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Brief Report

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Trends and Disparities in Stage-Specific Incidence of Hepatocellular Carcinoma among US Adults, 2004–2019

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Hepatocellular cancer · Incidence · Stage · Racial disparity

Abstract
Introduction: The aim of this study was to determine the stage-specific incidence trend of hepatocellular carcinoma (HCC) among US adults. ***Methods:*** The age-adjusted incidence rate was extracted from Surveillance, Epidemiology, and End Results database for localized, regional, and distant HCC. Trend analyses were conducted in the overall population and stratified by demographic and sociodemographic variables. The annual percentage change (APC) in 2014–2019 was estimated to determine the stage-specific incidence trend. ***Results:*** Although the incidence of localized HCC significantly declined, the incidence for regional and distant HCC plateaued in 2014–2019 (APCs, 4.4% [95% CI, −0.2% to 9.3%] and −0.7% [95% CI, −1.8% to 0.5%], respectively) with age and race/ethnicity disparities. More pronounced increases for regional and distant HCC were observed among the elderly (APCs, 8.4% [95% CI, 4.8–12.2%] and 2.2% [95% CI, 1.7–2.7%] for regional and distant HCC, respectively), non-Hispanic white individuals (APCs, 4.0% [95% CI, 2.9–5.1%] and 1.5% [95% CI, 0.7–2.4%] for regional and distant HCC, respectively). ***Conclusions:*** Disparities in incidence trends may reflect the inequalities in access to primary health care. More efforts are still in great demand for the vulnerable population.

Introduction

Hepatocellular carcinoma (HCC), the dominant type of primary liver cancer (90%), is the fourth leading cause of cancer-related death worldwide [1]. It is estimated that there will be 41,260 new liver cancer cases and 30,520 deaths in 2022 [2]. The incidence of HCC had been increasing in the US since the 1980s, associated with the peak-HCV cohort during 1945–1965 [3]. Recent studies documented a nation-wide decline in incidence during 2015–2018 with racial disparities [4, 5].

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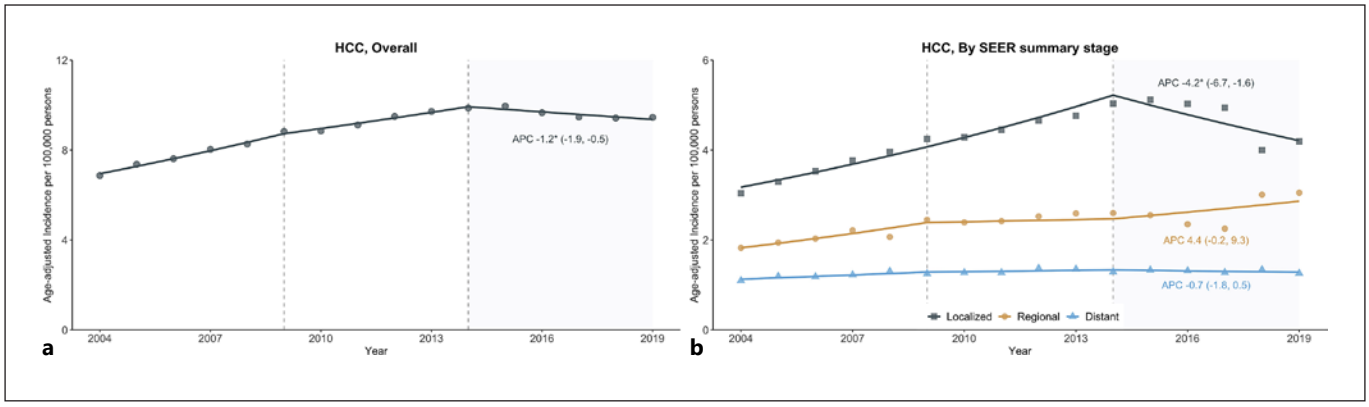

Fig. 1. Age-adjusted incidence trends of HCC (**a**) and stratified by stage (**b**) among the overall population during 2004–2019. APCs during 2014–2019 and their 95% confidence interval have been shown in the graph; asterisks represent that the APC was statistically significantly different from zero. APC, annual percentage change.

The tumor stage is crucial for HCC treatment and survival. Localized liver cancer has a chance of curative surgery with an average 5-year survival of 35%, while distant liver cancer can only benefit from systemic treatment or liver transplant and has a 3% 5-year survival [2]. Nevertheless, trends in the incidence of HCC by Surveillance, Epidemiology, and End Results (SEER) summary stages (localized, regional, and distant) are not well described, which presents challenges for the next precise management. Hence, we sought to determine the national trend in the incidence of HCC by SEER summary stage in the USA during 2004–2019.

Materials and Methods

We used data from SEER 17 registers database to estimate the stage-specific incidence among US adults aged ≥20 years during 2004–2019. HCC was identified by topography code C22.0 and morphology codes 8170/3-8175/3 per the International Classification of Diseases for Oncology (third edition). The incidence (per 100,000 persons) was age adjusted to 2000 US standard population and adjusted to reporting delay. Stage-stratified incidence trends (localized, regional, and distant) were quantified as an annual percentage change (APC) estimated by fitting joinpoint regression models and stratified by sex, age, race/ethnicity, rural-urban continuum, median household income, SEER registry, pretreatment alpha fetoprotein (AFP) level, and fibrosis score. The incidence trend was separated into three periods (2004–2009, 2009–2014, and 2014–2019) according to the joinpoints of the overall trend (all stages combined), and the average APCs were calculated for each period. We also estimated the trend of liver cholangiocarcinoma and combined HCC and cholangiocarcinoma in 2014–2019 to provide more information. We conducted two sensitivity analyses. We excluded the registers with significantly increasing incidence trends in HCC with unknown stages to determine the impact of inaccurate staging. Additionally, we used the SEER 22 register database, which represents approximately 47.9% of the US population, to estimate the stage-specific incidence. See Supplementary for details.

Analyses were conducted using the SEER*Stat version 8.4.0 (National Cancer Institute) and the Joinpoint Regression Program (National Cancer Institute) version 4.9.1.0. All p values were two-sided, and statistical significance was claimed when it was less than 0.05 for the overall population. The comparison between APCs during 2014–2019 was conducted among those subgroups with significant APCs, where multiple test correction was applied.

Results

Totally, 93,910 HCC cases were recorded, including 45,287 (48.2%) localized, 25,473 (27.1%) regional, 13,339 (27.1%) distant, and 9,811 (10.4%) unstaged cases. Overall, the incidence of HCC increased from 2004 through 2014 and then significantly decreased from 2014 through 2019 (APC −1.2% [95% CI, −1.9 to −0.5%], shown in Fig. 1a). The same pattern was also found for localized HCC, significantly decreased with an APC of −4.7% (95% CI, −7.5 to −1.8%) in 2014–2019 after an increase. By contrast, the incidence of regional HCC fluctuated largely during 2014 (APC, 4.4% [95% CI, −0.2% to 9.3%]) and increased in 2017–2019, while a plateau in incidence of distant HCC (APC −0.7% [95% CI, −1.8% to 0.5%]) was observed during 2014–2019 after a substantial climb in 2004–2014 (shown in Fig. 1b).

Stratified analyses showed that the incidence patterns of localized HCC steadily elevated until 2014, followed by a significant decrease or leveling off among a vast majority of

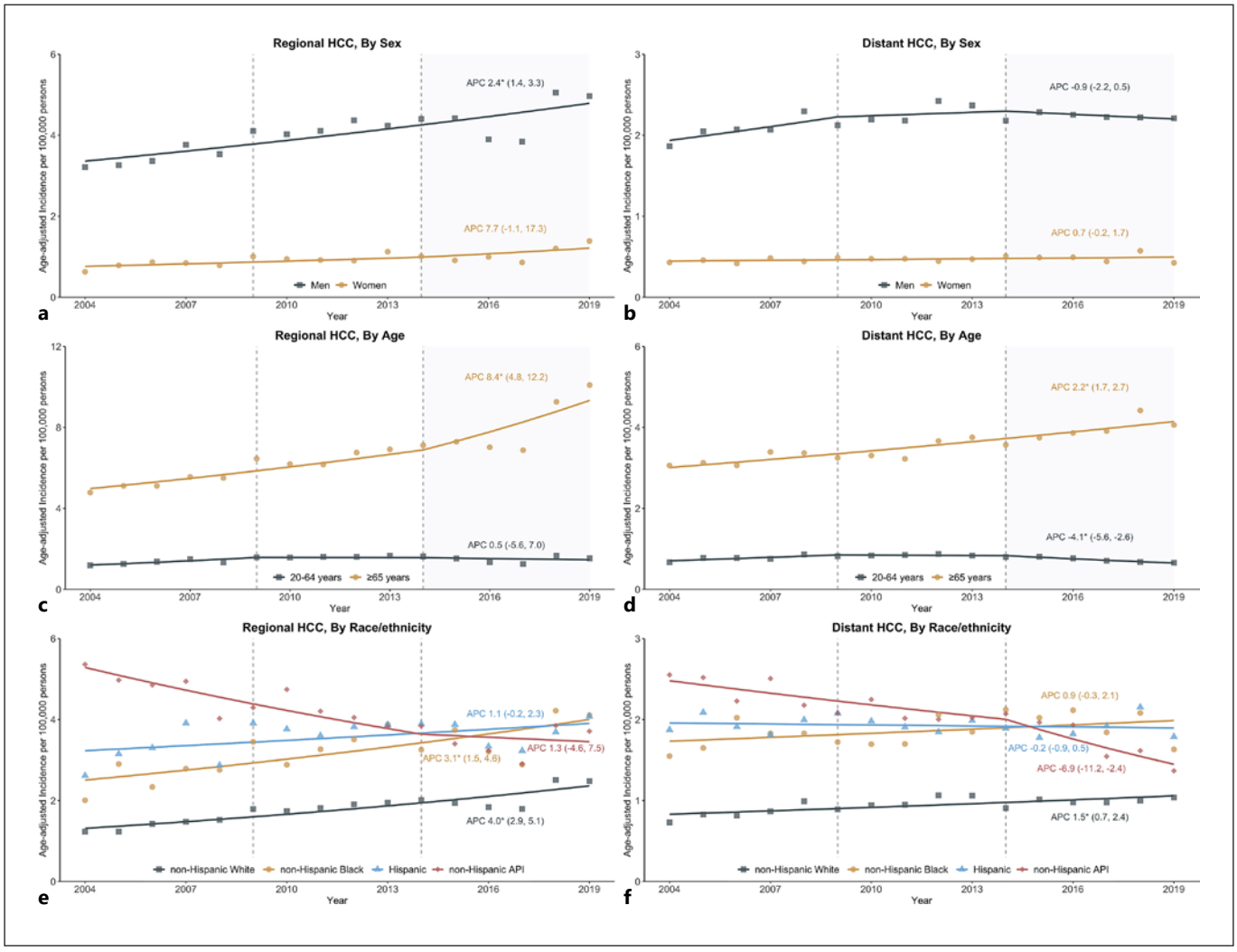

Fig. 2. Age-adjusted incidence trends of regional and distant HCC by sex (**a**–**b**), age (**c**–**d**), and race and ethnicity (**e**–**f**) during 2004–2019. APCs during 2014–2019 and their 95% confidence interval have been shown in the graph; asterisks represent that the APC was statistically significantly different from zero. APC, annual percentage change; API, Asian/Pacific Islander.

subgroups (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000528374). However, incidence patterns of regional and distant HCC did not differ by sex but by age and race/ethnicity (shown in Fig. 2a–f). From 2014 to 2019, the incidence among individuals aged ≥65 years significantly increased with an APC of 8.4% (95% CI, 4.8–12.2%) for regional HCC and an APC of 2.2% (95% CI, 1.7–2.7%) for distant HCC but not among individuals aged 20–64 years (APCs, for regional HCC, 0.5% [95% CI, −5.6% to 7.0%] and for distant HCC, −4.1% [95% CI, −5.6 to −2.6%]). For regional HCC, the incidence rate among non-Hispanic white and non-Hispanic black significantly increased with an equal trend (APCs 4.0% [95% CI, 2.9–5.1%] and 3.1% [95% CI, 1.5–4.6%], respectively, P for interaction = 0.35), while it plateaued among Hispanic and non-Hispanic API individuals. Meanwhile, significant increases in the incidence rate for distant HCC were observed only among non-Hispanic white individuals (APC 1.5% [95% CI, 0.7–2.4%]). The incidence patterns by urbanicity, socioeconomic status, and geography were shown in online supplementary Tables 1–3. Sensitivity analysis shows the robustness of our findings (online suppl. eTable 4). Stratified analyses by pretreatment AFP level and fibrosis score were shown in online supplementary Table 5,

while the trends of liver cholangiocarcinoma and combined HCC and cholangiocarcinoma were presented in online supplementary Table 6.

Discussion

Collectively, we found that the incidence rate of localized HCC was no longer increasing, while the plateau in the incidence of regional and distant HCC was primarily related to the increasing incidence rates among the elderly and non-Hispanic white. Recent studies have well documented the decrease in HCC incidence during 2015–2018 [3, 4], which was parallel with our result about localized HCC. There are improvements in HCV prevention and treatments, such as avoiding HCV transmission through contaminated blood, interferon therapy, and direct-acting antivirals for HCV infection [6]. Additionally, the shifting of etiology, from HCV infection to non-alcoholic fatty liver disease (NAFLD), may also contribute to the incidence pattern. The incidence of NAFLD-related liver cancer has increased when virus-driven HCC has declined. However, up to 20–30% of NAFLD-related HCC developed without the background of cirrhosis, which posed challenges for the early diagnosis of HCC [7]. This should raise alarm. However, the disparities in stage-specific incidence trends may reflect the inequalities in access to primary health care among different race/ethnicity and age groups, for example, in screening or early diagnosis of HCC, even HCV infection and management of liver diseases, such as NAFLD and liver cirrhosis. Also, race-based disproportional exposure or difference in susceptibility to known and unknown risk factors may also contribute to the disparities. The underlying difference in risk factors and pathogenesis of HCC among different race/ethnicity groups should be investigated.

A limitation of this study is the lack of information on extensive HCC risk factors or biomarkers, and investigations for identifying the risk determinants remain to be conducted in other large population-based cohorts. In summary, the rising incidence rates for regional and distant HCC indicated that more efforts of disease prevention and health promotion are still in great demand for the susceptible population.

Statement of Ethics Statement

The study was exempted from ethical review because the data were deidentified and publicly available.

Conflict of Interest Statement

The authors disclose no competing interests.

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Author Contributions

Haoting Shi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Haoting Shi: concept design; drafted the manuscript; acquired, analyzed, or interpreted the data; and statistical analysis. Jingxuan Huang and Shi Zhao: statistical analysis and acquired, analyzed, or interpreted the data. Yiwen Jin: acquired, analyzed, or interpreted the data. Rong Cai: obtained funding and supervision. Jinjun Ran: concept design, obtained funding, and supervision. All authors contributed to the administrative, technical, or material support and have approved the final draft submitted.

Data Availability Statements

All data used in this work were publicly available, shown at https://seer.cancer.gov/. Further inquiries can be directed to the corresponding author.

References

1 Hepatocellular carcinoma. Nat Rev Dis Primers. 2021;7:7.
2 Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics. CA Cancer J Clin. 2022 Jan;72(1):7–33.
3 Kulik L, El-Serag HB. Epidemiology and management of hepatocellular carcinoma. Gastroenterology. 2019;156(2):477–91.e1.
4 Alvarez CS, Petrick JL, Parisi D, McMahon BJ, Graubard BI, McGlynn KA. Racial/ethnic disparities in hepatocellular carcinoma incidence and mortality rates in the United States, 1992–2018. Hepatology. 2022;76(3):589–98.
5 Shiels MS, O'Brien TR. Declining US hepatocellular carcinoma rates. Clin Gastroenterol Hepatol. 2022;20(2):e330–4.
6 Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018;391(10127):1301–14.
7 Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. Lancet. 2022 Oct 15;400(10360):1345–62.