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Examining the evolving landscape of liver cancer burden in the United States from 1990 to 2019

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Abstract

Introduction Liver cancer (LC) is frequently preceded by cirrhosis and poses a significant public health challenge in the United States (US). Recent decades have seen notable shifts in the epidemiological patterns of LC, yet national data guiding the optimal allocation of resources and preventive efforts remain limited. This study aims to investigate the current trends, risk factors, and outcomes of LC in the US.

Methods This study utilized the Global Burden of Disease (GBD) dataset to collect data on the annual incident cases, deaths, Disability-Adjusted Life Years (DALYs), age-standardized incidence rates (ASIR), age-standardized death rates, and age-standardized DALY rates of primary LC and its etiologies and risk factors, between 1990 and 2019. Percentage changes in incident cases, DALYs, and deaths and the estimated annual percentage change (EAPC) in ASIR and deaths rates of LC were calculated to conduct temporal analysis. Linear regression was applied for the calculation of EAPCs. Correlations of EAPC with socio-demographic index (SDI) were separately evaluated by Pearson correlation analyses.

Results We observed a marked increase in the ASIR of LC, increasing from 2.22 (95% CI: 2.15–2.27) per 100,000 people in 1990 to 5.23 (95% CI: 4.28–6.29) per 100,000 people in 2019, a percentage change of 135.4%. LC due to hepatitis C followed by alcohol use were the primary factors driving this increase. The ASIR and age-standardized death rates of LC showed a significant average annual increase of 3.0% (95% CI: 2.7–3.2) and 2.6% (95% CI: 2.5–2.8), respectively. There was a significant negative correlation between the SDI and the EAPC in ASIR (ρ = -0.40, p = 0.004) and age-standardized death rates (ρ = -0.46, p < 0.001). In 2019, drug and alcohol use, followed by elevated body mass index (BMI) were the primary risk factors for age-standardized DALY rates attributable to LC.

Conclusion The increased burden of LC in the US highlights the need for interventions. This is particularly important given that LC is mostly influenced by modifiable risk factors, such as drug and alcohol use, and elevated BMI. Our findings highlight the urgent need for public health interventions targeting socio-economic, lifestyle, and modifiable risk factors to mitigate the escalating burden of LC.

Keywords Burden of disease, Hepatocellular carcinoma, United States, DALYs, Risk factors, Hepatitis B, Hepatitis C, Alcohol use

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Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related deaths worldwide, accounting for over 80% of primary liver cancers with an annual death toll ranging from 600,000 to 900,000 [1, 2]. Most liver cancer (LC) cases are reported in resource-limited countries, particularly in Eastern Asia and sub-Saharan Africa [3]. However, the incidence of HCC has been on the rise in the United States (US). While the median age of LC onset exceeds sixty years in North America and Europe, it ranges between thirty to sixty years in Asia and Africa [1]. The etiologies of LC vary by region, with common risk factors including hepatitis B, hepatitis C, exposure to dietary toxins, metabolic dysfunction-associated steatotic liver disease (MASLD), and alcohol consumption [1, 4, 5]. In North America, Europe, and Japan, hepatitis C emerges as a primary risk factor for LC, whereas hepatitis B predominates in China, South Korea, and Taiwan [1, 6]. Given the preventability of these risk factors and the improved outcomes associated with early LC detection, understanding LC is crucial for improving public health outcomes.

Despite advancements in detection and monitoring, recent studies have highlighted a concerning rise in LC incidence in the US. For example, Cao et al. found a more than 300% increase in LC cases from 1990 to 2019, with an age-standardized incidence rate (ASIR) of 5.23 per 100,000 individuals in 2019 [7]. Similarly, Zhang et al. observed an increase in LC rates between 2001 and 2015 among individuals aged over fifty [8]. Predictive age-period-cohort models anticipate a continuing rise in LC rates until 2030, attributed to declining hepatitis C rates with a concomitant increase in fatty liver disease [9]. The overall escalating burden of LC in the US remains a significant concern despite some studies showing declining LC rates and incidence-based mortality in specific US populations, possibly due to improvements in HCV detection [10, 11].

A limited number of studies have focused exclusively on the LC disease burden in the US, reporting different trends [12–14]. Some studies have utilized the Global Burden of Disease (GBD) Database to analyze global and national LC trends from 1990 to 2019, showing an increase in the ASIR of LC in the US against a backdrop of a global decrease [1, 7]. These studies were limited in addressing the causes, risk factors, public health implications, and discussing potential solutions to the rising LC rates nationally.

Our study aims to address these gaps in the literature, highlighting the different risk factors contributing to the increased incidence of LC in the US and proposing effective measures to counter this trend. Utilizing data from the 2019 GBD Database, we focus specifically on US-centric LC trends and their underlying causes. To our knowledge, this is the first study using the 2019 GBD Database to exclusively explore temporal LC trends in the US and the contributing risk factors. The insights from our research could significantly inform public health policies aimed at reducing the prevalence of LC in the US.

Methods

Data source

This study is an observational, longitudinal analysis utilizing data from the GBD 2019 study. The GBD study is a comprehensive regional and global research program that assesses mortality and disability from major diseases, injuries, and risk factors. The study is conducted by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington in Seattle, and is financially supported by various institutions, including the World Bank, the National Institutes of Health, and predominantly the Bill & Melinda Gates Foundation. The GBD 2019 study compiled data from a diverse range of high-quality sources, including censuses, household surveys, disease registries, health service utilization data, and vital statistics records. These sources are carefully selected, validated, and subjected to rigorous statistical analysis, including adjustments for potential biases and inconsistencies. The study also incorporates expert input and uses advanced modeling techniques to enhance the accuracy of its estimates. Additionally, the methodologies undergo thorough peer review and transparent documentation, further ensuring the reliability and external validation of its findings. [15]

Measures

We obtained data on incidence, deaths, and Disability-Adjusted Life Years (DALYs) for LC as a whole and secondary to specific etiologies from 1990 to 2019 from the Global Health Data Exchange (GHDx) query tool [16]. The GBD identified five primary etiologies for liver cancer: hepatitis B, hepatitis C, alcohol use, nonalcoholic steatohepatitis (NASH), and other causes, which included etiologies such as liver flukes, obesity, and aflatoxins. Incident cases and deaths were defined based on ICD-9 codes 155-155.1, 155.3-155.9, 211.5 and ICD-10 codes C22-C22.8 and D13.4.

While the GBD studies continue to use the terms Non-Alcoholic Fatty Liver Disease (NAFLD) and NASH, our study has chosen to adopt the multi-society consensus on updated terminology established in June 2023. We refer to these conditions as MASLD and Metabolic Associated Steatohepatitis (MASH).

Estimation of incidence, deaths, and DALYs

- Incidence Cases: The number of new cases within a specified time frame, presented as total raw counts.
- ASIR: Incidence rates adjusted for age distribution, reported per 100,000 individuals.
- Death Cases: The number of deaths derived from vital registration data and household surveys, reported as total raw counts.
- Age-Standardized Death Rates: Death rates adjusted for age distribution, reported per 100,000 individuals.
- DALYs raw count: The combined measure of years lived with a disability and years of life lost, reported as total raw counts.
- Age-Standardized DALY Rates: DALY rates adjusted for age distribution, reported per 100,000 individuals.

Study location

Our analysis focused on the United States, encompassing all 50 states and the District of Columbia as per the GBD study.

Risk factors

We included all risk factors related with liver cancer DALYs from the GBD 2019 dataset, including alcohol, drug use, elevated Body-mass index, high fasting plasma glucose levels, and smoking.

Socio-demographic index (SDI)

The SDI, a composite measure of development status correlated with health outcomes, was used. It is calculated as the geometric mean of indices of income, education, and fertility rate. The SDI values range from 0 (minimum) to 1 (maximum), and data for all states as well as the District of Columbia in 2019 were sourced from the GHDx.

Statistical analysis

The GBD study employs advanced methodologies like the Cause of Death Ensemble model (CODEm), spatiotemporal Gaussian process regression (ST-GPR), and DisMod-MR for initial data processing. We accessed this processed data through the GBD website for further analysis.

Our analysis included presenting incident cases, raw DALYs count, raw deaths count, ASIR, age-standardized DALYs rate, and age-standardized deaths rates of primary liver cancer, with 95% uncertainty intervals (UIs). We also report the annual proportion of incident cases, DALYs, and deaths by etiology. The percentage changes in these metrics from 1990 to 2019 were computed as:

$$Percent\ change = \frac{measures\ in\ 2019 - measures\ in\ 1990}{measures\ in\ 1990} x\ 100\%$$

Additionally, we determined the Estimated Annual Percentage Changes (EAPCs) in age-standardized incidence and death rates, along with their 95% confidence intervals (CIs), using a regression line fitted to the natural logarithm of the rates against calendar years as:

$$y = \alpha + \beta x + \epsilon$$

where y = ln (ASR) and x = calendar year. The EAPC was calculated as:

$$100 \times (exp(\beta) - 1)$$

and trends were classified as upward or downward based on the EAPC and its 95% CI. Correlations between EAPC values in ASIR and age-standardized death rates with SDI values in 2019 were evaluated using Pearson correlation analyses. All analyses as well as graphical illustrations were conducted using R programming version 4.3.2 [17]. A P-value of < 0.05 was considered statistically significant.

Results

Trends in the incidence primary liver cancer and its underlying etiologies

Table 1 shows the total incidence of liver cancer exhibited a marked increase from 1990 to 2019. The total cases for both genders combined escalated from 6,874 in 1990 to 27,895 in 2019, a significant increase of 305.8%. This rise was particularly notable in males (358.0%) compared to females (213.1%).

Focusing on the ASIR, ASIR of liver cancer showed a significant average annual increase of 2.97% (95% CI: 2.74–3.19) during this period with an overall substantial increase of 135.4%, going from 2.22 (CI: 2.15–2.27) per 100,000 people to 5.23 (CI: 4.28–6.29) per 100,000 people. This increase was more pronounced in males (147.2%) than in females (92.6%).

Furthermore, in the case of liver cancer due to alcohol use, the overall ASIR increased by 156.9%, with a more significant rise in males (152.4%) compared to females (93.3%). For liver cancer due to hepatitis B, the ASIR rose by 113.7% overall, with males experiencing a higher increase (121.0%) than females (74.4%).

Figure 1 shows the trends of liver cancer due to specific etiologies. The ASIR for liver cancer due to hepatitis C showed an increase of 139.7%, with a larger rise in males (162.9%) compared to females (102.2%). For liver cancer due to MASH, the overall ASIR increased by 148.0%, with males

Table 1 All age incidence raw number, age-standardized incidence rate, and percentage change for different subcategories of Liver Cancer in 1990 and 2019

Cause	Gender	Total raw incidence counts in 1990 (95% UI)	Total raw incidence counts in 2019 (95% UI)	Percentage change	Age-standardized incidence rate in 1990 (95% UI)	Age-standardized incidence rate in 2019 (95% UI)	Percentage change
Liver cancer	Both	6874 (6639–7029)	27,895 (22785–33513)	305.8%	2.22 (2.15–2.27)	5.23 (4.28–6.29)	135.4%
	Female	2478 (2330–2571)	7760 (6299–9376)	213.1%	1.38 (1.31–1.43)	2.67 (2.16–3.22)	92.6%
	Male	4396 (4269–4506)	20,135 (15289–25526)	358.0%	3.27 (3.18–3.36)	8.09 (6.15–10.26)	147.2%
Liver cancer due to alcohol use	Both	2022 (1789–2247)	8928 (6833–11477)	341.5%	0.65 (0.57–0.72)	1.66 (1.27–2.15)	156.9%
	Female	330 (277–382)	1029 (781–1338)	211.9%	0.18 (0.15–0.21)	0.35 (0.27–0.46)	93.3%
	Male	1692 (1509–1866)	7899 (5894–10299)	366.8%	1.24 (1.11–1.37)	3.14 (2.34–4.09)	152.4%
Liver cancer due to hepatitis B	Both	965 (839–1110)	3443 (2613–4474)	256.7%	0.32 (0.28–0.37)	0.69 (0.53–0.89)	113.7%
	Female	277 (238–318)	764 (593–968)	176.2%	0.16 (0.14–0.19)	0.29 (0.22–0.36)	74.4%
	Male	689 (597–798)	2679 (1914–3593)	289.0%	0.51 (0.45–0.59)	1.13 (0.82–1.51)	121.0%
Liver cancer due to hepatitis C	Both	2485 (2235–2716)	10,409 (8344–12654)	318.9%	0.78 (0.71–0.86)	1.88 (1.51–2.28)	139.7%
	Female	1195 (1075–1292)	3942 (3177–4848)	230.0%	0.64 (0.58–0.69)	1.30 (1.04–1.61)	102.2%
	Male	1290 (1147–1435)	6467 (4744–8563)	401.2%	0.96 (0.86–1.07)	2.54 (1.86–3.35)	162.9%
Liver cancer due to MASH	Both	661 (569–767)	2791 (2184–3465)	322.1%	0.20 (0.18–0.24)	0.51 (0.40–0.63)	148.0%
	Female	324 (276–375)	1099 (845–1389)	239.5%	0.17 (0.15–0.20)	0.36 (0.28–0.46)	114.1%
	Male	337 (287–394)	1691 (1218–2252)	401.4%	0.25 (0.21–0.29)	0.67 (0.49–0.89)	168.2%
Liver cancer due to other causes	Both	741 (657–825)	2325 (1857–2896)	213.7%	0.26 (0.23–0.29)	0.49 (0.39–0.60)	85.9%
	Female	354 (311–397)	926 (731–1155)	162.0%	0.23 (0.20–0.25)	0.37 (0.30–0.46)	62.3%
	Male	388 (339–438)	1399 (1021–1863)	260.8%	0.30 (0.27–0.34)	0.61 (0.46–0.80)	102.9%

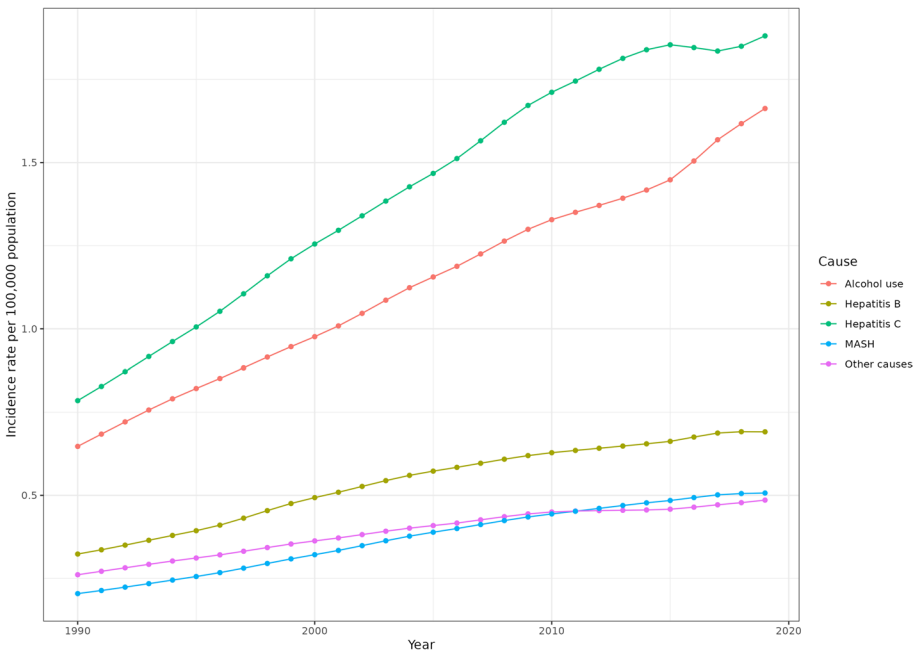

Fig. 1 Age-standardized Liver Cancer Incidence Rates by Cause from 1990 to 2019

showing a notably higher increase (168.2%) compared to females (114.1%). Finally, for liver cancer due to other causes, the ASIR rose by 85.9% overall, with males experiencing a higher increase (102.9%) compared to females (62.3%).

Trends in mortality of primary liver cancer and its underlying etiologies

Table 2 shows the total deaths from liver cancer witnessed a significant increase from 1990 to 2019, rising from 6,454 to 23,807, an overall increase of 268.9%. This trend was markedly more pronounced in males, who experienced a 312.9% increase, compared to a 198.6% increase in females.

Regarding the age-standardized death rates, there was a notable average annual increase of 2.6% (95% CI: 2.5–2.8) over this period. The overall age-standardized death rates for liver cancer rose by 112.4%, from 2.04 (CI: 1.96–2.09) to 4.33 (CI: 3.86–4.75) per 100,000 people. This pattern of higher increases in males compared to females was consistent across various causes of liver cancer.

Specifically, liver cancer due to alcohol use saw a 128.1% increase in age-standardized death rates, with similar trends observed for liver cancer due to hepatitis B (90.2% increase), hepatitis C (115.8% increase), MASH (125.0% increase), and other causes (74.2% increase). Each of these categories showed a greater rate of increase in males, aligning with the overall trend.

Trends in DALYs of primary liver cancer and its underlying etiologies

Table 3 shows that there was a substantial increase in the total DALYs for liver cancer across all categories from 1990 to 2019. For instance, the overall total DALYs for liver cancer in both genders rose from 152,279 (CI: 148,428 – 155,467) to 551,263 (CI: 491,021–603,899), marking a 262.0% increase. This increase was more pronounced in males, who experienced a 301.3% surge, as opposed to females, with a 189.4% rise.

The age-standardized DALY rates for liver cancer nearly doubled, with an overall increase of 108.7%, moving from 51.35 (CI: 50.17–52.40) to 107.18 (CI: 95.59–117.45) per 100,000 people, with an estimated annual percentage change of 2.57% (95% CI: 2.41–2.74). Breaking this down by gender, males saw their age-standardized DALY rates climb from 73.92 (CI: 71.97–75.68) to 162.25 (CI: 139.16–182.92), a substantial increase of 119.5%. Females experienced a significant increase as well, from 32.42 (CI: 31.12–33.41) to 56.87 (CI: 52.36–61.57), translating to a 75.4% rise.

For liver cancer due to alcohol use, the age-standardized DALY rates spiked by 130.6%, hepatitis B was associated with an 83.4% increase, hepatitis C saw a 119.6% rise, MASH-related liver cancer went up by 127.0%, and Fig. 2 shows state-specific data in 1990 and 2019. Data showed that in 1990, Oklahoma and Mississippi

Table 2 All age death raw number, age-standardized death rate, and percentage change for different subcategories of Liver Cancer in 1990 and 2019

Cause	Gender	Total raw Death counts in 1990 (95% UI)	Total raw Death counts in 2019 (95% UI)	Percentage change	Age-standardized Death rate in 1990 (95% UI)	Age-standardized Death rate in 2019 (95% UI)	Percentage change
Liver cancer	Both	6454 (6183–6616)	23,807 (21185–26096)	268.9%	2.04 (1.96–2.09)	4.33 (3.86–4.75)	112.4%
	Female	2486 (2316–2590)	7421 (6702–8064)	198.6%	1.33 (1.25–1.38)	2.43 (2.22–2.63)	83.0%
	Male	3968 (3847–4069)	16,386 (14018–18488)	312.9%	2.95 (2.86–3.03)	6.49 (5.55–7.32)	119.7%
Liver cancer due to alcohol use	Both	1875 (1656–2089)	7384 (6001–8768)	293.9%	0.59 (0.52–0.65)	1.35 (1.10–1.60)	128.1%
	Female	331 (278–384)	972 (798–1157)	193.5%	0.18 (0.15–0.20)	0.32 (0.26–0.38)	81.5%
	Male	1543 (1375–1703)	6412 (5147–7656)	315.5%	1.13 (1.01–1.25)	2.52 (2.03–3.00)	122.2%
Liver cancer due to hepatitis B	Both	848 (735–976)	2742 (2216–3353)	223.6%	0.28 (0.24–0.32)	0.53 (0.43–0.65)	90.2%
	Female	262 (224–303)	687 (576–818)	162.3%	0.15 (0.13–0.17)	0.24 (0.21–0.29)	63.1%
	Male	586 (506–679)	2055 (1604–2574)	251.0%	0.44 (0.38–0.50)	0.85 (0.66–1.05)	94.2%
Liver cancer due to hepatitis C	Both	2436 (2192–2666)	9231 (7939–10567)	278.9%	0.76 (0.68–0.83)	1.63 (1.40–1.87)	115.8%
	Female	1235 (1103–1341)	3842 (3379–4283)	211.0%	0.64 (0.58–0.70)	1.22 (1.08–1.36)	90.0%
	Male	1201 (1067–1338)	5390 (4339–6446)	348.7%	0.90 (0.80–1.00)	2.10 (1.70–2.51)	133.1%
Liver cancer due to MASH	Both	656 (564–764)	2534 (2081–3047)	286.4%	0.20 (0.17–0.23)	0.45 (0.37–0.54)	125.0%
	Female	338 (287–393)	1092 (912–1288)	222.9%	0.17 (0.15–0.20)	0.34 (0.29–0.40)	102.2%
	Male	318 (270–372)	1442 (1103–1793)	354.1%	0.24 (0.20–0.28)	0.57 (0.43–0.70)	139.2%
Liver cancer due to other causes	Both	640 (559–723)	1915 (1597–2255)	199.4%	0.21 (0.19–0.24)	0.37 (0.31–0.44)	74.2%
	Female	319 (278–363)	829 (699–970)	159.7%	0.19 (0.17–0.21)	0.30 (0.26–0.34)	58.6%
	Male	321 (278–365)	1086 (844–1341)	238.9%	0.25 (0.22–0.28)	0.46 (0.36–0.56)	85.2%

Table 3 All age DALY raw number, age-standardized DALYs rate, and percentage change for different subcategories of Liver Cancer in 1990 and 2019

Cause	Gender	Total raw DALY counts in 1990 (95% UI)	Total raw DALY counts in 2019 (95% UI)	Percentage change	Age-standardized DALYs rate in 1990 (95% UI)	Age-standardized DALYs rate in 2019 (95% UI)	Percentage change
Liver cancer	Both	152,279 (148428–155467)	551,263 (491021–603899)	262.0%	51.35 (50.17–52.40)	107.18 (95.59–117.45)	108.7%
	Female	53,471 (51010–55147)	154,739 (142012–167331)	189.4%	32.42 (31.12–33.41)	56.87 (52.36–61.57)	75.4%
	Male	98,808 (96227–101066)	396,524 (339605–446729)	301.3%	73.92 (71.97–75.68)	162.25 (139.16–182.92)	119.5%
Liver cancer due to alcohol use	Both	44,239 (39191–49163)	176,991 (144023–211258)	300.1%	14.65 (12.98–16.35)	33.79 (27.58–40.41)	130.6%
	Female	7062 (5938–8225)	20,816 (16987–24862)	194.7%	4.14 (3.48–4.81)	7.43 (6.12–8.86)	79.5%
	Male	37,176 (33140–41076)	156,175 (125407–187748)	320.1%	27.41 (24.43–30.30)	62.80 (50.64–75.65)	129.1%
Liver cancer due to hepatitis B	Both	24,008 (20964–27378)	72,865 (58771–89847)	203.5%	8.30 (7.24–9.49)	15.22 (12.40–18.54)	83.4%
	Female	6770 (5859–7757)	16,754 (14114–20027)	147.5%	4.29 (3.72–4.92)	6.73 (5.72–7.91)	56.9%
	Male	17,238 (15020–19812)	56,110 (43617–70127)	225.5%	12.84 (11.17–14.67)	24.33 (19.13–30.14)	89.5%
Liver cancer due to hepatitis C	Both	51,425 (46179–56454)	199,612 (169775–231284)	288.2%	16.86 (15.12–18.49)	37.02 (31.37–42.80)	119.6%
	Female	24,197 (21914–26196)	76,361 (67571–85361)	215.6%	13.96 (12.72–15.14)	26.45 (23.37–29.59)	89.5%
	Male	27,228 (24105–30353)	123,251 (97872–149295)	352.7%	20.36 (18.02–22.67)	48.65 (38.74–58.82)	138.9%
Liver cancer due to MASH	Both	13,378 (11618–15462)	51,959 (42091–62315)	288.4%	4.30 (3.74–4.96)	9.76 (7.94–11.63)	127.0%
	Female	6397 (5541–7379)	20,512 (17194–24199)	220.6%	3.60 (3.14–4.13)	7.17 (6.06–8.40)	99.2%
	Male	6981 (5989–8117)	31,446 (23703–39028)	350.5%	5.16 (4.45–5.98)	12.63 (9.62–15.66)	144.8%
Liver cancer due to other causes	Both	19,228 (17317–21208)	49,837 (41803–58644)	159.2%	7.24 (6.57–7.95)	11.39 (9.75–13.09)	57.3%
	Female	9045 (8130–10027)	20,295 (17374–23382)	124.4%	6.43 (5.83–7.11)	9.07 (8.01–10.24)	41.1%
	Male	10,184 (9116–11381)	29541 (23190–36222	190.1%	8.15 (7.32–9.08)	13.85 (11.07–16.73)	69.9%

as having the lowest age-standardized DALY rates, with a DALYs rate per 100,000 people of 35.71 (CI: 33.00–38.62) and 37.17 (CI: 34.37–40.06), respectively, while the highest DALYs were in the District of Columbia and Hawaii with a DALY rate of 110.55 (CI: 98.84, 121.17) and 94.32 (CI: 87.32- 101.81) per 100,000 individuals, respectively. Fast forward to 2019, and Nebraska along with Arkansas emerged as the states with the lowest age-standardized DALY rates (81.31, CI: 64.91–100.92) and (89.59, CI: 68.84–114.80), respectively. The highest rates were reported in the District of Columbia and Hawaii with 153.54 (CI: 121.62–190.13) and 152.53 (CI: 120.11–190.20) DALYs per 100,000 individuals, respectively.

Risk factors associated with primary liver cancer DALYs

Figure 3 presents the age-standardized DALY rates per 100,000 persons in 2019, attributed to various risk factors. According to the GBD dataset, there are five key risk factors associated with the rate of DALYs for liver cancer. Our analysis indicates that the burden from all five risk factors has increased from 1990 to 2019.

In 1990, the primary risk factors contributing to the age-standardized liver cancer DALYs per 100,000

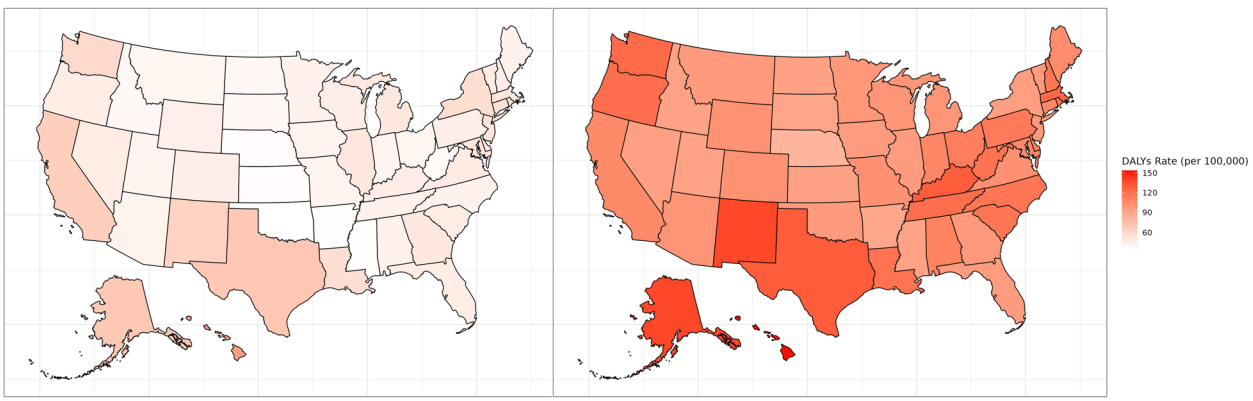

Fig. 2 Age-standardized DALY Rates in 1990 and 2019 by State

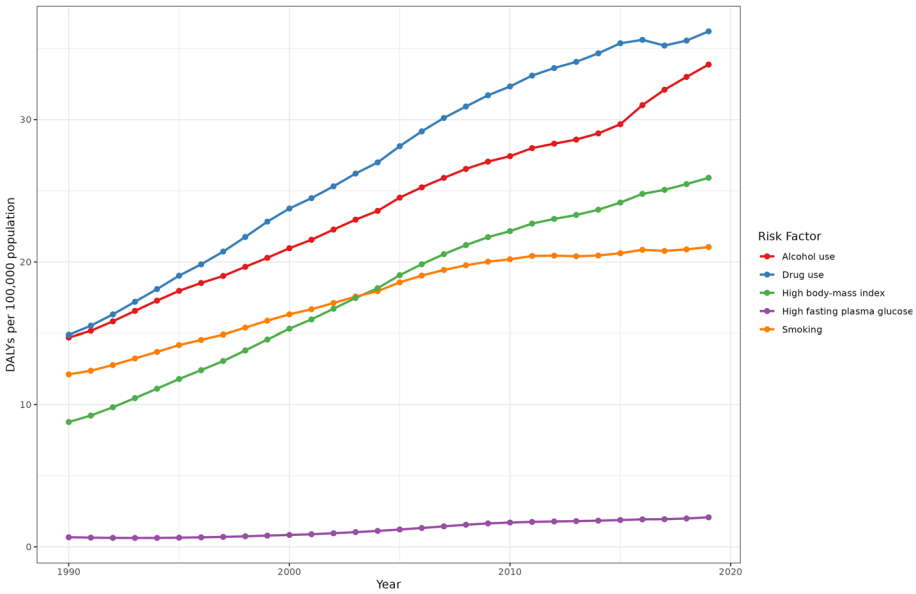

Fig. 3 Age standardized DALYs Rate Attributable to Risk Factors

individuals were drug use, alcohol use, and smoking. By 2019, this profile shifted; while drug use and alcohol use remained leading contributors, high BMI emerged as a significant risk factor, replacing smoking in the top three.

Estimated annual percentage change in age-standardized incidence and death rates by state, and the relationship between the SDI and liver cancer EAPCs

Regarding the annual changes in ASIR and age-standardized death rates, all regions reported yearly increases in both metrics. Kentucky experienced the most significant annual increase in ASIR at 4.1%, while Texas had the smallest at 2.0% per year. Similarly, in terms of age-standardized death rates, Kentucky again showed the highest annual rate of increase at 3.9%, contrasting with Texas, which had the lowest at 1.7%.

Figures 4 and 5 illustrate the relationship between the SDI in 2019 and the EAPC in ASIR and death rates, respectively. In Fig. 4, the EAPC in ASIR is plotted against the SDI, with the size of each point representing the rate of incident cases per 100,000 in each state in 2019. The figure shows a significant moderate negative correlation between the SDI and the EAPC in ASIR (ρ = -0.40, $p = 0.004$). This suggests that states with higher SDI values tend to have a smaller increase or even a decrease in ASIR over time, as indicated by the downward trend of the EAPC as the SDI increases.

Similarly, Fig. 5 presents the relationship between the EAPC in age-standardized death rates and the SDI in 2019, with the size of each point indicating the death rate per 100,000 in that year. The figure demonstrates a significant moderate negative correlation between the SDI and the EAPC in death rates (ρ = -0.46, $p < 0.001$). This indicates that states with higher SDI values tend to experience a smaller increase or a decrease in age-standardized death rates, reinforcing the trend observed in ASIR.

Discussion

This study offers an in-depth analysis of the evolving landscape of LC in the US from 1990 to 2019, investigating temporal trends, risk factors, and outcomes. This period saw a significant 305.8% increase in LC incidence, with a concomitant increase in ASIR by an average annual rate of around 3.0% and an overall of 135.4% over these 29 years. The study also highlights substantial rises in ASIR for LC stemming from alcohol use, hepatitis B and C, MASH, and other etiologies. Furthermore, LC-related age-standardized death rates increased by an average annual rate of 2.6% leading to a 112.4% overall increase. DALYs due to LC increased from 152,279 to 551,263 years, with an estimated annual percentage change of around 2.6%. LC incidence, deaths, and DALYs were all disproportionately associated with significantly higher rates in males. Examining state-specific data showed different trends with a negative correlation between the SDI and ASIR and age-standardized death rates of LC, suggesting potential socioeconomic influences.

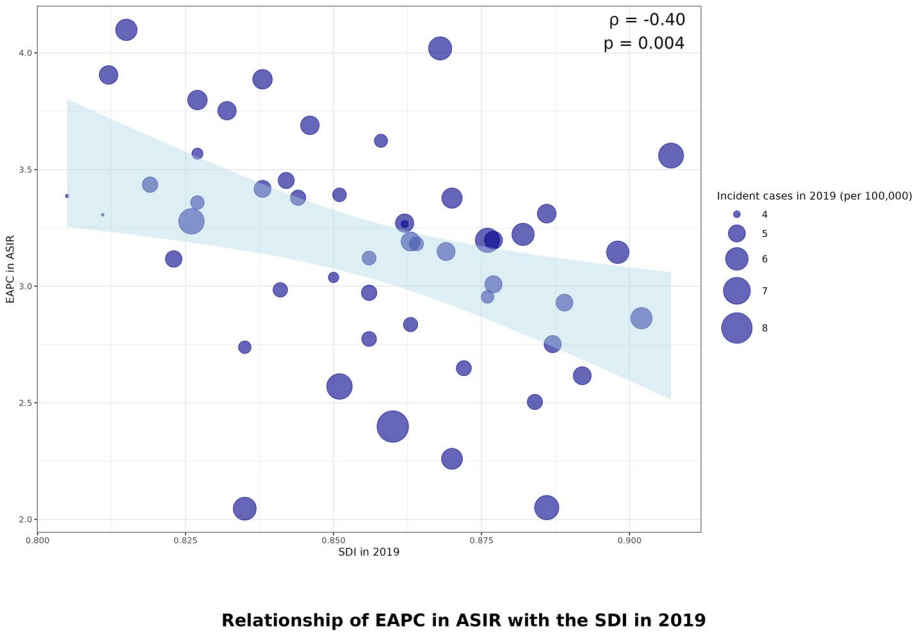

Fig. 4 Relationship Between the EAPC in ASIR and the Sociodemographic Index

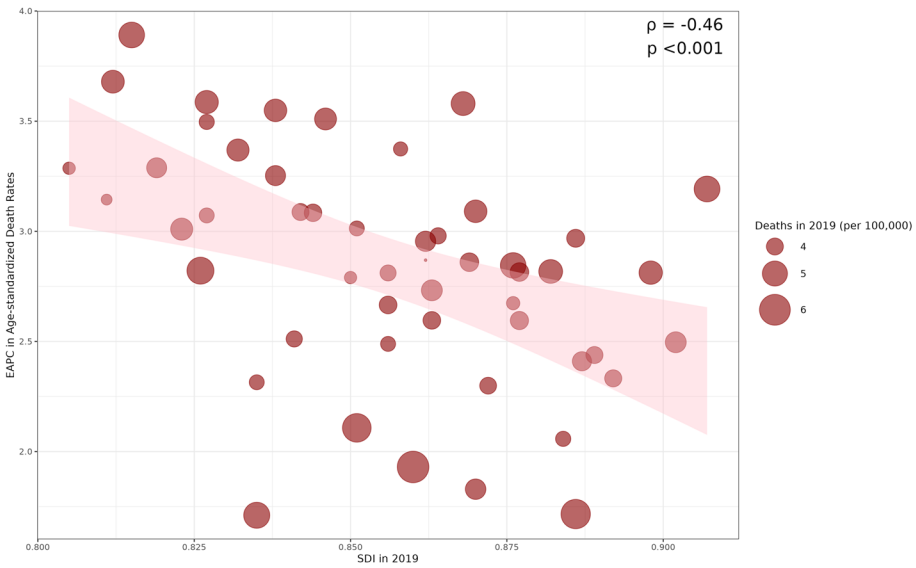

Fig. 5 Relationship Between the EAPC in Age-Standardized Death Rates and the Sociodemographic Index

Comparison with prior literature

Our study provides significant insights into the increasing incidence, mortality, and DALYs of LC in the US from 1990 to 2019, aligning with findings from other studies on the disease's evolving dynamics within national and global health systems. Specifically, our study identifies an overall increase in the incidence and mortality of LC in the US paralleling findings by Cao et al. [7] who observed a similar increase in the burden of LC. Furthermore, the correlation between LC incidence and aging is evident in our study, reflecting the impact of demographic shifts, such as the substantial increase in the elderly population in the US [18]. Comparatively, a similar trend can be seen in the work by Siegel et al. highlighting the

disproportionate rise in LC mortality rates compared to other cancers [19].

HCV continues to be a leading cause of liver cancer in the US, maintaining a consistent trend from 1990 to 2019. This finding diverges from global trends, where HBV is the predominant cause of LC. Our analysis reveals a significant increase in LC incidence and mortality related to HCV, alcohol use, and MASH, paralleling global trends. Data from the Surveillance, Epidemiology, and End Results (SEER) program further support our results, showing an increasing trend in the age-adjusted incidence rates of liver and intrahepatic bile duct cancer in the US [20].

However, our study identifies notable differences from global patterns. For instance, while a decreasing trend in both ASIR and age-standardized death rates of primary liver cancer worldwide was previously found [7], our study found an opposing trend in the US, especially among cases related to alcohol consumption, which may stem from various factors. Globally, the declining ASIR of primary liver cancer might be attributed to enhanced prevention and control of major risk factors, such as HBV and HCV infections. Conversely, the US has experienced a marked increase in acute HCV infections, particularly from 2010 to 2019, significantly influenced by the opioid overdose epidemic and resultant injection drug use among young adults [21–23]. Moreover, while the availability of anti-hepatitis C medications could theoretically reduce the incidence of HCV-induced liver cancer, the persistent rise in liver cancer cases in the US may be due in part to improved diagnosis and surveillance systems, which have led to better detection of liver cancer cases that might have been missed in the past. This enhanced detection could contribute to the observed trends, in contrast to global patterns where such diagnostic advances may not be as widespread [24, 25]. Therefore, the unique challenges faced by the US, coupled with better detection capabilities, highlights the need for a tailored approach to the prevention and management of liver cancer in the country.

Interpretation of epidemiological trends and risk factors

The rise in incidence, mortality, and DALYs of LC in the United States is closely linked to evolving risk factors highlighting the dynamic nature of this public health challenge. The increase in chronic and heavy alcohol use is a recognized risk factor for LC, especially with reported shifts towards beverages with higher alcohol content and patterns of binge drinking [26, 27].

HBV poses a significant risk in immigrant populations from high-prevalence areas, compounded by issues such as limited healthcare access, lack of awareness, and suboptimal vaccination rates [28–30]. Similarly, HCV remains a major factor in the increase in LC incidence and has been largely fuelled by increased injection drug use [31, 32]. The advent of direct-acting antivirals offers a beacon of hope by potentially mitigating LC risk among individuals with HCV [33].

By 2019, a shift in primary risk factors was evident, with high BMI emerging as a significant contributor to liver cancer. The increasing prevalence of MASLD with potential progression to MASH may be closely linked to the obesity crisis, type 2 diabetes mellitus, and metabolic syndrome [34, 35]. The consistent increase in obesity rates, as reported by NHANES, along with the rising incidence and prevalence of diabetes highlight the growing concern for MASLD-related LC [36].

In comparison to global trends, where liver cancer is often linked to viral hepatitis, particularly in developing countries, the U.S. presents a distinct pattern driven by lifestyle-related risk factors. Obesity and diabetes have emerged as major contributors to liver cancer in the U.S., with nearly 37% of cases attributable to these conditions [37]. The rising prevalence of MASH, closely associated with obesity and diabetes, further exacerbates this trend [38]. Moreover, the demographic distribution of liver cancer in the U.S. reveals significant disparities, with higher mortality rates observed among American Indians and Alaska Natives, populations that also face a high prevalence of obesity and metabolic disorders [37]. These trends underscore the urgent need for targeted public health interventions to mitigate these key modifiable risk factors for liver cancer. It is thus imperative to adopt a comprehensive approach that encompasses both traditional risk factors, such as alcohol use and viral hepatitis, and emerging issues like obesity and metabolic disorders. These divergent trends from global patterns raise important questions about the effectiveness of current public health strategies in the U.S. This further emphasizes the urgent need for targeted interventions that consider the specific socio-economic and behavioral factors contributing to the rise in liver cancer, particularly those related to obesity, diabetes, and substance use.

Gender disparities

LC incidence and mortality exhibit notable gender discrepancies, with males significantly more affected than females [39]. The difference may stem from biological, behavioral, and socio-economic factors. The biological protective effects of estrogen in females and the potential facilitation of disease progression by androgens in males may influence these disparities [40]. Behaviorally, men are more prone to engage in risky habits like heavy alcohol use, smoking, and unsafe injection practices [31]. They also have a higher prevalence of HBV and

HCV infections, which might be related to these behaviours [41]. Men are at higher risk of socioeconomic challenges and may face more barriers to healthcare access or exhibit reluctance in seeking medical care, leading to advanced disease stages and worse outcomes [12]. Finally, occupational exposures to carcinogens, more prevalent in male-dominated sectors, may further contribute to the higher liver cancer rates in men [42].

Regional variations and socio-demographic factors

LC rates in the US exhibit significant regional variation, closely linked to socio-demographic factors. Higher SDI regions typically report lower EAPC for age-standardized incidence and death rates of liver cancer. This trend is likely driven by healthier lifestyle choices, such as improved diet, lower obesity rates, and moderated alcohol consumption, which are more prevalent in higher SDI areas [43, 44]. Conversely, regions with lower SDI scores often face significant healthcare access barriers, lower HBV vaccination rates, and higher engagement in risky behaviors, all of which contribute to a greater prevalence of LC [45]. The opioid crisis further exacerbates this issue, as it has led to a marked increase in chronic HCV infections through injection drug use, disproportionately affecting lower-income and rural populations [46].

Beyond SDI, race, ethnicity, and income levels play a pivotal role in shaping LC trends. Ethnic groups with higher HBV prevalence or genetic predispositions face increased risks, while income disparities contribute to unequal access to healthcare services, including screening and early intervention [47]. For instance, lower-income populations may have limited access to healthcare facilities, resulting in delayed diagnoses and poorer outcomes. Additionally, socioeconomic factors such as education level, employment status, and neighborhood environments can influence lifestyle choices and access to preventive measures, further compounding LC risk in disadvantaged communities [48]. The intersection of these socioeconomic factors with behavioral risks, such as poor diet, sedentary lifestyle, and substance use, underscores the complex and multifaceted nature of LC trends in the US.

The absence of a more detailed exploration of these socioeconomic influences in the current study may limit our understanding of how these factors contribute to liver cancer trends and outcomes. Future research should focus on disentangling the relative contributions of these socio-economic factors, examining their interplay with regional and demographic variables, and identifying specific interventions that can mitigate their impact. By addressing these socio-economic disparities, public health strategies can be better tailored to target high-risk populations, thereby reducing the burden of liver cancer more effectively across different regions and communities.

Public health implications

Effective prevention strategies demand a comprehensive strategy that addresses gender disparities, regional variations, and socio-demographic factors. This may include tailored public health measures, targeted screenings, and education initiatives. Emphasizing lifestyle modifications like a healthy diet and regular exercise is key in preventing MASLD, with weight loss being shown to diminish liver fat and inflammation, reducing the risk of MASLD progression [49, 50]. Medications such as vitamin E and bariatric surgery show potential benefits in severe MASLD and MASH [51–54].

Routine screening for MASLD in high-risk populations is crucial for early detection and intervention [52]. Additionally, public health policies should address alcohol consumption with initiatives to limit alcohol advertising and promoting responsible drinking [26, 55]. Tackling the opioid epidemic is also vital for preventing HCV transmission through harm reduction programs, such as needle exchange and supervised injection facilities. These have proven to be effective in preventing HCV transmission among people who inject drugs (PWID) [56, 57]. Medication-Assisted Treatment (MAT) for individuals with opioid use disorder reduces opioid use, improves treatment retention, and prevents blood borne virus transmission, including HCV [58].

HBV vaccination programs and tobacco control, targeting specific risk populations, alongside widespread HCV screening and access to direct-acting antivirals, are foundational in mitigating liver cancer risks. Tobacco control has been shown to be an independent risk factor [59]. Widespread HCV screening and testing, especially among at-risk populations like baby boomers and PWID, align with CDC recommendations [60]. Access to highly effective DAA therapy is key to preventing HCV-related liver complications, with their high cure rates reducing the risk of cirrhosis and liver cancer [61]. Expanding access to these treatments, particularly in vulnerable populations, is critical for preventing HCV progression. Moreover, comprehensive policies should include regular medical check-ups for early detection of liver conditions, in line with recommendations from national and internation health organizations.

Strengths and limitations

This study offers a comprehensive analysis of liver cancer, tackling different risk factors and utilizes current

data for targeted recommendations provides a holistic view of LC etiology and epidemiology. However, the study may be limited in regional variations in data quality and reporting standards. There is also a possibility of underreporting or misclassification of liver cancer cases, especially in regions with less developed healthcare infrastructures. The study's secondary data reliance might introduce biases, and its observational nature limits causality establishment. Additionally, the study does not incorporate predictive analyses that could help explain the observed trends in liver cancer incidence and mortality, particularly in the context of recent public health interventions and advancements in treatment. This omission represents a gap that future research should aim to address.

Future research

Future studies should explore the biological bases for gender and regional liver cancer disparities and assess public health interventions' efficacy. Investigating emerging risk factors and the impact of technological advancements in detection and treatment is essential. Longitudinal studies tracking lifestyle and healthcare access changes, especially in underserved populations, are critical for refining liver cancer prevention and management strategies. To address regional variations more effectively, future research should utilize additional data sources to compare and analyze state-level differences in liver cancer trends. This will help clarify trends and guide targeted public health strategies.

Conclusion

This study emphasizes the need for multifaceted public health strategies to combat liver cancer, highlighting the significance of gender, regional, and socio-demographic factors. The pronounced increase in liver cancer incidence, mortality, and DALYs exemplifies the urgent need to address the interplay of these risk factors. Our findings support the imperative for ongoing research to understand the underlying biological, behavioral, and environmental determinants of liver cancer. Future efforts should focus on prevention, early detection, and personalized interventions to reduce LC burden, leveraging technological innovations and addressing emerging risk factors.

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Authors' contributions
(A=Study Design, B=Data collection, C=Statistical analysis, D=Data interpretation, E=Manuscript preparation, F=Literature search, G=Manuscript review).
Omar Al Ta'ani: ABCDEFG, Yazan Al-Ajlouni: AEFG, Balaji Jagdish:EFG, Himsikhar Khataniar: EFG, Wesam Aleyadeh: EFG, Farah Al-Bitar: EFG, Tavankit Singh: AEFG.

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Availability of data and materials
The data underlying the findings of this study are derived from the GBD study, which is publicly available and can be accessed through the Institute for Health Metrics and Evaluation (IHME) website. The GBD provides an extensive range of health-related data globally, including estimates of mortality, morbidity, and risk factors across a wide array of diseases and conditions.To access the specific dataset utilized in our study, interested parties can visit the IHME GBD Data Tool page on https://vizhub.healthdata.org/gbd-compare/#. This tool allows users to interact with the data, facilitating the exploration of health trends globally, regionally, and at the country level. The dataset is available for open access under the terms specified by the IHME, which supports the use of GBD data for research and policy analysis purposes.

Declarations

Ethics approval and consent to participate
Given that we utilized publicly accessible data, no IRB or individual consent was needed.

Consent for publication
Given that we utilized publicly accessible data, individual consent for publication is not required.

Competing interests
The authors declare no competing interests.

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