The changing epidemiology of hepatocellular carcinoma in Asia versus United States and Europe

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Abstract: Hepatocellular carcinoma (HCC) is a major disease worldwide. There were 782,000 estimated new cases globally in 2012 with the majority (76%) occurring in Asia, especially China. Although the etiologies are similar, the prevalence of each HCC risk factor varies in different geographic regions. In China, hepatitis B virus (HBV) infection is the major cause of HCC, whereas in Japan, United States (US) and Europe, hepatitis C virus (HCV) infection predominates. With the epidemic of obesity and diabetes, non-alcoholic fatty liver disease (NAFLD), especially its more aggressive form non-alcoholic steatohepatitis (NASH), has now become a major contributor to HCC. It is anticipated that NAFLD/NASH is likely to overtake viral hepatitis as the leading contributor to HCC in the future. Prior success in reducing HCC cases through hepatitis B immunization program and effective HBV treatments is likely to be offset by rising significance of NASH-associated HCC. In view of this, appropriate measures such as aggressive monitoring clinical course and prognosis of patients with HCC from NASH, studying pathogenesis and mechanism by which NASH promotes HCC, and developing novel interventions and treatment strategy for these patients would be important to address this important public health challenge.

Keywords: hepatocellular carcinoma; viral hepatitis; alcohol-related liver disease; non-alcohol fatty liver disorder


Received: 9th November 2016; Accepted: 29th January 2017; Published Online: 18th April 2017

Introduction

Primary liver disease is a major health problem in the world with liver cancer contributing to the largest disease burden among all liver diseases. Liver cancer is the fifth most common cancer diagnosed in men and the second largest contributor to cancer mortality[1]. Hepatocellular carcinoma (HCC) is the most common histologic subtype of all liver cancers. In 2012, a total of 782,000 new cases of HCC were estimated in the world. Seventy-six percent of these cases occurred in Asia (with 50% in China alone), compared to 8% in Europe and 4% in North America[1].

The highest incidence rates of HCC were found in East Asia with an age-standardized rate (ASR) of 31.9 per 100,000 in men and 10.2 per 100,000 in women, respectively[1]. It was followed closely by Southeast Asia with an ASR of 22.2 per 100,000 in men and 7.2 per 100,000 in women[1]. Males were found to have a higher HCC incidence than females, with the male/female ratios somewhere between 2:1 and 4:1[1]. This observed gender difference may be due to the differences in exposure to various HCC risk factors. The prognosis of HCC was very poor with the mortality-to-incidence ratio as high as 0.95[1]. The geographic patterns in incidence and mortality apparently were quite similar all over the world.

Chronic infections with hepatitis B virus (HBV) or hepatitis C virus (HCV) are the biggest risk factors for HCC, contributing to more than 60% of all HCC cases globally[2]. In areas with the HBV endemic, the virus is generally acquired via vertical or perinatal transmission. In contrast, HCV infection can be acquired at any age in life either via contaminated blood transfusion or in-
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Intravenous injection of illicit drugs by drug abusers. In China, HBV infection is the major cause of HCC, whereas in Japan, US and Europe, HCV infection predominates.[3-6].

In recent years, with the global epidemic of obesity and diabetes, several published studies have now associated these two common medical conditions as risk factors for HCC.[7-11] While the underlying mechanism is not totally understood, this observed association may be due to an increased risk of developing non-alcoholic fatty liver disease (NAFLD) in patients with obesity and diabetes.[12].

NAFLD is the hepatic manifestation of obesity and related metabolic disorders. NAFLD and its more severe form NASH (non-alcoholic steatohepatitis) were originally assumed to be largely confined to industrialized Western countries.[12]. In the US and other industrialized countries, NAFLD is the most common liver disorder, affecting 20%–30% of the general population.[13,14]. However, social and lifestyle changes in Asia, such as increasing consumption of fast food and low physical activity, have resulted in over-nutrition and predisposition to NAFLD and related metabolic syndrome in Asian populations. Similar to the Western counterparts, NAFLD is now commonly observed in Asian countries with prevalence ranging from 15%–45%.[15]. NASH likely accounts for a substantial portion of the cryptogenic HCC without known etiology.[16].

In most Asian countries, the significance of chronic HBV infection is declining, but it is likely to be offset by rising significance of NASH-associated HCC in the future. For example, from a registry of 1,351 HCC cases in Singapore, the proportion of cases associated with chronic HBV infection has dropped from 71.9% in the pre-2010 era to 57.1% post-2010. The proportion of non-viral, non-alcohol-related HCCs (which connotes NASH etiology, in general) have risen from 16.6% to 27.8% over the same periods.[17].

As seen from these data, there are large geographic variations in the epidemiology of HCC in the world. This review attempts to describe and compare the differences in incidence and risk factors of HCC as well as time trends in Asia versus US and Europe.

Incidence of hepatocellular carcinoma

Tables 1A and 1B summarized the incidence rates and ASR of HCC in various regions and countries. By region, the highest incidence rates of HCC were found in East Asia, followed by Southeast Asia. More than 50% of the HCC occurred in China.

The following is a more detailed description of incidence of HCC for China, Japan, US and Europe:

China

Liver cancer is ranked as the third most common cancer in China. From the data of 72 local population-based cancer registries (2009–2011), which represented 2.9% of the China population, a total of 466,000 new cases of HCC were estimated for 2015. Among these new cases, 73.7% were in men (343,700) and 26.2% (122,300) were in women. Despite ranking third in incidence, HCC actually has the highest mortality with the estimated deaths of 422,100 (310,600 men and 111,500 women).[18].

For the age subgroups, more liver cases occurred in the 45–59 age group than other age subgroups (estimated new liver cases: <30 versus 30–44 versus 45–59 versus 60–74)

Table 1A. Incidence and age-standardized rate of HCC in various regions

<table>
<thead>
<tr>
<th>Region</th>
<th>No. of new cases* (total)</th>
<th>No. of new cases* (male)</th>
<th>No. of new cases* (female)</th>
<th>ASR (total)</th>
<th>ASR (male)</th>
<th>ASR (female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLOBAL</td>
<td>782</td>
<td>554</td>
<td>228</td>
<td>10.1</td>
<td>15.3</td>
<td>5.4</td>
</tr>
<tr>
<td>ASIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastern Asia</td>
<td>466</td>
<td>342</td>
<td>124</td>
<td>20.9</td>
<td>31.9</td>
<td>10.2</td>
</tr>
<tr>
<td>South-Eastern Asia</td>
<td>80</td>
<td>58</td>
<td>21</td>
<td>14.2</td>
<td>22.2</td>
<td>7.2</td>
</tr>
<tr>
<td>EUROPE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southern Europe</td>
<td>20</td>
<td>14</td>
<td>6</td>
<td>5.9</td>
<td>9.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Western Europe</td>
<td>20</td>
<td>15</td>
<td>5</td>
<td>4.9</td>
<td>8</td>
<td>2.2</td>
</tr>
<tr>
<td>Northern Europe</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>3.1</td>
<td>4.6</td>
<td>1.8</td>
</tr>
<tr>
<td>NORTH AMERICA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>33</td>
<td>24</td>
<td>9</td>
<td>5.8</td>
<td>9.3</td>
<td>2.7</td>
</tr>
</tbody>
</table>

*in '000; ASR = Age-adjusted rate per 100,000

52
versus ≥75 = 4,400 versus 41,300 versus 130,400 versus 116,100 versus 51,600 in men; estimated death cases: <30 versus 30–44 versus 45–59 versus 60–74 versus ≥75 = 700 versus 5,800 versus 26,900 versus 44,800 versus 33,200 in men). For individuals aged <60 years, HCC is the most commonly diagnosed cancer and the leading cause of cancer death in men, followed by lung and stomach cancer[18].

The same report from Chen et al.[18] also analyzed data from 22 local China registries for a trend analysis (2000–2011). There was a downward trend observed for HCC for both genders. In contrast, there was an increase trend for cancers of pancreas, colon, brain/central nervous system (CNS), prostate, bladder and leukemia along with a stable trend for lung cancer[18]. Although a decreasing trend is observed, it is important to note that the overall number of new HCC cases continues to increase. It is projected that the total HCC cases in China may reach 494,000 and 560,000 in 2020 and 2025, respectively[1].

Japan (third in men and fifth in women)[5]. From the data of the Osaka Cancer Registry (1981–2003), the incidence of HCC was found to be higher in men than women. Over the past two decades, the age-standardized incidence of HCC in men had increased from 29.2 per 100,000 in 1981 to 41.9 per 100,000 in 1987. However, from 1988 to 1995, the incidence continued to fluctuate within this observed range until a slowly deceasing trend was observed from 1996 to 2012[19]. For women, the age-standardized incidence peaked around 1995–2000 but declined thereafter from 2001–2012[1].

Korea
HCC is ranked as the third most common cancer and the third leading cause of cancer mortality in Korea[5]. The age-standardized incidence of HCC was 16.2 per 100,000 (25.8 and 8.7 per 100,000 in men and women, respectively)[1].

Taiwan
HCC is ranked as the third most common cancer and the second leading cause of cancer mortality in Taiwan. A total of 11,422 new cases of HCC were estimated in 2012 in Taiwan with an ASR of 31.4 per 100,000[1].

Table 1B. Incidence and age-standardized rate of HCC in key representative countries

<table>
<thead>
<tr>
<th>Region</th>
<th>No. of new cases* (total)</th>
<th>No. of new cases* (male)</th>
<th>No. of new cases* (female)</th>
<th>ASR (total)</th>
<th>ASR (male)</th>
<th>ASR (female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>394</td>
<td>293</td>
<td>101</td>
<td>22.3</td>
<td>33.7</td>
<td>10.9</td>
</tr>
<tr>
<td>Japan</td>
<td>36</td>
<td>24</td>
<td>12</td>
<td>9.3</td>
<td>14.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Korea</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>16.2</td>
<td>25.8</td>
<td>8.7</td>
</tr>
<tr>
<td>Vietnam</td>
<td>22</td>
<td>17</td>
<td>5</td>
<td>24.6</td>
<td>40.2</td>
<td>10.9</td>
</tr>
<tr>
<td>Indonesia</td>
<td>18</td>
<td>13</td>
<td>5</td>
<td>8.4</td>
<td>13.4</td>
<td>4.0</td>
</tr>
<tr>
<td>Thailand</td>
<td>21</td>
<td>15</td>
<td>6</td>
<td>22.3</td>
<td>34.8</td>
<td>11.3</td>
</tr>
<tr>
<td>Singapore</td>
<td>0.7</td>
<td>0.6</td>
<td>0.1</td>
<td>9.7</td>
<td>15.8</td>
<td>4.1</td>
</tr>
<tr>
<td>Philippines</td>
<td>7</td>
<td>5</td>
<td>2</td>
<td>11.4</td>
<td>17.1</td>
<td>6.5</td>
</tr>
<tr>
<td>EUROPE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>11</td>
<td>7</td>
<td>4</td>
<td>7.1</td>
<td>11.0</td>
<td>3.6</td>
</tr>
<tr>
<td>France</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>6.6</td>
<td>11.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Spain</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>5.9</td>
<td>9.9</td>
<td>2.4</td>
</tr>
<tr>
<td>UK</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>3.2</td>
<td>4.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Germany</td>
<td>9</td>
<td>6</td>
<td>3</td>
<td>4.6</td>
<td>7.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Greece</td>
<td>1</td>
<td>0.7</td>
<td>0.3</td>
<td>3.4</td>
<td>5.3</td>
<td>1.8</td>
</tr>
<tr>
<td>NORTH AMERICA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>29</td>
<td>21</td>
<td>8</td>
<td>7.9</td>
<td>12.0</td>
<td>4.2</td>
</tr>
</tbody>
</table>

*in '000; ASR = Age-adjusted rate per 100,000

#ref[5]
United States

In 2013, a total of 29,473 people in the US were diagnosed with HCC (21,143 men and 8,330 women)\textsuperscript{[20]}. The ASR was 7.9 per 100,000 (12.0 and 4.2 per 100,000 in men and women, respectively)\textsuperscript{[20]}. By racial and ethnic differences, Hispanic was found to have the highest ASR, followed by Asian and Pacific Islander, and then African-American (ASR: White versus African-American versus Asian and Pacific Islander versus American Indian and Alaska Native versus Hispanic = 7.1 versus 10.4 versus 12.3 versus 9.3 versus 12.8 per 100,000, respectively)\textsuperscript{[20]}. The relative five-year survival rate for HCC is 13.6% (95% CI, 13.3%–13.8%)\textsuperscript{[20]}.

Secular trends in age-adjusted incidence based on the Surveillance, Epidemiology, and End Results (SEER) data (1973–2011) showed that, overall, the incidence of HCC is on the increase (HCC incidence, 1973 versus 2011: 1.5 versus 6.2 cases per 100,000)\textsuperscript{[21]}. Although HCC incidence continues to increase, a slowing of the rate of increase occurred around 2006, suggesting a plateau of the HCC epidemic\textsuperscript{[21]}. Subgroup analysis showed that the greatest increase in incidence of HCC was seen especially in Hispanics and African-Americans in the 45–65 years age group (time interval 1993–1995 versus 2005–2007: White 2.0 versus 3.7, African-American 4.0 versus 7.6, Asian 8.4 versus 10.3, and Hispanic 4.3 versus 8.2, respectively)\textsuperscript{[22]}.

Europe

Compared to other parts of the world, Southern Europe has an intermediate incidence of HCC and Northern Europe has the lowest incidence rate. By country, the highest rates of HCC for men in Europe occurred in France, followed by Italy and Spain. Specific ASR for the top six HCC countries in Europe are as follows: France versus Italy versus Spain versus Germany versus Greece versus United Kingdom (UK) = 11.3 versus 11.0 versus 9.9 versus 7.2 versus 5.3 versus 4.6 per 100,000 in men; 2.5 versus 3.6 versus 2.4 versus 2.3 versus 1.8 versus 1.9 per 100,000 in women, respectively\textsuperscript{[21]}.

Risk factors of hepatocellular carcinoma

Table 2 lists the prevalence of HBV, HCV infection, NAFLD and alcoholic liver disease (ALD) in China, Japan, US and Europe. Below is a more detailed description of the various key HCC risk factors for these countries:

<table>
<thead>
<tr>
<th></th>
<th>HBV (%)</th>
<th>HCV (%)</th>
<th>NAFLD (%)</th>
<th>ALD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>7.2</td>
<td>0.7</td>
<td>15</td>
<td>2.3–6.1</td>
</tr>
<tr>
<td>Japan</td>
<td>1.0</td>
<td>1.6</td>
<td>30</td>
<td>NA</td>
</tr>
<tr>
<td>US</td>
<td>0.3–0.7</td>
<td>0.8–1.2</td>
<td>30</td>
<td>2.0</td>
</tr>
<tr>
<td>Europe</td>
<td>0.5–0.7</td>
<td>0.1–3.3</td>
<td>20–30</td>
<td>NA</td>
</tr>
</tbody>
</table>

China

Within liver diseases as a whole, NAFLD (49.3%) is most common, followed by HBV (22.9%), alcoholic liver disease (ALD) (14.8%), HCV (3.2%), and other miscellaneous liver disorders (9.9%)\textsuperscript{[3]}. For HBV infection, owing to the universal HBV immunization program which started in China in 1992, hepatitis B surface antigen (HBsAg) carrier rates have been significantly reduced in the general Chinese population, dropping from 9.8% in 1992 to 7.2% in 2006\textsuperscript{[23]}. The HBsAg carrier rates in children (<10 years old) were also reduced to just 1.5%, and hepatitis B surface antibody (HBsAb) was found in 60% of Chinese children under 13 years of age in 2006. Although the HBsAg carrier rates have been reduced dramatically especially among children, there are still about 97 million Chinese people who remain to be HBV carriers, with 20 million likely to suffer from active chronic HBV infection and/or cirrhosis or HCC\textsuperscript{[24]}.

For HCV infection, following the implementation of mandatory anti-HCV screening along with the administration of special precautions to prevent blood-borne disease transmission in 1993, new cases of HCV infection have also been decreased significantly in China. A nationwide survey conducted in 2006 showed that the prevalence of anti-HCV was only 0.43%\textsuperscript{[3]}. While the true prevalence of anti-HCV is unknown, some Chinese experts estimated that about 10 million people in China are infected with HCV\textsuperscript{[3]}.

Alcohol consumption has increased considerably in China over the past several decades. Unfortunately, there were no large-scale epidemiologic surveys for ALD conducted in China. The point prevalence of ALD in some areas of China has been reported to be between 2.3%–6.1% (median 4.5%)\textsuperscript{[25]}. Due to the large increase in alcohol consumption, ALD has now become the second most common cause of end-stage liver disease (ESLD) in China after viral hepatitis\textsuperscript{[26]}.

According to data from several epidemiologic studies, the prevalence of NAFLD is estimated to be around...
15% among Chinese adults (95% CI: 6.3%–27.0%) and 1.3% among children and adolescents\(^5,27\). For equivalent levels of over-nutrition, Asians seem to be more prone to NAFLD, metabolic syndrome or diabetes than their Western counterparts due perhaps to the differences in body composition, especially muscle and fat distribution\(^15\).

**Japan**

The etiology of HCC differs significantly in Japan than other Asian countries. Chronic HCV infection is more common than HBV. In 2002–2007, HCV accounted for 72% of all new cases of HCC, whereas HBV only contributed to 18% and non-HBV non-HCV (NBNC) responsible for the remaining 10%\(^3\).

It is important to note that Japan actually did not introduce any hepatitis B immunization program in the country. Recent viral hepatitis surveys in Japan showed that the prevalence of HBV carrier was higher than HCV among Japanese <65 years of age\(^24\). A reversal of epidemiology of HCC in Japan from predominantly HCV-related to HBV-related may be possible in the future.

Prevalence of NAFLD in Japan was noted to increase from 13% before 1990 to 30% in 1998\(^15\). From a study conducted by Okanoue et al., NAFLD was found to be in 32% of men and 17% of women in 2008\(^29\).

**Korea**

In Korea, concerning the etiological agents, 74.2% of patients with HCC have HBV infection, 8.6% have HCV infection and 6.9% have heavy alcoholism\(^5\).

**Taiwan**

From 1995 to 2000, HBV infection accounted for 59% of HCC and HCV infection accounted for 31% of HCC, with HBV–HCV coinfection accounting for 4%\(^5\).

**United States**

Chronic HBV and HCV are the major risk factors for HCC in the US. Data from national US surveys indicated that around 0.9–2.2 million people have chronic HBV infection and 2.7–3.5 million people suffer from chronic HCV infection\(^30-33\). Nevertheless, with the implementation of universal HBV vaccination program in 1991, the prevalence of chronic HBV infection has reduced dramatically among the young populations. However, over the past several decades, there have been a high number of immigrants with chronic HBV who migrated to the US from HBV endemic countries. For example, based on Centers for Disease Control’s 2008 Morbidity and Mortality Weekly Report (MMWR), people living with chronic HBV accounted for as high as 70% of all HBV infections in the US and most were immigrants\(^34\).

NAFLD is the hepatic manifestation of obesity and related metabolic disorders. With the epidemic of obesity and diabetes, NAFLD has now become the most common liver disorder in the US, affecting about 30% of the general population and 90% of those with morbid obesity\(^12\).

**Europe**

Etiologies of HCC in Europe are not any different from other countries. Excessive alcohol consumption, HBV/ HCV infections and metabolic syndromes due to obesity are the major causes of cirrhosis and primary liver cancer in Europe\(^6\).

Chronic HBV infection affects about 0.5%–0.7% of the European population and the prevalence rates of chronic HCV are 0.1%–3.3%. The prevalence of NAFLD is estimated to be 2%–44% in the general European population, but much higher in patients with Type 2 diabetes, with a NAFLD rate of 42.6%–69.5%\(^6\).

Europe apparently has the highest prevalence of alcohol consumption. Alcohol can lead to liver cirrhosis, which in turn can result into HCC. For example, 69% of HCC cases in France are caused by excessive alcohol consumption despite viral etiology is also on the rise\(^35\). A nationwide population-based hospital registry in Denmark estimated that the prevalence of alcoholic cirrhosis was 1.33 and 0.7 per 1,000 population for men and women, respectively\(^36\).

A population-based cohort study using Clinical Practice Research Datalink and linked English Hospital Episode Statistics in UK estimated that the incidence rate of cirrhosis between 1998 and 2009 by etiology was 16.53, 3.44, and 7.70 per 100,000 person-years for alcohol, viral hepatitis and cryptogenic, respectively\(^37\).

**Molecular classification—Asia versus Europe**

Considerable amount of research has been developed to classify HCC into transcriptomic subtypes in recent years. Using a set of 16 genes, Boyault et al. identified six HCC subtypes in a cohort of European samples with unique gene signature: G1 (IGF2 over-expression), G2 (PIK3CA mutations), G3 (TP53 mutations), G4 (TCF1-mutations), G5 (β-catenin mutations) and G6 (β-catenin mutations with
E-cadherin under-expression[38]. Of note is that G1 and G2 were both associated with HBV and were quite distinct from other subtypes.

Using this approach, Allen et al. analyzed 82 HCC samples (35 Chinese, 47 other Asians) from Singapore[39]. Subtype distribution among this Asian cohort was as follows: G1 (13.4%), G2 (24.4%), G3 (15.9%), G4 (24.4%), G5 (14.6%), and G6 (7.3%). Viral hepatitis infections were very common, with 43.9% of these samples had HBV, 26.8% had HCV, and 1.2% had both. The corresponding distribution among its European counterparts was as follows: G1 (9.2%), G2 (14.2%), G3 (12.5%), G4 (34.2%), G5 (20.0%), and G6 (10.0%). Overall, results were generally similar between the two cohorts except the Asian samples seemed to be higher in G1–G3 (53.7%) versus G4–G6 tumors (46.3%) and this was consistent with the higher proportion of HBV patients in Asian versus Europe samples (43.9% versus 30.0%, respectively). Among the 35 patients of Chinese descent, G4 (28.6%) and G2 (20.0%) were the most common, whereas of the 47 patients with other Asian heritage, the highest were G2 (27.7%) and G4 (21.3%).

**Discussion**

HCC has long been a major public health problem, especially in Asia. China alone contributes to about half of all new HCC cases worldwide. In the US and Europe, the incidence of HCC continues to increase slightly over time, whereas in China, a downward trend is observed. However, the overall number of new HCC cases continues to increase in China; it is projected that total HCC cases in China may reach 494,000 and 560,000 in 2020 and 2025, respectively. In Japan, the incidence of HCC peaked around 1988–1995 for men and 1995–2000 for women and declined thereafter for both genders.

The high burden of HCC in China is mainly due to the high prevalence of chronic HBV infection. The prevalence of HBV infection is higher in China than other countries. However, owing to the successful national HBV immunization program and effective HBV treatment, chronic HBV infection in most Asian countries besides Japan has been declining. In Japan, US and Europe, chronic HCV infection is more common than HBV infection. In Japan, the peak period of HCV-related HCC has passed, whereas in the US, HCV-related HCC incidence is still rising.

Meanwhile, ALD is also quite common as drinking problem is quite prominent in China and Europe. ALD is also an important risk factor of HCC. While modest social drinking is acceptable, caution should be applied for people who are prone to excess consumption.

A more worrisome finding is the high prevalence of NAFLD in all regions. The prevalence of NAFLD was 15% in China, and 30% for Japan, US, and Europe. NAFLD is believed to closely relate to metabolic syndrome and insulin resistance. With the rising epidemic of obesity and diabetes in many parts of the world, NAFLD is increasing quickly in developed and developing countries. It is noted that up to 80% of obese people would have NAFLD. As it progresses, its more severe form NASH would present severe inflammation and fibrosis, which can lead to cirrhosis and/or HCC.

In most Asian countries, the significance of chronic HBV infection is declining, but it is likely to be offset by rising significance of NASH-associated HCC. As seen from a registry of HCC cases in Singapore, while the proportion of HBV-related cases dropped, the proportion of non-viral, non-alcohol-related HCCs (which connotes NASH etiology, in general) was observed to increase[17]. Due to the high prevalence of NAFLD in all regions, NAFLD/NASH is likely to overtake viral hepatitis as the leading cause of HCC in the coming years.

Another potential problem is the co-existing of more than one risk factor of HCC. For example, there exist some individuals who may suffer from viral hepatitis, yet have NAFLD from obesity/diabetes along with an alcohol drinking problem. The effects of multiple risk factors are multiplicative, and the probability of developing HCC in these patients is many folds higher than those with just a single risk factor of HCC alone.

The rise of NAFLD and its more severe form NASH is particularly worrisome. Measures to actively combat obesity and manage diabetes are critical. Public health measures to promote a healthy lifestyle, with a balanced diet, regular exercise and avoiding excess sugary intake, would be useful. For patients with NAFLD, actively monitoring disease progression, stringent diet and regular exercise would help control the disease. In fact, in some cases, these measures may even be helpful to reverse the disease course.

To reduce HCC incidence from NASH, proper measures may include monitoring the clinical course and prognoses of patients with HCC from NASH, and studying the pathogenesis and mechanism by which NASH promotes HCC.
In addition, developing novel intervention and treatment strategy for these patients would be helpful to address this important public health challenge.

**Conclusion**

In summary, HCC is a deadly disease with a very high mortality. Despite various past efforts which have been placed to reduce its incidence, it remains a major public health problem in many parts of the world, especially China and many Asian countries. Meanwhile, epidemiology of HCC in Asia is likely to change. Importance of chronic HBV infection is declining, now it is likely to be offset by rising significance of NASH. Accordingly, initiating appropriate public health measures in an attempt to proper control the key risk factors, especially NAFLD/NASH, would be warranted in combating this important challenge.

**Conflict of interest**

The author declares no potential conflict of interest with respect to the research, authorship and/or publication of this article.

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