Gastroenterology 2023;164:766–782

Global Epidemiology and Genetics of Hepatocellular Carcinoma







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Hepatocellular carcinoma (HCC) is one of the leading cancers worldwide. Classically, HCC develops in genetically susceptible individuals who are exposed to risk factors, especially in the presence of liver cirrhosis. Significant temporal and geographic variations exist for HCC and its etiologies. Over time, the burden of HCC has shifted from the low–moderate to the high sociodemographic index regions, reflecting the transition from viral to nonviral causes. Geographically, the hepatitis viruses predominate as the causes of HCC in Asia and Africa. Although there are genetic conditions that confer increased risk for HCC, these diagnoses are rarely recognized outside North America and Europe. In this review, we will evaluate the epidemiologic trends and risk factors of HCC, and discuss the genetics of HCC, including monogenic diseases, single-nucleotide polymorphisms, gut microbiome, and somatic mutations.

Keywords: Hepatocellular Carcinoma; Epidemiology; Genetics.

Liver cancer is the eighth most common and third leading cause of cancer death.[1] Hepatocellular carcinoma (HCC) accounts for 80% of all liver cancers.[2] In 2019, there were approximately 747,000 cases of HCC worldwide, representing a 70% rise since 1990, and 480,000 deaths were attributable to HCC.[3] Overall survival of HCC is poor, with a median survival of 6–10 months.[4,5] The main risk factors are viral hepatitis, alcohol-related liver disease (ALD), and nonalcoholic liver diseases. Over the years, the global burden of HCC shifted from the low–moderate sociodemographic index (SDI) regions to the high SDI regions, mirroring the transition from viral to nonviral etiologies.[6–8] Some of the trends may be accounted for by longer life expectancy and better HCC surveillance in the high SDI regions compared with the low–moderate SDI regions.[9–11] We will review the epidemiologic trends of HCC in the various world regions, particularly countries with the highest burden of HCC and its risk factors. The epidemiologic analysis will be based mostly on estimates from the 2019 Global Burden of Disease study (represented in Figure 1 and Supplementary Table 1) and, to a lesser extent, region- and country-specific data.

Hepatocellular Carcinoma Risk Factors

Viral Hepatitis

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are hepatotropic viruses that can be transmitted vertically from mother to child or horizontally through sex and contaminated needles.[12,13] Approximately 10%–25% of chronic HBV infections will lead to HCC, and HCC develops at an annual rate of 2%–4% in HCV-related cirrhosis.[13,14] Globally, more than 350 million people are chronically infected with HBV and HCV[15,16] and 80%–90% of them are unaware of their diagnosis.[17]

In 2016, the World Health Organization called for the eradication of viral hepatitis by 2030, aiming for 90% and 65% reductions in incidence and mortality, respectively.[18] To this end, the World Health Organization proposed a care continuum of prevention, diagnosis, and treatment.[18]

Abbreviations used in this paper: **AA, aristolochic acid; AIO, African iron overload; ALD, alcohol-related liver disease; DAA, direct-acting antiviral; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HH, hereditary hemochromatosis; HT1, hereditary tyrosinemia type 1; ITH, intratumoral heterogeneity; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OR, odds ratio; PCT, porphyria cutanea tarda; SDI, sociodemographic index; SNP, single-nucleotide polymorphism; SSA, sub-Saharan Africa; WD, Wilson disease.**

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2023.01.033

Horizontal spread of the hepatitis viruses can be reduced with harm-reduction interventions, such as needle and syringe programs and opiate agonist therapies.[18] Approximately 90%–95% of vertically transmitted HBV infections can be prevented by the 3-dose hepatitis B vaccine.[18,19] In 2019, the 3-dose hepatitis B vaccine achieved a global coverage of 85%.[17] HBV vaccination has been associated with reductions in HCC incidence.[20] In Taiwan, where HBV was once endemic, incidence of HCC declined by 80% after universal HBV vaccination.[21] Besides HBV vaccines, treating chronic hepatitis B with nucleoside analogues has also been found to reduce HCC risk by 45%–80%.[22–25]

For HCV, treating existing HCV infections with direct-acting antiviral (DAA) therapies is the most effective way to prevent new cases, with cure rates exceeding 90%.[26] Achieving sustained virologic response has also been found to reduce HCC risk by >70%.[27] However, large-scale HCV testing and treatment might not be cost-effective in low-endemic countries. The more pragmatic approach is microelimination, in which efforts are focused on high-risk subpopulations, such as people who inject drugs, HIV-positive individuals, men who have sex with men, prisoners, certain birth cohorts, and migrants from endemic regions.[28,29]

Nonalcoholic Steatohepatitis

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in the world. Its global prevalence in 2016 was approximately 25%, with a projected 15%–56% rise by 2030.[30,31] Approximately 10%–20% of people with NAFLD will develop nonalcoholic steatohepatitis (NASH) and 21%–26% of people with NASH will develop liver cirrhosis within 8 years, of which up to 3% are diagnosed with HCC every year.[32–34] Noncirrhotic HCC is more common in NASH than the other etiologies; 39% of NASH-associated HCCs develop in the absence of cirrhosis, compared with 22%, 6%, and 9% for HBV, HCV, and ALD, respectively.[33,35] Compared with the other etiologies, people with NASH-related HCC are older (mean difference, 5.6 years); have higher body mass index (mean difference, 3 kg/m^2); and have higher rates of type 2 diabetes mellitus (odds ratio [OR], 4.3), hypertension (OR, 2.8), hyperlipidemia (OR, 3.4), and cardiovascular disease (OR, 2.2).[35] Patients with NASH are less likely to undergo HCC surveillance than those with other causes (OR, 0.4), as most individuals are unaware of their diagnosis.[35] Obesity and diabetes are important risk factors for both NASH and NASH-related HCC.[36,37] With the growing epidemics of obesity and diabetes, NASH-related HCC cases are rising rapidly and NASH is now the fastest growing cause of HCC worldwide.[33] We do not have any effective therapy for NASH. Intensive lifestyle modifications, such as weight loss and cardiovascular risk control, are the main measures to slow disease progression and, when weight loss is significant, to reverse steatohepatitis.[33,38–40] Recently, both the American Diabetes Association and European Association for the Study of Diabetes recommended screening for NAFLD in patients with type 2 diabetes mellitus.[41]

Alcohol-Related Liver Disease

Alcohol is an independent risk factor for HCC, with a greater risk ratio conferred by higher levels of consumption.[42,43] Although there are no safe limits for alcohol consumption, most guidelines recommend lower thresholds for women than for men; for example, the Centers for Disease Control and Prevention recommend limiting daily alcohol intake to 2 drinks for men and 1 drink for women.[44,45] Alcohol also synergizes with other risk factors (such as viral hepatitis) to accelerate hepatocarcinogenesis.[46–48] ALD accounts for one-fifth of all HCCs.[3] Risk is 10-fold higher in the presence of liver cirrhosis (risk ratio, 2.4 vs 22.4).[49] Every year, 3% of people with alcoholic cirrhosis will develop HCC.[50] People with ALD-related HCC have the shortest median survival compared with the other HCC causes (6 vs 8–10 months), due to a poorer performance status, worse liver function, more advanced HCC at presentation, and alcohol nonabstinence excluding them from liver transplantation.[51,52] The main treatment for ALD is alcohol cessation, which reduces the cancer risk by 6%–7% for every year of abstinence.[50]

Aflatoxin

Aflatoxin is a carcinogenic mycotoxin produced by the *Aspergillus* mold, which thrives on maize and groundnuts.[53] Five billion people are exposed to aflatoxin in the world, especially those living in rural areas of sub-Saharan Africa (SSA), Southeast Asia, and China, where maize and groundnut are the staple foods.[53] Aflatoxin exposure is associated with 5%–28% of HCC worldwide, and shares a similar geographic distribution with HBV, where co-exposure can raise the relative risk of HCC by 4–10 times.[53,54] The active metabolite of aflatoxin forms DNA adducts and induces G>T transversions characteristic of the aflatoxin-specific mutation signature (signature 24).[55,56] The main risk-mitigation strategies for aflatoxin exposure are dietary diversification and strict regulations. At present, 99 countries have imposed regulations on mycotoxin contamination in food production.[57] Food producers throughout North America and Europe comply with strict regulations and food sampling protocols to minimize aflatoxin contamination.[57] Unfortunately, regulations are lacking in SSA countries, where aflatoxin-contaminated foods are widely consumed.[57,58] Only 15 African countries, containing 59% of the African population, have mycotoxin regulations.[57]

Aristolochic acid

Aristolochic acid (AA) is a potent nephrotoxin and mutagen found in plants in the genus Aristolochia and used in Chinese herbal medicine.[59] Exposure to AA leads to T>A transversions in HCC and the unique molecular signature 22.[60] An analysis of The Cancer Genome Atlas database signature 22 in 47% and 56% of the HCCs in China and Southeast Asia, respectively, far exceeding those of Europe (2%) and North America (5%).[60] Since the early 2000s, the sales of AA-containing products were banned in many countries.[61] However, AA-containing products are being manufactured and sold worldwide under loose regulations

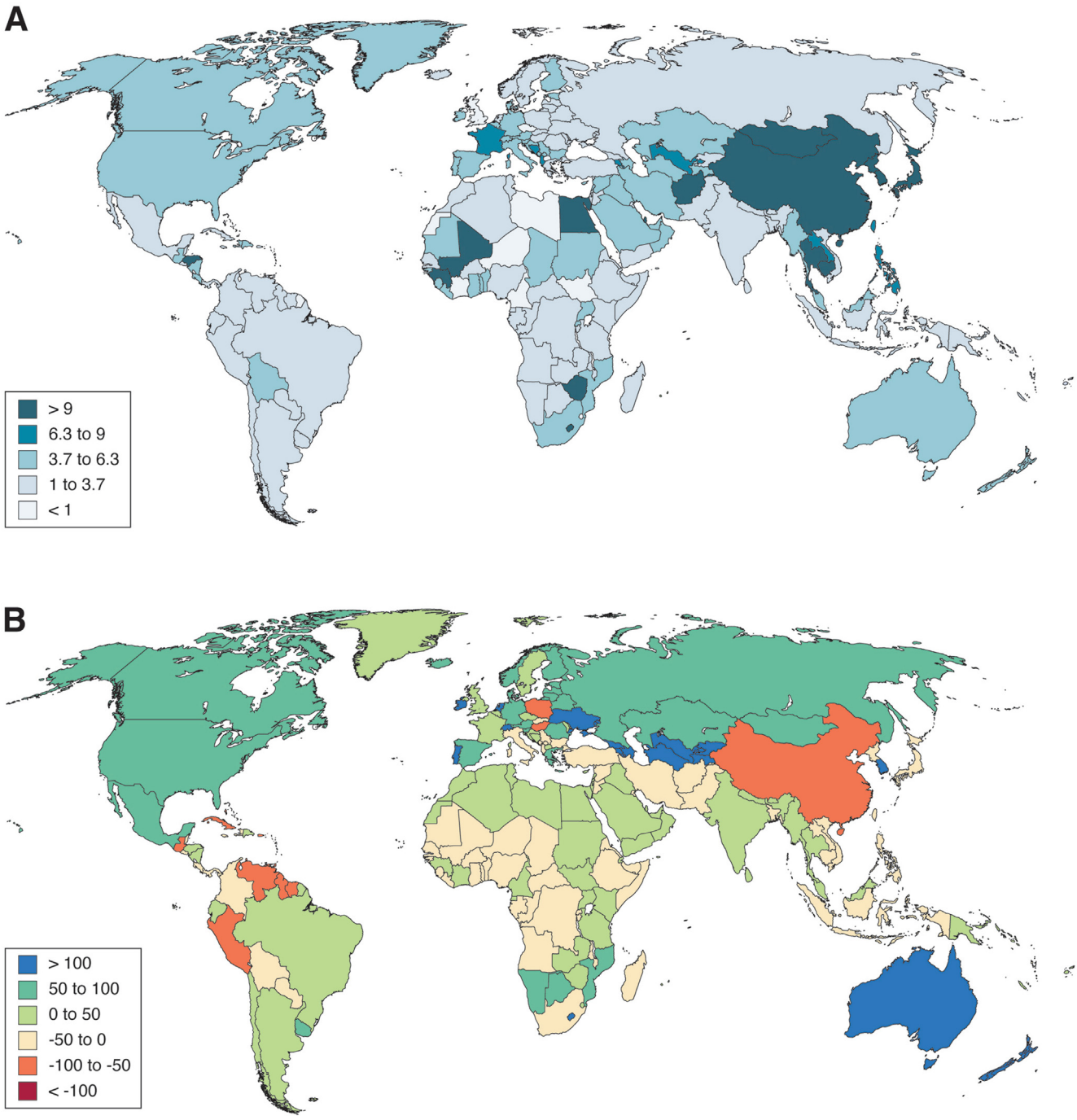

Figure 1. Regional variations of hepatocellular carcinoma (HCC) between 1990 and 2019. The epidemiologic data were obtained from the Global Burden of Disease study.[6] *Map* was generated by StatPlanet Interactive Mapping and Visualization Software. *(A)* Age-standardized incidence rates (per 100,000 people) in 2019. *(B)* Temporal changes in age-standardized incidence rates between 1990 and 2019, represented as a percentage.

and the AA signature 22 continues to be detected in new HCC cases.[60]

Iron Overload

Iron overload arises when iron homeostasis is disrupted. Excess iron stores can trigger reactive oxygen species production and lipid peroxidation, which damage cells and activate hepatic stellate cells, leading to accelerated liver fibrosis and hepatocarcinogenesis.[62,63] African iron overload (AIO) is an acquired iron overload that is associated with HCC (OR, 3.1–10.6).[64,65] AIO affects 10% of the people living in rural SSA, where iron-rich traditional beers are commonly consumed.[66,67] However, most traditional beer drinkers (80%) do not develop AIO.[66] Preliminary studies suggest that germline variants in iron regulatory genes might account for a potential hereditary component of AIO.[66] An example is

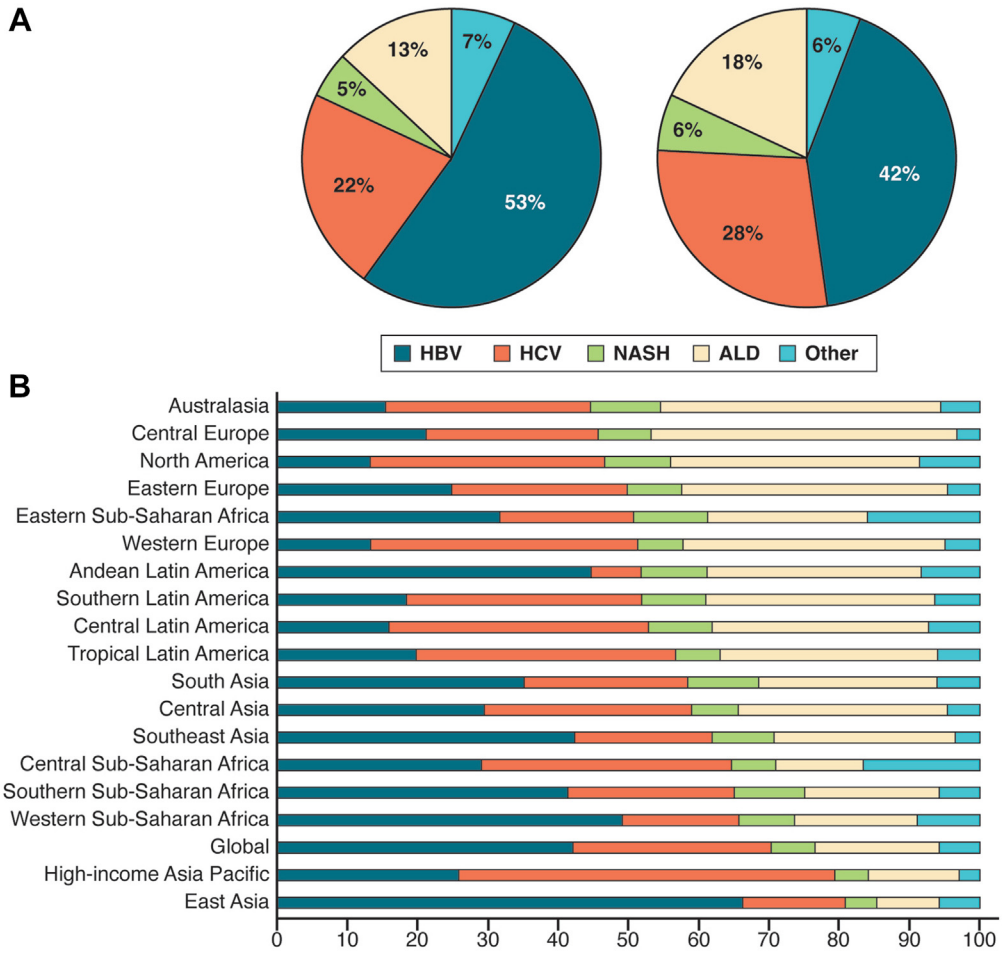

Figure 2. Temporal and geographical differences in HCC etiologies based on prevalence data from the Global Burden of Disease study.[6] (*A*) Distribution of HCC etiologies showing a transition from viral hepatitis to nonviral etiologies between 1990 (*left*) and 2019 (*right*). (*B*) Distribution of HCC etiologies in the various world regions in 2019. Viral hepatitis is the main cause of HCC in Asia and most African regions. Nonviral causes, that is, NASH and ALD, contribute to the majority of HCC in North America, Europe, Latin America, and Australasia.

SLC40A1 Q248H, which has an allele frequency of 0.09 among people of SSA descent and is associated with the risk of AIO (OR, 1.6).[66]

Region- and Country-Specific Epidemiology, Risk Factors, and Interventions

Asia Pacific

The Asia Pacific region has an HCC prevalence of approximately 530,000, accounting for more than one-half of the global HCC burden in 2019 (Figure 2).[3] Almost 80% of the cases are caused by HBV and HCV, reflecting the high endemicity of the region.[3,6,68]

China

China has the world's greatest HCC burden.[3] In 2019, more than 290,000 people in China were diagnosed with HCC and another 188,000 died from HCC.[3] HBV is the leading cause of HCC in China and accounts for approximately 190,000 cases of HCC.[3] Over the years, China achieved a steady reduction in HCC incidence and mortality of 2% every year, with a projected 50% reduction in HCC incidence by 2050.[69,70]

In 2019, more than 114 million people in China were affected by HBV and another 9 million people were chronically infected with HCV.[3] Mother-to-child transmission is the main route of HBV transmission due to the high seroprevalence (10%) among women in the 1980–1990s, and unsafe injectables are the predominant source of new HCV infections, with the highest infection rates among people who inject drugs (55%–65%).[71-73] China has achieved >90% coverage for infant hepatitis B immunization, antenatal HBV screening, and passive–active immunization for at-risk newborns, preventing 80–90 million chronic HBV infections.[74–76] For HCV, the Chinese government has been actively raising awareness among the public and at-risk populations, increasing HCV screening coverage, integrating primary care in the care cascade, and improving DAA accessibility via price negotiations and national subsidies.[72] However, upscaling these elimination efforts may not always be feasible, considering the large population size of China. Microelimination of HCV in high-risk populations might be a more cost-effective approach to achieve higher diagnosis and treatment rates.[77,78]

In 2019, both NASH and ALD accounted for approximately 13% of the HCC cases in China.[3] The rapid economic development in China has led to higher alcohol consumption (from 4 L of alcohol per capita in 2005 to 7 L in 2016), more

sedentary lifestyle, and rising rates of obesity and diabetes (by 2%–3% between 2014 and 2018).[48,79] These have led to a rise in both NASH and ALD; NAFLD (no data for NASH) increased from 24% to 33% between the early 2000s and 2018, and ALD prevalence doubled between 2002 and 2013.[80–82] In 2020, NASH and ALD affected 2%–6% and 1%–8% of the general population, respectively, with an expected 48% rise in NASH prevalence by 2030.[31,83] In 2016, the government initiated the "Healthy China 2030" national campaign to encourage healthy living, hoping to reverse the rising trends of NASH and ALD.[79]

Mongolia

Mongolia has the world's highest mortality rate of HCC, substantially above the global average (115 vs 6 per 100,000 people).[3] Almost one-half of all of the cancer deaths in Mongolia are attributable to HCC, due to high seroprevalence of the viral hepatitis (approximately 10%) and lack of HCC surveillance.[3,84,85] With the implementation of blood product screening, free childhood hepatitis B vaccination, and HBV and HCV testing with linkage to care and subsidized treatment, the proportion of viral hepatitis–related HCC has decreased from almost 98% in 2010 (based on Mongolia's national cancer records) to 60% in 2019 (based on Global Burden of Disease estimates).[3,86,87] Unfortunately, the decline in viral hepatitis–related HCC was offset by the quadrupling of alcohol-related HCC between 1990 and 2019.[3,88] Alcohol has become the second leading cause of HCC-related deaths, with alcohol-related liver cirrhosis causing 7 times more deaths than HBV- and HCV-related liver cirrhosis combined.[88]

Japan

Japan has the second highest prevalence of HCC worldwide, with an estimated 34,000 HCC-related deaths in 2019.[1,6] HCC prevalence has risen over the years, driven by the growth in NASH and ALD.[3,89] Between 1996 and 2019, non-viral–related HCC nearly quadrupled from 12% to 46%, in tandem with the rise in obesity, metabolic syndrome, and alcoholism in Japan.[3,90,91] The prevalence rate of NAFLD almost doubled from 13% (in the early 1990s) to 25%–35% (in the early 2000s), and is predicted to affect 45% of the population in 2040.[92,93] Similarly, the prevalence of alcohol dependence has risen by nearly 50% between 2003 and 2013, and drinkers are getting younger.[94] In 2013, the Japanese government implemented "Health Japan 21" to promote healthy living and reduce rates of obesity, drinking, diabetes, and other comorbidities.[95]

With more than half a million people living with HCV, HCV is the main cause of HCC in Japan.[96] HCV infection is 10 times more common among those older than 55 years due to birth cohort effects (eg, 1920s *Schistosoma japonicum* outbreak, post-war intravenous drug abuse, and the 1960s outbreak of contaminated blood transfusions).[97–99] To control the birth cohort effects, the government implemented blood product screening in 1999, nationwide viral hepatitis screening (in 2002), and DAA subsidies (in 2014).[100,101] The seroprevalence of HCV has been on a decline, from 0.7% to 0.4% between 2015 and 2020.[97,102] Based on a recent epidemiologic study in Kyusu, the proportion of incident HCC cases attributable to HCV decreased from 73% (1996–2001) to 14% (2014–2019).[90]

Australia

Australia has one of the lowest HCC burdens in the region, however, the prevalence of HCC has increased more than 5-fold from approximately 400 to 2,300 between 1990 and 2019.[3,6] HCC is the fastest growing cancer in Australia, with an overall 5-year survival of 20%.[103] The HCC mortality rate has also tripled between the 1980s and 2010s, causing 7 deaths per 100,000 people.[104] Overall, HCV and ALD are the main etiologies and account for approximately 40% and 30% of the HCC cases, respectively.[3,105] HCV seroprevalence in Australia has fallen steadily from 0.8% in 2015 to 0.5% in 2020[96]; 99% of HCV infections have been diagnosed and 7% are treated every year.[102] Australia has become a best-practice model for HCV elimination.[106] Key models of care include providing unrestricted access to DAA, point-of-care testing, and testing and treatment by general practitioners and in pharmacies and prisons.[74,107] The various etiologies are distributed unevenly across the different subpopulations of Australia.[105,108] In general, immigrants from viral hepatitis endemic regions, Aboriginal Australians, and those born during the peak HCV period (1955–1975) had significantly higher proportions of viral hepatitis–related HCC, and the local populations were affected more by ALD- and NASH-related HCC due to higher alcohol consumption and obesity rates (>60% of the adult Australian population).[104,105,108]

Sub-Saharan Africa

SSA has an estimated 23,000–32,000 cases of HCC.[1,3] Notably, SSA has the world's youngest population of HCC, with a median age of 45 years compared with the global median age of 65 years.[8,109] HBV is the main etiology and accounts for 40%–55% of the cases.[3,110] SSA has the world's highest proportion of aflatoxin-related HCC (40%), with an estimated 11,000–60,000 cases of aflatoxin-related HCC in 2010.[53] High HBV endemicity with oncogenic HBV genotypes, high HIV co-infection rates, and chronic exposure to aflatoxin have been cited as reasons for the younger HCC population.[111–113] In addition, SSA has the poorest HCC survival worldwide (median survival of 2.5 vs 6–10 months) due to late presentation, lack of HCC surveillance among at-risk populations, and inadequate treatment expertise.[8] In a retrospective study by the Africa Liver Cancer Consortium, 95% of the 1315 patients with HCC were diagnosed with advanced HCC (Barcelona Clinic Liver Cancer stages C and D).[110] Of those who presented early, only 13 were resected and 5 received chemoembolization.[110] None of them underwent transplantation or local ablation.[110] Significant racial disparity exists for HCC, with the Black African population having 3–6 times higher mortality than the White African population, attributable to lower socioeconomic status and health literacy.[114]

SSA is a high HBV-endemic region (6%–6.5% seroprevalence) and accounts for nearly 25% of the global HBV

burden.[115,116] SSA also has higher rates of HDV (2%–67%) and HIV coinfections (10%–25%), which contribute to faster disease progression and a younger HCC population.[117,118] Up to 90% of the HBV infections in SSA are transmitted horizontally during childhood via unsafe blood transfusion, unsafe needle practices, and cultural practices, such as tribal scarification and male circumcision.[119] Elimination efforts are lacking in SSA and only 3 SSA countries have national guidelines on HBV.[115,120] SSA has one of the lowest coverage of hepatitis B vaccine; 77% of the infants in SSA received the 3-dose vaccine series, falling short of the global coverage of 84%.[120] Likewise, only 7% of the newborns in SSA received the birth-dose vaccine compared with the global coverage of 43%.[120] Administration of birth-dose vaccine within 24 hours has been challenging, especially in rural areas where vaccine stability is compromised from cold-chain breaks.[120,121] In terms of testing and treating HBV, <1% of people with HBV infections have been diagnosed and only 0.1% are treated.[120,122] Better public awareness, broader hepatitis B vaccination coverage, harm reduction services, and accessible testing (eg, point-of-care tests) with linkage to care are crucial to HBV elimination. In 2019, South Africa published its first national guidelines on viral hepatitis.[123]

North America

United States. The United States has the world's third highest prevalence of HCC, with an estimated 43,000 cases in 2019.[1,3] HCC is the fastest growing cancer in the United States, with a more than 3-fold increase in new cases between 1980 and 2015.[124] In 2022, the North American Association of Central Cancer Registries reported 41,260 new HCC cases and 30,520 HCC deaths in the United States.[124]

In 2015, NASH affected 1.5%–6.5% of the general population in the United States, with an expected 63% rise by 2030.[30,125] Over the years, NASH has become the leading etiology of HCC in the United States.[52] According to the Surveillance, Epidemiology and End Results-Medicare databases (2004–2009 and 2011–2015), the proportion of NASH-related HCC grew from 14% (2004–2009) to 36% (2011–2015), in parallel with the rise in obesity and diabetes.[52,126] NASH is also the fastest growing cause of HCC in liver transplant recipients, ranked second after HCV.[127] People with NASH-related HCC have a poorer survival compared with those with HBV-related HCC (8 vs 10 months), due to the lower HCC surveillance rate before diagnosis (5% vs 24%), more advanced disease at diagnosis (tumors >5 cm: 46% vs 37% and distant metastasis: 17% vs 10%), greater comorbidities (Charlson Comorbidity Index >2: 12% vs 5%), and lower treatment rate (27% vs 40%).[4,52]

An estimated 28 million people in the United States had alcohol use disorder in 2020, nearly twice as many as 2015, when 15.7 million people were affected.[128,129] Between 2004 and 2015, the proportion of ALD-related HCC increased from 16% (2004–2009) to 18% (2011–2015).[52] The mortality rate of ALD-related HCC increased from 0.09 to 0.16 per 100,000 people between 2007 and 2017, which was the greatest increase among the HCC causes.[130] ALD-related HCC has the lowest median survival (6 months) and treatment rate (19%) among all causes of HCC.[4] In 2018, the US Preventive Services Taskforce recommended routine screening for alcohol use disorder in primary care settings to facilitate early counseling and interventions.[131]

The United States has a relatively low seroprevalence of HBV (1% in 2020) and HCV (0%–1% in 2016).[102] HBV and HCV contribute to 5% and 34% of the HCC cases, respectively.[52] People with cirrhosis due to viral hepatitis were more likely to undergo regular HCC surveillance and present with early-stage HCC amenable to curative treatment.[52] Based on the 2011–2015 Surveillance, Epidemiology and End Results-Medicare data, regular HCC surveillance was performed in 25% of HBV-related cirrhosis and 27% of HCV-related cirrhosis, more than those caused by NASH (5%) and ALD (20%).[52] Twenty-five percent of people with HBV or HCV-related HCC presented with early-stage HCC, more commonly than those with NASH (13%) and ALD (20%).[52] Twenty-eight percent of the HBV-related HCC and 34% of the HBV-related HCC were treated with the curative intent, compared with HCC due to NASH (18%) and ALD (20%).[52] Hence, the rise in mortality rate between 2007 and 2017 was substantially lower for HBV- (6%) and HCV-related HCC (27%) than those of NASH- (39%) and ALD-related HCC (78%).[130]

Latin America

In 2019, there were approximately 18,000 cases of HCC and 20,000 HCC-related deaths in Latin America.[6] In 2017, the main causes of HCC were HCV (48%), ALD (22%), HBV (14%), and NASH (9%).[132] Since then, the proportion of NASH-related HCC has quadrupled from 9% to 37% and has become the leading cause of HCC in 2021; other causes were HCV (21%), HBV (12%), and ALD (17%).[133] Latin America has the highest prevalence of NASH (6%–18%) worldwide.[134] This is contributed to by the high prevalence of obesity and diabetes in the region, coupled with an increased NASH risk (OR, 3.5) conferred by the *PNPLA3* I148M variant (present in nearly one-half of the Hispanic population).[135,136] HCC surveillance before diagnosis has been suboptimal in Latin America and did not improve over the years.[133] Fewer than one-half of the HCCs were diagnosed during surveillance.[132,133] Hence, most people (57%) presented with advanced disease not amenable to curative therapy.[133] Even among those with curable disease, one-third did not receive curative therapy.[133]

Europe

HCC is uncommon in Europe, with an estimated 85,000–90,000 prevalent cases and 60,000–80,000 HCC deaths.[1,6] ALD is the leading cause of HCC and accounted for 37% of the cases in 2019, while HCV, HBV, and NASH constituted 35%, 17%, and 7% of the HCC cases, respectively.[3,137] ALD-related cirrhosis is also the leading cause for liver transplantation in Europe, accounting for 20% of the liver transplantations in 2016.[138,139] Europe has the highest alcohol consumption worldwide (11–12 L of alcohol per

capita per year vs the global average of 6.5 L).[48] Despite this, Europe has been at the forefront of alcohol-control policies and is the only region to achieve the World Health Organization target of a 10% target reduction in harmful alcohol use.[140] Since 1990, alcohol use in Europe decreased from 12 L to 9 L per capita per year and the prevalence of alcohol use disorder remained stable at 20 million cases.[3,141]

In 2015, almost 25% of the population in Europe had NAFLD, with a predicted 90%–125% rise by 2030.[30,31] There has also been an increase in the proportion of liver transplantations performed for NASH, from 1.2% in 2002 to 8.4% in 2016.[142] Between 1990 and 2019, the number of NASH-related HCCs nearly tripled, affecting 6100 people.[102] NAFLD has become a costly disease, with an annual cost of approximately €354–€1,163 per patient.[143] Unfortunately, a recent cross-sectional study on 29 European countries revealed that none of the countries had written strategies or action plans against NASH.[144]

Each year, another 19,000 and 300,000 people in Europe are infected with HBV and HCV, respectively, considerably lower than the global estimates (1.5 million).[18] Most European countries have achieved substantial improvements in the infection rates due to effective elimination programs and DAA therapies.[6,137] Since 2000, the United Kingdom, Greece, and Slovenia have experienced a >5% annual reduction in HBV seroprevalence.[145] Nonetheless, viral hepatitis remains an important cause of HCC, especially in European countries with a high proportion of older adult and foreign-born immigrants.[146]

Host Susceptibility: Age, Sex, and Genetic Predisposition

Hepatocarcinogenesis involves risk-factor exposure in a susceptible host, development of liver cirrhosis, and accumulation of somatic alterations (Figure 3). Host susceptibility includes older age, male sex, and genetic predisposition. Aging correlates positively with HCC risk (hazard ratio, 1.4–2.5 per 5 years).[147] Most HCCs are sporadic and older adults are most affected.[148] The median age at HCC diagnosis is 60 years, with the highest incidence occurring between 60 and 74 years.[6] The male to female ratio of HCC is 11, and male patients have faster disease progression, poorer treatment response, and higher mortality rates.[149,150] Some studies have suggested that the estrogen axis protects against HCC by modulating the inflammatory microenvironment, while the androgen receptor regulates genes that can drive β-catenin/T cell factor–dependent hepatocarcinogenesis.[149,150]

Genetic Predisposition: Monogenic and Polygenic

Genetic susceptibility to HCC can be subdivided into monogenic and polygenic predisposition. Monogenic disorders with HCC risks include hereditary hemochromatosis (HH), Wilson disease (WD), hereditary tyrosinemia type 1 (HT1), porphyria cutanea tarda (PCT), and α-1-antitrypsin deficiency. Their regional prevalence, diagnosis, and management are summarized in Supplementary Tables 2–7.

Hereditary hemochromatosis. HH is an autosomal recessive disease driven by mutations in the *HFE* gene (p.C282Y, p.H63D, and p.S65C), with a prevalence of 1 in 300 in the Western population; the various genotype frequencies are summarized in Supplementary Table 2.[151] Clinical penetrance is approximately 2% and the affected individuals can manifest with elevated serum ferritin and iron saturation, liver cirrhosis, cardiomyopathy, and endocrinopathies.[152] People with HH and liver cirrhosis have a 20-fold greater lifetime risk of developing HCC and a 4% annual incidence rate.[153,154] HCC risks are greater in those with more severe iron overload, cirrhosis, and concomitant viral hepatitis.[152] HCC surveillance is recommended in all patients with HH with cirrhosis.[155]

Wilson disease. WD is an autosomal recessive disorder of copper metabolism caused by mutations in *ATP7B* encoding for copper-transporting ATPase. The global prevalence of WD is estimated at 1 in 10,000–30,000, mainly in White populations.[156] Patients accumulate copper in several organs, including the liver, brain, and cornea. WD-associated liver injury can manifest as asymptomatic transaminitis or acute or chronic hepatitis, with cirrhosis reported in 17%–37% of patients.[157,158] HCC is rare in WD, even in those with liver cirrhosis, with an annual incidence of 0.09%–0.14%.[159] Hence, HCC surveillance in WD is controversial.

Hereditary tyrosinemia type 1. HT1 is an autosomal recessive disorder caused by a deficiency in fumarylacetoacetate hydrolase. Toxic metabolites accumulate in the liver, destabilizing chromosomes and cell processes.[160] HT1 can manifest as acute liver failure in the first 2 months of life and has a low survival rate (29%).[160] In survivors with untreated HT1, HCC can develop at an incidence rate of almost 40%, as early as age 4–5 years.[160,161] Patients should be screened regularly with α-fetoprotein levels and ultrasound.[160] Those who develop HCC should be considered for liver resection and transplantation; a retrospective study of 16 children with HT1 who underwent liver transplantation had a survival rate of 86% at a median follow-up of 6.6 years.[162]

Porphyria cutanea tarda. PCT is the most common porphyria, characterized by deficient uroporphyrinogen decarboxylase and abnormal heme synthesis.[163] Most cases are sporadic due to susceptibility factors, such as heavy alcohol use (>40 g/d), HCV infection, and *HFE* mutation.[164,165] Familial PCT, an autosomal dominant disorder involving the *UROD* gene, constitutes 20%–25% of all cases.[163] Hepatic accumulation of porphyrins can lead to liver injury and cirrhosis. Elevated HCC risk (5- to 21-fold) is observed in individuals with PCT.[163] The actual risk conferred by porphyrin accumulation is confounded by the high prevalence of heavy alcohol use (60%–90%), HCV infections (70%–80%), and *HFE* mutations (21%–73%).[163] It is unclear whether patients with PCT should be routinely screened for HCC.

α-1-Antitrypsin deficiency. α-1-Antitrypsin deficiency is an autosomal recessive disorder of the *SERPINA1* gene. There are 3 major alleles: M (normal), S (abnormal),

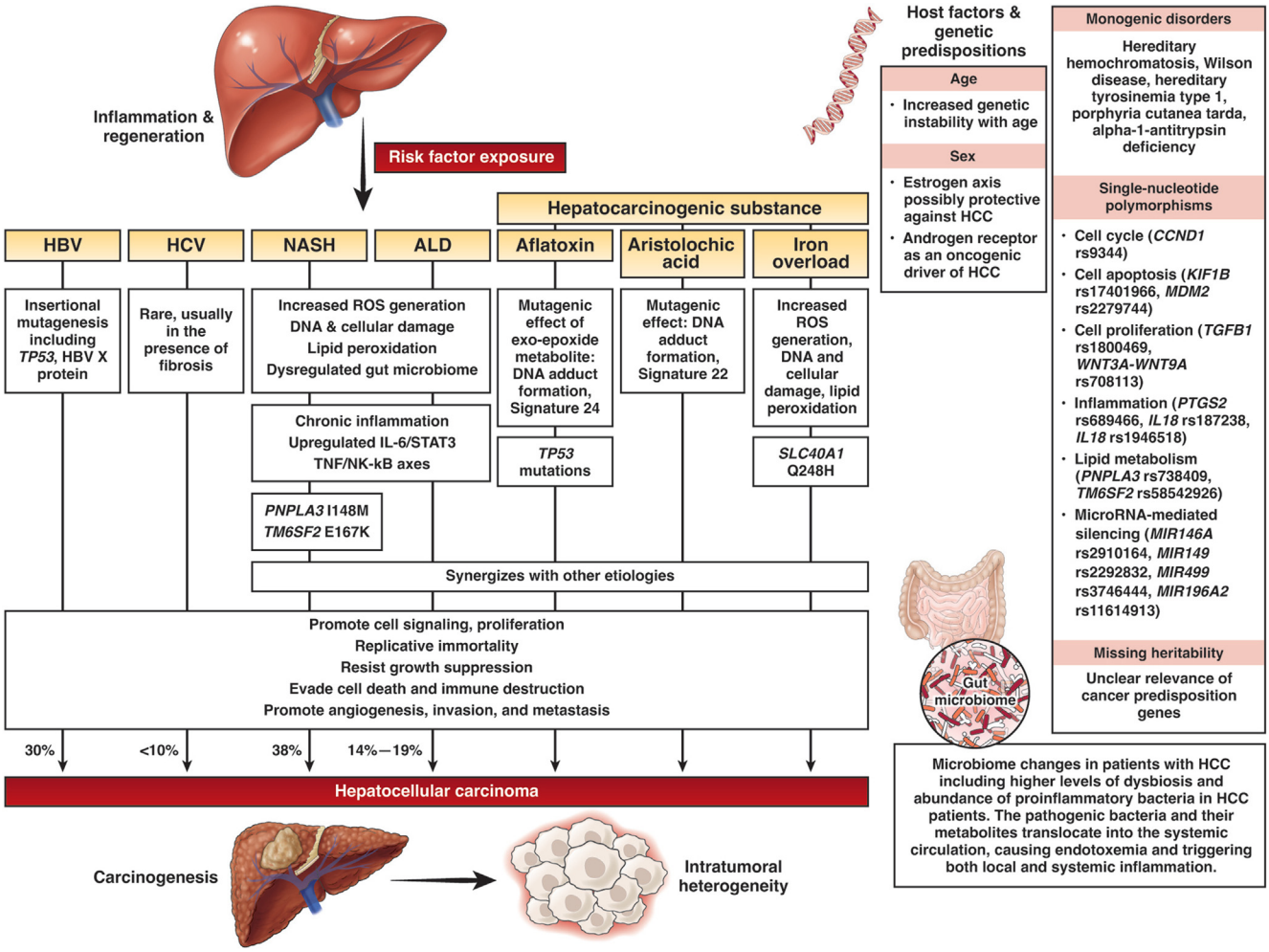

Figure 3. Pathogenesis of HCC. This process begins with the exposure to environmental risk factors that induce chronic inflammation in the liver, further aggravated by gut dysbiosis. Eventually, the liver becomes cirrhotic and this forms the "soil" for hepatocarcinogenesis. On a molecular level, chronic inflammation and exposure to oxidative stress dysregulate the cellular process. This leads to up-regulation of cell signaling pathways, reactivation of telomerase, and epigenetic dysregulation. Coupled with the inhibition of DNA damage repair pathways and p53 apoptotic pathways, these processes result in uncontrolled cell proliferation, migration, and other cancer hallmarks. Most HCCs contain trunk mutations in *TERT*, *TP53*, and *CTNNB1*. Diverse branch mutations result in genomic intratumoral heterogeneity. Hepatocarcinogenesis is accelerated in genetically predisposed individuals who carry SNPs in these molecular pathways and possibly pathogenic variants in the DNA repair genes.

and Z (abnormal, most severe). In those with abnormal alleles, misfolded A1AT proteins aggregate within the hepatocytes and induce inflammation. The risk of liver disease varies based on the degree of deficiency, with Pi*ZZ homozygotes being most affected.[166] In the largest study of Pi*ZZ individuals (n = 1595), liver cirrhosis and HCC were seen in 7% and 2% of the patients, respectively.[167] Of those diagnosed with HCC, more than half did not have cirrhosis at diagnosis.[167] Given the high prevalence, it is recommended to monitor all Pi*ZZ carriers for liver disease and also for HCC if the patient turns cirrhotic.

Single-Nucleotide Polymorphisms

Genome-wide association studies have identified 32 single-nucleotide polymorphisms (SNPs) in 24 loci with an association with HCC (Supplementary Table 8). Most SNPs are derived from pathways of cell cycle (*CCND1* rs9344), cell apoptosis (*KIF1B* rs17401966, *MDM2* rs2279744), cell proliferation (*TGFB1* rs1800469, *WNT3A-WNT9A* rs708113), inflammation (*PTGS2* rs689466, *IL18* rs187238, *IL18* rs1946518), lipid metabolism (*PNPLA3* rs738409, *TM6SF2* rs58542926), and microRNA-mediated silencing (*MIR146A* rs2910164, *MIR149* rs2292832, *MIR499* rs3746444, *MIR196A2* rs11614913).[168–170] Two widely studied SNPs are *TM6SF2* rs58542926 (c.449 C>T, p.E167K) and *PNPLA3* rs738409 (c.444 C>G, p.I148M). *TM6SF2* encodes for an endoplasmic reticulum membrane protein involved in the secretion of very-low-density lipoproteins and lipid metabolism, while *PNPLA3* encodes for the adiponutrin protein. *TM6SF2* rs58542926 and *PNPLA3* rs738409 have allele frequencies of 0.1 and 0.3,

Table 1. Hepatocellular Carcinoma Surveillance Recommendations

Recommendation	Society		
	European Association for the Study of the Liver[222]	American Association for the Study of Liver Diseases[223]	Asian Pacific Association for the Study of the Liver[100]
Recommended	Cirrhotic patients, regardless of etiology Noncirrhotic patients with chronic HBV and intermediate–high risk of HCC (PAGE-B score ≥10) Noncirrhotic patients with advanced fibrosis (Metavir F3), depending on individual risk assessment Patients waiting for liver transplant	Cirrhotic patients, regardless of etiology Noncirrhotic patients with chronic HBV with 1 of the following features: • Asian male older than 40 y • Asian female older than 50 y • African and/or North American Black • Family history of HCC	Cirrhotic patients, regardless of etiology Noncirrhotic patients with chronic HBV with 1 of the following features: • Asian male older than age 40 y • Asian female older than age 50 y • Africans older than age 20 y • Family history of HCC
Not recommended/ uncertain	Noncirrhotic patients with NAFLD	Patients with chronic HBV infection who are younger than 40 y (male patients) or 50 y (female patients) Noncirrhotic patients with HCV and advanced fibrosis Noncirrhotic patients with NAFLD	Patients with chronic HBV infection who are younger than 40 y (male patients) or 50 y (female patients) Noncirrhotic patients with HCV and advanced fibrosis Noncirrhotic patients with NAFLD

respectively.[171] Implicated as genetic modifiers of NASH and ALD, both SNPs are loss-of-function mutations associated with intrahepatic fat deposition.[172,173] Risks of HCC are raised for both *TM6SF2* rs58542926 (OR, 1.6–1.8) and *PNPLA3* rs738409 (OR, 1.4).[170,174–176] Polygenic risk scores based on these risk variants have been found to predict HCC in patients with NASH and dysmetabolism.[177] When combined, the risk variants account for a significant population attributable fraction of HCC.[177] Further validation of these risk scores in multiethnic cohorts will be useful before their clinical use as risk-stratification tools.[178]

Cancer Predisposition Genes

The missing heritability of HCC has also been interrogated using multigene panels containing cancer predisposition genes.[179] Several prospective studies have identified germline pathogenic variants in 11%–15% of patients with HCC.[179,180] Most were pathogenic variants of DNA repair genes, mostly those from the homologous recombination and mismatch repair pathways.[179,180] DNA repair genes have been implicated in well-studied cancer syndromes, such as hereditary breast and ovarian cancer and Lynch syndrome.

The relationship between these cancer susceptibility genes and HCC is unclear.[180] We will need to validate these associations in larger populations around the world and determine their functional effects via functional studies and, ideally, via tumor loss of heterozygosity. In addition, platinum agents and PARP inhibitors have not demonstrated efficacy in HCCs.[181] A proposed mechanism is the tumor overexpression of the c-Met receptor tyrosine kinase, which phosphorylates PARP and reduces its affinity for the PARP inhibitor.[182] As our understanding of the resistance mechanisms improves, we may then develop combination therapies containing PARP inhibitors against homologous recombination–deficient HCCs.

Although some have proposed universal genetic testing for individuals with HCC, the prevalence of pathogenic germline variant of 11%–14% is likely overestimated due to ascertainment bias.[180] In familial cases of HCC, patients should be evaluated for possible genetic etiologies, as well as environmental exposures and health behaviors.

Somatic Mutations in Hepatocellular Carcinoma

Liver cirrhosis is the main determinant of HCC. Up to 90% of HCC cases occur in cirrhotic livers and the annual HCC incidence is 7- to 45-fold higher in liver cirrhosis.[56,183] The cirrhotic liver accumulates somatic genetic alterations before acquiring the hallmark capabilities of cancer.[184,185] On average, HCC tumors harbor 50–70 nonsilent mutations, of which 2–6 are driver mutations.[186] Commonly altered pathways include telomere maintenance (60%), Wnt/β-catenin (54%), PI3K/AKT/mTOR (51%), TP53 cell cycle (49%), Ras/MAPK (43%), epigenetic regulation (32%), chromatin remodeling (28%), and oxidative stress (12%); the numbers in parentheses refer to the alteration frequencies reported in the exome sequencing study performed by Schulze et al[187] on 243 HCC tumors. A detailed discussion of these pathways can be found in the Supplementary Material.

The enrichment of somatic mutations of the HCC depends on the etiology and risk factor.[188] For instance, HBV- and aflatoxin-related HCCs have a higher frequency of somatic mutations in cell cycle control and apoptosis (*TP53*, *CTNNB1*), and the ALD-related HCCs are enriched in *CTNNB1, TERT, CDKN2A, SMARCA2,* and *HGF* mutations.[187,188] Ethnicity might also play a role in shaping the genomic landscape of the HCC. An analysis of the Mongolian

HCC identified unique drivers (*GTF2IRD2B*, *PNRC2,* and *SPTA1*) in addition to the common drivers (*TP53*, *CTNNB1*).[189]

Intratumoral Heterogeneity

A key limitation to HCC genomics is intratumoral heterogeneity (ITH) and, hence, our failure to have any predictive biomarkers in HCC. Seen in 30%–40% of treatment-naïve HCCs, ITH arises when tumor cells accumulate mutations in separate parts of the tumor and diversify into distinct subclonal populations.[190] These subclones modify their microenvironment to their survival advantage and, in turn, are influenced by its selective pressures. The interactions between the cancer cells and the tumor microenvironment are complex and dynamic.[191] Although genomic ITH remains relatively stable across different stages of HCC, phenotypic ITH, such as RNA expressions and immune-cell compositions, diverges quickly in patients with stage II HCC.[192,193] Recent advances in spatial omics and multiplexed imaging have enabled the systematic quantification of the spatial architecture and multicellular interactions in the tumor microenvironment.[194] These methods can now be used to simultaneously measure the expression levels of thousands of messenger RNAs and tens of protein markers at different subregions of the same microenvironment.[195–197] Automated and quantitative profiling of single-cell phenotypes from these images may be used to derive compact representations of disease phenotypes.[198–200] These spatial multimodal data can also be integrated using artificial intelligence to derive joint molecular and phenotypic markers.[201,202] Characterizing ITH is important for predicting and preempting treatment resistance, and for monitoring treatment response.[203] However, it may be technically challenging, as multiregional biopsies may not always be feasible due to procedural risks. Liquid biopsies, such as circulating tumor DNA and cells, have been proposed as minimally invasive tools for mutation profiling and biomarker development.[204]

Gut Microbiome

An emerging cause of hepatocarcinogenesis is the gut microbiome. Referred to as the "last undiscovered human organ," the gut microbiome encompasses the genetic makeup of all microbes within the human gastrointestinal tract.[205] The gut microbiome guides local immune responses against pathogenic microbes.[205] Several human studies have observed microbiome changes in patients with HCC, including higher levels of dysbiosis and pro-inflammatory bacteria.[206–209] This dysbiosis is closely linked to leaky gut, another prominent feature in HCC that enables bacterial metabolites to readily reach the liver through the portal circulation.[210] The endotoxemia stimulates local and systemic inflammation, causing fibrosis and organ failure.[205] Deoxycholic acid is a bacterial metabolite converted from cholic acid by intestinal bacteria, which can activate the mTOR pathway, increase TLR2 expression on hepatic stellate cells, and enhance tumor-promoting cellular senescence.[211–213] Several clinical trials are ongoing to evaluate the effect of microbiota-mediated therapies on cancer treatment outcomes.[214,215] Other potential therapeutic applications include preventing tumor cachexia, ameliorating chemotherapy-induced gastrointestinal adverse effects, and enhancing treatment efficacies.[216,217] These studies will provide many opportunities for the microbiome-based diagnosis, treatment, and prevention of HCC.

Hepatocellular Carcinoma Surveillance

Almost half of all HCCs are diagnosed late, with regional or distant spread.[218] Compared with localized HCC, the advanced cases have few curative-intent therapies and poorer survival.[218] Crucial for early diagnosis and improved survival, HCC surveillance with abdominal ultrasound and serum α-fetoprotein are recommended in populations with HCC incidence exceeding 1.5% per year (Table 1).[100,219,220] This includes all patients with liver cirrhosis and non-cirrhotic patients with chronic HBV infections.[221] Routine screening in noncirrhotic NASH remains debatable. Despite the growing prevalence of this subpopulation, the small risk (0.02%) of noncirrhotic NASH HCC does not warrant routine HCC screening.[220]

Conclusions

HCC is a major health issue in the world. The landscape is now transiting from viral hepatitis to ALD and NASH, and continues to change as we unravel the complex genetics surrounding hepatocarcinogenesis. Importantly, we must not lose sight of potential health inequities that may arise during our campaign against HCC. A united effort from the various stakeholders is pivotal to the progress in HCC epidemiology.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2023.01.033.

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Received August 16, 2022. Accepted January 29, 2023.

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Author Contributions
All authors made substantial contributions to the data analysis, drafting, and critical revision of the manuscript.

Conflicts of interest
The authors disclose no conflicts.