Sex and Race Disparities in the Incidence of Hepatocellular Carcinoma in the United States Examined through Age–Period–Cohort Analysis
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ABSTRACT

Background: Incidence rates for hepatocellular carcinoma (HCC) vary considerably by age, sex, and race/ethnicity. We assessed whether the underlying reasons for variations in HCC among subgroups of the population by age, sex, race/ethnicity, and birth cohort are uniform or whether they interact with one another or have changed over time.

Methods: Data were from the U.S. Cancer Statistics registry. We assessed annual trends within population subgroups and examined for secular trends in the male-to-female ratio for HCC incidence. We used jointpoint regression to compute annual percent change and average annual percent change (AAPC) and corresponding 95% confidence intervals (CI). We also used age–period–cohort models to disentangle period and cohort effects.

Results: Between 2001 and 2015, HCC rates increased in men and women ≥50 years, remained stable among women ages 40 to 49 years, but decreased among males ages 40 to 44 years (AAPC = −2.47%; 95% CI, −3.15% to −1.80%) and 45 to 49 years (AAPC = −3.49%; 95% CI, −4.78% to −2.17%). As a result, the male-to-female incidence rate ratio (IRR) among persons aged <50 years decreased from 4.63 in 2001 to 2.42 in 2015 but remained stable over time among persons aged ≥50 years. HCC rates were lower among successive cohorts of males born after circa 1956, whereas HCC rates among females born circa 1991 were higher than those among females born circa 1956 (IRR = 1.67; 95% CI, 1.05–2.65).

Conclusions: As a result of decreasing incidence among males aged <50 years and strong cohort effect, the epidemiology of HCC is changing from a disease with striking male predominance to one with less male predominance.

Impact: The sex and racial disparities and strong birth cohort effect on HCC risk identified in this study have important implications for population-based HCC prevention efforts.

Introduction

In the United States, incidence and mortality rates for liver cancer have tripled since the 1980s (1). Hepatocellular carcinoma (HCC) is the predominant histologic type, accounting for greater than 85% of all liver cancers. HCC rates are projected to increase through 2030 (2).

HCC incidence rates vary considerably by age, sex, and race/ethnicity. HCC is rare among persons less than 40 years of age but increases linearly with increasing age before reaching a plateau at approximately 70 years of age. HCC predominantly occurs in males (male-to-female ratio up to 4:to-1; ref. 3) and is 2-to-4-fold more common in Hispanics and Asians/Pacific Islanders (API) compared with non-Hispanic Whites (NHW; refs. 4, 5). We recently showed that Hispanics now have the highest HCC incidence rates in the United States, surpassing APIs as the racial/ethnicity group at highest risk for HCC (6). Although overall HCC incidence rates are increasing in the United States, a recent study analyzing data from 13 registries in the Surveillance, Epidemiology, and End Results (SEER) program found that HCC incidence rates among adults ages 40 to 49 years in the United States decreased from the mid-2000s to 2015, regardless of sex and race/ethnicity (7).

The underlying reasons for variations in HCC incidence based on age, sex, and race/ethnicity are not completely understood. Hypothesized causes include differences in the prevalence, time of onset, or severity of known risk factors for HCC related to external factors, genetic susceptibility (8), hormonal factors, and other intrinsic exposures with differential distribution based on age, sex, or race/ethnicity. For example, hepatitis B virus (HBV) infection is the most common underlying cause of HCC among Asians, whereas hepatitis C virus (HCV) infection, obesity, alcohol consumption, and other metabolic disorders are the most important risk factors for HCC among non-Asians (9). The interaction among these factors (age, sex, and race/ethnicity) and patterns over time are also unclear. Understanding these interactions could shed light on the nature of acquired risk factors and their acquisition/incubation periods as well as hormonal factors.

Therefore, we analyzed data from the U.S. Cancer Statistics (USCS) registry, which covers the entire U.S. population. Leveraging this population-based resource, we assessed whether HCC incidence rates among subgroups of the population by age, sex, and race/ethnicity are uniform or whether they interact with each other and whether these relationships have changed over time. Examining data from all 50 states provides a more representative picture of HCC trends in the United States than shown in prior SEER-based studies (7). Furthermore, we used age–period–cohort models to disentangle factors that equally influence all age groups at a particular calendar time (period effects) and those that vary by birth generation (cohort effects). Period effects reflect population exposures, such as diagnostic methods or...
treatment of risk factors. Cohort effects reflect changes in the prevalence of exposure to causal factors that differ across successive generations, such as the HCV epidemic affecting persons born between 1945 and 1965 in the United States, HBV infection and vaccination among Asian immigrants and first generations, and increased obesity and metabolic syndrome in recent generations.

Materials and Methods
Data source
Incident primary HCC cases diagnosed between 2001 and 2015 were identified in the USCS registry (10). The two primary data sources for the USCS registry are the Centers for Disease Control and Prevention (CDC) National Program of Cancer Registries (NPCR), which includes all population-based state cancer registries, and SEER, which includes 14 population-based cancer registries and three supplemental registries. The USCS includes cancer incidence data for all 50 states and the District of Columbia, and each contributing registry uses uniform methodologies for data collection and reporting (11). Data are continuously updated and monitored annually for quality. The data include information on demographic (e.g., age, sex, race/ethnicity) and tumor (e.g., year of diagnosis, site, histology, tumor stage) characteristics. We identified HCC cases within the USCS registry using a combination of International Classification of Diseases for Oncology, Third Edition (ICD-O-3) site code C22.0 and ICD-O-3 histology codes 8170–8175. We tested an alternate designation (C22.1 and C22.2) and the results were not different.

Statistical analysis
We calculated annual age-standardized incidence rates (ASR) of HCC overall and stratified by sex and race/ethnicity. Rates were standardized to those of the U.S. population in 2000 using the direct method and reported per 100,000 person-years (PY). Corresponding 95% confidence intervals (CI) were calculated using the modification described in Tiwari and colleagues (12). We also examined age-specific HCC rates based on defined age groups at the time of cancer diagnosis. Five major racial/ethnic groups were included: NHWs, non-Hispanic Blacks (NHB), American Indians and Alaska Natives (AI/AN), APIs, and Hispanics. Male-to-female incidence rate ratios (IRR) for HCC were calculated and associated 95% CIs were calculated using the modification described in Tiwari and colleagues (12). We evaluated secular trends in HCC incidence rates via the NCI’s Joinpoint program (version 4.7.0.0; available from: http://surveillance.cancer.gov/joinpoint), which tests whether an apparent change in trend is statistically significant using a Monte Carlo Permutation method. We tested a single line model (i.e., no joinpoints), and then assessed if more joinpoints should be added to the model based on their statistical significance. We allowed a maximum of two joinpoints with a minimum of four observations per segment. The best joinpoint model was identified using log-transformed data. We obtained the annual percent change (APC) in incidence rates over a single linear segment and the average annual percent change (AAPC) over the entire study period for each joinpoint model. The 95% CIs were calculated using a normal approximation (13).

Finally, we used NCI’s Age-Period-Cohort Web tool (https://analyisitools.nci.nih.gov/apc/) to fit age-period–cohort models to examine secular trends in HCC incidence rates based on age at diagnosis (age), year of diagnosis (period), and year of birth (cohort). The tool produces estimates of net drifts (APC in the expected age-adjusted rates over time), local drifts (APC in the expected age-specific rates over time), and cohort rate ratios (ratio of age-specific rates in each birth cohort relative to the reference cohort) and enables statistical testing of the equality of observed trends (14). We used thirteen 5-year age groups (20–24 through 85–90) and three 5-year calendar periods (2001–2005, 2006–2010, 2011–2015), spanning 16 partially overlapping birth cohorts referenced by mid-year of birth (1916–1991). Default reference groups were used for comparisons, that is, the median calendar period (2006–2010) and the median birth cohort (1956). The median birth cohort also corresponds to the peak HCV epidemic cohort whose members were born between 1945 and 1965. The post-peak HCV epidemic cohort generally includes persons born after 1966. Age–period–cohort models were assessed on the basis of overdispersion ($\sigma^2$), with values near 1.0 indicating successful fit (15).

Results
There were 248,374 incident cases of HCC diagnosed in the USCS registry between 2001 and 2015 (Table 1). Approximately 9% of HCC cases were aged <50 years at their cancer diagnosis; the remaining cases were evenly split (~30% in each) among the 50 to 59, 60 to 69, and ≥70 years age groups. Most HCC cases were male (76.9%) and NHW (59.1%). The overall ASR of HCC for the study period was 4.93/100,000 PYs (95% CI, 4.91–4.95). For males, females, and all racial/ethnic subgroups, ASRs for HCC were lowest in the <50-year age group and increased with increasing age (Table 1). Among males and females, ASRs for HCC were highest in APIs (males, 17.6/100,000 PYs; female, 5.79/100,000 PYs) and lowest in NHWs (males, 6.35/100,000 PYs; females, 1.56/100,000 PYs). Across all age groups, NHWs had the lowest age-specific rates for HCC (Table 1).

The overall male-to-female IRR for the study period was 3.43 (95% CI, 3.40–3.47). The male-to-female IRR was highest among persons ages 50 to 59 years at diagnosis (IRR = 5.41) and lowest among persons aged ≥70 years (IRR = 2.92). When examined by race/ethnicity, the male-to-female IRR was highest among NHBs and NHWs and lowest among AI/ANs. A similar relationship (highest in 50–59 and lowest in ≥70 age groups) was seen following age-group analysis of each racial/ethnic subgroup (Table 1). The ASR for HCC increased from 3.30/100,000 PYs (95% CI, 3.23–3.37) in 2001 to 5.86/100,000 PYs (95% CI, 5.78–5.84) in 2015, representing an AAPC of 4.35% (95% CI, 3.91%–4.78%). Joinpoint regression identified one significant inflection point (2009), that is, two distinct linear segments (trends; Table 2). ASRs for HCC rose by 5.97% (95% CI, 5.34%–6.61%) annually between 2001 and 2009 and by 2.22% (95% CI, 1.45%–3.00%) annually between 2009 and 2015. Similar secular trends were observed for males (AAPC = 4.16%; 95% CI, 3.67%–4.66%) and females (AAPC = 4.26%; 95% CI, 3.60%–4.93%), meaning that the overall male-to-female IRR remained stable over the study period (male-to-female IRR, ~3.8; Fig. 1).

Age-specific rates for HCC increased over time in age groups ≥50 years (Table 2). The largest AAPCs were observed in persons ages 55 to 59 years (AAPC = 8.01%; 95% CI, 6.93%–9.11%) and 60 to 64 years (AAPC = 9.84%; 95% CI, 8.98%–10.7%) between 2001 and 2015. Conversely, age-specific rates for HCC decreased between 2001 and 2015 among persons ages 40 to 44 years (AAPC = −1.80%; 95% CI, −2.50% to −1.10%) and 45 to 49 years (AAPC = −2.99%; 95% CI, −4.19% to −1.77%). When stratified by sex, there was no change in age-specific rates for HCC in males ages 40 to 44 and 45 to 49 years, whereas there were statistically significant decreases in age-specific HCC rates in males ages 40 to 44 (AAPC = −2.47%; 95% CI, −3.15% to −1.80%) and 45 to 49 (AAPC = −3.49%; 95% CI, −4.78% to −2.17%) years between 2001 and 2015 (Fig. 2). As a result, the male-to-female IRR among persons aged <50 years decreased from 4.63 in
Table 2. Counts and incidence rates of HCC in the United States between 2001 and 2015 based on USCS registry data, overall and by age group, sex, and race/ethnicity.

| All | Incident HCCs | Rate/100,000 PYs (95% CI) | Males | Incident HCCs | Rate/100,000 PYs (95% CI) | Females | Incident HCCs | Rate/100,000 PYs (95% CI) | Male:Female IRR |
|-----|---------------|--------------------------|-------|---------------|--------------------------|---------|---------------|--------------------------|----------------|
| All  | 248,374       | 4.93 (4.91–4.95)         | 190,894 | 8.15 (8.12–8.19) | 57,480  | 2.14 (2.12–2.15) | 3.43 (3.40–3.47) |
| <50  | 21,457        | 0.69 (0.68–0.70)         | 17,037  | 1.08 (1.06–1.09) | 4,420  | 0.29 (0.28–0.29) | 3.77 (3.35–3.90) |
| 50–59| 76,349        | 12.8 (12.7–12.9)         | 63,927  | 22.0 (21.9–22.2) | 12,422 | 4.07 (4.00–4.15) | 5.41 (5.31–5.51) |
| 60–69| 74,461        | 18.2 (18.1–18.4)         | 58,896  | 30.4 (30.2–30.6) | 15,565 | 7.26 (7.14–7.37) | 4.19 (4.11–4.26) |
| >70  | 76,107        | 18.3 (18.2–18.4)         | 51,034  | 29.3 (29.6–30.1)| 25,073 | 10.2 (10.1–10.4)| 2.92 (2.87–2.96) |

2001 to 2.42 in 2015 but remained stable over time among persons aged ≥50 years (Supplementary Fig. S1).

Between 2001 and 2015, ASRs for HCC increased among NHWs (AAPC = 4.49%; 95% CI, 4.04%–4.94%), NHBs (AAPC = 4.69%; 95% CI, 3.99%–5.40%), Hispanics (AAPC = 2.48%; 95% CI, 1.68%–3.28%), and AI/ANs (AAPC = 5.91%; 95% CI, 4.37%–7.48%) and decreased among APIs (AAPC = −0.91%; 95% CI, −1.34% to −0.48%; Table 2). The overall male-to-female IRR remained stable over time among all racial/ethnic subgroups, the male-to-female IRRs remained relatively stable over time (Supplementary Fig. S4). In all racial/ethnic subgroups, the male-to-female IRRs remained stable over time in persons aged ≥50 years (Supplementary Fig. S5).

Age-period-cohort models

Although the overall net drift in HCC rates (i.e., expected change in ASRs over time) was +2.63% (95% CI, 2.32%–2.93%) per calendar year, the local trends (i.e., age-specific annual HCC incidence rate percentage change) were consistent with the observed over time decreasing rates among persons ages 40 to 49 years and increasing percentages change) were consistent with the observed over time decreasing rates among persons born after 1956 were statistically significantly lower and decreased with successive generations through 1976, after which rates stabilized. HCC incidence rates among persons born circa 1986 were 28% (IRR = 0.72; 95% CI, 0.55–0.94) lower than those born circa 1956. However, relative to the 1956 birth cohort, incidence rates among those born circa 1991 were not different (IRR = 0.81; 95% CI, 0.57–1.15).
Table 2. APC and AAPC in HCC incidence rates by demographic characteristics: USCS registry data 2001 to 2015.

| Characteristics | Joinpoint segment year start | Joinpoint segment year end | APC         | P         | AAPC        | P         |
|-----------------|-------------------------------|-----------------------------|-------------|-----------|-------------|-----------|
| Overall         | 2001                          | 2009                        | 5.97 (5.34–6.61) | <0.01     | 4.35 (3.91–4.78) | <0.01     |
| Overall         | 2009                          | 2015                        | 2.22 (1.45–3.00) | <0.01     |             |           |
| Sex             |                               |                             |             |           |             |           |
| Female          | 2001                          | 2010                        | 5.22 (4.48–5.97) | <0.01     | 4.26 (3.60–4.93) | <0.01     |
| Male            | 2001                          | 2010                        | 5.22 (4.48–5.97) | <0.01     | 4.26 (3.60–4.93) | <0.01     |
| Age in years    |                               |                             |             |           |             |           |
| 20–24           | 2001                          | 2015                        | 1.05 (–2.26–4.47) | 0.51      | 1.05 (–2.26–4.47) | 0.51      |
| 25–29           | 2001                          | 2015                        | 1.02 (–0.72–2.80) | 0.23      | 1.02 (–0.72–2.80) | 0.23      |
| 30–34           | 2001                          | 2015                        | 0.27 (–1.51–2.08) | 0.75      | 0.27 (–1.51–2.08) | 0.75      |
| 35–39           | 2001                          | 2006                        | 2.44 (–5.64–11.22) | 0.51      | 0.27 (–4.93–5.76) | 0.92      |
| 40–44           | 2001                          | 2015                        | –1.80 (–2.50 to –1.10) | <0.01     | –1.80 (–2.50 to –1.10) | <0.01     |
| 45–49           | 2001                          | 2009                        | –0.58 (–2.06–0.93) | 0.41      | –2.99 (–4.19 to –1.77) | <0.01     |
| 50–54           | 2001                          | 2009                        | –6.11 (–8.55 to –3.60) | <0.01     | 2.30 (0.66–3.98) | 0.01      |
| 55–59           | 2001                          | 2009                        | 12.24 (8.81–15.77) | <0.01     | 12.24 (8.81–15.77) | <0.01     |
| 60–64           | 2001                          | 2009                        | –0.11 (–3.46–3.36) | 0.94      | 2.30 (0.66–3.98) | 0.01      |
| 65–69           | 2001                          | 2009                        | –1.55 (–3.64–0.58) | 0.14      | 12.24 (8.81–15.77) | <0.01     |
| 70–74           | 2001                          | 2009                        | 2.30 (–0.34–4.80) | 0.06      | 2.30 (–0.34–4.80) | 0.06      |
| 75–79           | 2001                          | 2009                        | 3.12 (2.79–3.45) | <0.01     | 3.12 (2.79–3.45) | <0.01     |
| 80–84           | 2001                          | 2009                        | 5.04 (3.48–6.63) | <0.01     | 5.04 (3.48–6.63) | <0.01     |
| 85+             | 2001                          | 2009                        | 1.90 (1.05–2.75) | <0.01     | 1.90 (1.05–2.75) | <0.01     |
| Race/ethnicity  | NHW                           | 2001                        | 6.01 (5.66–6.36) | <0.01     | 4.49 (4.04–4.94) | <0.01     |
| Race/ethnicity  | NHW                           | 2009                        | 3.68 (2.40–4.97) | <0.01     | 3.68 (2.40–4.97) | <0.01     |
| Race/ethnicity  | NHB                           | 2001                        | 3.68 (2.40–4.97) | <0.01     | 3.68 (2.40–4.97) | <0.01     |
| Race/ethnicity  | NHB                           | 2009                        | 1.51 (0.32–2.77) | 0.02      | 1.51 (0.32–2.77) | 0.02      |
| Race/ethnicity  | Hispanic                      | 2001                        | 3.79 (2.78–4.81) | <0.01     | 2.48 (1.68–3.28) | <0.01     |
| Race/ethnicity  | Hispanic                      | 2010                        | 1.06 (–1.57–1.91) | 0.85      | 2.48 (1.68–3.28) | <0.01     |
| Race/ethnicity  | AI/AN                         | 2001                        | 5.91 (4.37–7.48) | <0.01     | 5.91 (4.37–7.48) | <0.01     |
| Race/ethnicity  | API                           | 2001                        | 0.94 (0.01–1.88) | 0.05      | –0.91 (–1.34 to –0.48) | <0.01     |
| Race/ethnicity  | API                           | 2007                        | –2.28 (–2.77 to –1.79) | <0.01     | –2.28 (–2.77 to –1.79) | <0.01     |

Both the age effect and period effect were similar in males and females. However, we observed a different birth cohort effect in females compared with males (Supplementary Fig. S7). Although HCC rates were lower among successive cohorts of males born after circa 1956, there was no decline in HCC rates among females born after 1956. Conversely, rates among females born circa 1991 were statistically significantly higher than those among females born circa 1956 (IRR = 1.67; 95% CI, 1.05–2.65).

Supplementary Figure S8 shows the birth cohort effects for HCC by race/ethnicity. For NHWs, NHBs, and Hispanics, HCC risk decreased and then plateaued among individuals born after 1956. For APIs, HCC risk continued to decrease over successive generations born after 1956.

Discussion

In this large population-based study, we found that HCC overall incidence rates in the United States increased from 3.30/100,000 in 2001 to 5.86/100,000 in 2015. The rate of this increase was highest between 2001 and 2009, where incidence rates increased by 5.97% annually. HCC incidence continued to rise between 2009 and 2015, albeit at a slower rate (2.22% per year). Although HCC incidence increased among persons aged ≥50 years, we confirmed findings from a recent study that showed decreasing HCC incidence among U.S. adults aged <50 years but we found that this decrease was limited to males (?). We also confirmed the male predominance in HCC regardless of race/ethnicity and age-group, and marked racial/
ethnic disparities in HCC incidence. However, while the male-to-female IRR remained stable during the study period among persons aged ≥50 years, the magnitude of the male predominance declined over time among adults aged <50 years due to decreasing rates of HCC in males ages 40 to 49 years. This male-to-female relationship was seen for NHWs, NHBs, and Hispanics but not for APIs where HCC decreased over time in both males and females <50 years, and the male-to-female IRR remained stable in all age groups. We have also confirmed the birth cohort effect on HCC risk—HCC incidence increased in successive generations born between 1916 and 1956, then declined after cohort 1956, but stabilized or increased since birth cohort 1976.

Overall, HCC incidence rates were over 3-fold higher among males than females. Consistent with previous data from SEER 13 registries (16), the magnitude of the male predominance was highest for persons ages 50 to 59 years and lowest for persons aged ≥70 years. These findings may point to a role of sex hormones and reproductive factors in HCC risk. Several studies suggested that androgens and estrogens and their corresponding receptors (AR and ER-α) play different roles in HBV-related HCC (17, 18). Elevated levels of estrogens are thought to play a protective role against HCC development, whereas androgens may promote tumorigenesis (19, 20). Differential expression of ARs and ERs has been reported in HCC cells and normal liver (21). Estrogens exert protective effects by modulating the production of inflammatory cytokines (IL1 and IL6). AR signaling pathways suppress the activity of p53 and the DNA damage repair process, thereby promoting hepatocarcinogenesis. However, even among persons aged ≥70 years, HCC incidence was almost 3-fold higher among males than females. Thus, although hormonal and reproductive factors may explain some of the sex effect in HCC, higher prevalence of known HCC risk factors among males than females (e.g.,...
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higher rates of HCV infection and heavy alcohol use) likely explains more of the male predominance of HCC.

The male-to-female IRR for HCC remained stable for persons aged ≥50 years over the study period, even though HCC incidence increased. This likely reflects the strong cohort effect that we and others have reported for HCC in males (22–24). HCC rates were highest for males from peak HCV epidemic birth cohorts due to higher HCV prevalence among males. Conversely, the declining male-to-female IRR among adults aged <50 years reflects the declining rates of HCV infection among males born in successive generations because peak HCV epidemic birth cohorts. We also found a drop in HCC in more recent birth cohorts in men but not women. This might be related to slower progression of HCV in women due to less alcohol and obesity as well as intrinsic factors, so there is a late surge in HCC among women (25). Similar findings were reported in Japan as their HCV-related factors started to drop (26). Going forward, higher rates of alcohol abuse, obesity, and diabetes in males than females will likely contribute to higher HCC rates for males but less striking than historical HCV-related disparities.

Consistent with prior studies (6), we found that the rate of increase in HCC incidence has slowed since 2009. Although we were unable to examine specifically the cause of the inflection point in 2009, we posit that it likely reflects the shift in risk factors from HBV to HCV, alcohol, and NAFLD. This is supported by our age–period–cohort analysis findings, which suggest a significant cohort effect driving the temporal trends. Likewise, as previously reported (6, 24, 27), we found highest overall incidence rates of HCC among APIs and Hispanics and lowest HCC rates among NHWs, NHBs, Hispanics, and AI/ANs. HCC rates decreased among APIs. Among APIs in the USCS registry, HCC incidence rates decreased at a rate of 2.28% per year between 2007 and 2015. These secular trends are supported by contrasting cohort effects within the racial/ethnic subgroups. HCC rates are highest for NHWs, NHBs, and Hispanics born circa 1956 (corresponding to the peak HCV epidemic period) and have plateaued in most recent birth cohorts. HCC in APIs are largely due to HBV infection and the increased HBV vaccination combined with improved antiviral treatment of chronic HBV with nucleoside analogs explain the continued decline in HCC among APIs (28). Recent API immigrants and subsequent generations of APIs born in the United States have substantially lower rates of HBV infection resulting in decrease HCC risk. The male-to-female IRR was highest among NHGs and NHBs and lowest among AI/ANs. As seen for overall HCC rates, incidence of HCC decreased among NHW, NHB, and Hispanic males aged <50 years, leading to a reduction in the male predominance over time in these race/ethnic subgroups. For APIs, HCC incidence decreased among males and females aged <50 years and the male-to-female IRR remained stable.

The strengths of our study include that the data used are more representative of the entire U.S. population than the SEER database, which is commonly used to describe HCC incidence trends. This is especially important given our finding that secular trends, and the cohort effect varied by race/ethnicity and with minority subgroups underrepresented in SEER. We carried out novel analyses including the male-to-female HCC IRR trend and the potential effect with race/ethnicity and age, and the age–period–cohort model. A limitation of our study is that it was based on cancer registry data and that no information on individual risk factors was available. As such, our study cannot provide any direct evidence about the role of specific exposures or interventions on the period and cohort effects we observed for the HCC incidence trends.

In summary, HCC rates are increasing in the United States; however, the historical characteristics may be changing (e.g., from a striking male predominance in HCC incidence rates to disease with less male predominance). It is difficult to precisely predict future HCC risk trends, due to the multifactorial nature and complexity of HCC pathogenesis, multiple risk factors, and other factors that accelerate progression.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: X. Zhang, A.P. Thrift
Development of methodology: X. Zhang, H.B. El-Serag
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): X. Zhang, H.B. El-Serag
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): X. Zhang, H.B. El-Serag, A.P. Thrift
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): X. Zhang, H.B. El-Serag
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References
1. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009;27:1485–91.
2. Ryerson AB, Ehemann CR, Altekruse SF, Ward JW, Jemal A, Sherman RL, et al. Annual report to the nation on the status of cancer, 1975–2012, featuring the increasing incidence of liver cancer. Cancer 2016;122:1312–37.
3. Wands J. Hepatocellular carcinoma and sex. N Engl J Med 2007;357:1974–6.
4. El-Serag HB, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: where are we? Where do we go? Hepatology 2014;60:1767–75.
5. El-Serag HB, Lau M, Esschbach K, Davila J, Goodwin J. Epidemiology of hepatocellular carcinoma in Hispanics in the United States. Arch Intern Med 2007;167:1983–9.
6. White DL, Thrift AP, Kanwal F, Davila J, El-Serag HB. Incidence of hepatocellular carcinoma in all 50 United States, from 2000 through 2012. Gastroenterology 2017;152:812–20.
7. Rich NE, Yopp AC, Singal AG, Murphy CC. Hepatocellular carcinoma incidence is decreasing among younger adults in the United States. Clin Gastroenterol Hepatol 2019 Apr 28 [Epub ahead of print].
8. Islami F, Miller KD, Siegel RL, Fedewa SA, Ward EM, Jemal A. Disparities in liver cancer occurrence in the United States by race/ethnicity and state. CA Cancer J Clin 2017;67:273–89.
9. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. Clin Liver Dis 2015;19:223–38.

10. National Program of Cancer Registries (NPCR) and Surveillance, Epidemiology & End Results (SEER). NPCR and SEER Incidence – U.S. Cancer Statistics Public Use Database Data Standards and Data Dictionary Washington (DC): U.S. Department of Health and Human Services; 2017. Available from: https://www.cdc.gov/cancer/uscs/public-use/pdf/npcr-seer-public-use-data-database-data-dictionary-2001-2015-508.pdf.

11. Wingo PA, Jamison PM, Hiatt RA, Gargiullo PM, Hutton M, et al. Building the infrastructure for nationwide cancer surveillance and control – a comparison between the National Program of Cancer Registries (NPCR) and the Surveillance, Epidemiology, and End Results (SEER) Program (United States). Cancer Causes Control 2003;14:175–93.

12. Tiwari RC, Clegg LX, Zou Z. Efficient interval estimation for age-adjusted cancer rates. Stat Methods Med Res 2006;15:547–69.

13. Walters KA, Li Y, Tiwari RC, Zou Z. A weighted-least-squares estimation approach to comparing trends in age-adjusted cancer rates across overlapping regions. J Data Sci 2011;8:631–44.

14. Rosenberg PS, Check DP, Anderson WF. A web tool for age-period-cohort analysis of cancer incidence and mortality rates. Cancer Epidemiol Biomarkers Prev 2014;23:2296–302.

15. McCullagh P, Nelder JA. Generalized linear models. New York: Chapman and Hall; 1989.

16. Liu P, Xu SH, Hu S, Cheng X, Gao T, Zhang C, et al. Age-specific sex difference in the incidence of hepatocellular carcinoma in the United States. Oncotarget 2017;8:68131–7.

17. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007;132:2557–76.

18. Kohi MP. Gender related differences in hepatocellular carcinoma: does sex matter? J Vasc Interv Radiol 2016;27:1338–41.

19. Huang FY, Wong DK, Seto WK, Lai CL, Yuen MF. Estradiol induces apoptosis via activation of miRNA-23a and p53: implication for gender difference in liver cancer development. Oncotarget 2015;6:34941–52.

20. Ren J, Chen GG, Liu Y, Su X, Hu B, Leung BC, et al. Cytochrome P450 1A2 metabolizes 17β-estradiol to suppress hepatocellular carcinoma. PLoS One 2016;11:e0153863.

21. Kalra M, Mayes J, Assefa S, Kaul AK, Kaul R. Role of sex steroid receptors in pathobiology of hepatocellular carcinoma. World J Gastroenterol 2008;14:5945–61.

22. Beal EW, Tumin D, Kabir A, Moris D, Zhang XF, Chakedia J, et al. Cohort contributions to race- and gender-specific trends in the incidence of hepatocellular carcinoma in the USA. World J Surg 2018;42:835–40.

23. Yan M, Ha J, Aguilar M, Bhuket T, Liu B, Gish RG, et al. Birth cohort-specific disparities in hepatocellular carcinoma stage at diagnosis, treatment, and long-term survival. J Hepatol 2016;64:326–32.

24. 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;34:1787–94.

25. Guy J, Peters MG. Liver disease in women: the influence of gender on epidemiology, natural history, and patient outcomes. Gastroenterol Hepatol 2013;9:633–9.

26. Yatsuhashi H. Past, present, and future of viral hepatitis C in Japan. Euroasian J Hepatogastroenterol 2016;6:49–51.

27. Pham C, Fong T-L, Zhang J, Liu L. Striking racial/ethnic disparities in liver cancer incidence rates and temporal trends in California, 1988–2012. J Natl Cancer Inst 2018;110:1259–69.

28. Gordon SC, Lamerato LE, Rupp LB, Li J, Holmberg SD, Moorman AC, et al. Antiviral therapy for chronic hepatitis B virus infection and development of hepatocellular carcinoma in a US population. Clin Gastroenterol Hepatol 2014;12:885–93.