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Epidemiological characteristics and precise prophylaxis and control of HBV-associated primary liver cancer

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Abstract

Primary liver cancer (PLC), which includes hepatocellular carcinoma (HCC, 93% in China; 75%-80% worldwide), intrahepatic cholangiocarcinoma (ICC, 4.3% in China; 10%-15% worldwide), and combined hepatocellular cholangiocarcinoma (CHC, 1.6% in China), is a global disease that brings a heavy burden to the world and the number of incidence cases is on the rise. Chronic liver injury caused by factors such as exposure to aflatoxin B1, infection with Clonorchis sinensis, heavy alcohol consumption, chronic infection with hepatitis C virus (HCV), and metabolic syndrome are all known risk factors for PLC. Notably, chronic infection with hepatitis B virus (HBV) is the major risk factor for HCC. Globally, PLC risk factors are changing from infectious causes to metabolic factors. Here, we update the mechanisms of HBV-related HCC (HBV-HCC) development, especially the effect of HBV evolution on the development of HCC. The HBV mutations, viral load, and HBV integration, together with parameters of poor liver function, are key components to define the highest-risk population of HBV-HCC. Antiviral therapy has been proven to be effective for the prevention of HBV-HCC in the highest-risk population. Non-invasive imaging combined with key markers is economical and convenient for screening early PLC. Surgical resection and liver transplantation are therapeutic options for HCC; however, postoperative recurrence reaches 70% in five years. Targeted therapy, immunotherapy, and radiotherapy can improve the survival of PLC. Active prophylaxes, including HBV vaccination, antiviral treatment, improving lifestyle to decrease chronic inflammation, and surveillance, are cost-effective in decreasing the disease burden of PLC.

Keywords: Primary liver cancer, hepatitis B virus, risk factor, hepatocellular carcinoma, prophylaxis of I-III grade

INTRODUCTION

Primary liver cancer (PLC) represents a spectrum of malignant hepatic neoplasms, including hepatocellular carcinoma (HCC) originating from hepatocytes, intrahepatic cholangiocarcinoma (ICC) arising from bile duct epithelial cells, and combined hepatocellular cholangiocarcinoma (CHC). The etiology of HCC is frequently associated with hepatitis B virus (HBV) or hepatitis C virus (HCV) infections[1]. In mainland China, the majority of PLC cases are HCC (93.0%), followed by ICC (4.3%) and CHC (1.6%), with HBV and HCV infections accounting for 84.4% and 3.2% of HCC cases, respectively[1,2]. Globally, the distribution and etiology of PLC vary significantly across different countries and ethnic populations. A comprehensive understanding of the global epidemiological characteristics of HBV infection and the mechanism by which HBV induces hepatocarcinogenesis is crucial for establishing a specific prevention and control technology system and realizing precise prevention and control.

THE GLOBAL EPIDEMIOLOGICAL CHARACTERISTICS OF PLC

According to the statistics from Globocan, PLC ranks sixth in incidence and the third leading cause of cancer-related death worldwide in 2022[3,4]. PLC is endemic in East Asia and sub-Saharan Africa. Asia accounts for 70% of the global burden of PLC in terms of both incidence and mortality. China has the highest number of cases, with 367,657 PLC cases reported in 2022[4-6]. In all regions worldwide, the incidence and mortality rates of PLC are higher in males than in females[2], with an age-standardized male-to-female ratio of 1.2 to 3.6[7]. It is speculated that by 2040, the number of PLC cases will reach 1.4 million, with 1.3 million PLC-related deaths[7]. A decline in both incidence and mortality rates of PLC has been observed in many high-risk regions, including China, South Korea, the Philippines, and Japan, since the 1990s[7-9]. HBV vaccination was introduced in high-risk countries in Southeast Asia in the 1980s[10]. This may have significantly reduced HBV infections and the incidence of HCC. Concurrently, with improvements in living standards, the rates of overweight individuals and diabetes are increasing in many regions[11]. In recent years, an upward trend in the incidence of PLC has been observed in several countries that were previously considered to be at low risk, including those in Europe, North America, Oceania, and most countries in South America[7,11,12]. Research from the National Cancer Center (NCC) indicates that between 2000 and 2011, the age-standardized incidence rate (ASIR) and age-standardized mortality rates (ASMR) for PLC in China showed a consistent decrease[13]. The decline in ASIR reflects the effectiveness of etiological prevention, whereas the decrease in ASMR reflects both the decline in the ASIR and the effects of clinical treatment, indicating that clinical treatment contributes little to the decrease in the ASMR from PLC. Primary prevention, or etiological prevention, plays a major role in reducing the ASMR from PLC in the population. The first condition for achieving primary prevention is to elucidate the modifiable etiologies that can be intervened.

HCC is the predominant form of PLC. The global incidence of HCC varies due to differing prevalence of risk factors. Sub-Saharan Africa and East Asia are the endemic areas where the majority (80%) of HCC occur, with chronic HBV infection and exposure to aflatoxin B1 (AFB1) being the major risk factors[14]. China accounts for more than 51% of the global number of HCC cases[15]. According to the global burden of disease from 1990 to 2015, HBV and HCV led to 432,000 HCC deaths (54%), alcohol caused 245,000 HCC deaths (30%), and other causes accounted for 133,000 HCC deaths (16%)[16]. ICC is a heterogeneous group of aggressive tumors of the biliary system, accounting for about 15% of PLC worldwide, with an incidence that is low in most high-income countries (0.3-2 cases per 100,000) but much higher (even 40-fold increase) in regions such as China and Thailand[16,17]. The incidence of ICC is highest in Asia, especially in South Korea (ASR = 2.80), Thailand (ASR = 2.19), and Japan (ASR = 0.95). The incidence of ICC increased in most of the countries between 1993 and 2012[12].

MAIN RISK FACTORS OF PLC

Any factor that can lead to persistent chronic liver injury is the etiology of PLC. The main cause of HCC in China is chronic HBV infection, followed by aflatoxin exposure, infection with Clonorchis sinensis (liver fluke), heavy alcohol consumption, metabolic syndrome, HCV infection, and smoking. Adding any of these risk factors to HBV infection or together with hepatitis D virus infection will substantially increase the risk of HCC; liver fluke, metabolic syndrome [obesity, diabetes mellitus, non-alcoholic fatty liver disease (NAFLD)], heavy alcohol consumption, HBV and HCV infections are the major risk factors for ICC[2]. Recent studies have demonstrated a clear association between metabolic dysfunction-associated fatty liver disease (MASLD) and ICC[18]; however, the direct causal chain between them has not been clearly verified[19,20].

HBV infection

Chronic HBV infection is mainly transmitted perinatally (mother-to-child) or horizontally (contacted with infected blood). Approximately 90% of chronic HBV infections are acquired during infancy or early childhood. Booster vaccinations during childhood are effective in preventing HBV infection. In addition to this, HBV is spread through needle-stick injuries, tattoos, and piercings. WHO estimates that 254 million people were living with chronic hepatitis B and that hepatitis B caused 1.1 million deaths in 2022[21]. Regions with a high burden of chronic hepatitis B infection mainly include the Western Pacific (97 million), Africa (65 million), and Southeast Asia (61 million)[21].

HCV infection

HCV is a blood-borne virus that is transmitted primarily through sharing unsterilized needles, transfusion of unscreened blood, and sexual contact with bleeding[22]. An estimated 50 million people worldwide will be chronically infected with HCV by 2024, with approximately 1 million new infections per year. Chronic HCV infection occurs in all regions, with the most severely affected regions in the Eastern Mediterranean region (12 million people chronically infected), the Southeast Asia region and the European region (9 million), the African region (8 million), the Western Pacific region (7 million), and the Americas region (5 million cases)[22]. HCV-associated HCC cases are highest in China, Japan, and the United States[23]. Countries with a high prevalence of chronic HCV infection in the 2021 GBD database include Mongolia, Cambodia, Chad, Uzbekistan, Gabon, Democratic Republic of the Congo, Central African Republic, Angola, Turkmenistan, Tajikistan, and Kyrgyzstan[4]. Unlike HBV, HCV does not integrate into the host genome but contributes to HCC occurrence through epigenetic dysregulation, including DNA methylation, histone modifications, encoded proteins, and HCV genetic variants[24]. Approximately 90% of HCV-associated HCC cases have liver cirrhosis, so it is hypothesized that HCV may promote tumorigenesis through repetitive liver injury, regeneration, and fibrosis[25]. Therefore, WHO recommends treatment with pan-genotypic direct antiviral agents (DAAs) for all adults, adolescents, and children under 3 years of age with chronic HCV infection[26].

Metabolic dysfunction-associated steatotic liver disease

The International Diabetes Federation (IDF) recently defined MASLD as a condition characterized by central obesity (measured by a waist circumference of ≥ 94 cm for European men and ≥ 80 cm for European women, with other ethnic groups having their own specific values) plus any two of the following four factors [triglyceride (TG) level > 1.7 mmol/L; high-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/L in men and < 1.3 mmol/L in women; systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg; and fasting blood glucose (FPG) ≥ 5.6 mmol/L or a diagnosis of type 2 diabetes][27]. In the Delphi Consensus on Nomenclature Updates for Fatty Liver Disease, launched on June 24, 2023, by the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the Latin American Association for the Study of the Hepatology (ALEH), 53 international

experts recommended that the name of NAFLD be changed to MASLD. The name change is intended to more accurately describe the metabolic basis of the disease and reduce the potential negative impact of the original term[28]. The name change aims to more accurately describe the metabolic basis of the disease and to minimize the potential negative impact of the original terminology[28]. The authors still described this risk factor according to the original source. One-quarter of the world's population is estimated to have NAFLD. The incidence of non-alcoholic steatohepatitis (NASH) is projected to increase by up to 56% over the next 10 years[29]. NAFLD is a common cause of chronic liver disease in Western countries and has been the fastest-growing cause of HCC in the United States, France, and the United Kingdom[29]. With the increasing prevalence of obesity, the incidence of NAFLD has been rising, which has led to an upward trend in the proportion of HCC cases caused by NAFLD[30]. Compared with virus-associated HCC, NAFLD-associated HCC tends to occur in older adults[31]. It can occur in the absence of cirrhosis[32] and has a low survival rate[33]. NAFLD is caused by metabolic syndrome and is strongly associated with type 2 diabetes and obesity. In the setting of insulin resistance, increased oxidative stress and altered lipid metabolism lead to chronic inflammation and contribute to the development of HCC[34]. The relative risk of diabetes leading to HCC ranges from 2-3. Insulin resistance and reactive oxygen species production are thought to play a role in hepatocarcinogenesis[5]. Diabetes combined with cirrhosis increases the risk of HCC in patients [35]. There is growing evidence that metabolic syndrome increases the risk of HCC[16]. A 2014 cohort study showed an overall 81% increased risk of HCC in cases of metabolic syndrome (relative risk: 1.81; 95%CI: 1.37-2.41)[36]. Modifiable risk factors for NAFLD include unhealthy lifestyles (over-nutrition, sedentary lifestyle, low physical activity) and sulfonylureas and insulin use[36-38]. In a multicenter prospective study of NAFLD patients from five regions in Asia, patients had a prevalence of unhealthy lifestyles of smoking (3.8%-22.6%) and soft drink consumption (22.6%-62.2%), as well as low levels of physical activity, with a median sedentary time of 42 h per week[39]. This suggests that adopting a healthy lifestyle and appropriately circumventing the use of specific drugs may have a preventive effect on NAFLD. In addition, statins for dyslipidemia reduce the risk by 37%-42%[39-41]. The development of NASH-HCC is linked to genetic mutations, immunological alterations, and changes in the microenvironment. Notable features include an increased prevalence of *TP53* and ACVR2A mutations in hepatocytes, alterations in the innate immune response, such as changes in dendritic cells and Kupffer cells[42], decreased cytotoxicity of natural killer (NK) cells, and the accumulation of neutrophils. Additionally, dysfunction in immune cell subsets has been observed, which includes single nucleotide polymorphisms (SNPs) in genes such as *PNPLA3*. Although the majority of HCC cases in NASH occur after the development of cirrhosis, 30%-40% of tumors develop in patients with advanced fibrosis but without cirrhosis, which is instructive for surveillance and early detection of HCC[43].

Alcohol

Excessive alcohol consumption has been widely recognized as a risk factor for PLC, although the relationship between small amounts of alcohol and PLC remains unclarified[44]. The annual incidence of HCC in patients with alcohol-associated cirrhosis ranges from 0.9% to 5.6%. Approximately 1/5 of HCC deaths globally in 2019 will be attributable to alcohol consumption. The highest per capita alcohol consumption is in Europe (12.3 liters in 2005 and 9.8 liters in 2016) and the Western Pacific (4.6 liters in 2005 and 7.3 liters in 2016)[45]. This fact is corroborated by the number of alcohol-related liver cancer deaths in these two regions [22,215 (18,146-26,413) deaths in Europe in 2019, and 27,623 (21,296-34,686) deaths in the Western Pacific][46]. In Europe and the United States, most HCC is associated with alcoholic liver disease (ALD)[47]. The factors that promote the progression of ALD to HCC include malnutrition caused by long-term drinking, hepatic stellate cells (HSCs) activation, damage caused by alcohol and its metabolites, oxidative stress in liver tissue, immune reaction, and genetic factors[48]. Heavy alcohol consumption and aldehyde dehydrogenase 2 (ALDH2) rs671 polymorphism significantly increased the risk of HBV-HCC development and mortality[49]. There exists a synergistic effect between HBV, HCV, and alcoholic

hepatotoxicity, especially HCV infection with alcohol intake[48,49].

Other factors

Aflatoxin exposure, schistosomiasis, water contamination, nicotine use, and genetic predisposition are thought to be other possible risk factors for PLC[14,47,50,51]. Globally, 5%-28% of HCC is associated with AFB1[52]. The incidence of HCC in HIV-infected patients has shown an increasing trend, especially in those patient groups co-infected with HBV or HCV[53]. The incidence of HCC in HIV-infected patients has shown an increasing trend, especially in those patient groups co-infected with HBV or HCV[14,53]. In addition to the above causative factors, many causes are still being discovered, and the synergistic mechanisms of carcinogenesis among these factors need to be further explored.

EVOLUTIONARY PATTERNS OF HBV IN THE "TRILOGY" OF HEPATOCELLULAR CARCINOGENESIS

HBV mutations at the core promoter and enhancer regions

Viral sequences from over 1,000 asymptomatic HBV-infected patients, particularly those seropositive for HBeAg, were used to identify "wild sequences", which served as controls for recognizing disease-associated HBV mutations. We characterized the HBV mutations at the core promoter and enhancer region at each stage of the HBV oncogenic "trilogy" and revealed 66 previously unreported HCC-associated HBV variants. Key mutations in HBV genotype C, including *C1673T*, *A1726C*, *A1727T*, *C1730G*, *C1766T*, *A1762T*/*G1764A*, *T1768A*, *C1773T*, and *C1799G*, were found to increase the risk of cirrhosis significantly. Multifactorial logistic regression analysis disclosed that age, abnormal aminotransferase (ALT), HBV DNA ≥ 104 copies/mL, and genotypes C, *C1653T*, *T1674C*/*G*, *T1753V*, and *A1762T*/*G1764A* were independent risk factors for HCC development. The haplotype *1653C-1674G*/*C-1753V-1762T*/*1764A*, a predominant HBV variant, was detected in HCC 6.28 times more frequently than in non-HCC-infected individuals, demonstrating high specificity and detection frequency, rendering it suitable for HCC prediction[54] [Table 1]. These studies contribute to the definition of the high-risk group for HCC.

Characteristics of HBV mutations in the pre-S region

Significant differences in the judgment of the HBV mutations in the preS region were observed, which was particularly distinct in different HBV genotypes. Asymptomatic HBV-infected carriers, chronic hepatitis B patients, cirrhotic patients, and HBV-HCC patients were used as mutual controls to screen the HBV mutations in the preS region and part of the S region. The *pre-S1* deletion, *pre-S2* deletion, and *pre-S2* start site mutations were substantially more frequent in HCC than in asymptomatic HBV carriers, chronic hepatitis B patients, and cirrhotic patients. HBV preS wild types were predominantly associated with an increased risk of cirrhosis, while their mutation types were mostly associated with an increased risk of developing HCC. Multifactorial logistic regression analysis confirmed that age, HBeAg conversion, ALT ≥ 45 U/L, and representative wild-type *T3116C* and *A2964C* were independent risk factors for increased risk of cirrhosis; age, HBV DNA ≥ 104 copies/mL, HBV genotype C, and HBV mutations including *C2964A*, *C3116T*, *C7A*, *T53C*, *pre-S2* start site variants, and *pre-S1* deletion were independent risk factors for HCC[55] [Table 1], confirming the advantages and feasibility of the HBV mutations in predicting various liver diseases in the "trilogy" of HBV-induced carcinogenesis.

Effect of combined HBV variants on the occurrence of HCC

HCC-associated HBV variants are numerous, and age- and sex-matched case-control studies revealed the independent effects of HBV core promoter and preS mutations on the risk of HCC. It was found that HBV genotype C, *preS 2* promoter mutations, *C105T*, *T1753V*, *A1762T*/*G1764A*, and other HBV variants were independent risk factors for HCC[56,57] [Table 1]. A systematic analysis of HBV variants with high specificity and detection rates in HCC revealed that the frequency of preS deletion, *C1653T*, *T1753V*, and *A1762T*/

Table 1. Key mutation sites of HBV/HCV-HCC

Viral type	Mutation sites	Country/Region	Reference
HBV	*C1673T*, *A1726C*, *A1727T*, *C1730G*, *C1766T*, *A1762T/G1764A*, *T1768A*, *C1773T*, *C1799G*,*1653C-1674G/C-1753V-1762T/1764A*	China	Yin *et al.* 2011[54]
HBV	*pre-S1* deletion, *pre-S2* deletion, *pre-S2* start site mutations,*C2964A*, *C3116T*, *C7A*, *T53C*, preS *PreS2* start *C3116T*, *C7A*, *T53C*	China	Yin *et al.* 2010[55]
HBV	*C105T*, *T1753V*, *A1762T/G1764A*	China	Liu *et al.* 2011[56] Xie *et al.* 2010[57]
HBV	*G40C*	China	Chen *et al.* 2021[62]
HBV	*G2950A/G2951A/A2962G/C2964A*, *C3116T/T31C*	China	Pu *et al.* 2022[63]
HBV	IL-17A rs2275913 (*G197A*), IL-17F rs763780 (*A7488G*)	Iran	Gheshlaghi *et al.* 2021[213]
HBV	rs3077(HLA-DP), rs9277535(HLA-DP)	China, Korea, Japan, Saudi Arabia, Thailand	Yu *et al.* 2015[214]
HBV	IL10RB-rs2834167, PAPL-rs423058A, DEPDC5-rs1012068	China	Ma *et al.* 2014[215]
HCV	*A028C*, *G209A*, *C219U/A*, *U264C*, *A271C/U*, *C378U/A*, *G435A/C*, *G481A*, *U303C/A*	Europe, America	Hu *et al.* 2009[205]
HCV	CHI3L1 (rs880633), intergenic (rs597533) polymorphisms	Egypt	Mangoud *et al.* 2021[216]
HCV	HCP5-rs2244546	Switzerland	Lange *et al.* 2013[217]

HBV: Hepatitis B virus; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; HLA-DP: human leukocyte antigen-DP; IL10RB: interleukin 10RB; PAPL: iron/zinc purple acid phosphatase-like protein; DEPDC5: DEP domain containing 5; CHI3L1: Chitinase-3-like protein 1; HCP5: histocompatibility leukocyte antigen complex P5.

G1764A mutations gradually increased at each node of the HBV oncogenic "trilogy" disease. The HCC-associated variants in the HBV pre-S region and core promoter/enhancer II accumulate during the progression of HBV chronic infection to HCC, and these variants and their combination can predict the development of HCC[58]. The HBV signature disease mutations *A1762T/G1764A* can be detected 10 years prior to the onset of HCC, and the combination of mutations increases the specificity of monitoring HCC development more dramatically than single-point mutations. It was found that *A1762T/G1764A* appeared earlier, and preS deletion, *C1653T*, and *T1753V* appeared later after the acquisition of HBV infection[59]. A cohort study found that combined variants predicted HCC development up to 6 years earlier[60]. Therefore, a combined detection technique for high-risk HBV variants was established, which has been used for the surveillance of HCC occurrence in HBV-infected patients, for defining high-risk groups, and for the development of HCC secondary prevention.

Predictive role of HBV variants in HCC recurrence

Analysis of HBV variants in different liver tissues revealed asynchronous degrees of HBV evolution in cancerous tissues, adjacent liver tissues, and peripheral blood in HCC patients. In cancerous tissues, evolution was slowest due to the weakest immune pressure; in peripheral blood, immune selection was strongest, and HBV evolution was the fastest; and in adjacent liver tissues, the degree of HBV evolution was intermediate. Adjacent liver tissue is the most important site for HBV synthesis, and the evolutionary trajectory of HBV undergoing different immune pressures in the microenvironment after "leaving the factory" is completely different, resulting in conflicting roles of serum and tumor tissues in predicting HCC metastasis. Inflammatory molecules trans-activate APOBEC3s, which promote genomic mutation of HBV during replication throughout the RNA reverse transcription stage. *APOBEC3B*-related HBV mutations are important risk factors for HCC development after evolutionary selections. Among these, cancer-driving HBV mutations, such as *A1762T/G1764A*, in serum predict postoperative recurrence and metastasis of HCC. This effect was absent both in cancerous and adjacent liver tissues[61]. During HBV-HCC recurrence and metastasis, the direction of immune selection of HBV mutations tends to promote cancer metastasis,

possibly because of immune selection in the tumor microenvironment (TME). For the first time, it was found that the G40C mutation in the pre-S region of HBV was able to independently promote the poor prognosis of HCC[62] [Table 1]. In this way, HBV evolution promotes not only HCC occurrence but also poor prognosis of HCC, which can play a guiding role in both tertiary prevention of HBV-induced carcinogenesis as markers for the prediction of HCC occurrence and prognosis as well as therapeutic efficacy.

MOLECULAR MECHANISMS OF HBV MAJOR VARIANT GENES IN PROMOTING CARCINOGENESIS

The Sleeping Beauty (SB) transposon animal model was first used to imitate the early stage of HBV infection and to integrate it into the host genome. It was found that *hepatitis B x* (*HBx*) genes with combined mutations upregulated more "yin" inflammatory cytokines and caused a higher rate of HCC and more metastasis than did the wild-type counterpart. Combined *HBx* mutations *C1653T-T1674G-A1762T/G1764A* cause the maximal level of proinflammatory cytokine, thus promoting hepatocarcinogenesis. Mutant *HBx* promotes HCC malignant transformation and stemness characteristics mainly by activating the expression of plasminogen activator inhibitor 1 (PAI-1) and cell division cyclin 20 (CDC20). These findings in the SB animal model were confirmed by subsequent cellular models and their xenograft animal models. PAI-1 has been shown to be a prognostic biomarker of HCC and a therapeutic target for HCC[63]. Meanwhile, our cohort study has also demonstrated that the frequency of combined *C3116T/T31C* mutations is significantly higher than that of preS 2 deletion (43.61% *vs.* 7.16%). Using the xenograft immunodeficiency animal model, we found that transfection of the large S gene carrying the major combined mutations *G2950A/G2951A/A2962G/C2964A* and *C3116T/T31C* in the preS region resulted in rapid tumor growth[63] [Table 1]. The mutant HBV large S gene was found to have a stronger ability to cause HCC and promote HCC metastasis and death than did the wild-type large S gene in the SB animal model. Both *G2950A/G2951A/A2962G/C2964A* and *C3116T/T31C* combination mutations activate inflammatory regulatory networks and metabolism-related signaling, inducing endoplasmic reticulum stress, affecting the body's response to hypoxia, and upregulating the interleukin-6 (IL-6) signal transducer and activator of transcription 3 (STAT3) signaling pathway in the SB animal model. Thus, the HBV mutations at the large S gene promote HCC occurrence and metastasis by amplifying the IL-6/STAT3 signaling pathway[64]. Oncogenic HBV mutations arise due to immune selection and amplify oncogenic and cancer progression-related inflammatory signaling pathways *in vivo*. Thus, HBV evolution through the "wild-type HBV - immune selection - mutant HBV - local inflammation - carcinogenesis" eventually promotes HCC evolution by amplifying the proinflammatory and oncogenic pathways.

Drivers of HBV evolution: genetically determined inflammatory immune mechanisms

Genome-wide association analysis was employed to uncover new susceptibility loci for HBV-HCC; the *STAT4* gene rs7574865 and the class II human leukocyte antigen (HLA)-DQ rs9275319 were identified to be the major susceptible genetic loci. *STAT4*, a crucial transcription factor and key regulator of the immune response, plays a significant role in transmitting signals from interleukin IL-12 and type I interferon (IFN-α or IFN-β) to induce IFN-γ, thereby influencing the immune response to HCC. The rs7574865 G allele, which affects *STAT4* expression, has been shown to significantly increase the risk of HCC. Notably, *STAT4* expression levels were significantly lower in cancerous tissues compared to paracancerous liver tissues, with the lowest levels observed in individuals with the rs7574865 GG genotype[65]. Additionally, a PRMT7-encoded gene intron region on chromosome 16q22.1 was identified to harbor an HCC-risk region, with the high-risk allele at rs73613962 exhibiting allele-specific enhancer activity. This "allele-specific enhancer" promotes PRMT7 expression through the binding of the transcription factor HNF4A, impacting HCC susceptibility via the P53 pathway[66]. We also discovered that rare genotypes of genetic polymorphisms of

HLA-II antigen genes (*HLA-DR*, *HLA-DP*, and *HLA-DQ*) were negatively associated with the chronicity of HBV infection. Dominant alleles of these genetic polymorphisms promote chronic infection and immune selection of viral variants, making HBV more likely to cause HCC in Chinese populations. A significant finding was that major and rare genotypes in Chinese and white European populations are interchanged: genetic loci promoting the chronicity of HBV infection (*HLA-DQ*, *HLA-DP*, *HLA-DR*, and *NFKBIA* genetic loci) are major genotypes in the Chinese genome and rare in Europeans, and vice versa[67-69]. Furthermore, SNPs in the promoters of the *NF-κB1* and *IκB* genes, which are part of the NF-κB pathway - a key inflammatory signaling network in the oncogenic process of HBV - were found to be responsible for the development of HCC in patients infected with HBV type C2. The polymorphism *NFKBIA* -881 (rs3138053, A>G) at the promoter region of the *IκB*, a key molecule of the NF-κB pathway, promotes the process of chronic inflammation and inflammation-carcinoma transformation[70]. Differences in the frequency of this polymorphic allele among different human races provide insights into the reason why the Chinese population is more susceptible to chronic HBV infection, which accounts for one-third of the world's cases, and more likely to develop HCC, which accounts for half of the world's cases. Genetic polymorphisms in NF-κB, *STAT3*, and other major inflammatory pathways in the HBV oncogenic pathway were also found to significantly interact with the pro-cancer HBV mutations in the development of HCC and cirrhosis[71,72]. Immunogenetic factors modulate the expression of immune/inflammatory molecules, influencing inflammatory-immune functions and predisposing individuals to develop chronic active hepatitis following HBV infection, thereby promoting the evolutionary development of HCC.

Inflammatory factors affect the balance between *APOBEC3B* - *UNG*

Immunogenetic traits, when interacting with environmental factors, foster the formation and maintenance of a chronic inflammatory microenvironment. This microenvironment serves as a driving force for the generation of HBV mutations and the selection of hepatocytes following somatic mutations. Dysregulation of the balance between APOBEC3s and uracil DNA glycosylase (*UNG*) is a central driver of somatic mutations in both the HBV genome and host cell genomes. The functional polymorphic locus of the *APOBEC3B* promoter rs2267401 has been shown to promote the generation of high-risk HBV mutations. Alleles that enhance *APOBEC3B* expression interact with alleles that reduce *UNG* enhancer function, significantly contributing to the development and poor prognosis of HCC. "Yin" inflammatory molecules, such as IL-6 and other *trans*-activators, activate *APOBEC3B* expression and reduce *UNG* expression. This leads to a dysregulation of the *APOBEC3B*-*UNG* balance, promoting somatic mutations and HBV mutations. The tumor inflammatory-immune microenvironment effectively selects the mutated cells and mutated viruses, promoting the evolutionary process of HCC through a process termed "mutation-selection-adaptation"[73]. We then depict a figure to show the current understanding of HBV-induced hepatocarcinogenesis [Figure 1]. The discovery of this mechanism further supports the theoretical basis of cancer evolution and development "Cancer Evo-Dev". The imbalance of APOBEC3s-*UNG* plays a significant role not only in HBV carcinogenesis but also in other tumors, such as cholangiocarcinoma, gallbladder carcinoma, and renal cell carcinoma. The *APOBEC3B* promoter with rs2267401-G was found to be associated with a decreased risk of cholangiocarcinoma but associated with an increased risk of gallbladder cancer, possibly due to the high expression of the transcriptional repressor TFAP2A in cholangiocarcinoma. Tumor necrosis factor α (TNFα) increases the expression level of *APOBEC3B* by repressing TFAP2A. The genotype rs12157810-C at the *APOBEC3A* promoter was associated with a decreased risk of cholangiocarcinoma and gallbladder cancer, mainly due to the fact that TNFα increases the binding of the transcription factor Ets-1p68 to the *APOBEC3A* promoter carrying the rs12157810-C allele, promoting *APOBEC3A* overexpression. The mutagenicity of *APOBEC3A* is nearly 1,000-fold higher than that of *APOBEC3B*, and high expression of *APOBEC3A* leads to widespread breakage of host genomic DNA and induces apoptosis, thereby reducing cancer risk[74]. Similar findings have been reported in renal cell carcinoma[75]. Therefore, the *APOBEC3A*/*APOBEC3B* promoter allelic genotype might take part in

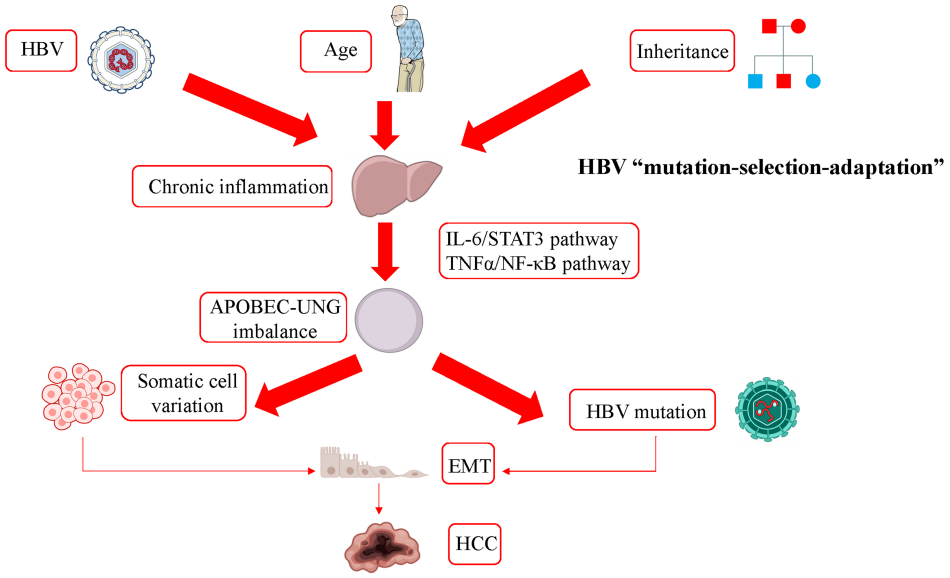

Figure 1. The mechanisms of HBV-induced hepatocarcinogenesis: the current understanding. The interplay between HBV infection, age, and genetic predisposition leads to chronic inflammation. Inflammatory mediators such as IL-6, STAT3, TNF-α, and NF-κB are activated in this process. These factors not only upregulate the expression of APOBEC but also downregulate the expression of the UNG, resulting in an APOBEC-UNG imbalance. This imbalance fosters both HBV mutation and somatic cell mutation. While most of the mutated HBV are eliminated by the immune system, a minority survives and integrates into the genome of these residual somatic cells. This integration triggers the activation of the EMT and oncogenic pathways, potentially leading to the development of HCC. Created with Biorender (https://www.biorender.com/) and Bioart (https://bioart.niaid.nih.gov/). HBV: Hepatitis B virus; HCC: hepatocellular carcinoma; IL-6: interleukin-6; STAT3: signal transducer and activator of transcription 3; TNF-α: tumor necrosis factor α; NF-κB: nuclear factor kappa B; APOBEC: apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like; UNG: uracil-N-glycosylase; EMT: epithelial-mesenchymal transition.

regulating the direction of cancer evolution in inflammatory environments through interactions with specific transcription factors inherent to a given tissue type. To identify cancer-promoting pathways after somatic mutation, organoid technology was applied to analyze the mechanism by which the proinflammatory microenvironment selects the stem-like progenitors of HCC, ICC, and CHC. We found that the stemness characteristics of cancer cells in tumor tissues were positively associated with the success rate of organoid culture. These stemness characteristics not only determine the primary and sorafenib-induced resistance of HCC but also play a central role in cancer recurrence and metastasis[76]. Histological techniques applied to analyze the expression profiles associated with malignant tumors, such as HCC and colorectal cancer, revealed that inflammation promotes the cancer stemness-related signaling pathway and tumor-specific protein expression regulation mechanism by modulating the driver mutations of APOBECs[77]. The abnormal regulation of these tumor growth genes is a target for cancer treatment.

In The Cancer Genome Atlas classification, HBV infection is significantly associated with Cluster 1, whereas HCV infection is significantly associated with Cluster 4[78]. In addition, other authors analyzed transcriptomic datasets composed of 99% HBV-related HCCs and showed that the molecular diversity of HBV-related HCCs spans from non-proliferative, well-differentiated tumors preserving a periportal or perivenous phenotype to poorly differentiated tumors enriched in metastasis signatures and stem cell markers[79].

ICC PATHOGENESIS

Many parts of the pathogenesis of ICC remain to be elucidated. Several meta-analyses have shown that HBV

and HCV infections significantly increase the risk of developing ICC[80-84]. For ICC, HBV may produce multiple inflammatory mediators through inflammation, including IL-6, TNF-α, cyclooxygenase-2, and Wnt. Furthermore, transforming growth factor β (TGF-β), vascular endothelial growth factor, hepatocyte growth factor, and several microRNAs were also found to be upregulated, creating an environment conducive to the generation of successive oncogene mutations and cell proliferation[85]. In addition to this, HBV may act as an oncogene to promote cancer development. Experiments in mice have shown that high expression of *HBx* protein may lead to the amplification of EpCAM(+) or OV6(+) tumor cells[86]. It has also been shown that amplification of the RNA editing enzyme *ADAR1* induced increased expression and caused aberrant editing of the p.M8V locus of the *KPC1* gene in ICC. This aberrant editing activates the *NF-κB* signaling pathway, which in turn promotes the progression of ICC[87].

SCREENING AND DIAGNOSIS

To find PLC patients at the early stage, screening of PLC is an important public health action in the endemic areas. The cost-effective ratio should be considered for this action, even in the high-risk population. Specific techniques used for PLC screening can be categorized as invasive and non-invasive. Non-invasive means include simple technical scoring, imaging means [computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), positron emission tomography-computed tomography (PET-CT), positron emission tomography - magnetic resonance imaging (PET-MRI)], and serum marker testing. US plus serum alpha-fetoprotein (AFP) is the most popular non-invasive protocol for HCC screening. The invasive screening means mainly refers to liver biopsy.

Screening

HCC screening is a long-term, cyclical and universal endeavor. Experts generally agree that early diagnosis is the key to successful treatment[88]. The selection of screening methods should take into account factors such as accuracy, operational difficulty, degree of impairment, and economic cost[89]. The monitoring of HCC can be divided into invasive and non-invasive methods. Invasive monitoring includes liver biopsy, which may lead to some complications and is also subject to potential bias due to variations in test samples and observer interpretation. Non-invasive methods encompass some simple counting methods [Fibrosis 4 Index (FIB-4)and NAFLD Fibrosis Score (NFS)], US, MRI, serum biomarkers, and shear wave elastography[90,91]. Currently, abdominal US and serum AFP testing remain the primary routine screening methods because they are well-established, inexpensive, and easy to perform and administer in areas with varying medical conditions. US combined with AFP screening is significantly more sensitive than either test alone[92]. According to current guidelines[92-96], HCC surveillance using US with or without serum AFP levels should be considered every 6 months in patients with NASH-associated cirrhosis in high-risk groups such as those with hepatitis viral infections, chronic alcohol consumption, obesity, and diabetes. However, US visualization may be less sensitive for HCC[97-99], especially in patients with early tumors[98,100,101], ascites, cirrhosis, and obesity[97,102,103]. In 2022, the Korean Liver Cancer Association (KLCA) and NCC guidelines also recommend dynamic contrast-enhanced CT or dynamic contrast-enhanced MRI as an alternative screening tool if liver ultrasound is limited or not indicated[104]. The use of simple and easy-to-generate parameters, such as fibrosis scores, can help screen patients with advanced liver fibrosis or cirrhosis who are at increased risk of developing HCC[105]. Due to the low prevalence of ICC in the population as a whole, screening is not recommended by medical societies, given the cost-effective ratio[106,107].

Diagnosis

In 2023, experts from the Italian Association for the Study of the Liver (AISF), the Italian Association of Medical Oncology (AIOM), and the Italian Association of Hepatobiliary and Pancreatic Surgery (AICEP), among others, jointly recommended that the diagnosis and therapeutic evaluation of patients with HCC should be carried out by a team of professionals working in a multidisciplinary manner and not

independently by a single specialist[108]. Non-invasive imaging findings are the standard for the diagnosis of HCC in patients with cirrhosis, and the typical imaging features of arterial versus venous flushing have good specificity and acceptable sensitivity and are recommended by national guidelines (AASLD or APASL guidelines)[109]. Enhanced CT or MRI should be performed in patients with nodules (especially < 2 cm in long diameter) or unexplained elevated serum AFP[110]. For individuals with US nodules or/and elevated serum AFP who do not yet meet diagnostic criteria, enhanced screening is recommended every 2-3 months, primarily using abdominal CT or MRI and specific contrast agents[111]. For tumors of > 2 cm in diameter, there is no significant difference in the sensitivity between MRI and CT[112]. However, early HCC (single nodule < 2.0 cm in diameter) is detected more frequently with MRI combined with gadoxetic acid disodium, a liver-specific MRI contrast agent, than with enhanced CT[113]. For nodules with a diameter of 1-2 cm, gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced MRI (EOB-MRI) and contrast-enhanced ultrasound (CEUS) have been included in China as screening tests for the diagnosis of nodes of undetermined size to improve the sensitivity for the diagnosis[114].

MRI provides more accurate and comprehensive information, which is better suited for early diagnosis. Biopsy should be performed to confirm the diagnosis of HCC as soon as atypical features of the liver lesion in terms of contrast uptake are observed[115]. Biopsy is the basis for the diagnosis of HCC[116], but biopsy may also produce a false-negative rate of about 30%[117].

Serum markers such as vitamin deficiency or antagonist II (PIVKA-II/DCP)-induced proteins can be used as complementary screening techniques. AFP-L3 is predominantly present in patients with HCC. The ratio of AFP-L3 to AFP eliminates the effects of other factors that contribute to the upregulation of AFP[118]. Gender, age, AFP-L3, AFP, and des-gamma-carboxy prothrombin (DCP) (GALAD) improve the sensitivity of early HCC detection, but increase false-positive results[119]. In addition, novel molecular markers such as the HBV mutations, circulating tumor DNA (ctDNA), tumor-associated methylation, circulating free DNA (cfDNA), and non-coding RNAs have been shown to have high accuracy in HCC screening[54,120,121]. ctDNA, in combination with *TP53* mutation, *RASSF1a* methylation, and *GSTP1*, could be used as a potential non-invasive screening method for HCC in patients with low AFP[122].

ICC is diagnosed primarily through imaging techniques. Multiple modality approaches, including CT, MRI, magnetic resonance cholangiopancreatography (MRCP), and PET, are often required to arrive at a final diagnosis and to screen patients for potential surgery[123]. US is usually the first test to detect ICC, which presents as a solid mass with variable echoes[124]. CT is considered the standard imaging method for preoperative evaluation. ICCs are usually of low density, have irregular borders and may be accompanied by peritoneal retraction. Contrast-enhanced scan is usually used to show ICC[125]. MRI is the most commonly used imaging method for periportal cholangiocarcinoma[123]. In some cases, the imaging features of ICC are similar to those of HCC and are, therefore, easily misdiagnosed[126]. Concurrent problems include the low diagnostic accuracy of current tumor markers, the difficulty in identifying benign and malignant biliary structures with imaging techniques, and confirmatory diagnostic modalities for invasive procedures[127]. Notably, the use of portal-phase flushing rather than conventional flushing in gadoxetic acid-enhanced MRI imaging may prevent the misdiagnosis of ICC as HCC in cirrhotic liver[128]. Deep migration learning models are considered the future direction for the diagnosis of lymph node metastasis, showing good predictive performance[129-131]. Lymph node metastasis may result in a significant increase in CD8+ T cell and NK-cell infiltration, reflecting an enhanced antitumor immune response, which might provide a direction for the prediction of lymph node metastasis of ICC[132].

TREATMENT

According to the Barcelona Liver Cancer Clinic (BCLC) algorithm, patients with HCC are classified into five clinical stages: very early stage (BCLC 0), early stage (BCLC A), intermediate stage (BCLC B), advanced stage (BCLC C), and terminal stage (BCLC D)[133]. Currently, locoregional therapy (LRT) is used for early to intermediate HCC, while sorafenib is used for advanced HCC. Recognition of the limitations of these treatments and the potential to enhance their efficacy has driven the exploration of combinative therapeutic options, particularly combining LRT with systemic therapy[134].

Surgical treatment

Surgical resection is the treatment of choice for cirrhosis-free patients with early-stage HCC according to Barcelona Clinical Liver Cancer Staging (BCLC 0 or A)[12]. According to the BCLC staging guidelines, hepatectomy is indicated in patients with a single tumor diameter of ≤ 2 cm and a Child-Pugh classification of A[133]. Differences in patient conditions may lead to different postoperative outcomes, with a 5-year overall survival (OS) of ~ 70% and perioperative mortality of < 2% in patients selected by strict criteria[95,135]. When HCC is found to be unsuitable for resection during surgical exploration, hepatic artery and portal vein catheterization chemotherapy or other intraoperative locoregional treatments may be considered[136]. Surgical resection is usually considered curative for HCC, but HCC also recurs from time to time in patients with multinodular disease, microvascular infiltrates and/or poorly differentiated tumors (5-year incidence of 50%-70%)[137]. Furthermore, patients associated with MASLD may avoid surgical resection due to the increased risk of perioperative complications[41,138]. Nevertheless, a meta-analysis based on 7,226 patients has shown that OS appeared to be better in patients with MASLD-associated than in those with virus-associated HCC (HR: 0.80; 95%CI: 0.67-0.96; $P = 0.017$)[139]. However, at the time of diagnosis, less than 10% of patients are eligible for surgery for liver resection or transplantation. LRT, the precise manipulation of liver tumors through minimally invasive image guidance, has become an integral part of HCC treatment[140]. Minimally invasive liver resection (MILS) is emerging as an alternative to open hepatectomy, which not only reduces intraoperative bleeding and hospital stay, but also has similar prognostic outcomes[141]. Robotic Liver Resection (RLR) frees up manpower and promises to be a new surgical modality. However, the high cost may be an important reason why RLR has not been performed on a large scale[141]. From November 2018 to June 2021, surgeon Broering D and the bedside surgical team completed 356 robotic donor hepatectomies with no donor deaths, only two open conversions, and an overall complication rate of just under 6% for all donor types (no grade 3 or higher complications). Due to the special capabilities of articulated instruments and magnified 3D vision, as well as considerable ergonomic advantages, RLR overcomes the drawbacks of inflexible fixation of surgical instruments and large oscillations of the visual field leverage effect of conventional laparoscopic surgery (LLR). However, the high cost may be an important reason why RLR has not been performed on a large scale[141]. The recognized cure for ICC is still surgical excision, which is only possible in 20% of cases at the time of diagnosis[142]. The aim of surgical treatment is complete margin-negative (R0) resection, and the functional residual capacity of the liver and the radical nature of the tumor, as well as the patient's physical status, are determinants of surgical success[143]. ICC patients who undergo staged laparoscopy (SL) have better perioperative outcomes and longer OS than those who do not[144,145]. The therapeutic efficacy of lymph node dissection (LND) for ICC is controversial and remains to be proven. The impact of LND on ICC and its extent seems to be closely related to the specific location of the tumor. A multicenter analysis showed that in hilar lesions, more extensive lymph node removal of level 2 (retro-pancreatic or common hepatic artery lymph nodes) could be recommended, whereas in peripheral lesions, LND might not be removed beyond the entrapment of level 1 (hepatoduodenal ligament lymph nodes)[146]. A multicenter cohort study involving 159 patients showed that LND did not significantly improve the prognosis of patients with clinically lymph node-negative ICC [median recurrence-free survival (12.0 months *vs.* 10.0 months; $P = 0.37$) and median OS (22.0 months *vs.* 26.0 months; $P = 0.47$) in the LND *vs.* non-LND groups][147]. Interestingly, in a meta-analysis involving 4,407 patients, LND did not improve

prognosis in patients with ICC (HR: 1.05; 95%CI: 0.83-1.32). Meanwhile, LND was significantly associated with superior OS in low-risk group patients (HR: 0.76; 95%CI: 0.59-0.98)[148].

According to the Milan criteria, LT is usually indicated for a single tumor of ≤ 5 cm or 2-3 tumors of ≤ 3 cm without vascular infiltration[149]. According to the BCLC staging guidelines, early LT is usually considered the best treatment for patients with HCC when a single tumor has a diameter of ≤ 2 cm and a Child-Pugh grade of C. In addition, early LT is often considered the best treatment for patients with HCC. LT has a median OS of > 10 years and a recurrence rate of ~ 10% in patients selected according to strict criteria[150]. LT is considered superior to resection in terms of long-term outcomes (70% recurrence rate and 7%-15% survival at 10 years)[151]. Living donor liver transplantation (LDLT) is considered the optimal therapeutic option for patients with HBV-HCC due to its shorter waiting period, better quality of donor liver, and almost negligible cold ischemia time[152]. However, patients with HCC may have to wait longer for reasons such as organ shortages, which can lead to patients being pushed off waiting lists due to tumor progression, and the likelihood of cure by resection is similar to LT when the dropout rate reaches 20% and above[153,154]. There is not sufficient evidence to use LT as the absolute standard of care for ICC. However, LT has demonstrated positive therapeutic effects in carefully screened patient populations, and prospective studies combining systemic neoadjuvant chemotherapy (NAC) with localized therapies in conjunction with LT have revealed some encouraging long-term efficacy[155]. For unresectable perihilar cholangiocarcinoma (pCCA), adjuvant radiotherapy combined with LT offers a new idea of resolution, with the largest consecutive series published by the Mayo Clinic showing that 221 patients underwent LT between 1993 and 2018, and that the 5-year OS of pCCA was 58%[156].

Adjuvant therapy

While waiting for LT, patients receive treatments known as bridging therapies to avoid HCC progression. Common bridging modalities include transarterial chemoembolization (TACE), ablation, and radiotherapy[14]. Bridging therapies significantly decrease the risk of HCC recurrence after liver transplantation[157,158]. Ablation is an adjuvant therapy that directly damages the tumor by chemical, thermal, or electrical means[159]. For patients with early-detected HCC (BCLC 0 or A) who are not candidates for surgery or transplantation, local ablation with radiofrequency ablation (RFA) or microwave (MWA) radiation is the standard of care, with selective transarterial radioembolization (TARE) or stereotactic radiotherapy (SBRT) as an alternative[103,121-123]. The AASLD and EASL guidelines have identified RFA as the primary first-line treatment for single tumors < 2 cm and as an alternative to surgery for early single tumors of 3-4 cm or for 2-3 tumors of < 3 cm[92,160]. For unresectable ICC measuring ≤ 3 cm without evidence of extrahepatic disease, the guidelines consider ablation as a palliative treatment option[106]. However, in patients with HCC tumors > 3 cm in diameter or serum AFP levels > 200 ng/ml, hepatectomy may perform better than RFA in terms of local disease control and long-term survival[161]. RFA results in a median OS of ~ 60 months and a 5-year recurrence rate of 50%-70% in HCC[162,163]. Currently, RFA and MWA are well-established thermal techniques, while other ablation techniques such as cryoablation (CRA), laser interstitial thermotherapy, and irreversible electroporation (IRE) are less commonly used[159]. TACE is the standard of care for intermediate-term HCC at Child-Pugh class B. In a prospective study of 175 patients with HCC, the mean time of chemoembolization was 58.1 min, and this duration was significantly correlated with the number of nodules[164]. TARE is a treatment technique that kills tumor cells by releasing radiation from microspheres with a radioactive substance, usually for intermediate-stage disease[165]. A meta-analysis demonstrated a median OS of 26-30 months for TACE, with no difference in OS between the two modalities[166]. An increasing number of patients with unresectable ICC are now being treated with TACE and TARE[167,168]. Drug-eluting bead transarterial chemoembolization (DEB-TACE) is an endovascular therapeutic technique specifically targeting unresectable HCC. This technique achieves effective control of drug release kinetics by encapsulating chemotherapeutic drugs within microspheres and releasing them

precisely in the lesion area[169]. The 2023 Korean Hepatocellular Carcinoma Association Expert Consensus states that DEB-TACE has less severe postembolization syndrome, shorter hospital stay, and similar survival compared to conventional TACE. However, DEB-TACE may not be indicated for HCC ≤ 3 cm[170]. In patients with locally advanced HCC or those who do not respond to TACE, hepatic arterial infusion chemotherapy (HAIC) with the FOLFOX regimen consisting of oxaliplatin, fluorouracil, and folinic acid or in combination with systemic therapy is recommended[171,172].

Adoption of adjunctive therapeutic techniques for postoperative ICC patients is thought to be beneficial to patient prognosis[147,173,174]. There is a cohort study showing that postoperative adjuvant therapy is associated with prolonged survival in patients with ICC, especially in the non-LND group (P = 0.02 for recurrence-free survival, P = 0.03 for OS)[147]. A meta-analysis involving 10,181 patients showed that chemotherapy significantly improves postoperative prognosis in ICC (HR: 0.57; 95%CI: 0.44-0.70)[173]. A study from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) involving 3,226 patients with lymph node-positive biliary tract cancers showed that the median survival time in the surgery-combination-chemotherapy group was significantly longer than in the surgery-alone group (median survival time of 19 months *vs.*10 months, $P < 0.01$)[174].

Systemic therapy

Systemic therapy is divided into targeted therapy and immunotherapy. The approach is suitable for treating advanced and intermediate-stage HCC patients who are not eligible for local treatment[14]. Six systemic therapies have been approved (atilizumab plus bevacizumab, sorafenib, levatinib, regorafenib, cabozantinib and ramorubicin)[14]. In the absence of contraindications (e.g., bleeding risk), multiple authoritative guidelines recommend atezolizumab plus bevacizumab as a first-line therapeutic option for HCC[92,175-177]. In recent years, the combination of interventional and systemic therapy has become an important tool in the treatment of PLC[178,179].

There are two types of multi-targeted kinase inhibitors: one with anti-proliferative and anti-angiogenic properties through inhibition of receptors, such as platelet-derived growth factor receptor (PDGFR) and vascular endothelial growth factor receptor (VEGFR) tyrosine kinases, and the other, monoclonal antibodies that inhibit VEGF/VEGFR pathway[180]. The former drugs include sorafenib, lenvatinib, cabozantinib, and regorafenib[181]. Sorafenib was the first adopted first-line treatment for patients with advanced HCC. Superior efficacy of sorafenib over placebo has been demonstrated in patients with advanced HCC (median OR: 10.7 months *vs.* 7.9 months; HR: 0.69; 95%CI: 0.55-0.87)[182]. Lenvatinib is an inhibitor of VEGF receptors 1-3, FGF receptors 1-4, PDGFRα, RET, and KIT. A randomized, non-inferiority trial enrolling 1,492 patients has demonstrated that in untreated advanced HCC, lenvatinib is proven to be non-inferior to sorafenib in terms of OS (Median OS: 13.6 months *vs.* 12.3 months; risk ratio: 0.92; 95%CI: 0.79-1.06). However, Lenvatinib adverse reactions are more frequent, mainly focusing on skin reactions, diarrhea, and hypertension[183]. In addition to these two drugs, first-line treatment options include the combination of Atezolizumab and Bevacizumab, which has been shown in phase 1b trials to have better OS outcomes and progression-free survival compared to sorafenib [OS: 67.2%; (95%CI: 61.3 to 73.1) for the former and 54.6%, (95%CI: 45.2 to 64.0) for the latter]. Second-line therapies mainly included regorafenib, Cabozantinib, and Ramucirumab[184-186]. Phase 3 clinical trial studies have shown that Regorafenib has the best median survival time (10.6 months), followed by Cabozantinib (10.2 months), and Ramucirumab was the worst (8.5 months); common adverse events mainly include hypertension and skin reactions. The most common immunotherapy is immune checkpoint inhibitors to enhance existing immune responses. The use of ICI is becoming increasingly common[187]. There are successful trials showing the ability of ICI to improve survival[188]. Drugs include PD-L1 antibodies (durvalumab, atezolizumab, and avelumab), anti-PD-1 antibodies (nivolumab, pembrolizumab, and camrelizumab), and anti-CTLA-4 antibodies (ipilimumab and

tremelimumab)[180]. Nivolumab, a PD-1 inhibitor, is currently used as a second-line systemic therapy for patients with advanced HCC. Median OS was 16.4 months (95%CI: 13.9-18.4) in the nivolumab group and 14.7 months (95%CI: 11.9-17.2) in the sorafenib group [risk ratio: 0.85; (95%CI: 0.72-1.02); $P = 0.075$]. Nivolumab is considered to have a better safety profile compared to sorafenib, although OS was not significantly improved[189].

The gemcitabine combined with cisplatin (GEMCIS) chemotherapy regimen has been selected for the first-line treatment of ICC[190]. Mutation-based therapies offer promising prospects for personalized treatment. Representative drugs include those targeting fibroblast growth factor receptors (FGFRs), isocitrate dehydrogenase-1 (IDH1), human epidermal growth factor receptor-2 (HER2), and the B-Raf proto-oncogene (BRAF)[191]. These drugs have positive therapeutic effects in ICC by specifically targeting genetic alterations[192]. ICC is associated with a rich and diverse TME[193,194]. TME may be associated with the generation of immune escape responses in CCA[195] and an important entry point for molecularly targeted therapies, immunotherapies, and combination therapies[196]. A growing body of research data support that various components of the tumor-responsive stroma (TRS) play a crucial role in the development of CCA[197,198]. Other studies have shown that regulation of PD-1 and PD-L1 is the key mechanism of immune escape in ICC[199].

PREVENTION

Antiviral therapy

Patients with active chronic hepatitis B, defined as HBV DNA greater than 2,000 IU/mL, alanine aminotransferase (ALT) above the upper limit of normal, or at least moderate hepatic necroinflammation or fibrosis, are candidates for treatment. In addition, candidates for treatment include patients with detectable HBV DNA, compensated or uncompensated cirrhosis, and a family history of HCC. Patients with extrahepatic manifestations are also candidates for treatment[200]. Those with serum HBeAg antibodies < 2,000 IU/mL, normal HBV DNA, and normal ALT are usually not candidates for treatment. However, they require lifelong follow-up due to the risk of reactivation and development of extrahepatic manifestations[201]. The cost of antiviral nucleotide analogs (NAs) has been reduced, especially in China, providing more HBV-infected individuals with the opportunity to receive anti-HBV treatment. Currently approved therapeutic agents include pegylated interferon (PEG-IFN) and NAs[202]. WHO recommends vaccination as a preventive measure against HBV infection[21].

HBV plays an important role in promoting hepatocarcinogenesis and unfavorable prognosis. We have demonstrated that the key mutations including *C1673T*, *A1726C*, *A1727T*, *C1730G*, *C1766T*, *A1762T/G1764A*, *T1768A*, *C1773T*, and *C1799G* in HBV genotype C significantly increased the risk of cirrhosis, and that the major HBV mutant haplotype *1653C-1674G/C1753V-1762T/1764A* was detected 6.28 times more frequently in HCC than in non-HCC HBV-infected patients, with high specificity and high frequency of detection, making it applicable to HCC prediction[54]. HBV genotype C, PreS2 promoter variants, *C105T*, *T1753V*, *A1762T/G1764A*, and other HBV variants were found to be independent risk factors for HCC[55-57]. Through a systematic analysis of HBV mutations with high specificity and detection rate in HCC, we have found that the frequencies of PreS deletion and the *C1653T*, *T1753V*, and *A1762T/G1764A* mutations gradually increase at each stage of "triology" of HBV-induced hepatocarcinogenesis. Upon HBV infection, *A1762T/G1764A* mutation appears earlier, while PreS deletion, *C1653T* and *T1753V* mutations appear later[59]. HCC-associated mutations in the HBV pre-S region and the core promoter/enhancer II region have been found to accumulate progressively during the progression of chronic HBV infection to HCC, and these mutations and their combination predict the development of HCC[58]. Our cohort study has demonstrated that these combined mutations predict HCC development 6 years earlier[60]. The application

of the combined detection technology of high-risk HBV mutations to monitor the occurrence of HCC in HBV-infected patients and to identify high-risk populations lays the foundation for the development of secondary prevention of HCC. HBV mutations are also predictive of HCC recurrence and poor prognosis. The presence of some HBV mutations such as *A1762T*/*G1764A* in serum not only predicts hepatocarcinogenesis, but also indicates the likelihood of HCC recurrence and metastasis, whereas HBV mutations in either cancerous or paracancerous tissues do not have such effects[61]. The *G40C* mutation in the pre-HBV S region also independently predicts a poor prognosis in HCC[62]. In this way, HBV evolution not only promotes HCC occurrence but also predicts a poor HCC prognosis, and thus serves as a marker for the prediction of HCC occurrence (diagnostic), prognosis (prognostic), and therapeutic efficacy (predictive), all of which play a guiding role in tertiary prevention of HBV-induced carcinogenesis.

Antiviral therapy for HCV includes Direct-Acting Antivirals (DAAs), PEG-IFN, NA, and ribavirin. The emergence of DAAs has led to an improvement in HCV antiviral therapy, with sustained viral response (SVR) rates of more than 90%[203]. Combination therapy is thought to have better efficacy. In a large cohort study of more than 3,000 first-treatment patients, IFN-ribavirin combined therapy was effective in reducing fibrosis and halting the progression of fibrosis in 92% of patients[204]. HCV mutations in the core genes including *A028C*, *G209A*, *C219U*/*A*, *U264C*, *A271C*/*U*, *C378U*/*A*, *G435A*/*C*, and *G481A* were significantly associated with an increased risk of HCC, whereas HCV *U303C*/*A* mutation was associated with a decreased risk of HCC[205]. There is a lack of studies on the association between characteristic HCV mutations and HCC. It remains to be explored whether the mechanism of HCV-HCC is similar to that described for HBV-HCC by Cancer Evo-Dev theory. This could be a potential breakthrough for future HCV surveillance and prevention.

Lifestyle interventions

Physical activity has a clear protective effect against HCC. Exercise not only significantly prevents the development of cancer, but also has a clear protective effect on all types of cancer-related deaths[206]. Physical activity is effective in improving insulin tolerance, promoting hepatic fatty acid metabolism, and modulating inflammatory molecules, which in turn has significant benefits for liver health. A large body of evidence has suggested that physical activity has a clear inhibitory effect on the development of PLC, particularly HCC, reducing the overall incidence of PLC by more than 20%. Non-professional sports of 7.5-15 h per week reduce the risk of PLC by 18%-27%, and moderate-intensity exercise reduces the risk of HCC by 23% and the risk of death from HCC by 19%[207]. Aggressive and effective clinical treatment combined with public health measures including aerobic exercise such as running and swimming is important for the tertiary prevention of HCC.

SPECIFIC PREVENTION AND TREATMENT FOR THE OCCURRENCE AND RECURRENCE OF HBV-HCC METASTASIS

Intrinsic factors resisting HCC recurrence and metastasis

From a study cohort of HBV-HCC patients with recurrence, tumor tissue samples were selected and subjected to high-throughput RNA sequencing, miRNA sequencing, and circRNA sequencing, resulting in the identification of 59,711 circRNA sequences, 55,752 of which were annotated in the CircAtlas database. The 3,959 novel circRNA sequences were analyzed using bioinformatics lineage enrichment analysis, identifying circRNAs significantly associated with recurrence and prognosis. Two of the most significant circRNAs, circKCNN2 and circGLS2, were experimentally validated. High expression of circKCNN2 in tumor tissues indicated a reduced risk of recurrence in patients. Ectopic expression of circKCNN2 in HCC cell lines significantly inhibited proliferation, migration, invasion, clonal formation, and *in vivo* tumorigenic capacity of HCC cells. The upstream transcriptional regulatory repressor nuclear factor Y α subunit (NFYA)

and downstream effector molecules miR-520c-3p, MBD2, and FGFR4 of circKCNN2 were identified, demonstrating that circKCNN2 upregulated MBD2 expression through the adsorption of miR-520c-3p to inhibit the malignant phenotype of HCC. Studies utilizing HCC cell lines and organoids revealed that short-term overexpression of circKCNN2 produced a synergistic antitumor effect with Lenvatinib by inhibiting FGFR4[208,209]. This research offers a novel intervention for tertiary prevention, such as the recurrence of HBV-HCC.

Establishment of innovative technologies for tumor-specific gene therapy for HCC and other tumors

By leveraging the gene transcriptional regulatory sequences - promoters and enhancers - of HCC and liver tissue-specific molecules such as AFP and albumin, we have developed a cancer-specific gene therapy for the treatment of HCC. This approach has enabled recombinant retroviral vectors to express exogenous genes within HCC tissues, not in extrahepatic tissues. Notably, the expression of immune-regulatory factors in tumor tissues has significantly improved the tumor immune microenvironment, while avoiding damage to normal tissues, such as bone marrow. This strategy exerts potent antitumor effects[210,211]. This study introduces an effective and specific new measure for HCC-based cancer-specific prevention and treatment, representing a valuable attempt at targeted therapy for the microenvironment of HCC.

Establishment of a predictive index system and specific preventive measures for postoperative recurrence of HBV-HCC

In our established postoperative follow-up cohort study of post-HBV HCC, we identified independent risk factors for HCC postoperative recurrence and death. These include tumor diameter greater than 3 cm, incomplete tumor envelope, numerous satellite foci, microvascular infiltration, low tumor differentiation, advanced Barcelona staging, elevated gamma-glutamyl transpeptidase levels, and viral concentrations exceeding 10^4 copies/mL. Anti-HBV treatment emerged as the sole independent protective factor against HCC recurrence and death. A subsequent standard randomized controlled clinical trial, coupled with a multifactorial Cox proportional hazards model analysis, confirmed that standard antiviral therapy with NAs significantly reduced HBV-HCC postoperative recurrence [HR, 95%CI; 0.41, 0.32-0.70] and prolonged HCC-related death (0.26, 0.14-0.50). Importantly, antiviral therapy significantly reduced deaths within two years after HCC (0.41, 0.27-0.62) and significantly improved liver function in HBV-HCC patients at six months postoperatively ($P < 0.0001$), facilitating rapid recovery of postoperative residual liver size and function. Overall, specific antiviral therapy improved four-year postoperative survival by 82.3%. However, antiviral therapy did not exhibit these effects in patients with the integration of the X gene of 3' truncated HBV (Ct-HBx) in the genome of the residual liver[212]. This finding has propelled postoperative antiviral therapy for HBV-HCC into clinical guidelines and raised a new question: the integration of Ct-HBx in the genome of the residual liver promotes recurrent metastasis, which can only be addressed by specifically splicing Ct-HBx in the genome of the residual liver in patients with Ct-HBx integration or by conducting specific gene therapy.

SUMMARY AND CONCLUSION

PLC as a global disease will likely continue to increase in number in the future, and although infectious factors are still the major risk factors, metabolic factors seem to be on the rise as the quality of life improves. China has the largest number of PLC cases, and HBV infection remains the major risk factor for HCC in the Chinese population. Cancer Evo-Dev has discovered the regulation of tumor suppressor genes, which provides new ideas for antitumor therapy. There is still a lack of studies on the relevance of HCV-characteristic mutated genes for HCC, and whether Cancer Evo-Dev can be applied to HCV-HCC remains to be clarified. Since the prognosis of PLC is extremely poor, its early monitoring and primary prevention are especially important. Abdominal ultrasound and serum marker tests are usually used as early screening tools for PLC because of their maturity and cheapness. However, its sensitivity remains suboptimal, and

monitoring of relevant virus-specific genotypes in patients on combination antiviral therapy for infectious hepatitis may be an important preventive measure to achieve precise prevention and control of HBV/HCV-HCC. Surgical resection and liver transplantation are often applied for early-stage PLC, while systemic drugs are often used for intermediate and late-stage PLC, and the combination of multiple methods is considered to be the main strategy to improve the survival rate and time of patients. Vaccination, adopting a good lifestyle (abstaining from smoking and alcohol, avoiding a sedentary lifestyle, and eating more fruits and vegetables), and increasing physical activity are effective in preventing PLC.

DECLARATIONS

Authors' contributions

Contributed to the conception and the design of the study, data search, and manuscript writing: Feng Y
Made contributions to conception and data search: Fang L
Supervised the article concept and revised the manuscript: Cao G

Availability of data and materials

Not applicable.

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Conflicts of interest

Cao G is the Editor-in-Chief of the journal *Hepatoma Research*. Cao G was not involved in any steps of editorial processing, notably including reviewers' selection, manuscript handling and decision making. The other authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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