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Attributable liver cancer deaths and disability-adjusted life years in China and worldwide: profiles and changing trends

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ABSTRACT

Objective: Liver cancer is a major health concern globally and in China. This analysis investigated deaths and disability-adjusted life years (DALYs) with respect to etiologies and risk factors for liver cancer in China and worldwide.

Methods: Global and China-specific data were collected on liver cancer deaths, DALYs, and age-standardized rates (ASRs) from the Global Burden of Disease Study 2019 database. Liver cancer etiologies were classified into five groups and risk factors were categorized into three levels. Each proportion of liver cancer burden was calculated in different geographic regions. The joinpoint regression model were used to assess the trends from 1990–2019.

Results: Liver cancer accounted for 484,577 deaths worldwide in 2019 with an ASR of 5.9 per 100,000 population. China had an elevated liver cancer death ASR in 2019 and males had an ASR 1.7 times the global rate. The global ASR for DALYs peaked at 75–79 years of age but peaked earlier in China. Hepatitis B virus was the prominent etiology globally (39.5%) and in China (62.5%), followed by hepatitis C virus and alcohol consumption. In high sociodemographic index countries, non-alcoholic steatohepatitis has gained an increasing contribution as an etiologic factor. The liver cancer burden due to various etiologies has decreased globally in both genders. However, metabolic risk factors, particularly obesity, have had a growing contribution to the liver cancer burden, especially among males.

Conclusions: Despite an overall decreasing trend in the liver cancer burden in China and worldwide, there has been a rising contribution from metabolic risk factors, highlighting the importance of implementing targeted prevention and control strategies that address regional and gender disparities.

KEYWORDS Liver cancer; deaths; risk factors; global; China

Introduction

Liver cancer is one of the most common cancers and poses a significant threat to the health of people worldwide. Liver cancer ranks sixth in cancer incidence and third in cancer mortality[1]. Approximately 75% of liver cancer cases occur in Asia, with China accounting for > 50% of the global burden[2,3]. The incidence of liver cancer has declined in many countries over the past few decades, especially in formerly high-burden countries in Asia[2,4]. Nevertheless, the incidence of liver cancer is increasing in some formerly low-rate areas, such as the United States[5]. Prevention and control measures for liver cancer clearly need to be strengthened.

Several modifiable risk factors have been well-established in liver cancer, including infectious factors [hepatitis B virus (HBV) and hepatitis C virus (HCV)], behavioral factors, and metabolic factors, the distribution of which varies widely across the globe[6-8]. The substantial variation in the disease burden of liver cancer in different geographic regions globally largely stems from the changing etiology of liver cancer, transitioning from virus-related liver disease patients to patients with non-viral causes, including alcohol- and metabolic dysfunction-related fatty liver diseases[7,8]. HBV infection is the leading cause of liver cancer, and deaths attributable to smoking and alcohol consumption are significantly higher in males than females[9]. Furthermore, lifestyle-related factors, such as alcohol consumption and obesity, are increasingly

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becoming prominent causes of liver cancer in Western countries. Aflatoxin exposure from contaminated food products is a significant risk factor for liver cancer in some geographic regions. Additionally, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (NASH) have emerged as important causes of liver cancer, especially in countries with high obesity rates[4,10,11].

With continuous changes in relevant risk factors and the widespread implementation and active promotion of primary and secondary prevention over the past few years, liver cancer disease burden trends have undergone significant changes globally. Despite a wealth of evidence relevant to liver cancer epidemiology, there is a lack of research comparing the high liver cancer disease burden in China and the average global level, which reflects unharmonized databases and dispersed information. Moreover, few studies have focused on both etiologies and risk factors, and the impact of weaker risk factors. The current study quantified the attributable liver cancer deaths and disability-adjusted life years (DALYs) in China and worldwide using detailed up-to-date data at the national level. The purpose of the study was to provide empirical evidence for understanding the current and over time liver cancer burden, as well as the liver cancer etiologies and risk factors in China and around the world. Furthermore, it can give evidence on achieving etiologic prevention and formulating targeted and effective liver cancer prevention and control policies globally and regionally.

Methods

Data source

The Global Burden of Disease (GBD) 2019, which included 204 countries and territories, estimated the incidence, deaths, and DALYs for 369 diseases and injuries in both genders. The general estimation methods for the GBD 2019 and the approach to estimating the liver cancer disease burden have been detailed in previous studies[12,13]. Liver cancer deaths were proportionally allocated to primary liver cancer and extrahepatic primary sites that metastasized to the liver, leading to fewer deaths attributed to liver cancer in the GBD 2019[13]. Multiple statistical methods were used to minimize data heterogeneity. The Cause of Death Ensemble model (CODEm) was utilized for Bayesian geospatial regression analysis to estimate mortality stratified by age, gender, location, and year. The GBD 2019 used the DALYs metric, which measures the gap between the current health of the population and a normative standard life expectancy spent in full health[12,13]. Our data were retrieved from the Global Health Data Exchange repository (http://ghdx.healthdata.org/gbd-results-tool), which is managed by the Institute for Health Metrics and Evaluation at the University of Washington (Seattle, WA, USA).

The GBD 2019 spatial range was divided into 4 categories: global; sociodemographic; epidemiologic similarity and geographic proximity; and individual countries or geographic regions. For the second category, the sociodemographic index (SDI), a composite indicator that measures per-capita income, average education level, and total fertility rate, was used to divide countries and regions into 5 super regions (low, low-middle, middle, high-middle, and high SDI). The third category, based on epidemiologic similarity and geographic closeness, divided the world into 21 geographic regions. The fourth category included 204 separate countries or geographic regions.

Etiologies and risk factors attributable to liver cancer

Within the GBD disease classification framework, the etiology of liver cancer was categorized into five groups (HBV, HCV, alcohol-related, NASH, and other causes). Etiologies described as "cryptogenic," "idiopathic," or "unknown" were grouped under "other causes." Additional liver disease etiologies, such as hemochromatosis, autoimmune hepatitis, and Wilson's disease, were also classified under "other causes." The proportions of liver cancer due to these five specific etiologies were calculated using five independent DisMod-MR 2.1 models. Each model was scaled to 100% within each age, gender, year, and location by dividing the estimates from each model by the sum of all five models.

The GBD 2019 introduced an innovative comparative risk assessment approach founded on a causal framework and a hierarchy of risk factors. The 87 risk factors encompassed within the GBD 2019 were broadly categorized into 5 hierarchical levels (0–4) according to the GBD 2019 criteria[14]. Risk factors for liver cancer outlined by the GBD 2019 included 0–3 levels. The level 0 risk factor was all risk factors combined. The level 1 risk factors were behavioral and metabolic factors. The level 2 risk factors included five risk factors (alcohol use, drug use, tobacco, high body-mass index [BMI], and high fasting plasma glucose). Level 3 included only one risk factor (smoking). The analysis primarily focused on evaluating the percentage contribution of the level 2 leading risk factors that could be attributed to liver cancer deaths and DALYs.

Statistical analysis

First, the global number and age-standardized rates (ASRs) of liver cancer deaths and DALYs by SDI and GBD regions were extracted. The proportion of liver cancer cases due to the five etiology groups included in the GBD and the global and China percentages of liver cancer deaths and DALYs due to the five etiology groups stratified by age groups and gender were determined. Next, the global proportion of liver cancer deaths and DALYs due to the five etiology groups and second-level risk factors based on the SDI and GBD regions was determined. Finally, the temporal change in attributable age-standardized death and DALY rates from 1990–2019 were analyzed using the joinpoint regression model. The average annual percentage change (AAPC) was used to quantify the overall time trend. An AAPC estimation and 95% CI lower boundary > 0 indicated an increasing trend. In contrast, a decreasing trend was noted if the AAPC estimation and 95% CI upper boundary were both < 0. Joinpoint regression model analysis was performed using the Joinpoint Regression Program (version 5.0; Statistical Research and Applications Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA). Statistical significance was defined as a two-tailed $P \leq 0.05$. Statistical analyses were conducted using R studio (version 4.3.3).

Results

Global liver cancer burden based on the SDI and GBD regions

Liver cancer caused 484,577 deaths globally in 2019 with an age-standardized death rate (ASDR) of 5.9 per 100,000 population. The ASDRs for males and females were 8.7 and 3.5 per 100,000 population, respectively. The number of liver cancer deaths in China was 187,700 and the total ASDR (9.4 per 100,000 population) was significantly higher than the worldwide ASDR. The number of liver cancer deaths among males was 14.6 per 100,000 population (1.7 times the global rate). Liver cancer death rates varied across different SDI countries. Among the 21 global regions, the high-income Asia Pacific area had the highest ASDR (10.8 per 100,000 population), followed by East Asia (9.4 per 100,000 population); Southern Latin America reported the lowest ASDR (2.4 per 100,000 population; **Table 1**).

The global liver cancer DALYs was approximately 12.5 million, with an age-standardized DALYs rate (ASDALYs) of 151.1 per 100,000 population in 2019. The ADALYs rate in China was 264.3 per 100,000 population. Males in China had a higher liver cancer burden than East Asia, whereas females had a lower liver cancer burden. The middle SDI countries exhibited the highest overall DALYs and ASDALYs for liver cancer, followed by the high and high-middle SDI countries. Asia, especially East (263.4 per 100,000 population), Central (213.5 per 100,000 population), and Southeast Asia (177.5 per 100,000 population), bore the brunt of the liver cancer burden; the high-income Asia Pacific area (238.6 per 100,000 population) was second only to East Asia (**Table 1**).

Global and China liver cancer deaths and DALYs by gender, age, and etiology

Globally, deaths and DALY rates increased as age advanced, indicating a significant liver cancer burden. Global male deaths reached a peak at 65–69 years of age. The disparity between male and female deaths was apparent with males exhibiting higher liver cancer deaths and DALYs rates in all age groups, and the deaths among females in older age groups increased. The trends in China death rates aligned with the global pattern with a pronounced increase in the older age group. The global ASR for DALYs in 2019 peaked in the 75–79 year age group for both males and females and peaked earlier in China for males and females in the 65–69 and 70–74 year age groups, respectively (**Figure 1**).

The distribution of liver cancer etiology varied significantly with age and gender. HBV was a leading cause of liver cancer across all age groups and was particularly pronounced in males worldwide and in China. Globally, the proportion of liver cancer cases caused by HCV was higher across all age groups compared to China and females had a higher burden of HCV infection than males. Notably, the contribution of alcohol use, NASH, and other liver cancer etiologies increased with age. HBV remained a dominant cause of liver cancer in China. The proportional impact of HCV, alcohol use, and NASH varied across different age groups, with a notable increase in the contribution of NASH in older age groups, especially among

Table 1 Deaths and DALYs of liver cancer worldwide, by SDI and GBD regions in 2019

Regions	Deaths						DALYs					
	Both		Male		Female		Both		Male		Female	
	Number	ASR	Number	ASR	Number	ASR	Number	ASR	Number	ASR	Number	ASR
World	484,576.6	5.9	333,672.6	8.7	150,904.1	3.5	12,528,421.5	151.1	9,048,722.6	225.3	3,479,698.9	81.3
China	187,699.6	9.4	139,025.6	14.6	48,674.0	4.8	5,325,460.7	264.3	4,145,795.1	414.9	1,179,665.6	115.9
SDI												
Low SDI country	20,756.0	3.9	13,029.5	5.1	7,726.5	2.8	663,783.6	101.2	406,359.2	128.9	257,424.4	74.2
Low-middle SDI country	572,40.7	4.2	36,287.4	5.5	20,953.3	3.0	1,616,487.8	109.0	1,049,300.3	144.6	567,187.5	75.2
Middle SDI country	196,958.9	7.9	141,249.6	11.7	55,709.3	4.4	5,463,765.1	206.9	4,102,975.5	315.5	1,360,789.7	103.0
High-middle SDI country	97,189.3	4.8	67,566.5	7.4	29,622.8	2.6	2,502,034.3	127.3	1,850,349.5	197.9	651,684.8	62.1
High SDI country	112,239.9	5.9	75,412.0	8.9	36,827.9	3.3	2,277,515.6	133.1	1,636,422.5	203.0	641,093.1	68.1
Region												
Central Europe	7,201.6	3.4	4,555.8	5.0	2,645.8	2.1	156,613.9	79.1	104,221.1	116.4	52,392.8	47.8
Eastern Europe	9,675.8	2.9	5,635.9	4.4	4,039.9	1.9	234,700.6	74.9	148,008.2	114.0	86,692.4	46.7
Western Europe	40,296.1	4.4	26,576.5	6.6	13,719.6	2.5	787,716.6	98.5	552,244.9	147.9	235,471.6	53.5
Central Asia	6,191.3	8.7	3,648.2	11.8	2,543.0	6.5	172,829.7	213.5	106,480.2	289.2	66,349.4	152.6
East Asia	193,863.9	9.4	143,103.3	14.4	50,760.7	4.8	5,491,479.5	263.4	4,264,611.4	412.7	1,226,868.1	116.2
South Asia	38,650.3	2.8	24,175.4	3.6	14,474.9	2.1	1,085,515.4	71.3	680,958.5	90.0	404,556.9	52.9
Southeast Asia	42,862.1	7.3	29,273.3	10.8	13,588.8	4.4	1,149,098.1	177.5	821,270.6	265.0	327,827.5	99.3
High-income Asia Pacific	49,684.6	10.8	33,264.7	16.9	16,419.9	5.5	920,379.3	238.6	673,678.6	380.9	246,700.7	105.6
Oceania	232.8	3.5	164.5	4.8	68.3	2.1	7,093.4	85.4	4,966.5	117.0	2,126.9	51.9
Australasia	2,006.0	4.1	1,336.1	5.9	669.9	2.5	43,655.0	98.1	30,413.4	142.9	13,241.6	56.3
High-income North America	26,479.4	4.3	18,143.1	6.4	8,336.3	2.4	608,194.5	105.5	435,713.6	158.9	172,480.9	56.6
Caribbean	1,694.9	3.3	1,065.7	4.4	629.2	2.3	41,275.6	80.7	26,381.3	108.0	14,894.3	55.9
Andean Latin America	1,840.0	3.3	918.5	3.5	921.6	3.2	44,339.6	77.3	23,035.9	82.5	21,303.7	72.2
Central Latin America	8,415.9	3.6	4,606.3	4.4	3,809.7	3.0	197,475.1	82.8	109,858.2	99.0	87,616.9	68.7
Tropical Latin America	5,939.5	2.5	3,776.3	3.6	2,163.2	1.6	142,718.9	58.6	92,266.0	82.4	50,452.9	38.6
Southern Latin America	2,027.2	2.4	1,256.0	3.5	771.3	1.6	43,534.4	53.6	27,961.5	75.9	15,572.9	35.0

Table 1 Continued

Regions	Deaths						DALYs					
	Both		Male		Female		Both		Male		Female	
	Number	ASR	Number	ASR	Number	ASR	Number	ASR	Number	ASR	Number	ASR
North Africa and Middle East	26,432.4	6.2	18,866.7	8.6	7,565.7	3.7	731,622.2	153.3	525,982.1	214.7	205,640.1	88.9
Central Sub-Saharan Africa	1,394.5	2.5	758.4	3.2	636.0	2.0	51,448.4	65.3	27,386.3	78.2	24,062.1	55.7
Eastern Sub-Saharan Africa	5,676.5	3.4	3,275.1	4.2	2,401.4	2.7	187,943.5	85.5	105,595.1	103.4	82,348.4	69.0
Southern Sub-Saharan Africa	4,039.9	7.1	2,571.0	10.5	1,468.9	4.6	122,194.8	188.8	82,434.3	281.3	39,760.5	114.2
Western Sub-Saharan Africa	9,971.9	5.3	6,701.6	7.5	3,270.3	3.3	308,593.0	130.8	205,254.7	184.2	103,338.3	81.9

DALYs, disability-adjusted life years; SDI, sociodemographic index; GBD, Global Burden of Diseases; ASR, age-standardized rates.

females (**Figure 2**); the proportional causes of DALYs were similar (**Figure S1**).

Attributable liver cancer deaths and DALYs worldwide

HBV and HCV were major contributors to liver cancer worldwide with the impact varying significantly across regions. Globally, HBV predominated in most regions, whereas in high SDI countries, HCV accounted for the highest proportion of causes. Liver cancer due to alcohol use represented a more pronounced proportion in high SDI countries than other countries. In East Asia and Oceania, the proportion of liver cancer cases attributable to HBV was significantly higher compared to other etiologies. In contrast, liver cancer due to HCV had a higher proportion, especially in the high-income Asia Pacific area. When stratified by gender, HBV and HCV were identified as the leading causes of liver cancer deaths for males and females in 2019, respectively. Alcohol use was generally higher among males than females, whereas the prevalence of NASH was generally higher in females than males (**Figure 3**).

Globally, alcohol use ranked as the predominant risk factor for liver cancer since the estimation included the etiology, followed by tobacco use. Tobacco use had the highest attributable fraction among risk factors in China. These risk factors revealed a complex interplay with the SDI and regions. Tobacco use, high BMI, and drug use were significant contributors to liver cancer in regions with a higher SDI. In Central Europe, the proportional alcohol use burden significantly surpassed other risk factors for liver cancer irrespective of gender. In Australia and high-income North America, high BMI and high fasting plasma glucose as metabolic factors, and drug use exhibited a higher proportion of risk compared to other regions (**Figure 3**); DALYs had similar proportions (**Figure S2**).

Trends of attributable liver cancer deaths and DALYs worldwide

Liver cancer deaths due to various etiologies declined worldwide (AAPC = −1.4) and in China (AAPC = −3.4) in both genders from 1990–2019. Liver cancer deaths attributed to all risk factors were also on a downward trend worldwide (AAPC = −0.7) and in China (AAPC = −2.8). Globally, metabolic factors had an increased (AAPC = 0.8)

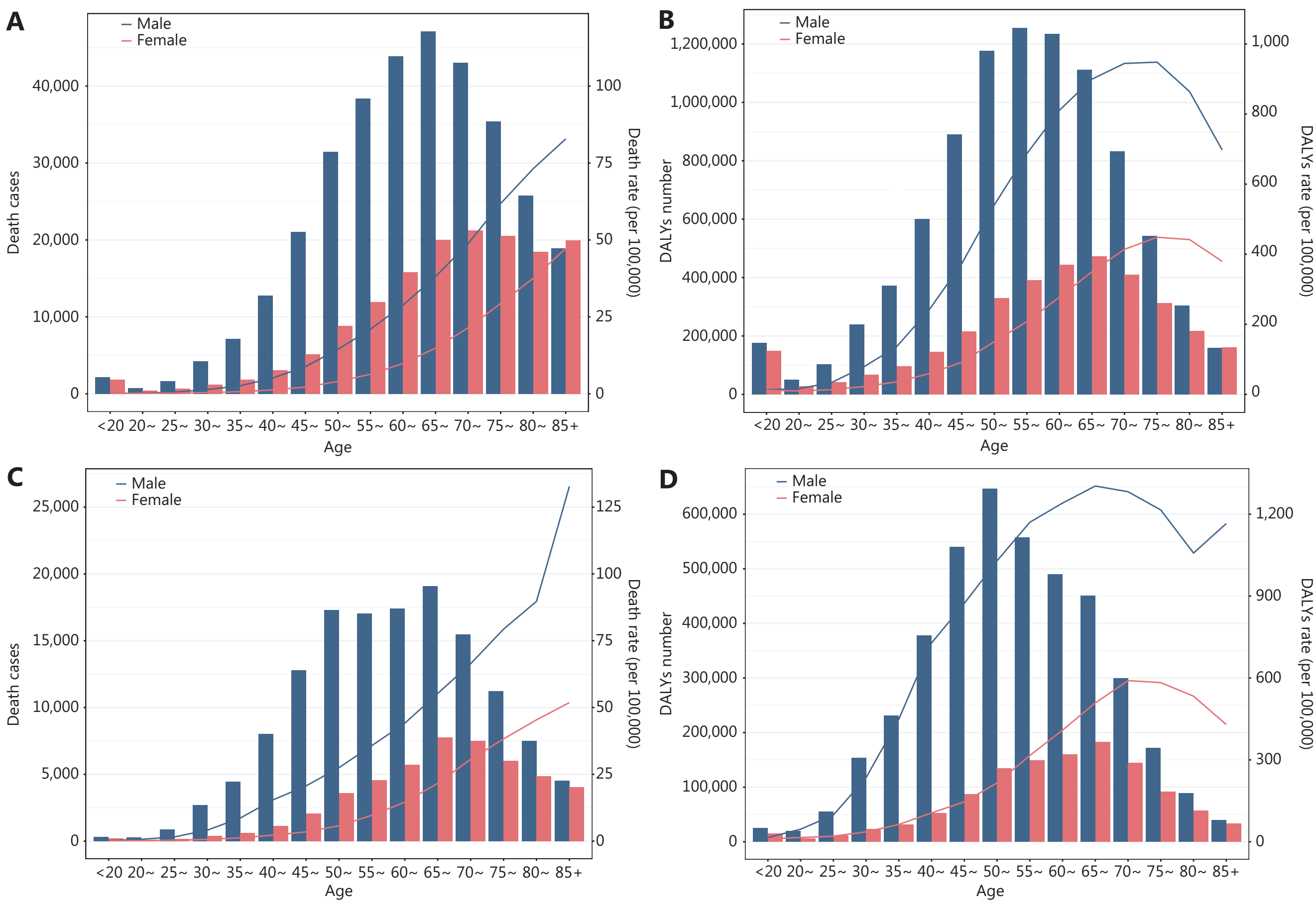

Figure 1 Age-specific deaths and DALYs numbers and rates of liver cancer worldwide and in China in 2019. (A) Global deaths. (B) Global DALYs. (C) China deaths. (D) China DALYs. DALYs, disability-adjusted life years.

contribution to liver cancer, especially in males (AAPC = 1.0). Metabolic factors had a decreased (AAPC = −0.9) contribution to liver cancer in China, especially in females (AAPC = −1.9). Among countries with different SDI levels, high-middle SDI countries had a decreasing trend for both etiologies and risk factors. Globally, there was a slight decline in liver cancer attributable to NASH among females, while high SDI countries had an increasing trend, especially in males. Liver cancer deaths attributed to various causes and risk factors were on the rise in high SDI countries with an upward trend of liver cancer due to HBV more pronounced among females. The liver cancer burden among females demonstrated a significant decrease in the majority of 21 regions, primarily due to a decline in viral infection factors. Approximately one-half of the regions had an increasing liver cancer burden caused by all risk factors, especially metabolic factors. Only Central Europe, East Asia, the Caribbean, and Andean Latin America showed declining trends (**Figure 4** and **Table S1**).

The trends in ASDALYs caused by etiologies and risk factors leading to liver cancer generally paralleled the death trends. Globally, ASDALYs due to metabolic factors leading to liver cancer were on the rise. While all causes and risk factors leading to liver cancer decreased in China, metabolic factors contributed less than other factors. In high SDI countries, the change in ASDALYs for liver cancer caused by tobacco decreased more among males. In both high and high-middle SDI countries, the liver cancer burden caused by metabolic factors exhibited increasing and decreasing trends, respectively, with the trends for liver cancer attributable to high blood fasting glucose more pronounced than high BMI. In Australia and high-income North America, both ASDRs and ASDALYs for liver cancer caused by all etiologies and risk factors had an upward trajectory. The variations in metabolic factors across

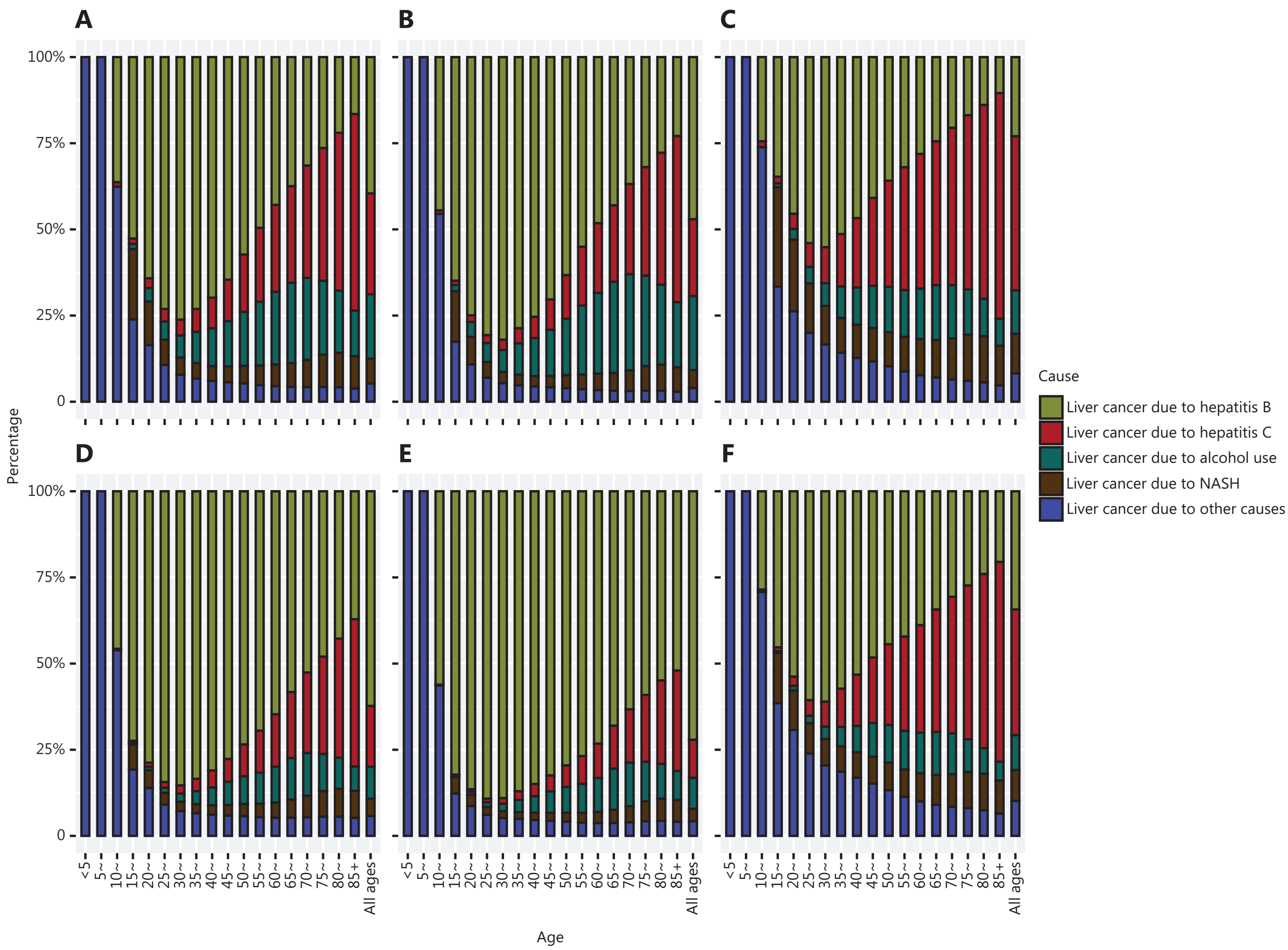

Figure 2 Proportional deaths burden of liver cancer etiologies by age groups worldwide and in China in 2019. (A) Global both genders. (B) Global males. (C) Global females. (D) China both genders. (E) China males. (F) China females.

regions were largely consistent with changes in high BMI, while changes in high blood fasting glucose had a significant upward trend in Central Asia and Australia (**Figure 4** and **Table S2**).

Discussion

Liver cancer remains a significant global health concern with a substantial disease burden, especially in Asia and China. According to the GBD 2019 database, the liver cancer burden in China was much higher than the global average and the peak age occurred earlier in males and females. There were significant disparities in the liver cancer burden attributable to various causes and risk factors in different regions globally. The overall liver cancer burden due to multiple causes generally declined in China and worldwide with a more pronounced decline in China. However, liver cancer attributed to metabolic factors was on the rise globally, especially in Central Asia, necessitating special attention. Regions and countries with high liver cancer burden should focus more on specific etiologic factors and take urgent actions.

The number of liver cancer deaths, ASDRs, DALYs, and ASDALYs in China were significantly higher than global levels. The global age distribution of liver cancer varied by region, gender, and etiology. Globally, the highest proportion of liver cancer cases occurred in individuals ≥ 75 years of age. In regions with higher disease burden, such as China, the mortality and DALYs peaks occurred approximately 5 years earlier than the global average[15]. Global and Chinese data indicated significant disparities in the liver cancer burden between males

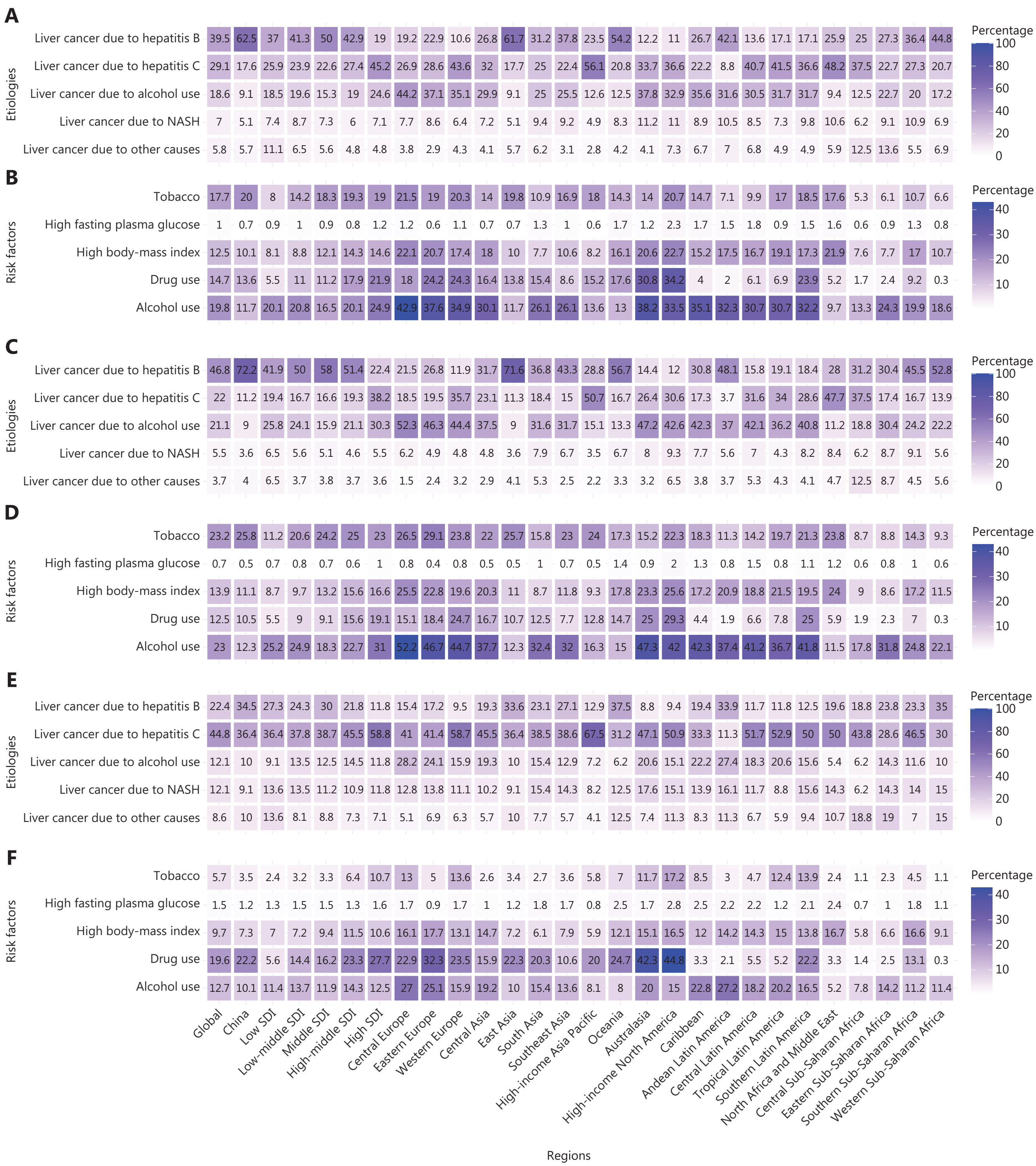

Figure 3 Proportion of deaths attributable to etiologies and risk factors of liver cancer by SDI and GBD regions in 2019. (A) Attributable to different etiologies for both genders. (B) Attributable to different risk factors for both genders. (C) Attributable to different etiologies for males. (D) Attributable to different risk factors for males. (E) Attributable to different etiologies for females. (F) Attributable to different risk factors for females. SDI, sociodemographic index; GBD, Global Burden of Diseases.

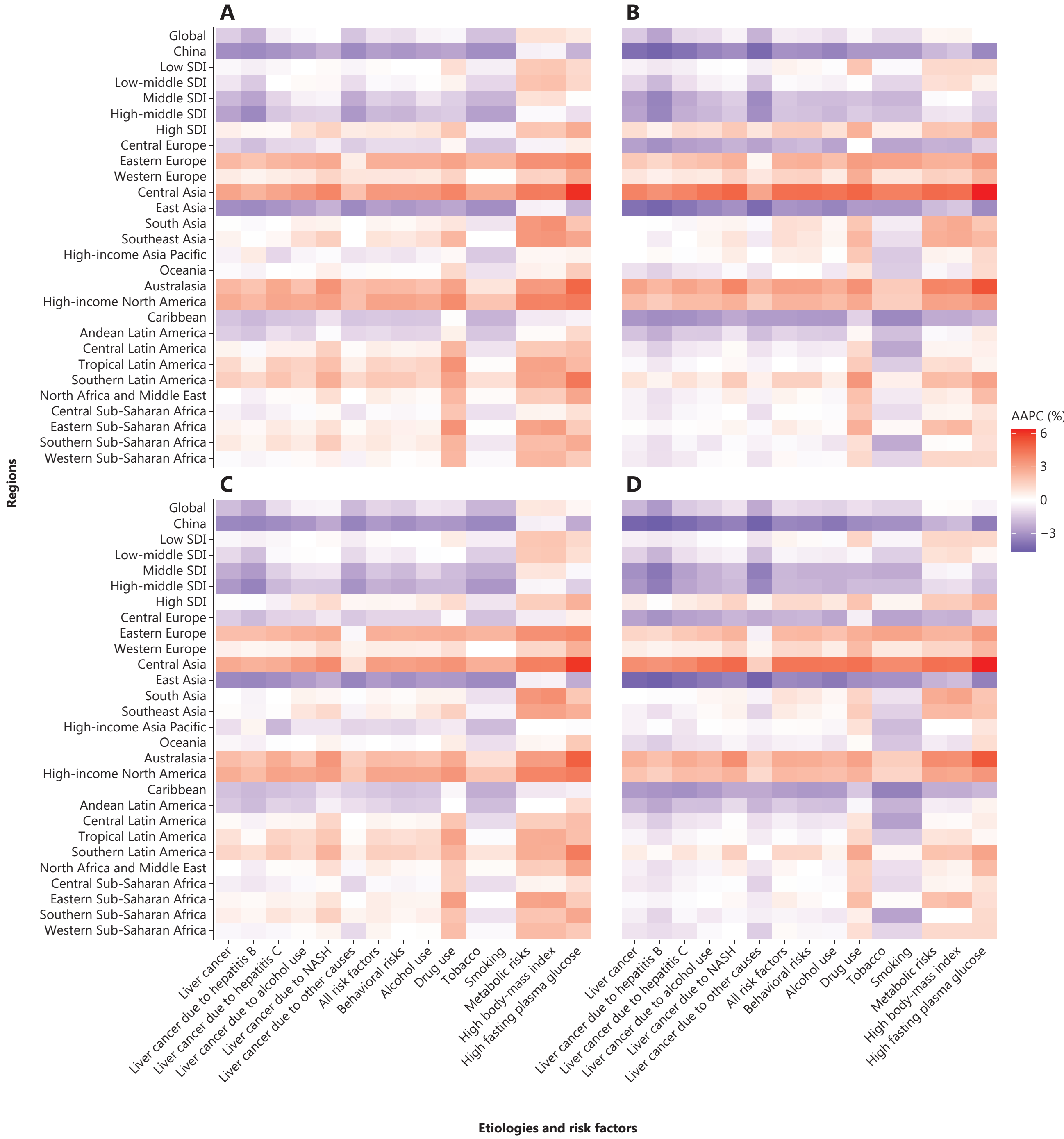

Figure 4 Trends in attributable age-standardized deaths and DALYs rates (per 100,000 population) for liver cancer by SDI and GBD regions, 1990–2019. (A) Trends in age-standardized death rates for males. (B) Trends in age-standardized death rates for females. (C) Trends in age-standardized DALY rates for males. (D) Trends in age-standardized DALY rates for females. DALYs, disability-adjusted life years; SDI, socio-demographic index; GBD, Global Burden of Diseases; AAPC, average annual percent change.

and females with the burden in males rising earlier and reaching peak values. The characterization of age-specific attributable liver cancer burden reflects the multifactorial nature of liver cancer risk factors over the lifespan, and was likely influenced by differences in predominant hepatitis viruses in populations, the age of virus acquisition, and the presence of other risk factors. Based on the population aging analyses of liver cancer etiologies, HCV, alcohol use, and NASH-induced liver cancer are considered aging-associated diseases[16]. Specifically, the proportion of liver cancer due to HCV rose significantly with age in both genders worldwide and in China. The ongoing demographic aging and increase in elderly-related diseases have contributed, in part, to the increasing burden of liver cancer[17].

China currently bears a heavy liver cancer burden and there are significant differences in the attributable liver cancer burden compared to other regions globally. HBV infection remains the most significant etiologic factor for liver cancer in the global population 15–69 years of age. The high incidence of liver cancer in Asia may be related to the fact that the region has three-fourths of the world's chronic HBV carriers[18]. It is estimated that the HBV surface antigen seroprevalence rate in China was 3.0% in 2021, which was much higher than the United States (0.3%)[19,20]. Although the number of liver cancer deaths and DALYs in the East Asia region, where China is located, were the highest, the burden trends were downward and there has been a significant improvement in liver cancer prevention and treatment over the past 30 years. This finding may be due to a series of measures implemented in China to prevent and control HBV infection, such as nationwide neonatal HBV vaccination, interruption of mother-to-child transmission, and promotion of antiviral therapy[3,21]. Globally, the proportion of liver cancer deaths attributed to HBV decreased and in high SDI regions did not rank first. Other related studies have reported a correlation between the age-standardized incidence rate (ASIR) of liver cancer caused by HBV and the SDI. In high SDI regions, the ASIRs of liver cancer caused by HBV are increasing, suggesting the need to strengthen liver disease management related to HBV in these specific regions[22].

HBV-related liver cancer accounted for > 50% of the cases in China, especially among males, and the declining trend was more pronounced among females. The observed differences in liver cancer burden between genders are primarily associated with variations in sex hormones and the prevalence of different risk factors[23,24]. Sex hormones and receptor signaling pathways may have a crucial role in the occurrence and development of liver cancer[23,25]. The interaction between hepatitis viruses and androgen receptors can lead to significant gender differences in the impact on liver cancer[26]. Liver cancer due to HCV was declining in both genders globally and in China as same as HBV-related liver cancer. The incidence of liver-related diseases in males with HBV or HCV infections was significantly higher than in females[27]. The burden of alcohol-induced liver cancer has gained significant attention in recent years. The proportion of liver cancer cases due to alcohol use was more than twice as high globally as in China, and the downward trend of liver cancer due to alcohol use was less pronounced globally than in China. Both globally and in China, liver cancer due to alcohol use in females declined more than males. Studies have indicated that females are more susceptible to alcohol-induced liver damage compared to males, although the exact mechanisms remain unclear[28,29]. Moreover, male alcohol-per-capita consumption was significantly higher than females[30]. The population attributable fractions (PAFs) of alcohol use were 19.8% and 11.7% worldwide and in China, which indicated a higher prevalence of alcohol consumption in other regions worldwide.

NASH has emerged as the fastest-growing cause of liver cancer incidence and mortality globally[24,31]. NASH is primarily characterized by obesity, insulin resistance, and metabolic disorders, representing a systemic metabolic disease associated with obesity[32]. The rapid increase in the liver cancer disease burden due to NASH corresponds to the increasing prevalence of obesity[33]. Notably, NASH contributed more to liver cancer in females than males, likely reflecting higher NASH prevalence among females, which may be related to the finding that the NASH prevalence is substantially higher in females[34]. Moreover, females with NASH exhibit a higher risk of developing liver cancer compared to males in elderly groups. This observation aligns with findings from multiple studies and may be attributed to a decrease in estrogen levels after menopause[34,35]. The contribution of NASH to liver cancer in the elderly becomes even more pronounced with the proportion of liver cancer due to HBV decreasing. This suggests that awareness, prevention, and control of NASH are particularly important in the elderly population.

Among the risk factors contributing to liver cancer, tobacco use in China accounted for the largest proportion. Based on the comparative risk assessment study in China, the PAF for liver cancer burden in males due to smoking is 15.7%[36].

For other regions, especially high SDI regions, the burden of DALYs from tobacco has declined, which may be related to the implementation of tobacco control policies. Smoking rates in the United States have been effectively controlled over the past 50 years, leading to a reduction in the burden attributable to tobacco[37,38]. In less developed regions represented by China, strict enforcement of tobacco control policies is urgently needed. Metabolic factors attributed to liver cancer in the GBD 2019 include high BMI and high fasting plasma glucose, both showing an increasing trend globally. The attributable risk of high BMI to liver cancer exceeds that of diabetes and the prevalence is projected to increase worldwide. Hence, early detection strategies for liver cancer are crucial for elderly females with NASH or obesity. In recent years, studies have shown that diabetes patients may have a higher risk of liver cancer incidence and mortality[39,40]. Liver cancer due to high fasting plasma glucose was on the rise, especially in Australia. The burden of liver cancer has been increasing in Australia in recent years, with an increase in liver cancer caused by HBV infections, potentially associated with increasing immigration[41].

The strength of the current study lies in the comprehensive analysis of the differences in liver cancer across global regions and within China, accounting for gender- and age-specific factors. Few studies have focused on the impact of weaker risk factors, such as smoking, on liver cancer, aside from infectious causes. For the first time, this study simultaneously focused on the burdens caused by etiologies and risk factors of liver cancer utilizing the framework of the same database, analyzing the temporal trends, and providing a comprehensive revelation of the attributable risks of current liver cancer. Understanding the trends in cancer burden over time can evaluate whether the liver cancer burden has improved or worsened in different regions over the long term. This finding allows for a systematic and comprehensive depiction of the current global attributable liver cancer burden, providing valuable recommendations for strengthening liver cancer prevention and control measures. In addition, DALYs is a comprehensive metric for measuring disease burden. DALYs not only considers deaths caused by diseases but also includes the decline in quality of life due to disabilities. This finding helps in thoroughly assessing the impact of cancer on individuals and society. Moreover, the multifaceted comparison of the attributable burden for different genders, age groups, and time trends globally and China is presented, making the current study the most comprehensive analysis of this data to date.

However, this study also had limitations. First, the GBD 2019 has certain data sourcing shortcomings. In instances where data from specific countries or regions were unavailable, the results of the GBD 2019 are model-dependent, potentially leading to disparities in data accuracy. Interpretations in specific regions should be made with caution. Second, the GBD 2019 used different estimation systems within the cause and risk factor frameworks. There might be overlapping risk factors, such as alcohol use, but this does not distort the attributable burden. Under the cause framework, weight coefficients divide the overall liver cancer burden into five distinct etiology parts. The values were weighted so that the proportions of the five causes sum to one. Therefore, in comparison, the value for HBV-related liver cancer does not equate to the PAF reported in epidemiologic studies. The risk factor analysis framework starts from 87 prevalent risk factors within the GBD framework. The percent of each risk factor could be considered as the PAF, which quantifies the proportion of cancers that could be prevented by eliminating a given risk factor and represents the unweighted result of the attributable burden. Additionally, the cancer statistics data have a lag, limiting the analysis to trends from 1990–2019.

Conclusions

The study underscores the landscape of liver cancer epidemiology in China and worldwide across regions, with China having an elevated burden but a pronounced declining trend. The global burden of liver cancer was on an overall decreasing trend, whether attributable to various etiologies or all risk factors. However, metabolic risk factors due to liver cancer were on the rise, especially in high SDI countries. These findings emphasize the need for public health interventions addressing obesity and related conditions globally. Overall, our findings emphasize the complexity of liver cancer etiology and the importance of region-specific preventive measures to mitigate the growing burden.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Mengdi Cao, Changfa Xia, Wanqing Chen.
Contributed data or analysis tools: Mengdi Cao.
Performed the analysis: Mengdi Cao.
Wrote the paper and revised: Mengdi Cao, Changfa Xia, Wanqing Chen.

Data availability statement

All data used in this study are publicly available from the Global Burden of Disease Study 2019 [https://vizhub.healthdata.org/gbd-results/].

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