Review Article

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Review of hepatocellular carcinoma: Epidemiology, etiology, and carcinogenesis

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Abstract:

Since the 1970s, the epidemic of hepatocellular carcinoma (HCC) has spread beyond the Eastern Asian predominance and has been increasing in Northern hemisphere, especially in the United States (US) and Western Europe. It occurs more commonly in males in the fourth and fifth decades of life. Among all cancers, HCC is one of the fastest growing causes of death in the US and poses a significant economic burden on healthcare. Chronic liver disease due to hepatitis B virus or hepatitis C virus and alcohol accounts for the majority of HCC cases. Incidence of nonalcoholic fatty liver disease has been on the risem and it has also been associated with the development of HCC. Its pathogenesis varies based on the underlying etiological factor although majority of cases develop in the setting of background cirrhosis. Carcinogenesis of HCC includes angiogenesis, chronic inflammation, and tumor macroenvironment and microenvironment. There is a significant role of both intrinsic genetic risk factors and extrinsic influences such as alcohol or viral infections that lead to the development of HCC. Understanding its etiopathogenesis helps select appropriate diagnostic tests and treatments.

Keywords:

Carcinogenesis, epidemiology, etiology, hepatocellular carcinoma, pathogenesis

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver.[1] The global burden of cancer in 2012 was an all-time high of 14 million cases and is predicted to grow to 22 million over the next two decades.[2] Liver cancers have the seventh highest age-adjusted incidence rate in the world, with 0.8 million cases diagnosed for the year 2012.[3] Its most common etiological factor in the world is hepatitis B virus (HBV) infection. The development of cirrhosis is associated with high risk for developing HCC with most common risk factors including alcohol, viral hepatitis such as hepatitis C virus (HCV), and nonalcoholic fatty liver disease (NAFLD). Due to the wide prevalence of HCC, it carries a significant economic burden on society at large, especially in the East Asian countries where HBV infection is endemic. This is the third most common cause of cancer-related death in the world and seventh most common cause in the United States (US).[3,4] Surveillance programs have also been implemented to screen for HCC in high-risk individuals, which is more cost-effective than the treatment of HCC.

The initial approach in the management of HCC is to determine if either surgical resection or liver transplantation is feasible. Since the majority of HCC cases develop in cirrhotic patients, surgical interventions can become challenging and the treatment has been directed toward liver transplantation. Certainly, prevention of the tumor seems to be a preferred strategy to tackle the shortage of donor organs. Hence, understanding the epidemiology, etiology, and pathogenesis of this economically burdening cancer is of prime significance for hepatologists and oncologists.

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Epidemiology

HCC is more common among males with a male:female ratio of 2.4 in its worldwide distribution.[5] The most common age at presentation is usually between 30 and 50 years.[6] HCC is predominant in Asian countries including China, Mongolia, Southeast Asia, and Sub-Saharan Western and Eastern Africa.[3] The prevalence of HCC in developed countries of the world is lower, except Japan, Italy, and France.

In the US surveillance, epidemiology, and end results (SEER) database program, HCC accounts for 65% of all cases of liver cancers.[7,8] The incidence rate of HCC has increased from 1.4/100,000 cases/year between 1976–1980 to 6.2/100,000 cases reported in 2011.[8] There are almost two times higher incidence of HCC among dark-skinned males compared to light-skinned males; a similar trend is seen among females with two times higher incidence rate among dark-skinned when compared to light-skinned.[8] The 5-year survival trend has improved by >60% from 1975 to 2005.[9,10]

A SEER-Medicare database, between 1991 and 1999, showed that the annual economic burden of HCC was 454.9 million US dollars.[11] This included healthcare cost and cost due to loss of productivity which was responsible for 89.2% and 10.8% of the total cost, respectively. Interestingly, HCC was most frequently found to be in individuals with lower socioeconomic status and among immigrant Hispanics, likely due to inadequate access to health care.[12]

Etiology

HCC has a multitude of etiological risk factors, with some that have shown to have a strong association with development of HCC. Hepatotropic viruses such as HBV, HCV, and hepatitis D virus (HDV) have a strong association with development of HCC; thus, the worldwide distribution of HCC mirrors the distributions of such viral infections.[13] Various other associated risk factors are summarized in Table 1. Around 80%–90% of HCC cases occur in the setting of underlying cirrhosis.[14] In addition, there is an incremental effect of presence of more than one risk factor responsible for HCC as the presence of HBV/HCV and HBV/HDV coinfections increases risk of HCC by two to six folds. Similarly, alcohol abuse further increases this risk.[15,16] Below, discussion will be focused on the most common risk factors for HCC.

Table 1: Risk Factors for Hepatocellular Carcinoma

Hepatitis B Virus Infection
Hepatitis C Virus Infection
Hepatitis D Virus Infection
Alcohol
Non-Alcoholic Fatty Liver Disease & Non-Alcoholic Steatohepatitis
Obesity and Diabetes
Aflatoxin
Hereditary Hemochromatosis
Smoking
Tyrosinemia
Glycogen Storage Disease Type 1a
Oral Contraceptives
Cirrhosis

Hepatitis-B virus

HBV is the most common cause for HCC worldwide accountable for an estimated 54% of all liver cancers.[17,18] Chronic infection with HBV increases the relative risk for developing HCC 15–20-fold with a mortality rate of approximately 30%–50% among all cases of chronic HBV infection.[19,20] Accordingly, regions endemic for chronic HBV infection have a similarly high incidence of HCC with >20 age cases per 100,000 males.[3,21] In these endemic regions, transmission of virus is mostly by vertical and perinatal exposure, compared to developed countries where the transmission is through sexual and parental contact with infected blood like in case of intravenous drug abusers.[21] In the US, around 10%–16% of HCC cases are attributed to HBV.[22,23] Approximately 10% of HIV-infected individuals are coinfected with chronic hepatitis B and are at higher risk of developing HCC than those with hepatitis B alone and in HIV patients with lower CD4+ counts.[24] A unique variant of HBV infection, occult HBV infection, occurs when the HBV-infected individual has the HBV viral particle but is tested negative for hepatitis B surface antigen; however, this can lead to cirrhosis and HCC.[25,26]

Based on genetic sequencing, human HBV is currently grouped into 10 genotypes (A-J).[27] The most prevalent genotypes in the US are A and C, except Western US, where B and C are the predominant genotypes.[28] Patients with genotypes C and D are more likely to progress to cirrhosis and HCC, as well as have poorer response to treatment with interferon (IFN) and/or lamivudine (compared to genotypes A and B).[29,30] Chronic HBV infection by genotype C puts one at risk of developing HCC, more than the other genotypes.[31]

Hepatitis-C virus

HCV is the second most common risk factor for HCC, with an estimated 10%–25% of all cases attributed to it around the world.[20,32] In developed countries including Japan and the US, HCV is most common causative agent.[33,34] Chronic HCV infection is associated with a 20–30-fold increased risk of developing HCC as compared to uninfected individuals. Approximately 2.5% of patients with chronic HCV infection develop HCC.[35] Even in the absence of an effective vaccine for

HCV, implementation of a combination of laboratory measures such as screening of blood and blood products, public health initiatives such as identification and counseling, and treatment of infected and high-risk individuals can reduce and possibly even eliminate HCV infection rates globally.[36] Nearly 80% of the HIV-infected individuals who get infected with HCV develop chronic hepatitis C and this coinfection puts them at higher risk for developing HCC.[37,38] In addition, HCV and HBV coinfection puts one at higher risk of developing HCC. In a study by Kruse *et al*., among the HCV-infected veteran population with or without additional HBV infection (detectable HBV DNA in serum or not), the incidence rate of developing HCC was higher in coinfected patients with and without detectable HBV DNA compared with HCV-monoinfected patients.[39] HCV viremia is associated with increased risk of developing HCC with studies from the last decade showing decreased risk of HCC by nearly 57%–75% among IFN-treated HCV patients.[22] With the newer HCV direct-acting agents, the impact on incidence of HCV-induced HCC is uncertain.

Alcohol

Alcohol-related cirrhosis is considered to be the third most common cause for HCC.[40] Alcohol works synergistically with hepatotropic viruses to increase the likelihood of developing HCC.[15] This effect was more pronounced in those individuals who consumed more than 60 g of alcohol per day. A study looking into the risk of developing HCC among heavy alcohol users with chronic HCV infection showed that individuals were at 2.3 (95% confidence interval: 1.67–3.26) times higher risk of developing HCC if they were heavy alcohol users (defined as alcohol use of 210–560 g/week).[41] Heavy alcohol in HBV patients increases the risk for HCC by almost three times; however, the differences can possibly due to different working definitions of heavy alcohol consumption. Alcohol can independently cause HCC by development of cirrhosis independent of the presence of viral hepatitis. HCC carcinogenesis induced by alcohol is associated with recurrent inflammation and cycles of hepatocyte necrosis and regeneration with oxidative stress, finally resulting in cirrhosis.[42]

Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis

NAFLD is the one of the most common causes of chronic liver disease in the US and has been consistently found to be causative of HCC, which occurs mainly in the setting of cirrhosis. The incidence has been on the rise in parallel with the rising rates of obesity, diabetes, and metabolic syndrome. Nonalcoholic steatohepatitis (NASH) has similar outcome as that of chronic HCV infection as demonstrated in a Japanese study comparing two groups, each having one underlying condition and having similar Child-Pugh class.[43] The 5-year risk of developing HCC in NASH group was 11.7% as compared to 30.4% in chronic HCV infection group. However, once HCC develops, the risk of mortality is same in both the groups. This has been demonstrated in an international, multicenter study which produced similar results.[44] Interestingly, NASH patients with no cirrhosis have no increased risk of HCC.[45]

Pathogenesis of Hepatocellular Carcinoma

First, we will review the tumor macroenvironment and the major risk factors of HCC and its pathogenesis. Second, the molecular landscape and the tumor microenvironment (TME) will be described.

Tumor macroenvironment

Development of HCC is caused by intrinsic factors that are genetic mutations either inherited or acquired and extrinsic risk factors such as alcohol, smoking, and hepatotropic viruses-B, C, and D. It is widely accepted that both these factors play a significant role in the development of HCC. In the tumor macroenvironment, hepatocytes undergo malignant transformation through mechanisms that prevent tumor destruction and evade apoptosis and promote tumor proliferation and neovascularization. Cirrhosis induces carcinogenic changes and is found in 90% of patients diagnosed with HCC. In the remaining 10% patients, noncirrhotic mechanisms of carcinogenesis are responsible for malignant disease.[14]

In cirrhotic livers, metabolic and oxidative injury causes cyclical inflammation, necrosis, and repeated compensatory regeneration, and increased turnover of hepatocytes over a period of decades leads to accumulation of genetic errors and mutations such as point mutations, deletions in TP53, AXIN1, and CTNNB1; chromosomal gains; telomere erosion; and telomerase reactivation.[46] They also undergo activation of protooncogenes such as RAS-MAPK pathway and β-catenin, resulting in the formation of monoclonal populations of dysplastic hepatocytes in foci and nodules.[46,47] It has been noted that the risk for HCC is greater when the cirrhosis is due to viral hepatitis compared to nonviral causes.[48] However, the risk of HCC in patients with cirrhosis due to hereditary hemochromatosis and primary biliary cholangitis (previously known as primary biliary cirrhosis) is comparable to those from viral causes.[49,50]

Hepatitis B

HBV is an enveloped partially double-stranded, circular DNA virus, from the genus Orthohepadnaviridae of the family Hepadnaviridae. HBV has a tropism for hepatocytes, into which it enters through the sodium taurocholate cotransporting polypeptide receptor.[51]

Following entry, its nucleocapsid is released into the cytosol and then is translocated along microtubules to the nucleus, wherein the HBV DNA is released from the nucleocapsid.[52] The HBV DNA is then converted into covalently closed circular DNA (cccDNA), which is organized into mini-chromosomes in the nucleus of the infected cell by binding to histones and nonhistones such as HBX protein and HBV core protein.[53,54] This mini-chromosomal structure of cccDNA is hypothesized to be resistant to antiviral therapy and thus responsible for relapse following treatment with antiviral drugs.[55]

HBV initiates the process of hepatic carcinogenesis by integrating into the host genome.[56] It can also induce carcinogenic changes by modulating the expression of liver-specific micro-RNAs like miR-155.[57] Integration of HBV DNA fragments in the host genome alters telomerase reverse transcriptase, which regulates expression of host genes.[58] Other proposed mechanisms include secretion of viral oncogenic proteins such as HBX and mutant pre-S2/S proteins.[59,60] HBX in particular has been closely studied and is now considered to be essential for HBV replication. It activates a wide range of targets such as RAS/MAPK1 and PI3k/AKT pathway and augments its invasive potential of HBx-infected cells.[61,62] It can act as a transactivator of other oncogenic genes such as c-myc protooncogene and it is self-generating by promoting HBV replication.[63,64]

Chronic liver damage induces fibrogenesis and inflammatory markers induce fibrosis in the liver leading to cirrhosis and presence of both cirrhosis and HBV infection further increases the risk of developing HCC.[14] Interestingly, noncirrhotic HBV-infected individuals have also shown to develop HCC. In a study of 44 patients with HBV-positive noncirrhotic HCC individuals as compared to chronic HBV carriers without HCC for risk factors of HCC, Liu *et al*. demonstrated a higher risk of developing HCC associated with male gender, higher viral loads, or BCP T1762/A1764 mutation. Among patients diagnosed with HCC, the HBV cirrhotics had a higher viral load than HBV noncirrhotics.[65]

Hepatitis C

The virus tends to cause chronic infection in 70%–80% of the infected cases in compared to HBV which induces chronicity in only 10% of infected cases.[66] HCV carcinogenesis is mediated by the viral-induced factors and host-induced immunologic response. The viral replication does not lead to cellular death, but the virus tends to harbor in the endoplasmic reticulum of the hepatocytes, replicating its RNA and inducing synthesis of its nonstructural proteins such as NS2, NS3, NS4A, NS5A, and NS5B, which form the RNA-dependent RNA polymerase and the viral envelope proteins.[42] Unlike HBV, HCV is a RNA virus that does not integrate its genomic material into the host genome. However, the current studies show that HCV gene products such as core protein, NS3, NS4B, and NS5A in tissue culture models can potentially lead to cellular transformation, but *in vivo* studies are yet to confirm these findings. HCV gene products such as core proteins alter the MAPK signaling pathway, thereby affecting cellular proliferation.[67] The NS5A protein inhibits the p53 pathway which affects cell cycles, cellular proliferation, and antitumor mechanisms.[68] The newer direct-acting antiviral agents are designed to be directed against HCV viral proteases. HCV viremia is associated with increased risk of developing HCC with studies from the last decade showing decreased risk of HCC by nearly 57%–75% among IFN-treated HCV patients.[22] With the newer direct-acting agents, overall incidence of HCV-induced HCC is likely to be significantly reduced.

HCV replication induces a unique immunologic host response within every individual. This response is mediated by factors such as tumor necrosis factor (TNF-α) and IFNs and results in cell injury, death, and regeneration. The hepatocytes undergo several such cycles of cellular death and regeneration, leading to scarring and fibrosis. The severity of fibrosis has been linked with the probability of harboring HCC although there have been studies that showed development of HCC, even in the absence or with low-grade fibrosis.[22] Furthermore, oxidative stress on the hepatocytes by reactive oxygen species (ROS) formation induced by the virus and host immune response leads to cell death and regeneration, subsequently leading to mutations in the hepatocytes and thereby development of HCC.

Alcohol

Ethyl alcohol or ethanol is one of the oldest known chemical carcinogens known to cause HCC.[40,42] Ethanol's metabolites, acetaldehyde and various ROS, produced by action of alcohol dehydrogenase and cytochrome P450 2E1 (CYP2E1), possess the capacity to induce chronic oxidative stress and chronic inflammation, leading to cirrhosis and eventually to malignancy.[69,70] In chronic liver injury from alcohol exposure, overproduction of ROS disrupts the interactions of DNA, RNA, lipids, and proteins, resulting in genomic instability and insufficient repair pathways.[69] Genetic variations in these enzymes are associated with differences in susceptibility to HCC.[71] Additional mechanisms proposed include iron overload, decreased vitamin A (retinoid acid) levels and downregulation of S-adenosyl methionine.[69] A comparison of whole exome sequencing of HCC tumors from European and Asian cohorts demonstrated differences based on risk factors.[72] Alcohol was the major risk factor in the European cohort and was associated with inactivation of chromatin remodelers;

however, in the Asian cohort, where HBV and HCV were the major etiological risk factors, mutations in chromatin remodeling were also present, but to a lesser extent. Further, p53 was also commonly detected in both cohorts but varied from 10% to 60% in the Asian/African versus 10%–20% in Western countries.[73,74]

Molecular landscape of hepatocellular carcinoma

The pathogenesis of etiologies of HCC has provided further understanding of the mutational background and molecular landscape of HCC. Further, techniques such as next-generation sequencing of HCC tumors have provided insight on the genetic landscape. Similar to other solid tumors, somatic mutations in HCC include C:G > T:A transitions. In addition, there are T:A > C:G transitions and C:G > A:T transversions that are unique to HCC.[75] The C:G > A:T transversions are more common in HBV-related HCC.[75] In early hepatocarcinogenesis, there is loss of insulin-like growth factor 2 receptor, resulting in unchecked proliferation.[34] CTNNB1 is most commonly mutated oncogene in HCC (~30%) but varies in frequency based on the etiology of HCC and more often mutated in HCV-related or nonviral-related HCC.[51] Alternately, TP53 is the most commonly mutated tumor suppressor gene and occurs more frequently in HBV-related HCC.[76] Other well-described pathways of HCC include the RAS/PI3K pathways. Whole exome sequencing has also revealed other novel pathways involving the chromatin remodeling, histone methylation, and oxidative stress.[76]

Tumor microenvironment

The TME is a complex network of tumor cells and stromal cells including angiogenic cells, immune cells, and cancer-related fibroblastic cells, in which signaling pathways and production of molecules and soluble factors promote carcinogenesis.[77] During chronic hepatic injury, fibrosis results from deposition of extracellular matrix (ECM), which leads to poor oxygen exchange. Hypoxia is further propagated with the secretion of pro-angiogenic factors by stromal cells and hypoxia-inducible factor-1α (HIF-1α) production is induced.[78] Excess ECM production and decreased turnover leads to a fibrotic environment and stimulates tumor growth, survival, and proliferation through enhanced integrin signaling.[77] Tumor-associated fibroblasts (TAFs) secrete factors that promote tumor growth and angiogenesis and are involved in cross-talk with cancer cells.[77,78] Immune cells, especially tumor infiltrating lymphocytes (TILs), are important for antitumor response; however, there is a predominance of circulating regulatory T-cells and myeloid-derived suppressive cells that dampen the immune response.[77] In addition, tumor-associated macrophages (TAMs) release chemokines and growth factors that suppress antitumor immunity.

Angiogenesis plays a key role in the carcinogenesis of HCC. HCC is characterized by an excess of angiogenic factors produced by tumor cells, vascular endothelial cells, immune cells, and surrounding TME. This creates a vascular network composed of leaky and abnormal vasculature resulting in hypovascular regions within the tumor, which promotes hypoxia and necrosis. Vascular endothelial growth factor (VEGF) is an important mediator in hepatocarcinogenesis and regulated by oncogenic gene mutations, hormones, and cytokines. Its overexpression results in leaky vessels and abnormal vascular structure and function. This creates a hypoxic and acidotic environment, which further stimulates VEGF overexpression. In addition, VEGF acts on the surrounding stromal environment consisting of hepatic stellate cells and Kupffer cells through VEGR receptors.[79] HIF-1α is stimulated by hypoxic conditions and play a synergistic role with other angiogenic factors, especially VEGF in counteracting apoptosis and promoting cell proliferation.[77,78] In addition, hypoxia induces autophagy which generates energy for tumor cells and its surrounding environment through catabolic breakdown of cellular elements to help promote cancer survival.[77] The TME is also composed of the ECM and stromal cells that releases VEGF. Other angiogenic molecules include angiopoietin (ANGPT) 1, ANGPT2, and basic fibroblast growth factor (bFGF), which promote dysfunctional vascular networks in HCC.[79] Ang-2 boosts the effect of VEGF on endothelial cells, which produce molecules that disrupt the basement membrane, further augmenting a hypoxic TME. bFGF and VEGF act synergistically to induce angiogenesis, and platelet-derived endothelial cell growth factor promotes cell migration and new vessel maturation.[77] These factors as well as transforming growth factor (TGF)-α, TGF-β, hepatocyte growth factor (HGF), endothelial growth factor (EGF), interleukin 4 (IL-4), IL-6, and IL-8 are elevated in HCC patients. Moreover, the PI3K/AKT pathways are activated in endothelial cells, and conversely, Dll4/Notch pathway is an antiangiogenic pathway, which may be downregulated in HCC.[77]

In cirrhosis, chronic inflammation mediated by persistent cytokine and chemokine production is a central process in development of dysplastic nodules and HCC.[34] TGF-β, HGF, and EGF are key growth factors that regulate the immune and inflammatory process.[77,78] There are increased Th2-like cytokines (IL-4, IL-5, IL-8, and IL10) compared to Th1-like cytokines (IL-1α, IL-1 β, IL-2, TNF-α) in a phenotype of more aggressive and metastatic HCC.[77] The role of chemokines (i.e., CXCL12, CX3CL1, and CCL20) is to regulate cell trafficking into and out of the TME by binding to a family of receptors (i.e., CCR, CXCR, CX3CR, and XCR).[77] The receptors are found on inflammatory, endothelial, and epithelial cells. For example, the CXCL12-CXCR4 axis regulates

angiogenesis.[77] Interactions with these receptors with cells of the TME mediate cancer progression, invasion, and metastasis.[78]

In summary, the epidemiology, etiology, and pathogenesis of HCC are complex. Further understanding of HCC and the etiological influence are imperative as this can provide improved strategies on the treatment of HCC based on its risk factors and pathways implicated by hepatocarcinogenesis.

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