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Burden of liver cancer in adolescents and young adults aged 15-49 years in China: a comprehensive analysis based on the Global Burden of Disease study (1990-2021)

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Abstract

Aim: Globally, primary liver cancer ranks as the third most common cause of mortality among cancer patients. China reports the highest number of cases in the world, with chronic hepatitis B virus (HBV) infection being the most common cause. Recent studies have shown an increasing risk among adolescents and young adults aged 15-49 years, posing a significant public health challenge.

Methods: This study uses the latest data from the Global Burden of Disease (GBD) 2021 to systematically evaluate the disease burden of liver cancer among individuals aged 15-49 years in China from 1990 to 2021.

Results: The results show an increase in liver cancer cases and deaths in this age group, with a decreasing trend in incidence and mortality rates. The highest incidence and mortality rates were observed in the 45-49-year age group, with a significant increase in disease burden in men and a decrease in women. The annual net decreases in incidence and mortality rates are 1.65% and 2.31%, respectively. In the Chinese adolescent population aged 15-49



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years, more than 80% of liver cancer cases are attributable to HBV. Other major risk factors include hepatitis C virus (HCV), alcohol consumption, non-alcoholic steatohepatitis (NASH), smoking, high body mass index (BMI), and high fasting plasma glucose.

Conclusion: Our study underscores the potential of HBV vaccination and lifestyle interventions in controlling Chinese adolescents' liver cancer incidence, and provides valuable insights for other countries and regions facing similar stages of development and major health challenges related to liver cancer.

Keywords: Primary liver cancer, adolescents and young adults, global burden of diseases, time trend, China

INTRODUCTION

Globally, primary liver cancer (PLC) is the sixth most commonly diagnosed cancer and the third leading cause of cancer-related mortality^[1]. According to the Global Cancer Statistics 2022, the incidence of liver cancer is highest in East Asia, particularly in Mongolia, where the rate reaches 96.8 cases per 100,000 persons^[2]. However, due to China's extremely high incidence rate combined with its large population base, the country reports the highest number of PLC cases in the world^[2,3].

The development of PLC is influenced by several risk factors, particularly chronic hepatitis B virus (HBV) and chronic hepatitis C virus (HCV) infections, which together account for more than 80% of PLC cases worldwide^[4-6]. Among these, HBV infection is the most prevalent cause of PLC, with the estimated relative risk (RR) of developing liver cancer among HBV-infected individuals compared to non-infected persons ranging from 15 to 20 times higher^[7,8]. The International Agency for Research on Cancer (IARC) has compiled results from 15 cohort studies (mean follow-up time ranging from 1.9 to 11.8 years), indicating a significant risk of hepatocellular carcinoma (HCC) associated with HBsAg positivity^[9]. In addition, a modeling study estimates the HBsAg positivity rate in China to be 6.1%^[10,11], compared to 2.4% in South Korea and below 1% in Japan, Australia, the United States, and the United Kingdom^[12]. These findings suggest that despite global progress in controlling HBV infection, the exposure of the Chinese population to HBV remains relatively high. Currently, it is widely recognized that injection of hepatitis B immunoglobulin after birth is the existing strategy for preventing HBV infection and related liver cancer^[13]. Universal vaccination against HBV can significantly reduce the prevalence of chronic HBV infection and may help reduce the incidence of liver cancer^[14]. Other known and emerging risk factors include high alcohol and tobacco use, obesity, and high plasma glucose, with the distribution and impact of these risk factors varying by region, demographic group, and context^[15-18].

While the public commonly perceives a severe burden of PLC among middle-aged and older adults, emerging research indicates an escalating risk of liver cancer among adolescents and young adults, posing significant challenges for public health^[19-21]. The rising incidence of liver cancer in this age group is particularly concerning because this age group represents a highly dynamic segment of the population with high population density and social vitality. This phenomenon is attributed to changes in lifestyle, increased environmental exposures, and genetic susceptibility, along with a rising rate of HBV infections observed in this cohort^[22]. Even alarming is the trend of younger onset, which adversely affects the work capacity of a number of young individuals, creating societal disruptions and increasing demands on resources allocated for liver cancer management and prevention^[21]. Early life exposures, including dietary factors, lifestyle, obesity, environmental exposures, and microbiome, have undergone significant changes^[23]. However, the research on the risk factors of liver cancer in adolescents and young adults is limited. Several previous studies have shown that the potential prevalence of liver cirrhosis is lower in patients with liver cancer in adolescents and young adults than that in patients with late-onset liver cancer, indicating the existence of

etiological differences^[24,25]. A case-control study involving HBV carriers showed that smoking was associated with early-onset liver cancer but not with late-onset liver cancer^[26]. A familial background of liver cancer raises the risk of the disease in those younger than 45. The increased risk is greater for HBV carriers than for non-HBV carriers^[27]. Non-alcoholic fatty liver disease and steatohepatitis, often linked to obesity, may also raise the possibility of liver cancer developing at a younger age^[28,29]. However, the impact of changes in smoking and drinking over the last several decades on the incidence of liver cancer in different age groups remains to be determined^[28,30]. The influence of liver cancer on adolescents and young adults is long-term. It may require a relatively long recovery period, and the body is exposed to persistent damage, including a decline in bodily functions. It imposes a considerable burden on the socioeconomic and healthcare systems^[31,32]. Despite the recent academic focus on liver cancer among younger populations, urbanization and changes in lifestyle have synergistically promoted the increase in the risk of liver cancer among young people through multiple mechanisms, including metabolism, environment exposures, risk factors, and medical accessibility, limited research has focused specifically on the disease in individuals aged 15-49^[19,21,33]. This adolescent and young age group represents a crucial stage of personal development and transition that the world is undergoing. However, at present, most studies mainly focus on the middle-aged and elderly population. Consequently, there is a research gap in understanding the incidence of liver cancer among young people. Standardized and comparable research methods are urgently needed to fully evaluate the liver cancer burden among Chinese adolescents and young adults^[21].

The Global Burden of Diseases (GBD), Injuries, and Risk Factors Study (2021) represents a comprehensive and systematic scientific research aimed at quantifying health losses attributed to various diseases, injuries, and risk factors in humans^[34]. This research presents an extensive collection of data, including incidence rates, mortality figures, and disability statistics from various nations, categorized temporally and by age group. This research utilizes GBD 2021 data to comprehensively analyze the disease burden of liver cancer among adolescents and young adults aged 15-49 years in China from 1990 to 2021, thus filling existing research gaps in China. We anticipate that this study will offer unique insights into trends in the burden of liver cancer in this age group in China during the specified time period, potentially guiding policy decisions for more precise cancer control based on empirical evidence. Our findings could ultimately reveal how HBV-related liver cancer affects young Chinese populations, while offering important implications for other developing regions confronting comparable liver cancer challenges.

METHODS

Data sources

The GBD 2021 study employed standardized analytical methods to systematically collate a comprehensive dataset of 369 types of health issues involved in 204 countries and regions worldwide from 1990 to 2021. This study created a multi-level disease assessment system based on gender, age, geographical region, and time dimensions, achieving standardized comparative analysis across populations, regions, and time periods. The Institute for Health Metrics and Evaluation (IHME) created this instrument, with its methodological framework and standardization procedures being comprehensively described in established GBD studies^[35-37]. The International Classification of Diseases (ICD) is utilized to define liver cancer. In the 9th and 10th revisions of ICD, the codes 155-155.963 and C22.0-C22.9 represent liver cancer, respectively. In this study, we extracted data on liver cancer for the Chinese population aged 15-49 years from GBD 2021 using the latest version of the GBD Results Tool (<https://vizhub.healthdata.org/gbd-results/>). As GBD data are anonymized and publicly available, this study was exempt from ethical approval.

Estimates of liver cancer burden among individuals aged 15-49 years in China

To evaluate the disease burden of liver cancer in China, the GBD 2021 study used a comprehensive set of 243 data sources. This integrates multiple data sources, covering national census data, results of tumor

epidemiological surveys, and official statistics from the Chinese Center for Disease Control and Prevention (CCDC). For specific details on the data sources, it will query the data source query function module in the Global Health Data Exchange Platform (GHDx). In the online database, we specified “deaths”, “incidence”, “disability-adjusted life years (DALYs)”, “years of life lost (YLLs)”, and “years lived with disability (YLDs)” as metrics, “liver cancer” as the cause, and “China” as the location for our analysis. We extracted data from the GBD 2021 online results tool to analyze the burden of liver cancer in Chinese adolescents and young adults (1990-2021) through age-standardized rates (ASRs, per 100,000 population), comprising incidence rates (ASIRs), mortality rates (ASMRs), DALY rates, YLL rates, and YLD rates.

Statistical analysis

Our analysis encompassed various metrics: incidence cases, deaths, incidence rates, mortality rates, age-standardized incidence and mortality rates, DALYs, YLLs due to premature mortality, and YLDs. DALYs represent the health gap comparing existing conditions against a theoretical benchmark of disease-free longevity for the entire population. This measure is derived through the aggregation of YLLs and YLDs. YLLs are determined by multiplying mortality counts by the remaining life expectancy at death, while YLDs are obtained through the product of incident cases, disability weights, and mean disability duration. We calculated the corresponding ASRs using the 1966 Segi-Doll world standard population (aged 15-49 years). The GBD study adopted the Monte Carlo simulation method. Through 1,000 sampling calculations, we obtained the upper and lower limits of the uncertainty interval (i.e., the 2.5th and 97.5th percentile values) to determine the 95% confidence interval (CI) range. In addition, we systematically analyzed the incidence and mortality of liver cancer among different gender and age groups in China, and quantitatively evaluated the changing trends of these epidemiological indicators from 1990 to 2021. The crude rates were calculated based on the global age structure for each year from 1990 to 2021. To address heterogeneity arising from sampling variability, we performed uncertainty interval estimation through 1,000 posterior distribution samples. Age-specific comparisons of hepatic carcinoma burden were made using crude rates with their corresponding 95% uncertainty ranges.

The temporal variation characteristics of the disease burden of liver cancer from 1990 to 2021 were analyzed based on the Joinpoint regression model. We quantified the long-term trend evolution by calculating the estimated average annual percentage change (EAPCs) of ASRs. Joinpoint regression models were used to quantify trends and test their statistical significance. The overall trend was represented by the annual percentage changes (APCs), the average annual percentage changes (AAPCs), and their 95% CIs. The Monte Carlo permutation method was used to test for the significant differences. Joinpoint regression is mainly used to identify the key turning points in the trend. It automatically determines the time points at which the incidence rate/mortality rate changes significantly through statistical tests. The regression model also fits multi-stage line graphs and clearly displays the trend changes. These calculations were based on the Joinpoint Regression Program (version 5.0.2, May 2023; Statistical Research and Applications Branch, National Cancer Institute).

Age-period-cohort model analysis was employed to assess potential social, historical, and environmental influences on the burden of liver cancer, with the aim of identifying independent effects of risk changes associated with age groups, different periods, and birth cohorts while avoiding confounding factors. The goal was to identify the early exposure in birth cohorts and warn of the long-term disease burdens. This enables precise attribution intervention and dynamic assessment of policies. Statistical modeling was conducted using the Poisson logarithmic linear regression model based on continuous 5-year age groups and continuous 5-year periods. By selecting the standard reference cohort and controlling for confounding factors in the control period, the longitudinal age-mortality curve was used to evaluate the true age effect. The period and cohort effects were evaluated using rate ratios (RRs) relative to the reference period and

Table 1. Percentage changes of incidence cases, deaths, and corresponding age-standardized rates for liver cancer in young adults aged 15- 49 years by sex in China, 1990-2021

Categories		Incidence cases (95%UI)	Age-standardized incidence rate, per 100,000 (95%UI)	Deaths (95%UI)	Age-standardized mortality rate, per 100,000 (95%UI)
Total	1990	30,185 (24,839-36,227)	10.58 (8.94-12.43)	27,360 (22,538-32,769)	10.75 (9.12-12.61)
	2021	38,509 (30,544-50,232)	9.52 (7.72-11.78)	28,127 (22,351-36,519)	8.35 (6.8-10.29)
	Change, %	27.58 (-15.69-102.23)	-10.02 (-37.89-31.77)	2.80 (-31.79-62.03)	-22.33 (-46.07-12.83)
Male	1990	24,710 (19,819-30,427)	15.06 (12.2-18.24)	22,389 (17,971-27,511)	15.19 (12.32-18.36)
	2021	33,413 (25,384-44,102)	14.34 (10.93-19.18)	24,420 (18,516-32,241)	12.40 (9.46-16.55)
	Change, %	35.22 (-16.57-122.52)	-4.78 (-40.08-57.21)	9.07 (-32.70-79.41)	-18.37 (-48.47-34.33)
Female	1990	5,475 (4,250-6,857)	6.04 (4.82-7.28)	4,971 (3,868-6,195)	6.33 (5.08-7.64)
	2021	5,096 (3,789-6,742)	4.89 (3.82-6.18)	3,707 (2,741-4,845)	4.57 (3.57-5.76)
	Change, %	-6.92 (-44.74-58.64)	-19.04 (-47.53-28.22)	-25.43 (-55.75-25.26)	-27.80 (-53.27-13.39)

UI: Uncertainty interval.

reference cohort, respectively. The period source of the cohort analysis is calculated by the observation year minus the age. The model used for age-period-cohort analysis in this study was developed by the Biostatistics Branch of the National Institutes of Health, USA.

The data processing and statistical analysis of this study were all performed using the R language programming environment (version 4.3.3). The statistical test adopted the two-sided test standard, and the significance level was set at $\alpha = 0.05$.

RESULTS

Analysis of incidence and mortality

Over the extended period from 1990 to 2021, China experienced a significant increase in both the number of incidence cases and deaths from liver cancer among individuals aged 15-49 years, as clearly illustrated in Table 1. Specifically, incidence cases of liver cancer increased by 27.58% from 30,185 in 1990 to 38,509 in 2021. At the same time, liver cancer deaths rose from 27,360 in 1990 to 28,127 in 2021, an increase of 2.80%.

Regarding ASRs, both the ASIR and ASMR exhibited declining trends. The ASIR decreased from 10.58 per 100,000 in 1990 to 9.52 per 100,000 in 2021, a reduction of 10.02%. Similarly, the ASMR decreased from 10.75 per 100,000 in 1990 to 8.35 per 100,000 in 2021, representing a 22.33% decrease. Over the past decades, different trends in incidence and mortality were observed between men and women. During the same period, the number of male cases increased by 35.22%, while female cases decreased by 6.92%. Similarly, deaths among men increased by 9.07%, whereas deaths among women decreased by a remarkable 25.43%. Concerning sex-specific ASRs, men showed consistently higher ASIR and ASMR than women throughout 1990-2021, although with declining trends for both sexes. Specifically, the ASIR decreased by 4.78% in men and by 19.04% in women during this period. The ASMR declined by 18.37% in men, while a more rapid decrease was 27.80% in women.

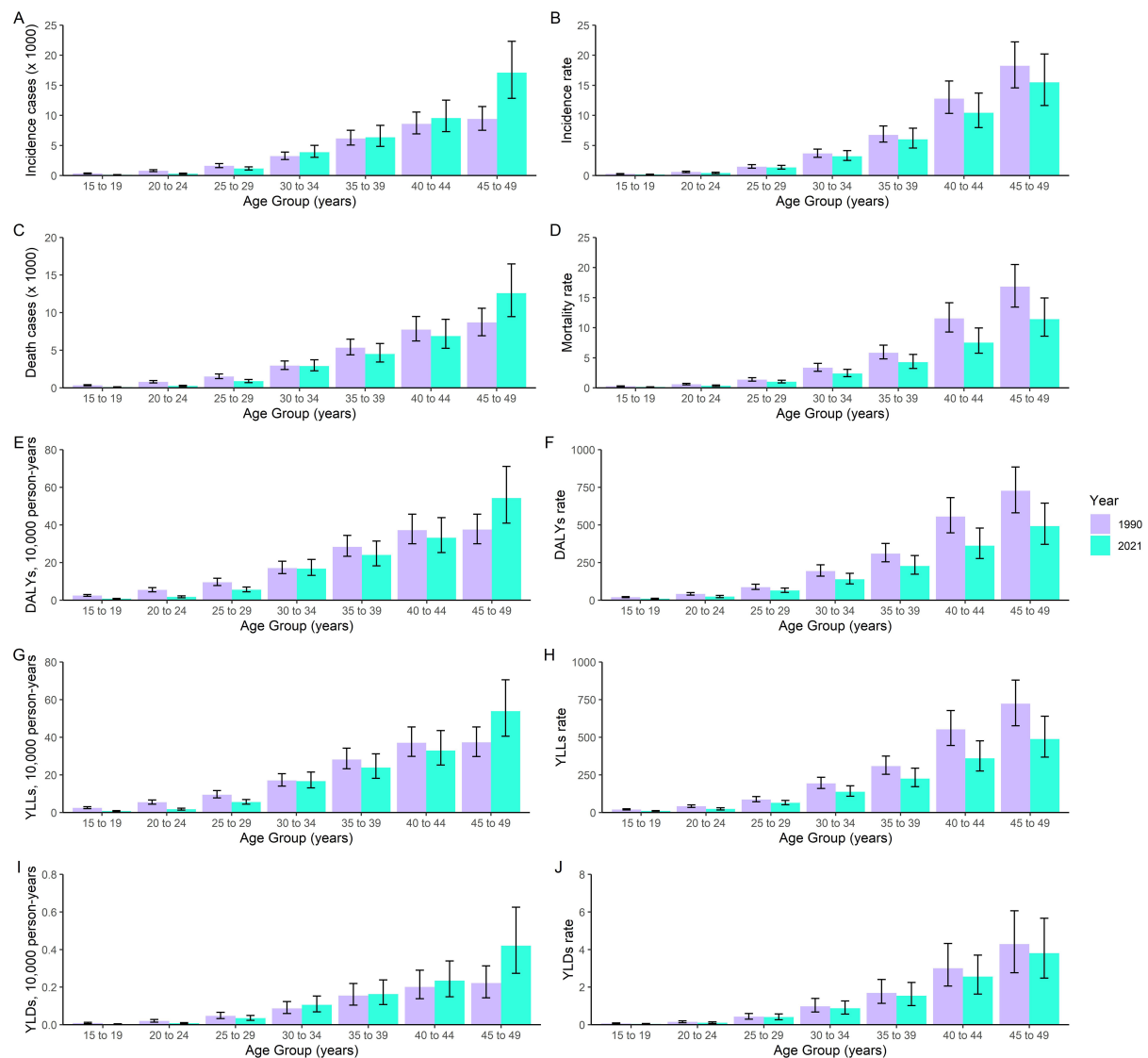


Figure 1. The rate of incidence, mortality, DALYs, YLLs due to premature mortality, YLDs, and corresponding numbers for liver cancer in each age group of adolescents and young adults in China, 1990-2021. (A) Incidence cases; (B) Incidence rate; (C) Death cases; (D) Mortality rate; (E) DALYs; (F) DALYs rate; (G) YLLs; (H) YLLs rate; (I) YLDs; (J) YLDs rate. DALYs: Disability-adjusted life-years; YLLs: years of life lost; YLDs: years lived with disability.

Different age groups demonstrated varied patterns of liver cancer incidence and mortality, as detailed in [Figure 1](#) and [Supplementary Tables 1 and 2](#). In both 1990 and 2021, the 45-49 age group consistently recorded the highest number of incidence cases and deaths among all age groups. Notably, this age group experienced a remarkable 81.37% increase in incidence cases and a 44.80% increase in deaths during this period. Interestingly, incidence cases showed a declining trend before the age of 30, followed by a gradual increase thereafter. Regarding deaths, only the 45-49 age group exhibited an upward trend. Generally, the growth rate of incidence cases and deaths accelerated with increasing age groups. [Supplementary Table 2](#) reveals that among Chinese youth, both incidence and mortality rates of liver cancer increased with age group progression, but showed declining trends from 1990 to 2021. Younger individuals generally experienced a more rapid decrease in incidence and mortality rates.

Table 2. Percentage changes of DALYs, YLLs due to premature mortality, YLDs and corresponding age-standardized rates for liver cancer in young adults aged 15- 49 years by sex in China, 1990-2021

Categories		DALYs, 10,000 person- years (95%UI)	Age- standardized DALY rate, per 100,000 (95%UI)	YLLs, 10,000 person- years (95%UI)	Age- standardized YLL rate, per 100,000 (95%UI)	YLDs, 10,000 person- years (95%UI)	Age- standardized YLD rate, per 100,000 (95%UI)
Total	1990	137.57 (113.49-164.77)	334.52 (281.08-393.14)	136.83 (112.87-163.71)	332.05 (279.18-389.6)	0.74 (0.50-1.03)	2.47 (1.69-3.40)
	2021	136.31 (108.32-176.91)	239.91 (191.98-299.37)	135.34 (107.45-175.62)	237.63 (190.4-296.93)	0.97 (0.63-1.41)	2.27 (1.53-3.15)
	Change, %	-0.92 (-34.26-55.88)	-28.28 (-51.17-6.51)	-1.09 (-34.37-55.59)	-28.44 (-51.13-6.36)	31.04 (-38.55-182.47)	-8.10 (-55.00-86.39)
Male	1990	112.11 (90.18-137.93)	483.97 (392.36-591.53)	111.50 (89.69-136.97)	480.48 (389.54-587.65)	0.61 (0.40-0.85)	3.49 (2.30-5.01)
	2021	118.37 (90.11-156.70)	368.19 (279.67-490.95)	117.53 (89.54-155.58)	364.78 (277.17-486.49)	0.84 (0.54-1.23)	3.40 (2.25-5.04)
	Change, %	5.58 (-34.67-73.77)	-23.92 (-52.72-25.13)	5.41 (-34.63-73.45)	-24.08 (-52.83-24.89)	38.38 (-36.39-210.37)	-2.58 (-55.09-119.13)
Female	1990	25.46 (19.79-31.73)	177.47 (142.84-214.58)	25.33 (19.69-31.54)	176.05 (141.9-212.8)	0.13 (0.09-0.19)	1.43 (0.96-1.99)
	2021	17.94 (13.27-23.49)	111.91 (87.16-141.96)	17.81 (13.19-23.32)	110.74 (86.25-140.35)	0.13 (0.09-0.19)	1.17 (0.77-1.69)
	Change, %	-29.55 (-58.17-18.74)	-36.94 (-59.38--0.62)	-29.70 (-58.18-18.48)	-37.10 (-59.47--1.09)	-1.94 (-55.80-115.96)	-18.18 (-61.31-76.04)

DALYs: Disability-adjusted life years; YLLs: years of life lost; YLDs: years lived with disability.

Analysis of DALYs

DALYs are used to quantify the overall burden that diseases, injuries, or risk factors impose on the health of a population. It combines the health losses caused by premature death and disability into a comprehensive value, facilitating the comparison of the impacts of different health problems or the assessment of the effectiveness of intervention measures. From 1990 to 2021, the DALYs for the 15-49 age group decreased from 137.57 person-years to 136.31, 10,000 person-years, a reduction of 0.92% [Table 2]. Similarly, the ASR of DALYs declined from 334.52 per 100,000 in 1990 to 239.91 per 100,000 in 2021, a decrease of 28.28%. Due to the relatively low relative survival rate of liver cancer, DALYs are primarily composed of YLLs. From 1990 to 2021, YLLs in the 15-49 age group decreased by 1.09%, while the ASR of YLLs declined by 28.44%. In contrast, YLDs in the 15-49 age group increased by 31.04%, while the ASR of YLDs decreased by 8.10%.

The disease burden trends differed between men and women. Contrary to the declining trend in DALYs and YLLs for the 15-49 age group, men experienced increases in DALYs and YLLs of 5.58% and 5.41%, respectively, while YLDs increased by 38.38%. Women exhibited declining trends across all measures, with DALYs and YLLs decreasing approximately five times more than men, and YLDs decreased by 1.94%. The reductions in ASRs for DALYs, YLLs, and YLDs were notably more pronounced in women than in men. These trends indicate a much higher burden of liver cancer in young men during this period.

The disease burden in different age groups mirrored the patterns observed in incidence and mortality rates. The 45-49 age group accounted for most of the liver cancer burden in Chinese youth [Figure 1 and Supplementary Table 3]. DALYs and YLLs began to increase in the 45-49 age group, whereas YLDs started to rise from the age of 30. The rates of DALYs, YLLs, and YLDs increased with age group. From 1990 to 2021, the rates of DALYs, YLLs, and YLDs decreased in all age groups, with higher reduction rates observed in younger age groups [Supplementary Table 4].

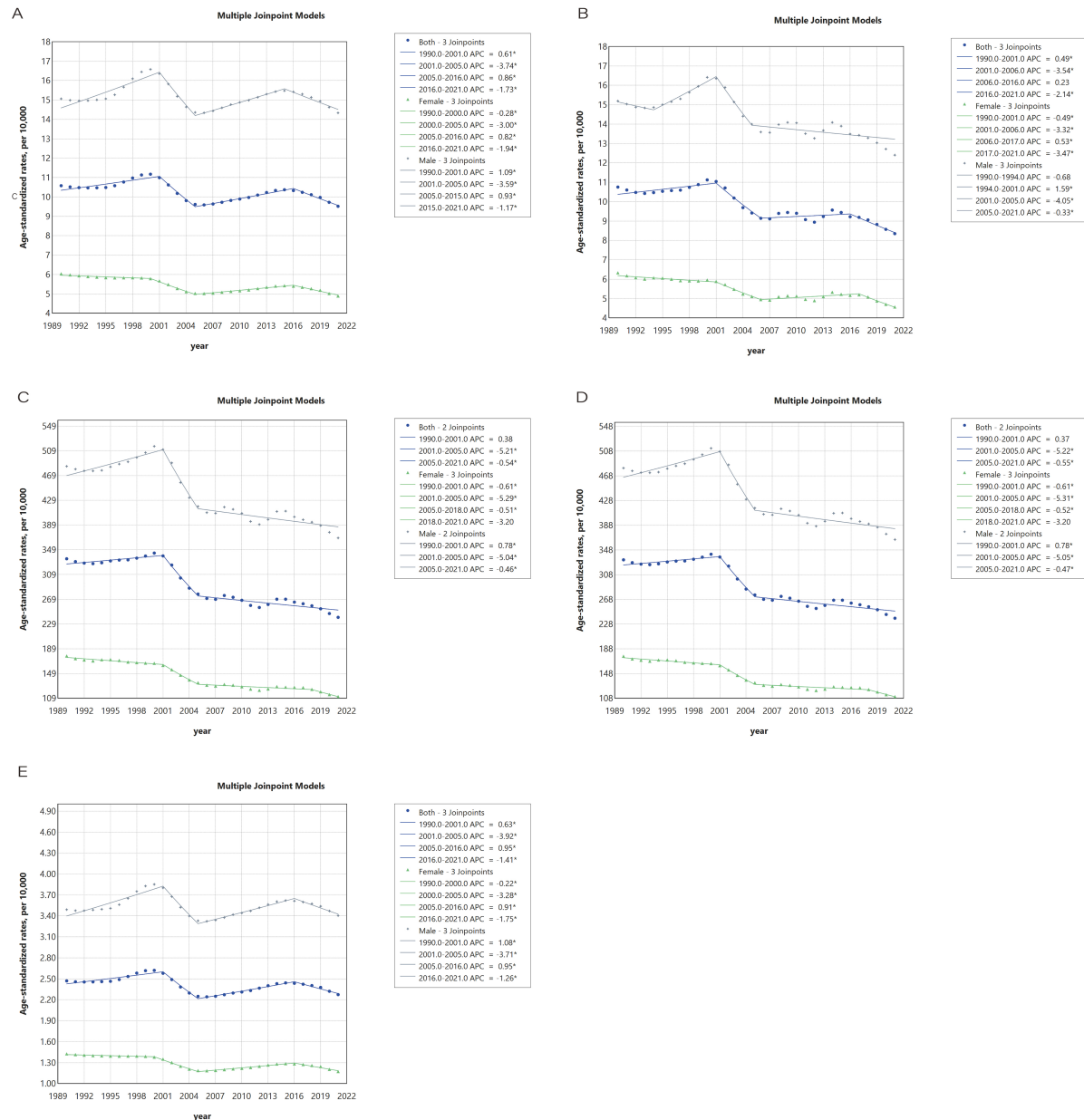


Figure 2. The trends of ASIR, ASMR, age-standardized DALY rate, age-standardized YLL due to premature mortality rate, and age-standardized YLD rate for liver cancer by sex in Joinpoint regression analysis, 1990-2021. (A) Age-standardized incidence rate; (B) Age-standardized mortality rate; (C) Age-standardized DALY rate; (D) Age-standardized YLL Rate; (E) Age-standardized YLD Rate. ASIR: Age-standardized incidence rate; ASMR: age-standardized mortality rate; DALY: disability-adjusted life-year; YLL: years of life lost; YLD: years lived with disability.

Temporal trends from 1990 to 2021

The time trends of liver cancer in Chinese youth exhibit sex disparities and temporal characteristics, as revealed by Joinpoint regression analysis. Overall, age-standardized incidence, mortality, DALYs, YLLs, and YLDs showed significant declining trends for both men and women [Figure 2 and Supplementary Table 5].

For women, the age-standardized incidence trend can be broadly divided into four periods: an increasing trend before 2001; a rapid decline between 2001 and 2005 with an APC of 3.59%; a slow increase from 2005 until 2015; and a subsequent decrease. The age-standardized mortality trend was more complex, decreasing before 1994, increasing until 2001, a rapid decline between 2001 and 2005 with an APC of 4.05%, and a significant decrease from 2005 to 2021. The trends in DALYs and YLLs were largely consistent, increasing until 2001, rapidly declining until 2005, and then declining slowly over the period 2005-2021. YLDs decreased only between 2001-2005 and 2016-2021, and increased to varying degrees in other periods.

Trends in women were slightly different. The age-standardized incidence rate for women has exhibited a downward trend, with the exception of a slight increase observed between 2005 and 2016. The most notable decrease occurred between 2000 and 2005, with an APC of 3.00%. The trend in age-standardized mortality was less complex, showing an increasing trend only between 2006 and 2017, with varying degrees of decline in other periods, notably an APC of 3.47% during 2017-2021. The trends in DALYs and YLLs mirrored those in mortality, with declining trends in all periods. YLDs increased only during 2005-2016, with declines in other periods.

These complex temporal trends provide crucial insights into the epidemiological characteristics of liver cancer among Chinese youth, facilitating a better understanding of the disease's dynamic progression and potential influencing factors.

Age-period-cohort analysis

To clarify the distinct contributions of chronological age, temporal trends, and generational effects on hepatic carcinoma rates among Chinese adolescents and young adults, we conducted an age-period-cohort analysis. The results showed that between 1990 and 2019, the net drift of liver cancer incidence among Chinese youth was -1.65% per year, while the net drift of mortality was -2.31% per year. The local drift of incidence exhibited a gradually increasing trend, albeit remaining negative throughout. The highest local drift occurred in the 45-49 age group (-0.59% per year). Local drift trends for incidence were similar for both sexes, with more pronounced changes in men.

The local drift of mortality also showed an increasing trend similar to that of incidence, while maintaining negative values. After controlling for period and cohort effects, we observed that the attributable effect of age on liver cancer incidence and mortality among Chinese youth increased progressively with age. The attribution effect of age on incidence rose from 0.35% in the 15-19 age group to 14.94% in the 45-49 age group. Notably, age attribution was more significant in males than in females, with a faster rate of increase in attribution for males. The association between age and mortality remained positively correlated, consistent with the pattern seen in incidence [Figure 3, Supplementary Figures 1 and 2, Supplementary Tables 6 and 7].

After controlling for age and cohort effects, we utilized the median level of 2000-2004 as a benchmark to quantify the period impact on incidence and mortality through ratios. Regarding period effects, it is noteworthy that the risk was higher than the median level during 1990-1999, and then remained below the median level until 2019. The period effect trends were generally consistent for both sexes [Figure 3, Supplementary Figures 1 and 2, Supplementary Tables 6 and 7].

After controlling for age and period effects, the birth cohort period of our study ranged from 1945 to 2000. Using the median level of the 1970 birth cohort as a reference, we calculated ratios to assess the cohort effect on liver cancer incidence and mortality among Chinese youth. The incidence ratio decreased from 1.16 for

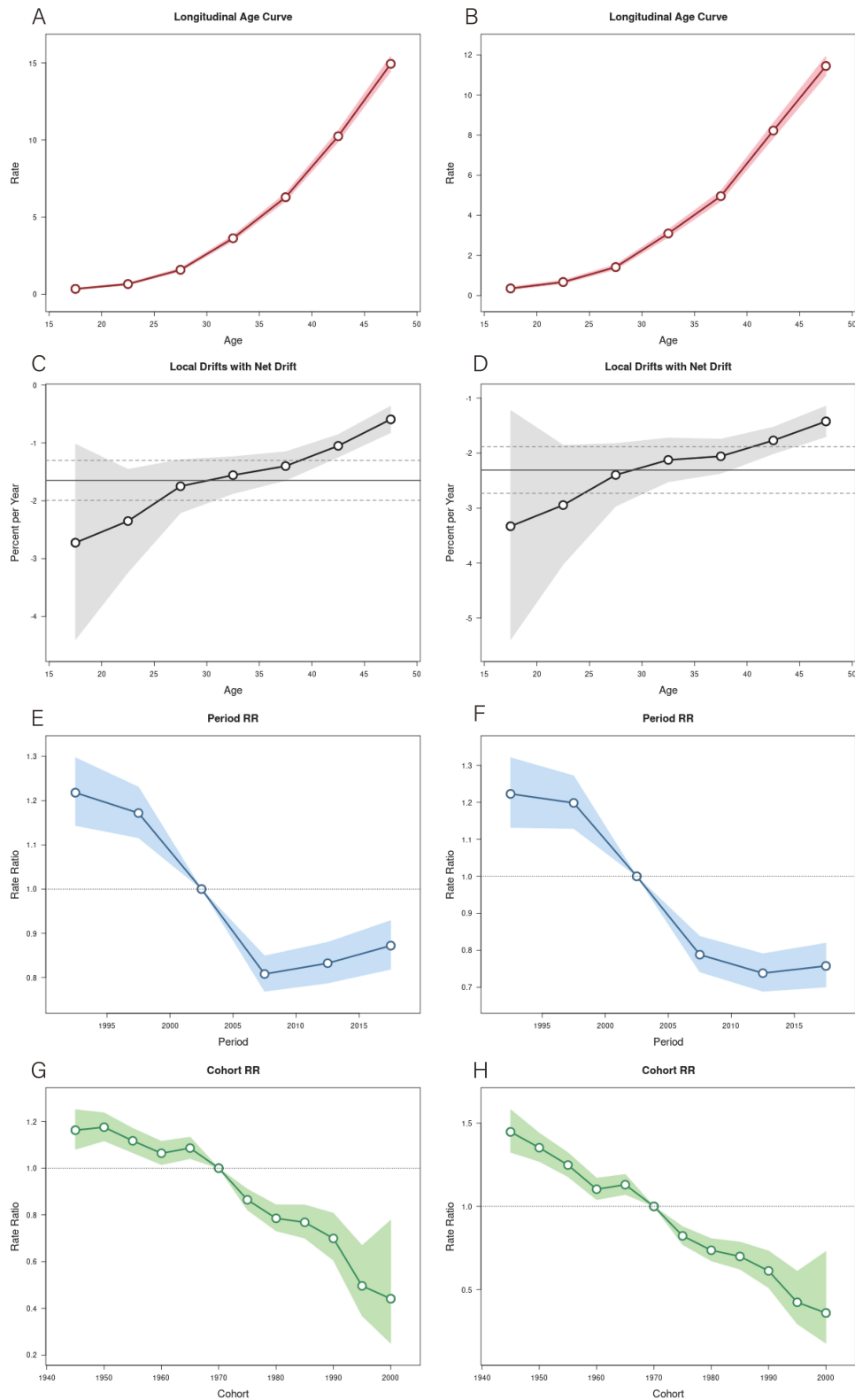


Figure 3. Age-period-cohort effect of liver cancer incidence and mortality in China, 1990-2021. (A) Longitudinal age curve of incidence; (B) Longitudinal age curve of mortality; (C) Local drift curve of incidence; (D) Local drift curve of mortality; (E) Period RR curve of incidence; (F) Period RR curve of mortality; (G) Cohort RR curve of incidence; (H) Cohort RR curve of mortality. RR: Rate ratio.

the 1945 cohort to 0.44 for the 2000 cohort. The cohort effect on mortality demonstrated a consistent declining trend with incidence. The ratio decreased from 1.45 for the 1945 cohort to 0.36 for the 2000 cohort. The cohort effect trends were generally consistent for both sexes [Figure 3, Supplementary Figures 1 and 2, Supplementary Tables 6 and 7].

Risk factors for liver cancer in China

The proportions of liver cancer attributable to specific etiology in China from 1990 to 2021 have been shown in Figure 4. In the Chinese adolescent population aged 15-49 years, over 80% of liver cancer cases are attributable to HBV. Subsequently, other causes, HCV, alcohol consumption, and non-alcoholic steatohepatitis (NASH), have demonstrated a relatively stable prevalence over time in China. In men, the proportion of liver cancer cases attributable to HBV is as high as 85%, which is a noteworthy phenomenon. In women, although HBV is also the leading cause, it is not as prevalent as in men, with a rate of 50%. With regard to age groups, the largest proportion of cases of liver cancer caused by HBV is observed in the 30-34 age group, which requires serious attention [Supplementary Figure 3].

Multiple risk factors have been confirmed that are associated with the burden of disease in liver cancer. Four of these are widely recognized and included in the GBD 2021 database: smoking, high body mass index (BMI), high alcohol consumption, and high fasting plasma glucose [Figure 5 and Supplementary Table 8]. The highest proportion of DALYs attributable to liver cancer was observed for smoking, which was consistent over the period, with no significant differences, and was predominantly concentrated in men [Supplementary Figure 4 and Supplementary Table 9]. A positive correlation was observed between the increase in high BMI over the years and the proportion of DALYs attributed to it, a trend that was consistent across both male and female populations [Supplementary Figure 5 and Supplementary Table 10]. In addition, the proportion of DALYs attributable to high BMI was consistently higher in women than in men from 2009 onwards. Similarly, high alcohol consumption demonstrated a consistent pattern with minimal significant variation over time and not much difference between men and women [Supplementary Figure 6 and Supplementary Table 11]. Finally, high fasting plasma glucose exhibited the lowest attribution to DALYs, with less than 1%. However, it is noteworthy that, similar to high BMI, a progressive increase in years showed a positive association with DALYs proportions, demonstrating higher prevalence among females relative to males [Supplementary Figure 7 and Supplementary Table 12].

DISCUSSION

In our study, we systematically evaluated the epidemiological characteristics and disease burden of liver cancer in the Chinese young adult population aged 15-49 years between 1990 and 2021, and identified and elucidated the pattern of temporal trends and potential age-period-cohort effects using a variety of analytical methods. The results of the study showed that, in terms of incidence and mortality, the total number of liver cancer incidence and mortality increased in the Chinese young adult population aged 15-49 years, while the ASIR and ASMR decreased. The highest incidence and mortality occurred in the 45-49 age group and continued to increase, with a decreasing trend in incidence and mortality among young people. For the burden of disease, men showed a significant increase in burden of disease, with increases in DALYs, YLLs, and YLDs, whereas all indicators decreased in women. The 45-49 age group was dominant for liver cancer, with a greater decrease in the younger age group. Temporal trends showed that, although there may have been slight variations between time points, overall, there were significant decreases in incidence, mortality, DALYs, YLLs, and YLDs for both men and women over the period.

In terms of time trend analysis, age-period-cohort analysis showed a net drift in incidence and mortality of liver cancer of -1.65% and -2.31% per year, respectively, in the young population. The local drift in incidence

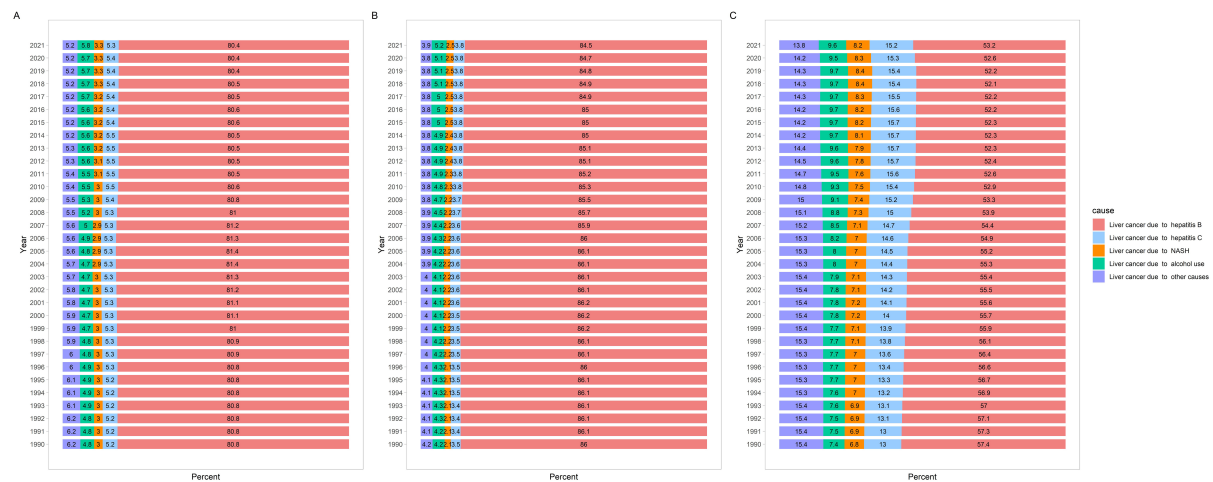


Figure 4. Contribution of HBV, HCV, alcohol use, NASH and other causes to absolute liver cancer incidence cases in China, 1990-2021. (A) Total; (B) Male; (C) Female. HBV: Hepatitis B virus; HCV: hepatitis C virus; NASH: non-alcoholic steatohepatitis.

rates increased progressively to negative values, with the highest rates in the 45-49 age group. Changes in incidence were more pronounced in men, with a significantly stronger effect with age for liver cancer, where the risk was above the median in the period 1990-1999 and consistently below the median thereafter. The effects of birth cohort on incidence decreased from 1.16 in 1945 to 0.44 in 2000, and that of deaths also decreased from 1.45 to 0.36, with generally consistent trends between the sexes. We also examined the proportions of liver cancer attributable to specific etiology in China from 1990 to 2021 in this population. The results show that over 80% of liver cancer is attributable to HBV in the Chinese adolescent population aged 15-49 years. Finally, we looked at several other risk factors, including smoking, high BMI, high alcohol consumption, and high fasting plasma glucose. Among these four GBD-estimated risk factors, smoking contributed the highest proportion of DALYs for liver cancer, with a predominant concentration in men. An increase in high BMI was positively associated with the number of DALYs. High alcohol consumption showed little variation and no substantial difference between men and women. High fasting plasma glucose had a small effect of less than 1%, but the annual increase of high fasting plasma glucose was positively associated with DALYs, and the prevalence of high fasting plasma glucose was higher in women than in men. Overall, these findings suggest that more precise and targeted interventions are needed to prevent and control liver cancer in the young Chinese population.

The global epidemiology of liver cancer shows marked regional variation. Contemporary research reveals that despite maintaining the highest ASRs for incidence, mortality, and DALYs in East Asia, the area has achieved substantial progress in reducing liver cancer burden since 1990, and regional differences still exist. The incidence rate, mortality rate, and DALYs of young men worldwide are significantly higher than those of young women, which are 3.1 times, 2.9 times, and 2.6 times higher than those of young women, respectively. The incidence rate, mortality rate, and the number and rate of DALYs of liver cancer increase with age. These results are consistent with our research results^[38,39].

PLC accounts for over one million cancer-related deaths annually, with projections indicating at least 55% growth within 15 years^[33]. A number of epidemiological studies have provided compelling evidence that the two primary risk factors for PLC are HBV and aflatoxin^[40,41]. These two factors have been shown to have a synergistic effect, increasing the risk of HCC by more than eightfold compared to HBV alone^[40,42,43]. Epidemiological evidence from Qidong's cancer surveillance system, combined with aflatoxin exposure

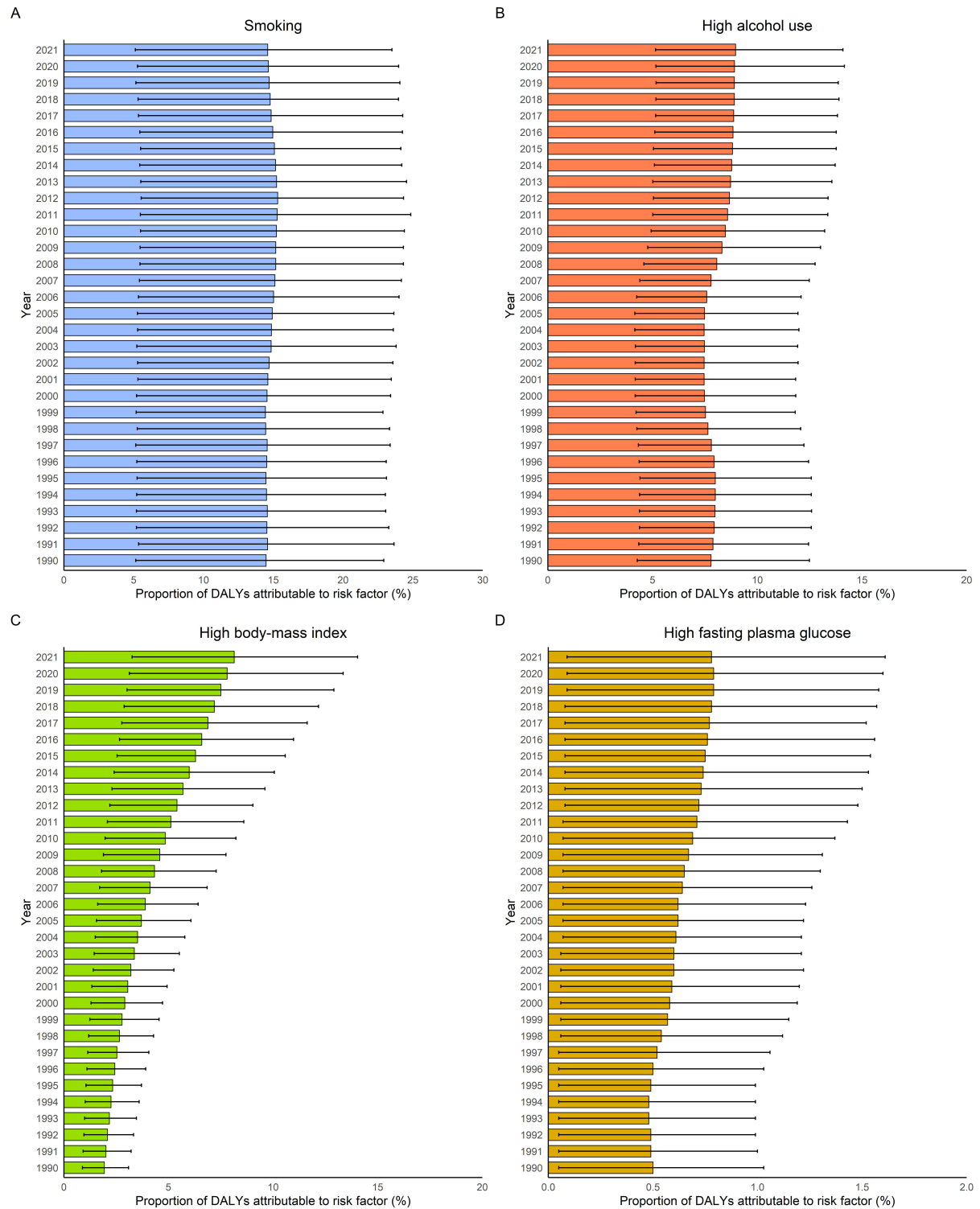


Figure 5. Proportion of liver cancer DALYs attributable to four risk factors in China, 1990-2021. (A) Smoking; (B) High alcohol use; (C) High body mass index; (D) High fasting plasma glucose. DALYs: Disability-adjusted life years.

biomarkers, suggests that declining aflatoxin levels over three decades may account for roughly 70% of the observed decrease in standardized liver cancer incidence^[44]. Over the past four decades in China, increased

dietary diversity appears to have accelerated the time to liver cancer diagnosis. This suggests that reducing exposure to this carcinogen could add several years of life before cancer diagnosis. It is feasible to reduce the incidence of liver cancer and delay its invariably fatal diagnosis by targeting interventions at aflatoxin^[45-47]. In addition to aflatoxin, it is worth mentioning that aristolochic acids in Chinese herbs, found in several aristolochic species, have been linked to DNA mutations and are strongly associated with HCC^[48,49]. Furthermore, high alcohol consumption also has a great impact on the increased risk of death from liver cancer. A meta-analysis of prospective studies showed that heavy drinking (≥ 3 cups/day) was associated with a 16% increased risk of liver cancer, but lower levels of drinking (< 3 cups/day) were not^[50]. Finally, several metabolic abnormalities, particularly metabolic syndrome, obesity, and type 2 diabetes, have been identified as significant contributors to liver cancer mortality risk^[51-54].

In China, HBV infection is the primary risk factor for the onset and death of liver cancer. Epidemiological investigations show that approximately 75 million Chinese residents have been infected with HBV, and only 17.33% of these individuals (3 million) were being treated with antivirals. Such people face a significant risk of premature death due to complications related to liver diseases^[55]. It is estimated that 263,000 deaths per year in China are attributable to liver cancer or cirrhosis, representing 37%-50% of global HBV-related mortality^[56]. In the context of the significant burden of liver cancer attributable to HBV in China's middle-aged and young adult population, it is worth considering the long-term efficacy of the hepatitis B vaccine in China as an area of potential research. A 37-year follow-up study, conducted from 1983 to 1990 in Qidong City as a group-randomized clinical trial, recruited participants into two groups: the neonatal vaccination group, in which all infants were vaccinated at birth, 1 and 6 months of age; and the control group, which received no intervention. The study revealed that the vaccine provided 72% (95%CI: 30-89) protection against the incidence of liver cancer. The protective efficacy against liver cancer mortality was 70% (95%CI: 0.23-0.88), and there was a 64% (95%CI: 0.27-0.82) benefit in preventing deaths related to liver disease^[57]. The administration of the hepatitis B vaccine at birth provides robust protection against the incidence of liver cancer and reduces mortality from HCC and liver disease^[14,57]. Another study similarly demonstrated that hepatitis B vaccination in infancy markedly reduced the seroprevalence of HBsAg in children and young adults, subsequently reducing the risk of PLC and other liver diseases in rural Chinese youth. Individuals born to mothers with HBsAg positivity who have completed the hepatitis B vaccination series should be considered for a booster dose during adolescence^[58].

In 1992, China commenced a nationwide hepatitis B vaccination project to prevent HBV infection, particularly among children and newborns in areas with a high prevalence of the disease^[59,60]. Since our research results show that over 80% of liver cancer cases in the Chinese adolescent population aged 15-49 years are attributable to HBV. Among the young population we studied, the proportion of HBV-related liver cancer was actually decreasing from 1990 to 2021, although the decline was not significant. If we focus on the entire age group or a longer period of time in the future, perhaps we can observe more significant differences. However, there are some regional disparities in vaccination coverage. In urban areas, vaccination coverage is typically high, reflecting greater public awareness and more convenient access to immunization services. Conversely, rural areas, particularly those in remote regions, exhibit comparatively lower vaccination coverage, possibly attributable to inadequate medical resources and inadequate dissemination of information^[61,62]. In Shanghai, the promotion of hepatitis B vaccination was synchronized with the national project, with implementation starting around 1992. As an economically developed region, Shanghai was able to ensure high vaccine coverage, resulting in a notable reduction in the incidence of hepatitis B^[63,64].

We believe this study provides a comprehensive picture of the burden of liver cancer in the young population in China. In this study, a variety of techniques were used to process the most recent data, allowing for comparisons to be made between different time periods and geographical locations. The heterogeneous characteristics such as gender differences, spatio-temporal evolution patterns, and age cohort effects revealed in this study have special guiding value for the prevention and control of liver cancer among young people in China. It should be pointed out that this study is limited by the inherent characteristics of the GBD 2021 database and therefore inherits the methodological limitations of the GBD research system. The relevant technical details have been thoroughly discussed in previous studies^[65-68]. For example, it should be noted that due to the necessary time lag generated during the statistical and reporting processes, the GBD framework has inherent limitations in reflecting real-time public health developments within the most recent three-year period. Furthermore, the existing analytical approach fails to fully elucidate the relationship between YLD and YLL uncertainty due to the interdependence between incidence and mortality. This may result in an underestimation of DALY uncertainty. First, we also need to consider the issues of comorbidities, which may introduce some uncalculatable and irremediable errors in the estimation of YLD. Second, the lack of detailed provincial data precluded a comprehensive summary and comparison of regional differences within China, which may have resulted in the overlook of disparities in the burden of liver cancer between regions. Third, a major limitation is the lack of reliable statistical models based on stratified populations, economic status, and public health resources in different regions. Those models would be extremely useful for understanding differences and guiding appropriate health policies and programs.

In conclusion, the absolute numbers of liver cancer cases, deaths, and DALYs among the young population in China show a steady increase from 1990 to 2021. However, the age-standardized incidence and mortality rates show a continuous decline. It is evident that there are notable differences in the risk factors associated with different sexes and disease contexts among this age group, which require further attention. The temporal and regional variations of the liver cancer epidemiology and its associated burden require the implementation of tailored interventions and the formulation of health policies adapted to local conditions. To reduce the liver cancer burden, a multifaceted approach is needed. This should include continuing to vaccinate against HBV, implementing targeted lifestyle interventions to reduce alcohol consumption and obesity, and expanding early screening programs for high-risk groups. Future research should examine regional disparities and the socioeconomic factors that influence liver cancer outcomes in order to inform more effective prevention strategies. The results of our research will facilitate the establishment of evidence-based protocols for liver cancer prevention and control in young adults.

DECLARATIONS

Authors' contributors

Designed the research and obtained funding: Xiang YB

Conducted the study: Zou YX, Li ZY, Zhou XH, Yang DN, Tuo JY, Shen QM, Tan YT, Li HL, Xiang YB

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Primary responsibility for the final content: Xiang YB

All authors reviewed, edited, and approved the final version of the paper.

Availability of data and materials

The datasets analyzed during the current study are available in the publicly available Global Burden of Disease datasets. The data can be found here: <http://ghdx.healthdata.org/gbd-results-tool>.

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Conflicts of interest

Xiang YB is an Editorial Board member of the journal *Hepatoma Research*. Xiang YB was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, or decision making. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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