

Chapter 1

The Epidemiology of Hepatocellular Carcinoma



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Key Learning Points

1. Hepatocellular carcinoma (HCC), the most common form of primary liver cancer, is predominantly a male disease, associated with increasing age and many types of chronic liver disease.
2. It is most prevalent in China and the Far East, Japan and sub-Saharan Africa.
3. This geographic variation is accounted for by the distribution of aetiological factors which include chronic hepatitis B virus infection (HBV), chronic hepatitis C virus (HCV) infection, alcoholic cirrhosis and obesity/metabolic syndrome—related to non-alcoholic fatty liver disease.
4. Vaccination against HBV and antiviral therapy for HCV will decrease the incidence of HCC in many populations and change the epidemiology.
5. In the West mortality from HCC is rising mainly due to fatty liver disease, consequent upon the increasing prevalence of obesity.

Areas of Controversy and Uncertainty

1. The long-term impact of obesity on the incidence of hepatocellular carcinoma in the West. The relationship between obesity-related HCC and cirrhosis is a major area of uncertainty.

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2. The long-term impact of antiviral treatment on the incidence of HCC both in the West (specifically hepatitis C) and the East (specifically hepatitis B).
3. The risk of HCC development after clearance of the hepatitis C virus by the action of direct-acting antiviral agents and the optimal strategy for surveillance amongst those who clear the virus.

Introduction and Magnitude of the Problem

In an increasingly globalised world, understanding the epidemiology of HCC has important implications for the clinical management of HCC.

Worldwide, primary liver cancer or hepatocellular carcinoma (HCC) is the sixth most commonly occurring cancer and the second largest contributor to cancer-related mortality. Due to the aggressive nature of the tumour, the associated underlying liver disease, late presentation and the limited range of therapeutic options, incidence and mortality rates are very close. It is the commonest of the two main primary malignancies of the liver, the other major hepatic cancer being cholangiocarcinoma (CC) which accounts for between 5 and 10% of malignant primary liver tumours, although it is increasingly recognised that there can be overlap of the features of HCC and CC.

Demography

The incidence of HCC can be broadly classified according to geographical region as high-, medium- and low-incidence areas (Fig. 1.1). The high-incidence areas include China, Southeast Asia, Japan and sub-Saharan Africa, with an incidence rate of over 20/100,000. Intermediate areas (incidence 5–20/100,000) include Southern Europe, and low-incidence areas include the USA, Scandinavia and Northern Europe [1].

In most areas of the world, the disease occurs predominantly in men over the age of 60 years, but the age at onset is significantly lower in sub-Saharan Africa. The reason for the male preponderance is unknown, but the regional variation in incidence is clearly accounted for by the geographic distribution of the major risk factors.

Risk Factors

The most striking feature of the epidemiology of HCC is the wide geographical variation in incidence (Fig. 1.2) which largely reflects the global distribution of the major aetiological factors, as described below. However, the relative importance and thereby the geographical distribution are changing rapidly with the development of new therapies and public health initiatives.

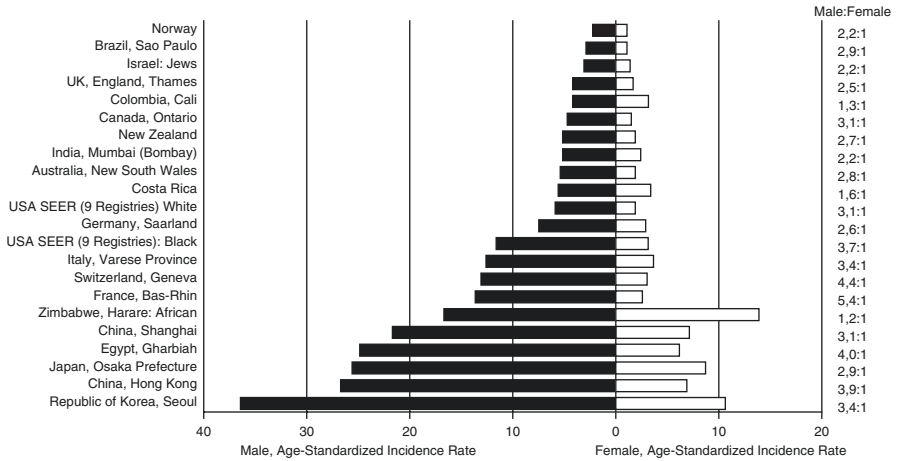


Fig. 1.1 Age-adjusted incidences per 100,000 of liver cancer among men and women by region, 2003–2007. Age-adjusted to world standard (Available at <http://ci5.iarc.fr>)

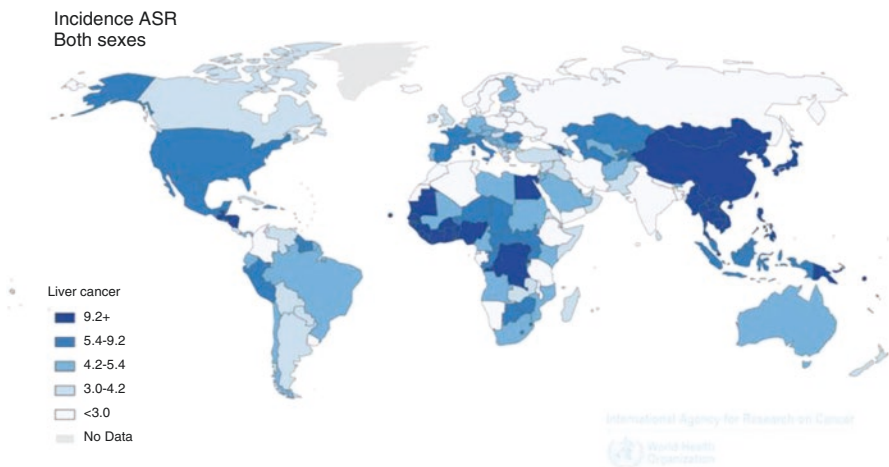
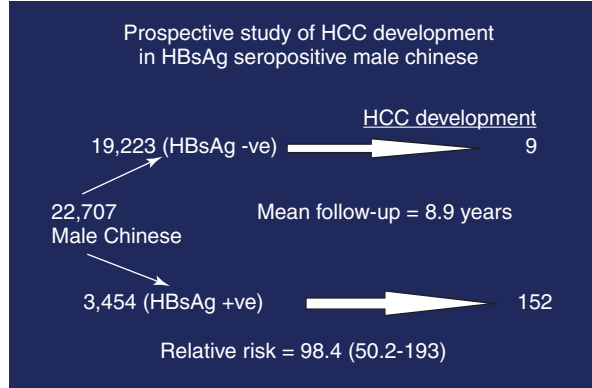


Fig. 1.2 Geographic variation in liver cancer incidence (age-standardised) (Available from <http://globocan.iarc.fr>)

The Hepatitis B Virus

The classic study of the natural history of hepatitis B virus infection and its relationship with HCC was reported from Taiwan [2]. This study followed up 22,707 HBV carriers for 5 years (Fig. 1.3). The annual incidence rate among those developing HCC was about 100-fold risk of the control group, thereby conclusively demonstrating the aetiological relevance of the HBV virus to HCC development and laying the basis for mass prevention strategies.

Fig. 1.3 The Taiwan prospective study of HCC development in patients with chronic hepatitis B virus infection. From Beasley et al. [2]



The natural history and global distribution of chronic HBV infection are now well documented [3, 4]. HBV is transmitted from mother to newborn at, or around, the time of birth, and this observation, combined with the Beasley study, led to a programme of mass vaccination against HBV, initiated in Taiwan in 1984 and supplemented by HBIG (hepatitis B immunoglobulin). The vaccine is extremely safe and effective, but, for a variety of reasons, vaccine-induced immunity coverage is much less than 100%, even in countries where universal vaccination is advocated.

The subsequent progress of this initiative in Taiwan and other countries and regions has been well documented. The latest analysis clearly shows that the prevalence of HB_sAg seropositivity has fallen from around 10% to less than 2% among those born in the immunisation period, and there has been a dramatic decrease in the incidence of HCC although the full impact will not be realised for another 30 years, when the first vaccines reach their sixth decade [5]. In the West most HBV-related disease arises from intravenous drug abuse or is sexually transmitted. First-generation immigrant populations coming from high HBV incidence areas to the West also tend to be over-represented with respect to HCC.

Obviously immunisation will have no impact on those who are already HBV carriers, but current evidence suggests that antiviral therapy significantly reduces the incidence of HCC [6]. Nonetheless, and in marked contradistinction to the current situation in HCV, sustained virus control is difficult and expensive to achieve. Thus, the combination of immunisation and antiviral therapy is likely to alter the epidemiology of HCC dramatically over the coming decades, although the gap between what is medically possible and what is, in financial and political terms, deliverable remains wide.

All therapeutic interventions are small when compared to the impact of immunisation and other methods by which the hepatitis B virus can be eliminated or controlled.

Hepatitis C Virus and the Changing Epidemiology of HCC in the West

Initially classified as ‘non-A/non-B’ virus infection, HCV was identified in 1989, and although such rigorous epidemiological studies as described above for HBV were never undertaken, case-control studies left little doubt that the virus was strongly associated with HCC. In the West HCV was acquired mainly through intravenous substance abuse or by blood transfusion. In Japan there was a major epidemic which led to around 35,000 cases developing per year for the 50 years following the end of the Second World War, after which there had been extensive use of infected blood [7].

In the last few years, effective therapy for HCV has been developed to the extent that complete “cure” can be obtained within a few months of treatment, and in several countries, the complete eradication of HCV is envisaged. After achievement of sustained virological remission, the risk of HCC decreases dramatically, further supporting the aetiological role of the virus [8].

Alcohol

Alcoholic cirrhosis has long been considered a major risk factor for HCC accounting for a high proportion of cases in the West. However, it now seems likely that, whilst there is a significant increase in HCC among patients with a history of high alcohol intake, some of this is related to associated factors such as coexisting HBV and HCV infection, which were not recognised in earlier studies, and the increasing recognition that alcohol likely acts in a synergistic manner to encourage HCC in patients with other underlying causes [9, 10, 11–13].

Aflatoxin

Aflatoxin B1 is a potent carcinogen derived from the mould *Aspergillus flavus* (hence aflatoxin) that grows in humid conditions on stored grain and ground nuts. It is a very likely contributor to the high incidence of HCC in sub-Saharan Africa and coastal regions of Southeast Asia and China [14]. Exposure to AFB1 is associated with a specific DNA mutation in the p53 gene (a 249ser mutation) [15]. It has a synergistic association with HBV in increasing the risk of HCC. The population attributable risk of AFB1 in sub-Saharan Africa is between 10 and 20%.

In general, in areas of the world where AFB1 exposure is high, chronic HBV infection is highly prevalent. As little can be done to alter the HBV chronic infection

state, once established, eradicating AFB1 from the food supply is an important strategy to reduce HCC incidence. In parts of Africa and China where AFB1 eradication programmes have been implemented, significant reductions in HCC rates have been documented [16].

Other Rarer Forms of Chronic Liver Disease

HCC is a recognised complication of all types of cirrhosis and chronic liver disease including primary biliary cirrhosis, Wilson's disease and alpha-1 antitrypsin deficiency. HCC is a major cause of mortality in haemochromatosis but can be prevented by venesection therapy if instituted before cirrhosis develops. This justifies careful screening of families with a history of haemochromatosis so as to achieve early diagnosis and to initiate appropriate therapy at a presymptomatic, pre-cirrhotic stage.

Obesity/Metabolic Syndrome and NAFLD

There remain between 10 and 30% of cases in which no aetiological factors can be identified. Such cases were previously referred to as “cryptogenic”. Over the past two decades, however, it has become apparent that in such cases there is a high incidence of obesity [17, 18] and diabetes. The associated liver disease is called non-alcoholic fatty liver disease (NAFLD) [19]. In a subgroup of this population, there is a fat-related inflammatory response that is likely to progress to serious liver disease—so-called non-alcoholic steatohepatitis (NASH). However, HCC may arise in NAFLD, without any associated chronic liver disease or cirrhosis [20]. Tobacco consumption probably imposes a risk, comparable to that of obesity.

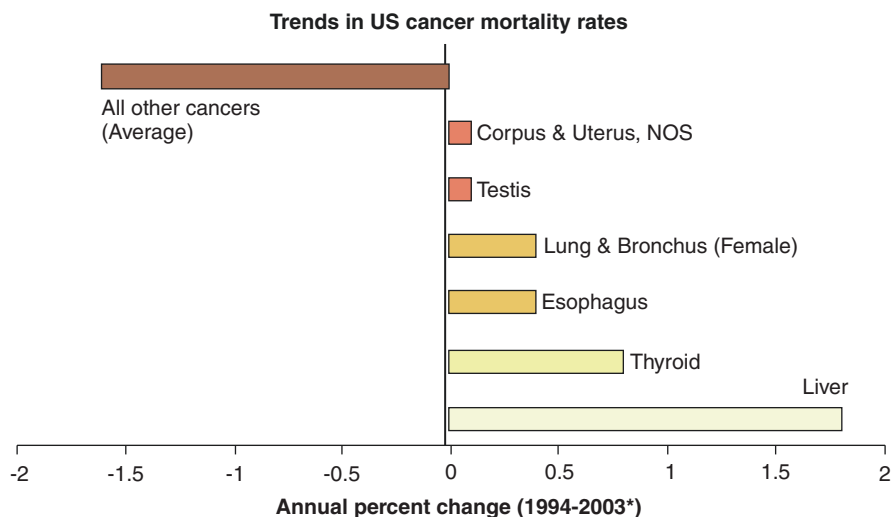
Implications of Epidemiology for Prevention

Epidemiological investigations have identified the relevant risk factors such that the major ones act as a target for preventative strategies. There is another and quite distinct epidemiological approach that may result in further preventative measures, and this relates to the analysis of large datasets that have been collected for purposes other than direct investigation of the prevention of HCC. This approach falls under the heading of “repurposing” of drugs. Thus, large-scale datasets reporting the incidence of HCCs in populations treated with various agents for purposes unrelated to their potential anticancer are an area of extensive research. Aspirin and non-steroidal anti-inflammatory drugs have well-documented activity in reducing the incidence of most gastrointestinal cancers, including HCC [21], and the

evidence that statins have an equivalent effect is now substantial [22]. Antidiabetic drugs such as metformin have also been proposed, but the most recent meta-analyses are less convincing [23].

The Changing Face of HCC Epidemiology

As suggested throughout this chapter, HCC is a preventable disease, and, over the last decade, evidence has emerged that preventative strategies are starting to have an impact on incidence. Chronic HBV infection rates, as a result of immunisation and antiviral treatment, are falling with resulting stabilisation or decrease in HCC rates across China and the Far East. In Japan and Southern Europe, the peak incidence of the post-war HCV epidemic is passing, and the later drug abuse-related epidemic in the West may be eradicated by direct-acting antiviral agents. Against these encouraging trends, it is sobering to note that HCC is now the most rapidly rising cause of cancer-related mortality at a time when the incidence of other cancers is falling by around 1–2% per annum (Fig. 1.4). The reason is clear. The major current aetiological factors are all related to the great addictions of Western societies, namely, alcohol, tobacco and, particularly, food. There is little prospect that this situation will change over the foreseeable future.



*Represents the annual percent change over the time interval
 National Cancer Institute Website.
 Available at: http://seer.cancer.gov/csr/1975_2003/sections.html. Accessed September 21, 2006.

Fig. 1.4 Change in cancer mortality rate in the USA. Note that “liver” is the most rapidly rising cause of cancer-related mortality at a time when the mortality from most cancers is decreasing

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