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REVIEW ARTICLE

Assessment of risk factors, and racial and ethnic differences in hepatocellular carcinoma

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Abstract

Despite improved screening and surveillance guidelines, significant race/ethnicity-specific disparities in hepatocellular carcinoma (HCC) continue to exist and disproportionately affect minority and disadvantaged populations. This trend indicates that social determinants, genetic, and environmental factors are driving the epidemic at the population level. Race and geography had independent associations with risk of mortality among patients with HCC. The present review discusses the risk factors and issues related to disparities in HCC. The underlying etiologies for these disparities are complex and multifactorial. Some of the risk factors for developing HCC include hepatitis B (HBV) and hepatitis C (HCV) viral infection, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, smoking and alcohol consumption. In addition, population genetics; socioeconomic and health care access; treatment and prevention differences; and genetic, behavioral, and biological influences can contribute to HCC. Acculturation of ethnic minorities, insurance status, and access to health care may further contribute to the observed disparities in HCC. By increasing awareness, better modalities for screening and surveillance, improving access to health care, and adapting targeted preventive and therapeutic interventions, disparities in HCC outcomes can be reduced or eliminated.

Introduction

Hepatocellular carcinoma (HCC) is one of the primary liver cancers predicted to be the sixth most commonly diagnosed cancer, and the third leading cause of cancer death worldwide in 2019, with about 841 000 new cases and 782 000 deaths annually. The worldwide HCC incidence is 10.1 cases per 100 000 person-years.[1,2] Globally, 80% of HCC cases occur in sub-Saharan Africa and eastern Asia. The burden of HCC in 2012 was 14 million and is expected to rise to 22 million in the next two decades.[3] HCC has an average 5-year survival of <15%.[3]

In the United States, HCC is the fifth leading cause of cancer-related deaths among men and ranks seventh among women.[4] In 2019, approximately 42 030 adults (29 480 men and 12 550 women) in the United States were diagnosed with primary liver cancer. The incidence of HCC in the United States has tripled over the last four decades. Between 2006 and 2015, the number of people diagnosed with the disease increased by approximately 3% annually. According to American Cancer Society, approximately 31 780 deaths (21 600 men and 10 180 women) from this disease has occurred in 2019. The overall death rate has more than doubled from 1980 to 2016.

Prominent risk factors for HCC vary depending on the region. Noticeably, the HCC incidence rates depend on the factors including race/ethnicity, gender, age, and geo-/demographic regions[5] and also by several risk factors such as cirrhosis, hepatitis B (HBV) infection, hepatitis C (HCV) infection, excessive alcohol consumption, nonalcoholic fatty liver disease (NAFLD), obesity, diabetes, glucose overload, metabolic syndrome, and environmental toxic intake (Fig. 1).[6–8] The development of HCC is complex, involving sustained inflammatory damage leading to hepatocyte necrosis, regeneration, and fibrotic deposition. A deeper understanding of the mechanisms and expanding access to high-quality prevention, early detection, and treatment for individuals will be required to reduce or prevent HCC disparities. The present review provides an overview of the risk factors and issues related with HCC disparities in epidemiology, detection, treatment, or outcomes.

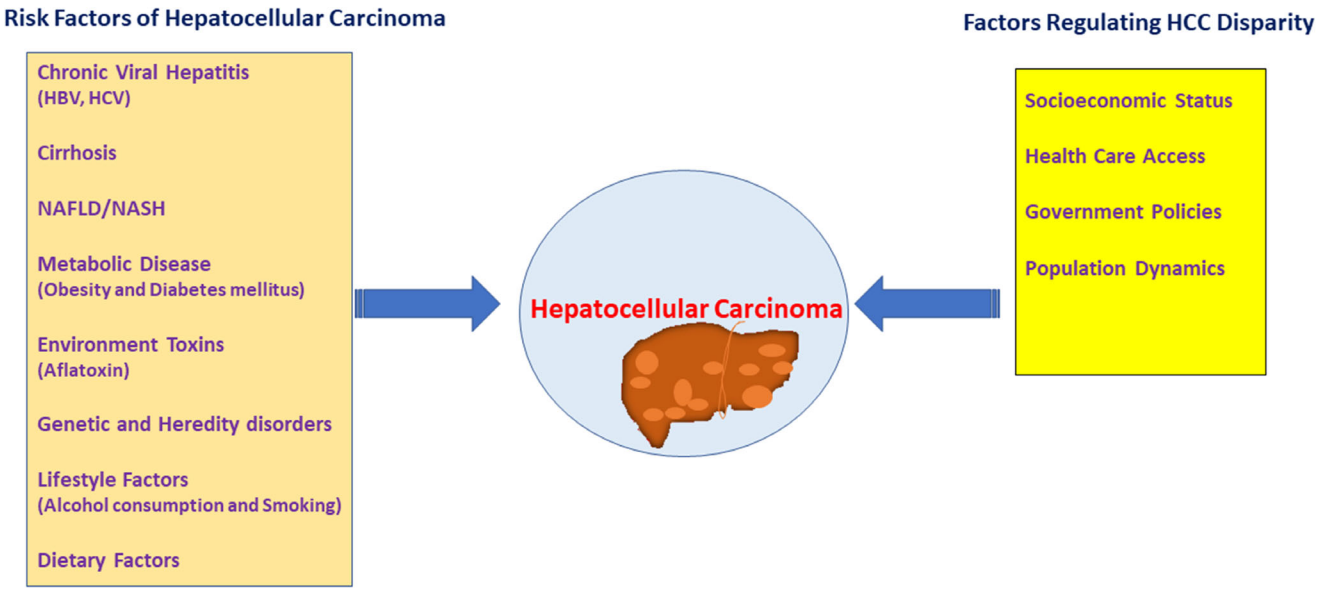

Figure 1 Risk factors of hepatocellular carcinoma (HCC) and factors regulating HCC disparities. Risk factors of HCC include chronic viral hepatitis (HBV, HCV), cirrhosis, NAFLD/NASH, metabolic disease (obesity and diabetes mellitus), environment toxins (Aflatoxin), genetic and heredity disorders, lifestyle factors, (alcohol consumption and smoking), and dietary factors. HCC disparities can be regulated by Socioechonomic status, health care access, government policies and population dynamics.

Gender, race, and ethnicity

Gender, racial, and ethnic disparities in the survival of patients with HCC continue to exist.[9] HCC cases are two to four times more common in males than in females. Liver cancer is the fifth most common cause of cancer death in men, whereas it is the seventh most common cause of cancer death in women. Clinical studies revealed that men have a higher risk of developing HCC by the progression of HBV and HCV, and elevated level of inflammatory cytokines (IL-6 and IL-1β) compared with the women worldwide.[10] This gender disparity is the result of different behavioral risk factors, such as smoking and drinking alcohol. Glutathione S-Transferase P1 (GSTP1) exon 6 polymorphism genotype was associated with an increase in the risk of HCC in male patients.[11]

HCC rates are two times higher in Asian Americans than African Americans (AA). HCC rates in AA are two times higher than those in Caucasian Americans (CAs).[12] In California, during 2009–2013, the age-adjusted HCC incidence was the highest in Asians/Pacific Islanders (APIs) and Hispanics (>100% higher than whites), especially those living in more ethnic neighborhoods (20–30% higher than less ethnic neighborhoods). In the United States, the HCC incidence was highest in Asians, followed by AA, Hispanics, and non-Hispanic whites. However, a recent observation noted the highest percent increase in HCC incidence among Hispanics, whereas its incidence decline in Asians.[4] The age-adjusted HCC incidence in the United States has increased in both men from 6.9 per 100 000 in 2000 to 10.8 in 2012 and women from 2.3 per 100 000 in 2000 to 3.2 in 2012, suggesting the majority (73%) of cases occur in men according to an average annual percentage change (APC) rate.[13] Hispanics and non-Hispanic whites have a severity of liver disease than Native Americans in the New Mexico region.[14] Blacks have a high occurrence of HCC than Hispanics and whites based on tumor stage and liver function.[15] These studies clearly suggest the existence of gender, racial, and ethnic disparities in HCC incidence.

Geographic disparities

The efforts in HCC management have been initiated to reduce regional disparities. When compared with the United States, HCC is much more common in sub-Saharan Africa and Southeast Asia. The highest rates of HCC occurred in eastern Asia compared with the other parts of the world.[1,16] Regions of Asia Pacific, Central Asia, East Asia, South Asia, and Southeast Asia have higher incidence rates of HCC compared with the other regions of the world.[17] The reason for highest incidence of HCC in Asia than other regions of the world was due to the endemic prevalence of HBV, which strongly predisposes to the development of chronic liver disease (CLD) and subsequent development of HCC.[18] Franco et al. using Surveillance Epidemiology and End Results data with 43 868 patients diagnosed from 2000 to 2012 reported that southern registries (Atlanta, Louisiana, and Rural and Greater Georgia) had steeper increases of age-adjusted HCC incidence (from 2.89 to 5.29 cases/100 000 people) than non-southern registries (from 3.58 to 5.54 cases/100 000 people).[19] Blacks were overconcentrated in southern registries (32% vs. 10%) where age-adjusted incidence rates of HCC were higher than non-southern registries.[19] Further studies are needed to understand the root causes of potential mortality risk among overall populations with HCC living in various regions of the world.

Cirrhosis

Cirrhosis is a major risk factor for the development of HCC and about 80% of patients with HCC have liver cirrhosis.[20] A diverse safety-net hospital population study in United States reported that cirrhosis patients were associated with 29.9% HCV, 13.4% HBV, 44.6% alcoholic cirrhosis and 8.9% nonalcoholic steatohepatitis (NASH).[14] Another study noted that cirrhosis-caused deaths among native Americans were associated with 52.6% of alcoholic liver disease (ALD), 10.7% of HCV infection and 1% of HBV infection.[21] Cirrhosis can be amalgamated with an over 30-fold increase in HCC risk with contrast to patients without cirrhosis.[13] According to a population-based study using the US Census and national mortality database, age-standardized cirrhosis-related mortality rates increased from 19.77/100 000 persons in 2007 to 23.67 in 2016 with an annual increase of 2.3% (95% confidence interval 2.0–2.7).[22] Mortality caused by cirrhosis was approximately threefold higher among non-Hispanic whites than all Asians.[23] Hispanic and Asian patients reported to have a higher risk of developing cirrhosis and HCC compared to Caucasian patients.[24] Among the AA, circulating miR-150 expression was found to be high in liver cirrhosis suggesting it may be used as a biomarker for the diagnosis and clinical progression of liver disease.[25] Since cirrhosis may develop into HCC, prevention of cirrhosis could be a novel strategy for the management of HCC.

Hepatitis B virus infection

Hepatitis B virus (HBV) infection is the main cause of HCC in the endemic regions of Asia, and the leading cause of morbidity and mortality worldwide with over 250 million people.[26] Chronic HBV-infected persons may have a 5- to 100-fold increase in the risk of developing HCC.[27] In early stages, HBV infection was asymptomatic, 15–40% of chronic HBV patients will develop cirrhosis or cirrhosis-related complications during their lifetime[28] and the greatest risk can be found in older male patients. Mortality for HBV-cirrhosis decreased with an average APC of 1.1% during 2007–2016.[22] Worldwide, an overall 44% of HCC cases were attributable to chronic HBV infection but the majority of cases occurring specifically in East Asia.[17] Disparities in HBV diagnosis, disease management, treatment, and prevention remain to exist for the AA and Hispanics. The commitments from governmental and public health organizations are needed to address these disparities effectively by screening and treating HBV by antiviral therapy.[29] US-born Hispanics have a greater risk for HCC development by HBV infection.[30] HBV accounts for 69% of cirrhosis in the region of sub-Saharan Africa.[31] HCC incidence increased by HBV DNA levels elevated in the person chronically infected with HBV. There are antiviral therapies that are very effective in suppressing HBV DNA levels but not eradicating the infection.[32] Antiviral therapy for HBV can significantly reduce HCC risk by over 50%.[33] HBV elimination strategies should focus on effective and implementable preventive and therapeutic strategies, which may include upscaling HBV birth-dose vaccination, vaccination of high-risk groups, full HBV vaccine coverage, prevention of mother-to-child transmission, and linkage of HBV-infected individuals to care with sustainable access to antiviral therapy.

Hepatitis C infection

An estimated 50–60% of HCC patients have hepatitis C (HCV) infection within the United States and in contrast to HBV, chronic HCV infection causes a 15- to 20-fold increase in the risk for HCC.[27] Overall, about 21% of all HCC cases had chronic HCV infection and were observed in Central Asia, Central Sub-Saharan Africa, and West Sub-Saharan Africa. Higher HCV incidence was observed in the region of North Africa, and the Middle East and Eastern Europe compared to rest of the world.[17] The APC in mortality rates for HCV-cirrhosis shifted from a 2.9% increase per year during 2007–2014 to a 6.5% decline per year during 2014–2016.[22] Hispanic and Asian patients have a higher risk of HCV for developing cirrhosis and HCC compared with Caucasian patients.[24] HCV infection is highly prevalent and causes high mortality rates in the AA population compared to the CA or other racial groups. In contrast to CA, increased expressions of miR-146a, miR-150, and miR-155 were found in HCV-infected AA patient sera and noted the higher expression of miR-150 in cirrhosis and HCC in AA patients, suggesting that circulating miR-150 may serve as a biomarker for liver disease progression in this population.[25] The incidence and mortality of HCV-induced HCC rate were higher in AA compared to the other racial/ethnic groups in the United States.[34] Significantly higher death rate by HCC was found in Latinos than non-Latinos in the United States. In New York City, 34.5% HCV infection was found in the Latinos compared to the non-Latinos (22.1%) suggesting that HCV infection was the major key factor for the burden of HCC among these races.[35] In the United States, AA patients have twice the prevalence of HCV seropositivity and develop HCC than whites.[36] Antiviral therapy for HCV can significantly reduce HCC risk by over 50%.[37] However, the long-term impact of viral clearance on future HCC risk with the current medicines in HCV patients is not yet known.

Lifestyle factors (alcohol consumption and smoking)

Alcohol use either as a primary factor or in combination with HBV, HCV or diabetes can result in the development of HCC. Alcohol consumption more than 80 g per day for 10 years increased fivefold of HCC risk.[4] The APC in mortality rates for ALD-cirrhosis increased 4.5% per year during 2007–2016.[22] Worldwide, about 26% of HCC can be attributed to alcohol drinking. More than 35% of the population attributable fraction for alcohol drinking were in Central and Eastern Europe and Tropical Latin America. Men had a higher prevalence of alcohol drinking compared with women.[17] According to the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), the greatest prevalence of heavy drinking (31.6%) was observed in Hispanics when compared with other race/ethnic minorities.[4] Most of the deaths by CLD were found in men (60.2% for US-born and 73.8% for foreign-born) due to ALD, whereas in women, the majority of CLD deaths were found due to cirrhosis or fibrosis (55.6% for US-born and 64.1% for foreign-born). In contrast to foreign-born women, the alcohol-related CLD deaths were higher in US-born women and also in

foreign-born Hispanics, the risk of HCC was due to increased alcohol consumption.[30]

The smoke from a cigarette contains more than 4000 chemicals, which could have various toxic, mutagenic, and carcinogenic effects.[38] Several epidemiological studies have revealed that smoking is a mild risk factor in the development of HCC.[39–43] A meta-analysis with 38 cohort studies and 58 case–control studies on liver cancer and cigarette smoking demonstrated that the adjusted relative risk for liver cancer was 1.51 (95% CI = 1.37–1.67) for current smokers, and 1.12 (95% CI = 0.78–1.60) for former smokers.[42] Some chemicals in tobacco smoke such as 4-aminobiphenyl and polycyclic aromatic hydrocarbons generate reactive species that can initiate HCC development.[44] There is a need to develop preventive measures against these risk factors that might help to reduce oxidative stress and to prevent cases of premature mortality in patients with HCC.

Nonalcoholic fatty liver disease

NAFLD is a condition/disorder in which fat mainly triglycerides builds up in the liver. Currently, NAFLD is the most common liver disease, with a worldwide prevalence of 25%. NASH is a type of NAFLD that occurs in the people who drink little to no alcohol. In the United States, NAFLD and NASH affect 30% and 5% of the population, respectively. If people have NASH, they develop inflammation, which leads to liver cell damage. NAFLD is considered as the hepatic manifestation of the metabolic syndrome, and is closely associated with obesity and diabetes. NAFLD is generally thought to be a nonprogressive hepatic steatosis associated with few hepatic complications. However, at least 20–30% of patients with NAFLD develop progressive liver disease with necroinflammation and fibrosis that can result in cirrhosis in 10–20% of cases.[45] The APC in mortality rates for NAFLD-cirrhosis increased 15.4 per year during 2007–2016.[22] Most of NAFLD patients with cirrhosis develop HCC, whereas 20% of NAFLD patients with HCC had no evidence of cirrhosis.[46] During 2004–2016, there was an increase in HCC owing to NASH as an indication for liver transplant in females, and it is also likely to rise in men as well.[47] Patients with NASH cirrhosis were significantly less likely to face the risk of HCC compared with patients with HCV, HBV, and alcoholic cirrhosis.[21] In a systematic review and meta-analysis, significant racial and ethnic disparities in NAFLD prevalence and severity in the United States were found, with the highest burden in Hispanics and lowest burden in blacks.[15] In Texas, the risk of HCC was the highest in Hispanics with cirrhosis than other race/ethnicity.[46] Although Hispanic individuals with NAFLD had more advanced fibrosis than other ethnic groups, higher central adiposity and visceral fat distribution are seen in Asians, which contribute to the increased risk of NASH development.[48] The prevalence of NAFLD along with the proportion of those with advanced liver disease is projected to increase because of ongoing obesity epidemic and the rise in diabetes. A deeper understanding of the mechanisms by which NAFLD regulate liver carcinogenesis and the identification of its genetic determinants will provide new diagnostic and therapeutic tools.

Obesity

Obesity contributes to 9% of HCC cases worldwide. Obesity evaluation is most commonly based on the patient's body mass index. It is a metabolic disorder that increases the HCC risk through chronic inflammation. Obesity is associated with a higher lipolytic rate, plasma FFAs and glycerol. Obesity not only induces cancer-causing chronic inflammation but also causes alterations in the endocrine system, which might altogether increase the risk of development of NAFLD and HCC.[49] Due to the high prevalence of overweight and obesity (>20%), the highest attributable fractions of liver cancer cases were found in Australia and North America but lowest attributable fractions (<5%) were observed in the parts of Asia.[17,50] The rising prevalence of NASH partly leads to the development of obesity and obesity-related diseases which in turn increase the risk of HCC.[51] Higher risk of HCC in Hispanic patients with HCV-cirrhosis and metabolic risk factors was reported in a retrospective cohort study of 3503 consecutive cirrhotic chronic hepatitis patients seen at Stanford University during 1997–2015.[52] The exact mechanisms linking the obesity with HCC risk are not well understood. However, recent studies have implicated several molecular pathways in obesity-associated HCC. These include insulin resistance leading to increased levels of insulin and insulin-like growth factors, adipose tissue remodeling, proinflammatory cytokine and adipokine secretion, chronic inflammation, and altered gut microbiota.[53–57] Better understanding and characterization of novel genetic and epigenetic alterations, which are important to obesity, may help understand the molecular pathogenesis of HCC and provide novel therapeutic targets for HCC treatment and prevention.

Diabetes

Diabetes is also one of the metabolic disorders, and about 7% of HCC cases can be attributed to diabetes worldwide.[17] A recent study estimated that patients with a history of diabetes exhibited a twofold to threefold higher liver cancer risk.[58] Using the data from the Nurses' Health Study (NHS), and the Health Professionals Follow-up Study, Type 2 diabetes (T2D) was associated with an increased HCC risk (multivariable HR, 4.59; 95% CI, 2.98–7.07), and this risk was enhanced with prolonged diabetes duration and with comorbid metabolic condition.[59] Multiethnic Cohort Study revealed that the HCC incidence rate was higher for US-born Hispanic men compared to foreign-born Hispanic men (44.7 vs. 23.1).[30] The highest risk of diabetes mellitus (39.1%) and metabolic syndrome (29.2%) were observed in older patients, AA, and women with HCV. Both diabetes mellitus and metabolic syndrome have been linked to the rising rates of NAFLD and NASH, which ultimately increase the higher risk of cirrhosis and HCC.[17,51] The lowest rate of diabetes mellitus (39.1%) and metabolic syndrome were found in non-Hispanic whites compared to other races in US population.[51] The etiological and pathophysiological relationship between diabetes and HCC linked hyperinsulinemia, insulin resistance, hyperglycemia, and activation of insulin-like growth factor signaling pathways. Metformin (1000 mg/day) use reduced HCC risk and modified the race/ethnicity disparity,[60] suggesting that metformin can be used as a preventive agent to modify HCC disparities in patients

with type II diabetes. Better understanding of genetic and epigenetic alterations in obesity may provide novel therapeutic targets for the management of HCC.

Environmental toxins

Aflatoxin is a family of toxins produced predominantly by two fungi: *Aspergillus flavus* and *Aspergillus parasiticus*. Contaminated animal and plant products are the major sources of aflatoxins. There are four aflatoxins (B1, B2, G1, and G2) that have been shown to act as carcinogen in both humans and animals, aflatoxin B1 (AFB1) is the most potent liver carcinogen. AFB1 exposure is a crucial factor to initiate HCC. Individuals exposed to high AFB1 levels showed mutations in the *p53* gene, a tumor suppressor. Mutations such as transversion in codon 249 were found in 50% of HCCs.[61] The enzyme cytochrome—P450 metabolizes AFB1 in the liver to produce intermediate metabolites (aflatoxin B1-8, 9-oxide, AFBO), which interact with the guanine base to cause mutational effects. Several naturally occurring biologically active agents such as phenethyl isothiocyanate (PEITC) and sulforaphane (SFN) have been found to possess chemoprotective properties against AFB-DNA adduct formation.[62]

Habitual betel (areca) quid chewing is associated with an increased risk of HCC.[63–66] Experimental studies have demonstrated persistent hepatocyte necroinflammation secondary to areca nut-derived nitrosamines that methylate and cyanoethylate DNA resulting in hepatotoxicity.[63] Betel leaves also contain a high concentration of safrole (15 mg/g fresh weight), which causes hepatocarcinogen.[67,68] Betel chewing increased cirrhosis and HCC risk in current chewers and ex-chewers, when compared with never-chewers.[69] Furthermore, a case–control study reported that betel quid chewing is an independent risk factor for HCC.[66] Several mechanisms that contribute to hepatic fibrosis have been hypothesized; (i) excess collagen production through NADPH oxidase by angiotensin-2 produced from hepatic stellate cells,[70] (ii) increase in circulating tissue inhibitor of metalloproteinase (TIMP-1),[71] (iii) presence of hypovitaminosis D as inhibition of chemically induced hepatocarcinogenesis by vitamin D through regulation of chromosomal aberration, DNA stand breaks and DNA adducts,[72,73] and (iv) production of nitric oxide/inducible nitric oxide synthase (iNOS) resulting in activation of stellate cells.[74,75] Stellate cells are intralobular connective tissue cells presenting lipocyte or myofibroblast-like phenotypes which participate in the homeostasis of liver extracellular matrix, regeneration, repair, fibrosis and control retinol metabolism, storage and release.

Contamination of groundwater with chemicals such as trichloroethylene (TCE), cadmium, lead, nickel, thallium, and arsenic, and human exposure to organic solvents like toluene, benzo [a]pyrene, and dioxin, and xylene have been shown to increase the risk of HCC.[76–81] Occupational exposure to chemicals like dichlorodiphenyl trichloroethane (DDT) and nitrosamines is another risk factor for HCC.[82–84] They exert their carcinogenic effects through regulation of CYP3A1 gene and via shortening of telomeres (critical in maintaining the integrity of chromosomes by capping at the end of each strand of DNA). However, further analyses by means of molecular epidemiology are needed to improve the understanding of cancer etiology induced by these carcinogens.

Genes

Compared to other risk factors, HCC disparities also caused by certain driver genes in which *CTNNB1*, *ALB*, *TP53* (males), and *AXIN1* (females) significantly linked to HCC gender, *TP53* and *CDKN2A* linked to race (in Asians than whites), and *RB1* linked to age. Therapeutically targeting these genes might prevent HCC disparities.[8] In HCC initiation and progression, long noncoding RNA FTX (Lnc-FTX) acts as an important regulator of HCC gender disparity. It is highly expressed in female livers than in male livers and is significantly downregulated in HCC tissues compared with normal liver tissues.[85] Lnc-FTX may suppress HCC tumor and patient survival, especially in females by a direct binding to miR-374a and MCM2.[85]

The expression of transcripts and proteins were distinctly altered in HCV-induced HCC in CA and AA subgroups. Both Affymetrix Human Transcriptome Array and quantitative RT-PCR data revealed that *SAA1*, *PCNA-AS1*, *DAB2*, and *IFI30* are differentially deregulated especially in AA compared with CAs. These observations suggest that during disease progression, pre-mRNA splicing machinery may be remodeled and therefore, it may play a major role in HCV-induced HCC racial disparity.[86] Further, sex may affect the risk and treatment outcome response in HCC. Sex-determining region on the Y chromosome (SRY) and its downstream Sox9 and PDGFRα pathways contributed to the male hepatocarcinogenesis providing a novel venue to the HCC gender disparity and sex-specific therapeutic strategies.[87] Next, the differential expression (higher) of circulatory miRNAs such as miR-146a, miR-150, and miR-155 was observed in HCV-mediated HCC of AAs when compared with that of CA patients' sera. However, miR-150 was highly prominent in cirrhosis and HCC in AA patients, suggesting it can be used as a diagnostic marker for the liver disease progression.[25] The expression of transferrin mRNA levels were 2- and 18-fold higher in cirrhotic and HCC of AA compared with CA patients, respectively. Also, apolipoprotein A1 (APOA1) expression level was sevenfold higher in HCC of AA compared with that of CA. Most interestingly, the hepatocyte nuclear factor4α (HNF4α) level was downregulated in AA, whereas higher regulation/induction of HNF4a was observed in CAs compared with that in AA. These studies suggest that a consequence of differential dysregulation of HNF4α transcriptional activity may lead to racial disparities in HCC,[34] and the development of HNF4α inhibitors may be useful to eliminate HCC racial disparities. We have recently demonstrated that HCC cells derived from AA expressed a higher level of SATB2 than those from CAs, and the expression of SATB2 was negatively correlated with tumor suppressive miR34a.[88] The data suggested that the higher expression of SATB2 may be responsible for the disparity in HCC outcomes. The better understanding of the epigenetic mechanisms and targeting the differentially expressed genes, novel therapeutics can be developed to reduce HCC disparities.

Disparities in socioeconomic status and health care access

HCC disproportionately affects disadvantaged populations, with the highest age-specific rates among racial/ethnic minorities. Furthermore, HCC cases are often clustered in areas of low

socioeconomic status (e.g. high unemployment, high poverty, and low education areas) compared to the general population.[89] Race/ethnicity was a significant independent prognostic factor in the HCC.[90] The synergistic effect of contributing factors, including demographic, socioeconomic, biological, and treatment differences, will significantly enhance the racial disparity observed in survival time of HCC patients.[90] Socioeconomic disparities in the survival of patients with HCC continue to exist, and these differences could result from inequities in access to care and in response to therapy.[91–93] Blacks and low-income individuals had the poorest long-term survival.[91] Black race was predictive of the poorest survival, whereas Asian race was associated with the best survival.[91] Neighborhood concentrated disadvantage, a robust measure of an adverse social environment, was found to be a geographically associated with HCC incidence.[94]

In the United States, significant racial and ethnic disparities in the outcome of patients with HCC persist despite the receipt of comparable treatment.[36,91,95] According to Surveillance Epidemiology and End Results data, blacks were significantly younger at diagnosis, more likely diagnosed with metastasis, and less likely to receive surgical therapies when compared with whites.[19] Among US-born people with HCC, minorities showed more advanced stage at diagnosis and had a disproportionately higher burden of treatment of end-stage liver disease-related mortality.[22,96] AA have twice the prevalence of HCV seropositivity and develop HCC at more than twice the rate as whites. AA are, however, less likely to respond to interferon therapy for HCV than are whites and have considerably lower likelihood of receiving liver transplantation.[36] Even among those who undergo transplantation, AA have lower 2- and 5-year graft and patient survival compared to whites.[36] In a retrospective study of patients diagnosed with HCC, racial/ethnic differences in outcomes of HCC were associated with differences in detection of tumors at early stages and receipt of curative treatment.[15] According to a study of 379 HCC patients (52.8% non-Hispanic White, 19.5% Hispanic White, 19.8% Black), insurance status and access to gastroenterology subspecialty care was found to be important drivers of racial/ethnic disparities in prognosis among HCC patients.[97] Patients admitted for HCC-related hospitalizations studies suggested that blacks were less likely to receive liver transplantation, hepatic resection, and ablation than whites and had higher in-hospital mortality.[98] Medicaid and uninsured HCC patients have more advanced tumor stage and are less likely to receive treatment.[97,99] Therefore, ensuring equal insurance coverage may improve access to care and mitigate some disparities in HCC outcomes. By interventional targeting of these factors, we can improve patient outcomes and reduce disparities.

Conclusions

There are differences in HCC presentation and outcomes between racial/ethnic groups. Several factors have been associated with the existence of the disparities among various racial/ethnic groups. Based on the published reports, it appears that blacks and Hispanics were less likely to be diagnosed with early-stage HCC and undergo curative treatment than whites. Blacks and Hispanics both were found to demonstrate worse absolute survival than whites. Differences in survival likely involve a combination of medical, financial, genetic, and sociodemographic factors, and tumor behavior. Our efforts should focus in improving early tumor detection and delivering curative treatment in order to improve HCC outcomes and reduce disparities. HBV elimination strategies will need to focus on effective and implementable preventive and therapeutic strategies such as upscaling HBV birth-dose vaccination, full HBV vaccine coverage, vaccination of high-risk groups, prevention of mother-to-child transmission, and identification of HBV-infected individuals and linkage to care with sustainable access to antiviral therapy. The metabolites derived from excessive glucose, insulin, and lipid may alter epigenetic gene regulation through histone modifications, DNA methylation, and RNA interference, leading to activation of proinflammatory signaling and deregulation of metabolic pathways. Dysregulated metabolic pathways can initiate and accelerate the development of HCC. A deeper understanding of signaling events during hepatocarcinogenesis may shed light in the identification of druggable epigenetic targets for the prevention and treatment of HCC in obese or diabetic patients. Finally, timely implementation of the unbiased health policies from local, state, and federal government may further improve racial/ethnic health disparities in HCC. Understanding the underlying mechanisms, improving socioeconomic conditions, preventing ALD combined with healthy diet and lifestyle, better environmental conditions, and access to health care are essential steps in implementing measures to reduce racially based inequities in the burden and management of HCC.

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