

The Etiology of Hepatocellular Carcinoma and Consequences for Treatment

ARUN J. SANYAL,^a SEUNG KEW YOON,^b RICCARDO LENCIONI^c

^aVirginia Commonwealth University Medical Center, Richmond, Virginia, USA; ^bThe Catholic University of Korea, Seoul, Korea; ^cPisa University School of Medicine, Pisa, Italy

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ABSTRACT

Most patients with hepatocellular carcinoma (HCC) have liver cirrhosis, which develops following long periods of chronic liver disease. Cirrhosis is characterized by a decrease in hepatocyte proliferation, indicating an exhaustion of the regenerative capacity of the liver, and results in an increase in fibrous tissue and a destruction of liver cells, which may ultimately lead to the development of cancerous nodules. Half of all cases of HCC are associated with hepatitis B virus infection, with a further 25% associated with hepatitis C virus. Other risk factors for developing HCC include alcoholic liver disease, nonalcoholic steatohepatitis, intake of aflatoxin-contaminated food, diabetes, and obesity. There are multiple factors involved in the etiology of

HCC, all of which have a direct impact on patient characteristics and disease course, and although a causative agent can often be identified, HCC remains an extremely complex condition associated with a poor prognosis. Additionally, the geographic variation in etiology means that information from different countries is needed in order to optimize surveillance methods and develop effective chemoprevention strategies. Unfortunately, there are still many gaps in our current understanding, and further research efforts are needed to fully elucidate the diverse mechanisms involved in the pathogenesis of HCC and offer optimal prevention strategies for those at risk. *The Oncologist* 2010;15(suppl 4):14–22

INTRODUCTION

Hepatocellular carcinoma (HCC) is the dominant form of primary liver cancer and is histologically and etiologically distinct from other forms of primary liver cancer [1]. Approximately 70%–90% of patients with HCC have an established background of chronic liver disease

and cirrhosis, with major risk factors for developing cirrhosis including chronic infection with hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease, and nonalcoholic steatohepatitis (NASH) [2, 3]. Additional risk factors for developing HCC include intake of aflatoxin-contaminated food, diabetes, obesity, certain

Correspondence: Arun J. Sanyal, M.D., F.A.C.P., Gastroenterology, Hepatology, Nutrition, Virginia Commonwealth University Medical Center, Richmond, Virginia, USA. Telephone: 804-828-6314; Fax: 804-828-2992; e-mail: asanyal@mcvh-vcu.edu Received January 22, 2010; accepted for publication October 6, 2010. ©AlphaMed Press 1083-7159/2010/\$30.00/0 doi: 10.1634/theoncologist.2010-S4-14

hereditary conditions such as hemochromatosis, and some metabolic disorders [2, 4, 5].

HCC is unusual among human cancers in that the causative agent is often clear. However, there are multiple etiologic factors affecting HCC, all of which vary by geographic location, have a direct impact on the characteristics of these patients, and influence the disease course, making HCC an extremely complex condition associated with a poor prognosis [6].

HCC carcinogenesis is a complex process that can involve various modifications to a number of molecular pathways as well as genetic alterations, and ultimately leads to malignant transformation and HCC disease progression [2, 7–11]. Here, we review the main mechanisms thought to be involved in hepatocarcinogenesis and discuss how these carcinogenic mechanisms differ according to the different etiologic risk factors.

RISK FACTORS

Cirrhosis

The primary risk factor for developing HCC is cirrhosis, the major causes of which are HBV and HCV infection. Indeed, there is evidence to show that 50% of all cases of HCC worldwide are associated with HBV infection, with a further 25% associated with HCV [12]. The annual incidence rates of HCC in patients with cirrhosis according to individual underlying disease are shown in Table 1. Although these incidence rates give an indication of the relative contributions of the underlying causes of cirrhosis to HCC progression, the development of cirrhosis and progression to HCC is complex and may involve a combination of etiologies, for example, patients coinfecting with both HCV and HBV [5].

Cirrhosis develops following long periods of chronic liver disease and is characterized by a decrease in hepatocyte proliferation, indicating an exhaustion of the regenerative capacity of the liver [13]. This is associated with an increase in fibrous tissue and a destruction of liver cells, which provides the soil for development of cancerous nodules [14]. Because liver cirrhosis can have a significant impact on liver reserve and is often an integral part of the morbidity and mortality associated with HCC, the presence and severity of cirrhosis must be defined in all patients in order to assess prognosis and make treatment recommendations.

To date, many studies have investigated the possible mechanisms involved in the development of HCC in patients with cirrhosis, and a number of mechanisms thought to accelerate cancer formation have been identified, includ-

Table 1. Annual incidence rates of hepatocellular carcinoma in patients with cirrhosis according to underlying disease [40, 75]

Underlying disease	Annual incidence (%)
Chronic hepatitis C	1–8
Chronic hepatitis B	1–15
Alcoholic liver disease	1
Nonalcoholic steatohepatitis	2.6
Hemochromatosis	2–6
Primary biliary cirrhosis	2
Autoimmune hepatitis	<0.2

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ing telomere dysfunction and alterations in the micro- and macroenvironment that stimulate cellular proliferation [2].

Telomerase plays an important role in maintaining telomere length and chromosomal stability in proliferating cells such as hepatocytes [15]. Shortening of telomere limits proliferation in these cells and is therefore thought to reduce the regenerative capacity of organs during aging and chronic disease [16]. In hepatocytes of a cirrhotic liver, telomeres are significantly shorter than in noncirrhotic tissue, and this shortening has been shown to correlate with fibrosis progression [16].

Telomere dysfunction has also been shown to increase the number of early-stage hepatic neoplasms in mouse models; however, this was accompanied by a decline in the occurrence of high-grade malignancies, suggesting that this mechanism alone is insufficient to drive disease progression to advanced HCC [17]. The effect of telomere dysfunction appears to be dependent on other factors, such as cell type and p53 status, with a combination of telomere dysfunction and p53 mutation accelerating tumor onset [18].

The decrease in hepatocyte proliferation that occurs during liver cirrhosis is thought to enhance cancer formation in cirrhotic livers. This was demonstrated in a rat model, in which the administration of various chemicals that inhibited hepatocyte proliferation also accelerated carcinogen-induced liver tumor formation [19]. Another characteristic of cirrhosis is the activation of stellate cells. This leads to an increase in the production of cytokines, growth factors, and products of oxidative stress [20], many of which have been shown to affect hepatocyte proliferation and so could play a role in tumor formation [2].

The main oncogenic pathways involved in HCC are phosphoinositol-3-kinase/Akt, myc, Wnt/ β -catenin, c-Met,

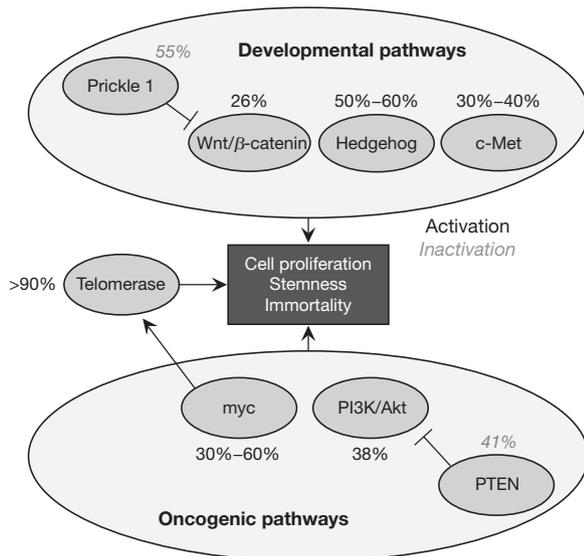


Figure 1. Main oncogenic pathways associated with hepatocarcinogenesis [2].

Abbreviations: PI3K, phosphoinositol-3-kinase; PTEN, phosphatase and tensin homologue deleted on chromosome ten.

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and hedgehog (Fig. 1) [2, 10, 11]. The latter three are developmental pathways, which suggests that some HCCs may arise from liver stem cells. The growth-inhibitory environment of a cirrhotic liver may activate and transform liver stem cells, and there is some evidence to suggest that a stem-cell gene-expression signature exists in a subset of human HCCs [21]. In liver cirrhosis, activation of Akt signaling is thought to promote tumor formation by suppressing transforming growth factor (TGF)- β -induced apoptosis [2]. Activation of this pathway has also been linked to activation of β -catenin signaling, so further driving the hepatocarcinogenic process.

Finally, a number of molecular alterations that affect DNA damage checkpoints have been described, which may promote tumor formation in the cirrhotic liver. These include loss of function of the *p53* tumor suppressor gene [22], inactivation of the p27 cell cycle regulator [23], loss of heterozygosity of the insulin-like growth factor 2 receptor locus [24], and loss of protein expression of the p16 cell cycle inhibitor [23].

HBV Infection

HBV infection causes acute and chronic liver disease, and has been shown to increase the risk for developing liver cancer 100-fold in chronic carriers [8]. Approximately 340,000 cases of liver cancer (54.4% of cases globally) are

attributable to HBV, with the majority of these in Africa, Asia, and the western Pacific region [25].

HBV is a partially double-stranded DNA-containing virus belonging to the *Hepadnaviridae* family. Infection with this virus is thought to cause HCC via both direct and indirect pathways. First, HBV infection causes hepatocyte injury and chronic necroinflammation, with subsequent hepatocyte proliferation, fibrosis, and cirrhosis. The continuous regeneration in cirrhosis leads to increased liver cell turnover and accumulation of mutations in the host genome that could result in genetic alterations, chromosomal rearrangements, activation of oncogenes, and inactivation of tumor suppressor genes [26]. However, HBV can also cause HCC in the absence of cirrhosis [2]. HBV is able to integrate its DNA into host cells and so may act as a mutagenic agent, causing secondary chromosomal rearrangement and increasing genomic instability [8]. In addition, the regulatory protein HBx is thought to transactivate genes involved in cell proliferation control, resulting in stimulation of the protein kinase C and nuclear factor kappa B pathways, as well as deregulation of cell cycle control and interference with cellular DNA repair and apoptosis [27].

HCV Infection

HCV infection causes chronic inflammation, cell death, proliferation, and cirrhosis of the liver [26]. Thus, HCV-related HCC is found almost exclusively in patients with cirrhosis [26]. The risk for developing HCC is \sim 17-fold higher in HCV-infected patients [28], although this risk varies depending on the degree of liver fibrosis at the time of HCV infection. Approximately 195,000 cases of liver cancer (31.1% of cases globally) are attributable to HCV, with northern and middle Africa being the areas of highest prevalence [25].

HCV belongs to the *Hepacivirus* genus of the *Flaviviridae* family [8]. Unlike HBV, HCV is an RNA-containing virus and so is unable to integrate into the host genome. HCV therefore causes HCC by various indirect mechanisms. For example, HCV core protein is thought to enter the host cell, where it localizes in the outer mitochondrial membrane as well as the endoplasmic reticulum and promotes oxidative stress. This results in activation of key signaling pathways such as the p38 mitogen-activated protein kinase and nuclear factor kappa B pathways, leading to up-regulation of genes involved in cytokine production and subsequent inflammation, alterations in apoptotic pathways, and tumor formation [7]. The nonstructural proteins of HCV, NS3, and NS5A are also thought to act as key mediators to induce oxidative stress and inflammation [7].

Interestingly, HCV infection has also been found to induce insulin resistance (IR), which in turn has been

closely linked to the development of fibrosis and type 2 diabetes in these patients [29]. Although the mechanisms involved in the development of IR are not fully understood, the immune response against HCV infection is thought to be involved and research suggests that the process may be multifactorial. Preclinical data from transgenic mice have demonstrated greater IR and higher levels of the proinflammatory cytokine tumor necrosis factor (TNF)- α in the presence of HCV core protein [30]. In humans, HCV infection is associated with significantly higher levels of HOMA-IR (homeostasis model assessment of IR), TNF- α , and interleukin 6 compared with healthy controls [31]. These proinflammatory cytokines are both known to induce IR [32], and there is evidence to suggest that Kupffer cells [7] stimulated by oxidative stress [33] and exposure to the HCV core protein [34] are a likely source. Although the mechanism has yet to be fully elucidated, one hypothesis concerning TNF- α -related IR proposes an inhibition of insulin receptor substrates [30]. Taken together, these data suggest that the process by which HCV infection can contribute to IR is complex and involves multiple mechanisms. Further evidence is needed to fully understand the relationship among HCV infection, immune response, IR, and HCC.

Finally, alcohol is an important cofactor in patients with HCV infection, with HCV reported in 4.6%–55.5% of alcoholics [35]. Patients with both HCV infection and alcohol abuse have been shown to develop more severe fibrosis and have higher rates of cirrhosis and HCC than nondrinkers [35]. The risk for developing HCC has also been shown to increase as levels of alcohol intake rise [28]. The mechanisms by which alcohol worsens HCV-related liver disease are not clear, although several possibilities have been proposed, including: greater HCV replication in the presence of alcohol; alcohol-associated changes in the hypervariable region of the viral genome, leading to more aggressive HCV-related liver disease and resistance to interferon therapy; and inhibition of hepatic expression of *Bcl-2* by alcohol, resulting in increased apoptosis and more severe liver injury [35]. However, the dominant mechanism for synergism between alcohol and HCV infection appears to be increased oxidative stress. As mentioned above, HCV core protein localizes at the mitochondrial membrane and promotes oxidative stress. Ethanol potentiates this mitochondrial injury by further increasing reactive oxygen species (ROS) production and enhancing hepatic glutathione oxidation. Moreover, alcohol and HCV core protein act synergistically in causing lipid peroxidation and increasing hepatic TGF- β and TNF- α expression [35].

Coinfection with HIV

HIV infection shortens the survival of patients with HCV-related cirrhosis [36]. In addition, hepatocarcinogenesis could be a more rapid and aggressive process in HIV/HCV coinfecting patients [37].

Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is a condition of unknown etiology that is characterized by a progressive destruction of the liver parenchyma, often leading to fibrosis and liver cirrhosis. Studies have shown that HCC occurs rarely in patients with AIH (<1%) and is almost exclusively restricted to patients with AIH and long-standing liver cirrhosis [38–40].

This surprisingly low incidence of HCC in patients with AIH suggests that there may be some pathologic mechanism preventing cancer progression. One hypothesis has highlighted the common use of immunosuppressants in these patients. Because these agents suppress cytokines such as interleukin 1 β and TNF- α , which are known to play an important role in tumor growth and proliferation, it has been suggested that downregulation of these cytokines might contribute to a protective mechanism from the development of HCC [40]. If confirmed, this could affect future therapeutic options afforded to patients with HCC. However, further characterization is needed before any definitive conclusions can be drawn.

Nonalcoholic Fatty Liver Disease and NASH

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disorder in western countries, with ~20% of individuals affected [41]. It occurs in the absence of alcohol use, although the hepatic histology appears consistent with alcoholic hepatitis [42], with changes in histology including hepatic steatosis, inflammation, hepatocyte injury as exemplified by cytologic ballooning and Mallory's hyaline, and fibrosis [43]. Thus, NAFLD comprises a spectrum of conditions ranging from fat alone to fat plus inflammation, fat plus ballooning degeneration, and NASH, the latter being the most serious form of NAFLD [42, 44].

Epidemiologic studies show that NAFLD is closely linked with the metabolic syndrome, particularly type 2 diabetes mellitus and obesity [45], with NAFLD occurring almost universally among diabetic patients who are morbidly obese [46]. Moreover, NASH in association with multiple components of the metabolic syndrome is thought to increase the risk for developing chronic liver disease, cirrhosis, and HCC [45]. Additionally, a recent study has shown that NAFLD is a principal risk factor in the development of HCC, irrespective of age [47].

Although the pathophysiologic mechanisms driving

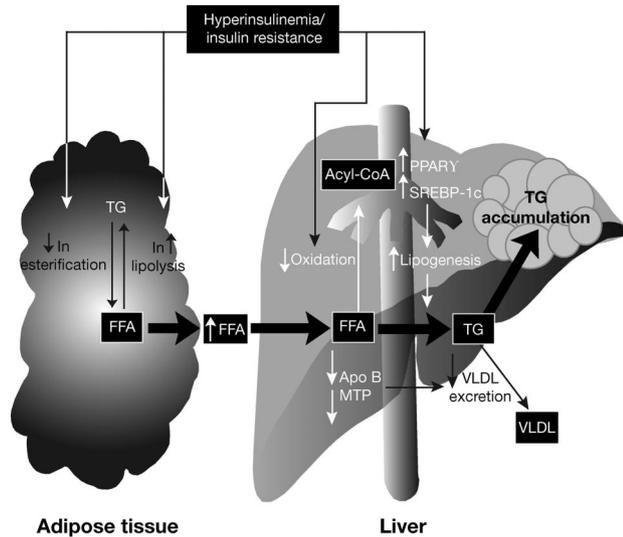


Figure 2. Insulin resistance and the development of non-alcoholic steatohepatitis [46].

Abbreviations: Apo B, apolipoprotein B; FFA, free fatty acids; MTP, microsomal triglyceride transfer protein; PPAR γ , peroxisome proliferator-activated receptor gamma; SREBP-1c, sterol regulatory element binding protein-1c; TG, triglycerides; VLDL, very low-density lipoprotein.

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NAFLD and the associated progressive hepatocellular damage are not fully understood, a number of processes have been described. A well-established driver of NAFLD is IR (Fig. 2). IR is a complex process that likely involves both insulin secretion and action, and is closely associated with obesity [46]. IR causes increased peripheral lipolysis and increases circulating fatty acids that are taken up by the liver. At the same time, there is an increase in de novo liponeogenesis in the hepatocytes and a reduction in the hepatic secretion of very-low-density lipoproteins, resulting in hepatic triglyceride accumulation or fatty liver.

Increased intrahepatic fatty acid levels are also thought to provide a source of oxidative stress, which may play an important role in the development from steatosis to steatohepatitis associated with progression to cirrhosis [48]. ROS produced by the mitochondria oxidize fat deposits to release lipid peroxidation products, which together with ROS impair the respiratory chain via oxidative damage to the mitochondrial genome [49]. ROS and lipid peroxidation products also increase the production of various cytokines, including TNF- α , TGF- β , and Fas ligand. Proinflammatory cytokines also activate hepatic stellate cells, which produce a collagen matrix and drive the development of fibrosis [9].

Table 2. Common causes of liver cirrhosis that could result in the development of hepatocellular carcinoma [52]

Most common causes of cirrhosis	Less common causes of cirrhosis
Alcohol (60%–70%)	Autoimmune chronic hepatitis
Biliary obstruction (5%–10%)	Drugs and toxins
Primary/secondary biliary cirrhosis	Genetic metabolic diseases
Chronic hepatitis B or C virus (10%)	Infection
Hemochromatosis	Vascular abnormalities
Nonalcoholic fatty liver disease (10%)	Veno-occlusive disease
	Idiopathic

From Heidelbaugh JJ, Bruderly M. Cirrhosis and chronic liver failure: Part I. Diagnosis and evaluation. *Am Fam Physician* 2006;74:756–762. Reproduced with permission from the American Academy of Family Physicians.

Other Risk Factors

HCC in noncirrhotic livers is rare and mostly occurs as a result of HBV infection, as described earlier [2]. However, HCC in noncirrhotic livers can also occur as a result of contamination of foodstuffs with aflatoxin B1 [50]. Aflatoxin B1 is a mycotoxin produced by the *Aspergillus* fungus that grows readily on food when stored in warm, damp conditions [2]. When ingested, it is metabolized into the active AFB₁-*exo*-8,9-epoxide, which binds to DNA to cause damage, including the production of mutations of the *p53* tumor suppressor gene. Indeed, this mutation has been reported in 50% of HCC tumors in southern Africa, where aflatoxin B1 is a known risk factor for developing HCC [51].

Another risk factor for developing HCC is alcoholic liver disease. Heavy alcohol intake (>50–70 g/day) is the most common cause of liver cirrhosis [52], and is a well-established risk factor for HCC, although it is unclear whether HCC risk is also affected by light to moderate alcohol intake [2]. As mentioned, heavy alcohol intake is thought to act synergistically with HCV to promote liver cirrhosis [28]. Similar results were seen for HBV, with a twofold higher odds ratio for each hepatitis virus infection for drinkers of >60 g/day [28].

Finally, a number of other risk factors for developing HCC exist, including primary biliary cirrhosis, silent chronic liver disease, and hereditary hemochromatosis [52]. Other less common causes of hepatic cirrhosis that could contribute to the development of HCC are shown in Table 2 and include genetic metabolic diseases, certain infections, and vascular and venous abnormalities. Implicated genetic disorders of the metabolism include α -1

antitrypsin deficiency; various amino acid, bile acid, carbohydrate, and lipid disorders; urea cycle defects; porphyria; and Wilson's disease. Infectious agents such as brucellosis, syphilis, echinococcosis, and schistosomiasis are known to cause cirrhosis, as are vascular abnormalities such as right-sided heart failure, pericarditis, hereditary hemorrhagic telangiectasia, and veno-occlusive diseases, for example, Budd-Chiari syndrome [52, 53].

SURVEILLANCE

Given the established links between liver cirrhosis and the development of HCC, there is a strong rationale for surveillance of patients with cirrhosis, and guidelines support observation of this group, regardless of etiology. The value of surveillance has already been demonstrated in Japan, where 80% of HCC cases are detected at an asymptomatic stage as a result of screening patients with known cirrhosis. In contrast, in the U.K., up to 40% of cases present with HCC as the first indication of underlying liver disease [54]. Furthermore, studies in China and Italy have shown that survival is improved by surveillance for HCC [55, 56].

Earlier diagnosis of HCC significantly affects treatment choices [54, 57–60] and treatment recommendations for patients with earlier-stage HCC are described in detail elsewhere in this issue [61]. The benefits of earlier diagnosis through surveillance were highlighted in a retrospective chart review of patients with HCV and HCC treated in the South Texas Veteran Healthcare System. That study showed that all screened patients were diagnosed with earlier-stage disease and were 10 times more likely to have received potentially curative treatment than unscreened patients [62].

The serum marker α -fetoprotein (AFP) has been used as a diagnostic test for HCC; however, it has limited sensitivity/specificity as a surveillance test when used alone. Ultrasound is a widely used method of detecting HCC, although it has been suggested that the reliability of this method is influenced by the expertise of the operator as well as the provision of dedicated equipment [54]. However, as expected, the levels of sensitivity and specificity are also dependent on the size of the tumor, with ultrasound able to detect 80%–95% of tumors 3–5 cm in diameter and 60%–80% of tumors <1 cm in diameter [54]. Combining ultrasound and AFP appears to improve detection rates, but also increases costs and the rate of false positives. The American Association for the Study of Liver Diseases guidelines recommend that surveillance for HCC be performed using ultrasonography at 6- to 12-month intervals and that AFP alone should not be used for screening unless ultrasound is not available [59].

Currently, the presence of cirrhosis is the key factor that

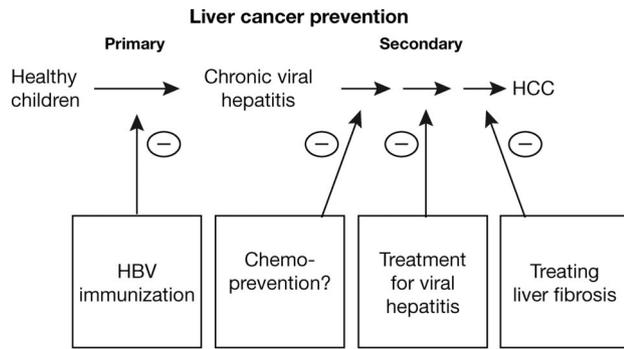
influences the decision to implement surveillance, irrespective of the etiology of the liver disease. However, guidelines also support surveillance for HCC in specific groups of individuals with HBV, even without cirrhosis (e.g., those with a family history of HCC) [59, 63, 64]. There is some suggestion that NAFLD/NASH may predispose to HCC in the absence of cirrhosis [65, 66], although more data are needed on this.

IMPACT OF ETIOLOGY ON TREATMENT

The complex etiology of HCC affects the possible treatment options offered to patients. For example, patients with compromised liver function as a result of cirrhosis are ineligible for surgical resection because of the risk for postoperative decompensation [54]. The coexistence of cirrhosis and associated liver dysfunction may also limit the nonsurgical treatment options available and is likely to be a large contributory factor to the poor prognosis of many HCC patients. The presence of comorbidities such as cardiac conditions or neurodegenerative disorders in patients with hemochromatosis, or diabetes, obesity, or cardiac conditions in patients with NASH, may influence treatment options for HCC, and the use of concomitant medications should also be carefully considered.

Patients with HBV or HCV require antiviral therapy to control viral replication and improve cirrhosis-related outcomes. For patients with HBV infection, antiviral therapy may also block the hepatocarcinogenic properties of viral proteins such as HBx [5, 67]. Indeed, prospective and retrospective studies of large numbers of patients with chronic HBV infection and advanced liver disease, including cirrhosis, have shown that treatment with the nucleotide analog lamivudine delays disease progression and also reduces the incidence of HCC [67, 68]. Because chemotherapy can reactivate the virus in HBV carriers, prophylactic lamivudine therapy during and 6 months after treatment is recommended in patients scheduled to receive chemotherapy [67].

Prevention of HCC is also an important goal, and opportunities exist for the further development of preventative measures (Fig. 3) [69]. The success of intervention was first demonstrated by the nationwide Taiwanese vaccination program against HBV, which was implemented in the 1980s and successfully reduced both the number of HBV carriers and the incidence of HCC in children, with recent evidence confirming that the benefit is maintained into early adulthood [70–73]. Subsequently, studies conducted in patients with HCV, with and without cirrhosis, have shown that treatment with interferon therapy is associated with a lower risk for developing HCC [74]. However, the potential role of interferon in future treatment strategies to



⊖ : interrupt or inhibit

Figure 3. Strategies for primary and secondary liver cancer prevention in healthy subjects and in those with chronic hepatitis infection [69].

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

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prevent HCC in HCV-infected patients remains controversial.

CONCLUSIONS

These findings show that the etiology of HCC is extremely complex, with many confounding factors affecting disease course and patient prognosis. For example, most patients with HCC have cirrhosis, which develops following long periods of chronic liver disease and results in increased fibrous tissue and a destruction of liver cells, and may ultimately promote tumor development. Both HBV and HCV infection increase the likelihood of developing liver cancer, with an incidence of 54.4% and 31.1% of liver cancer cases globally, respectively. Additional risk factors for developing HCC include NAFLD/NASH, alcoholic liver disease, intake of aflatoxin-contaminated food, diabetes, and obesity. The presence of multiple components, such as alcohol abuse in patients with HCV or obesity in patients with

NAFLD, also appears to further drive the hepatocarcinogenic process.

A broad range of mechanisms involved in the pathogenesis of HCC have been identified, including telomere dysfunction, activation of oncogenic pathways, abrogation of DNA damage checkpoints, activation of proinflammatory pathways, and induction of the oxidative stress response. However, the exact role of each of these pathways is thought to vary according to the etiologic agent, and significant gaps remain in the data available. Further research efforts are therefore needed to fully elucidate the diverse mechanisms involved in the pathogenesis of HCC as well as the possible interactions between different etiologic agents. The geographic variation in etiology means that further information from different countries around the world is also needed if we are to improve our global understanding in this area and develop effective surveillance programs and chemoprevention strategies. Indeed, a better understanding of the etiology of HCC may offer us the best chance of achieving earlier diagnosis and intervention, which would ultimately improve the outlook for those at risk for developing HCC.

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AUTHOR CONTRIBUTIONS

Conception/Design: Arun J. Sanyal, Seung Kew Yoon, Riccardo Lencioni
Data analysis and interpretation: Arun J. Sanyal, Seung Kew Yoon, Riccardo Lencioni
Manuscript writing: Arun J. Sanyal, Seung Kew Yoon, Riccardo Lencioni
Final approval of manuscript: Arun J. Sanyal, Seung Kew Yoon, Riccardo Lencioni

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