

## Epidemiology and Risk Factors of Hepatocellular Carcinoma in Asia

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### PREFACE (INTRODUCTION)

Primary liver cancer, which consists predominantly of hepatocellular carcinoma (HCC), is a major contributor to cancer incidence and mortality. HCC is the fifth most common cancer worldwide and the third most common cause of cancer mortality. It results in about 0.7 million deaths per year worldwide. Because of its poor prognosis, this number of deaths is almost the same as the number of cases being diagnosed each year (about 0.6 million)<sup>[1-3]</sup>.

There is a growing understanding on the molecular mechanisms inducing hepatocarcinogenesis, which almost never occurs in healthy liver. But, the cancer risk increases sharply in response to chronic liver injury at the cirrhosis stage<sup>[3]</sup>. Risk factors those may provide final and critical assaults for pathogenesis of HCC in diseased and inflamed livers have been elucidated. But, more studies would be needed regarding cellular and molecular mechanisms underlying hepatocarcinogenesis in different races and population groups.

The incidence and prevalence of HCC exhibit marked variations among geographic regions, racial and ethnic groups, and between men and women. Most of the HCC patients are detected in Asian and sub-Saharan African countries. Incidence of HCC has been decreasing in some areas of Asia with high prevalence of HCC. This is especially seen in some cities or specific regions of Asian countries<sup>[4]</sup>. It is assumed that effective HBV vaccination programs and the better control of aflatoxin exposure in the high HCC incidence areas are contributing to the decreased HCC incidence. On the other hand, the incidence of HCC is increasing, mainly because of the increasing prevalence of hepatitis C virus (HCV) infection and immigration of people from countries with high endemicity for hepatitis B virus (HBV) infection. In spite of this variability regarding incidence of HCC in different Asian countries, the total numbers of patients with HCC are increasing in these countries. Increased incidence of HCC, availability of improved diagnostic modalities for HCC, and increased survival resulting from better control and management strategies may have contributed to this phenomenon. Although these changes have been occurred in global context, the nature and characteristics of management strategies are variable among different countries of Asia and even in different parts of same country or region.

### ABSTRACT

The dominant form of primary liver cancer is hepatocellular carcinoma (HCC). Its incidence varies widely among different geographical areas (from <2 to >50 per 100,000 males/year), reaching peak values in some countries of Southeast Asia. The incidence, prevalence and risk factors of HCC exhibit marked differences among different countries of Asia and also among different regions of the same country. The numbers of patients with HCC are increasing in many Asian countries. It is expected that the incidence of HCC will also increase in the foreseeable future because the burden of chronic liver disease is increasing owing to increasing rates of hepatitis B and C prevalence, obesity-related fatty liver diseases, alcoholism, and other risk factors. Better understandings about epidemiology and risk factors of HCC in Asian countries would allow development of more effective control and management strategies against HCC in these countries.

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**Key words:** Hepatocellular carcinoma; Risk factor; Asia; Increased incidence

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The two most important risk factors for HCC are chronic HBV and HCV infection in the world. This is true in Asia as well. HBV is the most common etiological agent related to pathogenesis of HCC in most Asian countries. But, Japan is an exception to this. More than 80% HCC patients of Japan are infected with the HCV. Increased HCV prevalence has also been reported from some other Asian countries including Mongolia and Pakistan. But, it would be premature to conclude if increased HCV prevalence in these countries reflects in increased incidence of HCC.

Extensive and systemic studies about epidemiology and risk factors of HCC have been accomplished in some Asian countries like Taiwan and Japan. About 50% of total global HCC patients reside in China. Some data about HCC are available from China as well. However, most data about HCC epidemiology have been originated from some specific areas in China. The real impact of HCC in this vast country is yet to be elucidated properly. Studies about epidemiology of HCC have been done by Indian investigators, but, there is lack of information about country-based study in India. Pilot studies about HCC epidemiology and risk factors can be retrieved from most Asian countries. But, the relevance of this information in the context of incidence of HCC in entire country is elusive. Few data about HCC epidemiology are available from most of the developing countries of Asia. Asia-Pacific Working Party on Prevention of hepatocellular Carcinoma publishes their meeting report. This provides comprehensive information about incidence and prevalence of HCC in Asian countries. We used those data for compiling this article. Also, data of pilot studies from different countries were incorporated in this article.

## INCIDENCE AND PREVALENCE OF HCC IN ASIAN COUNTRIES

The estimated numbers of patients with HCC in 2000 have been shown in table 1. According to the estimates of World Health Organization (WHO) in 2008, there are about 749,000 new cases of HCC per year around the world<sup>[5]</sup>. Most of the patients with HCC die within one year; thus the case-fatality rate is about 1.0. According to the recent statistics of WHO (2008), there are 695,000 deaths per year from liver cancer<sup>[5]</sup>. More than 85% of newly-diagnosed liver cancer occurs in Asia, especially in developing countries of Asia. The incidence of HCC in WHO Western Pacific Region is almost 7-8 times of that of combined incidence of USA and European countries.

**Table 1** Patients with hepatocellular carcinoma in different parts of the world.

Region	Patients with HCC (Men)	Patients with HCC (Women)	Total patients with HCC
Asia	323,203	123,000	446,203
Europe	32,551	17,345	49,896
Africa	27,364	14,421	41,785
Oceania	978	452	1,430
North America	8,202	4,333	12,535
Central and South America	8,267	7,182	15,449
Total	400,565	166,733	567,298

Epidemiological data indicates that China alone accounts for 53.5% of cases of HCC worldwide<sup>[6]</sup>. From the statistics (2000-2005), the overall prevalence of HCC in China is 26-32 per 100,000 persons<sup>[7]</sup>. However, there are marked variations in the prevalence of HCC among different parts of China. The prevalence of HCC is 70-80 per 100,000 persons along east coastal regions. On the other hand low prevalence of HCC (<10 per 100,000) has been recorded in the Western regions of China. HCC in Chinese people increases

with age, and for every age group, males have a higher incidence of HCC compared to females<sup>[6]</sup>. The age-standardized incidence rates of HCC are 58 per 100,000 persons for male and 22 per 100,000 persons for female in China. The incidence of HCC is relatively low in female below 40 years (<3 per 100,000 population). However, it is 21 per 100,000 persons for men between 35-40 years. The incidence of HCC becomes as high as >160 per 100,000 persons for males and 94 per 100,000 persons for female after the age of 70 years. It may be extremely difficult to provide a nation-wide data of HCC incidence and prevalence in China, because the health care delivery system is highly variable in different parts of China. In some urban areas, reliable data may be provided. However, data are not available from some remote areas of China. This is not a China-specific factor, but, this is relevant in many Asian countries. Due to recent economic developments, more data about HCC prevalence have been accumulating from China that would provide proper insights about HCC epidemiology in global context.

There are around 8,000 new cases of HCC each year with approximately 7,000 deaths per year in Taiwan (<http://crs.cph.ntu.edu.tw/>). In Taiwan, the age-standardized incidence rates of HCC are 53 per 100,000 persons for men and 21 per 100,000 persons for women. Taiwan is one of the pioneer regions of the world that initiated detailed epidemiological studies about HCC prevalence before more than 3 decades. Also, vaccination against HBV was started in early 1980s in Taiwan and thus the impact of HBV vaccination on HCC incidence can be studied in Taiwan. Taiwan is an economically-developed region with an advanced health care delivery system.

According to 2005 statistics of Hong Kong, the age-standardized rates for HCC incidence for men and women are 30 and 8.3 per 100,000 persons, respectively (Hong Kong Cancer Registry, 2005). The age-standardized mortality rates for men and women are 25 and 7.2 per 100,000 persons. Thus, the numbers of HCC patients are increasing in Hong Kong. The males are more prone to develop HCC compared to the females. Also, the incidence of HCC increases sharply around the age of 40 years. The median age for development of HCC for men and women is 63 and 71 years, respectively<sup>[8]</sup>.

Compared to China, Taiwan and Hong Kong, the incidence and prevalence of HCC is considerably lower in India<sup>[9]</sup>. However, there is paucity of information about population-based survey in many part of this huge country. 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. It seems that considerable numbers of HCC patients in India have been detected in Southern part of India in the Chennai area. But, studies are yet to provide data about HCC from different parts of India.

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 for men and 6 for women per 100,000 persons, respectively. However, age-standardized incidence of HCC seems to be higher in both male and female in Japan. Similar to the situation in China and Hong Kong, incidence as well as the mortality starts to increase from the age of 40 years<sup>[10]</sup>. This phenomenon is consistently observed from 1980 to 2000. Approximately, about 30,000 persons die annually due to HCC in Japan.

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. Overall, the annual death rates from HCC are 22 per 100,000 persons in 2006<sup>[6]</sup>.

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.

According to the National Cancer Registry in Kuala Lumpur for 2008, HCC is the 8<sup>th</sup> 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<sup>[6]</sup>.

In Philippines, HCC 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 about 2-3 times more in males than females. HCC seems to be 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 mean age of development of HCC is 60 years<sup>[6]</sup>.

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 Singapore is decreasing. It fell 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. Singapore has Chinese, Malay and Indian populations. The incidence for HCC is the highest in Chinese compared with Malays ( $P=0.048$ ) and Indians ( $P=0.023$ ).

HCC 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<sup>[6]</sup>.

Few studies have been conducted about incidence and prevalence of HCC in many Asian countries, such as Bangladesh, Pakistan, Iran, and Countries of Arabian peninsula. However, the main etiological factors of HCC; infection with HBV and HCV are common in all of these countries. Due to lack of data from these countries, we would not provide detailed information about incidence and prevalence of HCC in these countries. However, several pilot studies conducted in these countries indicate that increased numbers of cases with HCC are diagnosed in different medical facilities of these countries.

#### **Changing epidemiology of HCC: numbers of patients with HCC are increasing in many Asian countries**

Compared to numbers of patients with HCC in early 1980s or 1990s, the numbers of HCC patients are increasing in 21<sup>st</sup> century in many Asian countries. In fact, there may be several factors underlying this: (1) increased incidence of HCC cases; (2) improved diagnosis of these patients; and (3) better management of HCC patients leading to increased survival and low mortality.

In China, increased numbers of HCC patients do not seem to be due to increased incidence of HCC cases in China. The incidence of HCC is almost static in China. Thus, increased numbers of HCC may be attributable to early diagnosis and improved management of HCC in some parts of China. In 1970s, almost all HCC patients died within one year of diagnosis. In fact, patients with large HCC could be diagnosed at that time. However, from the 1990s onwards, the mortality rate has been decreased to around 10-15 per 100,000 persons, which is lower than the incidence rate. Data from Shanghai have shown that 5 year survival rates have increased from about 48% to 64% for HCC <5 cm in maximum diameter during last 2 decades<sup>[6]</sup>. The numbers of HCC cases may be increased further

in China if modern early diagnosis and effective treatment are implemented in different regions of China.

A study from Taiwan has also supported what that has been shown in Shanghai. The highest survival rate was seen in patients diagnosed during 1998-2002, followed by patients diagnosed during the period 1994-1997, 1990-1993, and 1986-1989. This is probably due to earlier detection of HCC and improved patient care<sup>[11]</sup>.

Early diagnosis and various therapeutic approaches have decreased mortality rate from HCC in most developed and advanced countries of Asia. However, the overall 5 year-survival rate has not been considerably improved. In addition, decreased 1-year or 3-year mortality has not been reflected in many Asian countries due to poor health care delivery system. Early diagnosis of HCC has been accomplished in some rich and advanced countries of Asia. Also, proper therapeutic maneuvers are available in limited numbers of Asian countries. People attending hospital with large HCC is a common feature in most Asian countries. Again, HCC is the first presenting symptom of liver diseases of many HBV and HCV-infected patients in many Asian countries.

#### **Risk factors of HCC: related to etiologies of HCC**

The major risk factor for the development of HCC is cirrhosis of the liver that may be caused by viral (chronic hepatitis B and hepatitis C), toxic (alcohol and aflatoxins), metabolic (diabetes and non-alcoholic fatty liver disease, hereditary haemochromatosis) and immune-related (primary biliary cirrhosis and autoimmune hepatitis) factors<sup>[4]</sup>.

Worldwide, chronic HBV infection is the most common cause of HCC. More than 50% cases worldwide and 70-80% cases of HCC in Asia are attributable to HBV<sup>[12-16]</sup>. Furthermore, the risk of HCC development is related to the disease status of chronic HBV infection. For example, the estimated annual risk of HCC in chronic carriers is 0.26% to 0.6%. The risk increases to 1% in patients with active hepatitis. It further increases to 2% to 3% in cirrhotic patients<sup>[17]</sup>. Certain viral status also poses a higher risk of HCC. Studies in Taiwan showed that genotype C chronic hepatitis B infection has a more aggressive progression than genotype B in HBeAg-positive patients<sup>[13]</sup>. Core promoter mutations (T1762/A1764) are also found to be related to a more progressive disease<sup>[14, 15]</sup>.

In the majority of HCC cases (70% to 90%) there is underlying liver cirrhosis. Patients with HBV-cirrhosis have 1000 times higher risk of developing HCC, compared to hepatitis B surface antigen (HBsAg)-negative individuals<sup>[16]</sup>. Thus, it is likely that the probability of acquiring HCC increases with severity of underlying liver disease. In Japan, the mean interval between HBV initial infection and the occurrence of HCC is 50 years. As most people in Japan are infected with the HBV at birth, HBV-related cirrhosis usually develops earlier than in Western Europe or North America. Due to lack of studies about HBV-related factors in hepatocarcinogenesis, it is difficult to assess the relative contribution of different HBV-related viral factors in the pathogenesis of HCC.

HCV-related HCC is more prevalent only in Japan among Asian countries. More than 80% of HCC cases from Japan are infected with HCV. The annual risk of developing HCC in HCV-infected patients depends on the presence and severity of the underlying liver disease<sup>[18]</sup>.

Combined HCV and HBV infection have a higher risk of developing HCC than those with a HCV or HBV alone. The HCC risk in subjects with both infections was investigated in a meta-analysis of 32 epidemiological studies between 1993 and 1997. The odd ratio (OR) for development of HCC in HBsAg positive, anti-HCV/HCV RNA negative subjects was 20.4; in HBsAg negative, anti-HCV/

HCV RNA positive subjects, 23.6; and subjects positive for both markers, the OR was 135. These data suggest a more than additive effect of HBV and HCV coinfection on HCC risk<sup>[18,19]</sup>. However, there are few people with HBV and HCV coinfection in Asian countries. Thus, the role of coinfection remains to be elucidated in hepatocarcinogenesis in Asia. Also combined infection of HBV and hepatitis D virus (HDV) is not common in Asian countries. Coinfection of hepatitis virus and human immune-deficiency virus (HIV) has been detected in many Asian countries. But, the impact of coinfection on hepatocarcinogenesis in Asian countries is yet to be elucidated.

Taken together, the main etiological factor of HCC in Asian countries is HBV, although HCV is the main etiological factor of HCC in Japan. Also, more cases of HCV have been detected in some Asian countries, such as Pakistan and Singapore. But, their role in the pathogenesis of HCC remains to be elucidated in future. It is natural that coinfection of hepatitis virus and HIV may be potentiating factor for HCC development in Asia. But, epidemiological data regarding these associations are yet to be explored.

The role schistosomiasis is not notable in HCC development in Asian countries.

Aflatoxins, a group of mycotoxins, are found in moldy foods and their presence indicates a consequence of poor storage of susceptible grains. HCC is common in population exposed to aflatoxins. A prospective population based cohort study in Shanghai, China, provided the first set of compelling human data linking dietary aflatoxins exposure to the development of HCC, especially in HBV-infected patients. Singapore and Shanghai historically are high-risk areas for HCC, both of which have been experiencing steadily decreasing incidence rates over the past 2 decades. Due to economic improvements, food contaminated with aflatoxin seems to be decreased in these cities. This may cause a reduction of HCC in some Asian cities<sup>[20,21]</sup>.

## RISK FACTORS THAT INFLUENCE HEPATOCARCINOGENESIS IN SUSCEPTIBLE PERSONS

Studies have suggested that excessive alcohol intake and tobacco inhalation may be related to HCC development, especially in people with risk factors. However, it is difficult to assess the real impact of these factors in the pathogenesis of HCC because most of the people of Asian countries and also other countries use these substances. Diabetes and obesity have also been shown as risk factors for HCC. In fact, HCC mainly develops in patients with chronic liver diseases. Lots of proinflammatory cytokines are detected in patients with diabetes and obesity. These pathological processes also contribute to inflammatory hepatic mucosal milieu and may thus contribute to HCC<sup>[4]</sup>.

In addition, oral contraceptives and arsenic have been implicated in the pathogenesis of HCC. Many people of Asian countries, especially the poor people of these countries consume arsenic-contaminated water. However, more studies will be required to assess the impact of these factors in HCC development.

## SUMMARY

Asia, the largest continent of the world, harbors the major bulk of global HCC patients. The continent is highly heterogeneous in regard to population size, racial distribution, ethnic backgrounds, culture and social behaviors, levels of education, health care delivery systems,

and economic conditions. In one hand, Asia comprises regions and countries like Taiwan, Hong Kong and Singapore. These are comparatively smaller in size and endowed with stable economy and highly advanced health care delivery system. Epidemiology of HCC has been methodologically studied in these countries for more than 3 decades. Japan, one of the richest countries of the world, harbors considerable numbers of HCC patients. The patients with HCC and with pre-HCC statuses are diagnosed methodologically and different advanced therapeutic approaches are applied to these patients. In addition, HBV and HCV-infected patients are periodically followed up and early diagnosis of HCC (<2 cm in diameter) is a common feature in Japan. Some Asian countries have moderate levels of health care delivery system. On the other hand, China that harbors more than 50% of global HCC patients have a heterogeneous health care delivery system that differs considerably among different regions and cities of China. On the other side, countries like India, Bangladesh, and Pakistan (with about 1.5 billion people) do not have efficient public health delivery system or national health insurance support. Also, the people of these countries are economically poor.

Under these realities, we have compiled this review that has shown that the rate of incidence of HCC is extremely high in China, Taiwan, Hong Kong, Korea and Thailand (more than 30 per 100,000 men). It is low in India (less than 3-4 per 100,000 men). Data about HCC incidence and prevalence could not be provided from many Asian countries due to lack of publications. Thus, the real challenge is to accumulate data about incidence and prevalence of HCC from all countries of Asia with international support.

HBV and HCV are two main etiological factors related to HCC in Asia. However, HBV seems to be the main etiological factor of HCC in Asian country. The prevalence of HCV infection has been increasing in some Asian countries, such as Pakistan. The influence of HCV on hepatocarcinogenesis in Pakistan should be studied in details. In addition, other risk factors of HCC such as obesity and diabetes mellitus are notable. The people of Asia have been suffering from life-style-related diseases. HIV infection is also increasing in Asian country. HCC development in HIV and hepatitis virus coinfection patients should be studied in details.

Studies about epidemiology and risk factors of HCC would provide proper insights for early diagnosis and management of these patients. Although several aspects of HCC patients in Asia are unknown, some critical points about these patients have become known. The major etiological factors are HBV and HCV. Screening of different subjects for HBV and HCV would allow diagnosis of more precancerous patients in Asian countries. Management of these patients would reduce HCC incidence and prevalence in Asia.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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