

## Epidemiology of hepatocellular carcinoma and its viral risk factors

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**Key words :** incidence, geographical distribution, time trends, effects of migration, sex distribution, age distribution, hepatitis B virus, hepatitis C virus.

### Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant tumour of the liver and is considered to be one of the major malignant diseases in the world today. It is the most prevalent tumour, or among the most prevalent tumours, in many of the most populous geographical regions and accounts for 4.1% of all new cancer cases each year. Relative to other tumours, HCC ranks fifth in overall frequency, fourth in men and seventh in women. The annual mortality rate from the tumour is virtually the same as its annual incidence, attesting to the rapid course and grave prognosis of HCC.

### Geographical distribution

The frequency with which HCC occurs varies considerably in different parts of the world. High incidences of HCC are found in eastern and south-eastern Asia, in some Western Pacific islands, and throughout sub-Saharan Africa, with age-adjusted frequencies as high as 113 per 100,000 of the population per annum. Intermediate incidences are found in the remainder of the Far East, in Spain, northern Italy, Greece, Romania, Peru and in parts of France, Switzerland, Czechoslovakia, Poland, and Russia. HCC is uncommon or even rare, with annual incidences of less than 3 per 100,000 of the population, in the remaining countries.

Even in those countries with a high incidence of HCC, the tumour is not necessarily uniformly common throughout the country. This is seen, for example in the People's Republic of China, where the highest incidences of HCC are found in the north-eastern province of Jilin, along the south-eastern seaboard, and in the Guanxi Autonomous Region. In Mozambique, HCC occurs most commonly in the province of Inhambane.

### Time trends in incidence

Time trends in the occurrence of malignant tumours must be interpreted with reserve because they may be influenced by a number of variables. Nevertheless, there

has undoubtedly been a significant increase in the incidence of HCC in Japan over the past three decades, especially among men. This increase has been attributed to the increasing importance of hepatitis C virus (HCV) as a cause of the tumour in Japan as a result of the widespread administration of contaminated blood transfusions and use of unsterilized needles and syringes. Lesser increases have been recorded in Scandinavia, Australia, Canada, North America, Mexico, France, Italy, and parts of the United Kingdom. In Italy and North America the increase is thought to result from an increase in chronic HCV infections, and this may also be true of some of the other countries. Increasing alcohol abuse may also be incriminated, for example in Scandinavia. A declining incidence of HCC has been reported in Spain, India, Israel, and Latin America.

In the long-term, the complete eradication of hepatitis B virus (HBV) infection following the universal inclusion of HBV vaccine in the Expanded Program of Immunization should result, after an appropriate interval, in the disappearance of HBV-related HCC. This outcome will take many years to be realised, but in the meantime there is cause for optimism. In Taiwan, where universal immunization of infants against HBV was commenced in 1986, there has already been a ten-fold decrease in the HBV carrier rate in immunized children and a recent analysis shows a 50% reduction in the incidence and mortality rate from HCC in these children. The development of a vaccine against HCV and the global implementation of immunization against this virus will further greatly decrease the global incidence of HCC. This prospect is more distant, however, because testing of HCV vaccine is not expected to begin for at least another 10 years.

### Effects of migration

Migrants from countries with a low incidence of HCC to those with a high incidence generally retain the low incidence of the tumour of their country of origin. These migrants almost always preserve their original behav-

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Presented at the International Symposium on Viral Hepatitis beyond the Millennium Session of December 9, 2000.

rial patterns and they usually enjoy a higher standard of living than do the natives. Exceptions to this general rule are Indians who have settled in Hong Kong or Singapore who acquire in time incidence rates similar to the native population and appreciably higher than those in their home country.

Migrants from developing countries with a high incidence of HCC to industrialized countries with a low or intermediate incidence of the tumour initially retain a high incidence of HCC. In black African immigrants, in whom chronic HBV infection is the major causal association of the tumour and in whom the infection is predominantly acquired in early childhood by the horizontal route, the initial high incidence of HCC declines rapidly with successive generations in the new environment. In contrast, in ethnic Chinese immigrants, in whom chronic HBV infection is also the major risk factor but in whom the infection is mainly acquired by the perinatal route, the initial high incidence of both the infection and the tumour declines far more gradually during successive generations in the new country.

### Sex distribution

HCC is generally more common in males than in females, with an global ratio of 2.1 :1.0. However, male predominance is more striking in populations with a high incidence of the tumour (mean ratio 3.7 :1.0, range 2.1 :1.0-5.7 :1.0) than in those with a low or intermediate incidence (mean ratio 2.4 :1.0, range 1.0 :1.0-5.0 :1.0). In populations in which HCC is common male predominance is generally more striking in the younger age groups, whereas in populations in which the tumour is uncommon the opposite is true. In the latter populations, the tumour may have an equal sex distribution in young patients. This phenomenon may be attributed in part to the occurrence of the fibrolamellar variant of HCC, which characteristically effects young people and has an equal sex distribution, and the more widespread use of contraceptive steroids, in these populations.

### Age distribution

In almost all populations the incidence of HCC increases progressively with advancing age, although there may be a levelling off or even a decline in incidence in the oldest age groups. The mean age at the time of diagnosis in patients in countries with a low or intermediate incidence of HCC ranges from the late fifties to the mid-sixties. In contrast, in sub-Saharan Africa and some parts of the People's Republic of China the patients are often considerably younger. This is seen to best effect in Mozambique, where 50% of the patients are less than 30 years of age and their mean age is 33 years. In Qidong county and parts of the Guanxi Autonomous Region in the People's Republic of China the mean age of the patients is 40 years.

## Epidemiology of viral risk factors for hepatocellular carcinoma

Of the five currently recognised hepatitis viruses only HBV and HCV are incriminated as risk factors for HCC. Hepatitis A and E virus infections do not cause any chronic sequelae. Although hepatitis D virus infection occurs in association with HBV infection, there is no unequivocal evidence that it increases the carcinogenic potential of HBV, perhaps because patients co-infected with the two viruses do not live long enough for malignant transformation to occur. Two recently recognised viruses, GB-C virus and TT virus, have not been proved to be hepatotropic, to replicate in the liver, or to cause liver disease, and there is no convincing evidence that have oncogenic potential.

### *Hepatitis B virus*

HBV was one of the first viruses to be implicated as a cause of human tumours and it is now believed to be, with tobacco, the most important environmental carcinogen to which humans are exposed. There are some 360 million carriers of HBV in the world today and approximately one-quarter of these will die from HCC. Chronic HBV infection is responsible for approximately 80% of the HCC that occurs with such a high incidence in ethnic Chinese and black African populations. HBV carrier rates in these populations may be as high as 15%, and the infection is predominantly acquired early in childhood, mainly as a result either of perinatal transmission from HBV e antigen-positive carrier mothers or of horizontal spread from recently infected and hence highly infectious young siblings or playmates. Approximately 80% of infections acquired at this early stage of life become chronic, and it is these early-onset carriers that face a lifetime relative risk for the development of HCC of over 100.

### *Hepatitis C virus*

Although HCV has been recognised for a few years only, the evidence for its oncogenic potential is almost as compelling as that for HBV. There are estimated to be 170 million individuals in the world today that are persistently infected with HCV and they too are at high risk of tumour formation. Annual rates for HCC development in these people may be as high as 8.9%. Those with cirrhosis are about four times more susceptible to malignant transformation as those with chronic hepatitis. In Japan, which has a high incidence of HCC, and Italy and Spain, which have intermediate incidences, HCV accounts for as much as 83% of HCCs. In other industrialized countries with an intermediate or low incidence of the tumour, HCV is playing an increasingly important role in the aetiology of HCC, often in association with alcohol abuse. In ethnic Chinese and black African populations in which HBV is the predominant risk factor, HCV plays a secondary causative role.

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