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Cancer Trends

Global trend of aetiology-based primary liver cancer incidence from 1990 to 2030: a modelling study

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Abstract

Background: Predictions of primary liver cancer (PLC) incidence rates and case numbers are critical to understand and plan for PLC disease burden.

Methods: Data on PLC incidence rates and case numbers from 1990 to 2017 were retrieved from the Global Burden of Disease database. The estimated average percentage change (EAPC) was calculated to quantify the trends of PLC age-standardized incidence rates (ASRs). Bayesian age-period-cohort models were constructed to project PLC incidence rates and case numbers through 2030.

Results: Globally, the PLC case number doubled from 472 300 in 1990 to 953 100 in 2017. The case number will further increase to 1 571 200 in 2030, and the ASR will increase from 11.80 per 100 000 in 2018 to 14.08 per 100 000 in 2030. The most pronounced increases are observed in people afflicted by non-alcoholic steatohepatitis (NASH) and in older people. The trends of PLC incidence rates between 1990 and 2030 are heterogeneous among countries and can be summarized as five scenarios: (i) 46 countries that have and will continue to experience a persistent increase (e.g. Australia); (ii) 21 countries that experienced an initial decrease (or remained stable) but are predicted to increase (e.g. China); (iii) 7 countries that experienced an initial increase but are predicted to remain stable (e.g. USA); (iv) 29 countries that experienced an initial increase but are predicted to decrease (e.g. Egypt); and (v) 82 countries that have and will continue to experience a persistent decrease (e.g. Japan).

Conclusion: PLC incidence rates and case numbers are anticipated to increase at the global level through 2030. The increases in people afflicted by NASH and among older people suggest a dearth of attention for these populations in current prevention strategies and highlight their priority in future schedules for global control of PLC.

Key words: Primary liver cancer, incidence, prediction, HBV, HCV, non-alcoholic steatohepatitis

Key Messages

- Liver cancer is still a major public health concern worldwide.
- Although efforts to combat hepatitis B virus and hepatitis C virus infections has been going on for decades, hepatitis viruses are still are the major causes of liver cancer.
- The increases in people afflicted by non-alcoholic steatohepatitis and among older people suggest a dearth of attention for these populations in current prevention strategies and highlight their priority in future schedules for global control of primary liver cancer.

Introduction

Primary liver cancer (PLC), which afflicts ~841 000 new patients and causes 782 000 cancer-related deaths annually, was estimated to be the sixth most commonly diagnosed cancer and the fourth leading cause of cancer-related death worldwide in 2018.[1] Considerable endeavours, such as vaccination for the hepatitis B virus (HBV) and administration of direct-acting antiviral drugs (DAAs) for the hepatitis C virus (HCV), have resulted in a significant decrease in the PLC disease burden in certain regions.[2–5] However, multiple risk factors other than HBV and HCV are involved in PLC development, presenting obstacles for global control of liver cancer.[6] Our previous study found that the incidence of PLC caused by different aetiologies along with their temporal trends over the last three decades were highly heterogeneous across the world.[3] Whereas past trends of incidence rate can serve as a crude proxy for shifting patterns of disease within a population, as well as evidence for changing risk factors,[7] predictions of incidence rate are more informative for the future PLC disease burden.

More importantly, the risk factors for PLC are also rapidly changing over time.[8] For example, between 1990 and 2017, the global adult per-capita consumption of alcohol increased from 5.9 L to 6.5 L, and is forecasted to reach 7.6 L by 2030.[9] The changing trend of risk factors might result in substantial alterations in both the PLC incidence rate and the number of cancer cases in the near future. Projections of these data are therefore of strong interest for epidemiologists and policy makers and are of great importance in understanding and planning for the disease burden. To address this need, we used data on PLC from 1990 to 2017 at the global and national levels to predict both the future number of PLC patients and the incidence rates through 2030. Our results further describe the global disease burden of PLC and assist the targeted development of the global health system to respond to the future challenges of PLC.

Methods

Study data

We collected annual PLC case data from 1990 to 2017 by sex, nation, age (17 age groups, from <5 to ≥80 years at 5-year intervals) and aetiology from the online Global Health Data Exchange query tool (http://ghdx.healthdata.org/gbd-results-tool).[10] Data from 195 countries or territories were available. Data on five aetiologies [hepatitis B, hepatitis C, alcohol use, non-alcoholic steatohepatitis (NASH), and other causes] of liver cancer were retrieved from the Global Burden of Disease (GBD) database. The general methods of the GBD study and the methods for the estimation of disease burden of PLC have been detailed in previous studies.[2,11] The liver cancer incidence in the GBD dataset was estimated in the following ways. (i) The mortality to incidence ratio (MIR) for liver cancer was estimated by using any data sources that reported both incidence and mortality, and the MIR for all locations was predicted using the Healthcare Access and Quality (HAQ) Index. (ii) Any incidence data were sought from individual cancer registries or aggregated databases of cancer registries, e.g. Cancer Incidence in Five Continents (CI5), Surveillance, Epidemiology, and End Results (SEER) and Cancer statistics for the Nordic countries (NORDCAN). All International Classification of Disease (ICD9) and ICD10

codes pertaining to PLC (155–155.963 and C22.0–9, respectively) were included in these estimates. (iii) The cancer registry incidence data were multiplied by the MIR to estimate liver cancer mortality. (iv) The liver cancer mortality estimates were added to liver cancer mortality data from vital registration system data (death certificates); in cases where high-quality mortality data were available but not reported by the registry, processed vital registration mortality data from the cause of death database were matched to the registry's incidence data. This was the case for certain registries in the following countries: Australia, Austria, Belgium, Bulgaria, Denmark, Estonia, Finland, Hungary, Iceland, Ireland, New Zealand, Norway, South Korea and Switzerland. Sources for cancer incidence and mortality-to-incidence ratio data by country, year and registry were detailed elsewhere.[12] (v) These combined data sources are the input for a 'CODEm' model (Cause of Death Ensemble model), where the covariates were used to predict liver cancer mortality for all locations, ages, sexes and years. (vi) Liver cancer mortality estimates were adjusted to the separate estimates of all-cause mortality. (vii) These adjusted liver cancer deaths were divided by the MIR estimates to determine liver cancer incidence. To determine the proportion of liver cancer cases due to the five aetiologies included in the GBD, a systematic literature search was performed in PubMed (Supplementary Box, available as Supplementary data at *IJE* online).[12] Studies were included if the study population was representative of liver cancer patients in the respective location. For each study, the proportions of liver cancer due to the four specific risk factors were calculated. The remaining risk factors were included under a combined 'other causes' group. The proportion data identified through the systematic literature review were used as input data for four separate DisMod-MR 2.1 models to determine the proportion of liver cancers due to the five subgroups for all locations, both sexes and all age groups. Since the proportion models are run independently of each other, the final proportion models were scaled to sum to 100% within each age, sex, year and location by dividing each proportion by the sum of the five.[12] We retrieved the corresponding population data, stratified by year (from 1990 to 2030), sex, nation (185 countries or territories) and age (17 age groups, from <5 to ≥80 years at 5-year intervals) from the United Nations Department of Economics and Social Affairs Population Division (https://population.un.org/wpp/Download/Standard/Population/).

Statistical analysis

Incidence trend of PLC, 1990–2017

We used the World 2000 standard population to standardize the PLC incidence rate at the global and national levels.[3] The estimated average percentage change (EAPC) was applied to quantify the PLC age-standardized incidence rate (ASR) trends between 1990 and 2017. The EAPC is a summative and widely used measure for ASR trends over specified intervals. A regression line was fitted to the natural logarithm of the rates, i.e. $y = \alpha + \beta x + \varepsilon$, where $y = \ln(\text{ASR})$ and $x =$ calendar year. The EAPC was calculated as $100\times(exp(\beta)-1)$ and its 95% confidence interval (CI) was also obtained from the linear regression model. The ASR was deemed to be increased if the EAPC estimation and the lower boundary of its 95% CI were both >0. In contrast, the ASR was decreased if the EAPC estimation and the upper boundary of its 95% CI were both <0. Otherwise, the ASR was deemed to be stable over time.

Projections of PLC incidence rates and case numbers, 2018–2030

Several methods, such as the age-period-cohort (APC) model, Joinpoint model and Poisson regression, have been previously proposed to predict cancer incidence or mortality based on cancer registry data.[13,14] To select a model with the best predictive performance, we first conducted a model comparison. The Bayesian age-period-cohort (BAPC) model, generalized additive model, smooth spline model, Joinpoint model and Poisson regression were conducted using PLC case data at the global and national levels. Data from China, Bolivia and Dominica, which represent high, medium and low PLC disease burdens, respectively, and the global data were used. We split the whole dataset into training sets (data between 1990 and 2012) and testing sets (data between 2013 and 2017), which were used to train and test the predictive models, respectively. Absolute percentage deviation (APD) was applied to assess model performance. The APD can be calculated as $\hat{Y} - Y/Y \times 100$, where $\hat{Y}$ denotes the predictive value and Y denotes the observational value. The APDs for all selected models are presented in Supplementary Figure 1, available as Supplementary data at *IJE* online. Because of the relatively lower absolute percentage deviation for the BAPC model, we used it for the projections of PLC incidence rates and case numbers through 2030.

The APC model[15] assumes there is a multiplicative effect of age, period and cohort,

$$Y_{ap} = \mu' \alpha'_a \beta'_p \gamma'_c, \quad (1)$$

where Y_{ap} denotes the incident case counts, α'_a denotes the age effect, β'_p denotes the period effect and γ'_c denotes the cohort effect. We use $a = 1, \ldots, A$ to represent age groups, $p = 1, \ldots, P$ to represent observation periods, and

$c = 5 \times (A - a) + p$ to represent the birth cohorts (in this study, $A = 17$, $P = 28$). By taking the logarithm, model (1) can be transformed into an additive model:

$$\log(Y_{ap}) = \mu + \alpha_a + \beta_p + \gamma_c, \tag{2}$$

where μ, α_a, β_p and γ_c are the logarithms of μ', α'_a, β'_p and γ'_c, respectively. Here, we focus on the prediction of Y_{ap}; therefore, the identifiability problem of APC models does not affect the estimation.[16] We conducted a BAPC analysis with integrated nested Laplace approximation (INLA). To ensure smoothing, BAPC models assume independent mean-zero normal distributions on the second differences of all effects. Specifically, the BAPC model assumes prior distribution of the age effect as follows:

$$f(\alpha|k_\alpha) \propto k_\alpha^{\frac{I-2}{2}} \exp\left\{-\frac{k_\alpha}{2}\sum_{i=3}^{I}[(\alpha_i - \alpha_{i-1}) - (\alpha_{i-1} - \alpha_{i-2})]^2\right\}, \tag{3}$$

Considering that we are interested in the incident case counts for age group a, with a t period into the future, the following equation can be applied:

$$\log(Y_{a,p+t}) = \mu + \alpha_a + \beta_{p+t} + \gamma_{c+t} + \delta_{a,p+t}, \tag{4}$$

Here, we add an independent random effect $\delta_{a,p+t} \sim N(0, k_\delta^{-1})$ to adjust for overdispersion.[17] Considering the smoothing assumption, the BAPC models assume prior distribution of the period effect as follows:

$$\begin{aligned}\beta_{p+t}|\beta_1, \ldots, \beta_p, k_\beta \sim N\Big((1+t)\beta_p \\ -t\beta_{p-1}, k_\beta^{-1}(1 + 2^2 + \cdots + t^2)\Big),\end{aligned} \tag{5}$$

The summary estimates (mean, standard deviation, 2.5% quantile, median and 97.5% quantile) of all variance parameters in the BAPC models are presented in Supplementary Table 1, available as Supplementary data at *IJE* online. All statistical analyses were performed using the R program (version 3.5.1, R core team, Vienna, Austria).

Results

Trends and projections of PLC incidence rates and case numbers at the global level, 1990–2030

Globally, the case numbers of PLC doubled from 472 300 in 1990 to 953 100 in 2017, although the corresponding ASR remained stable during the same period (Table 1). The case numbers of PLC will further increase to 1 571 200 [95% credible interval (CrI): 1 425 100, 1 717 300] in 2030, with the ASR increasing from 11.80 per 100 000 in 2017 to 14.08 per 100 000 (95% CrI: 12.78, 15.37) in 2030 (EAPC = 1.22, 95% CI: 1.14, 1.30, $P < 0.001$) (Table 2; Figure 1). Males experienced a more pronounced increase in ASR than females from 1990 to 2017. The increasing trend in males will continue from 2018 to 2030, with the case number and ASR increasing to 1 159 900 and 22.14 per 100 000, respectively (Table 2; Supplementary Figures 2 and 3, available as Supplementary data at *IJE* online). Although females experienced a remarkable decrease in ASR from 1990 to 2017, the decreasing trend will be reversed in the next decade (Tables 1 and 2; Supplementary Figure 4, available as Supplementary data at *IJE* online). In 1990, liver cancer due to hepatitis B (LCHB) accounted for 46.5% of the total PLC cases worldwide. This proportion decreased to 42.4% in 2017 and will further decrease to 40.7% in 2030 (Tables 1 and 2). The declining trend in the ASR of LCHB is predicted to be overturned after 2017, and the case number of LCHB will nearly triple from 1990 to 2030. (Tables 1 and 2; Figures 1 and 2). A similar pattern was detected for liver cancer due to other causes (LCOT), which experienced a significant decrease in ASR from 1990 to 2017; however, an increase will be observed in the next decade. For liver cancer due to hepatitis C (LCHC), alcohol use (LCAL) and NASH (LCNS), the increasing trend will be accelerated between 2018 and 2030 (Tables 1 and 2; Figure 1). The most pronounced increase in ASR was and will be observed in LCNS in both the past and the future. For children and adolescents (aged 0–19 years), both the case number and overall ASR consistently decreased and will continue to decrease from 1990 to 2030. However, an unfavourable trend was found for LCHC, LCAL, LCNS and LCOT in this population after 2012 (Figure 3). For young adults (aged 20–39 years), the ASR decreased between 1990 and 2017, whereas the decreasing trend slowed in the next decade (Tables 1 and 2). For middle-aged adults (aged 40–59 years), a significant decrease in ASR was found between 1990 and 2017, whereas this decreasing trend will be overturned in the next decades (Tables 1 and 2). For elderly people (aged ≥60 years), the ASR increased between 1990 and 2017, and this increasing trend will accelerate between 2018 and 2030 (Tables 1 and 2). Correspondingly, the number of PLC cases will approximately double during this period (Tables 1 and 2; Figure 3).

Trends and projections of PLC incidence rates and case numbers in developed countries, 1990–2030

Generally, PLC incidence rates were relatively lower in developed countries than the global average (Figure 4). However, we found an unfavourable increase in both the past and the future in most of these countries. For example, PLC incidence increased by 3.81% (95% CI: 3.60%, 4.03%, $P < 0.001$) annually in the UK between 1990 and

Table 1. The number and ASR of PLC in 1990 and 2017, by sex, aetiology, age and country. The UIs of case numbers and ASRs from 1990 to 2017 were calculated from the DisMod-MR 2.1 models; the case number and ASR of liver cancer in 1990 and 2017 were retrieved from the GBD dataset

	Case numbers (×1000)		ASR (/100 000)		EAPC of ASR (95% CI)[a,b]
	1990 (95% UI)	2017 (95% UI)	1990 (95% UI)	2017 (95% UI)	1990–2017
Sex					
Both	472.3 (444.9, 512.5)	953.1 (916.5, 997.0)	11.05 (10.42, 11.97)	11.80 (11.35, 12.34)	−0.07 (−0.20, 0.06)
Male	322.9 (295.7, 356.8)	689.5 (653.6, 734.2)	15.78 (14.48, 17.47)	17.91 (17.03, 19.06)	0.14 (0.00, 0.27)*
Female	149.4 (134.3, 159.9)	263.5 (253.7, 274.8)	6.71 (6.05, 7.17)	6.19 (5.96, 6.46)	−0.54 (-0.65, −0.43)
Aetiology					
Hepatitis B	219.8 (201.2, 241.6)	404.0 (378.3, 434.1)	4.93 (4.51, 5.42)	4.93 (4.62, 5.29)	−0.41 (−0.58, −0.24)
Hepatitis C	118.8 (110.1, 130.0)	257.9 (241.3, 274.5)	2.94 (2.74, 3.22)	3.25 (3.04, 3.46)	0.15 (0.05, 0.26)
Alcohol use	66.5 (58.0, 77.5)	143.9 (127.2, 165.0)	1.60 (1.40, 1.86)	1.79 (1.59, 2.05)	0.19 (0.11, 0.27)
NASH	28.3 (24.9, 32.3)	72.2 (64.6, 79.9)	0.69 (0.61, 0.79)	0.91 (0.81, 1.00)	0.76 (0.66, 0.86)
Other causes	38.9 (34.2, 43.6)	75.1 (67.5, 83.3)	0.89 (0.79, 1.00)	0.93 (0.84, 1.03)	−0.21 (−0.35, −0.07)
Age (years)[c]					
0–19	5.0 (4.9, 5.1)	3.4 (3.3, 3.5)	0.93 (0.92, 0.93)	0.55 (0.54, 0.56)	−2.17 (−2.29, −2.05)
20–39	57.1 (56.7, 57.5)	48.0 (47.6, 48.3)	14.91 (14.87, 14.95)	8.65 (8.61, 8.68)	−2.58 (−2.84, −2.31)
40–59	174.4 (173.7, 175.1)	313.5 (312.5, 314.4)	81.03 (80.86, 81.19)	75.80 (75.65, 75.93)	−0.51 (−0.62, −0.41)
≥60	235.9 (235.0, 236.9)	588.0 (586.5, 589.5)	252.26 (251.62, 252.90)	328.18 (327.66, 328.68)	0.71 (0.58, 0.84)
Country					
China	258.0 (240.2, 272.8)	515.9 (486.2, 546.2)	27.16 (25.31, 28.69)	26.04 (24.57, 27.54)	−0.64 (−0.84, −0.44)
Japan	31.3 (30.8, 31.7)	43.2 (36.0, 48.4)	17.84 (17.58, 18.08)	11.97 (10.07, 13.33)	−1.70 (−1.92, −1.48)
USA	9.6 (9.3, 9.9)	35.2 (33.9, 36.6)	2.98 (2.89, 3.09)	6.69 (6.45, 6.96)	3.07 (2.80, 3.34)
Germany	4.3 (4.1, 4.4)	10.9 (10.6, 11.1)	3.33 (3.31, 3.36)	5.95 (5.92, 5.99)	1.78 (1.57, 2.00)
Brazil	4.4 (4.2, 4.6)	11.3 (11.0, 11.6)	5.26 (5.21, 5.30)	5.05 (5.03, 5.08)	−0.30 (−0.47, −0.14)
Egypt	4.1 (3.9, 4.3)	12.6 (12.3, 12.9)	11.32 (11.23, 11.42)	17.51 (17.41, 17.60)	2.25 (1.98, 2.52)

*$P < 0.05$.

[a]The CIs of EAPCs were calculated from the linear regression models as described in the Methods section in the manuscript.

[b]The EAPCs of ASRs were calculated based on the point estimate of ASR in each single year.

[c]The incidence rates for age groups have not been standardized by age.

2017. The incidence rate in the UK was predicted to be further increased between 2018 and 2030 (EAPC = 1.06, 95% CI: 1.01, 1.12, $P < 0.001$). The major aetiologies for PLC constitute HCV infection and alcohol consumption in developed countries. In Western Europe and Australia, LCAL was dominant, whereas in North America and Japan, LCHC was dominant. Of note is the striking increase in LCNS in these countries from 1990 to 2030, although the absolute case number and incidence were still low. In addition, LCHB, which was less frequently diagnosed, was increased with a relatively large magnitude. For example, in 1990–2017, the incidence rates of LCHB and LCNS increased ∼3- and 4-fold in the UK, respectively. The increasing trend was estimated to remain up to 2030.

Trends and projections of PLC incidence rates and case numbers in developing countries, 1990–2030

For 2017 and 2030, the highest ASRs of PLC were observed in Mongolia (93.44 per 100 000 in 2017 and 73.63 per 100 000 in 2030), followed by Gambia and Guinea in 2017 and Mali and Gambia in 2030 (Figure 4). The most pronounced decrease will be observed in Niger (EAPC = −8.12, 95% CI: −8.20, −8.03, $P < 0.001$); the greatest increase will be observed in Iran (EAPC = 4.61, 95% CI: 4.57, 4.65, $P < 0.001$). In developing countries, HBV infection was the dominant aetiology for PLC. Fortunately, the incidence of LCHB was decreased in most developing countries. This decreasing trend will be persistent in the next decade. According to the past and the future trends, however, LCHC and LCNS have become emerging concerns in these countries. For example, incidence of LCHC and LCNS increased by 0.16% (95% CI: 0.03%, 0.29%, $P = 0.016$) and 0.43% (95% CI: 0.29%, 0.57%, $P < 0.001$) per year during 1990–2017, respectively, in The Philippines. In 2018–2030, these increases were predicted to accelerate in that country.

Disease burden of PLC in countries showing different scenarios

All 185 countries or territories were categorized into five scenarios in terms of the changing pattern of ASR from 1990 to 2030, with the year 2017 as the demarcation.

Table 2. The predictive number and ASR of PLC in 2018 and 2030, by sex, aetiology, age and country. The CrIs [also known as high-density interval (HDI)] of case numbers and ASRs from 2018 to 2030 were calculated from the BAPC models; the case number and ASR of liver cancer in 2030 were estimated by BAPC model

	Case numbers (×1000)		ASR (/100 000)		EAPC of ASR (95% CI)[a,b]
	2018 (95% CrI)	2030 (95% CrI)	2018 (95% CrI)	2030 (95% CrI)	2018–2030
Sex					
Both	964.2 (958.5, 971.1)	1571.2 (1425.1, 1717.3)	12.20 (12.15, 12.25)	14.08 (12.78, 15.37)	1.22 (1.14, 1.30)
Male	695.3 (684.6, 709.5)	1159.9 (1045.0, 1274.8)	18.65 (18.57, 18.73)	22.14 (19.98, 24.31)	1.45 (1.36, 1.54)
Female	268.8 (258.9, 277.9)	394.1 (359.2, 429.0)	6.22 (6.19, 6.25)	6.46 (5.90, 7.03)	0.34 (0.29, 0.40)
Aetiology					
Hepatitis B	409.8 (406.3, 412.1)	640.1 (568.9, 711.2)	5.20 (5.14, 5.26)	5.97 (5.31, 6.62)	1.16 (1.06, 1.27)
Hepatitis C	260.1 (258.3, 264.1)	421.3 (386.8, 455.9)	3.24 (3.18, 3.40)	3.65 (3.35, 3.94)	1.00 (0.96, 1.03)
Alcohol use	146.3 (143.0, 149.4)	229.2 (211.2, 247.2)	1.83 (1.79, 1.88)	2.05 (1.89, 2.20)	0.92 (0.89, 0.95)
NASH	74.5 (72.6, 76.6)	136.8 (123.5, 150.1)	0.92 (0.87, 0.98)	1.18 (1.07, 1.30)	2.12 (2.08, 2.16)
Other causes	77.2 (76.5, 78.3)	129.1 (114.5, 143.7)	0.97 (0.91, 1.03)	1.18 (1.05, 1.31)	1.69 (1.64, 1.75)
Age (years)[c]					
0–19	3.6 (3.4, 3.8)	3.4 (2.6, 4.1)	0.55 (0.54, 0.56)	0.51 (0.39, 0.59)	−0.74 (−0.78, −0.69)
20–39	50.4 (49.9, 50.9)	54.8 (49.7, 60.0)	8.65 (8.61, 8.68)	7.25 (6.90, 8.43)	−0.44 (−0.84, −0.05)
40–59	320.9 (314.5, 324.4)	353.8 (320.9, 386.6)	75.80 (75.65, 75.93)	80.04 (65.66, 88.46)	0.64 (0.33, 0.94)
≥60	598.4 (590.3, 605.8)	1159.2 (1051.7, 1266.7)	328.18 (327.66, 328.68)	448.76 (406.20, 485.37)	2.39 (2.31, 2.47)
Country					
China	519.8 (512.9, 526.4)	1029.1 (876.4, 1181.8)	28.33 (27.87, 28.84)	38.58 (32.98, 44.18)	2.63 (2.53, 2.74)
Japan	38.1 (37.5, 38.9)	31.1 (27.0, 35.2)	11.30 (11.07, 11.43)	7.56 (6.59, 8.53)	−3.36 (−3.46, −3.25)
USA	39.2 (37.9, 41.6)	47.3 (41.1, 53.5)	6.80 (6.65, 6.96)	6.80 (5.92, 7.68)	0 (−0.04, 0.05)
Germany	14.3 (12.6, 16.1)	16.7 (14.2, 19.3)	6.07 (5.98, 6.13)	7.70 (6.59, 8.81)	1.96 (1.92, 2.00)
Brazil	18.7 (17.0, 20.4)	21.2 (18.8, 23.5)	5.14 (5.03, 5.22)	6.17 (5.51, 6.83)	1.54 (1.51, 1.56)
Egypt	13.4 (13.0, 13.9)	15.5 (12.6, 18.3)	17.30 (17.11, 17.49)	14.05 (11.54, 16.56)	−1.73 (−1.80, −1.66)

$P < 0.05$.

[a]The CIs of EAPCs were calculated from the linear regression models as described in the Methods section in the manuscript.

[b]The EAPCs of ASRs were calculated based on the point estimate of ASR in each single year.

[c]The incidence rates for age groups have not been standardized by age.

The five scenarios are (i) 46 countries that have and will continue to experience a persistent increase (e.g. India, the UK and Australia); (ii) 21 countries that experienced an initial decrease (or remained stable) but are predicted to increase (e.g. China, Brazil and Mali); (iii) 7 countries that experienced an initial increase but are predicted to remain stable (e.g. USA, Romania and Honduras); (iv) 29 countries that experienced an initial increase but are predicted to decrease (e.g. Egypt, Indonesia and Mongolia); and (v) 82 countries that have and will continue to experience a persistent decrease (e.g. Japan, South Korea and The Philippines) (Figure 5; Supplementary Figure 5, available as Supplementary data at *IJE* online). Figure 5 displays the top 20 countries or territories with the highest PLC case numbers in 2017. These countries or territories are located in different regions and experience various PLC incidence patterns between 1990 and 2030. Among them, we selected countries in terms of their locations and PLC changing patterns to further detail the temporal trends of PLC incidence rates and case numbers. Data from China, Japan, USA, Germany, Brazil and Egypt were ultimately included.

China accounted for 54.1% of the PLC cases worldwide in 2017, and this proportion is expected to increase to 65.5% in 2030. The case numbers of PLC will nearly double between 2018 and 2030, and the incidence rate of PLC is estimated to increase from 26.04 per 100 000 to 38.58 per 100 000 (95% CrI: 32.98, 44.18) in China during the same period (Tables 1 and 2; Supplementary Figures 7 and 8, available as Supplementary data at *IJE* online). The increasing trend was consistent between sexes and among aetiologies, with the most pronounced increase observed in LCNS (Supplementary Figure 9, available as Supplementary data at *IJE* online). In Japan, the PLC case number increased until 2010, and then a decrease was seen. This decrease will persist until 2030 (Tables 1 and 2; Supplementary Figure 10, available as Supplementary data at *IJE* online). The ASR of PLC was decreased in the past and will continue to decrease in the future, independent of sex, age and aetiology (Supplementary Figure 11, available as Supplementary data at *IJE* online). The most pronounced decline will be observed in LCHC in Japan (Supplementary Figure 9, available as Supplementary

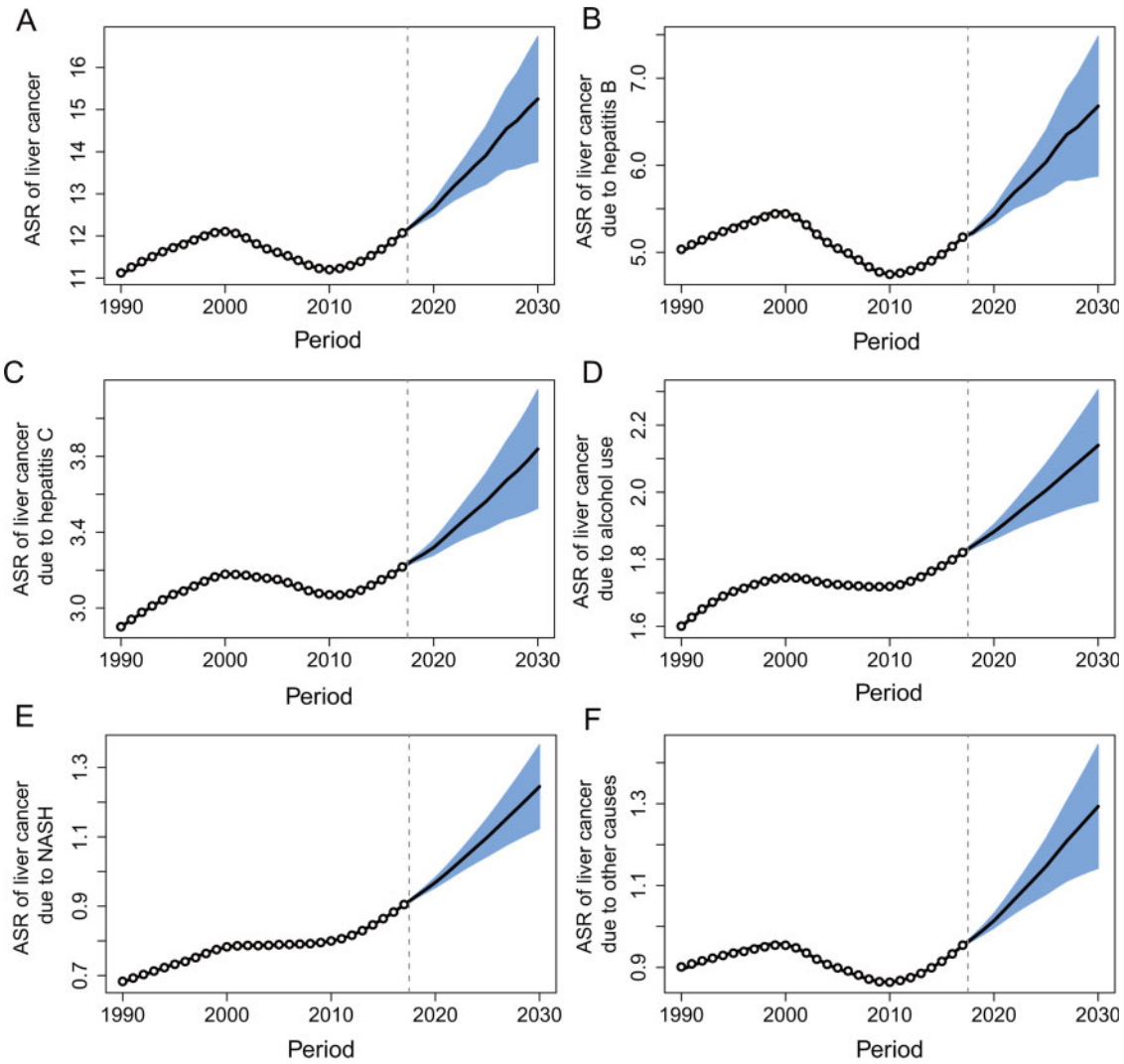

Figure 1. (**A**–**F**) The temporal trends of ASRs (per 100 000) of PLC between 1990 and 2017 and their projections up to 2030 at the global level. The open dots represent the observed values, and the fan shape denotes the predictive distribution between the 2.5 and 97.5% quantiles. The predictive mean value is shown as a solid line. The vertical dashed line indicates where the prediction starts.

dataat *IJE* online). In the USA, the number of PLC cases increased nearly 4-fold between 1990 and 2017, and the ASR increased by 3.07% per year during this period (Tables 1 and 2; Supplementary Figures 12 and 13, available as Supplementary data at *IJE* online). However, the increasing trend in the ASR was estimated to cease after 2017, although the ASRs of LCNS and LCOT are predicted to continue increasing (Supplementary Figures 9 and 13, available as Supplementary data at *IJE* online). Both the case numbers and ASR of PLC were found to continuously increase from 1990 to 2030 in Germany (Tables 1 and 2; Supplementary Figures 14 and S15, available as Supplementary data at *IJE* online). The greatest increase will be observed in LCNS (Supplementary Figure 9, available as Supplementary data at *IJE* online). In Brazil, the ASR of PLC decreased between 1990 and 2017; however, this downward trend is expected to reverse in the coming decade and the case numbers of PLC were observed to persistently increase during the study period (Tables 1 and 2; Supplementary Figures 16 and 17, available as Supplementary data at *IJE* online). In contrast, in Egypt, the ASR of PLC increased between 1990 and 2017, whereas this rate is estimated to decrease between 2018 and 2030 in spite of the consistent increase in case numbers (Tables 1 and 2; Supplementary Figures 18 and 19, available as Supplementary data at *IJE* online). The changing trends of PLC case numbers by age in these six countries are presented in Supplementary Figures 20–25, available as Supplementary data at *IJE* online. In China, Brazil and Egypt, a decreasing case number trend was observed in children and adolescents, whereas an increasing trend was observed in middle-aged and elderly people. In Japan, the PLC case numbers will decrease in all four age groups from 2018 to 2030. In contrast, the PLC case numbers will increase in

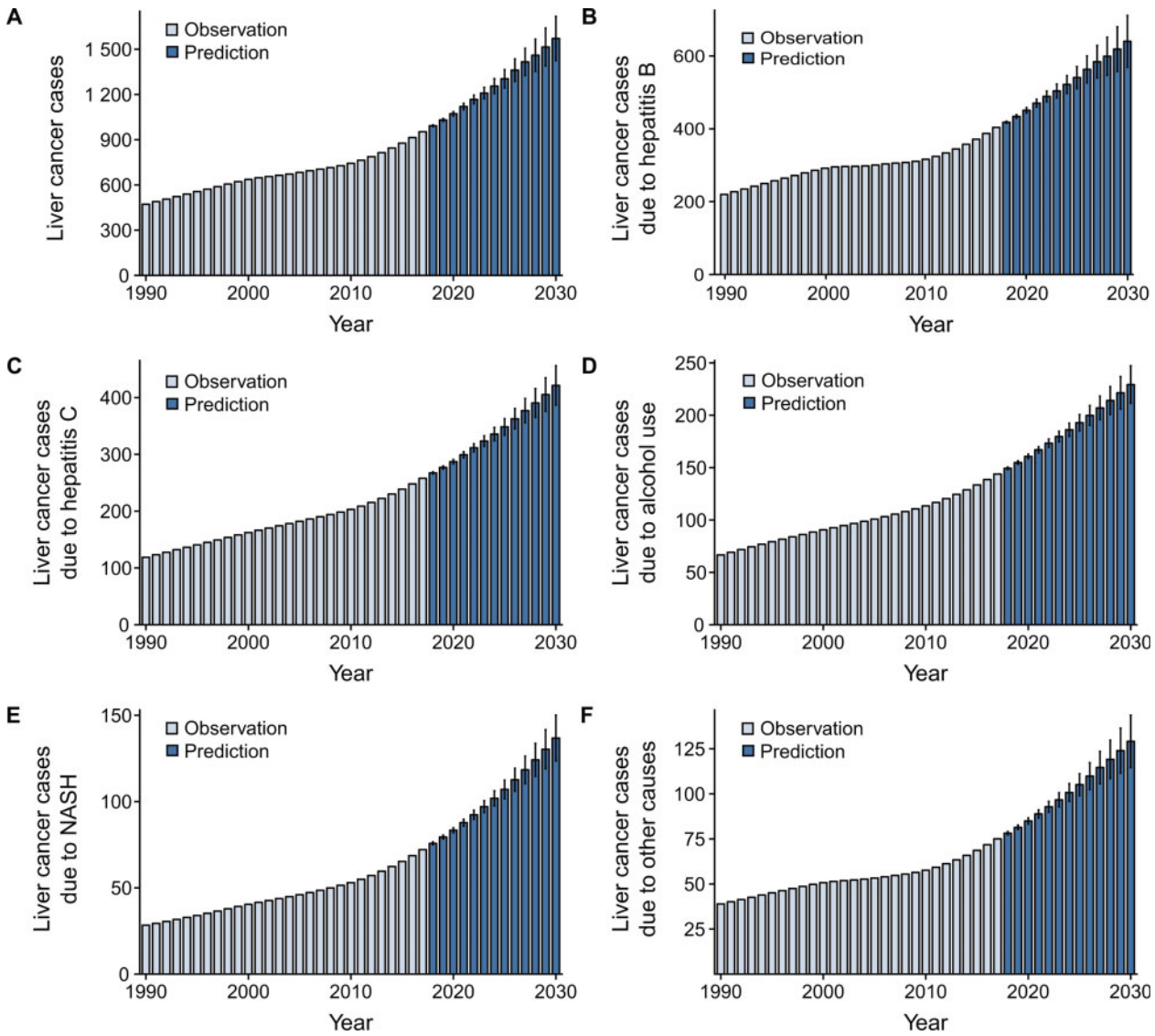

Figure 2. (**A**–**F**) The changing trends of case numbers of PLC between 1990 and 2017 and the predictions of case numbers through 2030. The error bar denotes the 95% CrI of the predictive value. The *y*-axes are on a scale of thousands.

Germany, regardless of age, during the same period. In the USA, a significant increase in PLC is expected in children, adolescents and older people, and a significant decrease will occur in middle-aged people between 2018 and 2030.

Sensitivity analysis

The data retrieved from the GBD dataset were estimated from mathematical models rather than observational data. We conducted sensitivity analyses considering the data uncertainty. First, we recalculated the EAPCs of PLC ASRs between 1990 and 2017. We incorporated the ASR uncertainty [i.e. the difference between the upper boundary of the 95% uncertainty interval (UI) and the lower boundary of the 95% UI] into the linear regression model as the weight. The results have no significant shifts compared with the original results (data not shown). Second, we repredicted the PLC cases through 2030 based on the cancer registry data in the CI5 *plus* database.[18] Considering the population coverage rate and time coverage of cancer registry, we selected the PLC case data from Australia (1993–2012), The Netherlands (1990–2012), Norway (1990–2012) and New Zealand (1990–2012) to predict the PLC cases by 2030 in these countries. The results are shown in Supplementary Figure 26, available as Supplementary data at *IJE* online. Although there are differences between the PLC ASRs based on two different datasets, the temporal trends of the predictive values are similar. This result to some extent suggests that the predictions based on GBD data are robust and credible.

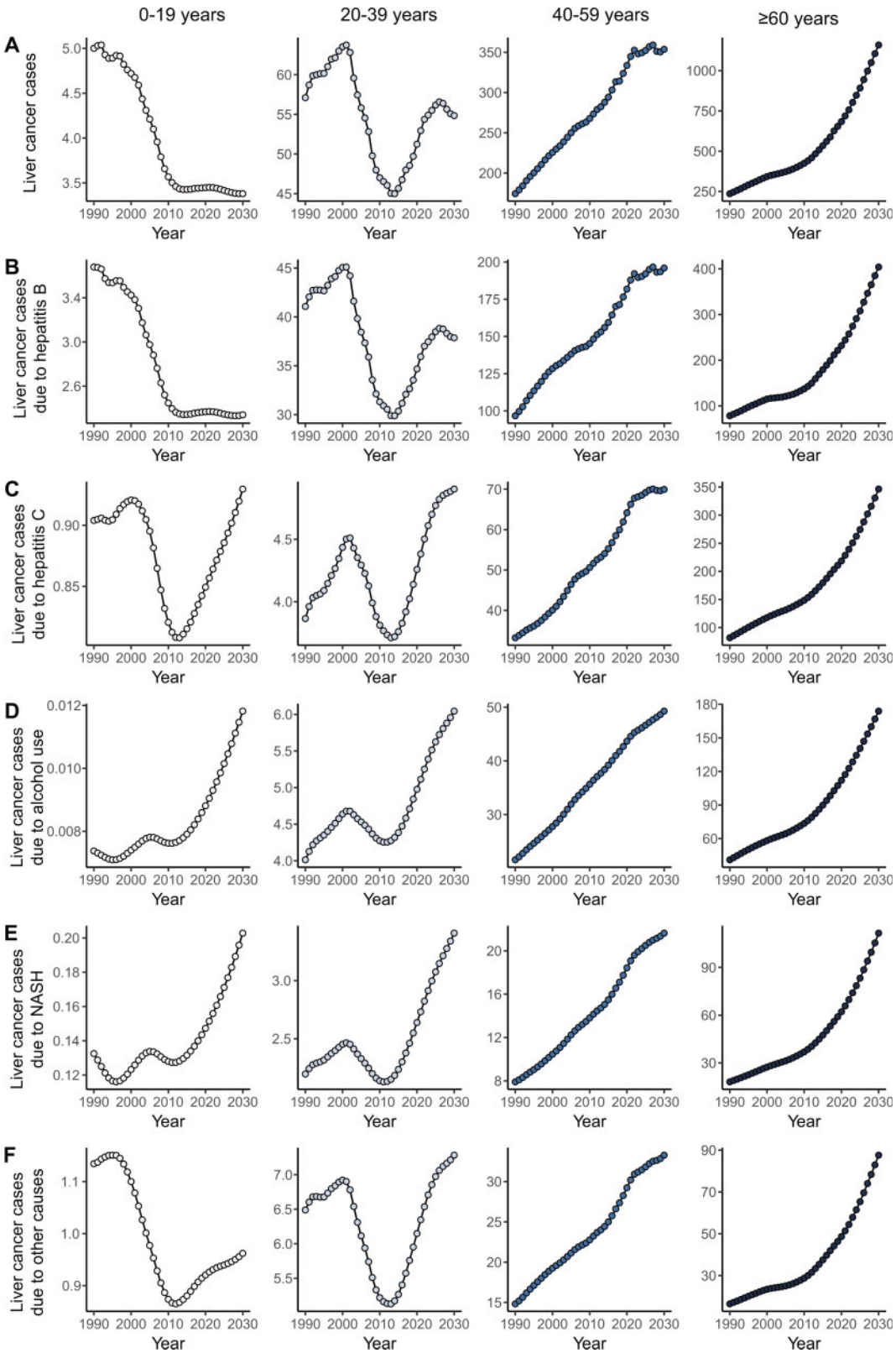

Figure 3. (**A**–**F**) The changing trends in case numbers of PLC, by age and aetiology, between 1990 and 2017 and the predictions of case numbers through 2030. The *y*-axes are on a scale of thousands.

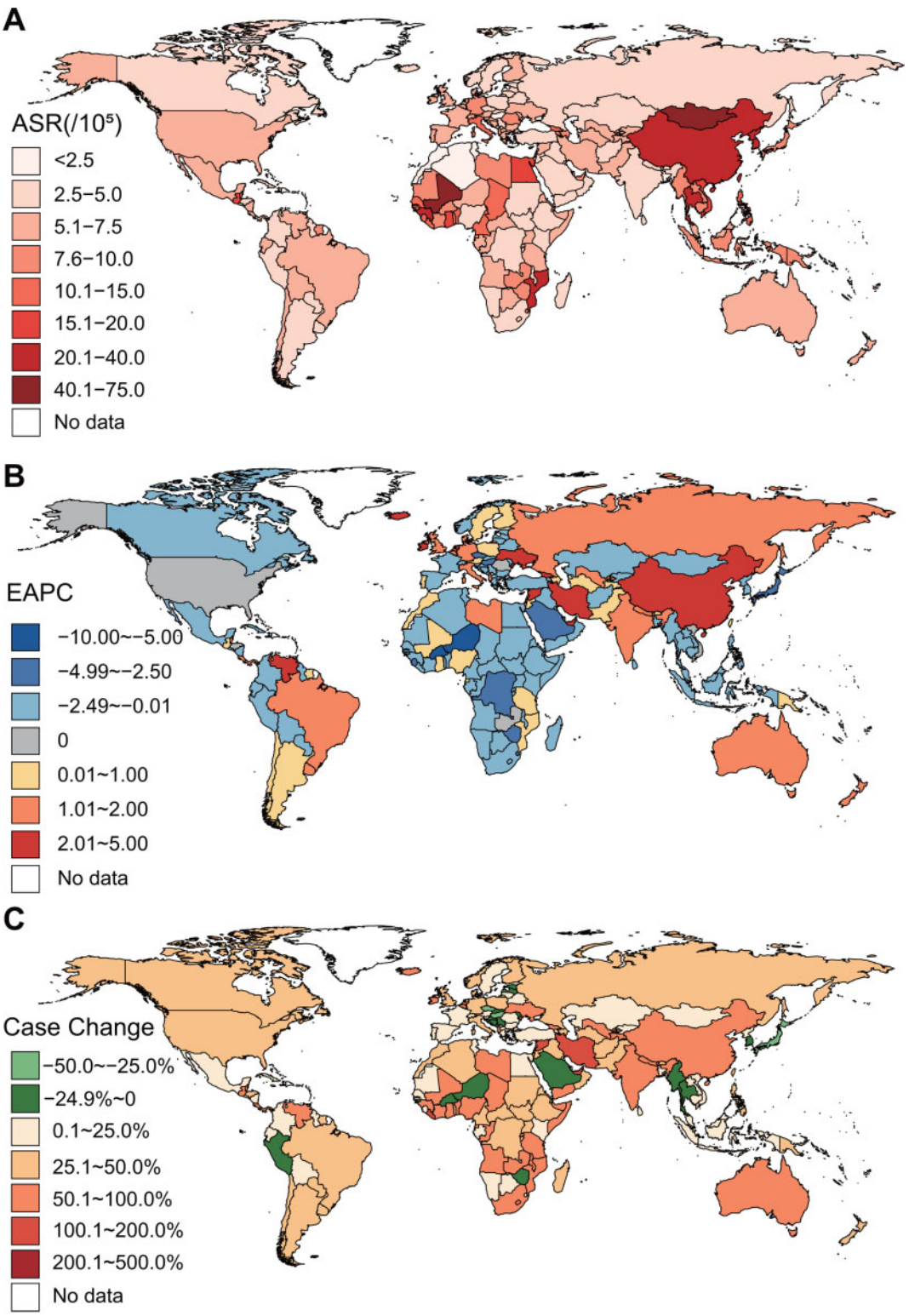

Figure 4. The global disease burden of PLC. (**A**) The global distribution of the ASR of PLC at the national level in 2030. (**B**) The EAPCs for the ASRs of PLC at the national level between 2018 and 2030. The statistically non-significant EAPCs were assigned to zero and are mapped in gray. (**C**) The percentage change in the case numbers of PLC between 2018 and 2030 at the national level.

Discussion

PLC has shown an increasing disease burden worldwide over the last decades.[2,19,20] In this study, we applied BAPC models to the long-term incidence data of PLC to predict PLC case numbers and incidence rates in the near future at both the global and national levels. Generally, the

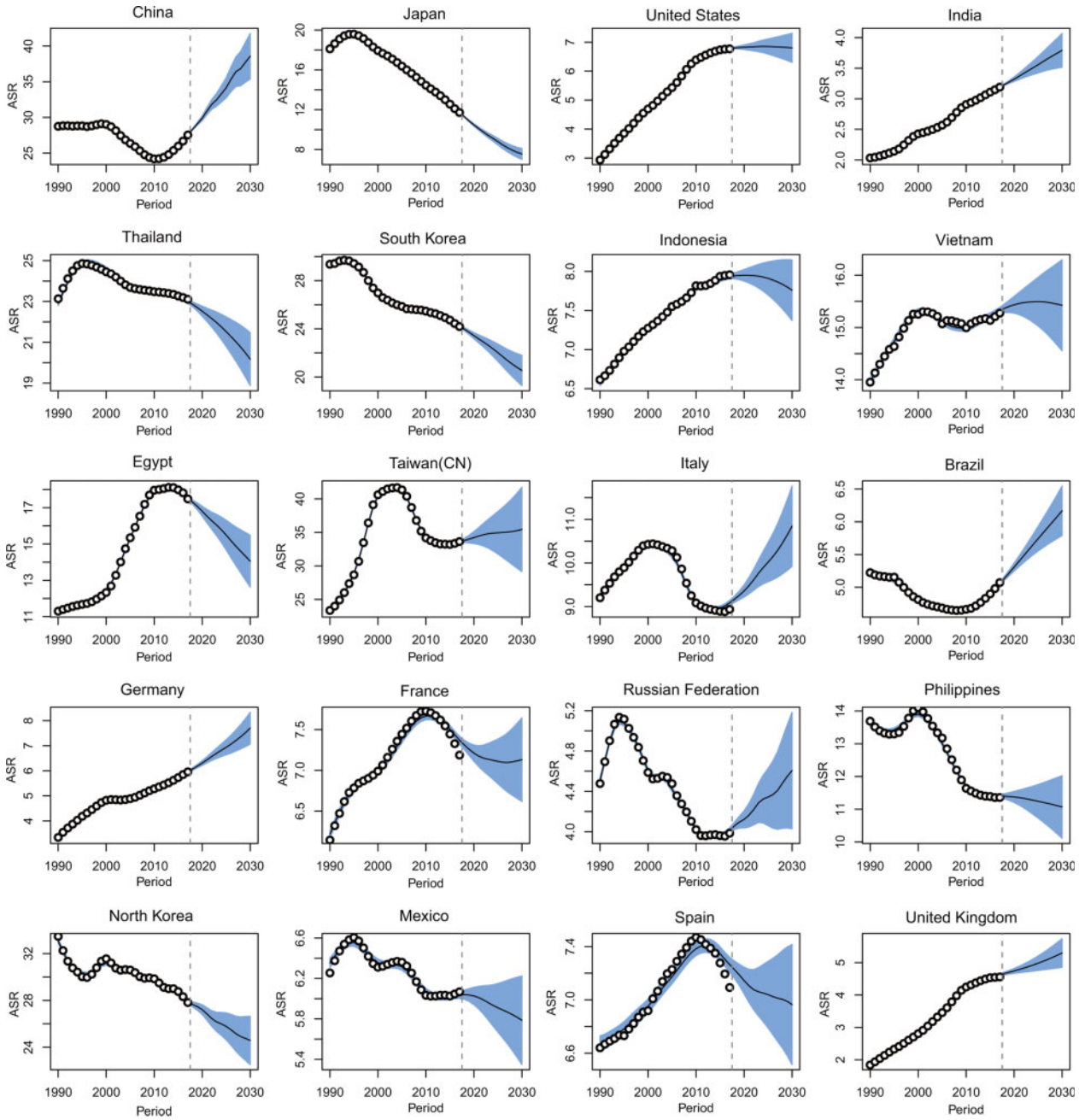

Figure 5. The temporal trends of ASRs of PLC between 1990 and 2017 and their projections through 2030 in countries with the top 20 highest disease burdens of liver cancer. The open dots represent the observed values, and the fan shape denotes the predictive distribution between the 2.5 and 97.5% quantiles. The predictive mean value is shown as a solid line. The vertical dashed line indicates where the prediction starts.

incidence rate of PLC is expected to increase between 2018 and 2030, regardless of sex and aetiology. The global PLC case numbers are expected to concomitantly increase by 65% during this period. More than 40% of the total PLC cases were attributable to hepatitis B, whereas the most pronounced increases in incidence will be observed in LCNS. Regarding age, a consistent decrease in PLC incidence and case number was found in children and adolescents. However, a consistent increase was observed in older people. The temporal trends of PLC in the past and in the future varied worldwide. Between 2018 and 2030, 56% of countries are expected to experience a decrease in PLC incidence, whereas 41% of countries are estimated to experience an increase. Future decreases were mostly observed in developing countries. In contrast, future increases were mostly observed in developed countries.

The aetiologies for PLC have been intensively investigated, and HBV and HCV infections, alcohol consumption and intake of aflatoxin-contaminated foodstuffs are well-known risk factors.[21,22] More than 80% of PLC cases are

attributable to these risk factors,[3] suggesting that PLC is largely preventable.[23] The campaign for HBV prevention has been feasible as a result of the release of the HBV vaccine in 1982.[1] By the end of 2017, 187 countries had introduced the HBV vaccine into their national immunization schedules, with global coverage of three doses of hepatitis B vaccine estimated at 84%.[24] The vaccine has substantially reduced the prevalence of HBV infection and the incidence of liver cancer, particularly in younger people in high-risk countries in East Asia, where mass vaccination was first introduced.[25] However, the HBV vaccine showed reduced protection for older people, possibly due to the lack of a HBV vaccination programme.[26] In our study, we found that the increase in both PLC incidence rate and case numbers was largely driven by an increase in the older population. For example, the PLC incidence is expected to increase in China, which is mainly attributed to the increase in PLC in the elderly population. The PLC burden, if no effective intervention is introduced, will continue to increase in older people, as predicted in the current study; therefore, more targeted prevention strategies are needed. Targeted prevention strategies could include (i) further expanding the HBV vaccination coverage rate among infants and children; (ii) increasing the 'catch-up' vaccination rate for young people; (iii) increasing access to screening and improving the timely diagnosis of HBV and HCV infection by extending basic public health services for older people; and (iv) increasing the coverage of HBV and HCV antiviral therapies. Moreover, in some HBV endemics, such as in Mongolia, the coinfection of HBV and hepatitis delta virus is highly prevalent and associated with more rapid progression of liver diseases than is seen in HBV monoinfection.[27] Hepatitis delta virus infection is less commonly treated by HBV oral-therapy, and it deserves more attention in the liver cancer prevention schedule.

HCV is also a leading cause of PLC. The advent of DAAs has fuelled optimism for the global control of HCV. However, after the initial phase of euphoria, dominated by the perception that HCV had been defeated, the sobering reality was that substantial challenges remain.[28] Currently, no vaccine is available to prevent HCV infection, and the efficacy of DAAs might be affected by drug resistance and high cost.[29] HCV and HCV-related PLC remain major public health concerns worldwide. Specifically, LCHC incidence is expected to increase in the near future, regardless of sex and age. Notably, in this study, we found that LCNS incidence showed the greatest magnitude of increase in both the past and the future. As a consequence of the pandemic spread of obesity, non-alcoholic fatty liver disease, particularly its histological phenotype NASH, is one of the primary causes of liver disease worldwide and will probably emerge as the leading cause of end-stage liver disease in the coming decades.[30] Given that there is still no approved drug for NASH,[31] attention should be paid by primary care physicians and health policy makers; preventing excessive weight gain during childhood and strengthening the available programmes for weight management are warranted.

We detected a variety of PLC incidence patterns between 1990 and 2030 from country to country. Of particular concern are the countries experiencing an unfavourable change between the past and the future. Surprisingly, in our study, we found that the PLC incidence in China was estimated to increase from 2018 to 2030, independent of aetiology. Our predictions are different from the results in Wu *et al.*'s study,[32] which might be mainly ascribed to the fact that their predictions were based on data from developed regions in China collected from 1983 to 2007. The unexpected increase in PLC in China largely drives the global increase in PLC burden and reveals the country's geographical heterogeneity. In our previous study,[33] we found that PLC incidence will be further decreased in the near future in Shanghai, a city that first initiated the campaigns for HBV vaccination and blocking HBV mother-to-infant transmission in China. We supposed that the increase in China might be explained by the following reasons: (i) the expansion of the aging population, resulting in increasing PLC cases;[34] (ii) the increasing prevalence of HCV infection among the older population;[35] and (iii) the 'lag effect' of the large HBV infection reservoir in this country,[35] i.e. a considerable proportion of people infected with HBV in their early life progressed to liver cancer over time. These underlying causes deserve further study and more attention might be placed on those developing areas in China. In contrast to China, we found an increasing trend of PLC incidence ceases in the coming decade in the USA, in which LCHC is dominant. This result supports a potential effect related to the peak-HCV cohort (1945–1965) that has not yet decreased but is anticipated to do so by 2020.[22] The wide coverage of DAAs in clinical practice to cure HCV infection might also contribute to the decrease in PLC incidence. However, we observed a persistent increase in LCNS and LCOT in the USA, which previously accounts for a relatively small proportion of the total PLC cases. These increases suggest that the PLC burden might change to increasing in the future if no effective strategies are adopted. In countries experiencing a sustained increase in PLC incidence, such as India, Germany and The Netherlands, PLC is expected to be one of most commonly diagnosed cancers in the future, although the current incidence is relatively low. More importantly, we observed an increase exclusively in younger people in

certain developed countries (e.g. Germany, The Netherlands, the USA and the UK), which was mainly driven by an increase in NASH and HBV infection. This trend might be fundamentally ascribed to the obesity pandemic[36] and the large immigrations from HBV-endemics in these countries.[37] There is currently no effective therapy for PLC and the 5-year survival rate of PLC patients has barely improved in the last decades.[38] The optimal way to combat PLC therefore is the primary prevention of risk factors, such as HBV vaccination. Unfortunately, there are hardly any scalable solutions currently to prevent people from drinking alcohol or becoming overweight. Our governments should play a strong leadership role in reinforcing the importance of addressing these problems and establishing more effective prevention strategies to combat them, e.g. by increasing the price of alcoholic beverages, reducing the availability of alcohol and restricting its marketing through taxation increases.[39] Individual weight management should be promoted at the community level.

Our study has limitations. First, the predictions were based on data from the GBD dataset, and the miscoding of liver metastases as PLC, the under-reporting of PLC, especially in low income regions, and the underestimation of PLC caused by specific aetiologies due to a lack of medical information can bias the estimates; however, this bias has been adjusted for by mapping the different coding systems to the GBD causes. Moreover, all predictions in the current study were calculated based on estimates of PLC cases from 1990 to 2017 rather than the observed data, and the results might be biased by mathematical approaches and should therefore be interpreted with caution. However, we also conducted a sensitivity analysis using the surveillance data from the International Agency for Research on Cancer. The predicting trends were comparable to results derived from GBD data. Second, due to the lack of relevant data, temporal trends in the incidence of PLC stratified by histology, such as hepatocellular carcinoma, were not assessed in the current study. Third, liver cancer caused by multi-aetiologies was not taken into account due to the data scarcity, and since many cancer registries are located in urban areas the representativeness of the registry for the general population can also be problematic. The accuracy of mortality data reported in cancer registries usually depends on the quality of the vital registration system. If the vital registration system is incomplete or of poor quality, the mortality-to-incidence ratio can be biased to lower ratios. Finally, the gradual expansion of DAAs worldwide might result in a considerable decrease in HCV prevalence and consequently bias the predictions in liver cancer incidence.[40] However, using the most up-to-date information and advanced modelling strategies, our study provides a more comprehensive understanding of the PLC burden from the past into the future.

In summary, the PLC incidence and case numbers are expected to increase further at the global level through 2030. The most pronounced increases were found among people afflicted by NASH and older people, suggesting that current prevention strategies should be focused on these populations, and these populations should be the priority for future strategies targeting the global control of liver cancer. Effective prevention measures are still needed to alleviate the PLC burden imposed by hepatitis virus infections.

Supplementary data

Supplementary data are available at *IJE* online.

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Data availability

The data used in this article are freely available at Global Burden of Disease online database (http://ghdx.healthdata.org/gbd-results-tool).

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Author contributions

X.C., T.Z., Z.L. and L.J. provided substantial contributions to the conception, design and drafting of the manuscript. Z.L., X.M.,

N.C., J.F. and Y.J. contributed substantially to the data collection. Z.L., K.X., C.S., X.M. and Y.J. provided substantial contributions to the data analyses. All authors contributed to the writing and revision of the manuscript. The funding agencies had no roles in writing or reviewing the manuscript.

Conflict of interest

None declared.

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