Hepatocellular Carcinoma

Second Edition

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HEPATOCELLULAR CARCINOMA

Diagnosis and Treatment

Second Edition

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To my daughters, Ophira and Feridey

Preface to 2nd 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 multi-head 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, non-metastatic HCC seems to bestow a survival advantage compared with no treatment. The high recurrence rates after resection have led numerous investigators to evaluate pre-resection and post-resection 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 non-toxic 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, since 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 1st 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.

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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1 Epidemiology of Hepatocellular Carcinoma

Donna L. White, PhD, MPH, Amir Firozi, MD, and Hashem B. El-Serag, MD, MPH

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ABSTRACT

Hepatocellular carcinoma (HCC) affects more than half a million individuals per year worldwide. It is a largely preventable disease. Most cases are related to hepatitis B virus infection in sub-Saharan Africa and Eastern Asia (except Japan). Hepatitis C virus has emerged as an important cause of HCC particularly in North America and some parts of Europe, where a recent sharp increase in HCC has been reported. There is growing evidence of an association between obesity and diabetes and increased risk of HCC; however, the causal link is still unclear. The striking geographic and racial variations in the occurrence of HCC are partly explained by the distribution of HBV and HCV infections. Additional established risk factors for HCC include older age, male sex, heavy alcohol intake, aflatoxin exposure, iron overload related to hemochromatosis, and possibly tobacco smoking. The

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role of diet except for alcohol drinking and aflatoxin contamination in the etiology of HCC in human populations is largely unknown. Host genetic factors are being examined but definitive data are lacking. Most of these risk factors operate by promoting the development of cirrhosis which is present in most HCC cases. The annual risk of HCC in cirrhosis ranges between 1 and 7%. This review discusses in detail the epidemiology of HCC from a global perspective.

Key Words: Hepatitis C; hepatitis B; cirrhosis; incidence; prevalence; risk; genetic association; coffee; insulin resistance; liver cancer; epidemiology; determinants; risk factors

1. GLOBAL INCIDENCE OF HEPATOCELLULAR CARCINOMA

1.1. Overview

Primary liver cancer is the fifth most common cancer worldwide and the third most common cause of cancer mortality *(1)*. Globally, over 560,000 people develop liver cancer each year and an almost equal number, 550,000, die of it. Liver cancer burden, however, is not evenly distributed throughout the world (Fig. 1). Most HCC cases (>80%) occur in either sub-Saharan Africa or in Eastern Asia. China alone accounts for more than 50% of the world's cases (age-standardized incidence rate (ASR) male: 35.2/100,000; female: 13.3/100,000). Other high-rate (>20/100,000) areas include Senegal (male: 28.47/100,000; female: 12.2/100,000), The Gambia (male: 39.67/100,000; female: 14.6/100,000), and South Korea (male: 48.8/100,000; female: 11.6/100,000).

North and South America, Northern Europe, and Oceania are low-rate (< 5.0/100,000) areas for liver cancer among most populations. Typical incidence rates in these areas are those of the United States (male: 4.21/100,000; female: 1.74/100,000), Canada (male: 3.2/100,000; female: 1.1/100,000), Colombia (male: 2.2/100,000; female: 2.0/100,000), the United Kingdom (male: 2.2/100,000; female: 1.1/100,000), and Australia (male: 3.6/100,000; female: 1.0/100,000). Southern European countries, typified by rates in Spain (male: 7.5/100,000; female: 2.4/100,000), Italy (male: 13.5/100,000; female: 4.6/100,000), and Greece (male: 12.1/100,000; female: 4.6/100,000), are of medium rate (5.0–20.0/100,000) *(2)*.

HCC accounts for between 85 and 90% of primary liver cancer. One noteworthy exception is the Khon Kaen region of Thailand, which has one of the world's highest rates of liver cancer ($ASR_{1993-1997}$ male: 88.0/100,000; female: 35.4/100,000) *(3)*. However, due to endemic infestation with liver

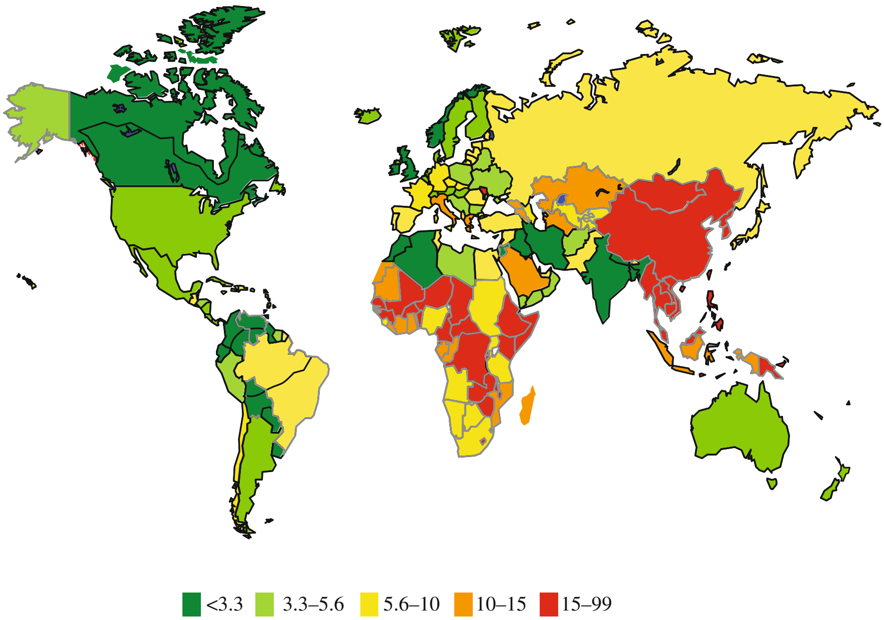

Fig. 1. Regional variations in the incidence rates of hepatocellular carcinoma categorized by age-adjusted incidence rates.

flukes, the major type of liver cancer in this region is intrahepatic cholangiocarcinoma rather than HCC *(4)*.

Encouraging trends in liver cancer incidence have been seen in some of these high-rate areas *(5)*. Between 1978–1982 and 1993–1997, decreases in incidence were reported among Chinese populations in Hong Kong, Shanghai, and Singapore *(3)*. In addition to these areas, Japan also began to experience declines in incidence rates among males for the first time between 1993 and 1997 (Fig. 2).

Many high-rate Asian countries now vaccinate all newborns against HBV and the effect on HCC rates has already become apparent. In Taiwan, where national newborn vaccination began in 1984, HCC rates among children aged 6–14 years declined significantly from 0.70/100,000 in 1981–1986 to 0.36/100,000 in 1990–1994 *(6)*. It is too soon yet for HBV vaccination to have had an effect on adult rates, but other public health measures may have 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 may have limited exposure to known hepatocarcinogen aflatoxin B1 (AFB1) in this area *(7)*. 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 decreased

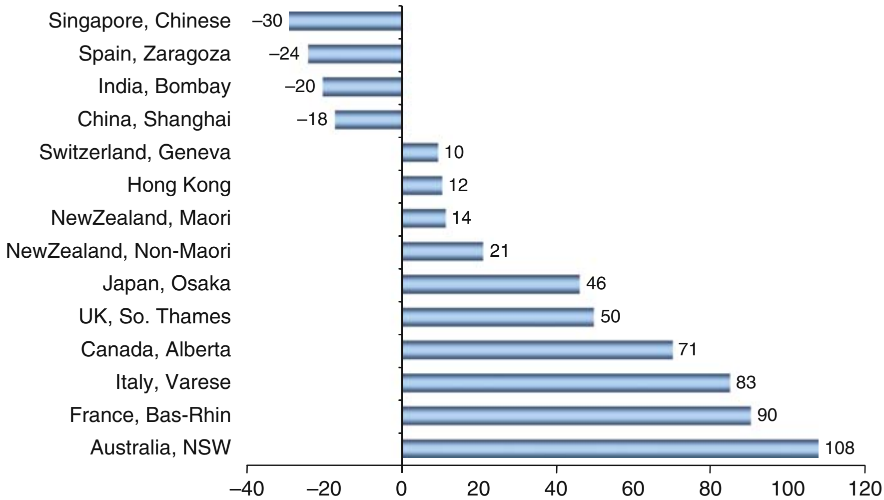

Fig. 2. Recent changes in the incidence of HCC. The incidence of HCC has been declining in some "high-incidence" areas, such as China and Hong Kong. On the other hand, HCC incidence in several "low and intermediate incidence" areas has been increasing. Modified from McGlynn et al. *(5)*.

consumption of microcystins, cyanobacteria-produced compounds demonstrated to be hepatocarcinogenic in experimental animals.

In contrast, registries in a number of low-rate areas reported increases in HCC incidence between 1978–1982 and 1993–1997. Included among these registries are those in the United States, the United Kingdom, and Australia. Reasons for both the decreased incidence in high-rate areas and the increased incidence in low-rate areas are not yet clear, suggesting that each area will be an important case study. It has been widely hypothesized, however, that increased incidence in low-rate areas may be related to greater prevalence of HCV infection within these areas.

1.2. Race/Ethnicity

HCC incidence rates also vary greatly among different populations living in the same region. For example, ethnic Indian, Chinese, and Malay populations of Singapore had age-adjusted rates ranging from 21.21/100,000 among Chinese males to 7.86/100,000 among Indian males between 1993 and 1997 *(3)*. The comparable rates for females were 5.13/100,000 among ethnic Chinese and 1.77/100,000 among ethnic Indians. Another example is the United States where, at all ages and among both genders, HCC rates are two times higher in Asians than in African-Americans, which are themselves two times higher than those in whites. The reason(s) for this interethnic variability likely include differences in prevalence and acquisition time of major risk factors for liver disease and HCC.

1.3. Gender

In almost all populations, males have higher liver cancer rates than females, with male:female ratios usually averaging between 2:1 and 4:1. At present, the largest discrepancies in rates (>4:1) are found in medium-risk European populations. Typical among these ratios are those reported from Geneva, Switzerland (4.1:1) and Varese, Italy (5.1:1). Among 10 French registries listed in volume VIII of *Cancer in Five Continents*, nine report male:female ratios >5:1. In contrast, typical ratios currently seen in high-risk populations are those of Qidong, China (3.2:1); Osaka, Japan (3.7:1); The Gambia (2.8:1); and Harare, Zimbabwe (2.4:1). Registries in Central and South America report some of the lowest sex ratios for liver cancer. Typical ratios in these regions are reported by Colombia (1.2:1) and Costa Rica (1.6:1).

The reasons for higher rates of liver cancer 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 increased iron stores. Higher levels of androgenic hormones, body mass index, and increased genetic susceptibility may also adversely affect male risk.

1.4. Age

The global age distribution of HCC varies by region, incidence rate, gender and, possibly, by etiology *(3)*. In almost all areas, female rates peak in the age group 5 years older than the peak age group for males. In low-risk populations (e.g., the United States, Canada, the United Kingdom), the highest age-specific rates occur among persons aged 75 and older. A similar pattern is seen among most high-risk Asian populations (e.g., Hong Kong, Shanghai). In contrast, male 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 became infected as adults, most HBV carriers became infected at very young ages.

Exceptions to these age patterns occur in Qidong, China, where liver cancer rates are among the world's highest. Age-specific incidence rates among males rise until age 45 and then plateau, while among females, rates rise until age 60 and then plateau. The explanation for these younger peak ages is unclear, but may be due to existence of other hepatocarcinogenic exposures.

1.5. Distribution of Risk Factors

Major risk factors for HCC vary by region. In most high-risk areas, the dominant risk factor is chronic HBV infection. In Asia, HBV infection is largely acquired by maternal–child transmission, while sibling-to-sibling transmission at young ages is more common in Africa. Consumption of aflatoxin B_1-contaminated foodstuffs is the other major HCC risk factor in most high-rate areas.

Unlike the rest of Asia, the dominant hepatitis virus in Japan is hepatitis C (HCV). HCV began to circulate in Japan shortly after World War II *(8)*. Consequently, HCC rates began to sharply increase in the mid-1970s with an anticipated peak in HCV-related HCC rates projected around 2015, though recent data suggests the peak might have already been reached.

In low-rate HCC areas, increasing numbers of persons living with cirrhosis is the likely explanation for rising HCC incidence. This has resulted from a combination of factors including rising incidence of cirrhosis due to HCV and, to a lesser extent, HBV infection, as well as a general improvement in survival among cirrhosis patients. It has been estimated that HCV began to infect large numbers of young adults in North America and South and Central Europe in the 1960s and the 1970s as a result of intravenous drug use *(9)*. 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. Currently, it is estimated that HCV-related HCC in low-rate countries will peak around 2010.

1.6. HCC in the United States

Age-adjusted HCC incidence rates increased more than 2-fold between 1985 and 2002 *(10)* (Fig. 3). Average annual, age-adjusted rate of HCC verified by histology or cytology increased from 1.3 per 100,000 during 1978–1980 to 3.3 per 100,000 during 1999–2001 *(11)*. The increase in HCC started in the mid-1980s with greatest proportional increases occurring during the late 1990s. The largest proportional increases occurred among whites (Hispanics and non-Hispanics), while the lowest proportional increases occurred among Asians. The mean age at diagnosis is approximately 65 years, 74% of cases occur in men, and the racial distribution is 48% white, 15% Hispanic, 13% African-American, and 24% other race/ethnicity (predominantly Asian). During recent years as incidence rates increased, the age distribution of HCC patients has shifted toward relatively younger ages, with greatest proportional increases between ages 45 and 60.

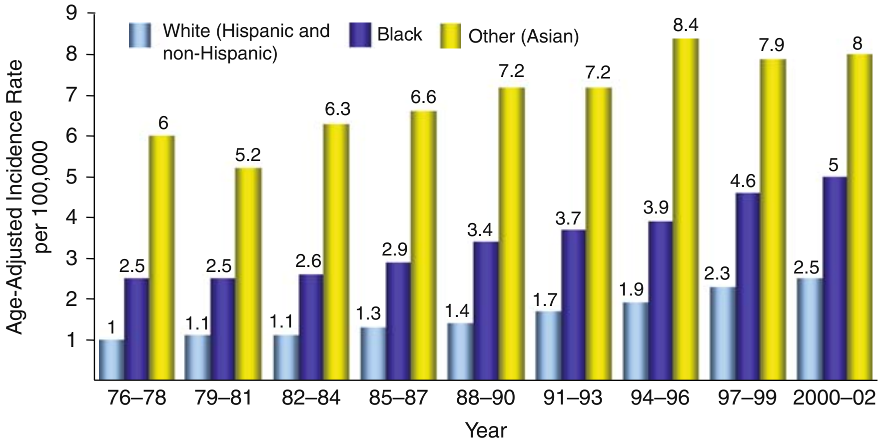

Fig. 3. Average yearly, age-adjusted incidence rates for HCC in the United States shown for 3-year intervals between 1975 and 2002. Whites include approximately 25% Hispanic while other race is predominantly Asian (88%).

Four published studies examined secular changes in HCC risk factors in the United States *(12–15)*. Two studies were from large, single referral centers where viral risk factor ascertainment was based on serology findings, while the other two were from national databases in which risk factors were ascertained from ICD-9 codes in billing or discharge records. In all four studies, the greatest proportional increases occurred in HCV-related HCC, while HBV-related HCC had the lowest and most stable rates. Overall, between 15 and 50% of HCC patients in the United States have no established risk factors.

2. RISK FACTORS OF HEPATOCELLULAR CARCINOMA

HCC is unique in that it largely occurs within an established background of chronic liver disease and cirrhosis (~70–90% of all detected HCC cases) (Fig. 4). Major causes of cirrhosis in patients with HCC include hepatitis B, hepatitis C, alcoholic liver disease, and possibly, non-alcoholic steatohepatitis.

2.1. Hepatitis B Virus

Globally, HBV is the most frequent underlying cause of HCC with an estimated 300 million persons with chronic infection worldwide. Case–control studies have demonstrated that chronic HBV carriers have a 5- to 15-fold increased risk of HCC compared to the general population.

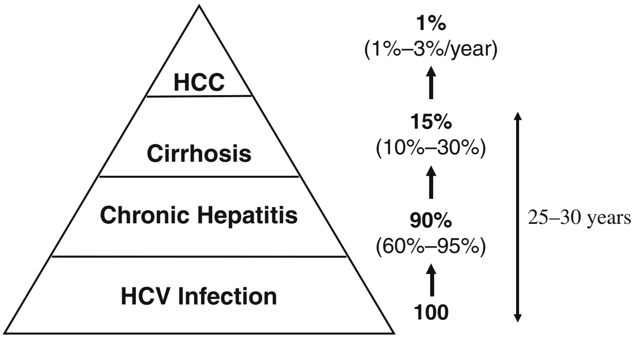

Fig. 4. Estimated progression rates to cirrhosis and hepatocellular carcinoma in hepatitis C infection.

The great majority, between 70 and 90%, of HBV-related HCC develops in a background of cirrhosis. HBV DNA is found in the host genome of both infected and malignant hepatic cells. HBV may, therefore, initiate malignant transformation through a direct carcinogenic mechanism by increasing likelihood of viral DNA insertion in or near proto-oncogenes or tumor-suppressor genes. However, despite initial excitement accompanying this discovery, subsequent research has failed to show a unifying mechanism by which integration of HBV DNA leads to HCC.

The increased HCC risk associated with HBV infection particularly applies to areas where HBV is endemic. In these areas, it is usually transmitted from mother to newborn (vertical transmission) and up to 90% of infected persons follow a chronic course. This pattern is different in areas with low-HCC incidence rates where HBV is acquired in adulthood through sexual and parenteral routes (horizontal transmission) with >90% of acute infections resolving spontaneously. The annual HCC incidence in chronic HBV carriers in Asia ranges between 0.4 and 0.6%. This figure is lower in Alaskan natives (0.26%/year) and lowest in Caucasian HBV carriers *(16)*.

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 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 genotype B *(17)*.

In the natural history of chronic HBV infection, spontaneous or treatment-induced development of antibodies against HBsAg and HBeAg leads to improved clinical outcomes. A meta-analysis of 12 studies with 1,187 patients who received interferon and 665 untreated patients followed for

5 years found lower HCC incidence in treated 1.9% (95% CI 0.8–3.0%) than untreated patients 3.2% (95% CI 1.8–4.5%). However, this difference was not statistically significant *(18)*.

Using sensitive amplification assays, many studies have demonstrated that HBV DNA persists as "occult HBV infection" for decades among persons with serological recovery (HBsAg negative) from acute infection. Occult HBV is associated with anti-HBc and/or anti-HBs *(19)*. However, in a significant proportion of individuals, neither anti-HBc nor anti-HBs can be detected. A single multinational investigation found prevalence of occult HBV in liver tissue to be 11% in Italy, 5–9% in Hong Kong, and 0% in the United Kingdom. Supporting an association with occult HBV, a high proportion of individuals with HCV infection who develop HCC have demonstrable HBV DNA and proteins in their neoplastic and adjacent non-neoplastic liver tissue. However, although some studies have linked development of HCC in individuals with chronic HCV infection to occult HBV, others have not found an association.

2.2. Hepatitis C Virus

Chronic HCV infection is a major risk factor for development of HCC. Markers of HCV infection are found in a variable proportion of HCC cases; for example, 44–66% in Italy, *(20, 21)* 27–58% in France, 60–75% in Spain, and 80–90% in Japan *(8)*. A higher but undefined proportion of HCC patients might have had HCV detected by PCR testing of liver tissue and/or serum, even if antibody to HCV (anti-HCV) was non-detectable. 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 (95% CI 14–22) *(22)*.

The likelihood of development of HCC among HCV-infected persons is difficult to determine due to the paucity of adequate long-term cohort studies; however, the best estimate is from 1 to 3% after 30 years (Fig. 5). HCV increases HCC risk by promoting fibrosis and eventually cirrhosis. Once HCV-related cirrhosis is established, HCC develops at an annual rate of 1–4%; though rates up to 7% have been reported in Japan. Rates of cirrhosis 25–30 years post-infection range between 15 and 35% *(23)*. The highest incidence rates were observed in HCV-contaminated blood or blood products recipients (14 and 1 per 1000 person-years for cirrhosis and HCC, respectively) and in hemophiliacs (5 and 0.7 per 1000 person-years). The lowest rates have been reported in women who received a one-time contaminated anti-D immune globulin treatment (1 and 0 per 1000 person-years, respectively).

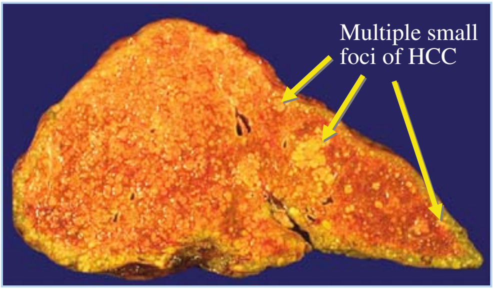

Fig. 5. Cirrhosis and hepatocellular carcinoma. Explanted liver showing features of cirrhosis and multiple small foci of HCC throughout the liver in a miliary pattern (*arrows*).

In HCV-infected patients, factors related to host and environment/lifestyle appear to be more important than viral factors in determining progression to cirrhosis. These factors include older age, older age at the time of acquisition of infection, male gender, heavy alcohol intake (>50g/day), diabetes, obesity, and coinfection with HIV or HBV *(24)*. There is no strong evidence that HCV viral factors like genotype, viral load, or quasispecies are important in determining the risk of progression to cirrhosis or HCC.

Successful antiviral therapy in patients with HCV-related cirrhosis may reduce future risk of HCC, but the evidence is weak. There is only one prospective, randomized, controlled trial that examined the effects of antiviral therapy on HCC, a Japanese trial in which 100 patients were randomized to receive either 6 million units of interferon alfa thrice weekly for 3–6 months or were followed without treatment *(25)*. After a 2- to 7-year follow-up period, HCC was significantly reduced in the treated (4%) compared to the non-treated control group (38%), a 93% reduction in adjusted risk. However, much of this risk reduction was a result of the unusually high HCC rate among these controls. Other studies, mostly retrospective and non-randomized, suggested moderately decreased HCC risk among HCV-infected patients treated with interferon *(26–37)*.

In general, reported preventive effects of interferon therapy were less marked in European compared to Japanese studies. However, the lack of randomization in most of these studies may exaggerate treatment benefits as it is likely that healthier patients tend to get treated more frequently than those with advanced liver disease (who are known to be more likely to develop HCC). In addition to a role in primary prevention of HCC among HCV-infected patients, a few Japanese reports suggest interferon may also be effective for secondary prevention in individuals who have previously undergone resection for HCC.

2.3. Alcohol

Heavy alcohol intake, defined as ingestion of >50–70 g/day for prolonged periods, is a well-established HCC risk factor. It is unclear whether risk of HCC is significantly altered in those with low or moderate alcohol intake. Although heavy intake is strongly associated with development of cirrhosis, there is little evidence of a direct carcinogenic effect of alcohol otherwise.

There is also evidence for a synergistic effect of heavy alcohol ingestion with HCV or HBV, with these factors presumably operating together to increase HCC risk by more actively promoting cirrhosis. For example, Donato et al. *(22)* reported that among alcohol drinkers, HCC risk increased in a linear fashion with daily intake >60 g. However, with concomitant presence of HCV infection, there was an additional 2-fold increase in HCC risk over that observed with alcohol usage alone (i.e., a positive synergistic effect).

2.4. Aflatoxin

Aflatoxin B_1 (AFB_1) is a mycotoxin produced by the *Aspergillus* fungus. This fungus grows readily on foodstuffs like corn and peanuts stored in warm, damp conditions. Animal experiments demonstrated that AFB_1 is a powerful hepatocarcinogen leading the International Agency for Research on Cancer (IARC) to classify it as carcinogenic *(30)*.

Once ingested, AFB_1 is metabolized to an active intermediate, AFB_1-*exo*-8,9-epoxide, which can bind to DNA and cause damage, including producing a characteristic mutation in the p53 tumor-suppressor gene (p53 249^{ser}) *(29)*. This mutation has been observed in 30–60% of HCC tumors in aflatoxin endemic areas *(27, 36)*.

Strong evidence that AFB_1 is a risk factor for HCC has been supplied by person-specific epidemiological studies performed in the last 15 years. These studies were permitted by development of assays for aflatoxin metabolites in urine, AFB_1-albumin adducts in serum, and detection of a signature aflatoxin DNA mutation in tissues.

Interaction between AFB_1 exposure and chronic HBV infection was revealed in short-term prospective studies in Shanghai, China. Urinary excretion of aflatoxin metabolites increased HCC risk 4-fold while HBV infection increased risk 7-fold. However, individuals who both excreted AFB_1 metabolites and were HBV carriers had a dramatic 60-fold increased risk of HCC *(38)*.

In most areas where AFB_1 exposure is a problem, chronic HBV infection is also highly prevalent. Though HBV vaccination is these areas should be the major preventive tactic, persons already chronically infected will not benefit from vaccination. However, HBV carriers could benefit by eliminating AFB_1 exposure. Efforts to accomplish this goal in China *(7)* and Africa *(36)* have been launched.

2.5. Non-alcoholic Fatty Liver Disease (NAFLD) and Non-alcoholic Steatohepatitis (NASH)

Studies in the United States evaluating risk factors for chronic liver disease or HCC have failed to identify HCV, HBV, or heavy alcohol intake in a large proportion of patients (30–40%). It has been suggested that many cryptogenic cirrhosis and HCC cases, in fact, represent more severe forms of non-alcoholic fatty liver disease (NAFLD), namely non-alcoholic steatohepatitis (NASH). Potential risk factors such as diabetes, obesity, and possibly HCV are likely to increase HCC risk at least partly by promoting NAFLD and NASH.

One difficulty in epidemiological studies attempting to elucidate the association between NASH and risk of HCC in humans, however, is that once either cirrhosis or HCC is established, it is difficult to identify pathological features of NASH. Several clinic-based case–control studies have, in fact, indicated that HCC patients with cryptogenic cirrhosis tend to have clinical and demographic features suggestive of NASH (predominance of women, diabetes, obesity) than age- and sex-matched HCC patients of well-defined viral or alcoholic etiology *(2–4)*. For example, Regimbeau et al. examined 210 patients who underwent resection for HCC of whom 18 (8.6%) had no identifiable cause for chronic liver disease and found higher prevalence of obesity (50% vs. 17% vs. 14%) and diabetes (56% vs. 17% vs. 11%) compared to patients with alcoholic and viral hepatitis, respectively *(39)*. Evidence of progression from NAFLD to HCC from prospective studies is scant. There are case reports *(5, 6)* and a small case series describing development of HCC several years following NASH diagnosis *(40)*. In a community-based retrospective cohort study, 420 patients diagnosed with NAFLD in Olmsted County, MN, were followed for a mean duration of 7.6 years. In that study, liver disease was the third leading cause of death (as compared with the 13th leading cause of death in the general Minnesota population) occurring in seven (1.7%) subjects. Twenty-one (5%) patients were diagnosed with cirrhosis of whom two developed HCC *(5, 6, 8)*.

2.6. Diabetes

Diabetes, particularly type II diabetes, has been proposed to be a risk factor for both chronic liver disease and HCC through development of NAFLD and NASH. It is known to contribute significantly to hepatic steatosis *(9, 10)* with development of increased levels of steatosis associated with more severe necroinflammatory activity *(11, 12)* and fibrosis *(16–18)*. Fibrosis progression rates have also appeared to be higher when marked steatosis was present *(19)*, with some studies suggesting that the increase in steatosis itself may be an indicator of fibrosis progression *(13)*. Additionally, liver disease occurs more frequently in those with more severe metabolic disturbances, with insulin resistance itself demonstrated to increase as liver disease progresses *(20)*.

Several case–control studies from the United States, Greece, Italy, Taiwan, and Japan examined the association between diabetes, mostly type II, and HCC. At least eight studies found a significant positive association between diabetes and HCC, two found a positive association that did not quite reach significance, and one found a significant negative association. A potential bias in cross-sectional and case–control studies, however, is difficulty in discerning temporal relationships between exposures (diabetes) and outcomes (HCC). This problem is relevant in evaluating HCC risk factors because 10–20% of patients with cirrhosis have overt diabetes and a larger percentage have impaired glucose tolerance. Thus, diabetes may also be the result of cirrhosis.

Cohort studies, which are intrinsically better suited to discern temporal relationships between exposure and disease, have also been conducted. All compared HCC incidence in cohorts of diabetic patients to either the expected incidence given HCC rates in the underlying population or the observed HCC incidence among a defined cohort without diabetes *(41)*. Three studies conducted among younger or smaller cohorts found either no or low number of HCC cases. At least four other cohort studies examined large number of patients for relatively long time periods, with three studies finding significantly increased risk of HCC with diabetes (risk ratios ranging between 2 and 3) *(21–23)*. We recently conducted a study of HCC incidence in a large cohort of VA patients ($n = 173{,}643$ with and $n = 650{,}620$ without diabetes). The findings of this study indicate HCC incidence doubled among patients with diabetes and was higher among those with longer duration of follow-up *(41)* (Fig. 7).

While most studies have been conducted in low-HCC rate areas, diabetes has also been found to be a significant risk factor in areas of high HCC incidence like Japan. Further, although other underlying risk factors like HCV may confound the association between diabetes and HCC, they do not seem to fully explain it. Taken together, available data suggest that diabetes is a moderately strong risk factor for HCC *(42)*. However, additional research is needed to more fully examine how any excess risk conveyed by diabetes is mediated by such potentially confounding factors as duration and treatment of diabetes, family history of diabetes, and current and historical levels of obesity and physical activity.

2.7. Obesity

Obesity, especially abdominal obesity, is strongly correlated with insulin resistance and type II diabetes, a state of clinically diagnosable advanced insulin resistance that has itself been associated with HCC risk. Some evidence in support of a direct contribution of obesity-mediated metabolic errors in hepatocarcinogenesis comes from experimental research in a genetically obese ob/ob knockout mouse model of NAFLD that demonstrated hepatic hyperplasia even at very early stages of disease and without evidence of cirrhosis *(25)*.

The effect of obesity on HCC risk has been examined in several cohort studies. In a large prospective cohort study of more than 900,000 individuals from around the United States followed for a 16-year period, liver cancer mortality rates were five times greater among men with the greatest baseline BMI (35–40) compared to those with normal BMI *(43)* (Fig. 6). In the same study, the risk of liver cancer was not as elevated in women with a relative risk of 1.68 (0.93–3.05). Two other population-based cohort studies from Sweden and Denmark found excess HCC risk (elevated relative risk of 2- to 3-fold) in obese men and women compared to those with normal BMI *(44, 45)*. The effects of obesity on HCC risk may vary according to the presence of other underlying risk factors for HCC; however, the data are consistent. In a large prospective cohort study in Taiwan, obesity (BMI 30+) conveyed excess risk of HCC even after controlling for other metabolic risk factors including presence of diabetes mellitus *(26)*. The greatest increase in risk with obesity was observed in the context of HCV infection (HR = 4.10, 95% CI 1.38–12.4). While a 2.4-fold excess risk that approached significance was also observed among persons who were negative for both HBV and HCV infection, obesity conveyed only a very modest and non-significant 1.4-fold excess risk among persons with HBV

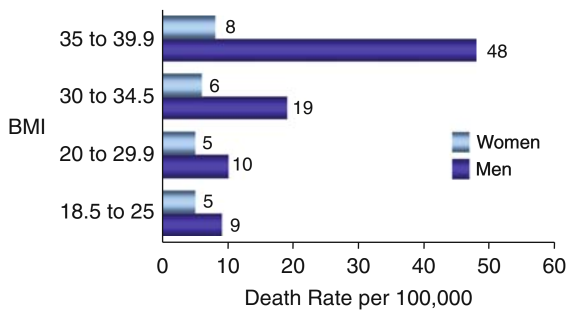

Fig. 6. Obesity and liver cancer. In both men and women, a higher body mass index (BMI) is significantly associated with higher rates of death due to cancer of the liver. Modified from Calle et al. *(43)*.

infection. There was, however, evidence of very strong synergism between obesity and diabetes which, when both conditions occurred together, conveyed a 100-fold excess HCC risk with obesity in the context of either HBV or HCV infection. In a retrospective study of over 19,000 registry-listed individuals in the United states with cirrhosis who received a liver transplant, the effect of obesity on HCC risk also varied according to disease etiology *(46)*. Specifically, obesity conveyed strong and significant excess risk of HCC even after controlling for presence of diabetes among transplant recipients with cryptogenic or alcoholic cirrhosis (OR = 11.1, 95% CI 1.5–87.4 and OR = 3.2, 95% CI 1.5–6.6, respectively). However, obesity was not an independent predictor of HCC risk among those with other disease etiologies including HCV or HBV infection, biliary cirrhosis, or autoimmume hepatitis.

Several case–control studies have also evaluated the association between BMI and risk of HCC. In a study in Japan conducted in chronically HCV-infected patients, the incidence of HCC was significantly increased among those with a higher BMI. Further, there was also evidence of a dose-dependent relationship with a significant 1.8-fold excess HCC risk in HCV+ cases who were overweight (BMI 25–<30) that increased to a 3.1-fold excess in those who were obese (BMI 30+) in comparison to lean HCV+ cases *(33)*. Another case–control study conducted in a regional medical center in the United States compared the prevalence of obesity among 70 HCC cases to that observed among 140 age- and gender-matched controls ($n = 70$ with cirrhosis and $n = 70$ without liver disease) *(47)*. HCC cases were significantly more likely to be obese than either patients with cirrhosis or normal controls (OR = 4.3, 95% CI 2.1–8.4 and OR = 47.8, 95% CI 9.6–74.5). Further, there was evidence of significant synergism or particularly increased risk of HCC among those with obesity (BMI 30+) who also had more than 100 drinks and smoked more than 100 cigarettes during their lifetime (OR = 7.4, 95% CI 2.1–14.6). Although this study did not include adjustment for presence of diabetes, the overall prevalence of diabetes was similar among the HCC case, cirrhotic case, and normal control groups.

Taken together the data suggest that obesity conveys excess risk of HCC beyond that conveyed by diabetes. However, the actual magnitude of risk and the specific subgroups of chronic liver disease patients in whom its presence may be most salient in promoting HCC risk varied across studies. Future research with evaluation of additional factors that may influence obesity-mediated risk of HCC including timing and duration of obesity as well as family history of obesity and diabetes may be helpful in identifying subgroups of obese chronic liver disease patients who may particularly benefit from enhanced surveillance and therapeutic interventions.

In conclusion, many developing countries are in the midst of a burgeoning obesity epidemic. This is particularly apparent in the United States where