Hepatocellular carcinoma in the Asia Pacific region

Man-Fung Yuen,* Jin-Lin Hou,† Anuchit Chutaputti,‡ on behalf of the Asia Pacific Working Party on Prevention of Hepatocellular Carcinoma

*Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, †Hepatology Unit, Nanfang Hospital, Guangzhou, China, and ‡Phramongkutklao Hospital, Thailand

Abstract

Primary liver cancer, particularly hepatocellular carcinoma (HCC) remains a significant disease worldwide. It is among the top three causes of cancer death in the Asia Pacific region because of the high prevalence of its main etiological agents, chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. In this region, the incidence of HCC has been static over recent decades. Older age is a major risk factor; the incidence increasing sharply after age 40 years. There is a male predilection, with male to female ratio of 3:1, except in elderly Japanese with equal sex incidence or female predominance. In most Asia-Pacific countries, chronic HBV infection accounts for 75–80% of cases; Japan, Singapore and Australia/New Zealand are exceptions because of higher prevalence of HCV infection. In spite of advances in surgery, liver transplantation and newer pharmacological/biological therapies, the survival rate has improved only slightly over recent decades, and this could be attributable to earlier diagnosis (‘lead-time bias’). The majority of patients present with advanced diseases, hence reducing the chance of curative treatment. The importance of HCC may decrease in two to three decades when the prevalence of chronic HBV infection decreases as a result of the universal HBV vaccination programs implemented in late 1980s in most Asia-Pacific countries, and because of reduced incidence of medical transmission of HCV. However, transmission of HCV by injection drug use, and rising prevalence of obesity and diabetes, both independent risk factors for HCC, may partly offset this decline.

Keywords

hepatocellular carcinoma, incidence, mortality and etiology, prevalence.

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Correspondence

Professor Man-Fung Yuen, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong. Email: mfyuen@hkucc.hku.hk

1Asia-Pacific Working Party on Prevention of Hepatocellular Carcinoma

Geoffrey C Farrell [Convenor], Australian National University Medical School, The Canberra Hospital, ACT, Australia

Henry L-Y Chan [Co-convenor and Secretary], Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong

Man-Fung Yuen, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong

Deepak N Amarapurkar, Bombay Hospital and Medical Research Center, Mumbai, India

Anuchit Chutaputti, Phramongkutklao Hospital, Thailand

Jian-Gao Fan, Department of Gastroenterology, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Jin-Lin Hou, Hepatology Unit, Nanfang Hospital, Guangzhou, China

Kwang-Hyub Han, Yonsei University College of Medicine, Seoul, Korea

Jia-Horng Kao, Hepatitis Research Center, National Taiwan University Hospital, Taipei, Taiwan

Seng-Gee Lim, National University Hospital, Singapore

Rosmawati Mohamed, University Malaya Medical Centre, Kuala Lumpur, Malaysia

Jose Sollano, University of Santo Tomas, Manila, Philippines

Yoshiyuki Ueno, Division of Gastroenterology, Tohoku University Graduate School of Medicine, Sendai, Japan
Background

Liver cancer, especially hepatocellular carcinoma (HCC), has long been one of the most important cancers in the world. From World Health Organization (WHO) statistics in 2000, it has been estimated that there are at least 564,000 new cases of HCC per year around the world.\(^1,2\) Of these, about 400,000 develop in men and 165,000 in women.\(^3\) Accordingly, HCC ranks highly in cancer frequency, the fifth most common cancer in men and the eighth in women.\(^4\) Because of its high mortality, the yearly fatality ratio is close to 1.0. This indicates that most patients who develop liver cancer will die within 1 year. According to the recent statistics of the WHO 2006, there are 662,000 deaths per year from liver cancer.\(^4\)

The incidence of liver cancer differs between different geographical regions, and also between countries or geo-economic zones within countries. It is a common cancer in the Asia-Pacific region and Africa with the age-standardized incidence of 14–36 per 100,000 men compared to 5–10 per 100,000 men in Europe, and 2–5 per 100,000 men in America, Australia and New Zealand.\(^5\) This unique variation in the incidence of liver cancer is closely linked to the risk factors of development of HCC, namely chronic infection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV). More than 70% of all newly diagnosed liver cancers occur in Asia, a region accounting for 75% of all those chronically infected with HBV in the world.\(^6\) Of particular importance, China alone accounts for 55% of cases of HCC worldwide.\(^7\)

In addition to examining recent data on the incidence and risk factors for HCC in our region, some other distinct characteristics, e.g. age of onset, gender predilection and change of incidence rate over time for HCC between different countries are also of great interest. In this article, we aim to examine the importance of this disease by reviewing the incidence, age of onset, gender distribution, risk factors, and mortality of liver cancer over time in different countries within the Asia Pacific region, with particular attention to China, Hong Kong, India, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan and Thailand (Fig. 1). This article is formatted to present data summarizes by colleagues from those countries and economic zones.

China

Data presented by Professor Jin-Lin Hou, Hepatology Unit, Nanfang Hospital, Guangzhou, China

From the statistics between year 2000 and 2005, the overall prevalence of HCC in China is 26–32 per 100,000 persons. However, in some areas the prevalence rate can be as high as to 70–80 per 100,000. This high prevalence has usually been observed along the east coastal areas, whilst prevalence is lower i.e. <10 per 100,000 population in provinces located in the western regions of China. According to the usual observation, the incidence of HCC in Chinese people increases with age, and for every age stratum, males have a higher incidence of HCC compared to females. The age-standardized incidence rates are 58 per 100,000 persons for men and 22 per 100,000 persons for women. Although the incidence of HCC is relatively low for women below the age of 40 years (<3 per 100,000 population), it is already at 21 per 100,000 persons for men between the ages of 35 and 40 years. This incidence increases proportionally with age in both sexes from the age of 40 onward, reaching >160 per 100,000 persons for males and 94 per 100,000 persons for females after the age of 70 years.

In the early 1970s, the incidence rate of HCC approximated the mortality rate, indicating patients died from HCC shortly after the diagnosis. From the 1990s onwards, the mortality rate has been around 10–15 per 100,000 persons, which is lower than the incidence rate; this suggests improved survival. This can likely be attributed to improvement in the treatment of HCC over the last 15 to 20 years in China, as exemplified by 5 year survival rates which have increased from <48% to 64% for HCC <5 cm in maximum diameter (data obtained in Shanghai over this period).

The major risk factor for HCC in China is clearly chronic HBV infection, followed by HCV infection. The odd ratios for different etiological agents are listed as follows: HBV: 12.45, HCV: 4.28, family history (may also be due to undiagnosed HBV): 3.45, aflatoxin B1: 2.82, alcohol intake: 1.88 (Fig. 2).\(^8\)

Hong Kong

Data presented by Professor Man-Fung Yuen, Queen Mary Hospital, The University of Hong Kong, Hong Kong

Hepatocellular carcinoma ranks the third most common cancer in men in Hong Kong, although there is a slight decrease in the age-standardized incidence rate from the mid-1990s onward. According to 2005 statistics, the age-standardized rates for men and women are 30 and 8.3 per 100,000 persons, respectively (Hong Kong Cancer Registry, 2005). The male : female ratio in patients with HCC is 3 : 1. Similar to the observations in China, the incidence increases sharply after the age of 40.\(^9\) The median age for development of HCC for men and women is 63 and 71 years, respectively.

The age-standardized mortality rates for men and women are 25 and 7.2 per 100,000 persons, again considerably lower than those for incidence rates of HCC. The median survival has increased from 3.5 weeks in 1980 to 11 months in 2006.\(^10,11\)

Concerning etiologies for HCC, several studies conducted in the period between 1981 and 2006 consistently showed that 75–80% case were related to chronic hepatitis B (CHB) infection.\(^10\) Chronic HCV infection accounted for 3–6%, while co-infection with HBV and HCV accounted for 0.4–3%; chronic alcohol intake accounted for another 5%.

India

Data presented by Dr. Deepak Amarapukar, Bombay Hospital and Medical Research Center, Mumbai, India

Age-standardized incidence rates of HCC in India for men and women are 0.9–3.4 and 0.2–1.8 per 100,000 persons, respectively. Among patients with background cirrhosis, the incidence rate increases to 1.6 per 100 person-year.\(^16\) Among HCC patients with cirrhosis, chronic HBV infection accounts for 71% and chronic HCV infection for 16%.\(^17\)
Depending on different areas in India, it has been estimated that 36–74% of patients with HCC are positive for HBsAg and 0–33% are positive for anti-HCV. The highest HBV prevalence has been found in Chennai. The incidence of HCC per 100 person-years was 2.4 for CHB patients, 2.4 for chronic hepatitis C (CHC) and 3.4 for patients with HBV/HCV co-infection. In patients with HCC and diabetes mellitus, a higher percentage of patients have a history of significant alcohol intake and non-alcoholic steatohepatitis (NASH) compared to those without diabetes. This observation indicates that confounding factors can be present for those with non-viral causes for HCC. In addition, diabetic patients with HCC have more advanced Child-Pugh scores, more advanced tumor lesions with larger tumor size and a higher chance of portal vein thrombosis or intra-hepatic bile duct involvement, lower chance of receiving resection or ablation therapy, and more importantly, lower mean survival. This suggests that diabetes exerts a negative effect on hepatocarcinogenesis, as recently reviewed by Teoh NC and Fan JG.
Japan

Data presented by Professor Yoshiyuki Ueno, Division of Gastroenterology, Tohoku University Graduate School of Medicine, Japan

According to statistics from the Center for Cancer Control and Information Services, National Cancer Center in Japan in 2000, HCC ranks the fourth most common cancer for both men and women. Incidence rates are approximately 8 and 6 per 100,000 persons, respectively. Similar to the situation in China and Hong Kong, incidence as well as the mortality starts to increase from the age of 40 years. This phenomenon is consistently observed from 1980 to 2000. The most recent data for annual number of deaths is from 2005, approximately 34,000. The population of Japan is 126,085,000 (male 61,511,000, female 64,574,000) (Statistics Bureau, Ministry of Internal Affairs and Communications, October 2007).

However, in contrast to China and Hong Kong, 79% of patients with HCC had chronic HCV infection and only 11% had chronic HBV infection. Sixty-three per cent of patients with HCC were older than 65 years. This may be related to the fact that the age of onset of HCC in patients with CHC is usually 10 years later than that of patients with CHB. The incidence of HCV-related HCC seems to decline after the year of 2000. This could be probably due to the decline in incidence of HCV infection after appropriate primary prevention has been initiated. The risk factors of HCC in Japan include elderly, male gender, advanced fibrosis, and positive viral hepatitis markers. However, a recent study demonstrated that male gender predominance is not applicable if the patients’ age is more than 70 years.

Korea

Data presented by Professor Kwang-Hyub Han, Yonsei University College of Medicine, Seoul, Korea

In Korea, HCC ranks the third common cancer and the third leading cause of cancer death. The age-standardized incidence rate and mortality rate are, respectively, 45 and 34 per 100,000 persons for men and 12 and 8.8 per 100,000 persons for women. These figures remain quite static between 1995 and 2003. Overall, the annual death rates from HCC are 23 per 100,000 persons in 2003 and 22 per 100,000 persons in 2006. The incidence increases with age, particularly after the age of 40 years. It reaches a maximum of nearly 160 per 100,000 men at the age of 55 years, before it starts to decline. The 5-year survival rate remains low at 9.6%.

Concerning the etiological agents, 72% of patients with HCC have CHB, 20% have CHC and less than 8% have other causes, including alcohol. Because of the implementation of a national HBV vaccination program in the late 1980s, the HBV carrier rates for males aged older than 20 years decrease from 8% in 1980s to only 4.2% in 2005. With that, it is expected that the incidence of HCC will start to decrease in 2 to 3 decades time.

Malaysia

Data presented by Professor Rosmawati Mohamed, University Malaya Medical Centre, Kuala Lumpur, Malaysia

According to the National Cancer Registry in Kuala Lumpur for 2008, HCC is the 8th most common cancer amongst Malaysian males. In patients with HCC, 59% are Chinese, 29% Malays and 5% Indians. The male to female ratio is 2.4 to 1. The age-standardized incidence rate is 3.6 per 100,000 persons for men and 1.6 per 100,000 persons for women. The incidence rates for both men and women start to increase after the age of 50 years.

According to statistics from the University Malaya Medical Center, of patients with HCC, 85% have CHB; 2% have CHC and 4% have chronic alcoholism. Only 13% and 16% were eligible for surgical resection and trans-catheter intra-arterial chemoembolization (TACE). A large number of patients (58%) can only receive symptomatic treatment. The overall 1-year and 3-year survival rates are 25% and 16% respectively.

Philippines

Data presented by Professor Jose D Sollano, University of Santo Tomas, Manila, Philippines

Hepatocellular carcinoma ranks as the fourth most common cancer with an age-standardized rate of 6.7 per 100,000 persons in 2005. The incidence rates are 14 per 100,000 persons for males and 4.8 per 100,000 persons for females. Overall, HCC ranks as the second most common cause of cancer death among all cancer types. The annual number of death from HCC was 7477 (country population of approximately 88 million). It is the second and seventh leading cause of cancer death for men and women, with age-standardized mortality rates of 11 and 3.2 per 100,000 persons, respectively. The 5-year survival was only 5.9%.

According to the statistics from the University of Santo Tomas, 2008, 55% of patients with HCC have CHB; 4.4% have CHC; 9.2% have chronic alcoholism; and 24.9% have cryptogenic cause. The mean age of development of HCC is 60 years. The male-to-female ratio is 3:1, and 74% of patients have a tumor size >5 cm at
the time of diagnosis. As such, surgical resection or liver transplantation can be done in only 3.7% of these patients, and 24% of patients with HCC receive TACE. More than 50% of patients only receive symptomatic treatment.

**Singapore**

**Data presented by Professor SG Lim, National University Hospital, Singapore**

According to the Singapore Cancer Registry 2002–2005, HCC is the fourth most common cancer in males. According to a study, the age-standardized incidence of HCC in the population fall by 58% (from 17 to 7.1 per 100 000 persons, \( P = 0.004 \)) in men and 47% (from 2.8 to 1.5 per 100 000 persons, \( P = 0.01 \)) in women from 1968–1972 to 1998–2002. The incidence for HCC is the highest in Chinese compared with Malays (\( P = 0.048 \)) and Indians (\( P = 0.023 \)).

The overall prevalence of chronic HBV infection in Singapore falls from 9–10% in 1980–81 to 4% in 1999. According to a cohort of 288 patients with HCC identified during 2002–2007 in the National University Hospital, 74% are male and 76% are ethnically Chinese; 35% have CHB; 13% have CHC and 31.4% are negative for CHB and CHC. The mean survival is 31 months.

**Taiwan**

**Data presented by Professor Jia-Horning Kao, Hepatitis Research Center, National Taiwan University Hospital, Taipei, Taiwan**

According to the Taiwan Cancer Registration System (http://crs.cph.ntu.edu.tw/), there are around 8000 new cases of HCC each year. The case number has increased gradually from 1994 to 2002. In 2002, the age-standardized incidence rates are 53 per 100 000 persons for men and 21 per 100 000 persons for women. The annual death number due to HCC is approximately 7000.

According to a study of 18 423 patients enrolled from 1981 to 2001 in Taiwan, 67% of male HCC are related to chronic HBV infection, but 55% of female HCC are related to chronic HCV infection. The mean age of patients with HBV-related HCC is 53 ± 14 years, and for those with HCV-related HCC it is 65 ± 9.1 years (\( P < 0.001 \)). Male-to-female ratio is 6.4 for HBV-related HCC, while it is 1.7 for HCV-related HCC (\( P < 0.001 \)). The percentage of HBV-related HCC progressively decreases from 82 to 66% in men, and from 67 to 41% in women over the study period. In summary, percentage of HBV-related HCC declines progressively over the last 20 years. However, this is not due to a decrease in prevalence of chronic HBV infection. Instead, it is caused by an increase in HCV-related HCC.

According to another study in Taiwan which recruited 11 312 patients with HCC between 1986 and 2002, patients diagnosed during 1998–2002 showed the highest survival rate, followed by patients diagnosed during the period 1994–1997, 1990–1993, and 1986–1989 (Table 1). This is probably due to earlier detection of HCC and improved patient care.

<table>
<thead>
<tr>
<th>Year</th>
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<td>1998–2001</td>
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**Thailand**

**Data presented by Dr. Anuchit Chutaputti, Phramongkutklao Hospital, Thailand**

Hepatocellular carcinoma is an endemic cancer in Thailand. It ranks as the number one among all cancers in men, with the incidence rate of 33 per 100 000 persons per year, and ranks as the third most common cancer in women, with an incidence of 13 per 100 000 per year. The incidence rate starts to rise at age of 35 years; it peaks around age of 60–65 years, with an incidence rate of ~180 per 100 000 persons.

The majority (80%) of HCC cases are related to chronic HBV infection, followed by CHC (15%) and others, such as alcoholic, metabolic liver disease, or aflatoxin exposure. Since HCC surveillance programs are still not widely available, the majority of cases are diagnosed in the advance stages.

**Discussion**

All assembled data presented from different countries of the Asia-Pacific region demonstrate that HCC is still a major cancer that causes substantial mortality, despite advancements in early diagnosis (in some countries) and of medical and surgical treatment. Overall, there appear to be slight improvements in survival rates, but these vary between countries and may depend on the stage of diagnosis as much as curative therapy. Incidence rates of HCC for males and females across the region are summarized in Table 2. The incidence rates over times in several countries are depicted in Fig. 3. The incidence of HCC remains the same over recent 20 years in most of the Asia-Pacific countries except in Singapore where incidence for both men and women fell over recent 30 years. China and Taiwan have reported an increasing incidence of HCC for both men and women. This may be due to increasing awareness of reporting and better screening services. In Australia, as in the United States, traditionally very low incidence regions, there has been a substantial increase (2 to 3-fold) in HCC incidence over the last 25 years, probably due mostly to immigration of people from Asia-Pacific and other regions with high prevalence rates of chronic HBV infection, but also due to the epidemics of CHC and possibly obesity and diabetes. It is acknowledged here that this Working Party was representative of the major (most populous) countries of the region. Unfortunately, resourcing logistics meant that some countries with high populations (Indonesia, Pakistan, Bangladesh) were not represented, and neither were Taiwan, and Japan.
numerous smaller nations (notably Papua New Guinea and other island states of the Pacific) that are known to have very high rates of HCC related to chronic HBV infection and possibly other environmental factors. It is hoped that the data that have been presented may be helpful in planning local and regional-based preventive strategies, and it is noted that hepatitis B vaccination has been part of a universal infant extended immunization program in Papua New Guinea for several years.33

Two observations have been noted consistently in all Asian countries. First, the male-to-female ratio for HCC is 3 : 1, with the exception of older women in Japan. Second, the incidence rate starts to increase from the age of 35 to 40 years, peaking in the sixth and seventh decades of life for men, possibly later for women. These observations on age-specific incidence have obvious implications for targeting a population for HCC screening programs, as discussed in a later review from discussions of this Working Party.

The main etiological agent for HCC in Asia is chronic HBV infection. In most countries, this usually accounts for 70–80% of the cases, with the exception of Japan where it only accounts for only 11% of HCC cases, while chronic hepatitis C accounts for nearly 80% of cases. Singapore appears to be another exception, where CHB only accounts for one third of cases of HCC, and in Australia and New Zealand chronic HCV infection also accounts for 30–40% of cases of HCC. Nevertheless, with the implementation of universal HBV vaccination in most of the Asia-Pacific countries, the authors anticipate a fall in incidence of HCC in the coming 20–30 years. Prevention of HCV infection from medical causes, as recommended by the Asia-Pacific Association for Study of the Liver (APASL) guidelines34 may have already caused the HCV-related HCC epidemic in Japan to peak (see age-specific prevalence data). Conversely, reports of increased numbers of IDU-transmitted HCV in the region, as in Australia and New Zealand, may greatly diminish the gains made by arresting medical transmission from contaminated blood.35 Finally, although CHB is the major cause for HCC in most of the countries of Asia-Pacific region, comprehensive data on the role of aflatoxin and other food and water-borne toxins, alcoholism and metabolic syndrome, especially obesity and diabetes on development of
HCC are lacking in the Asia Pacific region. Future studies are recommended to delineate the exact risk for HCC for these entities on their own and with the presence of other risk factors e.g. chronic HBV and HCV infections and excessive alcohol consumption. The impact of high rates of alcohol abuse in Asia (as in the rest of the world) and the recent (10–15 year) obesity and type 2 diabetes epidemic in Asia may impact adversely on HCC incidence in the next 25 years; the conundrum of non-viral associated HCC will be discussed in a later article in these Working Party reports.

In conclusion, HCC remains a highly prevalent disease associated with high mortality in the Asia-Pacific region. Chronic hepatitis B is the major etiologic agent for the development of HCC, but HCV infection is most important in Japan and plays a substantial role in Australia, New Zealand, and Singapore, and possibly in some other countries not specifically canvassed in this review (e.g., Pakistan, Bangladesh, Myanmar). The incidence of HCC increases with male gender and age older than 40 years. It is expected to decrease two to three decades later when the prevalence of CHB infection becomes lower as a result of the universal HBV vaccination implemented in late 1980s in most the Asia-Pacific countries.

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References


