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Comparison of time trends in the incidence of primary liver cancer between China and the United States: an age-period-cohort analysis of the Global Burden of Disease 2019

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Abstract

Background: China and the United States (US) ranked first and third in terms of new liver cancer cases and deaths globally in 2020. Therefore, a comprehensive assessment of trends in the incidence of primary liver cancer with four major etiological factors between China and the US during the past 30 years with age-period-cohort (APC) analyses is warranted.

Methods: Data were obtained from the Global Burden of Disease 2019, and period/cohort relative risks were estimated by APC modeling from 1990 to 2019.

Results: In 2019, there were 211,000 new liver cancer cases in China and 28,000 in the US, accounting for 39.4% and 5.2% of global liver cancer cases, respectively. For China, the age-standardized incidence rate (ASIR) consecutively decreased before 2005 but increased slightly since then, whereas the ASIR continuously increased in the US. Among the four etiological factors of liver cancer, the fastest reduction in incidence was observed in hepatitis B virus-related liver cancer among Chinese women, and the fastest increase was in nonalcoholic steatosis hepatitis (NASH)-related liver cancer among American men. The greatest reduction in the incidence of liver cancer was observed at the age of 53 years in Chinese men (−5.2%/year) and 33 years in Chinese women (−6.6%/year), while it peaked at 58 years old in both American men and women (4.5%/year *vs*. 2.8%/year). Furthermore, the period risks of alcohol- and NASH-related liver cancer among Chinese men have been elevated since 2013. Simultaneously, leveled-off period risks were observed in hepatitis C viral-related liver cancer in both American men and women.

Conclusions: Currently, both viral and lifestyle factors have been and will continue to play an important role in the time trends of liver cancer in both countries. More tailored and efficient preventive strategies should be designed to target both viral and lifestyle factors to prevent and control liver cancer.

Keywords: Alcohol use-related liver cancer; China; Global Burden of Disease; Hepatitis; Hepatitis B virus; Hepatitis C; Incidence; Liver neoplasms; Life Style; Middle aged; Non-alcoholic fatty liver disease; United States

Introduction

Enormous efforts have been implemented to prevent primary liver cancer (PLC) in the past three decades; however, it remains one of the top ten cancers in both incidence and mortality globally.[1] Based on the report of the International Agency for Research on Cancer (IARC) 2020, there are approximately 906,000 new cases and 830,000 deaths attributed to liver cancer.[1] China ranks top one both for new liver cases and deaths worldwide, and US ranks the third.[2] China has the largest number of liver cancer patients not only because of its large population but also due to the high prevalence of etiological factors.[3] It has been estimated that approximately one-fifth of the population in China is affected by different types of liver diseases, prominently hepatitis B and hepatitis C.[4] Due to the national immunization program of hepatitis B virus (HBV) in the late 1980s in China, the incidence of HBV-related liver cancer (LCHB) started to decrease. However, changing dietary preference (eg, overnutrition) and reduced physical activities have increased the prevalence of nonalcoholic steatohepatitis (NASH), which has gradually become one of the major factors leading to the development of liver cancer. In

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addition, increased alcohol consumption is also associated with an increase in alcohol-related liver disease and cancer.[4]

It has been observed that the incidence of PLC varies considerably across the world. The incidence in East Asia is almost five- to ten-fold higher than that in America. In the US, it confronts the double burden of viral- and lifestyle-related liver cancer. In particular, hepatitis C viral infection-related liver cancer (LCHC) and NASH have been increasing, which might be a major driving force of the growing prevalence of liver cancer in the US. Previous studies indicated that the incidence of liver cancer decreased in China.[5] However, a substantial increase in incidence has been observed in the US.[6] In a recent study, Liu *et al*[3] described that the US experienced a significant increase in liver cancer and that China was categorized as a "remain stable or minor decrease" country by cluster analysis. Previous research has mainly focused on liver cancer incidence over the past two or three decades and described the trends among the total population across all age groups,[3,5-7] which in fact ignored cohort and period effects. From an epidemiological perspective, period effects, such as changes in social, cultural, natural disasters, or physical environments, affected the population of all ages.[8] Cohort effects, defined as all those born at a specific calendar year, were independent of aging. Therefore, dissecting the cohort and period effects from age over a long time period can assist policy makers in identifying the risk population and the etiological factors of disease of interest.[9] Additionally, both China and the US have invested research funds in liver cancer prevention and control,[4] thus it is of particular interest to contrast and compare the differences in age, period, and cohort effects stratified by gender between the two countries.

Therefore, using data from the Global Burden of Disease (GBD) 2019, we compared trends of PLC incidence between China and the US during 1990 to 2019 and assessed their associations with age, period, and birth cohort. To evaluate the effectiveness of public health preventive strategies, further etiological analyses with HBV, hepatitis C virus (HCV), alcohol consumption, and NASH-related liver cancer using the age-period-cohort (APC) model were conducted.

Methods

Data sources

This was an analysis based on existing data from GBD 2019. All new case numbers and incidence rate data were obtained, including 285 causes of death across 195 countries and territories from 1980 to 2019 (http://ghdx.healthdata.org).[10] Methods used in the estimation of liver cancer incidence using GBD data were reported previously.[11,12] Original data of China were mainly reported from the Disease Surveillance Point (DSP), Maternal and Child Surveillance System and the Chinese Center for Diseases Control and Prevention Cause of Death Reporting System. The liver incidence data of the US were mainly derived from Surveillance, Epidemiology and End Results and IARC's Cancer Incidence in Five Continents.[3,5]

LCHB, LCHC, alcohol use-related liver cancer (LCAL), and NASH cases were classified based on the International Classification of Diseases and Injuries, Ninth and Tenth revisions (all ICD-9 and ICD-10 codes pertaining to PLC [155–155.963 and C22.0–9, respectively] were included in these estimates). The proportion of liver cancer cases due to the four etiology groups included in GBD (hepatitis B, hepatitis C, alcohol consumption, and NASH) was also directly downloaded from the GBD databases. The equation of age-standardized incidence rates (ASIRs) is listed below:

$$\mathrm{ASIR} = \frac{\sum_{i=1}^{A} a_i w_i}{\sum_{i=1}^{A} w_i} \sum_{i=1}^{A} \left(a_i \times \frac{w_i}{\sum_{i=1}^{A} w_i} \right).$$

The ASIR (per 100,000) in accordance with the direct method is calculated by summing the population weighted age-specific rates (a_i, where i represents the ith age group, A refers the number of age groups), where the population weight is defined as the share of standardized population weights (wi) in the correspondence subgroup i.[3] All ASIRs were estimated based on the GBD 2019 global age-standard population.

All data were deidentified and aggregated from the GBD website. Therefore, a waiver of informed consent and human project protection were reviewed and approved by the University of Washington Institutional Review Board.

Statistical analysis

The APC method was applied to assess the effects of age, period (year of incidence), and cohort (year of birth) on PLC incidence. The age effect includes the differential risks associated with membership in different age groups. The period effect indicates the variation in risk under certain periods or years that affects all age groups. The cohort effect represents the risk factors for the PLC for those individuals in the same birth year. The APC method can separate the effects of age, period, and cohort. Additionally, it provides the net drift, longitudinal age trend and age, period, and cohort deviations. More detailed information could be identified in previous publications.[8,13]

To perform the APC analyses, the incidence and population data were categorized into consecutive 5-year calendar year periods from 1993 to 2017 and sequential 5-year age groups from 15 to 19 years to 75 to 79 years (individuals who were <15 years old or >80 years old were censored). The APC Web Tool (Biostatistics Branch, National Cancer Institute, Bethesda, MD, USA) was adopted to obtain all the estimable parameters. The middle age group, period, and birth cohort were set as the reference through all APC analyses. The lower of the two central values was set as the reference if categories were an even number. The Wald chi-square test was applied to detect the significance of estimated parameters and functions, and a general linear model was adopted to compare the disparity between the slope of the period relative risk (RR) and cohort RR by estimating the effect of interaction between gender and calendar year/birth cohort. All statistical tests were two-sided, and P values <0.05 were considered statistically significant.

Results

Trends of incidence rate of PLC

The characteristics of the PLC ASIR, new cases, and relative proportion in both China and the US in 1990 and 2019 are shown in Table 1. Additionally, the trends of PLC incidence in both China and the US are demonstrated in Figure 1 and Supplementary Figure 1, http://links.lww.com/CM9/A930. From 1990 to 2019, the number of liver cancer cases increased from 373,000 to 535,000 worldwide. In 2019, there were 211,000 and 27,800 new PLC cases in China and the US, respectively, which accounted for 39.4% and 5.2% of all liver cancer cases globally. Additionally, new cases of liver cancer in men were almost three times that in women in both countries (75.8% *vs.* 24.2% in China and 71.9% *vs.* 24.2% in the US). Due to the large population size and a higher risk profile, new cases of liver cancer in China accounted for 42.4% (male) and 32.1% (female) of PLCs worldwide, respectively. Between 1990 and 2019, the relative proportion of new cases from LCHB, LCHC, LCAL, and NASH all decreased in China, with a notable reduction in viral-related liver cancer. However, both Chinese men and women still accounted for the highest proportion of viral-related liver cancer worldwide. In the past three decades, the overall incidence of PLC in the US was generally low. However, the ASIR of PLCs among both males and females gradually increased by varying degrees in the US. The US males experienced a significant increase in ASIR (from 3.3 to 8.1 per 100,000) and cause-specific PLC (122% for LCHB, 165% for LCHC, 158% for LCAL, and 168% for NASH).

Net drifts and local drifts of incidence in different age groups

Net drift represents the overall annual percentage change over the whole observation period, and local drift represents the annual percentage changes in incidence rate for each age group [Figure 2]. The overall net drift decreased in China but increased in the US during the study period. Notably, Chinese females experienced a faster reduction than males (−5.95% [95% confidence interval [CI]: −6.16% to −5.75%] *vs.* −4.52% [95% CI: −4.65% to −4.40%]), while US females had a slower increase than males (2.13% [95% CI: 1.99%–2.27%] *vs.* 2.44% [95% CI: 2.14%–2.75%]). Similar patterns were also observed in four etiological factors of PLC [Supplementary Figure 2, http://links.lww.com/CM9/A930]. In particular, the fastest decrease was observed in LCHB among Chinese women (−6.16%, 95% CI: −6.36% to −5.96%), and the fastest increase was observed in NASH-related liver cancer among US men (3.10%, 95% CI: 2.76%–3.44%).

Values of local drift in the US were mainly >0 for most age groups, particularly for people aged between 48 and 68 years old (annual increasing incidence varied between

Table 1: Characteristics of PLCs in China and the US during 1990 to 2019.

Parameters	Males of China		Males of US		Females of China		Females of US	
	1990	2019	1990	2019	1990	2019	1990	2019
Total ($N \times 1,000,000$)	610 (493, 741)	725 (577, 902)	124 (120, 127)	161 (122, 204)	573 (466, 705)	698 (563, 858)	130 (122, 135)	167 (135, 201)
Percentage of global (%)	22.7	18.7	4.6	4.2	21.6	18.1	4.9	4.3
Liver cancer								
ASIR (per 100,000)	36.4 (29.6, 44.2)	16.4 (13.1, 20.2)	3.3 (3.2, 3.4)	8.1 (6.1, 10.3)	15.0 (12.3, 18.3)	4.9 (4.0, 6.1)	1.4 (1.3, 1.4)	2.7 (2.2, 3.2)
N (×1000)	170 (138, 207)	160 (127, 199)	4.4 (4.3, 4.5)	20 (15, 26)	67 (54, 82)	51 (41, 62)	2.5 (2.3, 2.6)	7.8 (6.3, 9.4)
Relative proportion* (%)	65.4	42.4	1.7	5.3	59.0	32.1	2.2	4.9
LCHB								
ASIR (per 100,000)	27.1 (21.7, 33.0)	11.8 (9.3, 14.6)	0.51 (0.4, 0.6)	1.13 (1.6, 1.8)	5.9 (4.6, 7.5)	1.7 (1.4, 2.21)	0.16 (0.14, 0.19)	0.29 (0.22, 0.36)
N (×1000)	131 (105, 160)	117 (92, 146)	0.7 (0.6, 0.8)	2.7 (1.9, 3.6)	27.5 (21.6, 34.9)	18.0 (13.7, 23.2)	0.28 (0.24, 0.32)	0.76 (0.59, 0.97)
Relative proportion* (%)	50.3	31.1	0.26	0.71	24.3	11.4	0.24	0.48
LCHC								
ASIR (per 100,000)	4.0 (3.1, 5.0)	1.85 (1.4, 2.3)	0.96 (0.9, 1.1)	2.54 (1.9, 3.4)	5.0 (4.1, 6.3)	1.7 (1.3, 2.1)	0.64 (0.6, 0.7)	1.3 (1.0, 1.6)
N (×1000)	14.8 (11.5, 19.1)	16.5 (12.5, 21.3)	1.3 (1.1, 1.4)	6.5 (4.7, 8.6)	20.6 (16.4, 25.7)	17.6 (13.8, 21.9)	1.8 (1.4, 2.2)	3.9 (3.2, 4.8)
Relative proportion* (%)	5.7	4.4	0.5	1.7	18.2	11.1	1.1	2.5
LCAL								
ASIR (per 100,000)	2.7 (2.0, 3.7)	1.4 (1.0, 1.9)	1.2 (1.1, 1.4)	3.1 (2.3, 4.1)	1.2 (0.9, 1.7)	0.5 (0.4, 0.7)	0.18 (0.18, 0.21)	0.35 (0.27, 0.46)
N (× 1000)	12.0 (8.5, 16.4)	14.0 (10.0, 19.3)	1.7 (1.5, 1.9)	7.9 (5.9, 10.3)	5.5 (3.9, 7.6)	5.2 (3.7, 7.1)	3.3 (2.8, 3.8)	1.03 (0.78, 1.34)
Relative proportion* (%)	4.6	3.7	0.65	2.1	4.9	3.3	0.29	0.65
Liver cancer due to NASH								
ASIR (per 100,000)	1.0 (0.8, 1.3)	0.6 (0.5, 0.8)	0.25 (0.21, 0.29)	0.67 (0.49, 0.89)	1.04 (0.8, 1.3)	0.43 (0.3, 0.6)	0.17 (0.15, 0.20)	0.36 (0.3, 0.5)
N (× 1000)	4.2 (3.2 5.4)	5.5 (4.1, 7.2)	0.34 (0.3, 0.4)	1.7 (1.2, 2.3)	4.6 (3.5, 5.9)	4.5 (3.4, 5.7)	0.32 (0.3, 0.4)	1.1 (0.8, 1.4)
Relative proportion* (%)	1.6	1.5	0.13	0.45	4.1	2.9	0.29	0.70

Data are presented as n (95% uncertainty interval) or percentage. *The relative proportion of global incidence resulting from liver cancer, LCHB, LCHC, alcohol use (LCAL), and NASH by sex. ASIR: Age-standardized incidence rate; LCAL: Alcohol use-related liver cancer; LCHB: HBV-related liver cancer; LCHC: Hepatitis C viral infection-related liver cancer; NASH: Nonalcoholic steato hepatitis; PLC: Primary liver cancer; US: United States.

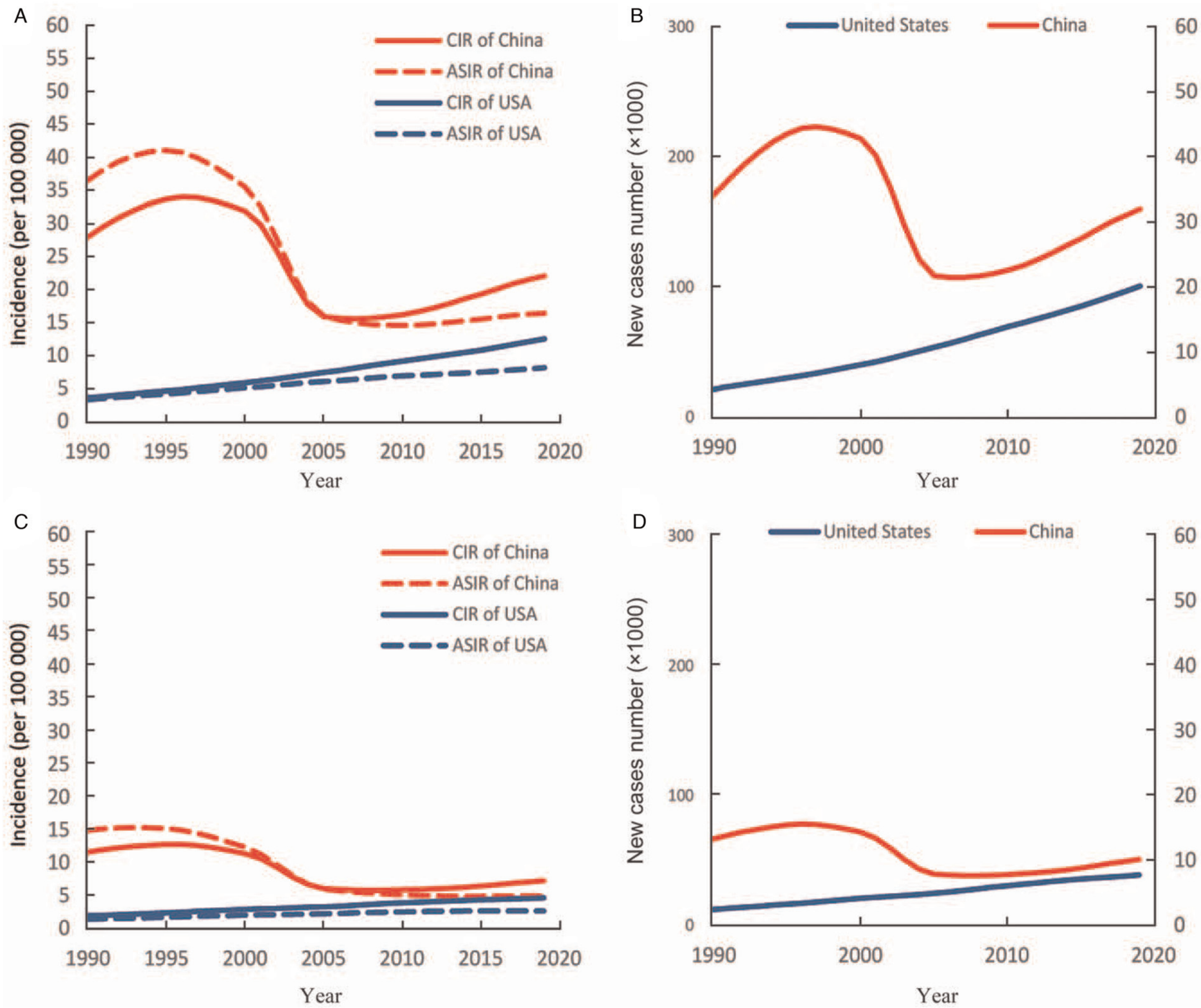

Figure 1: Time trends of PLC, CIR, and ASIR by sex in China and the US during 1990 to 2019. The solid line indicates the CIRof liver cancer, and the dashed line indicates the ASIR of liver cancer. In addition, the red line indicates China, and the blue line indicates the US. (A) and (B) refer to males and (C) and (D) refer to females. (B) and (D) represent the estimated absolute number of new cases in both countries during 1990 to 2019. ASIR: Age-standardized incidence rate; CIR: Crude incidence rate; PLC: Primary liver cancer; US: United States.

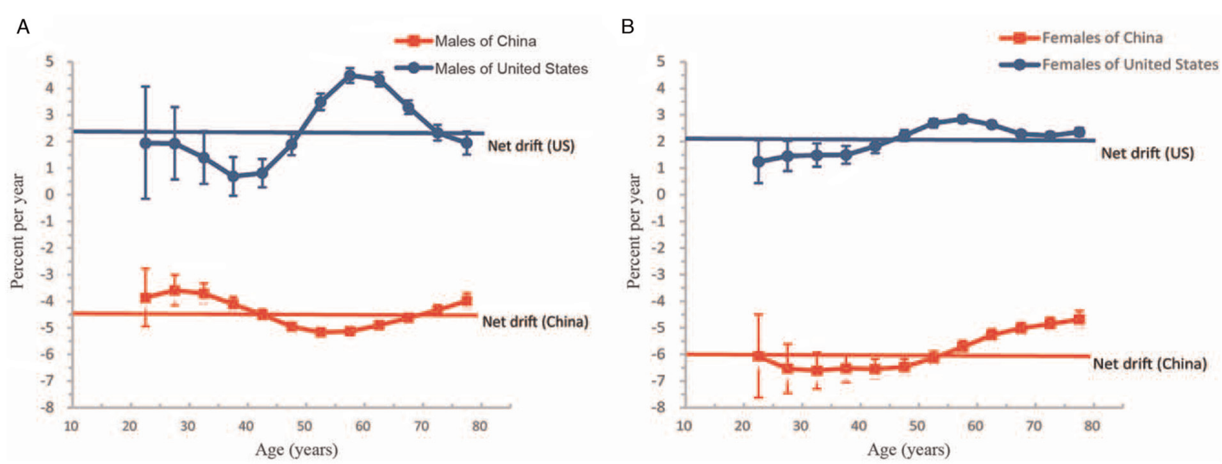

Figure 2: Net drift and local drift of PLC incidence by sex in China and the US during 1990 to 2019. Net drift demonstrated the overall annual percentage change. If the value was <0, it indicated a reduction in liver cancer incidence over the study period. The local drift value demonstrated an annual percentage change in each age group. If the value was <0 across all age groups, it indicated a substantial reduction in liver cancer incidence over the study period. The red line refers to China, and the blue line refers to the US. The hinges indicate 95% UI of the corresponding age. (A) represents the data derived from males and (B) represents the data derived from females. ASIR: Age-standardized incidence rate; CIR: Crude incidence rate; PLC: Primary liver cancer; UI: Uncertainty interval; US: United States.

3.29% and 4.48%), and the value peaked at approximately 58 years old in both men and women. However, the annual change was much higher in men than in women (4.5%/year *vs*. 2.8%/year). Values of local drift in China were mainly below 0 for most age groups, which indicates that all age groups experienced a reduction in the incidence of PLC. The greatest reduction was observed at the age of 53 years in men (−5.2%/year) and the age of 33 years in women (−6.6%/year). The corresponding patterns were illustrated separately for LCHB-, LCAL-, and NASH-related liver cancer in both China and the US [Supplementary Figure 2, http://links.lww.com/CM9/A930].

APC effects on PLC incidence

The period effect of China substantially improved from 1997 to 2012. However, the favorite period effect was blunted since 2007 among Chinese men [Figure 3]. In the US, more favorable period trends were observed since 2012, which was mainly attributable to women. For the birth cohort effect, the risk of PLC was enhanced dramatically in Americans born after 1975, whereas the increase started a decade early among women. For China, a significant decrease was observed in those born in 1915 and later.

The four-cause analysis of period and cohort effects in all subgroups showed similar patterns corresponding to their counterparts [men: Supplementary Figure 3, http://links.lww.com/CM9/A930 and women: Supplementary Figure 4, http://links.lww.com/CM9/A930]. In the period effect analysis [Supplementary Figure 3A, 3C, 3E, and 3G, http://links.lww.com/CM9/A930 and Supplementary Figure 4A, 4C, 4E, and 4G, http://links.lww.com/CM9/A930], the most striking reduction in the incidence of LCHB was identified in China before 2007, particularly in women. However, an upward trend and a stalled trend appeared since 2012 for Chinese men and women with four etiological factors individually [Supplementary Figure 3, http://links.lww.com/CM9/A930]. Generally, US had continuously upward trends for four types of liver cancer, with a notable effect on NASH. A stalled trend was demonstrated in LCHC among both men and women in the US since 2012. In terms of cohort effects [Supplementary Figure 3B, 3D, 3F, and 3H, http://links.lww.com/CM9/A930 and Supplementary Figure 4B, 4D, 4F, and

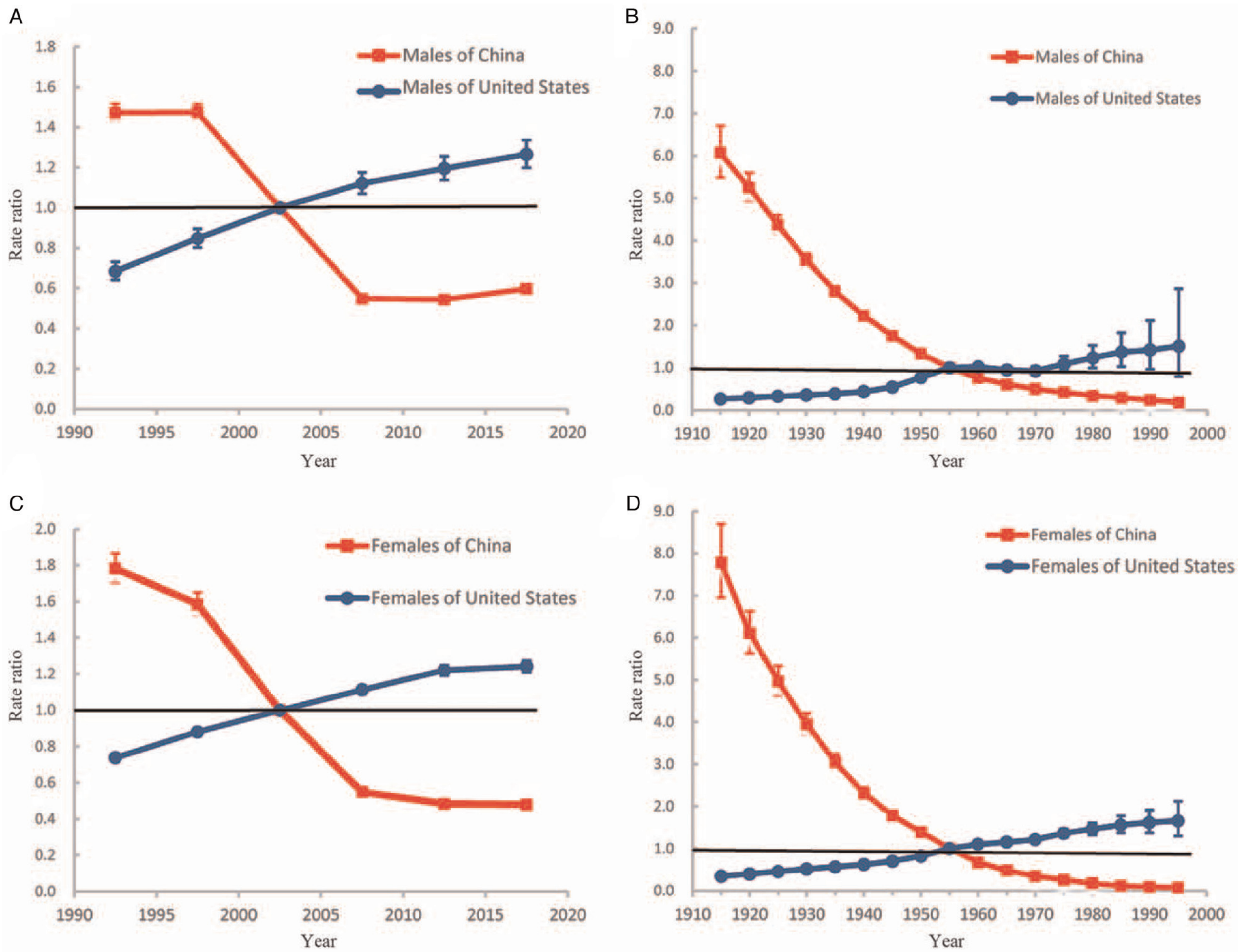

Figure 3: Period effects and cohort effects of PLC by sex in China and the US during 1990 to 2019. The red line indicates China, and the blue line indicates the US. The hinges indicate 95% UI of the corresponding period/birth cohort. (A) and (B) represent the data derived from males, and(B) and(D) represent the data derived from females. (A)and(C) represent the period effects, and (B) and (D) represent the birth cohort effects. PLC: Primary liver cancer; UI: Uncertainty interval; US: United States.

4H, http://links.lww.com/CM9/A930], a significant decreasing trend was observed in LCHB in China, and the predominant increase was detected in NASH-related liver cancer, followed by LCHC of the US across successive birth cohorts.

Discussion

China and the US ranked first and third in terms of estimated numbers of new liver cancer cases and deaths globally in 2020. Over the past 30 years, substantial improvements in four cause-specific PLCs were observed before 2012 in China, particularly among women. More favorable trends of four-cause-specific PLC have been demonstrated in the US since 2012, particularly LCHC. However, both countries face the increasing prevalence of alcohol- and NASH-related liver cancer, particularly among men.

The reduction in PLC incidence in China may be attributable to multiple factors, including HBV vaccination for new-borns, reduced consumption of aflatoxin-contaminated food or drinking water, prenatal examination of HBV and HCV, and effective population-based cancer prevention programs in high-risk areas.[14] Based on the HBV cohort study in Qidong, Jiangsu Province, HBV-infected patients had a 16 times higher risk of being diagnosed with liver cancer.[15] From the local drift analyses, decreasing trends of liver cancer incidence were observed in both men and women aged 28 to 35 years old with LCHB, which was plausibly attributed to HBV vaccination for newborns.[15] It is worth noting that the period effects of the four etiological factors of PLC all increased among Chinese males, but a decelerated reduction was observed among women since 2012, which was consistent with previous studies.[5] This phenomenon was partially attributable to the implementation of third-generation anti-HCV tests in China,[16] expanding the number of surveillance hospitals, and reducing lifestyle-related infections such as ear piercing and drug abuse.[17] Another possible reason might be the low coverage of diagnosis and treatment of hepatitis B currently. Liu *et al*[3] estimated that only 16.1 million (19%) chronic HBV-infected populations were diagnosed in China (*vs*. 90% in the 2030 targets).[18] When people are diagnosed with liver cancer and simultaneously found to be HBV positive, the number of LCHBs might increase. Additionally, China launched the national preconception health examination project in 2010 to provide free checkups for reproductive couples (including free HBV serological testing). Along with increasing health literacy, more aging family members went for further checkups. With enhanced accessibility, increased medical workforce skills, and improved economic status, the incidence of LCHB is projected to increase in the long run. A similar situation might occur to LCHC as well. Despite direct-acting antivirals (DAAs) being approved by the China Food and Drug Administration in 2017, the cost of treatment has not yet been covered in the medical insurance system.[4] Thus, China is facing huge challenges to achieve the goal of eliminating viral hepatitis by 2030. In addition, we observed that Chinese women were less vulnerable to PLC, which might be attributable to a better lifestyle (less alcohol consumption and tobacco smoking, low level of obesity, etc) and relatively lower prevalence of HBV infection.[19]

The trends of four causes in the US showed a similar pattern to the previous study.[20] The ASIR of four causes increased dramatically during 1993 to 2012, and more favorable trends were observed since 2012. Makarova-Rusher *et al*[21] calculated the population attributable fractions for risk factors for HCC and found that approximately 32% of HCC was attributable to metabolic disorder, followed by HCV, which accounted for approximately 20.5%, 13.4% to alcohol consumption, 9% to smoking, and 4.3% to HBV in 2016 in the US. However, in the present study, HCV, HBV, alcohol use, and NASH accounted for 40.6%, 14.3%, 24.4%, and 11.7% of PLCs, respectively. The disparity could be due to the different data sources and different definitions of liver cancer. The prevalence of HCV infection increased by 250% from 2010 to 2014, and >3 million people in the US were living with chronic hepatitis C.[22] It was estimated that approximately 2.4 million HBV carriers live in the US in 2021.[23] In addition, universal screening of pregnant women for hepatitis B was initiated in 2009,[24] and screening for HCV infection in adolescents and adults was recommended by the US Preventive Services Task Force in 2020.[25,26] Prediction analyses using the APC model demonstrated that Asians/Pacific Islanders experienced a striking decline in the incidence of HCC. Particularly, in light of the increasing awareness of the risk of HBV infection and implementation of various prevention policies, LCHB could be controlled by fast action with higher HBV vaccination coverage. For HCV infection, even though DAA was approved by the US Food and Drug Administration in 2014, the cost of DAA is still very high, with per patient costs ranging from $66,000 to $154,000 with sofosbuvir-ledipasvir. Therefore, the gap between willingness to treat and willingness to pay would be a huge challenge in the near future for patients with HCV infection.

The local drift peaking at approximately 53 to 63 years old could be partially explained by HCV infection of “baby boomers” and other risk factors for PLC,[27] such as obesity and excessive alcohol consumption.[6,28] Intriguingly, the period effects of LCAL and NASH have been uplifted in both China and the US since 2012, which indicated that westernized and sedentary lifestyle-related liver cancer will become a new challenge for both China and the US. Although the alcohol consumption in China was not as high as that in European countries, the consumption amount bounced up along with the dramatic economic development and increasing availability of various imported alcoholic products in the past three decades; in addition, the attitude to drinking among women has been more open now in China.[29,30] The growing speed of alcohol consumption in China is the fastest worldwide, with 56% males and 15% females as current drinkers.[31] Meanwhile, alcohol abuse among adolescents is an additional concern in China.[32] Currently, the prevalence of alcohol consumption and population-averaged standard drinks daily in China are lower than those in the US,[33] except for the standard drinks daily (defined as 10 g of pure ethyl alcohol) among men.[33] However, with an elevated socio-demographic index (SDI), the prevalence and average use of alcohol would increase as well. In comparison, alcohol consumption in the US increased to 2.35 gallons of ethanol per capita in 2018,[34] and alcoholic cirrhosis was the second most common risk factor for HCC in the US.[27] Additionally, alcohol-related liver cirrhosis was the major attributable risk for liver cancer among people aged 25 to 34 years old,[35] and the condition brought a substantial economic burden as well.[27] NASH is a serious type of nonalcoholic fatty liver disease (NAFLD) that can further progress to liver cancer and trigger extrahepatic syndrome and affect approximately 6% of the population globally.[36] One-third of NAFLD-related liver cancers are noncirrhotic based on histology. The prevalence of NASH was >20% in obese adults and at least 5% among those who were overweight ht.[37,38] However, no NASH-specific drugs have been approved.[36] Both Chinese and US adults and adolescents are facing the rapidly increasing prevalence of obesity and overweight, metabolic syndrome, and sedentary lifestyle;[39,40] moreover, NASH-related liver cancer has experienced the fastest increase in both China and the US.[20,41] Due to the growing unawareness of the public and the complexity of its diagnosis, we assume that more NAFLD-related disease burden would occur in the future due to improving economic and health care circumstances.

Based on the present analyses, similarities and disparities in liver cancer incidence were compared and contrasted between China and the US, the most representative countries in low–middle SDI countries and high SDI countries, respectively. Viral- and lifestyle-related liver cancer would be the double burden of liver cancer in the long term. Therefore, designing appropriate intervention policies to control viral-related liver cancer, such as prenatal screening of HBV and HCV, preventing transmission of HBV and HCV from mother to child, and enhancing willingness to test for HBV and HCV, are critical to achieve the goal of eliminating chronic viral hepatitis by 2030. For the remaining two lifestyle-related PLCs, maintaining a healthy lifestyle would reduce metabolic disorders and obesity-related liver injury and cirrhosis and further lead to a reduction in the PLC burden. For instance, reducing both alcohol consumption and hypercaloric diets and increasing physical activities are highly recommended.

To our knowledge, this is the first study that comprehensively compared the time trends of incidences of PLCs between China and the US using GBD 2019 data via APC methods. Additionally, due to the disparities of physiological and social behavior preference, we confirmed that the incidence of liver cancer and four etiological factors were lower among females than among males in both countries.[42] Our results indicated that interventions should focus on men since men's incidence was almost three times as high as women's. Several limitations of this study should be discussed as follows: (1) the accuracy and reliability of the present study depend on the quality of data collection in each country, which may affect our estimation. For example, limited medical information and miscoding of metastatic liver cancer as PLC may overestimate the numbers of liver cancer cases; (2) other risk factors for PLC, such as tobacco, anatoxin B1, and aristolochic acids, were not analyzed in the present study, which might have an impact on our observation; and (3) concurrent etiological liver cancer was not considered due to limitations of GBD data. For instance, alcohol use, a poor diet, or metabolic disorders might interact with HBV/ HCV infections and would increase the risk of liver cancer.

In conclusion, PLC is and will be the major cancer burden in the near future for both China and the US. However, it is largely a preventable disease. We should continue to prevent and control viral-related liver cancer through vaccination for HBV infection and effective treatment for HCV-related hepatitis and through broad-based efforts to strengthen the health system and advocacy preventive networks in each country. In addition, reducing alcohol consumption, controlling overweight and obesity, maintaining a healthy diet, and increasing physical activities at the population level will be the most effective ways to prevent lifestyle-related liver cancer.

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Conflicts of interest

None.

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