The National Burden of Hepatocellular Carcinoma Across Different Geographical Regions in The United States Between 2001 and 2020

Authors: Yazan Abboud¹, MD, Raj Malhotra², BS, Muhammad Hassaan Arif Maan³, MD, Anna Mathew³, BS, Ibrahim Abboud³, BS, Chun-Wei Pan³, MD, Saqr Alsakarneh⁴, MD, Fouad Jaber⁵, MD, Islam Mohamed⁶, MD, David Kim⁷, MD, Nikolaos T. Pyrsopoulos⁵, MD, PhD, MBA

Abstract:

Background:

While prior data showed an increasing incidence of Hepatocellular carcinoma (HCC) in the US, there are limited comprehensive and comparative data on the geographical variations of HCC trends in different demographic-specific populations.
Aim:

Evaluate sex and age-specific incidence rates and time trends in different geographical regions in the United States.

Methods:

- **Age-adjusted** HCC incidence rates were collected from the United States Cancer Statistics (USCS) database which covers approximately 98% of the population in the United States. HCC rates were stratified by sex, age, and geographical region. **Annual percentage change (APC) and average APC (AAPC)** were estimated using Joinpoint Regression. A pairwise comparison was conducted between sex-specific trends.

Results:

There were 467,344 patients diagnosed with HCC in the United States in the USCS database between 2001 and 2020. The rates and trends varied by geographical region. When looking at the West region (115,336 patients), incidence rates of HCC were overall increasing and also increasing in older adults. However, when evaluating younger adults, HCC incidence rates decreased in **men but not in women** with a sex-specific absolute **AAPC-difference of 2.15** (P=0.005). When evaluating the Midwest region (84,612 patients), similar results were seen. While incidence rates were increasing in the overall population and in older adults as well, they were decreasing in younger men but not in women with a sex-specific absolute **AAPC-difference of 1.61** (P<0.001). For the Northeast region (87,259 patients), the analysis showed similar results with decreasing HCC incidence rates in younger men but not counterpart women (Sex-specific AAPC-difference= 3.26, P<0.001). Lastly, when evaluating the south (180,137 patients), the results were also decreasing in younger men but not in women (Sex-specific AAPC-difference= 2.55, P<0.001).
Conclusion:

Nationwide analysis covering around 98% of the US population shows an increasing incidence of HCC across all geographical regions, most notably in the South. While younger men experienced decreasing HCC incidence, younger women had a stable trend and this was noted across all regions as well. Our study offers insight into the epidemiology of HCC in different demographic groups across various US geographical regions. While the reasons contributing to our findings are unclear, they can be related to sex and regional disparities in healthcare access and utilization. Future research is warranted to characterize the temporal change in HCC risk factors across different US regions.

Keywords: Hepatocellular carcinoma; Incidence; Epidemiology; Health disparity; Geography

Core Tip: In this retrospective study of the United States Cancer Statistics database (which covers ~98% of the US population), we analyzed sex and age-specific Hepatocellular Carcinoma (HCC) incidence across different US regions between 2001-2020. HCC incidence rates were significantly increasing in the West, Midwest, Northeast, and South of the US, most notably in the South. While younger men experienced decreasing HCC incidence, younger women had non-decreasing incidence, and this was noted across all regions. While this can be due to regional disparities in healthcare access/utilization, future research is needed to investigate regional HCC risk factors, especially in younger adults.
INTRODUCTION:

Hepatocellular carcinoma (HCC) accounts for around 80% of liver cancers and its incidence has tripled since 1980[1]. Although HCC can occur sporadically, almost 90% of cases can be attributed to underlying liver diseases such as hepatitis C virus (HCV), hepatitis B virus (HBV), alcohol-associated liver disease, and metabolic dysfunction associated steatotic liver disease (MASLD). With the routine vaccination against HBV and an increase in the proportion of HCV patients with sustained virologic response, coupled with increased prevalence of MASLD, epidemiological changes in HCC risk factors are expected in the coming years[2].

HCC burden is unequally distributed with disparities occurring at various steps of the cancer care continuum including implementation of screening programs, access to specialist care, timely diagnosis, and treatment. HCC is usually rare under the age of 40 years, and its incidence increases with age before plateauing around the age of 70 years[3]. The incidence of HCC is disproportionately greater in males, with associated mortality reported to be three times higher than in women[4]. These differences are attributed to a variation in the prevalence of risk factors such as alcohol use, smoking, viral hepatitis, and MASLD which disproportionally affect men and women. The evolving trends in sex- and age-specific HCC incidence rates call for further exploration and analysis of data at a national level to guide future interventions.

American Cancer Society projects cancer deaths in 2024 from liver and bile duct cancer to be the highest in California (3580), followed by Texas (2960) and Florida (2180)[1]. Limited data comparing regional variation in HCC incidence show rates are highest in Texas, followed by
Hawaii, New Mexico, and California; argued to be in part due to their racial/ethnic diversity[5]. While recent data showed an increasing overall incidence of HCC with variations based on age and sex[4], literature is scarce on demographic-specific trends across geographic regions. Understanding the epidemiological differences at a national level is imperative to identify regional variabilities in epidemiology and study their impact on HCC-associated morbidity and mortality. Therefore, we aimed to perform a comprehensive analysis of HCC incidence rates and time trends stratified by sex and age in different geographical regions in the US using the United States Cancer Statistics (USCS) database.

MATERIALS AND METHODS:

We report a time trend comprehensive analysis of national incidence rates of HCC in the US between 2001 and 2020 across various regions in the US using publicly available and de-identified data from the USCS database which covers nearly 98% of the US population[6]. HCC incidence rates were age-adjusted to the standard 2000 US population using SEER*Stat software (version 8.4.2, National Cancer Institute "NCI"). The rates were categorized by sex and age into younger and older adults (defined with an age cutoff 55 years)[4]. HCC incidence rates were also stratified by geographical region in the US into West, Midwest, Northeast, and South. Time-trends were reported as annual percentage change(APC) and average APC (AAPC) and were generated using Joinpoint Regression Software (version 5.0.2, NCI) via the weighted Bayesian Information Criteria “BIC” method (which is a data-driven analytical method used to estimate trends over time that is recommended to be used in large databases)[7-9]. A pairwise comparison was done between the sex-specific trends using the tests of parallelism and coincidence with a two-sided P-value cutoff at 0.05[10].

RESULTS:
During the study period of 2001-2020, there were 467,344 patients diagnosed with HCC in the US. The majority of the patients were men (74.0%) and were diagnosed in the South (38.5%). HCC incidence rates and time trends varied between the cohorts across different geographical regions.

In the West regions (115,336 patients; %26.9 women), HCC incidence rate per 100,000 population significantly increased in the overall population from 5.57 to 6.48 between 2001 and 2020, and also in older adults (95,152 patients; 28.2% women) from 19.66 to 26.31 between 2001 and 2020 (Figure 1). However, in younger adults (19,160 patients; 19.8% women), while HCC incidence rates decreased in men from 3.77 to 1.97 between 2001 and 2020 (AAPC= -2.92, P<0.001), the rates did not decrease in women (AAPC= -0.78, P=0.10) with a significant difference between the sexes (Sex-specific absolute AAPC-difference= 2.15, P<0.005) (Table 1 and Figure 2).

When evaluating the Midwest (84,612 patients; %26.8 women), similar results were seen where HCC incidence rates per 100,000 population were significantly increasing in the overall population from 3.84 to 5.16 between 2001 and 2020, and also in older adults (70,631 patients; 27.5% women) from 13.65 to 20.83 between 2001 and 2020 (Figure 1). However, in younger adults (13,169 patients; 22.3% women), while HCC incidence rates were decreasing in men from 2.40 to 1.61 between 2001 and 2020 (AAPC= -1.95, P=0.002), the rates did not decrease in women (AAPC= -0.35, P=0.65) with an absolute sex-specific AAPC-difference of 1.61, P=0.1 (Table 1 and Figure 2).

In the Northeast (87,259 patients; 24.9% women), similar results were also seen where HCC incidence rates per 100,000 population were increasing in the overall population from 5.01 to 5.74, and in older adults (72,391 patients; 225.8% women) from 17.36 to 23.41, between 2001 and 2020 (Figure 1). However, in younger adults (14,225 patients; 19.4% women), HCC rates were decreasing in men from 3.70 to 1.73 between
2001 and 2020 (AAPC= -3.38, P<0.001), and this was not seen in women who experienced a stable trend (AAPC= -0.13, P=0.87) with an absolute sex-specific AAPC-difference of 3.26, P<0.001 (Table 1 and Figure 2).

Lastly, in the south (180,137 patients; 25.5% women), similar results were also seen with increasing HCC rates per 100,000 population in the overall population from 4.31 to 6.81 between 2001 and 2020, and also in older adults from 14.69 to 27.68 between 2001 and 2020 (Figure 1). However, younger adults (467,344 patients; 20.8% women) experienced decreasing HCC incidence rates in men from 3.28 in 2001 to 2.14 in 2020 (AAPC= -2.05, P<0.001), but not in women who had a stable trend (AAPC= -0.05, P=0.95) with an absolute sex-specific AAPC-difference of 2.55, P<0.001 (Table 1 and Figure 2).

**DISCUSSION**

Our nationwide analysis of data covering nearly all HCC patients in the US shows increasing overall incidence of HCC in older adults across all geographical US regions, most notably in the South. However, in younger adults, HCC incidence was decreasing in men but not in counterpart women, and that sex-specific difference was seen across all geographical regions in the United States.

As of 2020, primary liver cancer is the fifth most common cancer in men worldwide, the ninth most common cancer in women worldwide, and the sixth most common cancer diagnosed overall[11]. According to the National Cancer Institute, in 2023, there were about 41,000 diagnoses and about 29,000 deaths related to primary liver cancer in the US. A recent analysis using the USCS database showed increasing overall HCC incidence, and decreasing rates in younger men but not women[4]. Recent data also suggests that HCC incidence is trending away from male predominance in younger adults, with a decreasing male-to-female incidence ratio[5]. We add to prior literature
showing that the greatest increase in overall HCC was in the South and the greatest decrease in HCC incidence in younger men was in the Northeast. We also show that the stable trend in younger women was noted across all US regions. These differences are multifactorial, in large part due to the racial and geographical disparities in access to and quality of care. The findings of non-decreasing HCC incidence rate in younger females may be attributable to the changing prevalence of risk factors over recent years across all regions of the US[4].

A prior analysis of the SEER database of 43,868 patients between 2000-2012 evaluating the most at-risk group in the US (Southern region) compared to other regions, showed that blacks comprised a larger proportion of HCC patients in the South compared to other areas (32.4% vs. 10.1%) and were diagnosed at a younger age, with more advanced stage at diagnosis and more metastases[12]. Furthermore, black patients were 58% less likely to receive liver transplant and 36% less likely to receive surgical therapy for HCC compared to patients of white race[13]. Of interest, this study also saw similar radial disparities in HCC outcomes in geographical regions outside the Southern US. Another analysis of the SEER database from 1975-2017 showed that HCC mortality rates were highest in the South, followed by the West, Northeast, and Midwest[14]. These differences are multifactorial, in large part due to the racial and geographical disparities in access to and quality of care[15]. Our study builds on these prior studies, using a significantly larger sample size over a more recent period and stratifying the analysis by sex and age, demonstrating that the greatest increase in HCC incidence was in the South.

The introduction of direct-acting-antiviral treatment for HBV and HCV along with the increasing obesity epidemic in the US has shifted the leading causes of HCC from viral hepatitis toward MASLD[16, 17]. However, access to treatment has been a subject of public health concern, as fewer Medicaid and Medicare recipients with HCV receive timely treatment compared to those privately insured[18]. Furthermore, black Medicaid recipients are less likely to receive direct-acting antiviral therapy than white counterparts[18, 19]. Viral hepatitis also disproportionately
affects the black population. A prior study using the National Health and Nutrition Examination Survey (NHANES) database found that African Americans had a two to three-fold higher prevalence of chronic HBV than the general population between 1999 and 2008\cite{20}. According to the US Census Bureau in 2021, nine of the ten poorest states are in the South. These factors could explain the greater increase in HCC incidence in the South. These findings demonstrate a need for targeted public health intervention and multidisciplinary care in this high-risk, underserved, largely uninsured population.

MASLD is a leading cause of HCC in Western countries\cite{21}. Sex differences in metabolic risk factors for HCC may explain the trends we observed. In the more recent years of our study period, in all regions but the Midwest, the HCC incidence rate in women older than 55 years of age has decreased less than that of men over 55 years of age. This could be explained in part by decreased estrogen levels in postmenopausal women. Estrogen may have protective effects on hepatic fibrinogenesis, causing later onset of HCC in the female population\cite{22, 23}. A single-center study reported significantly higher rates of MASLD in older women compared to younger women and older men\cite{24}. Patients without screenable etiologies to cirrhosis are disproportionately identified later in the disease course; postmenopausal women may be part of this population\cite{25, 26}. Having said that, it is hard to blame a single risk factor for the observed findings, especially with the variation in environmental exposures, biologics, and socioeconomic status between different cohorts in the US in different regions.

Our study has several strengths which include the stratified analysis by age and sex across different geographical regions, in addition to the large sample size (467,344 patients), recent period (2001-2020), and the use of joinpoint regression with the BIC method and comparative analysis. With that in mind, our study is limited in the lack of clinical variables to assess for HCC risk factors. However, our manuscript is observational, and its epidemiological retrospective design is hypothesis-generating and aims to guide future efforts toward further
investigations of the contributions leading to increasing HCC incidence across different US populations and geographical locations. Our study suffer from other limitations inherent in large databases such as loss of records and coding reliability[27]. However, all the data used in our analysis were obtained from the USCS database which is the official source of cancer incidence data in the US and undergoes many processes to ensure high-quality standardization and coding per the standards of the North American Association of Central Cancer Registries.

CONCLUSION

Our study offers insight into the epidemiology of HCC in different demographic groups across various US geographical regions. While overall HCC incidence was increasing across all geographical regions, Southern states experienced the steepest increase. The non-decreasing trend in younger women was noted across different regions, compared to counterpart younger men who experienced a decreasing trend. The reasons contributing to our findings are unclear and can be related to sex and regional disparities in healthcare access and utilization. Future research is warranted to characterize the temporal change in HCC risk factors across different US regions.