Review Article

Epidemiology, mutational landscape and staging of hepatocellular carcinoma

Sarah E. Fenton, Michael C. Burns, Aparna Kalyan

Division of Hematology and Oncology, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA

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Correspondence to: Aparna Kalyan, MBBS. Assistant Professor, Division of Hematology Oncology, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL 60611, USA. Email: Aparna.kalyan@northwestern.edu.

Abstract: Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver and rates of diagnosis have been fluctuating worldwide. In Western countries, HCC is driven primarily by the hepatitis C virus (HCV), alcohol use and non-alcoholic fatty liver disease (NAFLD). Hence, it is not surprising that the increased incidence of both HCV and NAFLD has been associated with a corresponding rise in rates of HCC. The introduction of antiviral medications could potentially change the landscape of HCC by reducing rates of HCV-associated HCC. In Eastern countries and Africa, HCC is driven primarily by hepatitis B virus (HBV), HCV, and to a lesser extent, aflatoxin exposure. The introduction of hepatitis B vaccines is expected to dramatically reduce hepatitis B induced liver damage and HCC. These varying etiologies of HCC result in different mutational landscapes, patient presentations and responses to treatment. This has made establishing a universal staging system difficult and several competing systems are available. Other than Sorafenib, there has also been a paucity of treatment options until the last two years, with immunotherapy and new-targeted tyrosine kinase inhibitors as potential treatment options. Management of HCC offers unique challenges during treatment, as there is often competing illness from underlying liver dysfunction and malignancy itself, both of which affects survival and treatment choice. The new era of treatment may offer additional options in this challenging field. In this review, we describe the underlying etiologies and associated mutational landscape, which drives the treatment options in this complex disease.

Keywords: Hepatocellular carcinoma (HCC); epidemiology; staging

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Introduction

Hepatocellular carcinoma (HCC) makes up 70–90% of primary liver cancers (1,2). Currently the third leading cause of cancer-related death, HCC is also one of the rapidly increasing causes of mortality in cancer patients (3,4). However, while rates of diagnosis are increasing in Western countries, they are decreasing in many Eastern countries (5). Over the last forty years, the incidence of HCC has quadrupled in the United States due to increased rates of hepatitis C virus (HCV) infection in the 1960-70s and non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) (*Figure 1*) (6-10). Fortunately, between 2009 and 2013, rates of HCC diagnosis and mortality have slowed with an anticipated decrease within the next twenty years due to decreased rates of HCV and improved antiviral options (6,7,10,11). Despite these improvements, certain patient populations, including men aged 55–64 across all ethnic backgrounds, continue to have increasing rates of HCC (5,10). In Western populations, HCC is predominantly driven by HCV and alcohol intake (*Figure 1*) (12,13). Despite decreasing rates

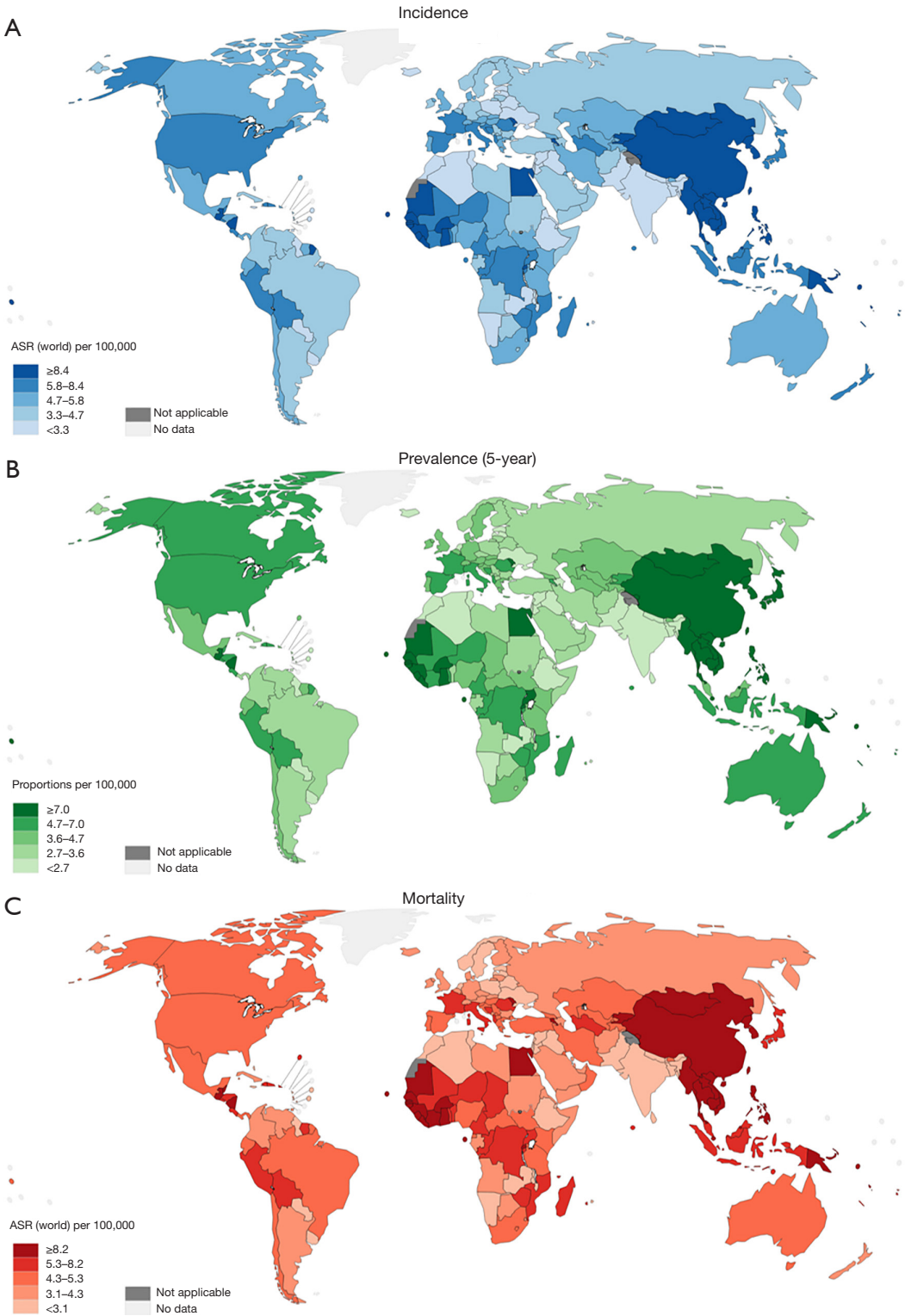

Figure 1 Geographical distribution of HCC. (A) Incidence, (B) prevalence (5-year), and (C) mortality for hepatocellular carcinoma by region. Age standardized rate (ASR) per 100,000 is shown. Data are from the International Agency for Research on Cancer (https://gco.iarc.fr/) (accessed on June 8, 2020). HCC, hepatocellular carcinoma.

of HCC in Eastern countries, the bulk of HCC diagnoses (approximately 80%) are still made in sub-Saharan Africa and eastern Asia (50% in China alone), where the most common risk factors include HBV and exposure to aflatoxin B1 (*Figure 1*) (2,12). In the United States, the mean age at diagnosis is 65 years old with 74% of HCC patients being male (14). Although 48% of HCC patients are Caucasian, the highest incidence is found in Pacific Islanders (11.7/100,000) (15,16).

HCC most often arises due to injury to the liver parenchyma, mediated by various insults that lead to the development of cirrhosis (*Figure 2*). Up to 80–90% of patients with HCC have concurrent cirrhosis (12), which increases a patient's risk of HCC by 30 fold (17). However, as will be discussed in the following paragraphs, several etiologies of HCC mediate tissue transformation without preceding cirrhosis (*Figure 2*). As the development of HCC is associated with multiple causes, certain genetic signatures have also been associated with different insults leading to HCC. Common signaling pathways associated with hepatocyte transformation include the p53, Ras, MAPK, JAK/STAT, Wnt/β-catenin and Hedghog pathways (18,19). In this review, we will discuss different etiologies of HCC, mutations associated with HCC formation and staging of HCC.

Etiologies of HCC

HCV

HCV is a member of the Flaviviridae family of RNA viruses and infection accounts for approximately 80% of HCC cases (20). Over 200 million people worldwide and 3.9 million adults in the US are infected with HCV (21,22). Six genotypes and multiple subtypes of each genotype have been identified (23). The rates of HCV-associated HCC is twice as high in Japan as the United States and Europe, likely due to the increased prevalence of genotype 1B HCV, a more resistant strain of the virus (15,24,25). Genotype 1b is also the most common subtype of HCV in Asia, while genotype 1a and 1b are most common in Europe, North and South America and genotype 4 is the most common subtype in Africa (23). Active infection with HCV increases the risk of HCC development by 15–20 fold (5-year cumulative risk of 17% in Western countries), and this risk is even greater in patients with HCV-induced cirrhosis where the annual risk of HCC is 1–8% (12,24,26-29). Although antiviral medications have been developed to eradicate HCV infection, only 50% of patients are aware of their HCV diagnosis, limiting the ability of these medications to reduce cirrhosis and HCC risk (30,31).

In the United States, 45–55% of new HCC cases are associated with HCV infection (32). Patients with risk factors including infection with HCV genotype 3, coinfection with HBV or the human immunodeficiency virus (HIV) have an increased risk of HCC (33-39). Heavy alcohol use in particular has a synergistic risk of HCC development in patients with HCV. Approximately 13–23% of HCC patients have alcohol related disorders (40,41). Additionally, the presence of the 61*G (rs4444903) single nucleotide polymorphism in the epidermal growth factor gene increases the risk of HCC development in patients with HCV (42). PNPLA3, a genetic predisposition identified primarily in Hispanic patients, increases the risk of HCC in patients with chronic HCV or NAFLD (5).

Rates of HCV eradication have increased precipitously with the introduction of direct-acting antivirals (DAAs) and interferon therapy. A sustained virologic response (SVR) is the most significant modifier of HCC development, reducing the risk by 50–80% (5,43-46). However, eradication of the virus does not completely eliminate the risk of future HCC formation, especially in patients with cirrhosis (47,48). A study of patients treated with DAAs through the Veterans' Affairs system found that patients with a SVR had a lower risk of HCC [HR 0.28, 95% confidence interval (CI): 0.22–0.36], but the risk of HCC remained higher in patients with cirrhosis (HR 4.71, 95% CI: 3.34–6.68) (46). A systemic review of 26 studies found that HCC risk was reduced to a similar extent by both DAA and interferon based therapy (49). In Western countries and Japan, HCV remains the most frequent etiology of HCC formation. Hopefully, as DAA and interferon therapy becomes more prevalent, rates of HCV induced cirrhosis and HCC will decrease in line with what has been seen with HBV vaccination.

Hepatitis B virus (HBV)

HBV is a DNA virus with eight genotypes (A-H). Genotype C is associated with severe liver disease and increased risk of HCC formation, and is the most common genotype in eastern Asian countries (14,50-54). HBV drives hepatocyte transformation and HCC through chronic necroinflammation and direct hepatocarcinogenesis secondary to virus specific factors (integration into the genome causing rapid cell cycling and instability among other causes) (55-58).

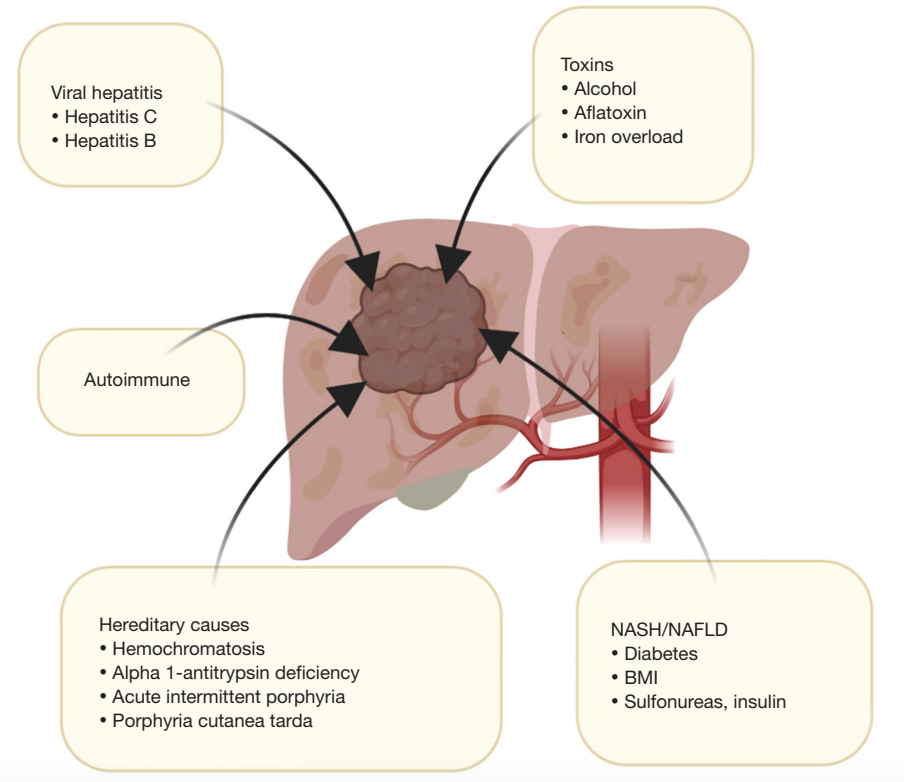

Figure 2 Etiologies of HCC include viral, autoimmune, exposures/toxins, hereditary causes and NASH/NAFLD. These etiologies may or may not act through mechanisms associated with cirrhosis. HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease.

Between 70% and 90% of HBV infected patients that develop HCC have underlying cirrhosis (12,59,60). Certain risk factors are associated with HCC formation even in the absence of cirrhosis, including: African American and Asian ethnicities, 1-antitrypsin deficiency, Wilson's disease, aflatoxin exposure and family history of HCC (61).

While HCV is the dominant risk factor in North America, HCC is more frequently driven by HBV in Africa and Asia, where HBV is often passed from mother to child via vertical transmission (62-64). In fact, the first documentation of the association between HBV and HCC was made in Taiwan in 1981 (65). Infection with HBV is associated with a 10% risk of HCC formation in Western countries and a 15% risk of HCC formation in Asia (24,29). In the United States, there are approximately 860,000 patients with chronic HBV infections, most of whom emigrated from countries with high endemic rates of HBV (66). Ten to fifteen percent of new HCC cases in the United States are due to HBV (32). The introduction of routine HBV vaccination is thought to contribute to this significant decrease in prevalence compared to other countries (32,67). A study in Taiwan found that HBV seropositivity rates decreased from 10–17% to 0.7–1.7% after the introduction of the HBV vaccine (68). Similar to HCV, DAA therapy has been developed for HBV but the decrease in HCC risk after successful treatment has not been defined, although early studies suggest it may be close to 50% (69,70). Risk factors associated with HCC formation after DAA use include older age, the presence of cirrhosis, thrombocytopenia, and increased liver stiffness (71-73).

Alcohol

Among patients with excessive alcohol intake (≥3 drinks/day), 1–2.5% will develop liver disease annually. Of these patients, 3–12% of patients annually will progress to cirrhosis, with a lifetime risk of 8–20% (74-76). Alcohol induced cirrhosis carries an 8-12% risk of progressing to HCC. The relative risk of HCC in heavy drinkers,

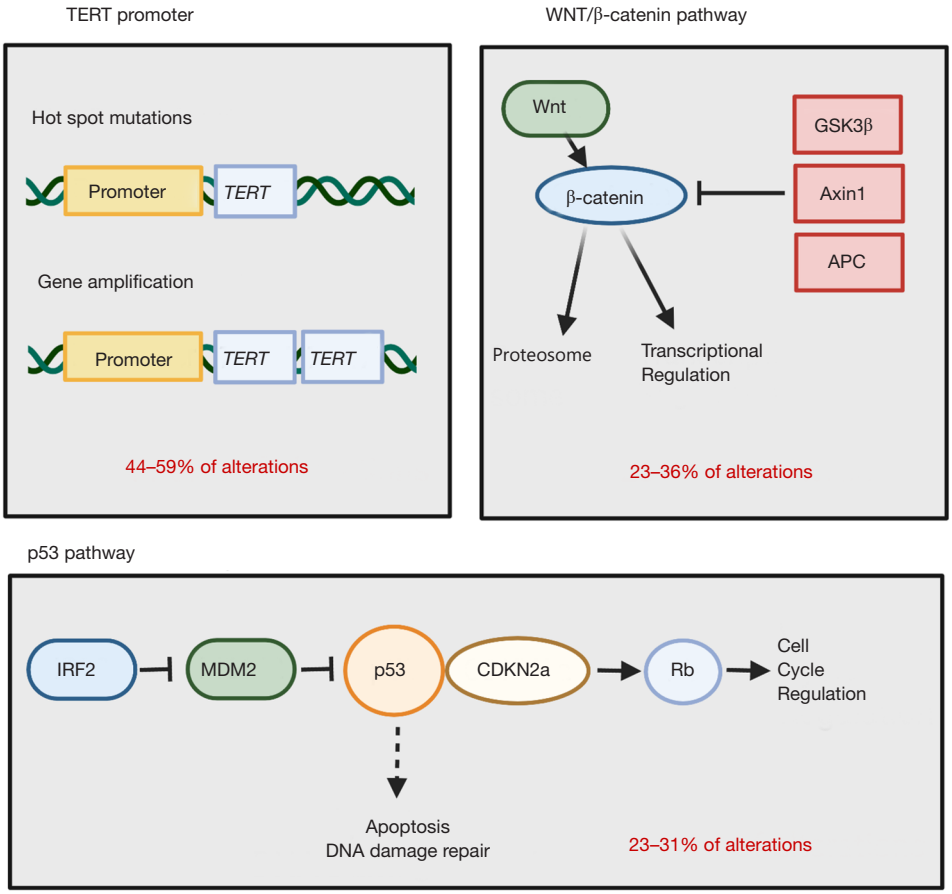

Figure 3 Somatic alterations commonly detected in HCC include those in the TERT promoter resulting in increased telomerase activity, the Wnt/β-catenin pathway resulting in gene dysregulation and the p53 pathway altering mechanisms involved in DNA damage repair and apoptosis. HCC, hepatocellular carcinoma.

regardless of the presence of cirrhosis, is 1.16 (95% CI: 1.01–1.34) (24,29,77). The risk of HCC decreases by 6–7%/year in abstinent patients; after twenty three years, the risk of HCC returns to that of nondrinkers, even in the setting of cirrhosis (78). Unfortunately, the presence of hepatitis, fatty liver, tobacco use or obesity in a patient with excessive alcohol consumption synergistically increases the risk of HCC (27,79-81). Specifically, the combination of HCV and excessive alcohol intake increases the risk of HCC compared to alcohol intake alone (HR 11.2, 95% CI: 2.3–55). Tumors related to combination of HCV and excessive alcohol intake are less differentiated, suggesting a more aggressive course (82,83).

NAFLD/NASH

Thirty to forty percent of new HCC cases are associated with metabolic disorders (metabolic syndrome, diabetes mellitus and obesity); however the exact mechanism of HCC in NAFLD/NASH is unknown (40,84,85). Up to one third of the population of the United States has NAFLD, with 10–20% ultimately developing cirrhosis (86-89), although up to 20% of patients with NAFLD and HCC show no evidence of cirrhosis (90). A VA study of patients with NAFLD found the hazard ratio of developing HCC was 7.62 (95% CI: 5.76–10.1) (90). However, in the United States, NAFLD is the most frequent cause of HCC in the absence of cirrhosis or liver fibrosis (91). Because NAFLD leads to cirrhosis and HCC to a much lesser extent than the risk factors discussed above and the mechanism is not as well defined, it is difficult to predict who may be at increased risk of hepatocyte transformation (14,92,93). Despite this, NAFLD/NASH is the fastest growing etiology of HCC in the United States and will continue to impact

fatality rates from HCC (94-97).

Risk factors associated with HCC formation include duration of type II diabetes mellitus, a high hemoglobin A1C, sulfonylurea use, or insulin therapy (98,99). A diagnosis of diabetes mellitus alone increases the risk of HCC two to three fold, regardless of the presence of hepatic damage (41). Interestingly, metformin use is associated with a 50% decreased risk of HCC through activation of the MAPK pathway and signaling through RAS/RAF/MEK/ERK, PI3K/AKT/mTOR and Wnt/β-catenin (98-104). The presence of a single nucleotide polymorphism in the palatin-like phospholipase domain-containing protein 3 (PNPLA3) or rs738409 may increase the risk of HCC in patients with NAFLD (105). Additionally, regardless of the etiology of HCC, the presence of an elevated body mass index (BMI) of 35–40 is associated with a 5-fold increase in liver cancer mortality (106).

Aflatoxin

Aflatoxin is produced by the molds *Aspergillus flavus* and *Aspergillus parasiticus* and is found in grains, maize, legumes, tree and grout nuts and the milk of animals that eat these products (67). Over 55 million people are exposed worldwide, predominantly in Mozambique, Vietnam, China and India (67). Between 4.6–28.2% of HCC cases are associated with aflatoxin exposure and this is particularly notable in patients with HBV and excessive alcohol use, where it synergistically increases the risk of HCC (107,108). Thirty to sixty percent of HCC tumors from areas known to have aflatoxin contain mutations associated with aflatoxin metabolite induced DNA damage, including mutations in codon 249 of p53 (G>T) (109-111).

Hereditary causes

Several hereditary disorders that cause liver damage are associated with HCC development. Hemochromatosis is an autosomal recessive disorder driven by missense mutations in the HFE gene (C282y and H63D) on chromosome six, where excess iron is reabsorbed and deposited in the liver among other tissues. Inheritance of hemochromatosis increases a patient's risk of HCC by 20 fold and carries a 21% lifetime risk of HCC development (24,29,112,113). Alpha 1-antitrypsin deficiency, acute intermittent porphyria and porphyria cutanea tarda are other hereditary conditions associated with liver damage and an increased risk of HCC (114,115).

Autoimmune hepatitis

Autoimmune hepatitis increases the risk of liver damage, cirrhosis and HCC but is lower compared to viral hepatitis. The incidence rate is 3.06 per 1,000 patient years (95% CI: 2.22–4.23) in patients without cirrhosis and 10.07 per 1,000 patient years (95% CI: 6.89–14.7) with cirrhosis (69,116). Multiple autoimmune relapses and ongoing alcohol abuse account for increased incidence of autoimmune mediated HCC (32).

Protective factors

Several lifestyle changes are associated with a decreased likelihood of HCC formation. Statin use decreases the risk of HCC in a dose dependent manner through 3-hydroxy-3-methylglytaryl coenzyme A inhibition (66,100,117), with Asian patients reaping the greatest benefit (100). As discussed above, metformin use is associated with decreased risk of HCC in patients with type II diabetes mellitus (102). HCC risk is also reduced by propranolol in patients with HCV related cirrhosis (118).

Mutational landscape

The most frequent somatic alterations observed in HCC occur in genes that are not clinically actionable, including the *TERT* promoter (44–59%), *TP53* (23–31%) and the WNT pathway oncogene *CTNNB1* (23–36%) (*Figure 3*) (119,120). Alterations at the *TERT* promoter by mutation, amplification, or hepatitis B DNA insertion serve to increase telomerase activity (121,122). Such *TERT* promoter point mutations have been shown to frequently co-occur with WNT pathway alterations, including activating mutations in *CTNNB1* (the gene encoding β-catenin) or loss of function alterations in the *AXIN1* (5–10%) and *APC* (1–2%) genes (123). Alterations in *CTNNB1* and *TERT* promoter, as well as the tumor suppressor *CDKN2A*, are also frequently enriched in alcohol-related HCC (124). These data suggest cooperativity between telomere maintenance and the WNT pathway in HCC. In contrast to *TERT* promoter mutations, mutations in *TP53* are associated with aflatoxin B1 exposure and HBV-related HCC and have been shown to be mutually exclusive with *CTNNB1* mutations (124,125). Tumor suppressor alterations in *TP53* and *CDKN2A* are often late occurring and associated with aggressive forms of HCC that carry a poor prognosis (125). Other less frequent genomic alterations in HCC occur in pathways regulating

chromatin modification (*ARID1A*, *ARID2*, *MLL1/MLL2/MLL3/MLL4*), receptor tyrosine kinase (RTK)-Ras-PI3K signaling cascades (*EGFR/ PDGFR/PIK3CA/PTEN/KRAS*) and oxidative stress (*NFE2L2/KEAP1*) (119,120).

Characterization of the recurrent genomic alterations described above has allowed for the identification of actionable therapeutic targets and provided the basis for the molecular subclassification of HCC (126,127). Two primary molecular subtypes of HCC have been described (120,128). The proliferative class is associated with a poor prognosis, chromosomal instability, and aberrant activation of the RTK-RAS-MAPK signaling cascade and PI3K-AKT-mTOR pathway. A second non-proliferative class, less aggressive clinically and driven by WNT signaling, retains similar physiology to normal hepatocytes and may have increased susceptibility to sorafenib (129). Finally, while anti-PD-1/PD-L1 immunotherapies are increasingly being used to treat HCC, correlative studies with nivolumab in advanced HCC (CheckMate 040) did not show a correlation with PD-L1 expression (130), and the molecular characterization of an immune-specific class of HCC remains an active area of investigation (131).

Staging

Unfortunately, HCC is often diagnosed at later stages due to its silent nature and lack of symptoms until the tumor burden is relatively high (14). Several staging systems have been developed in an attempt to provide prognostic information based on tumor and patient characteristics, direct therapies and to stratify patients in clinical trials. At least thirteen staging systems have been developed in an attempt to codify this information, more than have been developed for any other type of cancer. Unfortunately, none of these systems have been definitively proven to be superior, likely due to the heterogeneous nature of HCC and the many etiologies that can lead to HCC formation (132).

The Barcelona Clinic Liver Cancer (BCLC) system is the most commonly used staging system worldwide (3). It splits patients into five stages based on the number and size of lesions, locoregional involvement, patient characteristics and liver function tests. Tumor extension incorporates the number of tumors, tumor size and presence of portal vein invasion or extra-hepatic metastasis (3). Each stage has an associated prognosis and treatment plan.

Conclusions

HCC remains a malignancy that places a high burden on healthcare systems and patients worldwide with a ratio of mortality to incidence of 0.95 (2). Several causes of HCC have been identified including HCV, HBV and NAFLD/NASH, among others. Interestingly, the incidence of these driving factors varies geographically, changing the mutational landscapes that predominate around the world. Because HCC is a multifactorial malignancy with different inciting events and mutational burdens, it is difficult to identify a consistent system of codification. Ultimately, further understanding of the genomic landscape will lead to changes in the treatment strategies.

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