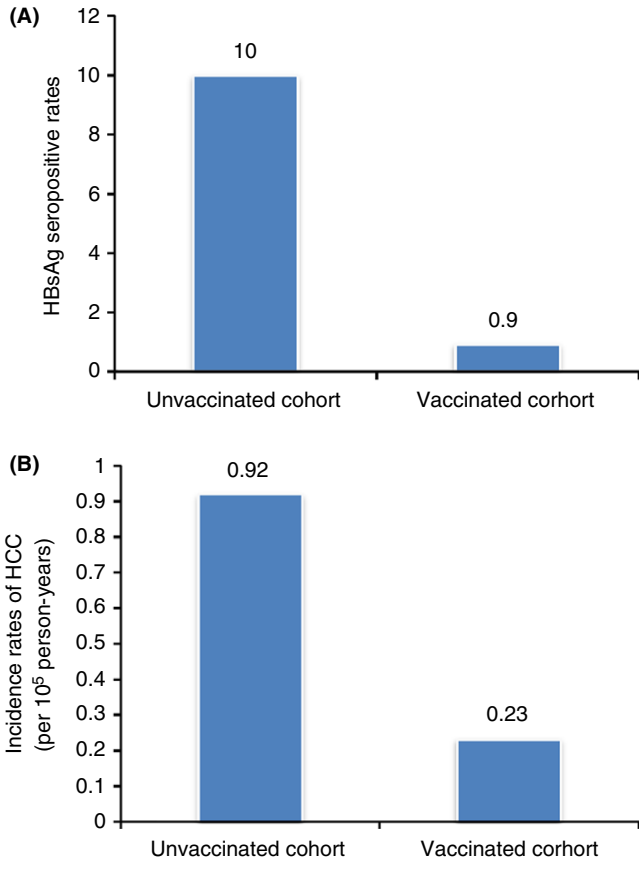

FIGURE 2 The HBsAg seropositive rate (A) and incidence rate of hepatocellular carcinoma (B) for children born before and after the launch of universal hepatitis B vaccination programme in Taiwan (modified from Ni et al[51] and Chang et al[55])

MTCT, anti-viral therapy in mid- or late pregnancy to interrupt MTCT has been suggested. A recent prospective study in Taiwan enrolled 118 HBeAg-positive pregnant women with high HBV DNA levels. Tenofovir disoproxil fumarate (TDF) 300 mg daily was prescribed from 30 to 32 weeks of gestation until 1 month postpartum. Compared to the mothers without anti-viral prophylaxis, the mothers received TDF had lower rates of infant HBsAg positivity at 6 months old (1.54% vs. 10.71%, $P = 0.0481$).[59] Furthermore, a randomised, controlled trial from China was reported recently. A total of 200 HBeAg-positive mothers with high HBV DNA level (>200 000 IU/mL) were randomised to receive TDF 300 mg daily from 30 to 32 weeks of gestation until postpartum week 4 or without TDF. At postpartum week 28, the rate of infant HBsAg positivity was significantly lower in the TDF group than in the control group (0 vs 7%, $P = 0.01$).[60]

The encouraging data imply that anti-viral prophylaxis in combination with immunoprophylaxis for HBeAg-positive mothers could decrease the rate of HBsAg positivity in their infants and may completely interrupt MTCT of HBV. However, several unresolved issues of HBV vaccination need further clarification. First, occult HBV infection after vaccination has been reported. In a prospective birth cohort study from China, HBV DNA was positive in 25% of HBsAg-negative and anti-HBs–positive neonates at 12 months of age. The first vaccine dose after 6 hours of birth was associated with the occurrence of occult HBV infection.[61] Thus, timely vaccination may reduce occult HBV infection following vaccination. Second, infants with vaccine escape mutants (S-gene mutations, such as G145R, P120S and P127S) infection have been reported despite previous vaccination.[62,63] The prevalence and prevention strategy of vaccine escape mutants should be investigated. Finally, the optimal timing to start anti-viral therapy and treatment duration for HBV viraemic mothers remain debatable. Recently, a meta-analysis demonstrated that any kind of NA in the third trimester of pregnancy has profound HBV suppression to reduce MTCT in HBV viraemic mothers.[64] The treatment duration for HBV viraemic mothers is unknown. As the safety of anti-viral therapy for infants during breastfeeding has not been well studied, current guideline suggested to discontinue anti-viral therapy at birth to 3 months postpartum.[43-45] For severe maternal disease, such as acute hepatitis flare or cirrhosis, treatment should be based on recommendations for nonpregnant women.[43]

5 | SECONDARY PREVENTION

Through long-term and profound viral suppression with NA, we can improve liver necroinflammation and regress hepatic fibrosis to prevent liver disease progression from chronic hepatitis to cirrhosis and eventually HCC.[65,66] Currently, 8 anti-viral agents are globally approved for the treatment of CHB, including standard interferon-α (IFN-α) or pegylated interferon-α (PEG-IFN-α) and 6 nucleos(t)ide analogues (NAs), including lamivudine (LAM), telbivudine (LdT), entecavir (ETV), adefovir dipivoxil (ADV), TDF and tenofovir alafenamide.[43-45,67] Current published data of anti-viral agents to prevent HCC development among CHB patients are summarised in Table 2.[68-76]

A finite duration of PEG-IFN-α provides durable host immune control over HBV and increases HBeAg/HBsAg loss or seroconversion over time in patients who respond to PEG-IFN-α therapy.[77] An earlier randomised control study showed that CHB patients with IFN therapy had lower incidence of HCC than untreated patients (1.5% vs. 12%, $P = 0.013$).[78] Furthermore, 3 meta-analyses also reported that IFN therapy reduced the risk of cirrhosis, cirrhotic complications and HCC incidence by 40%-50%.[69-71]

Regarding NAs, the Cirrhosis Asian Lamivudine Multicentre study first provided the evidence that LAM therapy was associated with a lower risk of HCC development and disease progression (HR: 0.49 and 0.45, respectively).[79] For the NAs with low genetic barrier to drug resistance (LAM and ADV), two meta-analyses indicated that the incidence of long-term complications (including decompensated cirrhosis, CHB-related death and HBV-related HCC) in patients receiving LAM or ADV treatment was reduced by 74%-78% compared to without treatment.[68,72] However, the risk of HCC remained higher in patients with resistance-related virological breakthrough than those with sustained virological response.[80] In a retrospective study, ETV-induced virological response was associated with a reduced risk of HCC in patients with prior LAM- or ADV-resistant mutants.[81]

Subsequent Asian studies further demonstrated the effect of NAs with high potency as well as minimal drug resistance (ETV and TDF) in the reduction in HBV-related HCC. A propensity score matching study from Japan revealed that CHB patients with ETV therapy had significantly lower 5-year cumulative HCC incidence than control group (3.7% vs. 13.7%, $P < 0.001$). ETV reduced 63% of HCC development.[74] In Hong Kong, compared to historical untreated cirrhotic patients, ETV-treated patients had significantly lower risks of HCC (HR: 0.55; 95% CI 0.31-0.99; $P = 0.049$).[73] In a large hospital-based cohort study in Taiwan, Cirrhosis Taiwanese Entecavir Multicenter (C-TEAM) study, 503 cirrhotic patients in the control group and 1123 in the ETV group were enrolled. ETV treatment was associated with 60% reduction in HCC risk (adjusted HR: 0.40, 95% CI: 0.28-0.57) in cirrhosis patients.[75] The protective effect of NAs in the development of HCC was also confirmed in a nationwide population-based study in Taiwan. CHB patients treated with NAs had a significantly lower 7-year incidence of HCC than patients without NAs treatment (7.32% vs. 22.7%, $P < 0.001$). After adjusting for competing mortality and other confounding factors, NAs treatment was associated with a reduced risk of HCC (adjusted HR: 0.37, 95% CI, 0.34-0.39; $P < .001$).[76] Furthermore, through the national healthcare database in Taiwan and excluded patients with LAM, ADV or LdT treatment, a total of 65 426 patients receiving ETV or TDF with a median follow-up of 25 (12.1-35.6) months were included in the study. The HCC annual incidence decreased with an adjusted incidence rate ratio of 0.73 (95% CI, 0.66-0.80) per yearly interval.[82] A long-term follow-up study for Caucasian CHB patients receiving ETV/TDF for more than 1 year was reported recently. The yearly HCC incidence rate significantly declined in patients with cirrhosis within and after the 5 years of follow-up (3.22% vs. 1.57%, $P = 0.039$).[83]

TABLE 2 Summary of published studies of anti-viral agents to prevent hepatocellular carcinoma development among chronic hepatitis B patients

Authors (published year)	Study design	No. of studies Anti-viral agent	Patients number Treated vs. Controls	Relative risk/risk difference (95% CI)	*P* value
Sung et al[68] (2008)	Meta-analysis	12 IFN	1292 vs. 1458	0.66 (0.48-0.89)	0.006
Sung et al[68] (2008)	Meta-analysis	5 NA	1267 vs. 1022	0.22 (0.10-0.50)	0.0003
Miyake et al[69] (2009)	Meta-analysis	8 IFN	553 vs 750	5.0% (9.4-0.5)	0.028
Yang et al[70] (2009)	Meta-analysis	11 IFN	1006 vs 1076	0.59 (0.43-0.81)	0.001
Wong et al[71] (2010)[a]	Meta-analysis	11 IFN	975 vs 1147	0.55 (0.43-0.70)	<0.001
Zhang et al[72] (2011)[a]	Meta-analysis	6 NA	2035 vs 1609	0.26 (0.15-0.47)	<0.001
Wong et al[73] (2013)	Retrospective, prospective cohort study	NA	482 vs 69 (cirrhosis patients)	0.55 (0.31-0.99)	0.049
Hosaka et al[74] (2013)	Retrospective nationwide cohort study with propensity score matching	NA	316 vs 316	0.37 (0.15-0.91)	0.03
Su et al[75] (2016)	Retrospective, prospective cohort study	NA	1315 vs 503 (cirrhosis patients)	0.40 (0.28-0.57)	<0.001
Wu et al[76] (2014)	Retrospective nationwide cohort study with propensity score matching	NA	21 595 vs 21 595	0.37 (0.34-0.39)	<0.001

IFN, interferon-based therapy; NA, nucleos(t)ide analogues.
[a]The outcomes include cirrhotic complications, HCC incidence and liver-related mortality.

In the natural history of CHB, the HCC risk is associated with high HBsAg level in CHB patients with low viraemia.[20] Previous studies showed that interferon was more effective than NAs for HBsAg decline.[84] A cohort study compared the HCC risk in CHB patients treated with PEG-IFN or NAs. The patients with PEG-IFN treatment had a lower HCC incidence than the ETV-treated patients ($P = 0.011$).[85] Therefore, the HBV DNA suppression and reduction in HBsAg may be complementary to each other in the prevention of HBV-related HCC.

Although effective anti-viral therapy may reduce the risk of HCC development in patients with chronic HBV infection, the challenges ahead include the presence of persistent intrahepatic cccDNA and a high viral relapse rate after discontinuation of NAs. Thus, even the treated patients remain at risk of HCC. New treatment strategies to cure CHB are urgently required.[86,87] In addition, whether HCC is prevented or delayed in cirrhotic patients with long-term NA therapy deserves further examinations.[88,89]

6 | TERTIARY PREVENTION

High recurrence is one of the major causes of unfavourable prognosis for HBV-related HCC patients. The cumulative recurrence rates of early-stage HCC at 5 years has been up to 75% after curative treatment with surgical resection or local ablation therapy.[90,91] Therefore, tertiary prevention is a clear clinical need for HBV-related HCC after curative treatment.[92,93]

Pioneering prospective randomised controlled studies for HBV-related HCC patients after curative treatment revealed that patients with adjuvant IFN therapy had decreased recurrence rate and improved overall survival than those without.[94,95] However, another randomised controlled trial conducted in Taiwan showed that adjuvant IFN did not reduce the post-operative recurrence of HBV-related HCC.[96] Furthermore, a meta-analysis also revealed that adjuvant IFN therapy following curative treatment of HCC cannot reduce early or late HCC recurrence.[97] Therefore, the effect of interferon-based therapies on tertiary prevention of HBV-related HCC remains controversial and need more studies.

Previous longitudinal follow-up studies indicated that high HBV viral load was an independent risk factor of HCC recurrence after curative treatment.[98-100] Thus, effective viral suppression with NA may prevent HBV-related HCC recurrence after curative treatment. Recent randomised controlled trials further found that NAs significantly decreased post-operative HCC recurrence.[101,102] The protective effect of NAs in reducing HBV-related HCC recurrence after curative therapies was also confirmed by a meta-analysis, including 13 studies with 6350 HCC patients. Patients with NAs therapy had a better recurrence-free survival (HR: 0.66; $P < 0.0001$) and overall

survival (HR: 0.56; $P < 0.0001$) than those without NAs therapy.[103] The nationwide claim database study in Taiwan also revealed that NAs treatment was independently associated with a reduced risk of HCC recurrence after surgical resection (HR: 0.67; $P < 0.001$) and radiofrequency ablation (HR: 0.69; $P < 0.005$).[104,105]

The effects of non-anti–viral adjuvant treatment on prevention of HCC recurrence remain largely unknown. Several nationwide cohort studies from Taiwan revealed that the use of concomitant medications with statin and nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin could reduce the risk of HCC recurrence in patients receiving curative HCC resection, regardless of HBV status.[104,106-108] Recently, a meta-analysis including 12 studies also demonstrated that NSAIDs significantly reduced the recurrent risk of HCC (HR: 0.79, 95% CI: 0.75-0.84).[109] The effects of non-anti–viral medicine on reduction risk of HCC recurrence should be confirmed through prospective studies or randomised clinical trials.

7 | CONCLUSIONS

After decades of tremendous efforts, HBV-related HCC is now a preventable disease (Figure 1). Universal hepatitis B vaccination and anti-viral prophylaxis for high viraemic mothers effectively interrupt MTCT of HBV to achieve the goal of primary prevention of HBV-related HCC. Accumulating evidence has shown that the risk of HCC development can be reduced by current anti-viral therapy in patients with chronic HBV infection, especially those with cirrhosis. However, safety profiles and resistance to long-term NAs therapy are possible concerns. HCC still occurs in some patients with long-term virological remission.[47] Successful secondary prevention of HBV-related HCC could be achieved by treating those who are chronically infected and monitoring for drug resistance. In addition, HCC surveillance is also mandatory in treated patients. Finally, tertiary prevention using NAs can reduce the risk of HCC recurrence after curative treatment. Through the strategies of three-level prevention, the global burden of HBV-related HCC would be substantially declined over time and even be eliminated in conjunction with HBV cure when all the unmet needs are met.[86,87]

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AUTHORSHIP

Guarantor of the article: Jia-Horng Kao is acting as the submission's guarantor.

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