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ORIGINAL ARTICLE

Global burden of liver cancer in males and females: Changing etiological basis and the growing contribution of NASH

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Abstract

Background and Aims: The etiology of liver diseases has changed in recent years, but its impact on the comparative burden of liver cancer between males and females is unclear. We estimated sex differences in the burden of liver cancer across 204 countries and territories from 2010 to 2019.

Approach and Results: We analyzed temporal trends in the burden of liver cancer using the methodology framework of the 2019 Global Burden of Disease study. We estimated annual frequencies and age-standardized rates (ASRs) of liver cancer incidence, death, and disability-adjusted life-years (DALYs) by sex, country, region, and etiology of liver disease. Globally in 2019, the frequency of incident cases, deaths, and DALYs due to liver cancer were 376,483, 333,672, and 9,048,723 in males, versus 157,881, 150,904, and 3,479,699 in females. From 2010 to 2019, the incidence ASRs in males increased while death and DALY ASRs remained stable; incidence, death, and DALY ASRs in females decreased. Death ASRs for both sexes increased only in the Americas and remained stable or declined in remaining regions. In 2019, hepatitis B was the leading cause of liver cancer death in males, and hepatitis C in females. From 2010 to 2019, NASH had the fastest growing death ASRs in males and females. The ratio of female-to-male death ASRs in 2019 was lowest in hepatitis B (0.2) and highest in NASH (0.9).

Conclusions: The overall burden of liver cancer is higher in males, although incidence and death ASRs from NASH-associated liver cancer in females approach that of males.

Rohit Loomba and Daniel Q Huang are co-senior authors.

INTRODUCTION

Liver cancer is the third leading cause of cancer-related deaths worldwide.[1,2] The epidemiology of liver cancer has changed significantly in the recent decade.[3–5] The burden of liver cancer due to HBV and HCV infection has declined due to the success of vaccination programs and increasing availability of antiviral therapy.[6–10] In contrast, NASH-associated liver cancer is the fastest growing cause of liver cancer, in parallel with the global obesity epidemic.[11–15] Global alcohol-per-capita consumption has also increased in the recent decade and contributed to an increase in the burden of alcohol-associated liver cancer.[5,12,16,17] However, the impact of these changes in etiology of liver diseases on the comparative burden of liver cancer between males and females is unclear.

Liver cancer due to HBV, HCV, and alcohol are associated with a higher disease burden in males compared with females.[18–22] However, emerging data suggest that the differences in liver cancer burden between males and females may be less pronounced among individuals with NASH, with several country-specific or region-specific studies finding minimal differences in liver cancer burden between male and female patients with NASH.[23–25] A comprehensive, updated global overview of the comparative burden of liver cancer between males and females has not been reported. Herein, we report sex differences in the temporal trends of liver cancer incidence, mortality, and disability-adjusted life-years (DALYs), and the contributions of various liver disease etiologies across 204 countries and territories from 2010 to 2019.

METHODS

Data source

This study used data from the Global Burden of Disease Study 2019 (GBD 2019), a systematic effort to estimate the burden caused by 369 diseases and 87 risk factors in 204 countries/territories.[1] The annual frequencies and age-standardized rates (ASRs) of liver cancer–related incidence, deaths, and DALYS, by sex, World Health Organization (WHO) region, and country from 2010 to 2019, were obtained from an online data source, the GlobalHealth Data Exchange (GHDx) query tool (http://ghdx.healthdata.org/gbd-results-tool). The GHDx is a data catalog created and maintained by the Institute for Health Metrics and Evaluation.

Estimation methods in the GBD 2019 study

The methods used to estimate the disease burden of liver cancer in the GBD 2019 study have been previously described.[1,5,26,27] Data were extracted from population-based cancer registries, vital registration systems, or verbal autopsy studies.[1] The GBD 2019 study provides quality assessment for the data from each county/territory, which was rated on a scale ranging from 0 (lowest quality) to 5 (highest quality). Quality ratings for the data from each country/ territory are included in Supporting Information S1.

To minimize data heterogeneity, different statistical methods including misclassification correction, garbage code redistribution, and noise reduction algorithms were used. Liver cancer–related mortality by age, sex, country/territory, and year was estimated via a Cause of Death Ensemble model, a form of Bayesian geospatial regression analysis. Incidence of liver cancer was then obtained by dividing mortality estimates by mortality-to-incidence ratios. DALYs were calculated as the sum of years of life lost and years lived with disability.[1]

The GBD study stratified causes of liver cancer cases into five etiology groups: HBV, HCV, alcohol, NASH, and other causes. The GBD collaborators performed a systematic literature search on PubMed and included population-based studies that provided data for the contribution of liver cancer etiologies to the overall incidence of liver cancer. The proportion of liver cancer cases secondary to each etiology was calculated for each study, and the pooled proportions were then used in five separate DisMod-MR 2.1 models (a Bayesian meta-regression-type model) to determine the overall proportion of liver cancers due to the five defined etiologies. Analysis was further stratified by country/territory, sex, and year. As the proportion models for age, sex, year, and location categories were run independently, the final proportions models were scaled to sum to 100% by dividing each proportion by the sum of the five proportion estimates for all etiologies of liver cancer. Liver cancer was attributed to NASH when the study specifically stated the etiology to be NASH or NAFLD. Cases in which the etiology was listed as “cryptogenic,” “idiopathic,” or “unknown” were included within the “other causes” category. The “other causes” category also included liver cancer secondary to autoimmune hepatitis, haemochromatosis, or Wilson disease. A sociodemographic index (SDI) was used to categorize countries/territories by development status—a measure that combines total fertility rate, average educational attainment in the population over age 15, and measures of income per capita (Supporting Information S2).

Data and statistical analysis

ASRs were derived using the direct method to the GBD 2019 population estimate with 5-year age groups.[1] All estimates were reported with the corresponding 95% uncertainty intervals (UIs), which were defined as the

2.5th and 97.5th ranked values across a total 1000 draws from a posterior distribution. The percentage change in any category from 2010 to 2019 was calculated by dividing the difference in values between 2010 and 2019 by the original value in 2010. The temporal change in ASRs from 2010 to 2019 was estimated by calculating the annual percentage change (APC) and corresponding 95% CIs using the Joinpoint Regression Program, version 4.6.0.0 (Statistical Research and Applications Branch, National Cancer Institute). When the APC and the lower boundary of the 95% CI were both positive, this was considered an increasing trend. When the APC and the upper boundary of the 95% CI were both negative, this was considered a decreasing trend. The ratio of female-to-male ASRs for liver cancer–related incidence and deaths were analyzed by country/territory, WHO region, and etiology of liver disease. Univariable and multivariable linear regression models were used to examine the association between country-level female-to-male ratios of overall liver cancer age-standardized death rates (ASDRs) and the geographical area of each country/territory, SDI, and etiology of liver disease. Statistical significance was defined as a two-tailed p value ≤ 0.05. Statistical analyses were conducted using Rstudio (Version 4.1.1).

RESULTS

Sex differences in the GBD 2019

Globally in 2019, there were 376,483 incident cases, 333,672 deaths, and 9,048,723 DALYs due to liver cancers in males, and 157,881 incident cases, 150,904 deaths, and 3,479,699 DALYs in females, respectively (Figure 1A; Tables 1–3). In 2019, the estimated age-standardized incident rates (ASIRs), ASDRs, and age-standardized DALYs (ASDALYs) of liver cancer in 2019 were 9.71 per 100,000 (95% UI 8.69–10.84), 8.73 per 100,000 (95% UI 7.88–9.60), and 225.28 per 100,000 (95% UI 200.39–250.17) in males, and 3.63 per 100,000 (95% UI 3.23–4.05), 3.46 per 100,000 (95% UI 3.08–3.83), and 81.28 per 100,000 (95% UI 72.72–90.34) in females, respectively (Figure 2A; Tables 1–3).

From 2010 to 2019, there was a 29% increase in incident cases of liver cancer in males, compared with a 23% increase in females. Over the same time period, the estimated annual percentage change (APC) of the ASIRs due to liver cancer increased in males (APC: 0.21%; 95% CI 0.20–0.23) but decreased in females (APC: −0.40%; 95% CI −0.44 to −0.36) (Table 1). During the study period, the frequency of deaths increased by 27% in males and 23% in females. From 2010 to 2019, ASDRs were stable in males (APC: 0.06%, 95% CI −0.10 to 0.22), but decreased in females (APC: −0.47%, 95% CI −0.57 to −0.37) (Table 2). Over the same time period, there was a 22% increase in DALYs in males, compared with 18% in females. ASDALYs remained stable in males (APC: −0.01%; 95% CI −0.34 to 0.33) and decreased in females (APC: −0.62%; 95% CI −0.77 to −0.46) (Table 3).

Sex differences in liver cancer burden, by WHO region

The estimated frequencies of incident liver cancer cases, deaths, DALYs, and rates (ASIRs, ASDRs, and ASDALYs) by sex and WHO region are summarized in Tables 1–3. The proportion of liver cancer deaths contributed by females in 2019 ranged from 28% in the Western Pacific to 37% in Africa (Figure 1B). In 2019, the Western Pacific region had the largest number of incident cases, deaths, and DALYs of liver cancer in males (217,921, 183,237, and 5,136,104, respectively) and females (77,563, 70,816 and 1,568,932, respectively) (Figure 1C,D). However, the Americas experienced the largest increase in the frequency of incident cases, deaths, and DALYs of liver cancers from 2010 to 2019 in both males (+45%, +48%, and +40%, respectively) and females (+33%, +33%, and +30%, respectively). From 2010 to 2019, the ASIRs in male patients increased in the Americas (APC: 1.43%; 95% CI 1.38–1.47) and the Western Pacific (APC: 0.37%, 95% CI 0.28–0.45) and decreased in all other WHO regions (Table 1). Over the same time period, the ASIRs in females increased only in the Americas (APC: 0.51%; 95% CI 0.49–0.54) and decreased in all other WHO regions. The ratio of female-to-male ASIRs in 2019 was 0.4 globally and ranged from 0.3 in the Western Pacific to 0.6 in the Eastern Mediterranean (Supporting Information S3A).

From 2010 to 2019, ASDRs in males increased in the Americas (APC: 1.56%; 95% CI 1.36–1.75), remained stable in the Western Pacific, and decreased in all other WHO regions, with the greatest decrease in Africa (APC: −0.91%; 95% CI −0.97 to −0.86) (Table 2). Among females, ASDRs increased only in the Americas (APC: 0.48%, 95% CI 0.32–0.64), and decreased in all other WHO regions, with the largest decrease in the Western Pacific (APC: −1.12%, 95% CI −1.25 to −0.98). The ratio of female-to-male ASDRs in 2019 was 0.4 globally and ranged from 0.3 in the Western Pacific to 0.5 in the Eastern Mediterranean (Figure 2B). By country, the ratio of female-to-male ASDRs in 2019 ranged from 0.09 (0.08–0.09) in Palau to 1.55 (1.54–1.56) in Pakistan (Figure 3A).

Sex differences in liver cancer burden, by SDI

The frequency of incident liver cancer cases, deaths, DALYs, and rates (ASIRs, ASDRs, and ASDALYs) by

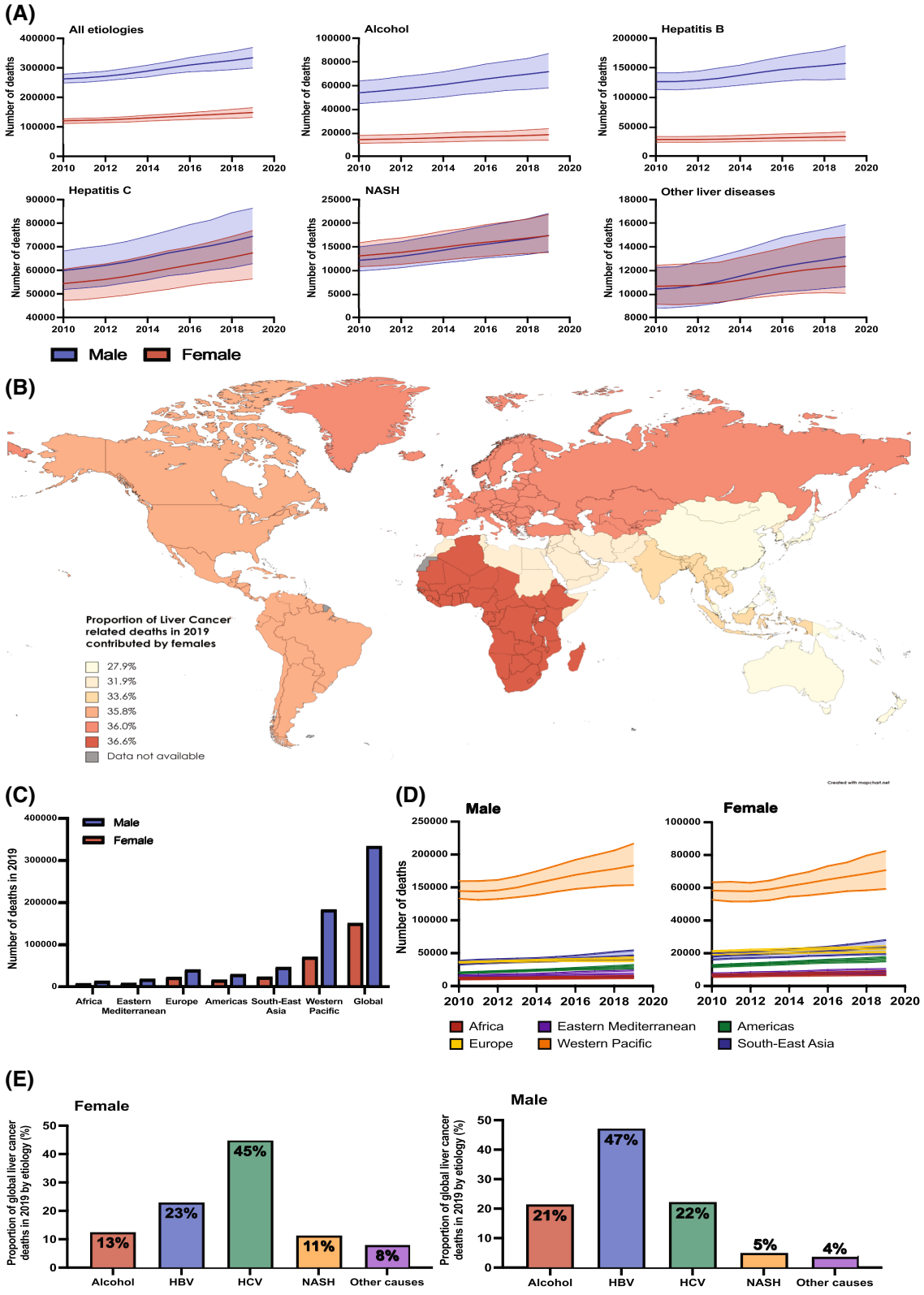

FIGURE 1 (A) Frequency of liver cancer deaths in males versus females from 2010 to 2019, by etiology of liver disease. (B) Proportion of liver cancer-related deaths contributed by females in 2019 by World Health Organization region. (C) Frequency of liver cancer–related deaths in males versus females in 2019 by World Health Organization region. (D) Frequency of liver cancer deaths in males versus females from 2010 to 2019 by World Health Organization region. (E) Contribution of global liver cancer deaths in male versus females in 2019, by etiology of liver disease

TABLE 1 Age-standardized incidence rates of liver cancer in 2010 and 2019, and the temporal trend of age-standardized incident rates from 2010 to 2019, stratified by sex

	Male			Female		
	2010 ASIR, per 100,000 (95% UI)	2019 ASIR, per 100,000 (95% UI)	APC in ASIR (95% CI)	2010 ASIR, per 100,000 (95% UI)	2019 ASIR, per 100,000 (95% UI)	APC in ASIR (95% CI)
Global	9.54 (9.03–10.13)	9.71 (8.69–10.84)	0.21 (0.20–0.23)	3.76 (3.49–3.96)	3.63 (3.23–4.05)	−0.40 (−0.44 to −0.36)
SDI						
Low SDI	5.10 (4.57–5.70)	4.79 (4.14–5.39)	−0.72 (−0.77 to −0.68)	2.75 (2.42–3.08)	2.65 (2.32–2.99)	−0.41 (−0.46 to −0.36)
Low–middle SDI	5.00 (4.60–5.41)	5.35 (4.77–5.96)	0.82 (0.58 to 1.06)	2.82 (2.50–3.11)	2.85 (2.44–3.31)	0.17 (0.13 to 0.21)
Middle SDI	11.37 (10.44–12.49)	12.41 (10.46–14.54)	1.07 (0.88 to 1.27)	4.49 (4.14–4.82)	4.43 (3.75–5.15)	−0.10 (−0.14 to −0.06)
High–middle SDI	8.35 (7.71–9.08)	8.29 (7.02–9.67)	−0.14 (−0.21 to −0.07)	3.00 (2.77–3.22)	2.75 (2.41–3.14)	−1.01 (−1.09 to −0.92)
High SDI	12.29 (11.72–12.75)	11.61 (10.44–12.95)	−0.74 (−0.85 to −0.62)	4.28 (3.84–4.52)	4.06 (3.56–4.53)	−0.63 (−0.73 to −0.53)
Region						
Africa	5.98 (5.37–6.60)	5.53 (4.90–6.21)	−0.86 (−0.89 to −0.83)	3.03 (2.68–3.38)	2.82 (2.44–3.22)	−0.82 (−0.85 to −0.79)
Eastern Mediterranean	8.70 (7.92–9.64)	8.20 (6.39–10.39)	−0.65 (−0.71 to −0.59)	4.67 (4.24–5.21)	4.57 (3.87–5.54)	−0.24 (−0.29 to −0.19)
Europe	6.81 (6.60–6.97)	6.69 (5.92–7.57)	−0.34 (−0.52 to −0.16)	2.57 (2.41–2.66)	2.56 (2.29–2.84)	−0.12 (−0.23 to −0.01)
Americas	5.00 (4.82–5.14)	5.67 (4.77–6.67)	1.43 (1.38 to 1.47)	2.31 (2.18–2.38)	2.41 (2.14–2.71)	0.51 (0.49 to 0.54)
Southeast Asia	5.60 (5.12–6.06)	5.52 (4.72–6.39)	−0.16 (−0.23 to −0.09)	2.77 (2.48–3.05)	2.65 (2.23–3.14)	−0.54 (−0.62 to −0.46)
Western Pacific	16.52 (15.10–18.15)	17.05 (14.51–20.13)	0.37 (0.28 to 0.45)	5.95 (5.34–6.46)	5.47 (4.57–6.41)	−0.98 (−1.03 to −0.92)
Etiology						
Alcohol	1.97 (1.65–2.30)	2.04 (1.65–2.46)	0.39 (0.34 to 0.44)	0.45 (0.36–0.56)	0.45 (0.35–0.57)	−0.08 (−0.20 to 0.05)
HBV	4.36 (3.89–4.85)	4.51 (3.78–5.31)	0.40 (0.33 to 0.47)	0.92 (0.78–1.08)	0.87 (0.71–1.07)	−0.62 (−0.66 to −0.59)
HCV	2.41 (2.12–2.72)	2.29 (1.94–2.66)	−0.60 (−0.65 to −0.55)	1.66 (1.45–1.85)	1.58 (1.35–1.81)	−0.59 (−0.65 to −0.53)
NASH	0.44 (0.36–0.54)	0.49 (0.40–0.62)	1.29 (1.13 to 1.44)	0.39 (0.32–0.48)	0.41 (0.32–0.50)	0.47 (0.43 to 0.51)
Other causes	0.37 (0.31–0.43)	0.39 (0.31–0.47)	0.68 (0.62 to 0.74)	0.34 (0.29–0.39)	0.32 (0.27–0.38)	−0.37 (−0.54 to −0.20)

Abbreviations: APC, annual percentage change; ASIR, age-standardized incidence rate; SDI, sociodemographic index.

TABLE 2 ASDRs of liver cancer in 2010 and 2019, and the temporal trend of ASIRs from 2010 to 2019, stratified by sex

	Male			Female		
	2010 ASDR, per 100,000 (95% UI)	2019 ASDR, per 100,000 (95% UI)	APC in ASDR (95% CI)	2010 ASDR, per 100,000 (95% UI)	2019 ASDR, per 100,000 (95% UI)	APC in ASDR (95% CI)
Global	8.78 (8.31–9.27)	8.73 (7.88–9.60)	0.06 (−0.10 to 0.22)	3.63 (3.36–3.83)	3.46 (3.08–3.83)	−0.47 (−0.57 to −0.37)
SDI						
Low SDI	5.48 (4.90–6.08)	5.12 (4.44–5.78)	−0.77 (−0.84 to −0.71)	2.94 (2.58–3.30)	2.82 (2.46–3.19)	−0.44 (−0.51 to −0.36)
Low–middle SDI	5.23 (4.79–5.63)	5.54 (4.99–6.14)	0.90 (0.66 to 1.15)	3.01 (2.66–3.32)	3.02 (2.58–3.53)	0.14 (−0.23 to 0.51)
Middle SDI	11.23 (10.37–12.31)	11.71 (9.76–13.67)	0.79 (0.48 to 1.10)	4.64 (4.29–4.98)	4.42 (3.76–5.13)	−0.35 (−0.58 to −0.13)
High–middle SDI	7.80 (7.24–8.41)	7.41 (6.4–8.49)	−0.53 (−0.84 to −0.21)	2.94 (2.73–3.16)	2.63 (2.31–2.98)	−1.27 (−1.36 to −1.17)
High SDI	9.49 (9.03–9.86)	8.86 (8.27–9.31)	−0.80 (−0.91 to −0.69)	3.47 (3.08–3.66)	3.29 (2.90–3.52)	−0.56 (−0.81 to −0.30)
Region						
Africa	6.46 (5.84–7.15)	5.94 (5.23–6.65)	−0.91 (−0.97 to −0.86)	3.25 (2.87–3.61)	3.02 (2.63–3.47)	−0.81 (−0.90 to −0.72)
Eastern Mediterranean	8.97 (8.12–9.96)	8.45 (6.59–10.76)	−0.71 (−0.96 to −0.46)	4.71 (4.21–5.24)	4.38 (3.68–5.23)	−0.74 (−1.00 to −0.47)
Europe	6.12 (5.90–6.26)	5.93 (5.52–6.40)	−0.44 (−0.62 to −0.25)	2.44 (2.28–2.53)	2.39 (2.20–2.55)	−0.27 (−0.41 to −0.13)
Americas	4.44 (4.26–4.57)	5.08 (4.55–5.54)	1.56 (1.36 to 1.75)	2.26 (2.13–2.34)	2.36 (2.17–2.54)	0.48 (0.32 to 0.64)
Southeast Asia	5.86 (5.34–6.31)	5.74 (4.90–6.72)	−0.27 (−0.43 to −0.11)	2.97 (2.66–3.28)	2.80 (2.31–3.34)	−0.66 (−1.07 to −0.24)
Western Pacific	14.66 (13.48–16.06)	14.51 (12.26–16.98)	0.04 (−0.39 to 0.48)	5.50 (4.94–5.97)	4.97 (4.17–5.79)	−1.12 (−1.25 to −0.98)
Etiology						
Alcohol	1.84 (1.54–2.18)	1.88 (1.53–2.28)	0.34 (0.24 to 0.44)	0.44 (0.35–0.54)	0.44 (0.33–0.55)	−0.11 (−0.23 to 0.01)
HBV	3.98 (3.56–4.46)	3.95 (3.30–4.67)	0.05 (−0.16 to 0.26)	0.86 (0.73–1.02)	0.80 (0.65–0.97)	−0.77 (−0.89 to −0.66)
HCV	2.20 (1.93–2.49)	2.09 (1.77–2.41)	−0.58 (−0.66 to −0.49)	1.63 (1.41–1.80)	1.54 (1.29–1.75)	−0.60 (−0.72 to −0.48)
NASH	0.43 (0.35–0.53)	0.47 (0.38–0.59)	1.22 (1.06 to 1.38)	0.39 (0.32–0.47)	0.40 (0.32–0.50)	0.37 (0.32 to 0.42)
Other causes	0.34 (0.28–0.39)	0.35 (0.28–0.42)	0.48 (0.29 to 0.67)	0.32 (0.27–0.37)	0.30 (0.25–0.35)	−0.52 (−0.66 to −0.38)

TABLE 3 Age-standardized disability-adjusted life-years rates of liver cancer in 2010 and 2019 and the temporal trend of ASIRs from 2010 to 2019, stratified by sex

	Male			Female		
	2010 ASDALYs, per 100,000 (95% UI)	2019 ASDALYs, per 100,000 (95% UI)	APC in ASDALYs (95% CI)	2010 ASDALYs, per 100,000 (95% UI)	2019 ASDALYs, per 100,000 (95% UI)	APC in ASDALYs (95% CI)
Global	227.93 (215.75–243.13)	225.28 (200.39–250.17)	−0.01 (−0.34 to 0.33)	86.10 (81.17–90.77)	81.28 (72.72–90.34)	−0.62 (−0.77 to −0.46)
SDI						
Low SDI	136.74 (121.53–152.71)	128.93 (110.41–147.16)	−0.64 (−0.69 to −0.58)	77.09 (68.19–86.80)	74.25 (64.19–84.99)	−0.39 (−0.45 to −0.33)
Low–middle SDI	137.63 (126.88–147.73)	144.59 (128.75–161.40)	0.79 (0.51 to 1.07)	75.43 (67.39–82.72)	75.21 (64.16–87.63)	0.04 (−0.33 to 0.40)
Middle SDI	304.83 (280.68–336.43)	315.48 (261.15–368.16)	0.72 (0.39 to 1.04)	109.86 (101.94–118.06)	103.05 (87.64–120.31)	−0.56 (−0.89 to −0.22)
High–middle SDI	208.61 (192.80–227.65)	197.90 (168.53–230.44)	−0.54 (−0.83 to −0.27)	70.61 (65.76–75.59)	62.08 (54.55–70.63)	−1.45 (−1.56 to −1.35)
High SDI	222.49 (215.16–230.17)	202.98 (190.92–212.64)	−1.04 (−1.16 to −0.92)	72.92 (67.86–75.67)	68.10 (62.77–71.81)	−0.82 (−1.01 to −0.64)
Region						
Africa	159.71 (143.26–177.91)	147.55 (128.90–167.95)	−0.84 (−0.91 to −0.76)	81.49 (71.50–90.71)	75.72 (64.08–88.92)	−0.79 (−0.88 to −0.69)
Eastern Mediterranean	232.57 (209.46–260.99)	211.89 (162.06–274.96)	−1.08 (−1.31 to −0.84)	116.66 (105.06–130.84)	107.72 (89.26–129.88)	−0.82 (−1.11 to −0.53)
Europe	143.25 (139.54–146.27)	137.32 (127.87–148.54)	−0.56 (−0.73 to −0.39)	54.86 (52.37–56.74)	53.50 (49.97–57.09)	−0.35 (−0.48 to −0.21)
Americas	109.10 (106.01–112.04)	121.68 (108.92–132.81)	1.28 (1.11 to 1.45)	52.84 (50.72–54.40)	54.73 (51.08–58.03)	0.33 (0.26 to 0.41)
Southeast Asia	148.66 (136.22–160.63)	143.52 (122.18–168.06)	−0.54 (−0.78 to −0.30)	69.75 (62.84–76.53)	65.43 (54.20–77.80)	−0.80 (−1.17 to −0.44)
Western Pacific	389.84 (356.83–432.97)	392.42 (325.58–469.09)	0.26 (−0.21 to 0.73)	127.26 (116.22–138.57)	114.37 (95.97–134.91)	−1.18 (−1.33 to −1.02)
Etiology						
Alcohol	42.94 (35.70–51.22)	43.69 (35.59–52.75)	0.29 (0.17 to 0.42)	10.14 (7.99–12.59)	10.00 (7.62–12.59)	−0.14 (−0.29 to 0.02)
HBV	119.28 (107.45–133.09)	117.92 (98.74–139.75)	0.05 (−0.43 to 0.53)	24.54 (21.02–28.37)	22.40 (18.33–27.17)	−1.01 (−1.16 to −0.85)
HCV	44.23 (37.90–50.63)	41.10 (34.22–48.07)	−0.82 (−1.02 to −0.62)	31.54 (27.45–35.26)	29.60 (25.09–34.03)	−0.70 (−0.83 to −0.57)
NASH	9.63 (7.96–11.81)	10.60 (8.50–13.16)	1.19 (1.02 to 1.36)	8.53 (7.13–10.24)	8.76 (7.15–10.87)	0.40 (0.25 to 0.54)
Other causes	11.86 (10.23–13.66)	11.98 (10.00–13.97)	0.30 (0.10 to 0.50)	11.36 (9.99–12.82)	10.52 (8.89–12.30)	−0.77 (−1.01 to −0.52)

Abbreviations: ASDALY, age-standardized disability-adjusted life-years rate.

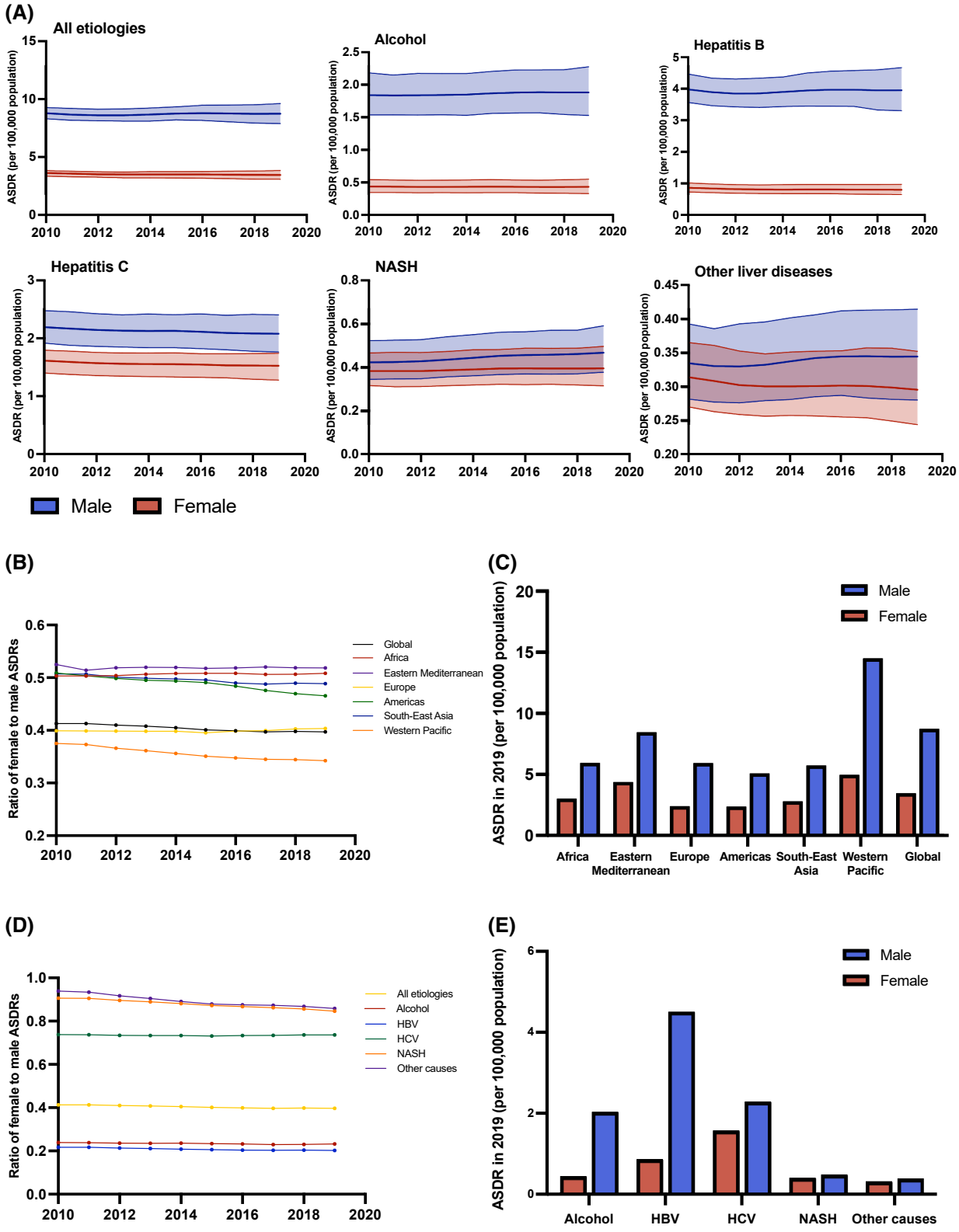

FIGURE 2 (A) Age-standardized death rates (ASDRs) of liver cancer in males versus females from 2010 to 2019 by etiology of liver disease. (B) Ratio of female-to-male ASDRs of liver cancer from 2010 to 2019 by World Health Organization region. (C) ASDRs of liver cancer in males versus females in 2019 by World Health Organization region. (D) ASDRs of liver cancer in males versus females in 2019 by etiology of liver disease. (D) Female-to-male ratios of ASDR of liver cancer from 2010 to 2019, by etiology of liver disease

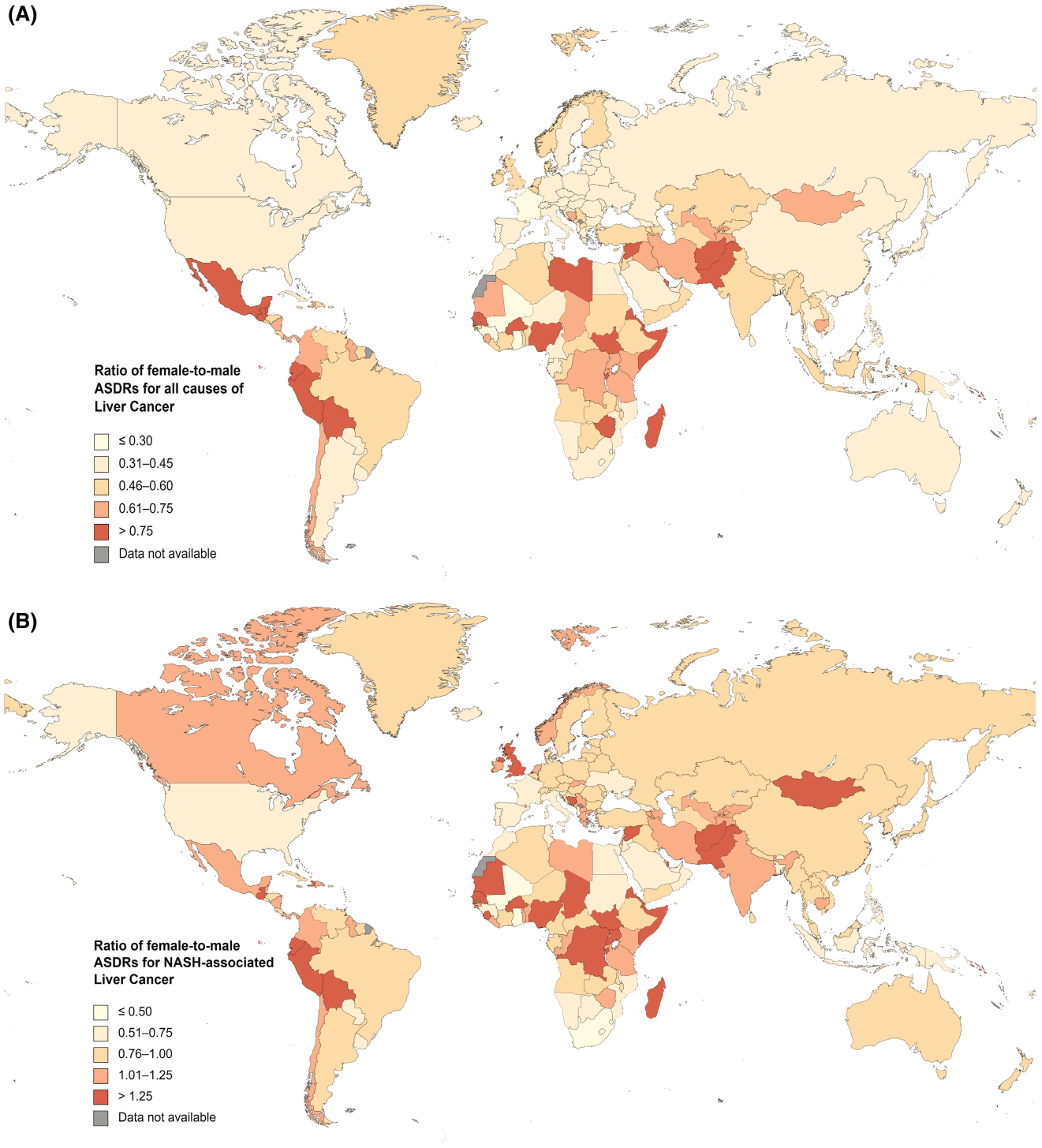

FIGURE 3 (A) Female-to-male ratios of ASDRs of liver cancer (from all etiologies) in 2019, by country/territory. (B) Female-to-male ratios of ASDRs of NASH-associated liver cancer in 2019, by country/territory

SDI and sex are summarized in Tables 1–3. In 2019, middle-SDI countries had the largest frequency of incident cases, deaths, and DALYs due to liver cancer in males (153,711, 141,250, and 4,102,975, respectively) and females (56,836, 55,709, and 1,360,790, respectively). The largest increase in incident cases and ASIRs of liver cancer from 2010 to 2019 was in the middle-SDI countries for males, and low–middle-SDI countries for females. The greatest increase in the frequency of deaths (+37%) and ASDRs (APC: 0.90, 95% CI 0.66–1.15) due to liver cancer were in low–middle-SDI countries for males. Among females, the greatest increase in the frequency of deaths (+34%) in females occurred in low–middle-SDI countries, while ASDRs

remained stable in low–middle-SDI countries and decreased in all other SDI groups.

Sex differences in the burden of liver cancer, by etiology

The frequency of incident liver cancer cases, deaths, DALYs, and rates (ASIRs, ASDRs, and ASDALYs) by etiology of liver disease and sex are summarized in Tables 1–3. In 2019, the leading causes of liver cancer deaths in males and females were HBV (47%) and HCV (45%), respectively (Figure 1E). However, between 2010 and 2019, NASH was the fastest growing etiology of incident liver cancer cases in both males (+44%) and females (+33%). Over the same time period, NASH was the etiology with the greatest increase in ASIRs in males (APC: 1.29%; 95% CI 1.13–1.44) and females (APC: 0.47%, 95% CI 0.43–0.51). In males, liver cancer ASIRs from HBV, alcohol, and other causes increased, while ASIRs from HCV-associated liver cancer decreased (APC: −0.60, 95% CI −0.65 to −0.55) (Table 1). Among females, ASIRs of all other etiologies apart from NASH either remained stable or decreased, with the largest decline in HBV-associated liver cancer (APC: −0.62%, 95% CI −0.66 to −0.59).

There was considerable variation by etiology of liver disease, and the ratio of female-to-male ASIRs due to liver cancer in 2019 was lowest in HBV (0.2), and highest in NASH (0.8) and other causes (0.8) (Supporting Information S3B).

From 2010 to 2019, NASH was the fastest growing etiology of liver cancer–related deaths in both males (+43%) and females (+33%) and had the greatest increase in ASDRs in both males (APC: 1.22%, 95% CI 1.06–1.38) and females (APC: 0.37%, 95% CI 0.32–0.42) (Table 2, Figure 1A, Supporting Information S3D,E). Among males, ASDRs of liver cancer due to alcohol and other causes increased; ASDRs of liver cancer due to HBV remained stable; and ASDRs of HCV decreased (APC: −0.58%, 95% CI −0.66 to −0.49). Among females, the ASDRs of liver cancers from all other etiologies apart from NASH either remained stable or decreased, with the greatest decrease in liver cancer due to HBV (APC: −0.77%, 95% CI −0.89 to −0.66). The ratio of female-to-male ASDRs due to liver cancer in 2019 was lowest in HBV (0.20), and highest in NASH (0.9) and other causes (0.9) (Figure 2D). DALYs due to NASH-associated liver cancer were similar between males and females, but higher in males for all other etiologies of liver disease (Table 3). In multivariable analysis of the country-level female-to-male ratio of ASDRs due to liver cancer in 2019, NASH (β: 2.193; SEM: 0.508; $p < 0.001$; Supporting Information S4) and other causes (β: 5.929; SEM: 0.816; $p < 0.001$) were associated with a higher female-to male ratios of ASDRs, whereas HBV was associated with a lower female-to-male ratio of ASDRs (β: −0.351; SEM: 0.097; $p < 0.001$), after adjusting for geographical area and SDI. High SDI (β: −0.087; SEM: 0.039; $p = 0.026$) and high–middle SDI (β: −0.061; SEM: 0.036; $p = 0.095$) were associated with lower female-to-male ratios of ASDRs due to liver cancer in 2019, whereas low SDI was associated with an increased female-to-male ratio of ASDRs (β: 0.149; SEM: 0.039; $p < 0.001$), after adjusting for geographical area and etiology of liver cancer.

Sex differences in the burden of liver cancer, by etiology and region

The ASIRs, ASDRs, ASDALYs, and APCs in these rates between 2010 and 2019 stratified by sex, etiology, and region are summarized in Supporting Informations S5–S7. Among males, the ASDRs of NASH-associated liver cancers increased in five of six WHO regions from 2010 to 2019, with the greatest increase in the Americas (APC: 1.86%; 95% CI 1.75–1.97), and declined only in Africa (APC: −0.36%; 95% CI; −0.53 to −0.19). Among females, the greatest increase in ASDRs of NASH-associated liver cancer was in the Eastern Mediterranean (APC: 0.82%; 95% CI 0.53–1.11). ASDRs due to NASH-associated liver cancer in females also increased in Europe and the Americas and remained stable in the other WHO regions. The ratio of female-to-male ASDRs in 2019 for NASH-associated liver cancer ranged from 0.8 in the Americas to 1.0 in Southeast Asia. By country, the ratio of female-to-male ASDRs in 2019 for NASH-associated liver cancer ranged from 0.17 (0.16–0.44) in Eswatini to 3.12 (2.95–3.52) in Senegal (Figure 3B). Among females, ASDRs from liver cancer due to alcohol, HBV, HCV, and other causes increased only in the Americas, and declined or remain stable in all other WHO regions (Supporting Information S6).

DISCUSSION

Main findings

Using data from the GBD 2019 study, we determined that the global burden of liver cancer remains higher in males versus females, with a greater number of incident cases (376,000 vs. 158,000), deaths (334,000 vs. 151,000), and DALYs (9,049,000 vs. 3,480,000) in 2019. Between 2010 and 2019, there was a greater increase in the frequency of incident cases, deaths, and DALYs in males compared with females. Among males, ASIRs due to liver cancer increased (APC: 0.21%) and ASDRs remained stable, whereas ASIRs (APC: −0.40%) and ASDRs (APC: −0.47%) declined in females. Although the Western Pacific accounted for the greatest number

of liver cancer deaths in 2019 among both males and females, ASDRs during the study period remained stable among males and declined among females (APC: −1.12%). In contrast, ASDRs for both males (APC: 1.56%) and females (APC: 0.48%) rose sharply only in the Americas and remained stable or declined in other world regions.

NASH was the fastest rising cause of age-adjusted cancer incidence and deaths in males (APCs: 1.29%; 1.22%) and females (APCs: 0.47%; 0.37%). The ASIRs (female-to-male ratio 0.8) and ASDRs (female-to-male ratio 0.9) due to NASH-associated liver cancer in 2019 of females approached that of males, unlike other etiologies of liver cancer where males had substantially higher ASIRs and ASDRs. We speculate that patients with NASH-associated liver cancer tend to be older, diminishing the protective influence of estrogen due to the onset of menopause in females, but this hypothesis requires validation.[14,20] The burden of NASH-associated liver cancer in females is rising rapidly.[5,28,29] There is a need to increase awareness among care providers that the risk of liver cancer among females with NASH approaches that of males, and HCC surveillance should be provided for both males and females with NASH cirrhosis when clinically appropriate.[23,30,31] Several experts in the field have proposed a change of nomenclature from NAFLD to metabolic associated fatty liver disease (MAFLD), which does not require the exclusion of concomitant liver diseases.[32,33] The rise in the burden of NASH-associated liver cancer in male and female patients is in parallel with the rising prevalence of obesity.[34] Worryingly, obesity rates are projected to increase in the future.[35–37] The rising obesity rates and increasing alcohol-per-capita consumption may result in an increase in the proportion of patients with liver cancer attributed to MAFLD in the future, should this new nomenclature be adopted.[32,33,38] Measures are required at a global level to reduce the prevalence of obesity and diabetes to slow the growth of NASH-associated liver cancer in both males and females.[39–41]

HBV was the first and second leading cause of liver cancer deaths in 2019 for male and females, respectively. The ASDRs for HBV-associated liver cancer remained stable over the study period among males and declined in females (APC: −0.77%). These data emphasize that continued efforts are required to continue to improve vaccination coverage, screening, and access to care for HBV.[6,8,10,42] HCV was the first and second leading cause of liver cancer deaths in 2019 for females and males, respectively. ASDRs for HCV-associated liver cancer in males (APC: −0.58%) and females (APC: −0.60%) declined over the study period, which may be related to the increasing availability of highly efficacious directly acting antiviral (DAA) therapy; however, a longer time period will be required to assess the impact of DAAs on liver cancer mortality rates in registry data.[43] Alcohol was the third leading cause of liver cancer death in 2019 for both males and females. The ASDRs for alcohol-associated liver cancer increased in males (APC: 0.34%) and declined in females (APC: −0.11%), highlighting the ongoing need for policies to reduce alcohol consumption in countries with high alcohol-per-capita consumption.[44] While ASDRs for alcohol-associated liver cancer in men increased from 2010 to 2019 in parallel with increasing alcohol consumption, there was no corresponding increase in ASDRs for alcohol-associated liver cancer in females. However, the male-to-female ratio of alcohol-per-capita consumption globally was around 2.8,[38] and the rise in global alcohol-per-capita consumption may have disproportionately increased the burden of alcohol-associated liver cancer in males compared with females. In addition, we speculate that the lack of a recorded increase in ASDRs from alcohol-associated liver cancer in females may have contributed by underdiagnosis and stigma, but more data are required to confirm this. It is notable that among females, the ASDRs from liver cancer due to alcohol, HBV, HCV, and other causes increased only in the Americas, and remained stable or declined in all other WHO regions, emphasizing the need for greater efforts to combat the rise of liver cancer among females in the Americas.

In context with current literature

Our study builds on previous studies of GBD 2015, GBD 2017, and GBD 2019[5,26,27] by providing an updated global perspective of sex differences in liver cancer burden by region, SDI, and etiology of liver disease. These data validate several country-specific and region- specific cohort studies that did not find significant differences in the burden of NASH-associated liver cancer between males and females.[23–25,45] In contrast, a study of patients with NAFLD from the United States Veterans Health Administration found an increased incidence of NAFLD-associated HCC in males versus females.[46] However, this study was conducted among US Armed Forces veterans, and more than 94% of included participants were male; hence, it is unclear whether its findings can be extrapolated to females in the general population.

Strengths and limitations

The current study provides an updated global perspective on the comparative burden of liver cancer between males and females in the recent decade. However, our study shares the same limitations as the GBD 2019

study. In particular, the availability of primary data was dependent on the quality of each country's registry.[1] In cases in which data were not available, the GBD 2019 study used statistical modeling to extrapolate data from past trends, possibly resulting in discrepancies in the accuracy of data. Therefore, reliable death certification is required for greater accuracy when estimating trends in disease burden. In addition, there was likely to be underreporting of data in regions such as Africa and Southeast Asia, due to a lack of disease awareness and access to care. It is likely that the burden of NASH-associated liver cancer was underestimated in the GBD 2019 study, as individuals with cryptogenic liver disease were classified under "other causes of liver cancer," given the lack of International Classification of Diseases codes for NASH. Although it is possible that some patients with cured HCV may have been wrongly classified as NASH, the GBD 2019 used the seroprevalence of hepatitis C IgG as a covariate to determine the proportion of liver cancer cases caused by HCV, which may have reduced this risk. It is possible that increasing awareness and registration of NASH as an etiological factor may have contributed to higher recorded rates of NASH-associated liver cancer incidence and deaths; however, the extent is unclear, and more data are required to determine this. Data regarding the histological subgroups of liver cancer such as HCC or cholangiocarcinoma were also lacking. Finally, the estimates in our study were obtained from a single database. However, the estimates of the ASRs of liver cancer mortality in the GBD 2019 study were found to be fairly similar to other data sources, such as the Global Cancer Observatory (GCO) by the International Agency for Research on Cancer and the Mortality Database by the WHO, although there were differing trends in several countries, such as in Africa and South America.[47] The GBD 2019 study used data from cancer registries, autopsy data, and published literature along with vital registration data, unlike the GCO and WHO mortality databases which relied on civil registration and vital registration data. In addition, the GBD 2019 study used complex modeling and adjustment methodology. These factors may have contributed to some differences in the estimates from the various databases.

The global burden of liver cancer was substantially higher in males compared with females. However, the burden of NASH-associated liver cancer in females approached that of males. The greatest increase in age-adjusted death rates due to liver cancer in both males and females occurred in the Americas. Measures are required to tackle metabolic risk factors to slow the rise of NASH-associated liver cancer in both males and females.

AUTHOR CONTRIBUTIONS

Study concept: Daniel Q. Huang and Rohit Loomba. *Data curation*: Darren Jun Hao Tan and Daniel Q. Huang. *Formal analysis and interpretation*: Darren Jun Hao Tan and Daniel Q. Huang. *Study supervision*: Daniel Q. Huang and Mark D. Muthiah. *Validation*: Cheng Han Ng and Wen Hui Lim. *Manuscript draft*: Darren Jun Hao Tan and Daniel Q. Huang. *Writing, review, and editing*: Darren Jun Hao Tan, Veronica Wendy Setiawan, Cheng Han Ng, Wen Hui Lim, Mark D. Muthiah, Eunice X. Tan, Yock Young Dan, Lewis R. Roberts, Rohit Loomba, and Daniel Q. Huang. All authors have read and approved the final version of the manuscript for submission.

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All authors have made substantial contributions to all of the following: (1) the study concept and design, acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be submitted. No writing assistance was obtained in the preparation of the manuscript. The manuscript, including related data, figures and tables has not been previously published and that the manuscript is not under consideration elsewhere.

The maps were created using mapchart.net.

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CONFLICT OF INTEREST

Daniel Huang consults for Eisai. Lewis R. Roberts advises and received grants from Bayer, Exact Sciences, and Gilead Sciences. He consults for AstraZeneca, Global Science, MJH Life Sciences, Novartis Venture Fund, Pontifax, and Roche. He advises Eisai, Genentech, GRAIL, Hepion, and The Lynx Group. He received grants from Boston Scientific, Fujifilm, Glycotest, RedHill, and TARGET PharmaSolutions. Rohit Loomba consults for and received grants from AstraZeneca, Bristol-Meyers Squibb, Eli Lilly, Galmed, Gilead, Intercept, Inventiva, Janssen, Madrigal, Merck, NGM Biopharmaceuticals, and Pfizer. He consults for Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, CohBar, Glympse Bio, Hightide, Inipharm, Ionis, Metacrine, Novartis, Novo Nordisk, Sagimet, Theratechnologies, 89 Bio, and Viking Therapeutics. He received grants from Allergan, Boehringer-Ingelheim, Galectin Therapeutics, Genfit, and Sonic Incytes. He is the co-founder of Liponexus Inc.

DATA AVAILABILITY STATEMENT

Data from the Global Burden of Disease study in 2019 can be accessed using the GlobalHealth Data

Exchange query tool (http://ghdx.healthdata.org/gbd-results-tool), which is maintained by the Institute for Health Metrics and Evaluation.

ETHICAL STATEMENT

The study was conducted in accordance with the Declaration of Helsinki. The study was exempt from internal review board review, as no confidential patient information was involved.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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