Title: International trends in primary liver cancer incidence from 1973 to 2007

Yue Zhang\textsuperscript{1}, Jian-Song Ren\textsuperscript{1}, Ju-Fang Shi\textsuperscript{1}, Ni Li\textsuperscript{1}, Yu-Ting Wang\textsuperscript{2}, Chun-Feng Qu\textsuperscript{2}, Yawei Zhang\textsuperscript{3} and Min Dai\textsuperscript{1*}

1. National Office for Cancer Prevention and Control, Cancer Institute & Hospital, Chinese Academy of Medical Sciences/Peking Union Medical College, Beijing 100021, China

2. State Key Laboratory of Molecular Oncology, Cancer Institute & Hospital, Chinese Academy of Medical Sciences, Beijing 100021, China

3. Yale School of Public Health, Yale School of Medicine, Yale Cancer Center, New Haven, CT 06510, USA

*Correspondence to: Min Dai, M. D., Ph.D.,

Email addresses:

Yue Zhang (zhangyue222@yeah.net)
Jian-Song Ren (renjiansong@sina.com)
Ju-Fang Shi (shijf@cicams.ac.cn)
Ni Li (lini1240@hotmail.com)
Yu-Ting Wang (wyt2051@163.com)
Chun-Feng Qu (quchf@cicams.ac.cn)
Yawei Zhang (yawei.zhang@yale.edu)
Min Dai (daiminlyon@gmail.com)
International trends in primary liver cancer incidence from 1973 to 2007

Abstract

Background: Primary liver cancer (PLC) is a common cancer worldwide, especially in developing countries. Several previous studies using different datasets had summarized the PLC incidence rates and trends in different populations. However, with the change of exposure to risk factors and the implementation of protective measures, the epidemiology of PLC worldwide may have changed.

Methods: We extended the analyses using the latest data from Cancer Incidence in Five Continents (CI5) over the 35-year period 1973–2007 from 24 populations in the Americas, Asia, Europe and Oceania by joinpoint regression analysis. We examined age-standardized rates of PLC by histologic subtypes for both males and females in 24 populations during the period 2003-2007.

Results: We found that during the period 2003-2007, the highest ASRs for PLC remained in some Asian populations, ranging from 19.0 to 26.7 per 100,000 in males and 4.8 to 8.7 per 100,000 in females. The international trends between 1973 and 2007 showed that ASRs for PLC were declining in several Asian populations. In contrast, ASRs for PLC were increasing in some European, American and Oceanian populations.

Conclusions: Although the reasons were not fully clear for these trends, public health measures in Asian populations and HCV transmission in European, American and Oceanian populations were likely to have contributed to these patterns. Meanwhile,
other possible risk factors such as the consumption of alcohol, obesity, and nonalcoholic fatty liver disease should also be concerned for the burden of PLC.

Key words: Liver neoplasms, incidence, international trends, HBV, HCV

Background

It was estimated that for the year 2012, primary liver cancer (PLC) incidence rates ranked fifth in men and ninth in women worldwide [1]. The number of incident cases of PLC was estimated to be 782,000 per year, including 554,000 in men and 228,000 in women [1]. PLC mortality rate ranked the second in both sexes in the world [1]. Five-year relative survival rate for USA tends to be 16.6% based on data from the US Surveillance Epidemiology and End Results (SEER) 18 (2004-2010) [2]. In China, the age-standardized 5-year relative survival rate for liver cancer was 10.1% [3]. PLC is the major form of liver cancer, which is composed of several histologic subtypes, including hepatocellular carcinoma (HCC), cholangiocarcinoma (CC), combined hepatocellular carcinoma and cholangiocarcinoma (cHCC-CC) [4].

Most of the PLC cases (85%) were diagnosed in developing countries. The highest incidence rates were reported in the regions of Southeast Asia and sub-Saharan Africa [5]. In these high-incidence populations except for Japan (hepatitis C virus, HCV), chronic infection with hepatitis B virus (HBV) and aflatoxin exposure were recognized as major risk factors for PLC. In high-incidence populations, however, PLC was mainly associated to the chronic infection with HCV. It was estimated that most cases of HCC (approximately 80%) were associated with HBV and/or HCV
infections [6]. Moreover, some recent studies indicated that alcohol-related liver
diseases, smoking, immigration, and obesity were also possible risk factors linking to
PLC [7-9].

Several previous studies [10-12] using different datasets had reported the
international trends in PLC incidence rates, one of which [12] reported the global PLC
incidence rates and trends for 1993-2002 (10-year period). However, with the change
of exposure status to risk factors and the implementation of protective measures, the
epidemiology of PLC worldwide may have changed. To give a longer-term and more
recent comprehensive picture to help understand the current status of PLC worldwide,
we extended the analyses for the 35-year period from 1973 to 2007 from 24
populations in Americas, Asia, Europe and Oceania. This data may provide more
useful evidence for evaluating the effect of previous measures of PLC prevention and
control and may facilitate the development of future measures.

Methods

Incidence data

To examine the changing trends in the incidence of PLC over time, age-standardized
(by Segi’s world standard population [13]) incidence rates (ASRs) by sex were
obtained from Volumes 4-10 of Cancer Incidence in Five Continents (CI5) from the
website of International Agency for Research on Cancer (IARC) [14-20]. Volumes
4-10 of CI5 generally provided data by 5-year periods: 1973-1977, 1978-1982,
2003 to 2007 by histologic subtypes (HCC, CC, other & unspecified carcinoma) were collected from 24 populations in four continents from Vol. 10 of CI5. Classification of PLC from Vols. 4, 5-8 and 9-10 of CI5 was coded according to the International Classification of Diseases (ICD) 8th (155), 9th (155) and 10th (C22) revisions, respectively.

Populations were chosen for inclusion in our study on the basis of the following criteria: (1) incidence for time periods at least as far back as 1983-1987; (2) an absence of changes in population coverage or of warnings regarding data quality reported in CI5 Vols. 4-10; and (3) a sufficiently large number of registered cases in CI5 Vol. 10 to enable analyses of recent rates by histologic subtypes (trends by histologic subtypes are not included in our study). Only one registry from each country was selected; if more than one registry met the basic criteria, the registry with the largest population was included in the analysis (except for China which included Hong Kong and Shanghai). Twenty four populations were selected: four from the Americas (Canada, British Columbia (BC); Colombia, Cali; USA, SEER: (9 registries: California: San Francisco; Connecticut; Georgia; Atlanta; Hawaii; Iowa; Michigan; Detroit; New Mexico; Utah; Washington: Seattle) Black/White), six from Asia (China, Hong Kong; China, Shanghai; India, Mumbai; Israel, Jews; Japan, Osaka Prefecture; Singapore, Chinese), five from Northern Europe (Denmark; Finland; Norway; Sweden; UK, England, North Western Region (NWR)), three from Western Europe (France, Bas-Rhin; Germany, Saarland; Switzerland, Geneva), four from elsewhere in Europe [21] (Southern and Central & Eastern Europe including
Italy, Varese Province; Poland, Cracow; Slovakia; Spain, Navarra), and two from Oceania (Australia, New South Wales (NSW); New Zealand). No African populations met all the inclusion criteria. However, four African populations (Algeria, Setif Wilaya; Egypt, Gharbiah; Uganda, Kyadondo; Zimbabwe, Harare: African) were chosen to describe the PLC incidence rates in the last time interval (2003-2007).

Incidence data for white and black populations in the US were not included in CI5 vols. 4 (1973-1977) and 5 (1978-1982), so we further referred to the US SEER dataset [22]. SEER program is a population-based cancer registration system covering 18 registries and 28% of the U.S. population. Long-term data from 1973 to 2010 were available from 9 registries that included approximately 9.4% of the U.S. population (based on 2010 census).

For New Zealand, we abstracted the data for 1983-1987 and 1988-2002 from CI5plus [23] which was part of CI5 databases and contained annual incidence data for a single registry or a group of populations in one country. The data for the last time period 2003-2007 were obtained from CI5 vol.10.

Data analysis

Incidence trends in ASRs of PLC were analyzed using Joinpoint regression (Joinpoint regression software, Version 3.5.3 - May 2012, available through the Surveillance Research Program of the US National Cancer Institute). Permutation method was used for significance test. Changes in annual incidence rates from PLC
were calculated as annual percentage change (APC) in each segment. In the final model, the Joinpoint analysis provided average annual percentage change (AAPC). The significant test of APC and AAPC to 0 was also conducted.

Age-standardized rates of PLC by histologic subtypes (HCC, CC and other & unspecified carcinoma) and sex for selected populations during the period 2003-2007 were integrated and calculated. Secular trends in ASRs were examined by registries and sexes for every five-year period during 1973-2007. PLC trends from New Zealand were described during five-year periods from 1983-1987 to 2003-2007. Figures displaying the incidence trends were prepared using a semi-log scale to facilitate the comparison of temporal trends as well as magnitude. These data were plotted at the midpoint of each five-year interval.

**Results**

ASRs for PLC in 2003-2007 were highest in some populations of Asia (China, Hong Kong; Japan; China, Shanghai; Singapore, Chinese) and Africa (Egypt and Zimbabwe), and much lower in most populations in Europe, Americas and Oceania (Tables 1 and 2). In Asian populations, ASRs for PLC were ranging from 19.0 to 26.7 per 100,000 in males and 4.8 to 8.7 per 100,000 in females, except India and Israel (Jews) (5.2 and 3.1 per 100,000 in males, 2.4 and 1.4 per 100,000 in females, respectively). In most populations in Americas, Europe and Oceania, PLC incidence rates varied between 2.2-7.8 per 100,000 for males and 1.0-3.7 per 100,000 for females except for France (13.6 per 100,000 for males and 2.5 per 100,000 for
females), Switzerland (13.1 per 100,000 for males and 3.0 per 100,000 for females),
Italy (12.6 per 100,000 for males and 3.7 per 100,000 for females), and USA, Black
population (11.6 per 100,000 for males and 3.1 per 100,000 for females).

Tables 1 and 2 also showed the results of Joinpoint analysis for ASRs in males and
females for all ages, respectively. The secular trends in liver cancer incidence among
24 populations from 1973 to 2007 were presented in Figure 1. The increasing trends
for both males and females in PLC incidence rates were seen in most of the
populations in Europe, Americas, and Oceania. UK, England, France, Germany,
Switzerland, Italy, Canada, Colombia, USA, Black, USA, White, Australia, and New
Zealand (1982-2007) showed a significant increasing trend across all the periods
(Tables 1 and 2 and Figure 1).

In males, ASRs for PLC in Germany, USA, Black, and USA, White increased
significantly from the period 1982-1987 (Table 1 and Figure 1.A). PLC incidence
rates in France, Canada, and Australia increased significantly from 1973-1977,
leveled off in the 1990s (Table 1 and Figure 1.A). ASRs for PLC in Spain
significantly increased by 28.9% per year from 1973-1977, significantly decreased by
1.8% per year from 1982-1987, whereas ASRs for PLC in Finland, Norway, Sweden,
Poland, and Slovakia leveled off in all the period (Table 1 and Figure 1.A). In females,
the pattern of PLC incidence in each population seemed to be similar except for
Denmark, Poland, and Spain (Table 2 and Figure 1.B). ASRs for PLC in Poland
significantly decreased by 3.1% per year from 1973-1977 to 2003-2007, whereas
ASRs for PLC in Denmark and Spain showed a stable trends from 1973-1977 to
However, in Asia, ASRs for PLC for both males and females showed significant decreasing trends in 2 of 6 populations (China, Shanghai; Singapore: Chinese) from 1973-1977 to 2003-2007 (Tables 1 and 2 and Figure 1.A and 1.B). The stable trends among males and females were seen in 3 of 6 populations (China, Hong Kong and Israel: Jews) from 1973-2007 to 2003-2007. ASRs for PLC in 1 of 6 populations (Japan) significantly increased by 23.0% in males and 23.5% in females from 1973-1977 and reached a plateau in 1990s (Tables 1 and 2 and Figure 1.A and 1.B). Whereas ASRs for PLC for females in India significantly increased by 5.3% from 1973-1977 and leveled off in 1980s (Table 2 and Figure 1.B).

According to the ASRs of PLC by histologic subtypes from 2003 to 2007, HCC was the dominant histologic subtype, followed by CC and other & unspecified carcinoma (Figure 2). The highest incidence rate of HCC was observed in China, Hong Kong (8.5 per 100,000 in males and 1.9 per 100,000 in females), and the lowest one was shown in UK England (0.9 per 100,000 in males and 0.3 per 100,000 in females). The highest incidence of CC was seen in France (2.0 per 100,000 in males and 0.7 per 100,000 in females), followed by other European countries including Spain (1.1 per 100,000 in males and 0.6 per 100,000 in females), Finland (1.0 per 100,000 in males and 0.7 per 100,000 in females), and Italy (1.0 per 100,000 in males and 0.6 per 100,000 in females). China, Hong Kong (0.9 per 100,000 in males and 0.7 per 100,000 in females) and Japan (0.9 per 100,000 in males and 0.5 per 100,000 in females) had the relatively higher incidence of CC than other Asian countries.
Discussion

International trends in PLC incidence rates during the period 1973–2007 showed that the PLC incidence increased in most of European, American and Oceanian populations although their age-standardized PLC incidence rates in 2003-2007 were much lower than these in Asia. Meanwhile, the incidence of PLC decreased in Asian populations although their age-standardized PLC incidence rates in 2003-2007 were the highest ones in the world.

PLC is a common cancer, particularly in Asia countries such as China, Japan, and Singapore (Chinese). Among these countries, PLC is closely associated with hepatitis virus infection (HBV infection in China and Singapore, HCV infection in Japan) and exposure to aflatoxin (in China). In our study, the decreasing trends in China and Singapore may be attributed to some public health measures [24-27]. The HBV vaccine was incorporated into the National Childhood Immunization Program by China and Singapore from the middle 1980s to the early 1990s. The immunization coverage with three doses of HBV vaccine was 70.7%-95% in 1999 [28, 29]. Several studies also reported the decreases in PLC incidence rates in China, particularly in Shanghai and in younger age groups [24, 30]. Another study in Taiwan showed that the age- and sex- adjusted rate ratios for individuals aged 5 to 29 years decreased by more than 80% for HCC incidence from 1977-1980 to 2001-2004 [25]. In Singapore, Chia et al [26] suggested that a general declining trend in liver cancer incidence was especially notable in local-born Chinese.
Although the measure had not an effect on general population, we expect it will play an important role in the reduction of PLC incidence rates in the coming decades. Moreover, dietary aflatoxin exposure declined in the high-incidence areas of PLC seemed to have contributed to the decrease in PLC incidence in China [31]. A study in Qidong, China [31], where aflatoxin were prevalent, had reported that the decreasing liver cancer incidence in population over 25 years could mainly be attributable to the reduction of exposure to aflatoxin from 1980 to 2008.

In Japan, there were different trends between 1973-1992 and 1988-2007. The increasing trends started in 1973-1977 and reached peak in 1988-1992. This was thought to be in part due to the spread of HCV infection, which began in the 1920s and increase after World War II with an explosion in parenteral amphetamine use and paid blood donation [32, 33]. Although APC did not significantly decrease during 1988-2007, the decline in PLC incidence had been continuously seen from 1988-1992 in our study. Stiffening of legal penalties against amphetamine use starting in 1954 and conversion from paid to voluntary blood donation in the late 1960s might have reduced HCV transmission [34]. After the discovery of HCV RNA, HCV screening test for first- and second-generation HCV antibodies started in 1989 and 1992, respectively [35]. These tests were adopted by Red Cross Blood Center for screening blood, which further decreased the risk of post-transfusion hepatitis. The Japanese government has taken urgent comprehensive countermeasures against hepatitis (HBV and HCV) and HCC since April 2002[33]. Therefore, these measures would provide a significant contribution to decrease the
number of patients suffering from HCV-related liver diseases including PLC.

In contrast, PLC was not a very common cancer in European, American and Oceanian countries where there were no epidemic regions of HBV infection. However, an increasing trend of PLC incidence rates was seen in most of these populations which were partly due to the widespread HCV infection associated with drug use, exposure to contaminated blood transfusion and/or needles used for medical purposes [36]. The natural history of PLC indicated that the time between exposure to HCV and development of HCC is about 30 years [37]. HCV infections were found in 30-50% in the United States and 44-66% of HCC patients in Italy [38]. Both of these countries had the highest PLC incidence rates in their own continent. The disparate time of HCV infection penetrating each country aroused the different peak time in PLC incidence rates. The increasing trends in PLC incidence rates in the United States could be attributed to the increased HCV exposures by contact with contaminated blood and injection drug use during the 1960s and 1970s [39]. HCV infection which was attributable to the introduction of disposable syringes and their re-use among without proper disinfection among intravenous drug use in Italy after 1970s was in part responsible for the upsurge of liver cancer incidence [40]. Meanwhile, in several studies conducted in Western countries, 30 to 40% of patients with hepatocellular carcinoma did not have chronic infection with HBV or HCV, suggesting the presence of other causes of disease[5]. Therefore, other factors including alcohol [41, 42], obesity [43, 44], and non-alcoholic fatty liver disease (NAFLD) [5] might be contributed to the increasing trend as well. In
population-based cohort studies in the United States and Scandinavia [44-46], HCC was 1.5 to 2.0 times as likely to develop in obese persons as in those who were not obese. NAFLD, which is present in up to 90% of all obese persons and up to 70% of persons with type 2 diabetes, has been proposed as a possible risk factor for hepatocellular carcinoma [47]. Although there were still some difficult problems in the latency period from exposure to these factors and PLC development, more emphasis should be recommended to control these factors.

The advent precise diagnostic tests may introduce a detection bias whereby increased recognition of the disease, rather than a true increase in its occurrence, accounts for a rising incidence [48]. Although ultrasonography, measurements of serum alpha-fetoprotein, and computed tomography (CT) scanning has been routine since the early 1980s, which should have led to an increase in the number of hepatic biopsies conducted, the percentage of histological confirmation of PLC has not increased significantly during the study period in these countries which had an increasing trend in PLC incidence rates. In addition, females in Poland (from 1973-1977 to 2003-2007) and males in Spain (from 1982-1987 to 2003-2007) had also exhibited a decreasing trend of PLC incidence. The reasons for this decreasing trend remained unclear.

This study has several strengths. The data were abstracted from large, well-established registries throughout the world. For the first time, data covering 35 years were analyzed to describe the variation of international trend in PLC incidence rates, which may stimulate further etiologic researches. In addition, incidence rates
of particular histologic subtypes of PLC in different populations were examined separately. This study, however, had limitations in that the trends by histologic subtypes of PLC were not studied. The variation of ICD coding might have an influence on the explanation of results. In our study, ICD coding contained ICD-8 (Malignant neoplasm of liver and intrahepatic bile ducts, specified as primary), ICD-9 (Malignant neoplasm of liver, specified as primary) and ICD-10 (Malignant neoplasm of liver and intrahepatic bile ducts, specified as primary). The CC was not included in ICD-9 (period from 1978-1982 to 1993-1997). Therefore, the changes in PLC rates mainly reflect changes of HCC. Our study was also limited by the lack of nationwide cancer registries in some countries and registration data might not accurately reflect the true patterns in their nations.

Conclusions

Our analysis on CI5 data suggested that ASRs for PLC were declining in several Asian countries where the highest incidence rates were still seen between 1973 to 1977 and 2003 to 2007. On the contrary, ASRs for PLC were increasing in some American, European and Oceanian countries. The implemented HBV vaccination program and screening test might play an important role in these deceasing trends in Asia. Although the reasons of the increasing trends in American, European and Oceanian populations were not fully clear, the variation was likely to be due to in part the increasing prevalence of HCV infection. However, unlikely HBV vaccine, there is a great challenge in the development of HCV vaccine. Therefore, it is a crucial task
that some integrated strategy including screening of blood donations, safe injection practices and avoidance of unnecessary injections should be taken to control HCV infections. Measures of controlling other risk factors such as alcohol, obesity, and NAFLD may help to reduce PLC incidence rates.

List of abbreviations

PLC: primary liver cancer; SEER: Surveillance Epidemiology and End Results; HCC: hepatocellular carcinoma; CC: cholangiocarcinoma; cHCC-CC: combined hepatocellular carcinoma and cholangiocarcinoma; ASRs: age-standardized incidence rates; HBV: hepatitis B virus; HCV: hepatitis C virus; CI5: Cancer Incidence in Five Continents; IARC: International Agency for Research on Cancer; ICD: International Classification of Diseases; BC: British Columbia; NWR: North Western Region; NSW: New South Wales; APC: annual percentage change; AAPC: average annual percentage change; HBsAg: hepatitis B surface antigen; NAFLD: nonalcoholic fatty liver disease

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

YZ participated in acquisition of data, analysis and interpretation of data and drafted the manuscript. JSR participated in acquisition of data, analysis and interpretation of
data and revised the manuscript. MD participated in the design of study, acquisition of
data, analysis and interpretation of data and revised the manuscript. JFS, NL, YTW,
CFQ and YWZ gave some substantial comments to draft the manuscript. All authors
read and approved the final manuscript.

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collection.
References


Table 1 International variation in primary liver cancer incidence rates for males, from 1973-1977 to 2003-2007

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*R: Rate is age-standardized to the world population, per 100,000 person-years. *Mean of MV% was calculated from 1978 to 2007.
AAPC: Average Annual Percent Change. *AAPC/AAPC is significantly different from 0 (two-side p<0.05)


2. The data of USA, SEER: Black/White (1973-1982) were from SEER 9 registries database. *The data of New Zealand (1983-2003) were from CISplus database. The other data which were not be footnoted were from CIS.

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1Rate is age-standardized to the world population, per 100,000 person-years. 2Mean of MV% was calculated from 1978 to 2007. 3AAPC, Average Annual Percent Change. 4AAPC is significantly different from 0 (two-side p<0.05). 5Germany, Saarland (1983-2007); 6USA, SEER: Black/White (1988-2007); 7New Zealand (1993-2007) 8The data of USA, SEER: Black/White (1973-1982) were from SEER 9 registries database. 9The data of New Zealand (1983-2003) were from CI5plus database. The other data which were not be footnoted were from CI5.
Figures

Figure 1. Trends in age-standardized primary liver cancer incidence rates by continent and area for the time period 1973-2007: A. Males B. Females

Figure 2. Age-standardized primary liver cancer incidence rates by histologic subtypes for selected populations for the time period 2003-2007
Figure 1. Trends in age-standardized primary liver cancer incidence rates by continent and area for the time period 1973-2007: A. Males B. Females
Figure 2. Age-standardized primary liver cancer incidence rates by histologic subtypes for selected populations for the time period 2003-2007.