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Brian I. Carr
Editor

Hepatocellular Carcinoma

Diagnosis and Treatment

Third Edition

Springer

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To my daughters, Ophira and Feridey
And to their sons, Rohan, Kunal and Oren

He used to say:
If I am not for myself, who will be for me?
And if I am only for myself, what am I?
And if not now, when?

—Hillel, Mishna Avot 1:14

Who is wise?
He who learns from every person.

—Ben Zoma, Mishna Avot 4:1

What we see changes what we know. What we know changes what we see.

—Jean Piaget

In questions of science, the authority of a thousand is not worth the humble reasoning of a single individual.

—Galileo Galilei

Preface to the Third Edition

In the interval between the second edition of this book in 2009 and this new, third edition, there have been immense advances in both the science and the clinical practice of hepatocellular carcinoma (HCC). The advances are already being built upon to enlarge our understanding of this complex and heterogeneous disease, which is increasing in some parts of the world and decreasing in others. As a result, the original chapters have been updated and more than a dozen new chapters were added, on the following topics: molecular profiling, molecular mechanisms in hepatocarcinogenesis, genomic phenotypes, miRNAs, gene signatures of risk factors, gut microbiota, microenvironment, tumor heterogeneity, circulating tumor cells, immune system and therapy, inflammation, obesity and NASH, staging systems, CT and bioenergetics. Many of the previous chapters have been completely rewritten, including those on local ablation, resection, transplantation, and the final summary chapter. The general scope of these advances is as follows:

1. The introduction into clinical practice of FDA-approved and effective drugs for HCV, with sustained virological responses obtainable for both HBV and HCV, together with high cure rates for HCV.
2. Initial clinical studies showing that the high tumor recurrence rates postresection can be reduced, not by anti-tumor therapy but, by treating underlying virus hepatitis. If confirmed, they will have major conceptual implications for our ideas about HCC therapy and antivirus therapy will be viewed as part of HCC therapy.
3. The underlying cirrhosis (non-HCC part of the liver) is increasingly being seen as not just a comorbid disease (although it is), but also as a source of prognostic information and determinant of HCC biology. Like items #1 and 2, it indicates that the microenvironment is a source of many HCC influences, including immunological, inflammatory, neovascular, cytokine and growth factor actions.
4. Systemic inflammation has become an important and independent prognosticator for many tumor types, including HCC and the simple 2-parameter Glasgow score and its variations are incorporated into clinical practice.
5. Molecular profiling is being used to identify HCC phenotypes, lineage subsets and hopefully, will support rational therapy selection (for example, Met-expressing tumors for Met inhibitor therapies). Furthermore, the increasing commercial availability of kits for purifying tumor cells or free tumor DNA in the blood circulation may provide a safe way of obtaining specific HCC information without the hazards of biopsy, as well as an easy and safe way to provide samples for molecular profiling at various phases of the HCC clinical course in the same patient.
6. Immune checkpoint inhibitors are taking center stage for therapy of many cancer types, with promising early results in HCC.
7. Extended criteria for transplanting larger HCCs and identification of prognostic subtypes are gaining traction.
8. ^{90}Yttrium microspheres regional therapy is being recognized as a safer alternative to TACE in the presence of portal vein invasion.

9. Several large phase III trials of new non-sorafenib (multi-)kinase inhibitors failed to meet their expected goals. However, many new targeted agents are currently being evaluated in clinical trials. Furthermore, trials are in progress that examine the combinations of either targeted therapies such as sorafenib with regional therapies (TACE or ^{90}Yttrium microspheres), or two or more therapies that target different pathways. In addition, ways of enhancing sorafenib effects or decreasing resistance to its actions are under investigation.
10. We are seeing the development of drugs against new, nongrowth signaling targets, including putative tumor stem cells, dendritic cells, tumor invasiveness proteins, growth-antagonizing microRNAs; the development of tumor vaccines and novel nuclides for internal radiation, such as ^{166}Holmium and ^{188}Rhenium, intensity modulated radiation and proton beam therapy.
11. There is a considerable increase in obesity-associated HCC and its different pathogenesis from virus-mediated HCC. This may supplant hepatitis as a cause of HCC in the Western world. The interplay of several factors in many HCC patients, such as HBV and alcohol, HBV and aflatoxin B_1 dietary exposure.
12. There has been a proliferation of proposed staging systems from several countries. Some systems are seemingly more applicable to patients in certain regions of the world than other systems.
13. The sorafenib phase III SHARP trial highlighted the discrepancy between tumor responses and patient survival, as shown by the minimal number of partial objective tumor responses (tumor size change) on the one hand and the finding of significant sorafenib survival benefits on the other. This has consequences for our thinking about the relevance of tumor size change in HCC (especially mediated by cytotoxic chemotherapy) and how we assess useful clinical endpoints for future HCC therapy trials. One result is a reconsideration of the value of 'stable disease' as a desirable endpoint in HCC management.
14. The pace of discovery is quickening, as is the interplay of the basic science and clinical applications. Perhaps the most profound changes have resulted from the availability of an effective vaccine against HBV or primary prevention (though not yet against HCV), and the new effective treatments for both HBV (non-curative) and HCV (curative). Thus, primary, secondary, and tertiary prevention are now available: primary prevention, by vaccination (HBV only); secondary prevention, by treatment of chronic carriers and decreasing the probability of developing cirrhosis and subsequent HCC; and tertiary prevention, by anti-hepatitis therapy resulting in the suppression or eradication of the hepatitis infection, with resultant decreases in postresection HCC recurrences.

Thus, the most significant recent translational advance has been in the area of hepatitis prevention (HBV) and treatment (HBV and HCV), with profound effects on the incidence and likely the biology of HCC caused by hepatitis B or C.

The book is divided into three parts: I, Causes, Biological and molecular basis; II, Diagnosis; III, Therapies. The final chapter provides an overview of current therapy.

November 2015 Brian I. Carr

Preface to the Second Edition

You are not obliged to complete the task,
Nor are you free to stop trying.

—Talmud, Avot

Hepatocellular carcinoma (HCC) used to be regarded as a rare disease. The increasing numbers of chronic HCV carriers in the USA and subsequent increased incidence of HCC seen in most large medical centers mean that it is no longer an uncommon disease for gastroenterologists or oncologists to encounter, and its incidence and epidemiology are changing (new chapter). This has been enhanced by the appreciation that obesity (NASH or NAFL)-associated cirrhosis is also a cause of HCC, as are many metabolic syndromes (new chapter), in addition to carcinogens in the environment (new chapter), hepatitis B (new chapter), and hepatitis C (new chapter). Associated with this has been a clearer understanding of the many mechanisms involved in carcinogenesis of the liver (new chapter). During the period when liver resection and systemic chemotherapy were the only real therapeutic modalities available, the outcomes were generally dismal, especially since most patients presented with advanced-stage tumors. Several recent factors seem to have changed this. They include the more frequent use of aggressive surveillance by ultrasound and CT scanning in patients who have chronic hepatitis or cirrhosis from any cause and thus are known to be at risk for subsequent development of HCC in order to detect tumors at an earlier and thus more treatable stage. Advances in CT scanning, particularly the introduction of multihead fast helical scans, mean that these vascular tumors can often be detected at an earlier stage or multiple lesions can now be appreciated, when only large single lesions were formally seen, so that unnecessary resections are not performed. Helical CTs have also largely replaced the more invasive CT arteriography. Furthermore, advances in MRI scanning (new chapter) have started to measure changes in tumor blood flow as a result of anti-angiogenic therapies (new chapter); so has dye-enhanced ultrasonography (new chapter). Liver transplantation has had a profound effect on the therapeutic landscape. There have always been two hopes for this modality, namely to eliminate cirrhosis as a limiting factor for surgical resection and also to extend the ability of the surgeon to remove ever-larger tumors confined to the liver. The organ shortage for patients with HCC who could be transplanted has been alleviated in part by two new factors. They are the MELD criteria, which give extra points to patients with small tumors, and the introduction of live donor transplants (new chapter), which obviate the need for long waits for a cadaveric donor. Regional chemotherapy and hepatic artery chemoembolization have been around for a long time and have been practiced mainly in the Far East and in Europe. There has not been a consensus on which drug or drug combinations are best or even whether embolization is important, and if so, what type and size of embolizing particle might be optimal. While there is still no consensus on these matters, it has recently become clear from two randomized controlled clinical trials that hepatic artery chemoembolization for unresectable, nonmetastatic HCC seems to bestow a survival advantage compared with no treatment. The high recurrence rates after resection have led numerous investigators to evaluate preresection and postresection chemotherapy in the hope of decreasing recurrence rates. Only

recently have clinical trials begun to provide evidence of enhanced survival for multimodality therapy involving resection with added chemotherapy or ^{131}I lipiodol. The introduction of ^{90}Y microspheres (Theraspheres) appears to offer the promise of relatively nontoxic tumoricidal internal radiotherapy to the liver and appears to be a major therapeutic addition to our treatment choices, and its role alone or in combination with other therapies is just beginning to be explored. The advent of multiple clinical trials for new agents that inhibit either the cell cycle or angiogenesis or both (new chapter) has diminished enthusiasm for chemotherapy, since these agents appear to be less toxic and may enhance survival, even for advanced disease. Some of these agents are taken orally, which makes them even more attractive. In addition, we are beginning to enter the phase of genomics (new chapter) and proteomics (new chapter) as applied to many tumor types, including HCC. This raises the possibility of being able to categorize patients into prognostic subsets, prior to any therapy. We are just at the beginning of the age of cell cycle modulating factors including hormones, growth factors, and growth factor receptor antagonists and agents that specifically alter defined aspects of the cell cycle. Since the mechanisms of many of these agents are known, we are entering the era of personalized medicine and the rational selection of suitable treatment drugs for an individual patient. For all these reasons, it seemed reasonable to us to produce a book that presents much of current therapy and current thinking on HCC. This is an exciting time to be in the field of HCC basic science as well as clinical management, as so many changes are simultaneously occurring at multiple levels of our understanding and management of the disease, and suddenly there are many new choices of therapy to offer our patients. All the original chapters have also been updated and enhanced.

Philadelphia, PA Brian I. Carr
March 2009

Preface to the First Edition

You are not obliged to complete the task,
nor are you free to desist from trying.

—Talmud, Avot

Hepatocellular carcinoma (HCC) used to be regarded as a rare disease.

The increasing numbers of chronic hepatitis C virus carriers in the United States and subsequent increased incidence of HCC seen in most large medical centers means that it is no longer an uncommon disease for most gastroenterologists or oncologists to encounter.

During the times when liver resection or systemic chemotherapy were the only real therapeutic modalities available, the outcomes were generally dismal, especially because most patients presented with advanced-stage tumors. Several recent factors seem to have changed this. They include the more frequent use of aggressive surveillance by ultrasound and computed tomography (CT) scanning in patients who have chronic hepatitis or cirrhosis from any cause (and thus are known to be at risk for subsequent development of HCC) to detect tumors at an earlier and therefore more treatable stage. Advances in CT scanning, particularly the introduction of multihead fast helical scans, mean that this vascular tumor can often be detected at an earlier stage, or multiple lesions can be diagnosed when only large single lesions were formerly seen, so that unnecessary resections are not performed.

During the times when liver resection or systemic chemotherapy were the only real therapeutic modalities available, the outcomes were generally dismal, especially because most patients presented with advanced-stage tumors. Several recent factors seem to have changed this. They include the more frequent use of aggressive surveillance by ultrasound and computed tomography (CT) scanning in patients who have chronic hepatitis or cirrhosis from any cause (and thus are known to be at risk for subsequent development of HCC) to detect tumors at an earlier and therefore more treatable stage. Advances in CT scanning, particularly the introduction of multihead fast helical scans, mean that this vascular tumor can often be detected at an earlier stage, or multiple lesions can be diagnosed when only large single lesions were formerly seen, so that unnecessary resections are not performed.

Liver transplantation has had a profound effect on the therapeutic landscape. There have always been two hopes for this modality: namely, to eliminate cirrhosis as a limiting factor for surgical resection and also to extend the ability of the surgeon to remove ever-larger tumors confined to the liver. Regional chemotherapy and hepatic artery chemoembolization have been around for a long time and have been practiced mainly in the Far East and Europe.

There has not been a consensus for which drug or drug combination is best or whether embolization is important and, if so, what type and size of particle are optimal. Although there is still no consensus on these matters, it has recently become clear from two randomized controlled clinical trials that hepatic artery chemoembolization for unresectable nonmetastatic HCC seems to bestow a survival advantage compared to no treatment. The high recurrence rates after resection have led numerous investigators to evaluate preresection and postresection chemotherapy in the hope of decreasing recurrence rates. Only recently have clinical trials begun to provide evidence of enhanced survival for multimodality therapy involving resection and either chemotherapy or 131I-lipiodol. The introduction of 90Yttrium microspheres, which

appear to offer the promise of relatively nontoxic tumoricidal therapy to the liver, appears to be a major therapeutic addition to our treatment choices, and its role alone or in combination with other therapies is just beginning to be explored.

In addition, we are beginning to enter the phase in which proteomics is applied to many tumor types, including HCC. This raises the possibility of being able to categorize patients into prognostic subsets, prior to any therapy. We are also just at the beginning of the age of cell cycle modulating factors including hormones, growth factors, and growth factor receptor antagonists and agents that specifically alter defined aspects of the cell cycle.

For these reasons, it seemed reasonable to produce a book that represents much of the current therapy and thinking on HCC. Admittedly, there is a bias toward expressing the experience of one center, the Liver Cancer Center at the University of Pittsburgh Starzl Transplant Institute, in which over 250 new cases of HCC have been seen each year for the last 15 years. This is an exciting time to be in the field of HCC basic science as well as clinical management because so many changes are simultaneously occurring at multiple levels of our understanding and management of the disease.

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Part I
Causes, Biological and Molecular Bases of HCC

Epidemiology of Hepatocellular Carcinoma

1

Donna L. White, Fasiha Kanwal, Li Jiao, and Hashem B. El-Serag

Contents

1.1 Global Incidence of Hepatocellular Carcinoma

1.1.1 Overview

Primary liver cancer or hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, with liver cancer accounting for 9.1 % of global cancer mortality [1]. In 2012, there were an estimated 782,000 incident HCC cases. Given an almost equally high number of deaths, 746,000, the mortality-to-incidence ratio is 0.95. Across time periods, regions and genders, liver cancer typically occurs in middle-aged and older adults. However, the burden of HCC is not evenly distributed throughout the world (Fig. 1.1). It also disproportionately impacts males (Fig. 1.2), with HCC the second leading cause of cancer mortality in men and the ninth leading cause in women [2].

Globally, the vast majority of HCC cases occur (>83 %) in less developed regions, particularly in Eastern and South-Eastern Asia and sub-Saharan Africa. China alone account for 50 % of all HCC cases, with an age-standardized incidence rate (ASR) of 22.3/100,000 person-years in 2012 [1]. However, four other countries have even higher ASRs—Mongolia (78.1/100,000), Lao People's Democratic Republic or Laos (52.6/100,000), The Gambia (25.8/100,000), and Egypt (25.6/100,000). Some typical rates from medium rate countries (i.e., HCC ASRs between 5 and 20/100,000) include Italy (7.6/100,000) and Spain (5.9/100,000). Notably, increasing numbers of countries that were formerly low rate (ASRs < 5/100,000) even a decade ago have now become medium rate countries, including the U.S. which had an ASR of 6.1/100,000 in 2012 (Fig. 1.3). Some rates from typical low rate countries include those from Argentina with an ASR of 3.3/100,000 and Israel with an ASR of 2.3 [1].

HCC accounts for between 85 and 90 % of primary liver cancers in adults [3]. One noteworthy exception is the Khon Kaen region of Thailand, which has one of the world's highest rates of liver cancer. However, due to endemic population infection with liver flukes, the major type of liver

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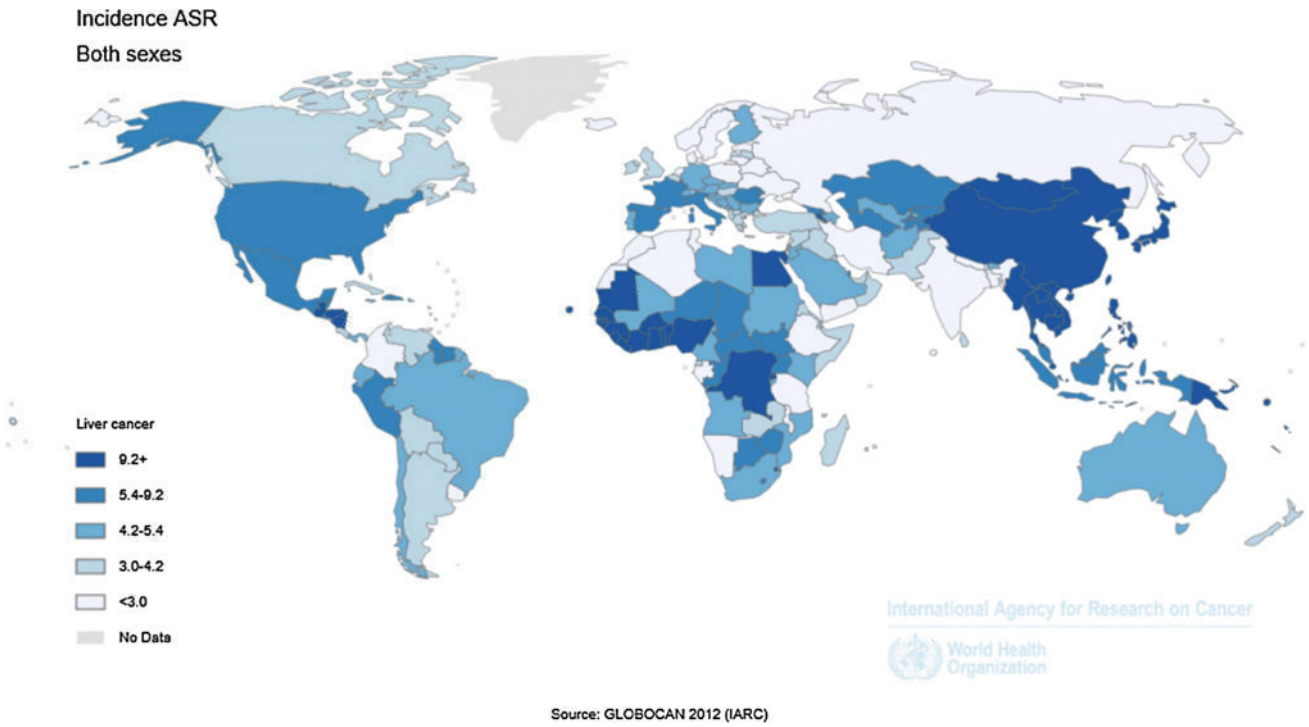

Fig. 1.1 Global map of age-standardized rates (ASR) of HCC in 2012

cancer in this region has historically been intrahepatic cholangiocarcinoma (ICCA) rather than HCC [4]. Mass drug administration and public health education campaigns that began in the early 1980s have resulted in a dramatic decreased prevalence of liver fluke infection in the population from 80 to 15 to 20 % by 1997 and remaining stable through 2013 [5]. This has led to subsequent substantial declines in ASRs for ICCA in this region with ASRs of 67.6/100,000 in males and 27.3/100,000 in females for the period 2004–2006, [6] levels already showing reductions from reported historical levels ranging between of 85–90/100,000 in males and between 32–39/100,000 in females [5]. Overall, ICCA remains the second most common primary hepatic malignancy worldwide, with over 750,000 million people residing in areas endemic for liver flukes and thus at ongoing exposure risk (e.g., Poland, Germany, Russia, Kazakhstan, and Western Siberia for *O. felineus*; Korea, China, Taiwan, and Vietnam for *C. Sinensis*, and North East Thailand, Laos, Cambodia for *O. Viverrini*) [7, 8] with an estimated 56.2 million persons globally infected with foodborne trematodes in 2005 [9].

Overall encouraging trends in HCC incidence have been seen in some high-rate areas. For example, between 1978 and 1982 and 1993 and 1997, decreases in incidence were reported among Chinese populations in Hong Kong, Shanghai, and Singapore [3] (Fig. 1.3). These rates continue to decline (e.g., China/Hong Kong ASR: 23.6/100,000 in 2001 vs. 18.9/100,000 in 2011) [1]. In addition to these areas, Japan also began to experience declines in incidence rates among males for the first time between 1993 and 1997.

Many high-rate Asian countries now vaccinate almost all newborns against hepatitis B virus (HBV) and the effect on HCC rates has already become apparent. In Taiwan, where government mandated national newborn vaccination began in 1984, HCC rates among children aged 6–14 years declined significantly over a short period from ASR: 0.70/100,000 in 1981–1986 to ASR: 0.36/100,000 in 1990–1994, [10] an effect that was presumed to be to vaccination. However, a national cohort analysis to evaluate the relative importance of age, time trend (period), and vaccination (cohort) on HCC incidence and mortality in Taiwanese children suggests HCC rates were already notably declining in boys and especially in girls in the 1980s prior to HBV vaccination, and that the first substantial vaccine-related decline in HCC rates was seen in boys starting 2000–2004 (i.e., a 15 year time lag) [11]. It is too soon yet for HBV vaccination to have had a substantial effect on adult rates which are highest in middle-aged and older adults, but other public health measures have likely contributed to declines in HCC incidence in high-risk areas of China. A Chinese government program started in the late 1980s to shift the staple diet of the Jiangsu Province from corn to rice reduced exposure to known hepatocarcinogen aflatoxin B1 (AFB1) in this area [12]. Similarly, another Chinese public health campaign initiated in the early 1970s to encourage drinking of well water rather than pond- or ditch water may have

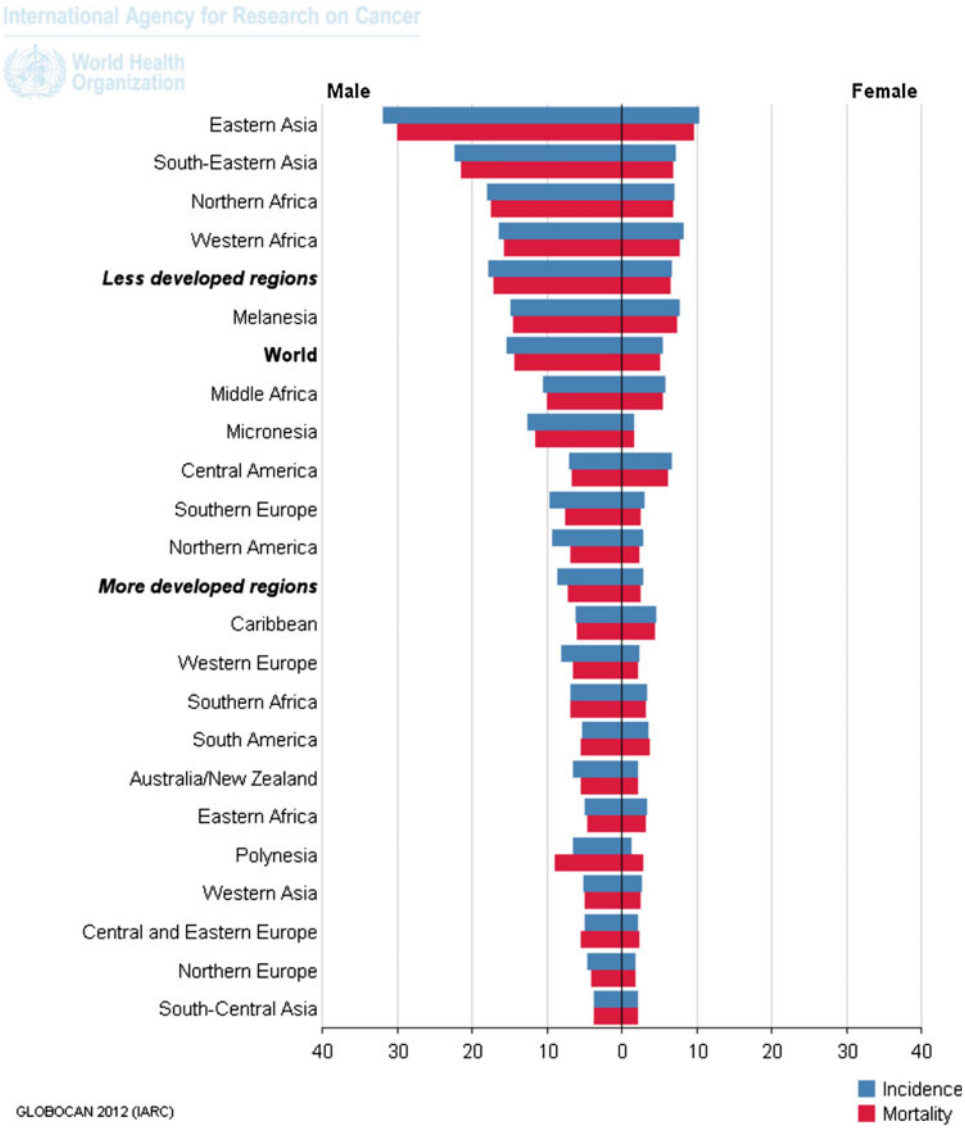

Fig. 1.2 Gender-specific and age-standardized HCC incidence and mortality rate by region and development status in 2012

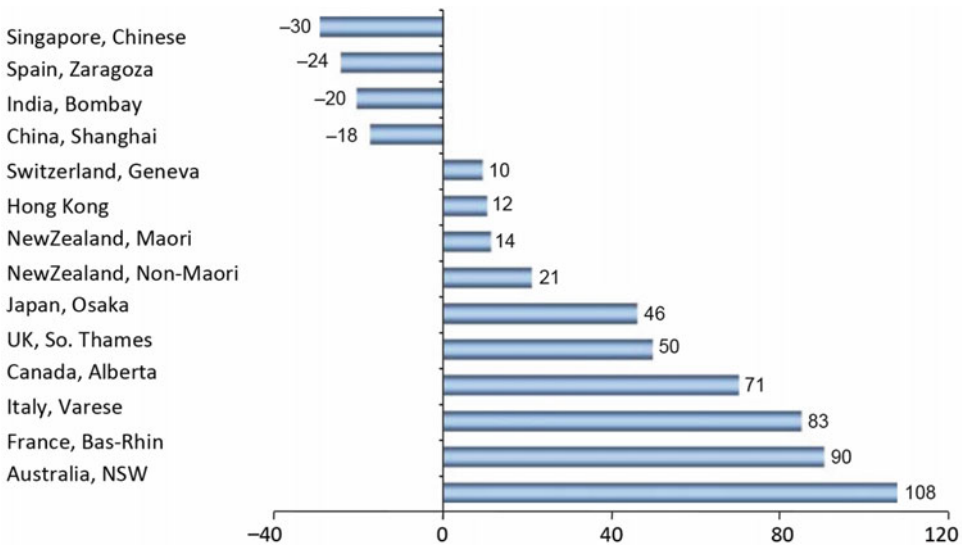

Fig. 1.3 Recent changes in the incidence of HCC. The incidence of HCC has been declining in some "high incidence" areas, such as China and Hong Kong. On the other hand, HCC incidence in several "low and intermediate incidence" areas has been increasing. Modified from McGlynn et al

decreased consumption of microcystins, blue-green algae (cyanobacteria) produced compounds demonstrated to be hepatocarcinogenic in experimental models [13].

In contrast, registries in a number of low- and medium rate areas reported sizable and continuing increases in HCC incidence between 1978–1982 and 1993–1997 [14] (Fig. 1.3). Included among these registries are those in the United States, the United Kingdom, and Australia. Reasons for both the decreased incidence in historically high-rate areas and the greatly increased incidence in formerly lower rate areas are not completely understood, suggesting that each will be an important case study. It has, however, been widely hypothesized that most of the increased incidence in many lower rate areas with ongoing low rates of HBV infection is due to the rapid aging of their hepatitis C virus (HCV) cohorts combined with substantial increasing rates of obesity and diabetes over the last few decades.

1.1.2 Race/Ethnicity

HCC incidence rates can vary greatly among different populations living within the same region. For example, in the United States at all ages and among both genders, age-standardized rates (ASRs) of liver cancer, expressed, per 100,000 are higher in Asians and Pacific Islanders (13.1) than in Hispanics (11.0), African-Americans (8.0), or Whites (4.5) [15]. The reason(s) for this interethnic variability likely include differences in prevalence and time of exposure for major risk factors for liver disease as well as for HCC, and potentially, in prevalence of salient genetic polymorphisms (e.g., the much lower prevalence among individuals of African ancestry of the highly favorable *IL28B* allele for HCV). Interestingly, liver cancer rates can also vary considerably individuals of the same race/ethnic group living across large geographical expanses, e.g., ASRs (expressed per 100,000) for Chinese males residing in China (Bejing): 16.7; Hong Kong: 26.7; Malyasia (Penang): 10.5; U.S. (Los Angeles): 18.4 [16] or even within the same country (e.g., very high ASRs in Mekong area including Khon Kaen in northern Thailand vs. considerably lower rates in Bangkok in southern Thailand). The reasons for this intra-ethnic variability likely include differences in exposure to and/or acquisition time of other liver disease risk factors (e.g., liver flukes, dietary aflatoxins, obesity, and alcohol use). However, they may also be impacted by relative differences in underlying population structure (e.g., age and gender) as well.

1.1.3 Gender

In essentially all populations, males have higher reported HCC rates than females, with male-to-female ratios usually averaging between 2:1 and 4:1 (Figure 1.2). As of 2012, some of the largest discrepancies in rates (>3.5:1) are found in medium rate European populations. Typical among these ratios are those reported in registries in Volume *X* of Cancer in Five Continents: Biela, Italy (3.9:1); Munich, Germany (3.6:1); Geneva, Switzerland (4.4:1) [17]. Among the 11 French registries, nine reported male:female ratios > 5:1. The gender ratio in the U.S., which is also medium risk, is lower (3.3:1). In contrast, typical gender ratios currently seen in high-rate populations are generally lower and include those of Qidong, China (3.0:1); Osaka, Japan (2.9:1); and Harare, Zimbabwe (1.2:1). Registries in Central and South America report some of the lowest sex ratios for liver cancer. Typical ratios in these regions are reported by Pasto, Colombia (1.2:1), and Costa Rica (1.6:1).

The reasons for higher rates of HCC in males may relate to gender-specific differences in exposure to risk factors. Men are more likely to be infected with HBV and HCV, consume alcohol, smoke cigarettes, and have visceral adiposity. Yet there are several compelling reasons to believe that sex-based biological differences (e.g., genetic, sex hormone levels) may also contribute to this pervasive dimorphism: dimorphism persists after adjustment for gender-based differences in other known risk factors, is observed in human children, and is evident in animal models. Further, use of some sex hormone modifying medications including androgenic anabolic steroids and earlier high dose formulations of oral contraception have been associated with young onset HCC in some case reports. However, the role that normal variation in sex hormone signaling plays in the substantial unexplained interindividual variability among individuals of the same gender and with similar major risk factors for HCC is not known.

The global age distribution of liver cancer varies by region, incidence rate, gender and, possibly, by etiology [18]. HCC overwhelmingly occurs in adulthood, most often as HCC arising in the background of one or more environmental or behavioral exposures known to increase liver cancer risk. Although the overwhelming majority of HCC are sporadic or have no similarly affected first-degree relative, family clusters [19] and also significant additional increases in HCC risk even after accounting for hepatitis status have been reported [20]. In contrast, the most common liver cancer in children is hepatoblastoma (∼2–3 cases/per

million persons) that arises in the background of a genetically determined disorder like Beckwith–Wiedemann syndrome, glycogen storage disease type I, or Tyrosinemia in infancy thru early childhood (most occurring within the first 18 months).

In adults, female HCC rates typically peak in the age group 5 years older than the peak age observed in comparable males. In low- and medium-risk populations (e.g., Canada, the United Kingdom, and the United States), the highest age-specific rates occur among persons aged 75 and older [18]. A similar pattern is seen among most high-risk Asian populations (e.g., Hong Kong, Shanghai). In contrast, male HCC rates in high-risk African populations (e.g., The Gambia, Mali) tend to peak between ages 60 and 65 before declining, while female rates peak between 65 and 70 before declining. These variable age-specific patterns are likely related to differences in the dominant hepatitis virus in the population, the age at viral infection and the existence of other risk factors. Notably, while most HCV carriers become infected as adults, most HBV carriers become infected at very young ages.

A historical exception was Qidong, China, where HCC rates are among the world's highest and where age-specific incidence rates among males rose until age 45 and then plateaued, while among females, rose until age 60 and then plateaued. The reasons for this unusually early onset are unclear, but could be due to existence of other hepatocarcinogenic exposures or differences in dose and timing of known hepatocarcinogens like dietary aflatoxin. However, by 2005–2008 the age of onset for the first time had increased to over 50 years, an effect hypothesized to be largely attributable to public health prevention measures in the region particularly dietary shift to prevent aflatoxin exposure [12].

1.1.4 HCC in the United States

Research conducted using the National Cancer Institute's (NCI) population-based Surveillance Epidemiology and End Results (SEER) registry data which cover >13 % of the U.S. population showed that overall annual age-adjusted HCC incidence rates (per 100,000) doubled from 1.4 in 1975–1977 to 4.8 in 2005–2007 [18] (Fig. 1.4) with large increases in incidence observed among Hispanics and the overall population aged 50–60 years old [21]. Rates continue to rise though not as dramatically, with an annual ~4 % increase in overall incidence observed between 2003 and 2012. This dramatic increase in rates is likely attributable to several factors including rising incidence of cirrhosis particularly due to HCV [22]; substantial recent increases in rates of obesity and thus metabolic syndrome associated

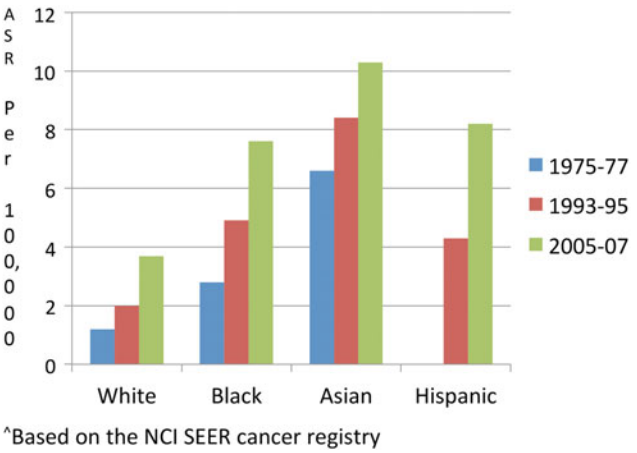

Fig. 1.4 Differences in age-standardized HCC rates by race/ethnicity in the U.S. by time period

complications like NAFLD and diabetes; population aging particularly among the HCV-infected; and a general improvement in survival among cirrhosis patients.

Overall, between 15 and 50 % of cirrhosis and HCC patients in the United States do not have a historically established risk factor like viral or autoimmune hepatitis, a genetic disorder, or an alcohol use disorder [14]. Most of these cryptogenic cases do, however, have some metabolic syndrome features like diabetes or obesity, and thus its hepatic manifestation, nonalcoholic fatty liver disease (NAFLD), is usually the presumptive underlying risk factor [23].

The overall epidemiological profile of incident HCC in the U.S. in 2012 based upon nationwide United States Cancer Statistics (USCS) registry data demonstrated: 73 % of all cases are male; 61 % are White (non-Hispanic); the 55–59 year old age-group has the largest number of incident HCC diagnoses (20 % of total); 89 % of cases are diagnosed at ages 50 and older; and the highest overall age-standardized incident rates (ASR), expressed per 100,000, are found in males who are Hispanic (17.8) closely followed by males who are Asian or Pacific Islanders (17.7). The burden of HCC in the U.S. is also not uniform, with most states with HCC rates in the upper quartile located in southwestern and western regions (Fig. 1.5). In 2012, Texas and Hawaii both reported the highest ASRs 13.7 [15]. Over the last decade, the largest age-specific increases in incidence have been in the 55–59 and 60–64 year old age groups (Fig. 1.6). The NCI's SEER data-based projections for the U.S. in 2015 are that 35,660 individuals in an incident diagnosis in 2015 at a median age of 63 years old, with current estimated overall 5-year survival based upon data from 2005 to 2011 of 17.2 % [24].

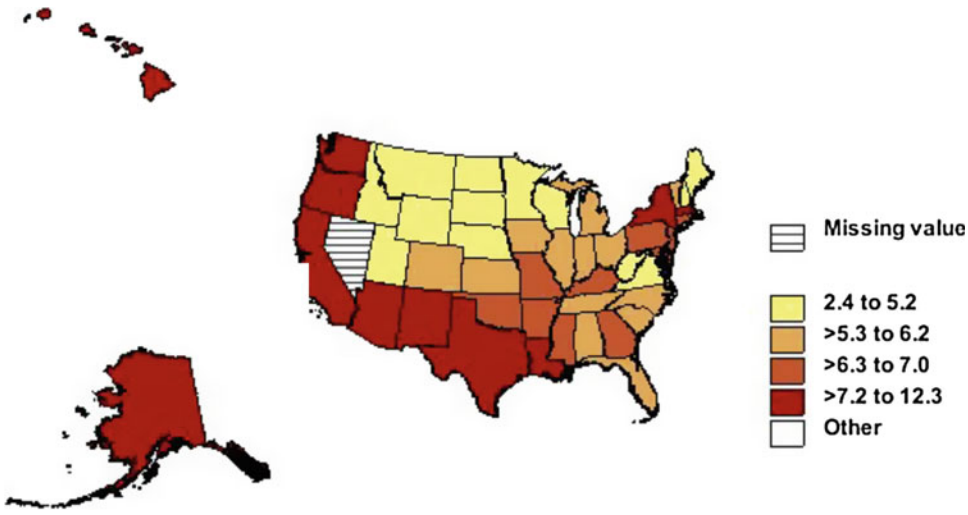

Fig. 1.5 Geographic distribution of age-standardized HCC rates in the U.S. in 2012

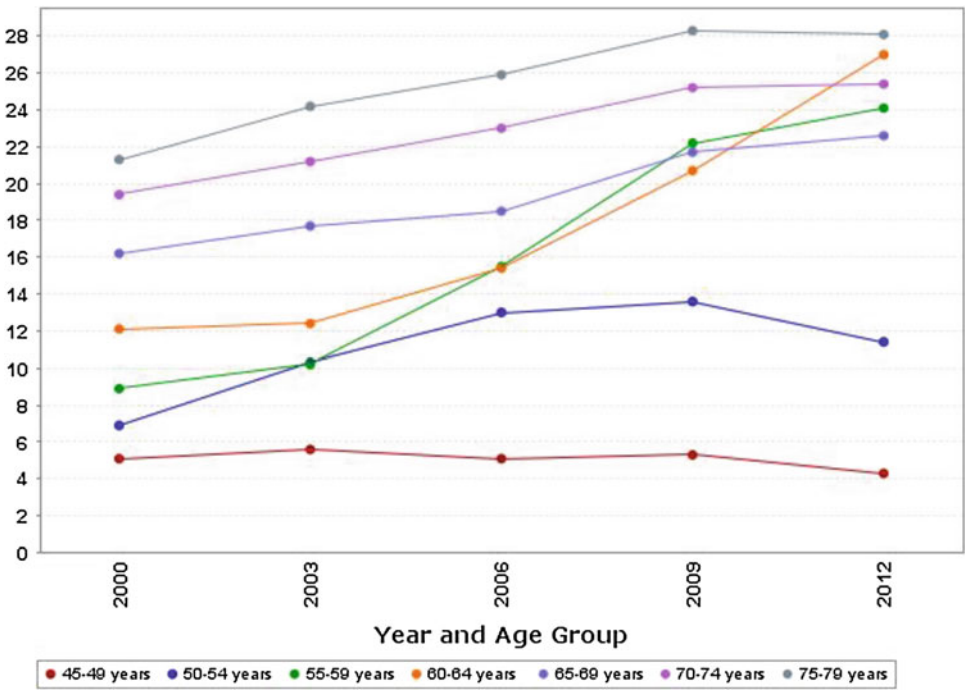

Fig. 1.6 Age-specific incidence rate of U.S. cancer registry reported HCC in the U.S. (2000–2012)

1.2 Risk Factors for Hepatocellular Carcinoma

HCC is unique in that it largely occurs within an established background of cirrhosis (~70–90 % of all detected HCC cases) (Fig. 1.7). The two major causes of cirrhosis and thus HCC globally include hepatitis B (Fig. 1.8) and hepatitis C (Fig. 1.9) virus infection, which collectively occur in close to 80 % of all HCC cases [25]. Other established as well as emerging risk factors include: alcohol and tobacco use; aflatoxin exposure; obesity, diabetes, and nonfatty liver disease; and diet. The distribution and impact of HCC risk factors often varies considerably across regions, populations and time periods. The epidemiological data linking these specific risk factors to HCC in particular is overviewed below. Our overview when sufficient data exists focuses primarily on findings reported in cohort studies, particularly those that are population-based and prospective and on meta-analyses of these prospective studies as this is considered the strongest direct observational epidemiologic data in support of a potential causal association.

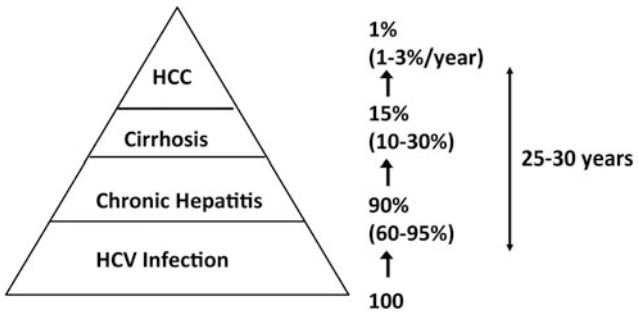

Fig. 1.7 Estimated progression rates to cirrhosis and hepatocellular carcinoma in hepatitis C infection

1.2.1 Hepatitis B Virus

Globally, HBV is the leading cause of HCC. An estimated 1 in 3 persons worldwide has been infected by HBV, and although only 5 % of these become chronic carriers, 25 % of chronic carriers develop serious liver disease like cirrhosis and HCC. Most HBV-related HCC cases occur in Asia and sub-Saharan Africa (Fig. 1.8), with China alone accounting for 73 % of the world's HBV-related HCC cases [2]. Chronic HBV infection affects an estimated 240 million persons worldwide, with more than 780,000 dying annually, primarily due to HBV-related liver disease [26].

In Asia, where HBV is endemic, infection is largely acquired by maternal–child transmission, while sibling-to-sibling transmission at young ages is more common in sub-Saharan Africa [27]. In these areas, up to 90 % of infected infants/children follow a lifelong chronic course. The pattern is different in areas with low endemicity, where HBV is typically acquired in adulthood through sexual and parenteral routes (horizontal transmission) and where with >90 % of acute infections in adults resolve spontaneously.

Epidemiological studies have demonstrated that chronic HBV carriers have a 5- to 15-fold increased risk of HCC compared to the general population. The great majority of HBV-related HCC (70–90 %) develops in a background of cirrhosis. A recent meta-analysis of 57 studies with treatment naïve HBV-infected cohorts found much higher annual HCC incidence in cirrhotics (3.16 vs. 0.10/100 person-years in cirrhotics vs. non-cirrhotics, respectively) [28]. It also found that although HCC incidence among HBV-related cirrhotics varied according to factors like gender, that it was largely similar in European and Asian populations.

Several other factors have been reported to increase HCC risk among HBV carriers including: male gender; older age (or longer duration of infection); Asian or African race; cirrhosis; family history of HCC; exposure to aflatoxin, alcohol, or tobacco; or coinfection with HCV or HDV. HCC risk is also increased in patients with higher levels of HBV

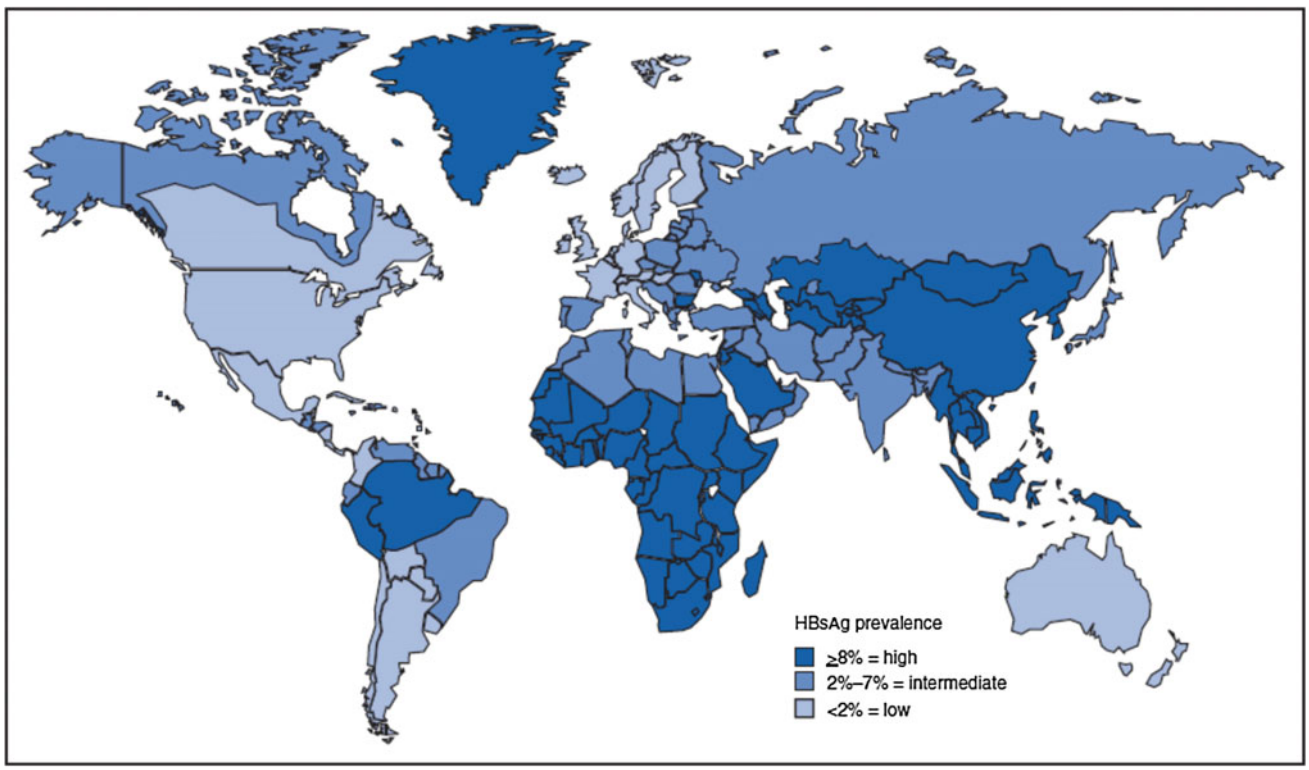

Fig. 1.8 Distribution of chronic hepatitis B virus (HBV) infection—worldwide, 2006. *Source* CDC. Travelers' health; yellow book. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2008. Available at http://wwwn.cdc.gov/travel/yellowbookch4-HepB.aspx

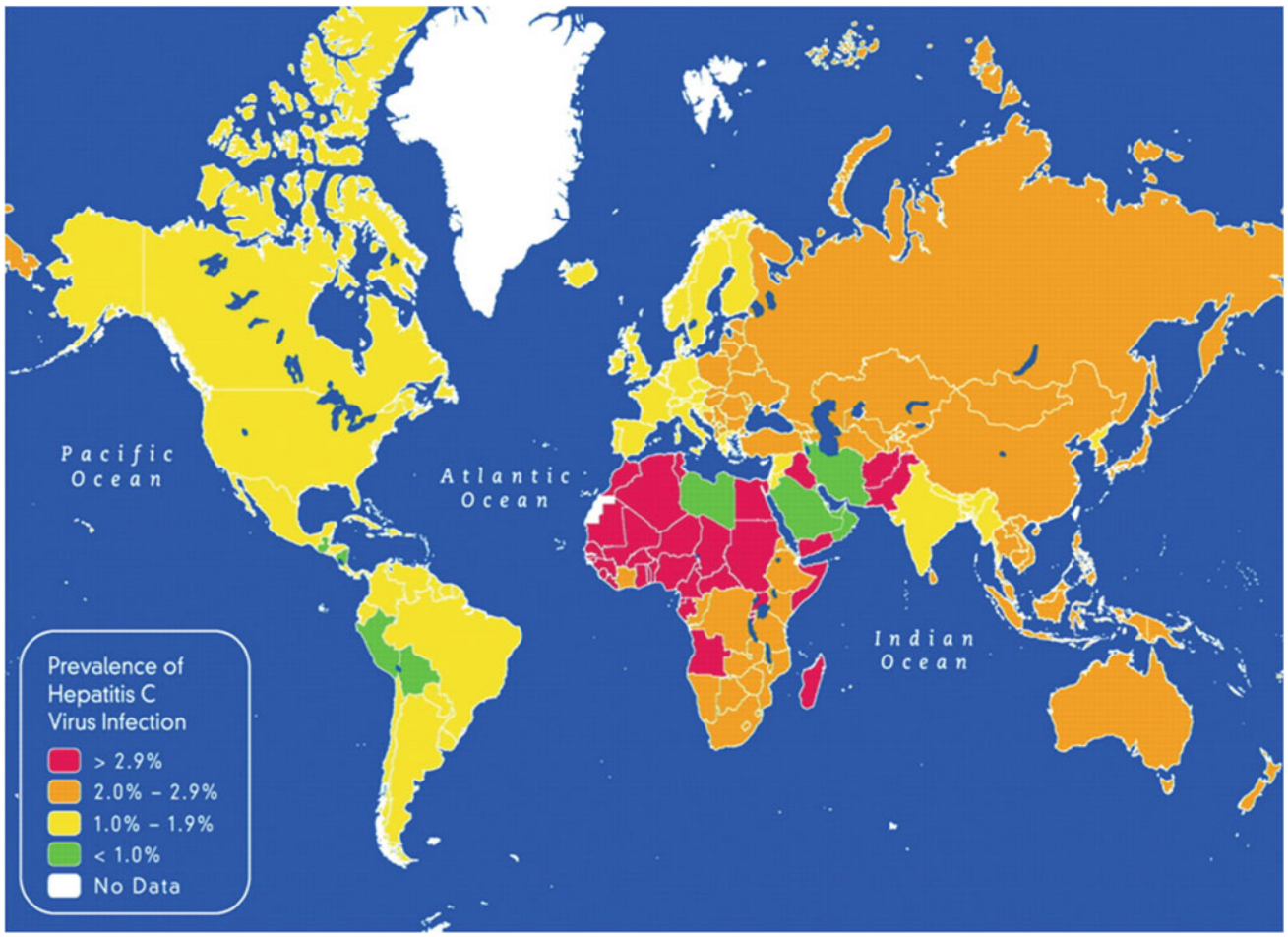

Fig. 1.9 Map of the global prevalence of chronic hepatitis C virus infection. *Source* Averhoff FM, et al. Clinical Infectious Diseases. 2012; 55: S10–S15

replication, as indicated by presence of HBeAg and high HBV DNA levels. In addition, it has been suggested in Asian studies that genotype C is associated with more severe liver disease than is genotype [29].

In the natural history of chronic HBV infection, spontaneous or treatment-induced development of antibodies against HBsAg and HBeAg leads to reduced HCC risk. A meta-analysis of 12 studies with 1187 patients who received interferon and 665 untreated patients followed for 5 years found lower cumulative HCC incidence in treated than untreated patients (1.9 % vs. 3.2 %, respectively), although this difference was not statistically significant [30]. However, statistically significant reduction in HCC risk was shown with use of the more recently available reverse transcriptase inhibitor medication Lamivudine, which reduced the risk of treated to untreated (odds ratio (OR) = 0.48). However, there was still notable HCC incidence during the median 43-month follow-up period among the treated (1.3/100 person-years in the treated vs. the untreated). These results are largely paralleled by results reported for other studies of single or combined use these medications and are evident in a more recent single cohort study with up to 8 years follow-up [31].

Another consideration is that that HBV DNA can persist as "occult HBV infection" for decades among persons with serological recovery (HBsAg negative). Occult HBV is associated with anti-HBc and/or anti-HBs [32]. However, in a significant proportion of individuals, neither anti-HBc nor anti-HBs can be detected. A recent meta-analysis of 8 prospective studies (6 in Asian populations) demonstrated significant increased HCC risk with occult infection compared to no infection (OR = 2.86) [33]. There was no association between occult HBV and HCC risk in the large HALT-C trial in HCV-related cirrhotics though a substantial number of cohort members had evidence of prior HBV infection.

The public health initiative in endemic countries to institute wide-scale vaccination of newborns for HBV started in the 1980s and is projected to dramatically lower HBV-associated HCC rates as that birth cohort, the eldest

now in their early 30 s, begins to age into higher risk ages for HCC onset. However, suboptimal vaccination rates and/or acquisition of immunity reported in some endemic countries or regions like Laos [34] suggests that without a viral cure, HBV-related HCC will continue to persist, albeit at dramatically lower rates, in the postvaccine generation pending discovery of a viral cure.

1.2.2 Hepatitis C Virus

HCV is the second leading cause of HCC worldwide, with most HCV-related HCC cases arising in Asia and North Africa (Fig. 1.9). Global HCV prevalence has grown over the last 15 years to over 185 million infected (~2.8 % global prevalence) [35], with recent estimated global prevalence of 46.2 % for genotype 1 (83.4 million, approximately one-third in East Asia) and 30.1 % for genotype 3 (54.3 million) [36]. The highest reported HCV prevalence in North Africa is in Egypt (~18 %) and in Asia in Mongolia (~10 %). It is also estimated that up to a million people die annually of HCV-related liver disease [37].

In contrast to HBV, vertical and early childhood infection is rare, and almost all new HCV infections arise in early adulthood. (Egypt is a notable exception; there were >5000 cases of vertical transmission in 2008 alone) [38]. Also in contrast to HBV, most infected adults (up to 80 %) develop chronic infection.

In Japan, in contrast to other high HCC rate Asian countries like China, HCV is the predominant viral cause of HCC. HCV was largely introduced there (as in Egypt) iatrogenically via use of intravenous antischistosomal therapy and began to widely disseminate shortly after World War II [39]. Consequently, HCV-related HCC rates began to sharply increase in Japan in the mid-1970s onward, although recent data suggest that the peak may already have been reached [40].

It has been estimated that HCV began to infect large numbers of young adults in North America and in South and Central Europe in the 1960s and 1970s, predominantly as a result of intravenous drug use [41]. The virus then moved into national blood supplies and circulated until a screening test was developed in 1990, after which time rates of new infection dropped dramatically. Consequently, most individuals in these chronically HCV-infected populations from developed countries have been infected for several decades and are rapidly graying into peak ages for liver disease onset. Accordingly, evidence-based model simulations suggested a peak incidence of HCV-related cirrhosis by 2020 with associated continued increases in HCC over the following decades [42]. These estimates, however, were made a few years prior to advent of highly efficacious direct acting antiviral (DAA) drug regimens that are interferon free, the first of which (sofosbuvir) became available for use the U.S. in 2014. Yet, given the very high cost of these new medications, combined with lack of awareness of underlying infection in almost all individuals with HCV infection until they are diagnosed with liver disease, their impact on the projected magnitude and timing of peak HCV-related HCC incidence rates in the U.S. (and globally) is not yet known.

HCV infection is consistently associated with substantially increased HCC risk in prospective and retrospective studies. For example, in a meta-analysis of 21 case-control studies in which second-generation enzyme immunoassay tests for anti-HCV were used, HCC risk was increased 17-fold in HCV-infected patients compared with HCV-negative controls. However, the likelihood of development of HCC among HCV-infected persons is difficult to determine due to the paucity of adequate long-term cohort studies; the best estimate is from 1 to 4 % after 30 years (Fig. 1.9). HCV increases HCC risk by promoting fibrosis and eventually cirrhosis, with rates of cirrhosis up to 30 % [43]. after several decades of infection [44]. Once cirrhosis is established, HCC develops at an annual rate of 2–5 % [45]. However, rates up to 7 % have been reported in Japan, with the historically highest incidence among recipients of contaminated blood or blood products (14 and 1 per 1000 person-years for cirrhosis and HCC, respectively) and in hemophiliacs (5 and 0.7 per 1000 person-years, respectively), and the lowest in women who received a one-time contaminated anti-D immune globulin treatment (1 and 0 per 1000 person-years, respectively).

In HCV-infected patients, factors related to host and environment/lifestyle appear to be more important than viral factors in determining progression to cirrhosis. Some of the key factors include: older age; older age at the time of infection; longer duration of infection; male gender; heavy alcohol intake (>50 g/day); obesity, diabetes, and fatty liver disease; and coinfection with HBV or HIV (with ~16–33 % coinfected in the U.S.) [46]. Although there is no strong evidence for an effect of most viral factors like viral load or quasispecies in HCC risk, our recent cohort based research in 111,000 chronically HCV-infected veterans using VA healthcare between 2002 and 2009 demonstrated 80 % excess HCC risk among those infected with genotype 3 in comparison to genotype 1 (HR = 1.80, 95 % CI: 1.61–2.03) [47]. We also found evidence suggestive of potential racial differences in risk of HCV-related progression within this VA cohort, with significantly increased HCC risk observed in Hispanics and significantly decreased risk among African Americans (HRs = 1.28 and 0.58, respectively) [48]. Globally, the most prevalent HCV genotypes are types 1 and 3, representing 46.2 % and 30.1 % of all cases, respectively. The less common genotypes (2, 4, 5 and 6) are disproportionately found in less developed countries [35].