Incidence of Hepatocellular Carcinoma Among Older Americans Attributable to Hepatitis C and Hepatitis B: 2001 Through 2013

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BACKGROUND: In the United States, incidence and mortality rates of hepatocellular carcinoma (HCC) are increasing in older individuals. Chronic infection with hepatitis C virus (HCV) and hepatitis B virus (HBV) are important causes of HCC; however, the contribution of viral hepatitis to recent trends in HCC incidence among older Americans is unclear. METHODS: Data from the Surveillance, Epidemiology, and End Results–Medicare linkage (SEER-Medicare) for the years 2001 through 2013 were used to identify HCC cases among individuals aged ≥66 years and Medicare files were used to assess the HCV and HBV status of these HCC cases. Age-standardized incidence rates of HCV-attributable, HBV-attributable, and HCV/HBV-unrelated HCC were estimated overall and by age group, sex, and race/ethnicity. The authors also calculated annual percent changes (APCs) in HCC incidence. RESULTS: Between 2001 and 2013, a total of 15,300 HCC cases occurred in this population. Overall HCC rates increased 43% from 16.3 to 23.3 per 100,000 population (APC, 3.40% per year), whereas HCV-attributable HCC rates nearly doubled from 4.2 to 8.2 per 100,000 population (APC, 5.62% per year). HCC rates increased more slowly for HBV-attributable HCC (1.3 to 1.8 per 100,000 population; APC, 3.17% per year) and HCV/HBV-unrelated HCC (11.3 to 14.1 per 100,000 population; APC, 2.35% per year). The percentage of HCC cases with evidence of HCV infection increased from 25.7% in 2001 through 2004 to 32.3% in 2011 through 2013, whereas the percentage with HBV remained stable at 8%. In 2013, higher rates for both HCV-attributable and HBV-attributable HCC were noted among individuals aged 66 to 75 years, men, and individuals of Asian ancestry. CONCLUSIONS: Among Americans aged ≥66 years, HCC rates increased rapidly between 2001 and 2013. Although HCV-attributable cases contributed substantially to this increase, rates of HBV-attributable and HCV/HBV-unrelated HCC also rose during this period. Cancer 2019;125:2621-2630. © 2019 American Cancer Society.

KEYWORDS: epidemiology, hepatitis, liver cancer, Medicare, trends.

INTRODUCTION
In the United States, liver cancer incidence and mortality rates increased substantially during 2003 through 2012. Nearly 75% of all liver cancer diagnoses are hepatocellular carcinomas (HCCs). During 2000 through 2010, temporal trends in HCC rates diverged by age group, with stable rates noted among individuals aged 35 to 49 years, but strong increases observed among those aged 50 to 64 years and ≥65 years. If current trends continue, it has been projected that HCC rates among individuals aged ≥65 years in the United States will increase 5.9% per year through 2030.

Chronic infection with hepatitis C virus (HCV) is an important driver of these rising liver cancer rates. HCV is associated with a 60-fold increase in HCC risk, and caused an estimated 31% of US liver cancer cases in 2015. Although available data do not support a precise determination of HCV prevalence in the United States, a recent estimate is that 2.5 to 4.7 million US residents have chronic HCV. Because HCV infection rates were high in the 1960s through the 1980s, and HCC risk rises with an increasing duration of HCV infection, rates of liver cancer due to HCV are rising over time.

Chronic infection with hepatitis B virus (HBV) is another important cause of liver cancer worldwide, increasing the risk 20-fold and causing an estimated 9% of cases in the United States. In 2012, an estimated 850,000 individuals were living with chronic HBV in the United States, with the highest prevalence reported among foreign-born Asian individuals. In addition to HCV and HBV, diabetes, obesity, metabolic syndrome, and excessive alcohol consumption also are associated with liver cancer, and also may have contributed to rising rates over time.

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We acknowledge the statistical support of Ms. Winnie Ricker and Mr. Nathan Appel (IMS Inc).

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.32129, Received: December 19, 2018; Revised: March 4, 2019; Accepted: March 16, 2019, Published online April 12, 2019 in Wiley Online Library (wileyonlinelibrary.com)
In the current study, we assessed HCC rates with data from the Surveillance, Epidemiology, and End Results (SEER)—Medicare database among Americans aged ≥66 years, an age range that included 44% of US HCC cases in 2015. We assessed trends in HCC rates, estimated HCV and HBV prevalence among HCC cases, and disaggregated HCC time trends by viral hepatitis status, sex, age group, and race/ethnicity during 2001 through 2013.

MATERIALS AND METHODS

Study Population

The current analysis was performed using data from the SEER-Medicare data set, a linkage of 2 population-based data sources: the SEER cancer registries and a database of US Medicare enrollees. In the United States, Medicare is the federally funded health insurance program that primarily covers individuals aged ≥65 years. SEER is a set of cancer registries funded by the National Cancer Institute, and includes information regarding tumor characteristics, patient demographics, and survival. The SEER-Medicare database includes Medicare claims during 1991 through 2014 for all cancer cases diagnosed between 1991 and 2013 as well as a 5% random sample of all Medicare enrollees from SEER areas.

HCC Cases

Invasive HCC cases that were diagnosed as a first primary cancer during 2001 through 2013 were identified by cancer registries and defined based on International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) site (C220) and histology (8170-8175) codes. The analysis was restricted to cases diagnosed among individuals aged 66 to 99 years at the time of diagnosis who had ≥12 months of Medicare coverage, including both Part A (inpatient) and Part B (health care provider) coverage outside of a health maintenance organization, prior to cancer diagnosis and at least 1 Medicare claim.

We ascertained infection with HCV or HBV from Medicare files for the period from 60 months before until 12 months after cancer diagnosis based on these International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes: HCV (including codes for acute HCV given the high probability of progression to chronic HCV): 070.41, 070.44, 070.51, 070.54, 070.7, 070.70, 070.71, or V02.62; and HBV (limited to codes for chronic HBV): 070.22, 070.23, 070.32, 070.33, 070.42, 070.52, or V02.61 (see Supporting Table 1). A positive HCV or HBV diagnosis required 1 inpatient claim or 2 physician or outpatient claims filed at least 30 days apart. No HCC cases were classified as HCV-infected or HBV-infected cases based on diagnoses recorded on or after the date of death. Claims related to the following conditions also were ascertained: diabetes mellitus (codes 250.0-250.9), alcohol-related liver disorders (codes 571.0, 571.1, 571.2, 571.3, and V11.3, or 571.6 in the presence of codes 291, 303, or 305.0), and rare genetic disorders (ie, tyrosinemia [code 270.2], alpha-1 antitrypsin deficiency [code 273.4], hemochromatosis [code 275.0], Wilson disease [code 275.1], and porphyrias [code 277.1]).

Five Percent Random Population Sample

A 5% random sample of all Medicare recipients (those with and without a cancer diagnosis) was ascertained for each calendar year, restricted to those enrollees who on July 1 of that year were aged 66 to 99 years; had ≥12 months of Medicare coverage, including both Part A and Part B coverage outside of a health maintenance organization; and had at least 1 claim.

Statistical Analysis

The percentages of HCC cases that were HCV-attributable, HBV-attributable, and both HCV-attributable and HBV-attributable were assessed by calendar period of HCC diagnosis (2001-2004, 2005-2007, 2008-2010, and 2011-2013), sex, age at diagnosis (66-75 years, 76-85 years, and 86-99 years), and race/ethnicity (non-Hispanic white [ie, white], non-Hispanic black [ie, black], Asian, Hispanic, or other/unknown). We considered cases with evidence of HBV or HCV infection as attributable to those infections based on prior analyses demonstrating that the prevalence of these viruses among HCC cases is nearly identical to the percentage of HCC cases caused by these viruses.

HCC incidence rates were estimated by dividing the number of HCC diagnoses by person-time from the 5% random sample, which was multiplied by 20 to represent the full Medicare population. Age-standardized rates were based on the 2000 US population age distribution. Temporal trends were assessed separately for HCV-attributable, HBV-attributable, and HCV/HBV-unrelated HCC cases, and stratified by sex, age group, and race/ethnicity during 2001 through 2013. Joinpoint regression was used to identify statistically significant changes in the slope of time trends in incidence rates (based on single-year data) and to estimate annual
percent changes (APCs) in rates in each group.\textsuperscript{15} For display purposes, we aggregated rates across 2-year or 3-year periods in figures.

To assess the extent to which SEER-Medicare rates represent rates from the full SEER population, HCC rates overall were compared with those for the full SEER population (individuals aged \( \geq 66 \) years) of included registries (ie, not restricted to eligible Medicare recipients).\textsuperscript{12} Furthermore, trends by HCV and HBV status were estimated requiring only one physician or outpatient claim for a diagnosis of HCV or HBV infection.

**RESULTS**

Between 2001 and 2013, a total of 15,300 cases of invasive HCC were diagnosed among eligible Medicare recipients (Table 1). Patients with HCC were more likely to be male than female, although a larger percentage of HCV-attributable cases occurred among women (39%) compared with HBV-attributable cases (29%) and HCV/HBV-unrelated cases (31%). The age distribution of HCV-attributable and HBV-attributable HCC cases was similar; in contrast, a smaller percentage of patients with HCV/HBV-unrelated HCC were aged 66 to 75 years, and a larger percentage of patients were aged \( \geq 86 \) years. The largest percentage of HCV-attributable (54%) and HCV/HBV-unrelated (76%) HCC cases occurred among white individuals, whereas the largest percentage of HBV-attributable HCC cases occurred among Asian individuals (53%). Claims for diabetes were most common among HCV/HBV-unrelated HCC cases (59%), and claims for alcohol-related liver disorders were most common among HCV-attributable cases (31%). HCC-related genetic disorders (2.7%) were uncommon across case groups.

The overall HCV prevalence among HCC cases was 29.5% (4518 cases) and that of HBV was 8.2% (1253 cases): 542 of these cases (3.5%) occurred among individuals who were infected with both HCV and HBV. HCV prevalence in HCC cases increased from 25.7% in 2001 through 2004 to 32.3% in 2011 through 2013, whereas HBV prevalence remained stable at 8% (Fig. 1A). These prevalence estimates are not mutually exclusive: individuals infected with both HBV and HCV were included in the prevalence estimates for both viruses. The prevalence of coinfection was 3.9% in 2001 through 2004 and 3.5% in 2011 through 2013. HCV prevalence among patients
with HCC increased in both men and women, with a higher HCV prevalence observed among women compared with men (36.7% vs 30.3% in 2011-2013). HCV prevalence among patients with HCC increased over time among those aged 66 to 75 years (32.2% in 2001-2004 vs 39.9% in 2011-2013) and patients aged 76 to 85 years (20.1% in 2001-2004 vs 25.9% in 2011-2013), but declined in the most recent period among individuals aged ≥86 years (17.5% in 2008-2010 and 14.4% in 2011-2013) (Fig. 1B). Temporal changes in HCV and HBV prevalence differed by race/ethnicity. HCV prevalence increased across time periods among white (20.4% in 2001-2004 and 26.7% in 2011-2013), black (40.3% in 2001-2004 vs 63.1% in 2011-2013), and Hispanic (26.0% in 2001-2004 vs 30.3% in 2011-2013) patients with HCC, and remained relatively stable among Asian

Figure 1. Prevalence of hepatitis C virus (HCV) and hepatitis B virus (HBV) infection among patients with hepatocellular carcinoma (HCC) in the Surveillance, Epidemiology, and End Results (SEER)–Medicare database from 2001 through 2013 shown by (A) sex, (B) age, and (C) race/ethnicity. Black bars indicate the percentage of patients with HCV; gray bars, percentage of patients with HBV; checkered bars, percentage of patients with HCV/ HBV coinfection.
patients (40.9% in 2001-2004 vs 41.1% in 2011-2013) and those of other or unknown race/ethnicity (31.7% in 2001-2004 vs 33.9% in 2011-2013) (Fig. 1C). There were no notable time trends in HBV prevalence noted among HCC cases across age and racial/ethnic groups; however, HBV prevalence among HCC cases was far higher among Asian patients (34.9% in 2011-2013) and those of other or unknown race/ethnicities (21.1%) compared with among white (2.7%), black (4.9%), or Hispanic (5.4%) patients with HCC.

Age-standardized rates of HCC increased from 16.3 per 100,000 population in 2001 to 23.3 per 100,000 population in 2013 (APC, 3.40% per year) (Fig. 2) (Table 2). Although the annual increase in incidence rates was most rapid for HCV-attributable HCC (APC, 5.62% per year), rates of HBV-attributable HCC (APC, 3.17% per year) and HCV/HBV-unrelated HCC (APC, 2.35% per year) also increased significantly over time. The absolute increase in age-standardized HCC rates between 2001 and 2013 was largest for HCV-attributable cases (4.01 per 100,000 population) and HCV/HBV-unrelated cases (2.80 per 100,000 population), and smaller for HBV-related cases (0.46 per 100,000 population).

HCC rates increased 3.16% per year among men and 3.14% per year among women; however, HCC rates were much higher among men compared with women in 2013 (36.6 vs 13.4 per 100,000 population in 2013) (Table 2) (Fig. 2). HCC rates increased across age groups (ages 66-75 years: 3.20% per year; ages 76-85 years: 3.86% per year; and age ≥ 86 years: 2.76% per year), and were highest among individuals aged 66 to 75 years. Rates of HCV/HBV-unrelated HCC increased significantly in each age group. HCV-attributable HCC rates increased significantly among those aged 66 to 75 years and 76 to 85 years, and HBV-attributable HCC increased significantly over time among individuals aged 76 to 85 years, although few cases occurred in individuals aged ≥86 years.

Age-standardized HCC rates varied substantially by race/ethnicity: in 2013, rates were nearly 3 times higher among Asian individuals (54.8 per 100,000 population) than among white individuals (19.7 per 100,000 population) (Table 2) (Fig. 2). Overall HCC rates increased significantly over time among white (APC, 3.69% per year), black (APC, 4.21% per year), and Hispanic (APC, 3.62% per year) individuals, but not among Asian individuals or those of other or unknown race/ethnicities. In 2013, Asians also had the highest rates of HCV-attributable (23.7 per 100,000 population) and HBV-attributable (19.5 per 100,000 population) HCC, whereas rates of HCV/HBV-unrelated HCC were highest among Hispanic individuals (24.9 per 100,000 population). HCV-attributable HCC rates increased significantly among white, black, and Hispanic individuals, whereas HBV-attributable HCC rates and HCV/HBV-unrelated HCC rates increased significantly only among white individuals. Rates of HCV-attributable and HBV-attributable HCC were stable among Asian individuals.

In the full SEER population, approximately 41% of all patients with HCC were aged ≥66 years during 2001 through 2013 (see Supporting Fig. 1). Comparing HCC rates in the SEER-Medicare database with those in the full SEER population, the SEER-Medicare rates were 10% to 14% lower, although the APCs were consistent (SEER-Medicare: 3.40% per year; and full SEER population: 3.29% per year) (see Supporting Fig. 2).

In a sensitivity analysis requiring only 1 inpatient, physician, or outpatient claim for a diagnosis of HCV or HBV, the HCV prevalence was 35.6% (5440 claims) and the HBV prevalence was 11.4% (1744 claims). Increases in prevalence were driven largely by an increase in HCV/HBV-coinfected HCC cases (1102 cases). In addition, APCs were consistent with those estimated in the primary analysis (HCV-attributable: 5.54% per year; HBV-attributable: 3.48% per year; and HCV/HBV-unrelated: 2.15% per year).

**DISCUSSION**

During 2001 through 2013, overall HCC rates among Americans of Medicare age increased by 3.4% per year, with the percentage of HCC cases attributable to HCV infection increasing from 26% to 32%. The rates of HCV-attributable HCC increased strongly overall (5.6% per year) and in the majority of demographic subgroups, contributing substantially to the increase in total HCC rates over time. Although rates of HBV-attributable HCC increased significantly over time (3.2% per year), absolute rates remained low. Rates of HCC unrelated to viral hepatitis also increased over time (2.4% per year), indicating that HCC driven by other causes unrelated to viral hepatitis also has contributed substantially to increasing overall trends.

Chronic infection with either HCV or HBV can lead to inflammation of the liver with resulting development of fibrosis and cirrhosis in some infected individuals. This process results in liver cells that are abnormal and at substantial risk of progressing to cancer. From 2011 through 2013, we estimated that approximately
Figure 2. Age-standardized hepatocellular carcinoma (HCC) incidence rates in the Surveillance, Epidemiology, and End Results (SEER)–Medicare database by sex, age, and race/ethnicity for 2001 through 2013. Circles indicate overall HCC rates; triangles, hepatitis C virus (HCV)/hepatitis B virus (HBV)-unrelated HCC rates; diamonds, HCV-attributable HCC rates; squares, HBV-attributable HCC rates. Note that rates of HCV-attributable and HBV-attributable HCC were not mutually exclusive.
## TABLE 2. APCs in Age-Standardized HCC Incidence Rates by HCV and HBV Viral Status in SEER-Medicare, 2001 Through 2013

| Demographic | All HCC Cases | HCV-Attributable HCC Cases | HBV-Attributable HCC Cases | HCV/HBV-Unrelated HCC Cases |
|-------------|---------------|---------------------------|---------------------------|-----------------------------|
|             | 2001 Rate     | 2013 Rate                 | APC (95% CI)a              | 2001 Rate                  | 2013 Rate                  | APC (95% CI)a              | 2001 Rate                  | 2013 Rate                  | APC (95% CI)a              | 2001 Rate                  | 2013 Rate                  | APC (95% CI)a              |
| Total       | 16.3          | 23.3                      | 3.40 (2.60 to 4.01)        | 4.19                       | 8.20                       | 5.62 (4.50 to 6.76)        | 1.32                       | 1.78                       | 3.17 (1.66 to 4.71)        | 11.3                       | 14.1                       | 2.35 (1.55 to 3.16)        |
| Sex         |               |                           |                           |                            |                            |                           |                            |                            |                           |                            |                            |                            |
| Male        | 27.7          | 36.6                      | 3.16 (2.50 to 3.82)        | 6.34                       | 11.9                       | 6.11 (4.55 to 7.68)        | 2.00                       | 2.93                       | 2.86 (1.00 to 4.76)        | 20.1                       | 23.2                       | 2.05 (1.09 to 3.01)        |
| Female      | 8.77          | 13.4                      | 3.14 (2.19 to 4.11)        | 2.69                       | 5.26                       | 4.37 (2.82 to 5.95)        | 0.82                       | 0.91                       | 3.39 (1.38 to 5.45)        | 5.68                       | 7.55                       | 2.18 (1.26 to 3.10)        |
| Age group, y|               |                           |                           |                            |                            |                           |                            |                            |                           |                            |                            |                            |
| 66-75       | 9.92          | 13.6                      | 3.20 (2.42 to 3.99)        | 3.11                       | 5.66                       | 5.43 (4.09 to 6.78)        | 1.16                       | 1.13                       | 1.48 (-0.46 to 3.46)       | 6.12                       | 7.37                       | 1.96 (0.84 to 3.09)        |
| 76-85       | 5.26          | 8.44                      | 3.86 (3.17 to 4.55)        | 0.93                       | 2.38                       | 6.24 (4.22 to 8.31)        | b                         | 0.61                       | 6.54 (2.95 to 10.3)        | 4.25                       | 5.70                       | 2.90 (2.22 to 3.59)        |
| ≥86         | 1.11          | 1.25                      | 2.76 (0.91 to 4.65)        | b                         | 0.16                       | 4.45 (-0.56 to 9.72)       | b                         | b                         | NE                         | 0.96                       | 1.05                       | 2.21 (0.39 to 4.06)        |
| Race/ethnicity |            |                           |                           |                            |                            |                           |                            |                            |                           |                            |                            |                            |
| White       | 12.8          | 19.7                      | 3.69 (3.16 to 4.22)        | 2.58                       | 5.80                       | 6.30 (5.09 to 7.53)        | 0.52                       | 0.58                       | 2.14 (0.01 to 4.31)        | 9.98                       | 13.6                       | 2.92 (2.18 to 3.66)        |
| Black       | 21.8          | 28.1                      | 4.21 (1.91 to 6.96)        | 8.90                       | 19.4                       | 9.04 (6.30 to 11.8)        | b                         | b                         | 3.73 (-3.44 to 11.4)       | 12.4                       | 8.04                       | -0.87 (-4.00 to 2.33)      |
| Asian       | 62.2          | 54.8                      | -0.35 (-1.94 to 1.15)      | 25.1                       | 23.7                       | -0.91 (-2.17 to 0.37)      | b                         | b                         | 1.06 (-1.21 to 3.38)       | 26.0                       | 20.2                       | -1.52 (-3.48 to 0.48)      |
| Hispanic    | 32.2          | 39.1                      | 3.62 (0.99 to 6.31)        | 16.9                       | 19.5                       | 6.76 (2.05 to 16.4)        | b                         | b                         | 1.96 (-2.05 to 5.92)       | 25.2                       | 24.9                       | 2.37 (-0.46 to 5.28)       |
| Other/unknown | 29.5          | 34.6                      | 0.05 (-2.47 to 2.64)       | 14.3                       | 14.3                       | 0.71 (-3.24 to 4.95)       | b                         | 4.84                       | 0.48 (-3.84 to 5.01)       | 18.6                       | 20.7                       | -0.99 (-3.80 to 1.90)      |

Abbreviations: APC, annual percent change; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NE, not evaluable; SEER, Surveillance, Epidemiology, and End Results.

aStatistically significant APCs are denoted in bold text.

bIncidence rates with <11 cases were suppressed.

cAPCs are shown for the entire period between 2001 and 2013. However, a statistically significant joinpoint for APC was detected for HCV-attributable HCC rates among patients aged ≥86 years (2001-2004: -17.6% per year; 2004-2009: 30.1% per year; and 2008-2013: -7.71% per year) and for HBV-attributable HCC rates among females (2001-2004: -8.53% per year; 2004-2009: 11.0% per year; and 2009-2013: -2.73% per year).
32% of HCC cases were HCV-attributable and 8% were HBV-attributable, similar to estimates published by the Global Burden of Disease group for the United States in 2015 (31% and 9%, respectively).\textsuperscript{5}

In the United States, HCV incidence was high in the 1960s through 1980s, most likely spread through injection drug use and the receipt of infected blood products prior to HCV screening of the blood supply.\textsuperscript{16} As a result, Americans born between 1945 and 1965 (ie, “baby boomers”) have a higher prevalence of chronic HCV infection compared with other birth cohorts.\textsuperscript{7} Prolonged chronic HCV infection in this aging birth cohort has resulted in particularly high rates of liver cancer. Only the oldest baby boomers (ie, 1945-1947 birth cohorts) are included in the current study; therefore, rising HCC rates presented herein largely reflect earlier birth cohorts.

Given the higher HCV prevalence noted among baby boomers, we might anticipate that rates of HCV-associated HCC in the Medicare population will continue to increase in coming years. However, that trend might be blunted by the availability of more effective therapy for chronic HCV.\textsuperscript{17} Until recently, treatment consisted of pegylated interferon-\( \alpha \) plus ribavirin, which produced a virological cure (“sustained virological response”) in only approximately 50% of patients overall and an even lower percentage of individuals with advanced fibrosis or cirrhosis (ie, those at highest risk of HCC). In 2011, first-generation direct antiviral agents for HCV were introduced and, in 2014, highly effective direct antiviral agent regimens pushed sustained virological response rates to >90%. The successful treatment of chronic HCV markedly reduces the risk of developing HCC\textsuperscript{18}; however, many infected individuals are unaware that they have chronic HCV.\textsuperscript{19,20} Future rates of HCV-associated HCC in the Medicare population will be affected by both the higher HCV prevalence among baby boomers and success in identifying and treating chronic HCV in this population.

The prevalence of chronic HBV in the United States was low (0.3% in 2007-2012) and did not change significantly from 1999 through 2012.\textsuperscript{21} Although current therapies for patients with chronic HBV generally are not curative, in observational studies, antiviral therapy in patients with immune-active chronic HBV has been found to reduce the risk of HCC by approximately 50%.\textsuperscript{22-24} Current initial therapy recommendations for patients with chronic HBV include pegylated interferon-\( \alpha \), entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide.\textsuperscript{23} However, even with effective treatment, HCC still may develop.\textsuperscript{25} Efforts currently are underway to develop new antiviral agents for HBV infection.\textsuperscript{22,24} It is interesting to note that although universal vaccination against HBV infection is recommended in the United States,\textsuperscript{26,27} it cannot impact HBV-attributable HCC occurring among individuals who already are chronic HBV carriers.

Although prior studies have reported on rising liver cancer rates,\textsuperscript{1,2} the current study has presented rates disaggregated based on the HBV and HCV status of cases, thereby providing insight into the etiologic drivers of the rising rates. The rate of HCV-attributable HCC nearly doubled during 2001 through 2013, increasing by 4% to 9% per year among men and women; those aged 66 to 85 years; and white, black, and Hispanic individuals. In contrast, HCV-attributable HCC rates were stable among Asian individuals and those of other or unknown race/ethnicity. Although rates of HBV-attributable HCC also increased significantly, the APCs generally were lower than those for HCV-attributable HCC, and HCV-attributable HCC rates were 3.5 times higher than HBV-attributable HCC rates in 2013. It is interesting to note that HBV-attributable HCC rates among Asians, the group with the highest rates, remained stable over time.

HCC rates unrelated to HCV or HBV infection increased overall, among both men and women and in all age groups. These increases appear to be more notable among white and Hispanic populations. Nonviral causes of HCC that may be contributing to rising HCC rates include alcohol consumption, obesity, diabetes, and nonalcoholic fatty liver disease (NAFLD), which is the hepatic manifestation of metabolic syndrome.\textsuperscript{10} The prevalence of alcohol abuse in the United States increased among all age groups between 2001 and 2002 and 2012 and 2013\textsuperscript{28} and there have been steady increases noted in the prevalence of obesity (37.0% of adults aged ≥60 years in 2011-2014), type II diabetes (25.2% of individuals aged ≥65 years in 2015), and NAFLD (31% of adults aged 20-74 years in 2011-2012).\textsuperscript{29,32} Associations between these risk factors and liver cancer are much weaker than those noted for HCV and HBV, and therefore the presence of one of these conditions among HCC cases cannot be concluded as causal.\textsuperscript{33} Nonetheless, alcohol abuse, obesity, diabetes, and NAFLD are far more common in the United States than chronic viral hepatitis. It should be noted that these nonviral risk factors may act synergistically with HCV and HBV infection,\textsuperscript{16} thereby further contributing to HCC cases attributable to viral hepatitis in this analysis.
The main strength of the current study was the use of linked data sets to distinguish between HCV-attributable, HBV-attributable, and HCV/HBV-unrelated HCC cases. With the exception of a single older study that focused on HCC rates in the 1990s, the current study is the only one to our knowledge that has estimated HCC incidence trends by viral hepatitis status. Although a recent study reported HCC mortality trends by viral status, this study relied on hepatitis information reported on death certificates, which is known to be vastly underreported: a prior study estimated that only 31% of all liver cancer deaths reported among individuals with chronic HCV infection listed HCV on the death certificate. In addition, the SEER-Medicare database is a large, nationally representative resource, and we have shown that HCC trends based on Medicare recipients closely represent rates from the same SEER cancer registries.

The main limitation of the current study was the use of medical claims, which do not capture HBV or HCV status with complete sensitivity or specificity and do not capture infection duration. To enhance specificity, we classified HCC cases as positive for HBV or HCV based on 1 inpatient claim or 2 physician or outpatient claims filed at least 30 days apart. An additional limitation of the current study was the lack of information regarding body mass index, cigarette smoking, and average alcohol consumption. We had limited power to detect significant changes in rates in some groups due to the small number of HCC cases. Finally, the age range of this analysis was restricted to Americans aged ≥66 years, and thus it did not capture the birth cohort with the highest HCV prevalence in the United States. The prevalence of HCV among patients with HCC is likely higher among Americans who were aged in their 40s and 50s during the study period, and HCV-attributable HCC rates for this birth cohort likely increased more rapidly than reported herein. However, it is important to note that approximately 41% of patients with HCC diagnosed in SEER during 2001 through 2013 were aged ≥66 years and therefore the Medicare-aged population captures a substantial percentage of HCC cases in the United States.

Among Americans aged ≥66 years, HCC rates increased rapidly between 2001 and 2013. HCV-attributable HCCs contributed substantially to this observed increase, with a smaller contribution observed by HBV-attributable HCCs. Interventions to treat and prevent viral hepatitis infections will affect future HCC rates among Medicare-aged Americans. Non-viral-related HCC cases will likely continue to increase in the United States, largely due to sustained increases in obesity and metabolic syndrome–related conditions. Interventions focused on modifiable risk factors for HCC, such as promoting a healthy body weight and reducing alcohol intake and cigarette smoking, also could have an impact on future HCC rates.

FUNDING SUPPORT

Funded by the Intramural Research Program of the National Cancer Institute. The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN262201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention’s National Program of Cancer Registries under agreement U58DP003862-01 awarded to the California Department of Public Health. The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended nor should be inferred. The authors acknowledge the efforts of the National Cancer Institute; the Office of Research, Development and Information, Centers for Medicare and Medicaid Services; Information Management Services (IMS) Inc; and the Surveillance, Epidemiology, and End Results (SEER) program tumor registries in the creation of the SEER-Medicare database.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Study conception and design: Meredith S. Shiels, Eric A. Engels, Elizabeth L. Yanik, and Thomas R. O’Brien. Data analysis: Meredith S. Shiels and Ruth M. Pfeiffer. Data interpretation and article preparation: Meredith S. Shiels, Eric A. Engels, Elizabeth L. Yanik, Katherine A. McGlynn, Ruth M. Pfeiffer, and Thomas R. O’Brien.

REFERENCES

1. Ryerson AB, Eheman CR, Altekruse SF, et al. Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. Cancer. 2016;122:1312-1337.
2. Altekruse SF, Henley SJ, Cucinelli JE, McGlynn KA. Changing hepatocellular carcinoma incidence and liver cancer mortality rates in the United States. Am J Gastroenterol. 2014;109:542-553.
3. Petrick JL, Kelly SP, Altekruse SF, McGlynn KA, Rosenberg PS. Future of hepatocellular carcinoma incidence in the United States forecast through 2030. J Clin Oncol. 2016;34:1787-1794.
4. Makarova-Rusher OV, Altekruse SF, McNeel TS, et al. Population attributable fractions of risk factors for hepatocellular carcinoma in the United States. Cancer. 2016;122:1757-1765.
5. Global Burden of Disease Liver Cancer Collaboration,Akinyemiju T, Aberra S, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the Global Burden of Disease Study 2015. JAMA Oncol. 2017;3:1683-1691.
6. Edlin BR, Eckhardt BJ, Shu MA, Holmberg SD, Swan T. Toward a more accurate estimate of the prevalence of hepatitis C in the United States. Hepatology. 2015;62:1353-1363.
7. Lazo M, Nwankwo C, Daya NR, et al. Confluence of epidemics of hepatitis C, diabetes, obesity, and chronic kidney disease in the United States population. Clin Gastroenterol Hepatol. 2017;15:1957-1964.e7.

8. Mitchell JK, Lemon SM, McGivern DR. How do persistent infections with hepatitis C virus cause liver cancer? Curr Opin Virol. 2015;14:101-108.

9. US Department of Health and Human Services. Hepatitis B basic information. https://www.hhs.gov/hepatitis/learn-about-viral-hepatitis/hepatitis-b-basics/index.html. Accessed February 5, 2019.

10. McGlynn KA, London WT. The global epidemiology of hepatocellular carcinoma: present and future. Clin Liver Dis. 2015;11:223-243, vii-v.

11. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Med Care. 2002;40(suppl 8):IV-3-18.

12. National Cancer Institute, Surveillance Research Program, Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence-SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov. 2017 Sub (2000-2015) <Katrina/Rita Population Adjustment->Linked To County Attributes-Total US, 1969-2016 Counties. Bethesda, MD: National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Surveillance Systems Branch; 2018.

13. Thomas DL, Seef I.B. Natural history of hepatitis C. Clin Liver Dis. 2005;9:383-398, vi.

14. Welzel TM, Graubard BI, Quraishi S, et al. Population-attributable fractions of risk factors for hepatocellular carcinoma in the United States. Am J Gastroenterol. 2013;108:1314-1321.

15. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for jointpoint regression with applications to cancer rates. Stat Med. 2000;19:335-351.

16. El-Serag HB. Epidemiology of viral hepatitits and hepatocellular carcinoma. Gastroenterology. 2012;142:1264-1273.e1.

17. Carter W, Connelly S, Struble K. Reinventing HCV treatment: past and future perspectives. J Clin Pharmacol. 2017;57:287-296.

18. El-Serag HB, Kanwal F, Richardson P, Kramer J. Risk of hepatocellular carcinoma after sustained virological response in veterans with hepatitis C virus infection. Hepatology. 2016;64:130-137.

19. Holmberg SD, Spradling PR, Moorman AC, Denniston MM. Hepatitis C in the United States. N Engl J Med. 2013;368:1859-1861.

20. Denniston MM, Klevens RM, McQuillan GM, Jiles RB. Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: National Health and Nutrition Examination Survey 2001-2008. Hepatology. 2012;55:1652-1661.

21. Roberts H, Kruszon-Moran D, Ly KN, et al. Prevalence of chronic hepatitis B virus (HBV) infection in U.S. households: National Health and Nutrition Examination Survey (NHANES), 1988-2012. Hepatology. 2016;63:388-397.

22. Emery JS, Feld J. Treatment of hepatitis B virus with combination therapy now and in the future. Best Pract Res Clin Gastroenterol. 2017;31:347-355.

23. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67:1560-1599.

24. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63:261-283.

25. Varbovitis I, Papatheodoridis GV. The assessment of hepatocellular carcinoma risk in patients with chronic hepatitis B under antiviral therapy. Clin Mol Hepatol. 2016;22:319-326.

26. Mast EE, Weinbaum CM, Fiore AE, et al; Advisory Committee on Immunization Practices (ACIP). Centers for Disease Control and Prevention (CDC). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. MMWR Recomm Rep. 2005;55:1-33; quiz CE1-4.

27. Mast EE, Margolis HS, Fiore AE, et al; Advisory Committee on Immunization Practices (ACIP). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. MMWR Recomm Rep. 2005;54:1-31.

28. Grant BF, Chou SP, Saha TD, et al. Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001-2002 to 2012-2013: results from the National Epidemiologic Survey on Alcohol and Related Conditions. JAMA Psychiatry. 2017;74:911-923.

29. Stokes A, Preston SH. The contribution of rising adiposity to the increasing prevalence of diabetes in the United States. Prev Med. 2017;101:91-95.

30. Ogden CL, Carroll MD, Fryar CD, Flegal KM. Prevalence of obesity among adults and youth: United States, 2011-2014. NCHS Data Brief. 2015;(219):1-8.

31. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2017.

32. Ruhl CE, Everhart JE. Fatty liver indices in the multiethnic United States National Health and Nutrition Examination Survey. Aliment Pharmacol Ther. 2015;41:65-76.

33. Campbell PT, Newton CC, Freedman ND, et al. Body mass index, waist circumference, diabetes, and risk of liver cancer for U.S. adults. Cancer Res. 2016;76:6076-6083.

34. Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: a population-based study. Gastroenterology. 2004;127:1372-1380.

35. Kim D, Li AA, Perumpail BJ, et al. Changing trends in etiology-based and ethnicity-based annual mortality rates of cirrhosis and hepatocellular carcinoma in the United States. Hepatology. 2019;69:1064-1074.

36. Mahtajan R, Xing J, Liu SJ, et al; Chronic Hepatitis Cohort Study (CHC-CS) Investigators. Mortality among persons in care with hepatitis C virus infection: the Chronic Hepatitis Cohort Study (CHC-CS), 2006-2010. Clin Infect Dis. 2014;58:1055-1061.