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HEPATIC CANCER (N PARIKH, SECTION EDITOR)

Racial and Sex Disparities in Hepatocellular Carcinoma in the USA

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Abstract

Purpose of Review In this review, we aim to provide a summary of the current literature on race and gender disparities in hepatocellular carcinoma (HCC) incidence, stage at diagnosis, treatment, and prognosis in the USA.

Recent Findings HCC incidence rates are rising in the USA in all racial/ethnic groups except for Asian/Pacific Islanders, with disproportionate rises and the highest rates among Hispanics compared to Blacks and non-Hispanic Whites. There are striking sex disparities in HCC incidence and mortality; however, with the shifting epidemiology of HCC risk factors in the USA, there is recent evidence that HCC is trending towards less male predominance, particularly among younger birth cohorts. Despite significant advances in HCC treatment over the past decade, disparities in HCC surveillance and treatment receipt persist among racial and ethnic minorities and the socioeconomically disadvantaged. Black patients continue to experience worse survival outcomes than non-Black patients with HCC.

Summary There are significant racial and gender disparities in HCC incidence, treatment, and mortality in the USA. Though these disparities are well-documented, data are still limited on the specific determinants driving disparities in HCC. To achieve health equity for all patients with HCC, we must advance beyond simply reporting on disparities and begin implementing targeted interventions to eliminate disparities.

Keywords Ethnicity · Racial · Sex · Disparities · Liver cancer

Introduction

Hepatocellular carcinoma (HCC) is one of the fastest rising causes of cancer-related death in the USA and a leading cause of death in patients with cirrhosis [1•]; however, the disease burden of HCC is unequally distributed, with men and racial/ethnic minorities disproportionately affected compared to women and non-minority populations. As has been observed in other cancers, disparities can occur at any point along the HCC care continuum, including under-recognition of cirrhosis, screening underuse, and delayed diagnosis or treatment, all of which may lead to poorer outcomes and increased mortality. HCC prognosis is significantly impacted by stage at diagnosis, with curative treatments available for patients diagnosed at an early stage. Though racial and gender disparities in HCC incidence and prognosis have been well-described over the past decade, data are limited on the specific determinants driving these disparities. The epidemiology of HCC in the USA is shifting, with fewer cases attributed to viral hepatitis, given the impact of effective direct-acting antivirals for hepatitis C and vaccination against hepatitis B, whereas the epidemic of non-alcoholic fatty liver disease (NAFLD) is rising exponentially [2]. Understanding the current landscape of racial and gender disparities in HCC is the first step to identify targets for intervention to reduce these disparities and promote equity for all patients with this deadly cancer. In this review, we will summarize the literature on the current landscape of racial and gender disparities in HCC.

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Disparities in HCC Incidence

Racial and Ethnic Disparities

HCC is one of the few cancers in the USA with rising incidence and mortality rates [3], and there is notable variation in disease burden by race/ethnicity. Historically, the highest HCC incidence rates were observed in Asian/Pacific Islanders [4], due in large part to high prevalence of hepatitis B virus (HBV) infection among immigrants from HBV-endemic areas; however, these rates plateaued around 2007 and began to decline in recent years (annual percent change [APC] − 1.59% and − 2.2% among men and women, respectively) [5•]. These declines are attributed to lower rates of HBV infection among subsequent generations born in the USA, HBV vaccination programs, and improvements in antiviral therapy for HBV [6]. Conversely, HCC incidence rates have risen in all other racial/ethnic groups, with disproportionate rises and the highest rates among Hispanic men (4.7% per year since 2000) compared to Blacks and non-Hispanic Whites [7, 8]. A study by Petrick et al. forecasted HCC incidence rates will continue to increase through the year 2030 in all racial/ethnic groups except Asian/Pacific Islanders [5•]. This rise is largely attributed to aging of the baby boomer birth cohort. Among younger adults (aged < 50), HCC incidence rates have begun to decline since the mid-2000s, with largest decreases noted among middle-aged Blacks (− 17.2% per year since 2012) compared to adults of similar age in other racial and groups [9]. Alaskan Natives have also historically had high prevalence of HCC due in large part to high rates of HBV infection in the 1970s [10], though incidence rates, particularly among young adults, have sharply declined in recent years due to a universal newborn and catch-up HBV vaccination program established in the 1980s [11, 12].

There is substantial geographic variation in HCC incidence in the USA, with Texas having the highest rates [13], followed by Hawaii, New Mexico, and California [14]. This is due in part to racial/ethnic diversity of citizens living in these states, with age-adjusted incidence rates highest among Hispanics in Texas (21.2 per 100,000) compared to 9.3 per 100,000 for Whites, 16.3 per 10,000 for Blacks, and 15.1 per 100,000 for Asian/Pacific Islanders [14]. Nativity, or country of birth, also appears to impact HCC risk [15]. Foreign-born Asian/Pacific Islanders have higher HCC risk, whereas US-born Hispanics have higher HCC incidence rates than their foreign-born counterparts [15]. The reasons for this have not been elucidated but are thought to be due to higher rates of known HCC risk factors (e.g., HCV infection, diabetes, metabolic syndrome, and non-alcoholic fatty liver disease [NAFLD]) in US-born Hispanics compared to those born outside the USA. Disparities in HCC incidence have also been observed based on neighborhood-level socioeconomic status [16, 17] and within subgroups of Asian/Pacific Islanders and Hispanics in California living in neighborhoods based on ethnic enclave status [18].

Sex Disparities

Sex disparities have been observed for most cancers; in fact, there are only a few examples of malignancies with higher incidence rates in women compared to men (i.e., thyroid, bladder, brain cancers) [19]. Sex disparities in HCC incidence are well-documented, with men having 2–8 times higher incidence rates than women across geographic regions, time period, and all racial/ethnic groups [20, 21]. There is some recent evidence that HCC is trending towards less male predominance, particularly among younger birth cohorts [22]. Since the year 2000, the male-to-female incidence rate ratio (IRR) has decreased in younger adults of all races/ethnicities but has remained stable in adults over 50 years [22].

However, despite this consistent observation, the specific factors driving this sex disparity are poorly understood. While there are gender differences in the distribution of certain HCC risk factors (e.g., alcohol use, viral hepatitis, diabetes, obesity) [23], these risk factors have varied in prevalence over time in the general population while the sex disparity has remained striking and consistent, suggesting that biological factors (e.g., sex hormones) also play a role in HCC risk. Though the role of sex hormones in HCC pathogenesis has primarily been investigated in animal models, there are data suggesting estrogen may be protective (via suppression of pro-inflammatory cytokines such as IL-6 [24]) and androgens deleterious (via signaling pathways leading to upregulation of vascular endothelial growth factor [VEGF] [25]). A retrospective cohort study of 928 men with chronic HBV and diabetes found higher serum testosterone levels were associated with increased HCC risk [26], whereas a small case-control study of 234 women found exogenous estrogen use was associated with reduced risk of HCC [27]. A large population-based study of circulating sex hormones in stored serum found no significant association between estrogen levels and HCC risk; however, sex hormone binding globulin (SHBG) and 4-androstendione levels were associated with higher and lower risk of HCC, respectively [28]. Further studies in large prospective cohorts of men and women with cirrhosis are needed to untangle the relative contribution of sex- and gender-related factors in HCC risk in order to address this sex disparity.

Disparities in HCC Risk Factors, Surveillance, and Stage at Diagnosis

Risk Factors

Between 80 and 90% of HCC in the USA occur in a background of cirrhosis [29]. The prevalence of underlying risk

factors for HCC, including underlying liver disease etiology, smoking, obesity, and diabetes, differ by race/ethnicity and gender [23, 30]. For example, an estimated 75–100 million Americans have non-alcoholic fatty liver disease (NAFLD), which has surpassed viral hepatitis and become the most common cause of chronic liver disease in the USA [31]. There are significant disparities in NAFLD prevalence and severity, with Hispanics having the highest prevalence of NAFLD and highest risk of progression to non-alcoholic steatohepatitis (NASH) compared to other racial/ethnic groups [32•]. Makarova-Rusher et al. evaluated the population attributable fraction (PAF) for various HCC risk factors using SEER-Medicare data, and found the PAF for metabolic disorders was highest among Hispanics (39.3%, 95% CI 31.9–40.4%) and Whites (34.8%, 95% CI 33.1–33.6%), whereas the PAF for HCV was highest among Black patients with HCC (36.1%, 95% CI 31.8–40.4%) [30]. There are also differences in the risk factors and presentation for HCC between men and women. Women tend to be older than men at time of HCC diagnosis with higher rates of NAFLD and metabolic syndrome, whereas viral hepatitis, alcohol use, and smoking are more commonly seen in men [33–35]. Targeted intervention at the underlying etiology of liver disease can guide HCC prevention strategies. It cannot be neglected that social determinants of health (e.g., poverty and environmental stressors) may lead to higher rates of HCC risk factors such as obesity and alcohol use in racial and ethnic minorities and the socioeconomically disadvantaged.

Surveillance

HCC surveillance is associated with early tumor detection and improved survival in patients with cirrhosis [36]. Unfortunately, despite professional society recommendations, HCC surveillance continues to be underutilized in the USA [37], particularly among racial/ethnic minorities and the socioeconomically disadvantaged [38]. There do not appear to be significant sex-related differences in HCC surveillance utilization [39]. Lower SES has been associated with decreased rates of cancer screening [40], even among patients receiving care in an integrated health system. Singal et al. found that only 13% of patients with cirrhosis received annual HCC surveillance at an urban safety-net hospital, with lower rates of consistent surveillance among Black patients and the underinsured [41]. Patient-reported barriers to surveillance include issues with scheduling, transportation, and financial burden [42]. Receipt of consistent and timely HCC surveillance is a key target for interventions to reduce disparities in HCC outcomes, as patients diagnosed at later tumor stages have limited treatment options and poor prognosis [43].

Tumor Stage at Diagnosis

Given disparities in surveillance, it is not unexpected that Black patients are more often diagnosed with HCC at an advanced stage compared to non-Black patients [44]. In an analysis of the SEER database, Ha et al. found Black patients had significantly higher odds (OR 1.20, 95% CI 1.10–1.30) and Asians had significantly lower odds (OR 0.87, 95% CI 0.80–0.94) of having advanced stage HCC at time of diagnosis compared to Whites [45]. Similarly, in a study of 1117 patients with HCC at two large health systems in Texas, we found Hispanic (OR 0.75, 95% CI 0.55–1.00) and Black patients (OR 0.74, 95% CI 0.56–0.98) were less likely to be diagnosed with early-stage HCC than white patients [46••]. Lastly, among 999 patients with HCC in Florida, Jones et al. found Blacks presented with more advanced stages with larger tumors, with 65.9% of Blacks beyond Milan criteria at diagnosis, compared to 54.6% of Asians, 49.7% of Hispanics, and 39.9% of Whites ($p < 0.01$) [47]. One of the major contributing factors to late-stage HCC detection among Black patients is that they are less likely to be adequately screened for HCC compared to other racial and ethnic groups, and patients connected with a hepatologist or gastroenterologist are more likely to receive routine surveillance [48]. Several studies have demonstrated sex disparities in tumor stage at diagnosis [34, 35]. In a retrospective study of 1100 patients with HCC, we found women with HCC were more likely than men to be detected at an early tumor stage (50.8% vs 42.1%; OR 1.55, 95% CI 1.16–2.08), even after adjusting for age, race/ethnicity, liver disease etiology, and liver function [36].

Disparities in HCC Treatment

HCC treatment is underutilized in the USA, including among patients with early-stage disease eligible for curative therapy (i.e., liver transplantation, surgical resection, and ablation) [49], with some of the lowest rates of curative treatment receipt observed among patients with low socioeconomic status [50] and racial and ethnic minorities [51]. Several population-based studies using data from SEER and the Nationwide Inpatient Sample (NIS) demonstrated Blacks and Hispanics have significantly lower rates of curative treatment receipt compared to Whites, even after adjusting for tumor stage at diagnosis [45, 52, 53]. Similarly, in a study of patients with HCC at two large health systems in Texas, we found Hispanics (OR 0.51, 95% CI 0.37–0.70) and Blacks (OR 0.60, 95% CI 0.4–0.81) were less likely to receive curative treatment than Whites, even after adjusting for insurance status and tumor stage at diagnosis [54•]. Significant racial and ethnic disparities in liver transplantation for HCC have also been reported, with Black [51, 55] and Hispanic [56] patients having less access to transplant compared to Whites. In a

study of data from the Texas Cancer Registry, Alawadi et al. also found Hispanics and Blacks were less likely to receive surgical treatment for HCC compared to Whites, but unexpectedly, rural residency was not associated with disparities in surgical treatment for HCC [57]. Finally, Stewart et al. found substantial inter-ethnic disparities in receipt of curative HCC treatment and survival among various Asian ethnic subgroups, even after accounting for tumor stage and socioeconomic status [58].

Women with HCC appear to receive curative treatment at similar or higher rates compared to men, which may be due in part to women being more likely to receive regular HCC surveillance [48] and therefore having a higher proportion of early-stage tumors, as well as lower rates of hepatic decompensation at time of HCC diagnosis [59]. In a study analyzing SEER data, Yang et al. found a higher proportion of women received surgical treatment than men (44% vs 36%, $p < 0.001$) [60]. Sobotka et al. analyzed data from the Nationwide Inpatient Sample and found women had higher odds of treatment with surgical resection (OR 1.31) and ablation (OR 1.22) compared to men; they found no significant difference in the rates of transarterial chemoembolization (TACE) between men and women [61]. In another study, Cauble et al. found women with HCC presented less often with decompensated cirrhosis (OR 0.79, $p < 0.001$); however, even among the subgroup of patients with compensated cirrhosis, women were offered curative therapy more often than men [59]. Women are less likely than men to undergo liver transplantation, both generally as well as for HCC [62, 63]. There are limited data on sex disparities in locoregional and systemic therapy in HCC.

Potential causes of treatment disparities are complex and likely related to a combination of patient-, provider-, and/or system-level factors. Patients may have misconceptions about cancer treatment that may impact their willingness to proceed with treatment. Financial toxicity, difficulty with transportation, language barriers, mistrust of providers and health systems, and other patient beliefs/preferences may all impact an individual patient's decision to proceed with treatment [64–66]. Provider biases and system-level factors (e.g., hospital volume and facilities) also play a role. For instance, Mokdad et al. found that 42% of patients in Texas with HCC received treatment at a safety-net health systems, facilities which care for a disproportionate number of racial and ethnic minorities and the socioeconomically disadvantaged [67]. Patients were less likely to receive curative treatment at the safety-net hospitals, even when diagnosed at an early stage (OR 0.51, 95% CI 0.40–0.66) and experienced worse overall survival (HR 1.30, 95% CI 1.22–1.39) than patients at non-safety-net hospitals [67]. Similarly, Hoehn et al. found liver transplantation and resection were performed less often for HCC at safety-net hospitals (50.7% vs 66.7%) [68]. While patient insurance status is associated with more advanced tumor stage at diagnosis and lower odds of HCC treatment receipt [69], "equal" healthcare coverage or insurance may still not translate into equitable access to care or outcomes. For example, in a study of Medicaid/Medicare enrollees with colorectal cancer, disparities in surgical treatment still persisted with fewer Black patients undergoing resection compared to Whites [70].

Disparities in HCC Prognosis and Survival

Black patients experience poorer survival than Whites for many cancers [71], including HCC. In the USA, studies demonstrating that Black patients and the socioeconomically disadvantaged experience worse survival than non-Black patients are ubiquitous [57]. One explanation for this finding is disparate use of HCC surveillance resulting in delayed detection, later stage diagnosis, and disparities in curative treatment as outlined above. Other factors driving disparities in outcomes may be liver disease etiology, liver disease severity, and other comorbid conditions. Black patients may also experience more fragmented care, which has also been associated with worse outcomes in HCC [72]. However, even among the subset of patients undergoing potentially curative therapy (e.g., surgical resection, liver transplantation, ablation), Black patients have significantly worse survival compared to other races and ethnicities [73]. In a study of the SEER database, Mathur et al. found Blacks had a 12% higher mortality rate (HR, 1.11; 95% CI, 1.03–1.20), Hispanics had a similar mortality rate (0.97; 0.91–1.04), and Asians had a 16% lower mortality rate (0.84; 0.79–0.89) compared to Whites [74]. In a study among 1117 patients with HCC from two US health systems, we found Black patients had worse mortality (HR 1.12, 95% CI 1.10–1.14) and Hispanics had lower mortality (HR 0.83, 95% CI 0.74–0.94) compared to Whites, even after adjusting for tumor stage, Child Pugh score, and HCC treatment receipt [54•]. Njei et al. found persistent disparities in survival even after liver transplantation, with Blacks having worse survival and Asian/Pacific Islanders having better survival compared to Whites [75]. Geographic disparities in HCC outcomes have also been reported, with worse outcomes in Southern states [72].

Age-adjusted mortality rates are higher in men than in women for most GI malignancies, including colorectal and esophageal cancers [76], and women also appear to have a survival advantage in HCC. In an analysis of SEER data, Yang et al. found women had better overall survival compared to men, independent of age, race, disease stage, or treatment [60]. Notably, the largest difference in overall survival was among patients aged 18 to 44 in which women had a 4-month survival benefit relative to age-matched men (HR 0.75, $p < 0.001$) [60]. Similarly, in a study of 1110 patients with HCC from two large health systems in the USA, we

found women had better overall survival than men (17.1 vs 12.0 months; HR 0.81, 95% CI 0.68–0.97), after adjusting for tumor stage, liver disease etiology, and liver function [34••]. This sex disparity was consistent across subgroups including liver disease etiology, BCLC stage, and type of HCC treatment; however, the survival benefit seen in women differed by age, with younger women having a survival benefit versus younger men (18.3 vs 11.2 months, $p = 0.02$), whereas no difference in survival was observed between older women and men (15.7 vs 15.5 months, $p = 0.45$) [34••]. These findings suggest that sex hormones may play a role in HCC prognosis; however, further studies are needed.

While some believe differences in HCC prognosis may extend beyond disparities in healthcare access, studies evaluating the doubling time of HCC tumors have not demonstrated significant sex or racial/ethnic differences in tumor biology or "aggressiveness," except more rapid growth in Asian populations with predominately HBV-related HCC [77, 78].

Future Directions Towards Eliminating Disparities

Though racial and gender differences in incidence and mortality have been described for many cancers, including HCC, few studies have evaluated the root causes and mechanisms underlying these disparities. Most studies on disparities in HCC are limited in scope and rely on administrative datasets lacking granular information on liver disease etiology, liver function, socioeconomic status, and psychosocial or behavioral factors. Furthermore, few studies in HCC have investigated the intersectionality of race and gender or race and socioeconomic status [79]. There are several challenges inherent to the study of cancer disparities including accurate ascertainment of race and ethnicity and classification of multi-ethnic individuals. Social determinants of health (e.g., poverty, environmental stress, health literacy, social support) are likely to heavily influence disparities in HCC incidence and mortality [80••]. Systemic racial inequity in the USA represents a public health crisis and large-scale interventions are needed to mitigate and reverse its effects on the health of vulnerable populations. Racism and discrimination are indeed social determinants of health that have negative downstream effects on health and access to healthcare [81]. Implicit biases and stereotypes may impact decision-making regarding screening and treatment, compounding disparities in marginalized populations with decreased healthcare access already facing other barriers [82]. Furthermore, it is increasingly recognized that seemingly "neutral" diagnostic and prognostic algorithms in medicine may perpetuate, rather than mitigate, racial and gender biases and disparities [83, 84]. For example, estimated glomerular filtration rate (eGFR) may overestimate kidney function in Black patients, potentially delaying referral for treatment or kidney transplantation [85], and the use of the Model for End Stage Liver Disease (MELD) score for organ allocation has disadvantaged women resulting in lower odds of liver transplantation and higher rates of waitlist death [86, 87]. While there is growing body of research on healthcare disparities, it is not sufficient to merely continue to identify and prove that disparities exist; rather, we must collectively take the critical next step to determine their root causes, implement interventions, and advocate for system-level change to eliminate disparities.

Conclusions

There are significant racial and gender disparities in the disease burden, treatment, and outcomes of HCC in the USA, with men and racial/ethnic minorities disproportionately impacted. Though some progress has been made, data are limited on the specific determinants driving disparities in HCC. As a scientific community, we must advance beyond simply reporting on disparities and instead begin implementing interventions to eliminate disparities to achieve equitable care for all patients with HCC.

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Compliance with Ethical Standards

Conflict of Interest Amit Singal has been on advisory boards and served as a consultant for Wako Diagnostics, Roche, Exact Sciences, Glycotest, Bayer, Eisai, Exelixis, BMS, Merck Genentech, and TARGET-Pharmasolutions. The other authors have no relevant conflicts 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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