Review of hepatocellular carcinoma: Epidemiology, etiology, and carcinogenesis

Yezaz Ahmed Ghouri, Idrees Mian, Julie H. Rowe

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 rise 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

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 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.

How to cite this article: Ghouri YA, Mian I, Rowe JH. Review of hepatocellular carcinoma: Epidemiology, etiology, and carcinogenesis. J Carcinog 2017;16:1.
Epidemiology

HCC is more common among males with a male:female ratio of 2.4 in its worldwide distribution. The most common age at presentation is usually between 30 and 50 years. HCC is predominant in Asian countries including China, Mongolia, Southeast Asia, and Sub-Saharan Western and Eastern Africa. 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. 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. 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. The 5-year survival trend has improved by >60% from 1975 to 2005.

A SEER-Medicare database, between 1991 and 1999, showed that the annual economic burden of HCC was 454.9 million US dollars. 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.

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. Various other associated risk factors are summarized in Table 1. Around 80%–90% of HCC cases occur in the setting of underlying cirrhosis. 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. Below, discussion will be focused on the most common risk factors for HCC.

Hepatitis-B virus

HBV is the most common cause for HCC worldwide accountable for an estimated 54% of all liver cancers. 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. Accordingly, regions endemic for chronic HBV infection have a similarly high incidence of HCC with >20 age cases per 100,000 males. 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. In the US, around 10%–16% of HCC cases are attributed to HBV. 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. 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.

Based on genetic sequencing, human HBV is currently grouped into 10 genotypes (A-J). The most prevalent genotypes in the US are A and C, except Western US, where B and C are the predominant genotypes. 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). Chronic HBV infection by genotype C puts one at risk of developing HCC, more than the other genotypes.

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. In developed countries including Japan and the US, HCV is most common causative agent. 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. 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. 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. 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 coinjected patients with and without detectable HBV DNA compared with HCV-monoinfected patients. 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. With the newer HCV direct-acting agents, the impact on incidence of HCV-induced HCC is uncertain.

**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.

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. 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. It has been noted that the risk for HCC is greater when the cirrhosis is due to viral hepatitis compared to nonviral causes. 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.

**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. 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. Interestingly, NASH patients with no cirrhosis have no increased risk of HCC.

**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.
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.[53] 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.[53]

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.[40,70] 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.\(^{[76]}\) 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.\(^{[52]}\) 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 acidic 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.\(^{[59]}\) 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.\(^{[77]}\)
angiogenesis.[27] Interactions with these receptors with cells of the TME mediate cancer progression, invasion, and metastasis.[28]

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.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Stuver S, Trichopolous D. Cancer of the liver and biliary tract. In: Adami HO, Hunter D, and Trichopolous D, editors. Textbook of Cancer Epidemiology. 2nd ed. Oxford University Press, New York; 2008.
2. Stewart BW, Wild CP, editors. World Cancer Report 2014. Lyon: International Agency for Research on Cancer; 2014.
3. World Health Organization, I.A.f.R.o.C. Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. Available from: http://www.globocan.iarc.fr/Pages/fact_sheets_population.aspx.
4. SEER Cancer Statistics Factsheets: Liver and Intrahepatic Bile Duct Cancer. National Cancer Institute; 2014. Available from: http://www.seer.cancer.gov/statfacts/html/livibd.html. [Last accessed on 2017 Apr].
5. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
6. Kumar V, Abbas AK, Fausto N, Robbins SL, and Cotran RS. Robbins and Cotran Pathologic Basis of Disease. 7th ed. Philadelphia:Elsevier Saunders; 2004.
7. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: Consider the population. J Clin Gastroenterol 2013;47 Suppl:S2.
8. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999;340:745-50.
9. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009;27:1485-91.
10. Njie B, Rotman Y, Ditah I, Lim JK. Emerging trends in hepatocellular carcinoma incidence and mortality. Hepatology 2015;61:191-9.
11. Lang K, Danchenko N, Gondek K, Shah S, Thompson D. The burden of illness associated with hepatocellular carcinoma in the United States. J Hepatol 2009;50:89-99.
12. Shebl FM, Capo-Ramos DE, Graubard BI, McGlynn KA, Altekruse SF. Socioeconomic status and hepatocellular carcinoma in the United States. Cancer Epidemiol Biomarkers Prev 2012;21:1330-5.
13. El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011;365:1118-27.
14. Zhang DY, Friedman SL. Fibrosis-dependent mechanisms of hepatocarcinogenesis. Hepatology 2012;56:769-75.
15. Donato F, Tagger A, Gelatti U, Parrinello G, Boffetta P, Albertini A, et al. Alcohol and hepatocellular carcinoma: The effect of lifetime intake and hepatitis virus infections in men and women. Am J Epidemiol 2002;155:323-31.
16. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: Incidence and risk factors. Gastroenterology 2004;127 5 Suppl 1:S35-50.
17. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer 2006;121:3030-44.
18. Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22 707 men in Taiwan. Lancet 1981;2:1129-33.
19. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat 2004;11:97-107.
20. Huang YT, Jen CL, Yang HI, Lee MH, Su J, Lu SN, et al. Lifetime risk and sex difference of hepatocellular carcinoma among patients with chronic hepatitis B and C. J Clin Oncol 2011;29:3643-50.
21. Bosch FX, Ribes J, Diaz M, Cléries R. Primary liver cancer: Worldwide incidence and trends. Gastroenterology 2004;127 5 Suppl 1:S5-16.
22. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012;142:1264-73.e1.
23. Dorfman JD, Schulic R, Choti MA, Geschwind JF, Kamel I, Torbenson M, et al. Differences in characteristics of patients with and without known risk factors for hepatocellular carcinoma in the United States. World J Gastroenterol 2007;13:781-4.
24. Konopnicki D, Mocroft A, de Wit S, Antunes F, Ledergerber B, Katlama C, et al. Hepatitis B and HIV: Prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. AIDS 2005;19:593-601.
25. Yotsuyanagi H, Shintani Y, Moriya K, Fujie H, Tsutsuji T, Kato T, et al. Virologic analysis of non-B, non-C hepatocellular carcinoma in Japan: Frequent involvement of hepatitis B virus. J Infect Dis 2000;181:1920-8.
26. Chen CH, Changchien CS, Lee CM, Tung WC, Hung CH, Hu TH, et al. A study on sequence variations in pre-S/surface, X and enhancer II/core promoter/precore regions of occult hepatitis B virus in non-B, non-C hepatocellular carcinoma patients in Taiwan. Int J Cancer 2009;125:621-9.
27. Tatematsu K, Tanaka Y, Kurbanoval F, Sugauchi F, Mano S, Maeshiro T, et al. A genetic variant of hepatitis B virus divergent from known human and ape genotypes isolated from a Japanese patient and provisionally assigned to new genotype J. J Virol 2009;83:10538-47.
28. Chu CJ, Keeffe EB, Han SH, Perrillo RP, Min AD, Soldevila-Pico C, et al. Hepatitis B virus genotypes in the United States: Results of a nationwide study. Gastroenterology 2003;125:444-51.
29. Erhardt A, Blondin D, Hauck K, Sagir A, Kohnle T, Heintges T, et al. Response to interferon alpha is hepatitis B virus genotype dependent: Genotype A is more sensitive to interferon than genotype B. J Virol 2004;78:10093-10099.
30. Sonneveld MJ, Rijkbosch V, Kakalogi Y, Simon K, Heathcote EJ, Tabak F, et al. Durable hepatitis B surface antigen decline in hepatitis B antigen-positive chronic hepatitis B patients treated with pegylated interferon-a2b: Relation to response and HBV genotype. Antivir Ther 2012;17:9-17.
31. Chan HL, Tse CH, Mo F, Koh J, Wong VW, Wong GL, et al. High viral load and hepatitis B virus subtype e are associated with increased risk of hepatocellular carcinoma. J Clin Oncol 2008;26:177-82.
32. Tanaka H, Tsukuma H, Yamano H, Oshima A, Shibata H. Prospective study on the risk of hepatocellular carcinoma among hepatitis C virus-positive blood donors focusing on demographic factors, alanine aminotransferase level at donation and interaction with hepatitis B virus. Int J Cancer 2004;112:1075-80.
33. Yoshizawa H. Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: Projection to other countries in the foreseeable future. Oncology 2002;62 Suppl 1:8-17.
34. El-Serag HB, Rudolph KL. Hepatocellular carcinoma:
Epidemiology and molecular carcinogenesis. Gastroenterology 2007;132:2557-76.
35. Bowen DG, Walker CM. Adaptive immune responses in acute and chronic hepatitis C virus infection. Nature 2005;436:946-52.
36. Wedemeyer H, Duberg AS, Buti M, Rosenberg WM, Franikova S, Esmat G, et al. Strategies to manage hepatitis C virus (HCV) disease burden. J Viral Hepat 2014;21 Suppl 1:60-89.
37. Soriano V, Vispo E, Labarga P, Medrano J, Barreiro P. Viral hepatitis and HIV co-infection. Antiviral Res 2010;85:303-15.
38. Clifford GM, Rickenbach M, Polesel J, Dal Maso L, Steffen L, Ledergerber B, et al. Influence of HIV-related immunodeficiency on the risk of hepatocellular carcinoma. AIDS 2008;22:2135-41.
39. Kruse RL, Kramer JR, Tyson GL, Duan Z, Chen L, El-Serag HB, et al. Clinical outcomes of hepatitis B virus infection in a United States cohort of hepatitis C virus-infected patients. Hepatology 2014;60:1871-8.
40. Bosch FX, Ribes J, Borràs J. Epidemiology of primary liver cancer. Semin Liver Dis 1999;19:271-85.
41. Hutchinson SJ, Bird SM, Goldberg DJ. Influence of alcohol on the progression of hepatitis C virus infection: A meta-analysis. Clin Gastroenterol Hepatol 2005;3:1150-9.
42. Farazi PA, DePinho RA. Hepatocellular carcinoma pathogenesis. From genes to environment. Nat Rev Cancer 2006;6:674-87.
43. Yatsui S, Hashimoto E, Tobari M, Tanaij M, Tokushige K, Shiratori K. Clinical features and outcomes of cirrhosis due to non-alcoholic steatohepatitis compared with cirrhosis caused by chronic hepatitis C. J Gastroenterol Hepatol 2009;24:248-54.
44. Bhalo N, Angulo P, van der Poorten D, Lee E, Hui JM, Saracco G, et al. The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: An international collaborative study. Hepatology 2011;54:1208-16.
45. Dam-Larsen S, Becker U, Franzmann MB, Larsen K, Christoffersen P, Bendtsen F. Final results of a long-term, clinical follow-up in fatty liver patients. Scand J Gastroenterol 2009;44:126-33.
46. Jhunjhunwala S, Jiang Z, Stawiski EW, Gnad F, Liu J, Mayba O, et al. Diverse modes of genomic alteration in hepatocellular carcinoma. Genome Biol 2014;15:436.
47. Thorgrinson SS, Grisham JW. Molecular pathogenesis of human hepatocellular carcinoma. Nat Genet 2002;31:339-46.
48. Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology 2010;51:1972-8.
49. Fargjon S, Mandelli C, Piperno A, Cesana B, Fracananzi AL, Fraquelli M, et al. Survival and prognostic factors in 212 Italian patients with genetic hemochromatosis. Hepatology 1992;15:655-9.
50. Caballeria L, Parés A, Castells A, Ginés A, Bru C, Rodés J. Hepatocellular carcinoma in primary biliary cirrhosis: Similar incidence to that in hepatitis C virus-related cirrhosis. Am J Gastroenterol 2001;96:1160-3.
51. Yan H, Peng B, He W, Zhong G, Qi Y, Ren B, et al. Molecular determinants of hepatitis B and D virus entry restriction in mouse sodium taurocholate cotransporting polypeptide. J Virol 2013;87:7977-91.
52. Rabe B, Delaene M, Bischof A, Foss M, Sominskaya I, Pumpens P, et al. Nuclear entry of hepatitis B virus capsids involves disintegration to protein dimers followed by nuclear reassociation to capsids. PLoS Pathog 2009;5:e1000563.
53. Bock CT, Schwind S, Locarnini S, Frye J, Manns MP, Trautwein C, et al. Structural organization of the hepatitis B virus minichromosome. J Mol Biol 2001;307:183-96.
54. Tang H, Delgermaa L, Huang F, Oishi N, Liu L, He F, et al. The transcriptional transactivation function of HBx protein is important for its augmentation role in hepatitis B virus replication. J Virol 2005;79:25548-56.
identifies etiological influences on mutation patterns and recurrent mutations in chromatin regulators. Nat Genet 2012;44:760-4.
75. Li S, Mao M. Next generation sequencing reveals genetic landscape of hepatocellular carcinomas. Cancer Lett 2013;340:247-53.
76. Nakagawa H, Shibata T. Comprehensive genome sequencing of the liver cancer genome. Cancer Lett 2013;340:234-40.
77. Hernandez-Gea V, Toffanin S, Friedman SL, Llovet JM. Role of the microenvironment in the pathogenesis and treatment of hepatocellular carcinoma. Gastroenterology 2013;144:512-27.
78. Wu SD, Ma YS, Fang Y, Liu LL, Fu D, Shen XZ. Role of the microenvironment in hepatocellular carcinoma development and progression. Cancer Treat Rev 2012;38:218-25.
79. Zhu AX, Duda DG, Sahani DV, Jain RK. HCC and angiogenesis: Possible targets and future directions. Nat Rev Clin Oncol 2011;8:292-301.

Authors Profile

Yezaz Ahmed Ghouri: Department of Internal Medicine, Division of Gastroenterology and Hepatology, University of Texas Medical Branch, Galveston, Texas, USA

Idrees Mian: Department of Hematology and Oncology, National Institute of Health, Bethesda, Maryland, USA

Julie H. Rowe: Department of Internal Medicine, Division of Oncology, University of Texas Health Science Center, McGovern Medical School, Houston, Texas, USA