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GI ONCOLOGY (R BRESALIER, SECTION EDITOR)

The Epidemiology of Hepatocellular Carcinoma in the USA

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Abstract

Purpose of Review To discuss current knowledge and recent findings regarding the epidemiology of hepatocellular carcinoma (HCC) in the USA.

Recent Finding The US incidence rate of HCC is increasing, although the pace may have somewhat slowed since 2010. In 2012, incidence rates of HCC in Hispanics surpassed those of Asians. The recent epidemiological changes in major risk factors for HCC include increasing hepatitis C virus post-sustained virologic response, suppressed hepatitis B virus on nucleoside analogues, and alcoholic and non-alcoholic fatty liver disease. Non-alcoholic fatty liver disease has the greatest proportion of the burden of the main risk factors for HCC in the USA, followed by alcoholic liver disease, and hepatitis C virus and hepatitis B virus infections.

Summary This review focuses on current knowledge regarding the recent epidemiological trends in HCC, with an emphasis on future directions.

Keywords Hepatocellular carcinoma · Epidemiology · Prevention

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide [1]. In the USA, the incidence rates have more than doubled over the past two decades [2] and is anticipated to continue to increase due to increasing patients with hepatitis C virus (HCV)-related cirrhosis, especially baby boomers in the peak HCV cohort (1945–1965) and increasing prevalence of non-alcoholic fatty liver disease (NAFLD) [3•]. Annual HCC-related deaths have doubled from 5112 in 1999 to 11,073 in 2016 [4]. Recent epidemiological changes in the HCC risk factors include an increasing number of post-sustained virologic response (SVR) HCV patients, medically suppressed hepatitis B virus (HBV)-infected patients with nucleotide analogues (NA), and NAFLD patients. However, still, viral hepatitis accounts for most (approximately 80%) HCC cases [5].

Recent studies found slowing or even plateauing of the increase in incidence and mortality rates for HCC during 2009–2013 [6], and a possible decrease is anticipated in the next two decades among patients younger than 65 years and those born after 1960 [7]. A recent study using the US Cancer Statistics Registry suggests that the increasing rate of HCC seems to have slowed from 2010 through 2012. The age-adjusted incidence rates of HCC increased from 4.4/100,000 in 2000 to 6.7/100,000 in 2012 with a 4.5% annual increase (95% confidence interval (CI), 4.3–4.7%) between 2000 and 2009. However, the increase rate has decreased to be 0.7% annually (95% CI, − 0.2 to 1.6%) from 2010 through 2012. Some demographic groups, such as men aged 55–64 years old, Hispanics, and those living in Texas, showed a faster-increasing incidence of HCC. In 2012, incidence rates among Hispanics surpassed those in Asians; and incidence rates in Texas surpassed those in Hawaii (9.71/100,000 vs 9.68/100,000) [3] (Fig. 1). The US-born Hispanics have higher incidence rates than foreign-born Hispanics, in part due to higher rates of HCV infection, alcoholic liver disease, metabolic syndrome, and NAFLD in US-born Hispanics [8–10].

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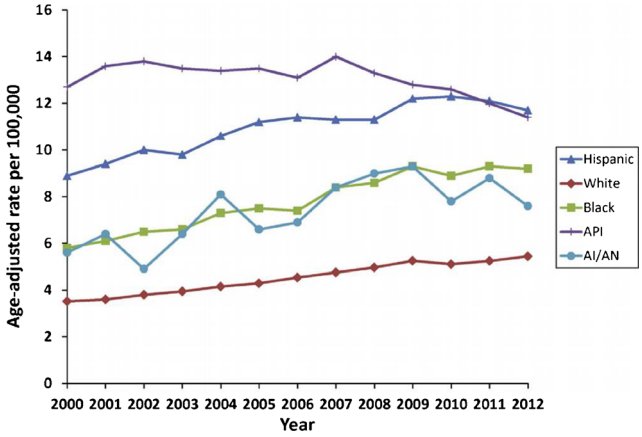

Fig. 1 Age-adjusted HCC incidence rates in the USA between 2000 and 2012 shown for several race/ethnicity groups. AI/AN, American Indian or Alaska Native

Risk Factors

The risk of developing HCC in cirrhotic patients varies with the underlying etiology. The highest 5-year cumulative risks are seen in HCV cirrhosis (17% in the West), hemochromatosis (21%), HBV cirrhosis (10% in the West and 15% in Asia), alcoholic cirrhosis (8%–12%), and biliary cirrhosis (4%) [11, 12].

Hepatitis B Virus

According to the National Health Nutrition Examination Survey, from 2011 to 2014, chronic HBV infection affected 0.86 million persons in the USA (prevalence 0.34%, 95% CI 0.24–0.43) [13]. In the USA, most patients with chronic HBV infection are foreign-born and from high endemic countries (odds ratio (OR) 3.46, 95% CI 0.78–15.3) [13]. Most HBV-infected individuals (70–90%) who develop HCC have underlying cirrhosis due to chronic necroinflammation, although a small proportion of HBV patients can develop HCC in the absence of cirrhosis [14]. The risk factors for HCC among HBV patients without cirrhosis include African American or Asian race, older than 40 years, hypertension, and family history of HCC [15]. The summarized incidence rates of HCC among chronic HBV patients from observational studies are 0.02–0.2 per 100 person-years in inactive carriers, 0.3–0.6 per 100 person-years in those without cirrhosis, and 2.2–3.7 per 100 person-years for those with compensated cirrhosis [16, 17]. Demographic factors (men, old age, Asian or African race/ethnicity, family history of HCC), viral factors (positivity of hepatitis B surface antigen and hepatitis B e antigen (HbeAg), duration of infection, higher levels of HBV DNA, HBV genotype, and co-infection with HCV, hepatitis D virus or HIV), and environmental factors (exposure to aflatoxin, smoking, and heavy alcohol use) are associated with the HCC risk among chronic HBV patients [16]. In North America and Western Europe, HBV patients with genotype D had a higher HCC incidence than those with genotype A. Genotype B HBV may be associated with HCC risk in young HBV patients without cirrhosis [18, 19]. Mutations in the region of the HBV genome that encodes the basal core promoter or the pre-core regions may play a role in HCC pathogenesis [20, 21]. Although successful nucleotide analogue (NA) treatment can reduce the risk of HCC, it is unclear whether prolonged viral suppression can eliminate the risk and how the risk of HCC may change following NA cessation. A cohort study in Europe, including 1951 adult Caucasian chronic HBV patients without HCC at baseline, suggests that the annual HCC incidence rate was 1.22% within and 0.73% after the first 5 years. The annual incidence rate did not significantly differ within and after the first 5 years in patients without cirrhosis (0.49% vs 0.47%, $P = 0.931$) while it significantly decreased in patients with cirrhosis (3.22% vs 1.57%, $P = 0.039$) [22].

Hepatitis C Virus

In the USA, the prevalence of HCV is estimated to be 1.67% (95% CI 1.53–1.90), or approximately 3.9 million adults (95% CI 3.5–4.4 million) [23]. The West census region had the highest region-specific prevalence (2.14%, 95% CI 1.96–2.48) [23]. The South had the highest number of persons with HCV antibodies ($n = 1.6$ million, 95% CI 1.4–1.8 million) [23]. The Midwest had the lowest region-specific prevalence (1.14%, 95% CI 1.04–1.30) [23]. Active HCV infection is estimated to have a 15–20-fold increased risk for HCC. When HCV-induced cirrhosis occurs, the annual risk for HCC is approximately 1–8% in those with untreated or uncured patients [24–26]. Male gender, Hispanic race/ethnicity, genotype 3, co-infection with HBV or HIV, obesity, diabetes, and heavy alcohol use are associated with HCC development in HCV patients [27, 28]. African Americans have a lower risk for cirrhosis and HCC compared to that of non-Hispanic whites [29]. The single-nucleotide polymorphism 61*G (rs4444903) in the epidermal growth factor gene may be associated with HCC pathogenesis among those with HCV infection [30]. However, SVR has become the major modifier of HCC in patients with HCV. The risk of HCC after SVR with interferon, while considerably reduced compared to no SVR, is at 0.33% per year [31]. However, the annual risk of HCC remained fairly high among patients with cirrhosis (1.39%, 95% CI 1.35–1.44) and those cured after age 64 (0.95%, 95% CI 0.89–1.02). Patients with diabetes (adjusted hazard ratio (HR) = 1.88, 1.21–2.91) or genotype 3 infection (adjusted HR = 1.62, 95% CI 0.96–2.73) were significantly more likely to develop HCC [31]. The effect of post-SVR by direct-acting antiviral (DAA) was examined in several studies including one that used the National Veterans Health

Administration databases from January 1, 2015, to December 31, 2015 [32]. There were 271 new cases of HCC among 22,500 patients treated with DAA (19,518 with SVR; 2982 without SVR). Compared to patients without SVR, those with SVR had a significantly lower risk of HCC (adjusted HR = 0.28, 95% CI 0.22–0.36, 0.90 vs 3.45 HCC/100 person-years). For patients with cirrhosis who reached SVR, the annual incidence of HCC was significantly higher than for those without cirrhosis (1.82 vs 0.34/100 person-years in patients without cirrhosis, adjusted HR 4.73, 95% CI 3.34–6.68). Although the SVR of HCV patients could affect the overall incidence of HCC in the population in the near future, the magnitude of the effect is still unclear, in part because most HCV patients are unaware of their infection, and thus, are not being treated. Current awareness of HCV infection in the USA is estimated to be around 50% [33]. Efforts to eliminate HCV encompass initiatives directed to screening, confirmation, linkage to care, and HCV treatment.

Metabolic Syndrome

According to data from a Surveillance, Epidemiology, and End Results analysis of the Medicare population, metabolic syndrome, diabetes mellitus, and obesity could be contributing to 36.6% of HCC cases [34]. Meta-analyses suggest increased HCC risks among patients with type 2 diabetes, independent of viral hepatitis or alcohol use (pooled OR ~ 2.5) [35, 36]. Long durations of diabetes, high HbA1c, sulphonylurea, and insulin therapy are associated with HCC risk, while metformin treatment may decrease HCC risk [37, 38]. According to a meta-analysis including 26 prospective cohort studies with total of 25,337 HCC cases, excess body weight (BMI ≥ 25 kg/m^2), and obesity (BMI ≥ 30 kg/m^2) were associated with HCC risk with the summary relative risk for a 5-unit increment in BMI of 1.39 kg/m^2 (95% CI 1.25–1.55) [39]. This increased HCC risk by higher BMI was the most prominent among persons with a BMI > 32 kg/m^2 [39]. This finding remained significant after adjusting for potential confounders including geographic locations, alcohol consumption, diabetes, HBV, or HCV infection [39]. Persons with HCV infection seem to have a stronger risk of HCC with obesity compared to persons with HBV infection [39].

Non-Alcoholic Fatty Liver Disease

NAFLD is the hepatic manifestation of metabolic syndrome, and it affects about a third of the US adult population [40, 41]. Epidemiological studies suggest an association between NAFLD or non-alcoholic steatohepatitis and HCC that is mostly limited to those with cirrhosis [42, 43]. Approximately 20–30% of persons with NAFLD develop progressive liver disease due to necroinflammation and fibrosis that can develop cirrhosis in 10–20% of cases [44]. The prevalence of NAFLD and risk of progression are the highest among Hispanics compared to other racial and ethnic groups [45]. NAFLD is the fastest-growing etiology of cirrhosis and indication for liver transplant in the USA [46]. From 2002 to 2012, the number of patients undergoing a liver transplant for HCC secondary to non-alcoholic steatohepatitis increased by nearly fourfold, twice greater than that of liver transplant patients with HCC secondary to HCV [46]. A few epidemiological studies about the association of NAFLD and HCC are limited by a small number of HCC cases; thus, subgroup analyses to risk stratify by potential risk factors were limited [47]. Recently, the largest published cohort study from a total of 130 facilities in the Veterans Health Administration from January 1, 2004, to December 31, 2008, confirmed the association between NAFLD and increased HCC risk. During 2,382,289 person-years of follow-up, NAFLD patients had a higher annual risk of HCC than controls (0.21/1000 person-year vs 0.02/1000 person-years, HR = 7.62, 95% CI 5.76–10.1). The incidence of HCC among NAFLD patients with cirrhosis was 10.6 per 1000 person-years. The risk of HCC was the highest in older Hispanics with cirrhosis (12.3 per 1000 person-years). It was also noteworthy that about 20% of NAFLD patients with HCC had no evidence of cirrhosis [48•]. In addition, a genetic single-nucleotide polymorphism of the patatin-like phospholipase domain-containing protein 3 (PNPLA3), or rs738409, may be associated with an increase in liver steatosis and the HCC risk [47].

Alcoholic Liver Disease

According to the National Health and Nutrition Examination Survey data, the prevalence of alcoholic liver disease was 1–2.5% during 1988–2008 [49]. Age-standardized mortality due to alcohol-related liver disease has increased from 7.76% in 2007 to 10.35% in 2016 according to results from the US Census and National Center for Health Statistics mortality records [50]. Alcoholic liver disease is a broad diagnosis that includes steatosis, fibrosis, alcoholic hepatitis, and cirrhosis. Higher alcohol consumption and alcoholic hepatitis are associated with developing cirrhosis. Among patients with alcoholic hepatitis, approximately 3–12% progress to cirrhosis annually [51]. A synergistic effect for the HCC risk between viral hepatitis and heavy alcohol use was reported [52, 53]. A similar synergism may also be present with diabetes. This effect is more pronounced in individuals who consumed more than 60 g of alcohol per day [52, 53]. A meta-analysis including 19 cohort studies for a total of 4445 HCC cases suggests that the pooled relative risk of HCC among heavy drinkers (≥ 3 drinks per day) was 1.16 (95% CI 1.01–1.34) compared to non-drinkers [54]. The dose–risk curve suggested a linear relationship with increasing alcohol intake in drinkers, with an estimated excess risk of 46% for 50 g of ethanol per day and 66% for 100 g per day [54].

Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is characterized by interface hepatitis, hypergammaglobulinemia, and autoantibodies [55–57]. Based on limited epidemiological data, the prevalence of AIH is estimated to be ~ 50–200 cases per 1 million in the Caucasian population in North America and Western Europe [56]. Clinical manifestations include no symptoms, severe acute hepatitis, cirrhosis, and, rarely, fulminant hepatic failure. The risk of HCC, while elevated compared to people with no liver disease, appears to be lower in patients with AIH cirrhosis than in patients with viral hepatitis cirrhosis. In a meta-analysis of 25 observational studies including 6528 patients, the pooled incidence rate for HCC in all patients with AIH was 3.06 per 1000 patient-years (95% CI 2.22–4.23) and 10.07 per 1000 patient-years (95% CI 6.89–14.7) among patients with AIH-related cirrhosis [58]. Almost all HCC cases among patients with AIH had cirrhosis prior to or at time of HCC diagnosis. Old age, male gender, Asian race, multiple AIH relapses, and ongoing alcohol abuse seem to be associated with increased risk for AIH-related HCC while the concomitant presence of primary sclerosing cholangitis was associated with low HCC risk [59].

Primary Biliary Cholangitis and Primary Sclerosing Cholangitis

The overall incidence of HCC among patients with primary biliary cholangitis (PBC) is generally low (0–11 per 1000 person-years), but higher in patients with PBC cirrhosis with 7–24 per 1000 person-years [60–64]. The incidence of HCC among patients with primary sclerosing cholangitis (PSC) is unknown but is likely very low [65]. On the basis of a retrospective analysis of more than 500 patients with PSC and 293 patient-years of follow-up, no patients developed HCC, while 35 patients developed cholangiocarcinoma and 3 patients developed gallbladder cancer [65]. Recently, Ali et al. reported that after a cumulative follow-up of 712 and 283 person-years pre- and post-hepatobiliary carcinoma diagnoses using medical records at the Mayo Clinic Rochester from 1995 to 2015, 78% of patients (54/79) developed cholangiocarcinoma, 21% (17/79) HCC, 6% (5/79) gallbladder cancer, and 3% (2/79) both cholangiocarcinoma and HCC [66]. Patients in the surveillance group had significantly higher 5-year overall survival compared with the no-surveillance group (68% vs 20%, $P < 0.001$) [66].

Natural History of HCC

There are very few studies on the natural history of untreated HCC in the USA. One report came from National Veterans Healthcare Administration data on 518 veterans who were diagnosed with HCC from 2004 to 2011 and received no palliative or curative treatment with follow-up ending in 2014 [67]. The mean age at HCC diagnosis was 65.7 years, and most of these patients had hepatitis C (60.6%). Almost all patients (99%) died within the study period, with a median overall survival of only 3.6 months. In the Barcelona Clinic Liver Cancer stage model for end-stage liver disease, alpha-fetoprotein level, and pre-diagnosis HCC surveillance were associated with survival. In other studies, the median overall survival time was up to 6.8 months in an Italian cohort of 320 untreated predominantly HCV-related HCC patients [68], and 9 months in data from the Italian Liver Cancer Group of 600 untreated predominantly HBV-related HCC patients [67, 69].

Controversies and Future Directions

Epidemiological Knowledge and Optimizing the Surveillance of HCC

The American Association for the Study of Liver Disease (AASLD) guidelines suggest that HCC surveillance is cost effective if the expected risk of HCC exceeds 1.5% per year [70, 71]. AASLD guidelines recommend HCC surveillance for all patients with cirrhosis and in chronic hepatitis B patients without cirrhosis, for Asian men aged ≥ 40, Asian women ≥ 50, and African/North American blacks aged ≥ 20 [72]. The elevated risk of HCC in Africans is based on studies from South Africa that African blacks with chronic HBV infection could develop HCC at an age prior to 40 years [73, 74]. The US-based data do not support the early age recommendation for African Americans. Furthermore, the race-based screening guidelines may need to be revised since Hispanics are currently at the highest risk for HCC.

However, how to optimize HCC surveillance by balancing the benefits and harms is still controversial. The pooled 3-year survival rate was 50.8% among the 4735 patients who underwent HCC surveillance, compared with only 27.9% among the 6115 patients without previous surveillance, with an OR of 1.90 (95% CI, 1.67–2.17; $P < 0.001$) [72]. In addition to improved survival, surveillance also led to an increase in the detection of early-stage HCC, with an OR of 2.11 (95% CI, 1.88–2.33) compared with no surveillance [72]. However, studies that supported the clinical utility of ultrasound and AFP were conducted before the DAA era and did not account for the rapidly changing etiologies of HCC risk factors and improvement of their management.

There are many efforts to personalize HCC surveillance to account for the current epidemiological risk factors. An adjusted AFP-based algorithm that included age, platelets, ALT values, and interaction terms (AFP and ALT, and AFP and platelets) was suggested and is currently externally

validated [75]. Furthermore, several consortia have been established to identify high-risk individuals for HCC. One is the Texas HCC consortium, which has a target to recruit over 3000 patients with cirrhosis (> 12,000 surveillance episodes and 200 expected HCC cases) from diverse etiologies (including cured HCV and NAFLD) with goals to develop an early detection algorithm that combines existing HCC blood-based biomarkers (e.g., AFP, AFP L3, DCP) and molecular markers from next-generation sequencing assays [76].

Hepatitis B Vaccination

National HBV vaccination programs have been the most successful public health preventive strategy to reduce the incidence of HCC in HBV-endemic areas, including East Asia and Spain. In these regions, HBV accounts for the majority of HCC cases and universal vaccination programs have significantly decreased the prevalence of chronic HBV infection with almost 100% penetration [77, 78]. For example, the world's first universal HBV vaccination program for infants was implemented in Taiwan in 1984. Since then, the chronic HBV infection rate decreased from 9.7% in university students born before June 1974 to < 1.0% in students born after 1992 [79]. According to a World Health Organization report, the global completion of 3-dose HBV vaccination in infancy increased from 3% in 1992 to 84% in 2015 [80]. However, there are still around 64 million high-risk adults in the USA who remain susceptible to HBV infection, especially men who have sex with men, injection drug users, injection drug users, people with diabetes, HCV patients, and populations with elevated AST/ALT [81].

Awareness of Viral Hepatitis

In 2014, the World Health Organization set a goal to reduce the incidence of chronic viral hepatitis by 90% and reduce the mortality rate by 65% between 2015 and 2030 [82]. Diagnosis and awareness of infection are the first essential steps toward achieving this goal. However, in the USA, the awareness of chronic HBV and HCV infection is estimated to be 33.9% and 55.6%, respectively [83]. Among HCV-infected baby boomers (born between 1945 and 1965), the awareness rate is 61.5%. Still, viral hepatitis accounts for most HCC cases (approximately 80%) [5]. Further research and active health policy are needed to identify persons at risk and provide appropriate management.

Chemoprevention Other than HBV and HCV Treatments

Metformin may reduce the HCC risks by 5′-adenosine monophosphate-activated protein kinase pathway activation that modifies several steps of RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, and Wnt/β-catenin signaling cascades [84]. In a systematic review and a meta-analysis including ten studies including 22,650 cases of HCC in 334,307 patients with type 2 diabetes, metformin use was associated with approximately 50% of the reduction in HCC incidence [38]. In addition, statins are also suggested to be associated with a lower risk for HCC development through 3-hydroxy-3-methylglutaryl coenzyme A inhibition [84]. A meta-analysis including 4298 cases of HCC among 1,459,417 patients suggests that statin users were less likely to develop HCC than statin non-users (adjusted OR 0.63, 95% CI 0.52–0.76) [85]. Interestingly, the risk reduction was greater in Asians (OR = 0.52; $P < 0.05$) than that in Western populations (OR = 0.67; $P < 0.05$), which may be in part due to interactions between statins and HBV infection [85]. Moreover, both metformin and statins have shown a dose-dependent protective effect. In addition, coffee drinking may be associated with a lower risk of HCC development. A meta-analysis including 18 cohort studies, including 2905 HCC cases, and 8 case-control studies, including 1825 HCC cases, suggests that an extra two cups per day of coffee was associated with a 35% reduction in the HCC risk (RR 0.65, 95% CI 0.59 to 0.72) [86]. Caffeinated coffee showed a higher reduction in the HCC risk (RR 0.73, 95% CI 0.63 to 0.85) than decaffeinated coffee (RR 0.86, 95% CI 0.74–1.00). The association remained significant after adjusting for other confounders such as viral hepatitis, diabetes, obesity, stage of liver disease, smoking, and alcohol use [86]. However, these chemopreventive roles of metformin, statins, and coffee are mainly from observational studies that could not account for all confounders and bias.

Conclusions

In summary, the incidence rate of HCC in the USA has been increasing in the past three decades, although the pace may be somewhat slowed. Since 2012, incidence rates of HCC in Hispanics surpassed those of Asians. The recent epidemiological changes in major risk factors for HCC include increasing post-SVR hepatitis C virus, suppressed hepatitis B virus on nucleoside analogues, alcoholic liver disease, and NAFLD. The greatest proportion of current burden for HCC in the USA is related to active HCV, while future burden may shift to NAFLD. Translating the epidemiological knowledge into HCC prevention is required through screening and risk stratification. Future research is needed to optimize HCC surveillance, based on an individual's risk factors, and discover and integrate molecular/genetic risk factors in the context of these emerging high-risk groups into clinical practice.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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