Liver Cancers

From Mechanisms to Management

Tim Cross
Daniel H. Palmer
Editors

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Dedicated to the Memory of Dr. CG 'Harry' Antoniades (1974–2018).

Foreword

There has been stunning progress in treating viral hepatitis over the last decade. Despite that, the number of patients across the world with liver disease is increasing annually, and in the United Kingdom, this has had a disproportionate and adverse effect on younger patients, such that chronic liver disease in England is now the second and fourth most common cause of years lost in women and men, respectively. Almost all of the increase over the past two decades can be attributed directly to the epidemic of obesity in first-world countries, although in many parts of the world alcohol continues to play an important aetiological role. There is also a strong, disproportionate effect of socio-economic deprivation on the prevalence of liver disease.

So it was inevitable that the numbers of patients presenting with hepatocellular carcinoma (HCC) would rise in parallel with those developing chronic liver disease. The increased numbers presenting to liver specialists with primary liver cancer have been almost overwhelming, while the change in the demographics underlying these tumours has been striking. No more of the young male immigrant born in the African or Asian continents with Hepatitis B virus acquired perinatally driving cirrhosis as we were taught. Now it is the elderly, slightly overweight, male diabetic in the clinic who has never consumed alcohol to excess and who may not even have cirrhosis.

These remarkable lifestyle-driven increases in cases presenting with hepatocellular carcinoma have made clinicians and more recently basic scientists look more closely at every aspect of the disease from the molecular pathways that precede disease or modify the clinical course, through screening (still contentious) or early detection to curative or palliative treatment and end-of-life care.

The proportion of patients that can be offered curative therapy is small but increasing. Recent data suggest that this proportion is greater in those centres with greater experience and turnover. The options for curative therapy are limited and by no means novel but earlier diagnosis, better case selection, and more experience mean that these older approaches (surgery or liver transplantation or both) are being used more appropriately with improved outcomes. The many options for therapy intended to halt or slow the disease for patients with more advanced disease have

also been used with increasing frequency and efficacy. But it is not clear which of these approaches is best for which patients nor is it clear if these approaches have additive benefit. Most centres report better survival now with non-curative therapy than a decade ago, reflecting greater availability of these approaches and again better selection based on growing experience. International meetings and the literature now report on potential pathways for novel approaches to primary liver cancer.

Those who deal with primary liver cancers will often be the same clinicians that are faced with benign tumours of the liver or with secondary malignancies.

HCC-UK was established 4 years ago to bring all of those interested in liver cancer. The faculty for this volume: *Liver Cancers: From Mechanisms to Management* are integral to HCC-UK and represent the best of UK specialist care in the field, so that every aspect of our current knowledge and clinical practice is covered.

Graeme Alexander
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Preface

There has been a well-documented rise in the prevalence of advanced liver disease over the last few decades. The culmination of this has been an increase in patients with cirrhosis and its complications. One of the most feared of these was hepatocellular carcinoma (HCC). At one time, this diagnosis heralded a universally grim prognosis, and the treatment options, particularly cure, in the absence of surgical resection, was rarely achieved. But the development of new technologies and the availabilities of new treatments, in particular, liver transplantation, have revolutionized treatment for these patients. Yet, the majority of patients still remain undiagnosed until the disease is at an incurable stage. For these patients, provided that their liver function and performance status permits, there are treatments that can extend life, and novel treatments appear tantalizingly close, in particular immune therapies. In addition, forms of targeted radiotherapies are appearing on the horizon (e.g., stereotactic body radiotherapy – SBRT) and could provide further treatment options for clinicians. So as the horizons for HCC are broadening so are treatment options for cholangiocarcinoma and other forms of malignancy that involve the liver. The contribution to be made by different specialities in a multidisciplinary team involving surgery, transplantation surgery, hepatology, medical oncology, clinical oncology, and palliative care is vital to ensure the best possible outcome for these patients and cannot be overemphasized.

This book is aimed at the hospital specialist in training in the medical or surgical specialities, nurse specialists, and consultants and researchers who just want an approachable and usable management guide. The chapters have been written by experts in their fields and focuses primarily on hepatocellular carcinoma whilst having comprehensive sections on cholangiocarcinoma, neuroendocrine tumours, and colorectal cancer liver metastases. Many authors are members of HCC-UK which is a UK group of clinicians and researchers with an interest in HCC who wish to improve the care and outcome for these patients. Professor Graeme Alexander must be thanked for having the vision to set up this group, and the intention is to work together to deliver management changing high-impact publications in the future. There was some constraint on what could be included and so detailed chapters on endoscopic therapies and radiotherapy will have to wait for further editions.

I am grateful to all the contributors for the time and effort they put into producing their chapters and also to the production team at Springer in particular Maha and Evgenia. Finally, this book is dedicated to the memory of Dr. CG 'Harry' Antoniades who died suddenly this year. He was reader in medicine at Imperial College London, St Mary's Hospital. He was an exceptional clinician and researcher, as well as a great friend and colleague. He will be deeply missed by all those who knew him. He leaves behind his wife Rebecca (herself an oncologist) and two wonderful children Amelie and Theo. Our thoughts and prayers are with them, and this book is a small token to show the respect and esteem in which he was held.

Liverpool, UK Tim Cross
April, 2018

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Part I
Hepatocellular Carcinoma

Chapter 1
The Epidemiology of Hepatocellular Carcinoma

Philip Johnson

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.

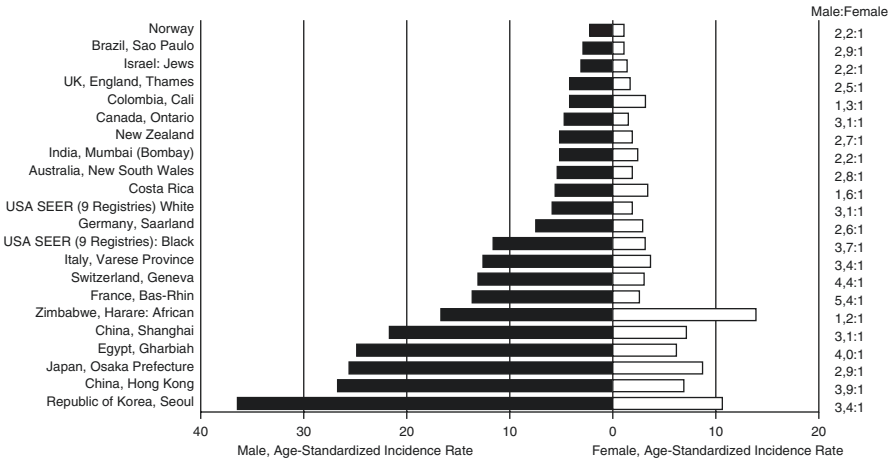


Fig. 1.1 Age-adjusted incidences per 100,000 of liver cancer among men and women by region, 2003–2007. Age-adjusted to world standard (Available at http://ci5.iarc.fr)

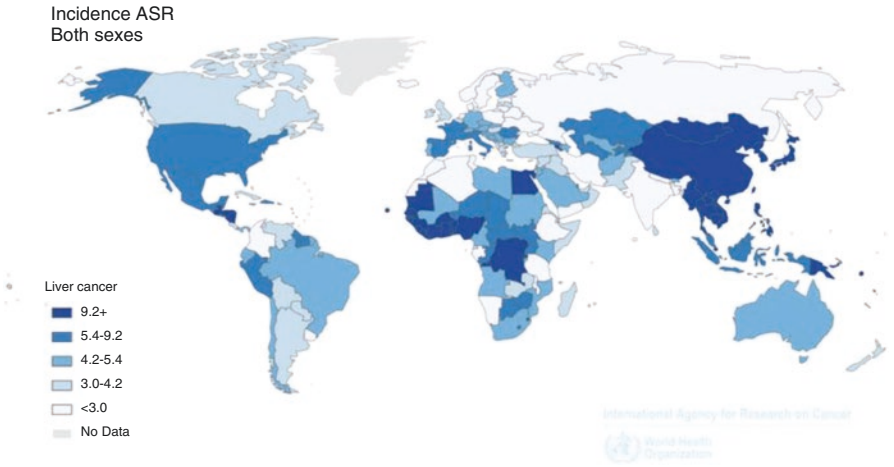


Fig. 1.2 Geographic variation in liver cancer incidence (age-standardised) (Available from http://globocan.iarc.fr)

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.

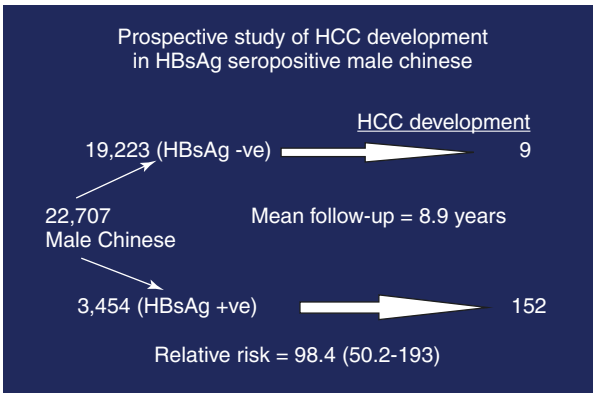


Fig. 1.3 The Taiwan prospective study of HCC development in patients with chronic hepatitis B virus infection. From Beasley et al. [2]

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 though 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.

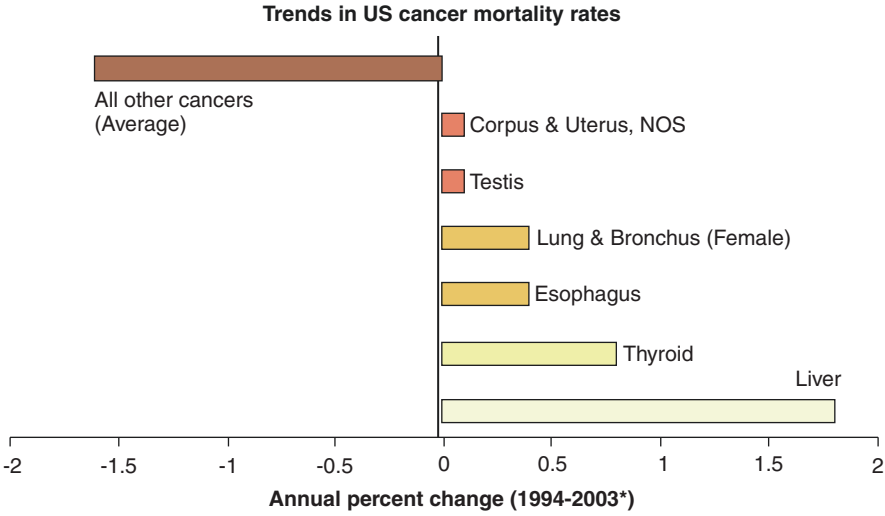
Implications of Epidemiology for Prevention

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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Chapter 2
Surveillance for Hepatocellular Carcinoma

Eleanor J. Taylor and Ian A. Rowe

Key Learning Points

1. Surveillance for the development of HCC in patients at risk, particularly those with cirrhosis, is logical with the aim to reduce overall mortality.
2. Six-monthly ultrasound scans (with or without AFP testing) is the current standard of care defined by professional societies.
3. The overall benefits of surveillance are small in populations of patients with cirrhosis, accounting for a reduction in overall mortality over 5 years of surveillance of approximately 1–2%.
4. The effectiveness of surveillance is reduced by eligible patients not entering surveillance programmes and by patients ineligible for curative treatments entering such programmes.
5. There are harms associated with surveillance that need to be communicated to the patient, together with the benefits that might be achieved.

Areas of Controversy and Uncertainty

1. The magnitude of the benefit of surveillance in patients with cirrhosis is uncertain and is subject to confounding.

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2. Models that predict benefits of surveillance are based on confounded retrospective estimates.
3. The significance of the harms of surveillance is uncertain.
4. There is a rationale for developing a randomised controlled trial of surveillance to address this uncertainty, but this is not be supported by the expert consensus.

The majority of hepatocellular carcinoma (HCC) globally is associated with chronic viral hepatitis, and it occurs most frequently in individuals with cirrhosis [1]. In the developed world, HCC associated with cirrhosis is the predominant form of the disease, accounting for at least 80% of cases [2]. Outcomes after diagnosis of HCC remain poor, particularly when HCC is diagnosed at late stage. It is for these reasons that surveillance for HCC, using regular 6-monthly ultrasound scans, is proposed as a method to improve outcomes for patients with cirrhosis. The aim of that surveillance is to improve overall survival of patients with cirrhosis.

In this chapter we will discuss the rationale for surveillance and the evidence that supports it, rates and barriers to the uptake of surveillance at the population level, and the expected outcomes of surveillance given current diagnostic and treatment methods.

The Rationale for Surveillance

Patients with chronic liver diseases, including viral hepatitis, alcohol-related liver disease and non-alcoholic fatty liver disease, as well as those with rarer metabolic diseases such as genetic haemochromatosis and autoimmune liver diseases, are at risk of developing cirrhosis. Treatment of the underlying cause of liver disease will usually prevent progression to cirrhosis and abrogate the risk of later developing complications of liver disease, including HCC. Those individuals who are not diagnosed with liver disease or those where treatment is for whatever reason unavailable or ineffective are at risk of disease progression through accumulation of liver fibrosis to cirrhosis. Once cirrhosis has developed, there is a risk of developing liver failure and also a risk of developing HCC. Since HCC is a major cause of mortality in this group, it is logical to consider surveillance to diagnose HCC early so that potentially curative treatments can be used to improve the overall survival of both the patient and the population with cirrhosis.

Typically surveillance is done using 6-monthly ultrasound scans and that is the method that is endorsed by the European Association for the Study of the Liver (EASL) as well as the United Kingdom National Institute for Health and Care Excellence (NICE) [3, 4]. There are however proponents for the addition of blood-based biomarkers of HCC development, most notably alpha-fetoprotein, to ultrasound to maximise early diagnosis. The additional benefits of AFP are frequently

discussed and it is listed as optional in some guidelines [5]. Whilst there is a small increase in the sensitivity of surveillance in general for early HCC by incorporating AFP, this comes at the cost of increasing the numbers of false-positive surveillance assessments [6]. This will also inevitably increase the rates of surveillance-associated harms that are discussed later.

The Target Population

Patients at risk of developing HCC are characterised as those with cirrhosis (from any cause) as well as those with advanced fibrosis from hepatitis C virus infection and those with hepatitis B virus (HBV) infection and associated risk factors including age, family history of HCC and active hepatitis. These groups are selected, largely on the basis of cost-effectiveness studies, as those with the most to gain from early diagnosis of HCC where the incidence is sufficient to warrant that intervention [3]. It is apparent that the annual incidence of HCC in each of the groups is different, ranging from 3% in those with hepatitis C cirrhosis to approximately 0.2% for those with HBV infection and associated risk factors. Given the low incidence in the non-cirrhotic HBV group, a number of investigators have tried to identify scores that will allow patients at high risk of HCC to be identified so that the whole group need not be entered into surveillance [7]. This is an attractive approach, but unless these scores can reliably identify groups with a *zero* risk of HCC development, it is challenging to implement given strong recommendations from the major professional associations [3, 5] for ongoing surveillance in this group.

Evidence of the Benefits of Surveillance

There have been two randomised controlled trials of surveillance done in China. These studies are not applicable to current practice, either because they did not use current methods of surveillance (i.e., 6-monthly ultrasound examinations) or because they included patients without cirrhosis. There are also a number of methodological concerns regarding these studies [8]. Consequently, they cannot be used to justify surveillance in Western patients with cirrhosis today.

There are a large number of retrospective studies from Europe, the United States and the Far East that suggest benefits of surveillance. These have been systematically reviewed by two groups, one of whom pooled the data that were extracted in a meta-analysis. The conclusions of the two reviews were similar in that they each concluded that it was probable that surveillance allows earlier diagnosis of HCC but diverged on the impact on mortality. One review concluded that the quality of the published evidence was very low, and there was uncertainty as to whether surveillance improved survival in patients with cirrhosis [9]. The second review concluded that surveillance improved survival in patients with cirrhosis based on the outcomes

of their meta-analysis [10], and this study has been used to support subsequent recommendations for surveillance in the American Association for the Study of Liver Diseases guideline for patients with HCC [5].

To understand the apparently contradictory findings of these reviews, it is critical to explore the evidence base further. The studies included in these reviews were all case control studies where the outcomes of patients with HCC were stratified by whether they had received surveillance or not. This design can therefore only assess whether surveillance improves outcomes in patients who have developed HCC and not those who have cirrhosis as a whole. Furthermore this design is subject to overestimation of the impact of surveillance since there will be confounding by a number of factors. These include confounding by the indication for surveillance where patients who are better suited to treatment for HCC are selected for surveillance, apparently improved survival as a consequence of lead time bias, as well as by length bias, each of which are well recognised in studies of other screening and surveillance programmes (Fig. 2.1). These factors are difficult to adjust for, and when adjustments for lead time bias in particular are made, there is a substantial reduction in the magnitude of the benefit that is apparent in those studies where this is done. Several studies have been published recently that aim to quantify the benefits of surveillance using a case control design with adjustments for lead time bias, and in those the absolute risk reduction in mortality at 3–5 years after the diagnosis of HCC is in the region of 10% [11, 12]. That is less than half of that reported in the meta-analysis and still subject to residual confounding from other sources.

It remains unclear from observational data therefore that surveillance using ultrasound will improve survival in patients with cirrhosis. Supportive evidence comes from both cost-effectiveness analyses and modelling studies of surveillance.

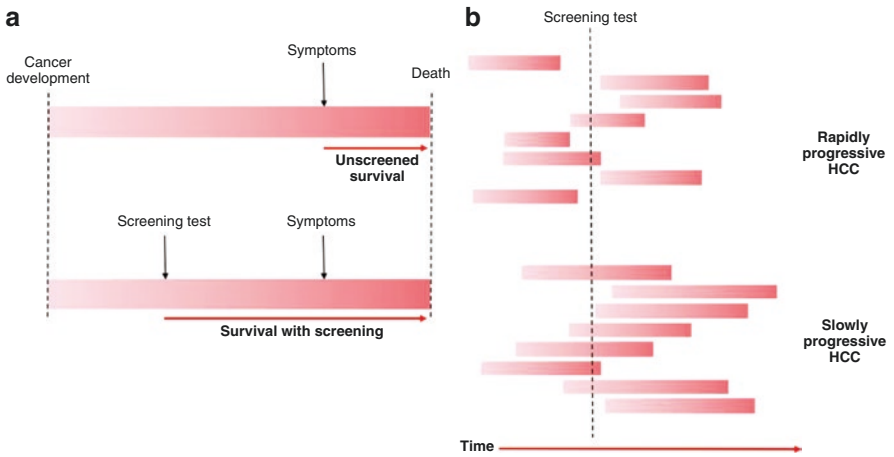

Fig. 2.1 Lead time and length bias in cancer screening. Lead time bias (**a**) defines an apparent improvement in survival as a consequence of early diagnosis of cancer due to screening or surveillance in the case of HCC although there is no change in the natural history of that cancer through treatment. Length bias (**b**) identifies the likelihood that more indolent cancers are diagnosed by screening or surveillance before symptoms present. Each of these biases serves to overestimate the efficacy of screening or surveillance interventions

These use published data to provide estimates of the likelihood of events in populations with cirrhosis and draw from the published literature estimates of treatment efficacy and are therefore subject to the same biases as the original observational studies.

Uptake of Surveillance at the Population Level

Despite low-quality evidence, surveillance is strongly recommended by all professional associations that represent physicians caring for patients with cirrhosis. Other expert bodies, including the US National Cancer Institute, do not recommend surveillance, but it is expected that most physicians would follow guidance issued by their professional societies. However, international studies, particularly from the United States and from the United Kingdom, suggest that only a minority of patients with cirrhosis receive surveillance. In the best characterised population, including individuals with cirrhosis due to HCV infection, rates of routine surveillance were calculated to be 42% in the first year after diagnosis and declined thereafter to 12% for individuals with at least 2 years of follow-up [13].

In the United Kingdom, a questionnaire study identified important deficits in surveillance for patients with cirrhosis. Whilst the majority of respondents reported that there was a surveillance programme in their hospital, there was often no mechanism to routinely recall the patient for follow-up imaging, and patients were not reliably informed of the reasons that surveillance was suggested [14].

Barriers to Effective Surveillance

Clinical effectiveness of an intervention, such as surveillance for HCC, defines how well that intervention performs in the real world. Even for an intervention that is 100% efficacious, factors that limit its use mean that the clinical effectiveness is often much less than 100%. Where there are questions about the efficacy of surveillance when it is done, any factors that reduce its use or that impair its performance will inevitably further reduce its clinical effectiveness (Fig. 2.2). Barriers to patients entering surveillance, patients entering surveillance where there are contraindications to anticancer treatment such as advanced liver or non-liver co-morbidities, and

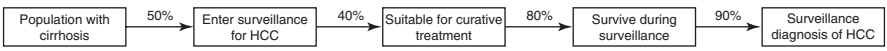

Fig. 2.2 Factors affecting the clinical effectiveness of surveillance for HCC. Multiple steps before a diagnosis of HCC in surveillance diminish the overall benefit of surveillance in the population. In this illustration estimated over 5 years, only 14% (=100×0.5×0.4×0.8×0.9) of the population with cirrhosis are eligible to benefit from surveillance. If 10% of those eligible to benefit from surveillance develop HCC and there is a 10% absolute risk reduction in mortality from a diagnosis of HCC in surveillance, then the anticipated survival benefit at the population level is 0.14% (=14×0.1×0.1)