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Original Article

Hepatocellular Carcinoma Incidence and Mortality in the USA by Sex, Age, and Race: A Nationwide Analysis of Two Decades

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Abstract

Background and Aims: While the incidence rates of hepatocellular carcinoma (HCC) are increasing, there are limited comprehensive data on demographic-specific incidence and mortality trends in the USA. We aimed to evaluate recent trends in HCC incidence and mortality among different demographic groups in the USA. ***Methods:*** Age-adjusted HCC incidence rates were calculated from the Centers for Disease Control's United States Cancer Statistics database, which combines incidence data on newly diagnosed cancer cases and covers approximately 98% of the population in the USA. Additionally, age-adjusted HCC mortality rates were obtained from the Centers for Disease Control's National Center for Health Statistics database, which offers comprehensive coverage spanning nearly 100% of deaths attributed to HCC in the USA. Rates were stratified by sex, age (older [≥55 years] and younger [<55 years] adults), race and ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, Non-Hispanic Asian/Pacific Islander, and Non-Hispanic American Indian/Alaska Native), and tumor stage at diagnosis (early and late). Annual and average annual percentage change (AAPC) were calculated using joinpoint regression. A sex-specific pairwise comparison was conducted. ***Results:*** Between 2001 and 2020, there were 467,346 patients diagnosed with HCC (26.0% women), with increasing incidence in both sexes without significant difference (p=0.65). In younger adults (78,169 patients), the incidence decreased in men but not in women (AAPC difference=−2.39, p=0.002). This was seen in various racial and ethnic groups, mostly driven by early-stage tumors (AAPC difference=−2.65, p=0.02). There were 329,973 deaths attributed to HCC between 2000 and 2020 (28.4% women). In younger adults (43,093 deaths), mortality decreased in men at a greater rate than in women (AAPC difference=1.61, p=0.007). This was seen in various racial and ethnic groups, most notably in non-Hispanic American Indian/Alaska Natives (AAPC difference=−4.51, p=0.01). ***Conclusions:*** Nationwide USA data, covering nearly all HCC cases, show an increasing incidence and mortality over the last two decades. In younger adults, there was a decreasing incidence in men but not in women, due to early-stage tumors. Mortality improved in younger men at a greater rate than in women, especially in Non-Hispanic American Indian/Alaska Natives. Future studies are warranted to identify the risk factors associated with the occurrence and outcomes of HCC in demographic-specific populations, especially younger women.

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Introduction

Primary liver cancer, predominantly hepatocellular carcinoma (HCC), significantly contributes to the rising burden of cancer in the USA and worldwide. It is the third leading cause of cancer-related deaths worldwide and the seventh in the USA.[1,2] Common risk factors associated with liver cancer include chronic viral hepatitis due to hepatitis B virus (HBV) or hepatitis C virus (HCV), alcohol, metabolic dysfunction-associated steatotic liver disease, which is often linked to obesity and metabolic syndrome, and environmental exposure to aflatoxins.[3,4] In the early stages, liver cancer is often asymptomatic, but eventual symptoms may include abdominal pain, weight loss, and malaise.[5]

Over the past two decades, there has been a significant increase in the incidence of primary liver cancer in the USA, with higher rates observed in men.[4] Its burden increases with age and disproportionately affects men, with mortality rates three times higher in men than in women.[6] The high-

Keywords: Liver cancer; Hepatocellular carcinoma; Incidence; Mortality; Epidemiology; Health disparity.

Abbreviations: AAPC, average annual percentage change; APC, annual percentage change; CDC, Center for Disease and Control; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis B virus; NCHS, National Center of Health Statistics; SEER, Surveillance Epidemiology and End Results; USCS, United States Cancer Statistics.

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er incidence in men can be partially attributed to a greater prevalence of risk factors such as alcohol abuse and chronic HBV and HCV infections.[6,7] A recent study of the Surveillance Epidemiology and End Results (SEER) database showed rising incidence and mortality of liver cancer in the USA from 1975 to 2017.[8] The most notable increase in incidence was observed in men and older adults. Another study found varying mortality rates of HCC across different age-specific populations in recent years. While mortality rates were found to be decreasing in younger individuals, they were increasing in older adults.[1] In addition, liver cancer trends among racial groups showed increasing incidence and mortality rates from 1975 to 2017, with variations across different race groups.[8]

Given the escalating incidence and mortality of HCC and the observed disparities among age and racial/ethnic groups, analyzing recent trends can aid in identifying high-risk populations, guiding early detection, intervention, and treatment, and ultimately improving patient outcomes. While current literature offers insight into the increasing incidence and mortality rates of HCC, there remains limited data pertaining to recent sex, age, and racial/ethnic group-specific incidence and mortality rates and time trends. This is especially important given the increasing incidence of several gastrointestinal cancers in younger adults, particularly in younger women.[9,10] Therefore, this study aimed to evaluate recent incidence and mortality rates and time trends of HCC in the USA, focusing on specific sex, age, and race/ethnicity using the following nationwide comprehensive databases: Center for Disease and Control (CDC)'s United States Cancer Statistics (USCS) and National Center of Health Statistics (NCHS). Our aims were to assess:

1. Overall and sex-specific incidence rates and time trends of HCC in different age groups;
2. Sex- and age-specific incidence rates and time trends of HCC across different racial and ethnic groups, to identify potential disparities;
3. Impact of tumor stage at diagnosis on sex- and age-specific incidence rates and time trends of HCC;
4. Overall and sex-specific mortality rates and time trends of HCC in different age groups;
5. Sex- and age-specific mortality rates and time trends of HCC across different racial and ethnic groups, to identify potential disparities.

Methods

This cross-sectional nationwide population-based time-trend analysis assessed the incidence and mortality rates of HCC in the USA over the last two decades using the CDC's USCS and NCHS databases. All data obtained for this study are publicly available and de-identified, and thus were exempted from review by the institutional review board based on the Policy of the National Human Research Protections Advisory Committee.

Data collection

Data on HCC incidence between January 1, 2001 and December 31, 2020 were obtained from the CDC's USCS database, which is the official source of cancer statistics in the USA, covering nearly 98% of the population.[11] This database compiles incidence data from cancer registries across all 50 states, the District of Columbia, and Puerto Rico, reporting on around 33 million cancer cases. All USCS data are ensured to have high-quality standardization and coding per the North American Association of Central Cancer Registries' Data Standards.[12]

Mortality data for HCC between January 2000 and December 2020 were obtained from the CDC's NCHS database, which is the most comprehensive source of mortality statistics in the USA, covering nearly 100% of deaths.[13] The mortality data are collected from vital registries across the USA, with the cause of death being determined based on death certificates and aligned with the International Classification of Disease. Regular data monitoring is conducted to ensure the maintenance of high-quality data.[13] Only cases in which HCC was the leading cause of death were included in the analysis. Patients aged <15 years were excluded from the analysis.

Definitions

The incidence rate of HCC was defined as the number of patients who were diagnosed with HCC per 100,000 population in a calendar year. Mortality rate was defined as the number of patients whose death was attributed to HCC per 100,000 population in a calendar year. The annual percentage change (APC) was defined as the percentage change in HCC incidence or mortality rate between subsequent years. The average APC (AAPC) was defined as the mean percentage change in HCC incidence or mortality rate per year for the entire study period. When the AAPC was statistically significant, the trend was reported as increasing or decreasing, whereas when the AAPC was not statistically significant, the trend was reported as stable (non-significant increase/decrease). Older and younger adults were defined as adults aged ≥55 years and those aged 15–54 years (<55 years), respectively.[14] HCC was defined using the primary site tab for the liver (C22.0) with malignant behavior only, without including tumors at the intrahepatic bile duct site. The racial and ethnic groups included were Non-Hispanic White (NHW), Non-Hispanic Black (NHB), Hispanic, Non-Hispanic American Indian/Alaska Native (NHAIAN), and Non-Hispanic Asian/Pacific Islander (NHAPI). Stage at diagnosis was defined as early stage (*in situ* and localized tumors) and late stage (tumors with regional or distant site/nodes involvement).

Statistical analysis

HCC incidence and mortality rates, age-adjusted to the standard 2000 population of the USA, were calculated using SEER*Stat software (v.8.4.1.2, National Cancer Institute "NCI"). These rates were categorized by sex, age, race/ethnicity, and tumor stage at diagnosis, as previously defined. Time-trends, calculated as APC and AAPC, were generated using Joinpoint Regression software (v.4.9.0.1, NCI) utilizing Monte Carlo permutation analysis to estimate the best-fit trend line, reflecting change in rates over time.[15,16] Pairwise comparison was conducted to analyze the sex-specific trends using tests of coincidence and parallelism, and the absolute AAPC-difference was assessed using parametric estimation and Taylor Series expansion, with a two-sided p-value cutoff of 0.05 utilized to determine statistical significance.[17]

Results

Overall and sex-specific HCC incidence rates and time trends

There were 467,346 patients diagnosed with HCC in the USCS database between 2001 and 2020, of which 26.0% were women. Overall, HCC incidence rates showed an increase in women from 2.38 per 100,000 population in 2001 to 3.09 in 2020, and also in men from 7.32 in 2001 to 9.82 in 2001. There was no significant difference between the sexes (AAPC=1.54 vs. 1.71; AAPC difference=0.17, p=0.65). Similar results were seen in older adults (385,300 patients;

26.9% women), with an increasing incidence in women from 8.94 to 12.29 per 100,000 population in 2021, and in men from 25.28 in 2001 to 40.38 in 2021 per 100,000 population (sex-specific AAPC difference=0.79, p=0.06). However, in younger adults (78,169 patients; 20.6% women), the incidence rates showed a significant decrease in men from 3.28 in 2001 to 1.93 in 2021 per 100,000 population but not in women, who had an incidence of 0.73 in 2001 and 0.70 in 2021 per 100,000 population. The sex-specific difference was significant (AAPC=−0.34 vs. −2.72; AAPC difference=−2.39, p=0.002). The trends were non-identical and non-parallel (p<0.001), suggesting that HCC incidence rates in younger men are decreasing at a greater rate compared to the stable trend observed in younger women (Table 1 and Fig. 1).

Overall and sex-specific HCC incidence rates and time trends in different racial/ethnic groups

In the NHW group (285,690 patients; 25.4% women), HCC incidence rates were similar to those observed in the overall population, increasing in both men and women without a significant difference (p=0.32) (Supplementary Table 1). In older adults (242,523 patients; 26.0% women), the rates were increasing in men at a greater rate than in women (p=0.02). However, in younger adults (41,143 patients; 21.0% women), similar findings to the overall population were seen, with decreasing trend observed in men but not in women (AAPC=−2.54 vs. 0.55; AAPC difference=−3.09, p<0.001) (Fig. 2). In the NHB group (67,137 patients; 25.1% women), the rates were increasing in men but not in women (p=0.69). In older NHB adults (53,193 patients; 25.2% women), the rates were increasing in both sexes without a significant difference (p=0.24). However, in younger NHB adults (13,488 patients; 24.0% women), the rates were decreasing in men at a greater rate compared to women (AAPC=−6.09 vs. 1.74; AAPC difference=−4.35, p<0.001). In Hispanics (71,120 patients; 27.6% women), while the overall incidence rates were stable in men and women (p=0.85), they were increasing in older adults (55,521 patients; 30.0% women; p=0.32). However, in younger Hispanics (14,561 patients; 17.2% women), the incidence rates were decreasing in men but not in women (AAPC=−3.20 vs. −1.50; AAPC difference=−1.71, p=0.10), with trends being non-identical (p<0.001) and non-parallel (p=0.02). In the NHAPI group (35,698 patients; 28.5% women), the rates were decreasing in both sexes without a significant difference (p=0.18), with similar findings seen in both older (27,943 patients; 31.3% women) and younger NHAPI adults (7,503 patients; 17.9% women). In the NHAIAN group (5,087 patients; 30.6% women), the incidence rates were increasing in both sexes without a significant difference (p=0.28), with similar results seen in older adults (4,065 patients; 32.2% women).

Overall and sex-specific HCC incidence rates and time trends based on the tumor stage at diagnosis

In patients diagnosed with early-stage HCC (198,040 patients; 26.9% women), the incidence rates were increasing in men and women without a significant difference (p=0.63), with similar results seen in older adults (163,891 patients; 27.7% women) (Supplementary Table 2). However, in younger adults (32,408 patients; 22.1% women), the rates were decreasing in men but not in women (AAPC=−1.52 vs. 1.12; AAPC difference=−2.65, p=0.02), with non-identical and non-parallel data (p<0.001) (Supplementary Fig. 1). On the other hand, in patients diagnosed with late-stage HCC (467,346 patients; 23.4% women), incidence rates were also increasing in both men and women without a significant difference (p=0.09). However, in older adults (146,384 patients; 24.1% women), the incidence rates were increasing in men at a greater rate than in women (AAPC difference=1.37, p<0.001), and there was no difference between the sexes in younger adults (32,628 patients; 19.4% women; p=0.28).

Overall and sex-specific HCC mortality rates and time trends

There were 329,973 deaths attributed to HCC in the USA between 2000 and 2020 (28.4% women). HCC mortality rates were significantly increasing in both men and women (AAPC=1.90 vs. 0.90; AAPC difference=1, p=0.001) (Table 2). In older adults (286,087 deaths; 29.7% women), mortality rates were increasing in both sexes, without a significant difference (p=0.11). However, in younger adults (43,093 deaths; 19.1% women), mortality rates were decreasing in both men and women (AAPC=−3.09 vs. −1.49; AAPC difference=1.61, p=0.007). The trends were non-identical and non-parallel (p<0.001), suggesting that HCC mortality rates in men differed and decreased at a significantly greater rate compared to their female counterparts (Fig. 3).

Overall and sex-specific HCC mortality rates and time trends in different racial/ethnic groups

In the NHW group (212,964 deaths; 28.4% women), mortality rates were increasing in both sexes, without a significant difference (p=0.25) (Supplementary Table 3). In older NHW adults (189,282 deaths; 29.4% women), the rates were increasing in men at a greater rate than in women (p=0.002). However, in younger NHW adults (23,270 deaths; 19.6% women), the rates were decreasing in men but not in women, with a significant AAPC difference of 1.95 (p=0.005) (Fig. 4). In NHB adults (48,376 deaths; 29.9% women), the rates were increasing in men but not in women (AAPC difference=1.10; p=0.02), with comparable results seen in older NHB adults (39,821 deaths; 27.8% women). However, in younger NHB adults (8,440 deaths; 22.0% women), the rates were decreasing in men at a greater rate compared to women, with an AAPC difference of −3.22 (p=0.07). In Hispanics (42,340 deaths; 29.3% women), the rates were increasing in men but not in women, with similar findings in older Hispanics (35,443 deaths; 31.7% women). In younger Hispanics (6,695 deaths; 16.3% women), the rates were decreasing in both sexes, without a significant difference (p=0.56). In the NHAPI group (22,263 deaths; 29.7% women), the rates were decreasing in both sexes in both older (18,175 deaths; 32.9% women) and younger (4,038 deaths; 15.2% women) adults. In older NHAIAN adults (2,555 deaths; 33.1% women), mortality rates were increasing in men but not in women, with an AAPC difference of 2.04 (p=0.009). On the other hand, in younger NHAIAN adults (477 deaths; 19.3% women), the rates were decreasing in men but not in women, with an AAPC difference of −4.51 (p=0.01).

Discussion

Our nationwide analysis of the USCS database, which covers approximately 98% of patients diagnosed with HCC in the USA, shows an increase in incidence over the past two decades in both men and women. Among younger adults, the incidence rates have been decreasing in men but not in women, with a significant difference between the sex-specific trends. An analysis specific to racial and ethnic groups showed increasing HCC incidence rates in most populations, except in NHAPI, who experienced decreasing trends. The difference between men and women was evident across various race/ethnic groups, except in NHAPI, and was primarily

Table 1. Sex-specific trends for HCC incidence among different age groups

Age group, y	Cases, *n*=467,346[a]	Trends[b]			Sex-specific AAPC difference (95% CI)[c]	Pairwise comparison *p*-values		
		Time period	APC (95% CI)	AAPC (95% CI)		Sex-specific AAPC difference	Coincidence[d]	Parallelism[e]
All ages								
Women	121,388 (25.79%)	2001–2014	3.14 (2.61 to 3.67)	1.54 (1.01 to 2.07)	0.17 (−0.59 to 0.93)	0.65	<0.001	0.004
		2014–2020	−1.84 (−3.21 to 0.45)					
Men	345,958 (74.03%)	2001–2007	5.27 (4.42 to 6.11)	1.71 (1.17 to 2.25)				
		2007–2014	2.77 (2.12 to 3.43)					
		2014–2018	−0.60 (−2.26 to 1.08)					
		2018–2020	−7.36 (−10.53 to −4.07)					
Aged≥55 years								
Women	103,720 (22.19%)	2001–2015	3.34 (2.84 to 3.83)	1.88 (1.32 to 2.46)	0.79 (−0.06 to 1.34)	0.06	<0.001	<0.001
		2015–2020	−2.07 (−3.90 to −0.22)					
Men	281,580 (60.25%)	2001–2014	4.99 (4.67 to 5.32)	2.67 (2.05 to 3.30)				
		2014–2018	0.27 (−1.87 to 2.46)					
		2018–2020	−6.90 (−10.89 to −2.73)					
Aged<55 years								
Women	16,067 (3.44%)	2001–2020	−0.34 (−1.34 to 0.68)	−0.34 (−1.34 to 0.68)	−2.39 (−3.91 to −0.87)	0.002	<0.001	0.002
Men	62,102 (13.29%)	2001–2020	−2.73 (−3.99 to −1.44)	−2.73 (−3.99 to −1.44)				

[a]Data are presented as count numbers followed by percentages of the count numbers from the total cases of HCC in the database. [b]Time trends were computed using joinpoint regression program (v4.9.0.1, NCI), with 3 maximum joinpoints allowed (4-line segments). [c]A negative value indicates a greater AAPC in women compared to men. [d]Tests whether sex-specific trends were identical. A significant *p*-value indicates that the trends were not identical (i.e. they had different incidence rates and coincidence was rejected). [e]Tests whether sex-specific trends were parallel. A significant *p*-value indicates that the trends were not parallel (i.e. parallelism was rejected). HCC, Hepatocellular Carcinoma; APC, Annual Percentage Change; AAPC, Average Annual Percentage Change.

attributed to tumors diagnosed at an early stage. Our analysis of the NCHS database, which encompasses almost 100% of deaths attributed to HCC in the USA, demonstrates a rise in HCC mortality rates in both sexes over the past two decades. However, while mortality rates in younger adults have improved, the decline in mortality among men was greater compared to their female counterparts, which was observed across different racial/ethnic groups, particularly among NHAIAN populations.

Previous data showed an increasing incidence of liver cancer in the USA across demographic-specific populations.[8] A nationwide analysis of the SEER database between 1992 and 2015, involving 51,188 patients diagnosed with HCC, showed an increase in incidence rates in both men and women aged 60 years or older; however, the study showed decreasing HCC incidence in younger adults, both men and women, since the mid-2000s.[18] While we reveal comparable findings in older adults and younger men, our study involves a significantly larger sample size (467,346 patients vs. 51,188 patients) with more recent data (2001–2020). Moreover, we provide a comparative analysis and show that the HCC incidence in younger women has not been decreasing and significantly differs from their male counterparts.

The increase in HCC incidence can be attributed to multiple factors. HBV and HCV have been global contributors to HCC; however, with the implementation of vaccinations and effective treatments against these viruses, their incidence rate and proportion of progression to HCC are expected to decrease in the coming years. This is evident in our findings showing a declining incidence of HCC in younger adults; however, the non-decreasing trend of HCC in younger women suggests the involvement of other factors. Metabolic risk fac-

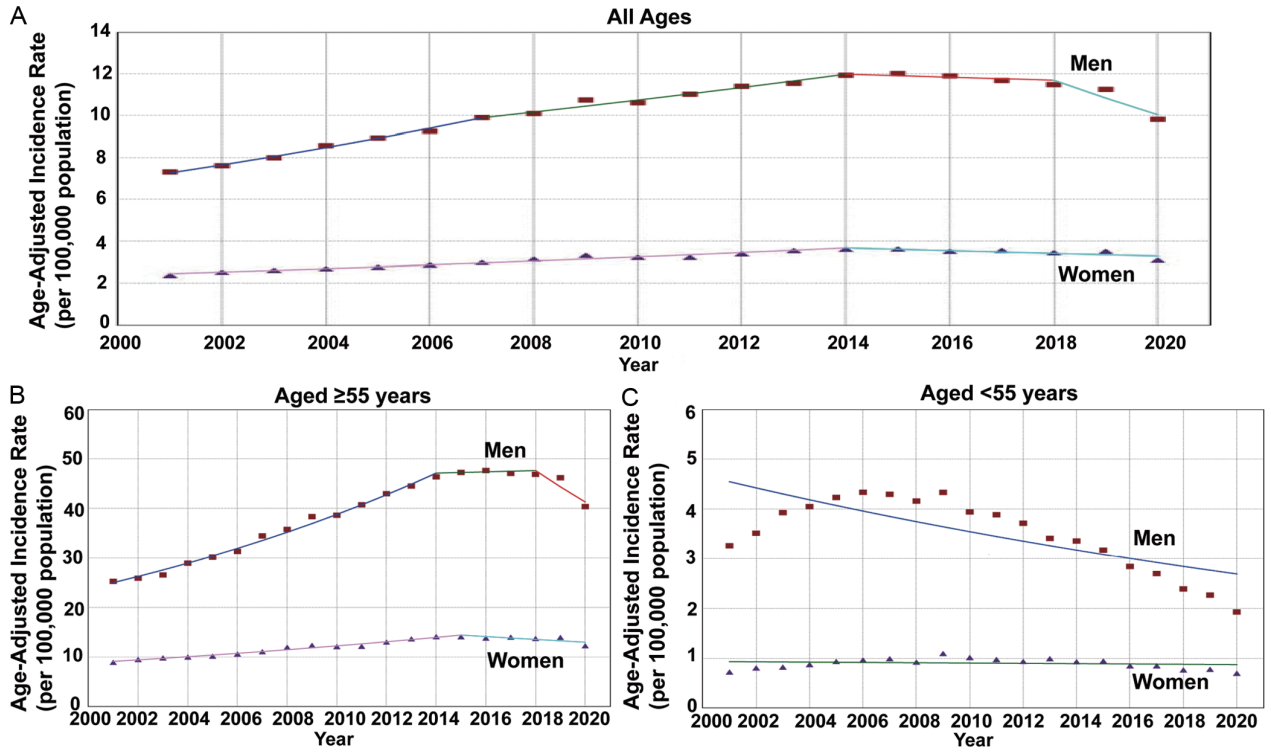

Fig. 1. Sex-specific trends and age-adjusted incidence rates per 100,000 population for Hepatocellular Carcinoma (HCC) among different age groups.

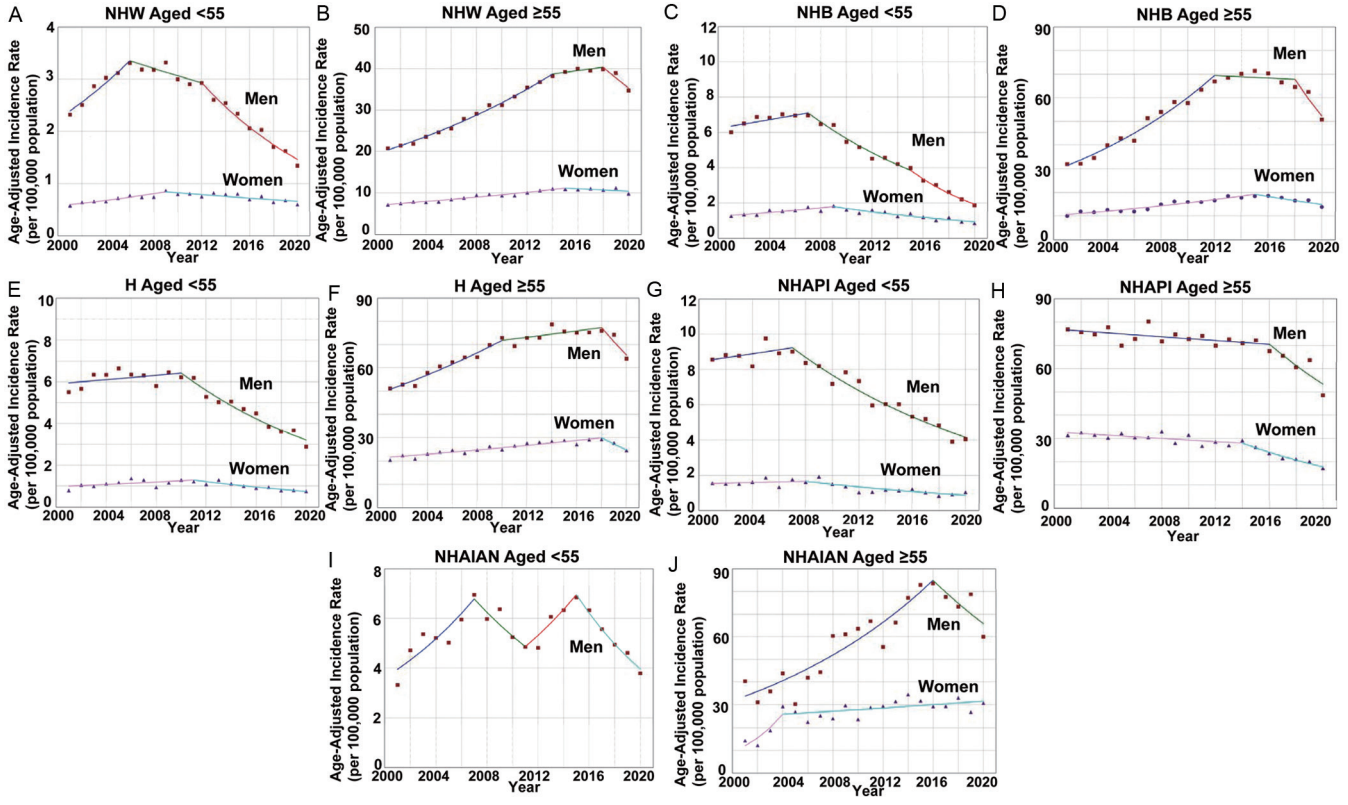

Fig. 2. Sex-specific trends and age-adjusted incidence rates per 100,000 population for Hepatocellular Carcinoma (HCC) among different age and racial/ethnic groups.

Table 2. Sex-specific trends for HCC mortality among different age groups

Age group, y	Deaths, *n*=329,973[a]	Trends[b]			Sex-specific AAPC difference (95% CI)[c]	Pairwise comparison *p*-values		
		Time period	APC (95% CI)	AAPC (95% CI)		Sex-specific AAPC difference	Coincidence[d]	Parallelism[e]
All ages								
Women	93,619 (28.4%)	2000–2009	0.62 (0.25 to 0.98)	0.90 (0.57 to 1.23)	1.01 (0.43 to 1.58)	0.001	<0.001	<0.001
		2009–2014	3.33 (2.18 to 4.48)					
		2014–2020	−0.67 (−1.20 to −0.14)					
Men	236,354 (71.6%)	2000–2004	0.97 (−0.52 to 2.47)	1.90 (1.43 to 2.37)				
		2004–2013	3.97 (3.53 to 4.40)					
		2013–2017	0.88 (−0.70 to 2.49)					
		2017–2020	−1.55 (−3.02 to −0.06)					
Aged≥55 years								
Women	85,049 (25.8%)	2000–2005	1.23 (0.45 to 2.01)	0.70 (0.18 to 1.22)	0.52 (−0.11 to 1.15)	0.11	<0.001	<0.001
		2005–2008	−0.54 (−3.75 to 2.79)					
		2008–2014	2.63 (1.93 to 3.33)					
		2014–2020	−1.01 (−1.47 to −0.54)					
Men	201,038 (60.9%)	2000–2007	2.13 (1.66 to 2.61)	1.22 (0.86 to 1.58)				
		2007–2012	3.20 (2.24 to 4.16)					
		2012–2017	0.22 (−0.61 to 1.06)					
		2017–2020	−2.42 (−3.66 to −1.16)					
Aged<55 years								
Women	8,250 (2.5%)	2000–2011	0.63 (−0.49 to 1.77)	−1.49 (−2.36 to −0.61)	−1.61 (−2.7 to −0.45)	0.007	<0.001	<0.001
		2011–2010	−4.02 (−5.57 to −2.44)					
Men	34,843 (10.6%)	2000–2004	5.84 (2.84 to 8.92)	−3.09 (−3.86 to −2.32)				
		2004–2012	−2.36 (−3.45 to −1.25)					
		2012–2020	−7.97 (−9.07 to −6.87)					

[a]Data are presented as death count numbers followed by percentages of the death count numbers from the total cases of deaths attributed to HCC in the database. [b]Time trends were computed using joinpoint regression program (v4.9.0.1, NCI), with 3 maximum joinpoints allowed (4-line segments). [c]A negative value indicates a greater AAPC in women compared to men. [d]Tests whether sex-specific trends were identical. A significant *p*-value indicates that the trends were not identical (i.e. they had different mortality rates and coincidence was rejected). [e]Tests whether sex-specific trends were parallel. A significant *p*-value indicates that the trends were not parallel (i.e. parallelism was rejected). HCC, Hepatocellular Carcinoma; APC, Annual Percentage Change; AAPC, Average Annual Percentage Change.

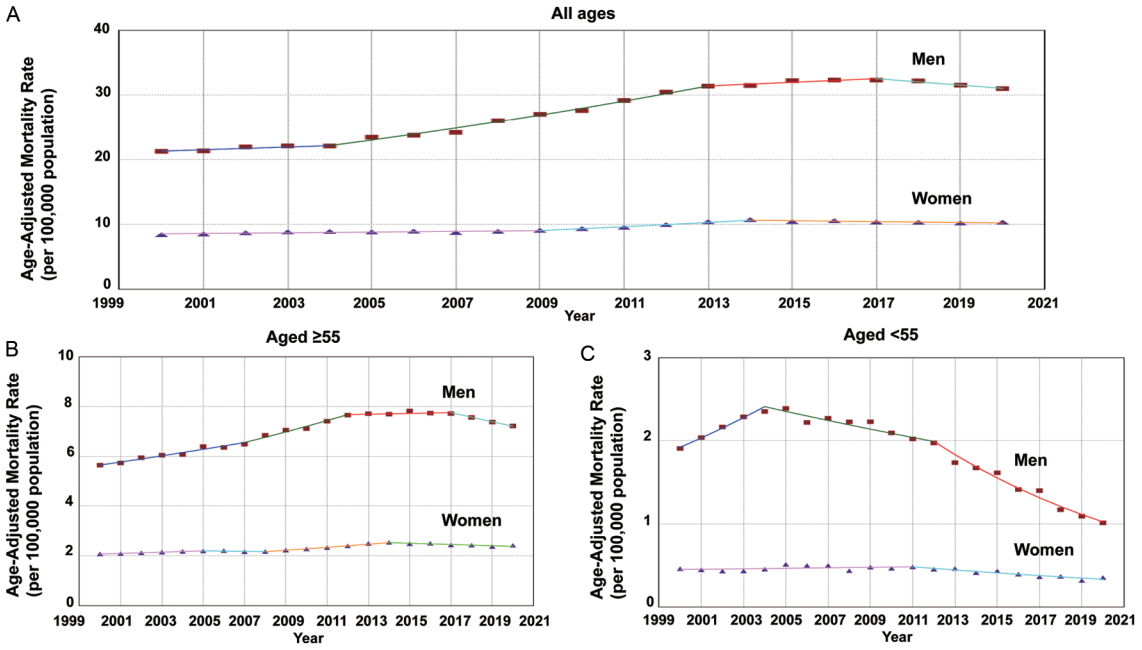

Fig. 3. Sex-specific trends and age-adjusted mortality rates per 100,000 population for Hepatocellular Carcinoma (HCC) among different age groups.

tors for HCC, such as obesity, type II diabetes, and non-alcoholic fatty liver disease, which was later termed "metabolic dysfunction-associated steatotic liver disease," were all found to be increasing.[6,19] A nationwide study of the National Health and Nutrition Examination Survey showed an increasing incidence of diabetes and obesity in younger adults in the

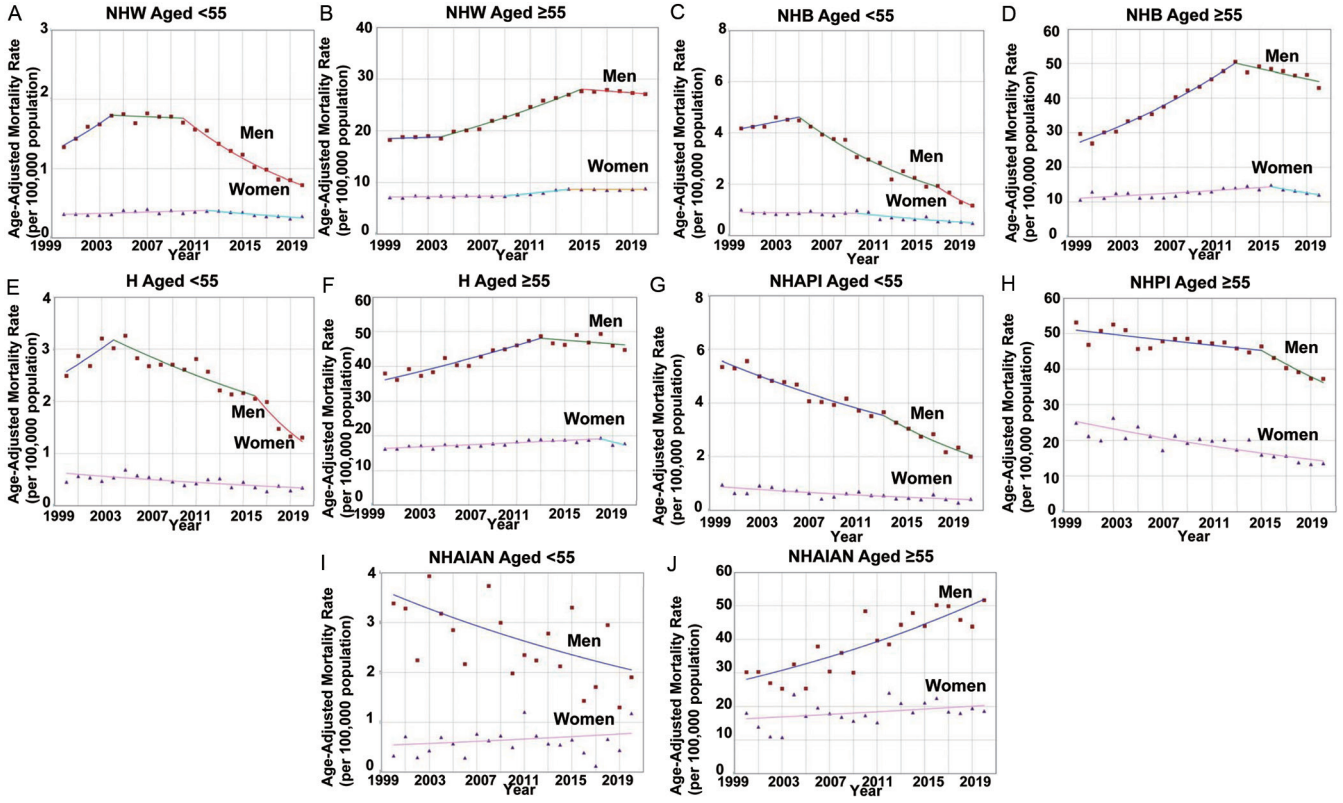

Fig. 4. Sex-specific trends and age-adjusted mortality rates per 100,000 population for Hepatocellular Carcinoma (HCC) among different age and racial/ethnic groups.

USA between 2009 and 2020.[20] Additionally, a systematic review of 245 articles projected an increased prevalence of metabolic dysfunction-associated steatotic liver disease by 2040, revealing a three-fold increase from 1990 to 2040, with a steeper rise in females compared to males.[21] Furthermore, alcohol consumption is known to be associated with a significantly increased risk of HCC.[6] A systematic review and meta-analysis of 68 studies showed an increasing incidence of alcohol consumption in younger cohorts, particularly among younger women.[22] All aforementioned risk factors might be disproportionally affecting women, contributing to the observed findings of non-decreased incidence and lesser improvement in mortality compared to men, despite effective treatments for HBV and HCV. Additionally, it is essential to approach the interpretation of these trends with great caution due to significant issues regarding the reliability and accuracy of HCC coding data. These challenges primarily arise from the complexity of distinguishing between primary and secondary liver neoplasms. Therefore, exercising caution in data interpretation is essential, particularly because the potential variability and changes in coding practices can influence the analysis.[23]

Men are known to have a higher incidence of HCC, with rates typically 2 to 4 times higher than in women.[6] Previous data have suggested that hormonal effects contribute to the sex disparities seen in HCC incidence. While androgens were found to be associated with a higher risk of HCC carcinoma,[24] estrogen was found to downregulate proinflammatory cytokines in Kupffer cells and induce apoptosis in HCC cells.[25] While previous studies have reported a decline in HCC incidence rate among younger adults, our findings contribute to the literature by highlighting sex differences across different age groups, specifically noting that the decline in HCC incidence was observed only in younger men. This may be attributed to the recently observed narrowing of sex differences in alcohol use, with data showing increased alcohol consumption in women but not in men. In addition, women experience worse alcohol-related outcomes, including liver-related injuries.[26] However, hormonal, behavioral, and environmental factors can also influence this sex disparity, suggesting the involvement of multiple factors in the molecular pathogenesis of HCC and raising questions about the varying impact of HCC risk factors across different sexes and age groups.

With regard to liver cancer-related mortality, previous literature reports notable increases in the mortality risk across both sexes and all racial/ethnic groups.[27] Non-comparative data from the SEER database between 1975 and 2017, covering 8.3% of the population in the USA, showed increasing mortality rates in both males and females.[8] Our study provides a comparative analysis of sex-specific mortality trends in different ages and specific racial and ethnic groups, covering nearly 100% of the population in the USA (329,973 deaths attributed to HCC) over a more recent period (2000–2020). We observed reductions in mortality rates in younger adults, with a more pronounced decrease observed in younger men compared to their female counterparts. This sex disparity in mortality was evident across various racial and ethnic groups, with NHAIAN showing the most notable difference.

Improved treatment options for cirrhosis in recent years have led to reduced cirrhosis-related mortality, and consequently, an increase in HCC incidence, especially in older adults, resulting in increasing HCC mortality rates.[1] The improved HCC outcomes in younger adults may be attributed to advancements in diagnostic modalities leading to early-stage diagnoses, along with improvements in therapeutic options. The slower improvement in mortality rates observed in younger women may be linked to the greater increase in incidence in this population compared to their male counterparts. Continuous monitoring of HCC mortality rates is essential for public health purposes, as it offers valuable insights into the effectiveness of recent treatment modalities.

HCC mortality depends on the stage of the disease in the patient, with earlier-stage disease exhibiting the most favorable prognosis.[28] Previous data shows a significant increase in the incidence of early-stage HCC between 2004 and 2015.[29] Our study expands upon existing literature by revealing a decline in HCC incidence among younger men but not women, which was mostly attributable to early-stage tumors. Previous literature indicated that younger women are more inclined to undergo regular HCC surveillance, which may lead to a higher percentage of early-stage tumors being detected.[30] Recent advancements in diagnostic modalities such as liver liquid biopsy, a non-invasive method used for the detection of tumor-derived biomarkers, along with imaging modalities such as contrast-enhanced ultrasound and magnetic resonance imaging, have increased the detection and accuracy of HCC diagnoses and surveillance in recent years.[31,32] This is evident from our findings in that the most notable increase in HCC cases was driven by tumors diagnosed at an early stage.

With regard to HCC trends in different racial and ethnic groups, a previous nationwide analysis conducted between 2000 and 2010 showed that while HCC incidence and mortality were increasing in older men and women of Black, Hispanic, and White races/ethnicities, patients of Asian/Pacific Islander race experienced decreasing incidence and mortality.[1] Our study provides a comprehensive evaluation of sex-specific incidence and mortality trends in racial/ethnic group-specific populations over the past two decades. Our analysis specific to racial/ethnic groups shows that HCC incidence rates were increasing in most populations except in NHAPI, who showed declining incidence rates in older as well as younger men and women. The disparity in incidence between younger men and women was evident across various racial/ethnic groups except NHAPI. We also demonstrate the disparity in mortality trends between men and women in different age groups, highlighting that mortality rates were decreasing in younger men of different racial/ethnic groups and were stable/decreasing at a lower rate in their female counterparts.

Our study has several strengths. First, it used data from two large comprehensive databases in the USA that cover nearly 98% of HCC cases (467,346 patients) and all deaths attributed to HCC (329,973 deaths) over the past two decades. Furthermore, we highlight that younger women have been experiencing a non-decreasing incidence of HCC compared to younger men and worse outcomes, exhibited by the lower improvement in HCC mortality rates. In addition, we utilized joinpoint regression analysis to provide a comprehensive evaluation of incidence and mortality rates by different variables including sex, age, race/ethnicity, and tumor stage at diagnosis, which will aid in shedding further light on the epidemiology of HCC in the USA.[33]

However, this study also has some limitations. The USCS and NCHS databases lack many variable data, which limited us from identifying risk factors associated with HCC incidence and mortality in different demographic-specific populations. Nevertheless, our study is hypothesis-generating and observational, and aims to guide future research and healthcare policymakers toward further investigations of this emergent topic. Furthermore, nationwide databases such as USCS and NCHS have inherent limitations such as the potential for record loss and coding reliability issues.[34] Despite these challenges, these databases are the

most comprehensive cancer incidence and mortality datasets in the USA that undergo stringent quality checks to ensure high-quality data before publication. Future studies are warranted to evaluate the risk factors associated with the incidence and mortality of HCC in different populations, especially younger women. Further research should evaluate new management options for HCC such as targeted chemotherapeutic agents like tyrosine kinase inhibitors (i.e. sorafenib, lenvatinib, and regorafenib) and immune checkpoint inhibitors (i.e. pembrolizumab and nivolumab), which have demonstrated promising results.[35]

Conclusions

In conclusion, our nationwide comprehensive analysis of the USCS database, which covers nearly all patients diagnosed with HCC, shows an increasing incidence of HCC rates between 2001 and 2020. Our analysis of younger adults shows decreasing HCC incidence in younger men but not in women. This trend was seen in various racial/ethnic groups, and was mostly attributed to tumors diagnosed at an early stage. Additionally, our evaluation of the NCHS database, which covers nearly all deaths attributed to HCC in the USA, showed increasing HCC mortality between 2000 and 2020. When evaluating younger adults, HCC mortality rates were found to have improved in men at a greater rate compared to women, and this was notable in various racial/ethnic groups, especially in NHAIAN. The reason for the disparity in incidence and mortality between men and women is unclear and may be attributed to known or yet-to-be-discovered modifiable or non-modifiable risk factors that might have been disproportionately affecting younger women. Future studies are warranted to identify the risk factors associated with the occurrence and outcomes of HCC in different populations, especially in younger women.

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Conflict of interest

NTP has been an associate editor of *Journal of Clinical and Translational Hepatology* since 2021. The other authors have no conflict of interests related to this publication.

Author contributions

Substantial contributions to the conception or design of the work, acquisition, analysis, and interpretation of data for the work, and drafting of the manuscript (YA); drafting of the manuscript and critical revision for important intellectual content (MI, HK); critical revision of the manuscript for important intellectual content (EMM, SA, FJ); amd substantial contributions to the conception or design of the work, and critical revision of the manuscript for important intellectual input (NTP).

Data sharing statement

The data used in this study are de-identified and publicly available, and can be requested and obtained from the USCS and NCHS websites.

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