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INTRODUCTION

Hepatocellular carcinoma (HCC) has been increasing in incidence over the last several decades. Previously limited to Eastern Asia, HCC has become increasingly prevalent in the northern and western hemispheres, particularly Western Europe and the United States.1 Today, it is the fifth and ninth most commonly diagnosed cancer in men and women, respectively, and the fourth leading cause of cancer mortality worldwide.2 There is a greater than 2-fold predilection toward males compared with females, especially between the ages of 55 and 64.3 The annual incidence in the United States has increased from 1.4 in 100,000 cases per year in 1976 to 1980 to 6.2 in 100,000 cases per year in 2011.1 Worldwide, the incidence was 10.1 in 100,000 in 2017, with an incidence of 24.2 per 100,000 in parts of Africa and 35.5 per 100,000 in Eastern Asia.4 According to the Centers for Disease Control and Prevention, the age-adjusted death...
rate owing to HCC has been increasing by 3% per year. It is estimated that over the next 2 decades, the global burden of HCC will increase to more than 22 million cases. In developing countries such as those in Asia and Africa where vaccination capabilities can remain limited in remote areas, HCC is largely attributed to underlying hepatitis B virus (HBV) infection, with more than 70% of HCC cases attributable to HBV. Until recently, in Europe and the United States, hepatitis C virus (HCV) cirrhosis was the most common underlying etiology of HCC, accounting for 60% of HCC cases. More recent data show that nonalcoholic steatohepatitis (NASH) is playing a greater role in HCC cases, with a 9% increase in HCC cases attributed to NASH between 2004 and 2009. The contribution of alcohol to the HCC burden is also significant at about 30%, with significant variability between different countries. Aflatoxin exposure is responsible for up to 40% of HCC cases in Africa, with a comparatively negligible contribution in Europe and North America. This worldwide heterogeneity of etiologic epidemiology is driven by several factors, including the availability of vaccination, the prevalence of the metabolic syndrome, and the prevalence of injection drug use. In this article, we discuss the evolving global epidemiology of HCC and the elements driving it.

CHRONIC HEPATITIS B
The Epidemiology of Chronic Hepatitis B

Despite the availability of effective vaccines since 1982 and effective antiviral therapy, HBV remains a prevalent global health problem. Two billion people have serologic evidence of past or ongoing HBV infection and an estimated 257 million people or 3.5% of the world’s population are chronically infected with HBV. It is well-known that HBV is associated with significant morbidity and mortality. The lifetime risk of cirrhosis, liver failure, and HCC in patients with HBV is reported to be between 15% and 40%. HBV is the leading cause of incident cases of liver cancer and deaths in the world (33%), followed by alcohol (30%), HCV (21%), and other causes (16%) (Fig. 1). Hepatitis B surface antigen (HBsAg) seroprevalence varies geographically.

Fig. 1. Global etiologies by percentage.
According to the 2017 World Health Organization (WHO) Global Hepatitis Report, the number of HBsAg-positive individuals was highest in the Western Pacific (115 million, prevalence estimate 6.2%; 95% uncertainty interval, 5.1%–7.6%) and Africa (60 million prevalence estimate 6.1%; 95% uncertainty interval, 4.6%–8.5%), which together accounted for 68% of the global burden.11 In May of 2016, the WHO adopted a global hepatitis strategy with the goal of eliminating viral hepatitis as a public health threat by 2030. This goal includes a target to decrease new cases of chronic HBV by 90%, decrease mortality owing to HBV and HCV by 65%, and to treat 80% of eligible persons with chronic HBV and HCV infections.14 Reaching these targets will ultimately decrease the incidence of HCC and its associated mortality.

Hepatitis B Virus as a Risk Factor for Hepatocellular Carcinoma

Among HBV-infected individuals, independent risk factors for HCC include HBeAg seropositivity, high viral load, and genotype C infection.13 Human immunodeficiency virus/HBV coinfection has a further impact because human immunodeficiency virus promotes a more aggressive natural history of hepatitis B, with often a younger age of disease onset with a more advanced fibrosis stage at diagnosis. The annual incidence of HCC correlates with the geographic HBsAg seroprevalence with the highest incidence found in sub-Saharan Africa and South East Asia.10 In Africa and East Africa, the population attributable fraction of HCC caused by HBV is reported to be approximately 60%, compared with lower rates in the western hemisphere.15 In sub-Saharan Africa HBV-related HCC is the most common malignancy among men in 12 countries and the most common cause of premature death. In the same region, HCC is the second most prevalent cancer in men and the third for women. HCC in Africa tends to occur in the late 30s and early 40s, at least a decade earlier than in Western countries.16 An analysis of the African population chronically infected with hepatitis B has elucidated genotype A, particularly subgenotype A1, to be associated with more aggressive liver disease, and more rapid progression to HCC.17 Although cirrhosis is the most common risk factor for HCC in the setting of chronic HBV, HCC can also develop independent of cirrhosis in HBV infection. High levels of HBV replication and chronicity of inflammation are known to independently increase the risk for HCC. Although infrequent, inactive HBV carriers or those with occult HBV infection can develop HCC in the absence of cirrhosis. A direct carcinogenic role of viral factors, HBV genotype, integration of viral DNA into the host genome, and direct effects of viral proteins are likely to contribute to the occurrence.18

The Impact of Hepatitis B Vaccination on the Global Epidemiology of Hepatocellular Carcinoma

The WHO recommended incorporation of HBV vaccination into the Expanded Program of immunization in 1991 as the most effective way to decrease the global burden of HBV. Universal vaccination has globally decreased HBsAg prevalence in children less than 5 years of age from 4.7% in the prevaccination era to 1.3% in 2015. However, the prevalence of HBsAg in the WHO Africa continent remains high at 3%.11 The WHO Western Pacific region has decreased their HBsAg prevalence in children less than 5 years of age to 0.9%. By 2013, universal HBV vaccination had prevented 14.2 million cases of chronic HBV infection among children aged 0 to 5 years worldwide and more than 1.3 million deaths.10 Universal HBV vaccination has also led to a significant decrease in HBV in Taiwan, where universal vaccination (introduced in 1984), together with a catchup vaccination program and improved maternal screening has led to a decrease in the prevalence of HBsAg positivity in children aged less than 15 years from 9.8% in 1984% to 0.3% in 2009.19,20 In turn, this process has led to a
A decrease in HCC incidence per $10^5$ person-years from 0.92 in unvaccinated to 0.23 in vaccinated cohorts.\textsuperscript{21} In many East Asian countries, the implementation of infant HBV immunization programs is expected to decrease HBV-related HCC in the future to a similar degree demonstrated in Taiwan.\textsuperscript{21} Universal HBV vaccination, vaccine catchup programs, and mass screening since 1981 have also eliminated acute symptomatic HBV infection and early-onset HCC as a public health threat among Alaskan Native children.\textsuperscript{10}

There are several countries that have yet to implement universal HBV vaccination and many individuals are still infected with HBV (approximately 257 million in 2015), mostly in Asia and sub-Saharan Africa, where the prevalence of HBsAg remains high.\textsuperscript{22} In Africa, HBV vaccine coverage is only 77%.\textsuperscript{23} A major limitation is the access to immunization and HBV treatment specifically in sub-Saharan Africa. The WHO Global Policy Report on the Prevention and Control of Viral Hepatitis reported that only 16.7% of WHO-AFRO countries have publicly funded HBV treatment available.\textsuperscript{24,25} Despite the WHO recommendation for use of birth dose vaccine for prevention of chronic HBV infection, as of 2019 only 10 of the 47 African nations have implemented this recommendation. Although an effective HBV vaccine has been available since 1982, there remains a wide range of vaccination rates and challenges associated with global HBV vaccination. It is imperative to recognize and address potential challenges associated with achieving the elimination of HBV, while also realizing that HBV and its associated complications are entirely vaccine preventable.\textsuperscript{10}

To achieve higher global vaccination rates, every country will need to assess the burden of HBV within its population and have knowledge of seroprevalence and potential high-risk groups. Prevention of mother-to-child transmission (MTCT) also plays a key role in the elimination of HBV.

**Mother-to-Child Transmission of Hepatitis B Virus**

In the absence of effective MTCT prophylaxis, HBV endemicity and chronicity is established in early childhood, with HBsAg seroprevalence studies showing no difference between children aged 5 to 9 years and adults.\textsuperscript{26} The risk of chronic HBV is strongly correlated with the age of acquisition of infection: 90% after neonatal infection (in children born to HBeAg-positive or highly viremic mothers), 20% to 50% with childhood infection (<5 years of age), and less than 5% for adults more than 20 years.\textsuperscript{10} HBV MTCT prevention strategies include antenatal HBsAg screening, third trimester antiviral therapy for women with high infectivity risk (HBeAg positive and/or HBV DNA >200,000 IU/mL), hepatitis B birth-dose (HepB-BD) vaccination, administration of hepatitis B immunoglobulin to the newborn, and full HBV vaccine coverage.\textsuperscript{27–29} In 2009, the WHO recommended HepB-BD vaccination with a monovalent HBV vaccine administered within 24 hours of delivery for all countries.\textsuperscript{14} However, globally in 2014, only 96 of 194 countries (49%) reported offering HepB-BD as part of their national immunization programs and fewer than 38% of babies born worldwide received HepB-BD within 24 hours after birth.\textsuperscript{10} Coverage of the HepB-BD vaccine in 2015 was only 38% worldwide and 10% in sub-Saharan Africa. The identification of HBsAg-positive pregnant women also provides the opportunity to identify potentially HBV-infected partners, siblings, and children and thereby link them to care, breaking the ongoing cycles of infection.

**Hepatitis Delta Virus and Hepatocellular Carcinoma**

Hepatitis delta virus (HDV) is a negative-sense RNA satellite virus of HBV that requires HBsAg for formation of new virions.\textsuperscript{30} HDV coexists with HBV and is related to the most severe form of liver failure attributable to chronic viral hepatitis.\textsuperscript{31} Accurate
data on HDV prevalence in many countries is lacking, leading to a global underestimation of disease burden. The WHO estimates that there are at least 20 million people infected with HDV worldwide, which represents 5% of HBV carriers. Key features of HDV remain unknown. Coinfection of HBV with HDV has been shown to increase the risk of HCC by 2-fold and the risk of cirrhosis 3-fold. It has been suggested that HDV accelerates the disease course compared with HBV monoinfection; however, the potential mechanisms underlying HDV-specific oncogenesis are poorly understood. Apart from enhancing fibrosis and inflammation, there is no evidence to suggest a direct oncogenic mechanism of HDV. Well-designed prospective studies are needed to further evaluate the oncogenic capacity of HBV/HDV co-infection.

NONALCOHOLIC FATTY LIVER DISEASE

The Epidemiology of Nonalcoholic Fatty Liver Disease

First described in the 1980s as an “unnamed disease,” nonalcoholic fatty liver disease (NAFLD) has now become the most common etiology of chronic liver disease in the United States, and is increasingly being recognized throughout the world as a frequent cause of liver disease in the setting of globally increasing rates of the metabolic syndrome. NAFLD is an entity that encompasses a wide range of manifestations from steatosis to NASH, with or without cirrhosis. It has been linked with multiple risk factors including metabolic syndrome, insulin resistance, altered gut flora and persistent inflammation. Notably, NAFLD is more common in the elderly, in whom it manifests with more advanced fibrosis staging at diagnosis and with additional associated comorbidities, such as glucose intolerance and cardiovascular disease, as compared with younger patients. One possible underlying mechanism is aging of the liver, resulting in impairment of metabolism and detoxification by hepatocytes, leading to liver injury and inflammation and the generation of pro-oncogenic substances.

The worldwide incidence of NAFLD ranges from 6% to 35% per year, with a prevalence estimated at 9% to 37%. The global disease burden of NAFLD is currently estimated at 1 billion cases, with the highest prevalence existing in Asia, closely followed by the United States. In the United States, the NAFLD burden has doubled over the past 2 decades to a current burden of 80 to 100 million cases, approximately 30% of the population, and has become the most rapidly growing etiology of cirrhosis. It is possible that the increasing prevalence may also in part relate to the advent of newer, more sensitive, noninvasive diagnostic modalities such as ultrasound examination, computed tomography scans, MRI, and elastography. NASH affects about 5% to 7% of the general population, with 3% to 15% of patients with NASH eventually progressing onto cirrhosis. Studies have shown that the risk of developing HCC in this patient population can be as high as 38% over 5 to 10 years. With the enhanced prevention and eradication of HBV and HCV respectively, NAFLD is predicted to supersede viral etiologies in its contribution to the HCC burden, particularly in developed countries around the world.

Progression of Nonalcoholic Fatty Liver Disease to Hepatocellular Carcinoma

Undoubtedly, the pathway of progression from NAFLD to NASH and similarly from NASH to HCC is complex with a pathophysiology that remains incompletely understood. Notable risk factors include genomic instability, obesity, and diabetes. Mechanisms related to these factors stimulate changes in signaling pathways leading to the evolution of dysplastic cells into malignant cells. A 2-hit hypothesis has been proposed, which suggests the initial risk is insulin resistance, which enhances lipolysis and increases serum free fatty acids. High levels of free fatty acids result in delivering
triglycerides from the liver to peripheral organs, inducing excess lipid synthesis and accumulation of lipids in the liver, or steatosis. The second hit—oxidative stress—is caused by an accumulation of triglycerides and, in turn, induces lipid peroxidation, proinflammatory factor release, and mitochondrial injury. This cascade of events culminates with hepatocellular damage, inflammation, and fibrosis described as NASH. More recently, a parallel hit hypothesis has been suggested. According to this theory, multiple concurrent processes are involved in the development of NASH, including genetic mutations, lipid metabolism disorders, oxidative stress, mitochondrial disorders, variable immune responses, and abnormal gut flora. Per this theory, inflammation is the first step in the cascade leading to fibrosis rather than steatosis. It is felt that much of the disruption in signaling pathways leading to NASH simultaneously lead to HCC. Important molecules orchestrating coordination between these signaling pathways lead to activation of pro-oncogenic processes and suppression of antioncogenic processes. Regardless of the pathophysiology causing NASH to develop, it is the culmination of cirrhotic architectural changes that is felt to be the common denominator in NASH-related HCC. Several clinical trials are ongoing at this time investigating the various pathways involved to determine treatment targets that may reduce progression to NASH and HCC.

Importantly, there is increasing evidence implicating noncirrhotic NAFLD in HCC development. Several studies have showed that in many patients with HCC of unknown etiology, that only risk factor for liver disease was the presence of metabolic syndrome, thus raising suspicion for underlying NAFLD. Many of those with HCC did have histologically confirmed steatosis in the absence of fibrosis or steatohepatitis. This finding suggests that steatosis alone may be implicated in the development of HCC. Notably, obesity has been identified as an independent risk factor for HCC, with an odds ratio of 2.6 (95% confidence interval [CI], 1.4–4.4). The pathogenesis of nonfibrotic NAFLD leading to HCC is yet to be confirmed at this time, although a few potential mechanisms related to the metabolic syndrome have been suggested: increased release of proinflammatory and pro-oncogenic cytokines, decreased expression of anti-inflammatory hormones, lipotoxicity interfering with cell signaling pathways, and hyperinsulinemia resulting in the activation of proliferative cell signaling cascades.

CHRONIC HEPATITIS C

The Epidemiology of Chronic Hepatitis C

HCV has been shown to be responsible for 10% to 25% of HCC cases worldwide. The risk of developing HCV-related HCC is 1.2% to 1.7% per year for patients with chronic hepatitis and 1.4% to 2.5% per year for those with cirrhosis. HCV endemicity is low in northern Europe and North America; intermediate in South America, Eastern Europe, Oceania, and in some Mediterranean countries; and high in some Eastern Asian countries and Western Africa. One of the highest areas of viremic prevalence is Egypt, with a prevalence of 6.3%, equivalent to 5.6 million HCV-infected individuals. Although prior studies among HCV-infected patients reported similar risk factors, for example, HCV genotype, the strongest determinants of HCC risk in these patients are currently the presence (vs absence) of cirrhosis and attaining a sustained virologic response (SVR). Unfortunately, unlike hepatitis B infection, a vaccine for HCV does not exist, making prevention strategies more limited.

Hepatitis C Virus as a Risk Factor for Hepatocellular Carcinoma

Attaining an SVR after HCV treatment is associated with a decreased risk of cirrhosis and its complications including HCC. Before the development of direct-acting
antivirals (DAA), HCV therapy consisted primarily of interferon (IFN)-based treatment. Depending on the HCV genotype and the IFN regimen with or without ribavirin, approximately 30% to 50% of patients treated with IFN achieved an SVR compared with more than 95% of patients achieving an SVR with DAA therapy.\(^5\) Despite the challenges with IFN therapy, studies have consistently demonstrated that, among HCV-infected patients, the risk of developing HCC significantly declined from 6.2% to 1.5% with IFN-based SVR\(^5\) and a similar reduction is observed for SVR from DAA agents\(^6\).

Early reports raised concern and controversy about an apparent unexpected increase in the number of HCC cases developing after DAA therapy for HCV, as well as higher than expected rates of recurrence after surgical resection in patients receiving DAA treatment.\(^5\) It was hypothesized that DAAs may adversely impact immune surveillance, resulting in higher HCC risk. Despite the results of these studies, subsequent data have emerged comparing HCC risk in DAA-cured patients with the risk in patients achieving SVR with IFN-based regimens. In a study by Li and colleagues\(^5\) among all treated persons, risk of HCC was similar in the DAA-treated and the IFN-treated cohorts (hazard ratio [HR], 1.07; 95% CI, 0.55–2.08) after adjusting for differences in patient populations, including higher proportions of cirrhosis and portal hypertension among DAA treated patients than those treated with IFN. Among persons with cirrhosis who achieved an SVR, neither HCC incidence nor HCC-free survival was significantly different in the DAA cohort compared with the IFN-treated cohort (21.2 per 1000 person-years vs 22.8 per 1000 person-years; \(P = .78\)). Collectively, recent data have shown that successful HCV eradication confers a benefit of decreased HCC incidence in DAA-treated patients.

There continues to be debate regarding the risk and aggressiveness of HCC recurrence after DAA therapy in patients with a history of HCC. However, a retrospective cohort study of patients with HCV-related HCC with complete response to resection, local ablation, transarterial chemoembolization, radioembolization, or radiation therapy found that DAA therapy was not associated with HCC recurrence (HR, 0.90; 95% CI, 0.70–1.16) or early HCC recurrence (HR, 0.96; 95% CI, 0.70–1.34).\(^5\) DAA therapy has also been associated with a significant reduction in risk of death as demonstrated by Singal and colleagues\(^5\) who, in an analysis of nearly 800 patients with HCV-related HCC, found that DAA therapy was associated with a significant decrease in the risk of death (HR, 0.54; 95% CI, 0.33–0.90). The association differed by SVR to DAA therapy, where risk of death was lower in patients with SVR to DAA therapy (HR, 0.29; 95% CI, 0.18–0.47) but not in patients without an SVR (HR, 1.13; 95% CI, 0.55–2.33).

DAA therapy, in addition to curing HCV, has shown benefit in terms of regression of liver fibrosis. However, despite HCV clearance, patients with bridging fibrosis or cirrhosis are still at risk of developing HCC. HCC may occur in patients with bridging fibrosis (METAVIR F3) owing to sampling variation in liver specimens, inaccurate evaluation by noninvasive tests, or the transition to cirrhosis after the F3 stage.\(^5\) All international guidelines endorse indefinite HCC surveillance after achieving an SVR in patients with cirrhosis diagnosed before the implementation of antiviral treatment and the development of an SVR.\(^5\) The necessity for periodic surveillance of patients with pretherapeutic bridging fibrosis (METAVIR F3) is more controversial. Recent dedicated analyses suggest that this strategy may not be cost effective in F3 patients owing to the lower HCC incidence observed after achieving an SVR than in patients with pretherapeutic documented cirrhosis.\(^5\)

Although the regression of cirrhosis is possible, the proportion of patients who will experience such an improvement is not known. Many patients may experience...
progression, particularly those with comorbidities. Recent large-scale longitudinal studies of noninvasive evaluations (eg, FIB-4 and APRI) suggest that even in cases of regression of these parameters, the risk of HCC remains high enough to justify surveillance.

The Impact of the Opioid Crisis on the Incidence of Acute Hepatitis C

It is worth mentioning that the population at risk for HCV has changed over the past several years. This has been reflected in the US Preventive Services Task Force recent changes in HCV screening recommendations. Previously it was felt that the recommendation to screen all adults born between 1945 and 1965 would capture the majority of the at-risk populations. More recently, there has been a sharp increase in the incidence of acute HCV infection. This increase can be almost entirely attributable to the epidemic of opioid use, which has created a crisis in communities across the United States. Over the last 2 decades, a nearly 4-fold increase in opioid sales has occurred from 1999 to 2008. Along with an increase in prescription opioid use and addiction, there has also been an acute increase in heroin use. Given these changes in 2019 the US Preventive Services Task Force released a draft recommendation summary to screen for HCV infection in adults ages 18 to 79 years of age.

The rapid increase in injection drug use has resulted in an abrupt increase in HCV transmission among populations at risk. After a remarkable decrease in acute HCV infection over the decade before, the number of acute HCV cases in the United States has nearly tripled between 2011 and 2015. Injection drug use continues to be the principle factor for HCV exposure. It is estimated that up to 1 in 3 persons who inject drugs will develop HCV infection within the first year of injecting drugs. Given the benefits associated with virologic cure, the current AASLD/IDSA HCV guidance document strongly recommends antiviral treatment for all adults with acute or chronic HCV infection (except those with a short life expectancy that cannot be remediated). This includes all persons with ongoing substance use (alcohol or drugs), because several studies have demonstrated that treatment-committed individuals in this disproportionally affected population achieve SVR rates with DAA therapy comparable with those without known, current substance use. Although it is unlikely that the opioid crisis is contributing to the current epidemiology of HCC, this factor deserves attention and a focus on antiviral treatment of this generally young population, with the hopes of preventing long-term complications of cirrhosis and HCC.

Alcoholic Liver Disease

Alcohol consumption has been linked to the development of many malignancies including HCC, with a 2.07 relative risk of development of HCC for alcohol abusers compared with nondrinkers. However, alcoholic liver disease in the absence of fibrosis or with very mild fibrosis has not been shown to be associated with an increased HCC risk. Although alcohol accounts for a significant proportion of primary HCC burden in cirrhosis, there is significant geographic variation. Alcohol is a risk factor for HCC development in 6% to 14% of patients in the Middle East and North Africa compared with 50% to 60% in Eastern Europe. The pathophysiology is believed to be related to the effect of alcohol in the disruption of liver architecture and function, with the eventual development of steatosis, steatohepatitis, and cirrhosis. A number of processes have been reported to contribute to carcinogenesis, including the formation of acetaldehyde and reactive oxygen species, increased production of cytochrome P450, and impairment DNA repair.
SUMMARY

HCC has been steadily increasing in incidence and is among the leading causes of morbidity and mortality in the United States and the world. Previously limited to developing countries, it is now impacting the northern and western hemispheres. With the burden of HCC expected to increase in the coming years, prevention of HCC through the modification of risk factors will be imperative. Owing to the current epidemic of metabolic syndrome, the population affected by NAFLD and NASH continues to increase and now comprises a significant portion with HCC.

The majority of efforts to prevent the progression from NASH to cirrhosis and HCC at this time focus on improving the metabolic syndrome and obesity, with an emphasis on dietary and lifestyle changes. As clinical trials for targeted pharmacologic therapy for the treatment of NASH are underway, there is promise that the future will bring medical therapies aimed to prevent fibrosis and decrease the risk for HCC development. The WHO goal of obtaining universal HBV vaccination by 2016 has led to a global effort to improve vaccination efforts, prevent MTCT and implement linkage to care to avoid the development of HCC in addition to cirrhosis.

Finally, the use of highly effective DAA therapies to reduce the burden of chronic HCV has decreased but not eliminated the risk of subsequent HCC development. Ongoing HCC risk factor identification and global attention to the prevention and treatment of chronic liver diseases will be critical to slowing the incidence of HCC.

REFERENCES


