PART 1
Learning from a Worldwide Perspective

1 Are patterns and prevalence changing?

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LEARNING POINTS

- Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, and in the absence of early detection through tumour surveillance, it is usually fatal with almost equal incidence and mortality rates in most parts of the world
- Most cases of HCC arise in those with established cirrhosis (annual rate of HCC in cirrhosis is 1–7%)
- Most cases of HCC are reported from hepatitis B virus (HBV) endemic areas in Southeast Asia and sub-Saharan Africa; many risk factors for HCC have been identified among those with chronic hepatitis C virus (HCV) or HBV
- There is a partly unexplained 2–4-fold increase in HCC risk in men, compared with women
- Viral hepatitis (HBV and HCV) is responsible for most cases of HCC worldwide
- The HCV epidemic in many regions, including the United States, has resulted in a recent dramatic increase in HCC incidence
- New risk factors for HCC include insulin resistance syndrome, manifesting as diabetes-related liver disease or obesity-related liver disease; given the high prevalence of these risk factors, even small increases in HCC risk may result in a considerable number of future HCC cases
- Apart from alcohol (which increases HCC risk) and coffee (which decreases HCC risk), the role of dietary factors is unclear

Liver cancer is the fifth most common cancer in men (522,000 cases, 7.9% of the total) and the seventh in women (225,000 cases, 6.5% of the total). Most of the burden is in developing countries, where almost 85% of the cases occur. Owing to its high fatality (overall ratio of mortality to incidence of 0.93), liver cancer is the third most common cause of death from cancer worldwide [1]. Hepatocellular carcinoma (HCC) accounts for 85–90% of all primary liver cancer (PLC) [2]. The aetiology of HCC, with more than 80% arising in patients infected by hepatitis B virus (HBV) or hepatitis C virus (HCV) [3], explains several features of the distinct geographic variations and temporal trends of liver cancer.

Figure 1.1 shows the considerable regional heterogeneity in the incidence of PLC worldwide. The highest age-standardised rates (ASRs) (more than 20 per 100,000 underlying population) are reported from countries in Southeast Asia (North and South Korea, China, Vietnam). These regions are endemic for HBV infection, with most PLC in these regions constituted by HCC. Exceptions to this generalisation include Thailand, where cholangiocarcinoma due to high exposure to liver flukes is the predominant form of PLC. Another exception is Japan, where HCV is the predominant risk factor for HCC in this high incidence area.

Owing to its very large population and high ASRs, China alone sees more than 55% of all PLC worldwide, with rates of 38–40 per 100,000 in males and 14–15 per 100,000 in females. Other high-incidence areas outside Southeast Asia include sub-Saharan African countries such as Cameroon and Mozambique. In general, countries in southern Europe have medium–high incidence rates (ASR in males: 10–15 per 100,000), with Italy on the high end with an ASR of 15.9 in men and 5.1 in women. Intermediate incidence areas (ASR: 5–10 per 100,000) include the United

Clinical Dilemmas in Primary Liver Cancer, First Edition. Edited by Roger Williams and Simon D. Taylor-Robinson.

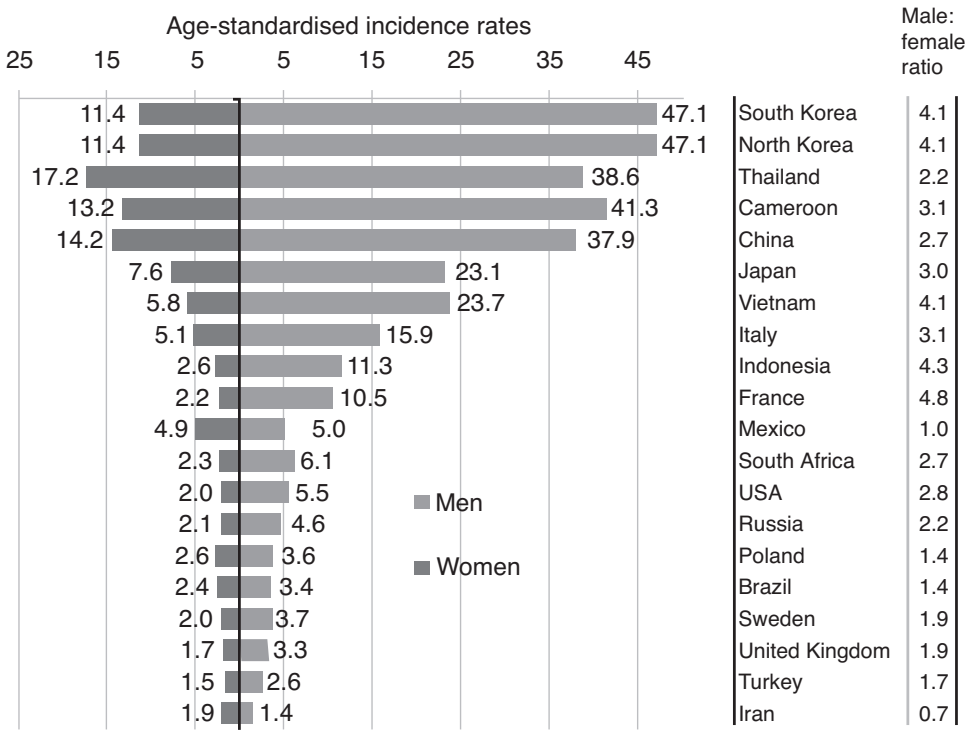

FIG 1.1 Age-standardised incidence rates of primary liver cancer per 100,000 population at risk. (GLOBOCAN 2002. The age-standardised rate is calculated using the 1960 world standard population.)

Kingdom (where cholangiocarcinoma is the commonest PLC), the United States, France and Germany. Low-incidence areas include South and Central America, Europe excluding the Mediterranean countries and North America (ASRs in males: less than 6 per 100,000).

There have been encouraging trends in liver cancer incidence in some high-rate areas [4], such as China, Japan and part of Europe, where HCC has been declining [5,6]. On the other hand, substantial increases in HCC incidence and mortality rates have been observed in areas previously considered low incidence in North America, Europe and Oceania. In these regions, HCV is the most frequent aetiologic risk factor, accounting for 30–50% of HCC cases. For example, incidence of HCC has tripled in the United States during the past two decades [7] and has become the most rapidly increasing cause of cancer-related deaths [8].

The median survival of PLC patients is estimated at less than 1 year [9]. There is considerable regional variation in mortality that tends to mirror those reported for incidence rates. In addition, there are also significant differences in the proportion of total cancer mortality attributable to PLC in different regions. For example, in Cameroon and Thailand, about one third of all cancer deaths are due to PLC, compared with less than 5% in most Western countries in Europe and North America.

Demographic features of HCC

Age

HCC is rare before age 40 and reaches a peak at around age 70. In low-risk populations (e.g. US, Canada, UK), the highest age-specific rates occur among persons 75 years and older. However, in Qidong, China, where HCC rates are among the world's highest, age-specific incidence rates among males rise until age 45 and then plateau. In all regions, female rates peak in the age group 5 years older than the peak age group for males. The variable age-specific patterns in different geographic regions 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.

Sex

There is a striking male predominance in HCC, with the highest male to female ratios seen in high and medium HCC incidence areas. HCC is more equally distributed among men and women in low-incidence countries in South and Central America. The prevalence of HBV, HCV, alcohol consumption and cigarette smoking is higher in men than in women. Some of the male predominance seen in HCC can be explained by higher cancer rates in males in general. A possible role of sex hormones in the development of HCC has also been suggested [10]. High serum testosterone levels have been associated with risk of HCC in nested case-control studies among HBV carriers in Taiwan and Shanghai [11].

Race/ethnicity

HCC incidence rates also vary substantially among different populations living in the same region. For example, ethnic Chinese populations of Singapore have considerably higher age-adjusted rates than Indians in the same region [12]. Another example, the age-adjusted HCC incidence rates in individuals of Asian/Pacific Islander ethnicity were almost three times higher than that in whites (ASRs 11.7 and 3.9, respectively), with Hispanics and blacks in between these two extremes (ASRs 8.0 and 7.0, respectively) [13]. Differences in the prevalence of the main risk factors may explain some of these differences; for example first generation immigrants from Southeast Asia have high HBV infection rates.

Risk factors for HCC

The main HCC risk factors are HBV, HCV, alcohol, aflatoxin and possible obesity and diabetes. Together HBV and HCV account for 80–90% of all HCC worldwide [3] (Table 1.1). Mendelian disorders (e.g. Wilson's disease, alpha-1 antitrypsin deficiency and hemochromatosis) account for a very small proportion of HCC. Cryptogenic or unknown aetiology HCC accounts for 15–30% of cases. Most HCC risk factors promote formation of cirrhosis, which is present in about 80–90% of HCC patients [14,15]. The risk of developing HCC in cirrhosis patients varies considerably with the underlying condition and severity of cirrhosis [16]. The highest 5-year cumulative risks are seen in HCV cirrhosis (30% in Japan and 17% in the West), hemochromatosis (21%), HBV cirrhosis (15% in Asia and 10% in the West), alcoholic cirrhosis (8%) and biliary cirrhosis (4%) [17].

TABLE 1.1 Estimated cases of primary liver cancer in 2002 attributable to HBV and HCV

	Primary liver cancer cases	HCV Attributable fraction (%)	HBV Attributable fraction (%)
Developed countries	110,800	23.3	19.9
Developing countries	515,300	58.8	33.4
Total	626,100	54.4	31.1

Source: Adapted from Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 2006; 118(12):3030–3044.

HBV

Approximately 350 million people around the world are estimated to be chronically infected by HBV [18]. Worldwide, chronic HBV infection accounts for approximately 50% of HCC cases [19] with considerable regional variation (70% in South Korea, 10–15% in Japan [20], 3% in Sweden, 9% in the United States and 55% in Greece [21]). The lifetime risk of HCC for a person with a chronic HBV infection is between 10% and 25% [22], which is 15–20-fold higher than non-infected controls [23,24]. HBV is a notorious cause for HCC in the absence of cirrhosis; however, the great majority (70–90%) of HBV-related HCC develops in livers already afflicted by cirrhosis [2].

The increased HCC risk associated with HBV infection particularly applies to areas where HBV infection is endemic. In these areas, HBV 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 more than 90% of acute infections resolving spontaneously. The annual HCC incidence in chronic HBV carriers in Asia ranges between 0.4% and 0.6%, but is considerably lower in Caucasian HBV carriers [25].

Several additional factors increase HCC risk among HBV carriers, including male sex, older age, longer duration of

infection, family history of HCC, exposure to aflatoxin, alcohol or tobacco or co-infection with HCV or delta hepatitis. HCC risk is also increased in patients with high levels of HBV hepatocellular replication, as indicated by high HBV DNA levels, presence of HBeAg [26] or HBV genotype C [27]. HBV DNA can also be detected in hepatitis B surface antigen (HBsAg)-negative individuals, but it has an unclear association with HCC risk There is moderately strong evidence that effective antiviral therapy that controls HBV infection in HBsAg-positive patients in viremic patients substantially reduces, but does not eliminate, HCC risk. One high-quality Taiwanese randomised controlled trial in patients with chronic HBV who had cirrhosis reported a significant reduction of HCC in patients treated with lamivudine for several years compared with placebo (3.9% vs. 7.4%; hazard ratio 0.49; $p = 0.047$) [28].

The risk of HCC is substantially lower in persons who are immune to HBV. For example, in the seminal study by Beasley et al. [29], the incidence of HCC was significantly lower in immune persons compared with carriers (5 vs. 495 per 100,000 per year) [29]. By using sensitive amplification assays, many studies have shown that HBV DNA persists as 'occult HBV infection' for decades among persons with serological recovery (HBsAg negative) from acute infection [30]. Although some studies have linked development of HCC in individuals with chronic HCV infection to occult HBV, others have not found an association. Frequently cited reports from Taiwan have described a reduction of HCC incidence rates in children 1–2 decades after the introduction of a universal vaccination programme against HBV [31].

Dietary aflatoxin

Aflatoxins are naturally occurring, potent hepatocarcinogenic mycotoxins produced by some *Aspergillus* species. They are moulds that grow on grains, corn, cassava, peanuts and fermented soy beans particularly under high moisture conditions in parts of sub-Saharan Africa and eastern Asia. Animal experiments demonstrated that AFB_1 is a powerful hepatocarcinogen, leading the International Agency for Research on Cancer to classify it as carcinogenic [32]. Once ingested, AFB_1 is metabolised to an active intermediate, AFB_1-*exo*-8,9-epoxide, which can bind to DNA and produce a characteristic mutation in the *p53* tumour suppressor gene ($p53\ 249^{ser}$) [33]. This mutation has been observed in 30–60% of HCC tumours in aflatoxin endemic areas [34,35]. Individuals infected by HBV and exposed to aflatoxin have an even higher risk of liver cancer, suggesting a synergistic effect between HBV and aflatoxin [36]. Though HBV vaccination in 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 have been launched to accomplish this goal in China [37] and Africa [35].

HCV

The global HCV prevalence is estimated to be 2% and as high as 10% in Egypt [38]. It has been estimated that HCV began to infect large numbers of young adults in Japan in the 1920s and in southern Europe in the 1940s and in North America in the 1960s and 1970s as a result of contaminated needles and/or injection drug use [39]. The virus then migrated into national blood supplies and circulated until a screening test was developed in 1990, after which the rates of new infection dropped dramatically.

The association between HCV infection and increased HCC risk is well established and has been shown in case-control as well as cohort studies. Markers of HCV infection are found in a variable proportion of HCC cases, for example 45–65% in Italy [40,41] and 80–90% in Japan [42]. HCC risk increased 17–20-fold in HCV-infected patients compared with HCV-negative controls [43].

The rate of HCC development in HCV-infected persons ranges from 1% to 3% after 30 years of chronic infection [44]. HCV increases HCC risk by promoting fibrosis and eventually cirrhosis. Once cirrhosis is established, the annual incidence of HCC is 1–4% [16]. In HCV-infected patients, factors related to host and environment or lifestyle appear to be more important than viral factors in determining progression to cirrhosis. These factors include: older age overall as well as older age at the time of HCV acquisition, male sex, heavy alcohol intake (more than 50 g/day), diabetes, obesity and co-infection with HIV or HBV [45]. On the other hand, HCV viral load and HCV genotype have not been associated with HCC risk.

Alcohol

Heavy alcohol intake, defined as ingestion of more than 50–70 g/day for several years, is a well-established HCC risk factor. It is unclear whether the risk of HCC is significantly altered in those with low or moderate alcohol intake. There is 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 [43].

Fatty liver disease. Many studies conducted in Western countries fail to identify a major risk factor (HBV, HCV, alcohol) for chronic liver disease or HCC in a large proportion of patients (30–40%). Non-alcoholic fatty liver disease (NAFLD), including its more advanced form non-alcoholic steatohepatitis (NASH), has been proposed as the aetiologic factor for many cases of cryptogenic HCC. Insulin resistance has been proposed as the major pathogenic mechanism for this disorder as well as its progression to NASH. Obesity and diabetes are the major clinical manifestations of the insulin resistance syndrome.

There is epidemiologic evidence in support of a potential association between NAFLD/NASH and a modest increase in HCC risk. The few available population-based cohort studies of patients with NAFLD/NASH provide a modest support for this association [46,47]. Cross-sectional and case-control studies are limited due to the requisite histopathological features for confirmed NAFLD/NASH diagnosis being less evident, or even absent, once cirrhosis is established. Indirect evidence to the NAFLD–HCC association is provided by multiple cross-sectional and case-control studies showing significantly higher prevalence of obesity and diabetes among patients with cryptogenic cirrhosis compared with controls with other causes of liver disease [48–51]. It is clear that development of cirrhosis related to NASH signals a considerable increase in HCC risk. Most studies that evaluated cryptogenic cirrhosis or documented NASH-related cirrhosis reported high HCC incidence. While the progression of NAFLD/NASH to cirrhosis and NAFLD/NASH-related HCC may very well be infrequent, given vast and increasing prevalence, obesity and diabetes could still contribute a large HCC.

Obesity

It has been estimated that up to 90% of all obese individuals (BMI >30 kg/m^2) and up to 70% of all people with diabetes have some type of fatty liver disease [52]. 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 4.5 higher in men with a BMI >35 kg/m^2 and 1.7 higher in women with a BMI >35 kg/m^2, compared with normal-weight individuals [53]. Two other population-based cohort studies from Sweden and Denmark found a 2–3-fold increased HCC risk in obese men and women compared with those with normal BMI [54,55]. Diabetes, particularly type 2, has been proposed to be a risk factor for both chronic liver disease and HCC. Several case-control studies have examined the association between diabetes and HCC. The majority found a statistically significant association with 50–100% increased HCC risk in the presence of diabetes. However, reverse causality is a concern in all these studies because in some cases diabetes might itself be a result of cirrhosis. A few cohort studies, better suited to evaluate temporality, have been conducted, showing that individuals with type 2 diabetes had on average a doubled risk to develop HCC, with one showing an association between longer duration of diabetes and increased HCC risk [41,56]. Additional research is needed to examine how any excess risk conveyed by diabetes is mediated by the duration and treatment of diabetes, a family history of diabetes, by obesity and by physical activity.

Tobacco smoking

The relationship between cigarette smoking and HCC has been examined in more than 50 studies in both low- and high-rate areas. In almost all countries, both positive association and lack of association findings have been reported. Taken together, available evidence suggests that any effect of smoking on HCC is likely to be weak and limited to a subset of the general population.

Diet

The role of diet, except for alcohol and coffee drinking, in the aetiology of HCC in human populations is largely unknown. Coffee drinking has been studied extensively in relation to HCC. Several epidemiological studies have previously reported coffee drinking reduces risk of elevated liver enzymes and of cirrhosis, while animal studies suggest that coffee reduces liver carcinogenesis. Further, coffee drinking has also been associated with reduced insulin levels as well as reduced risk of type 2 diabetes, in itself considered to be a risk factor for HCC [57].

Both case-control and cohort studies conducted in Japan and Southern Europe specifically evaluated the relationship between coffee consumption and HCC risk, most reporting a significantly reduced risk of HCC with increased consumption [58–60].

Future trends

HBV continues to be the major HCC risk factor worldwide, although its importance will most likely decrease during the coming decades because of the widespread use of the HBV vaccine in the newborns in HBV endemic and HCC high-incidence areas. This effect may become more tangible as the first individuals to get immunised grow older. HCV has been the dominant viral cause in HCC in North America, some Western countries and Japan. Obesity and diabetes are increasing at a fast pace throughout the world, and if they are established as HCC risk factors, whether independently or in the presence of viral hepatitis or alcohol abuse, these conditions would plausibly account for more HCC cases in the future.

References

1. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0. IARC Cancer Base No. 5. IARC Press, Lyon; 2001. Available from: http://globocan.iarc.fr .
2. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 2007; 132(7):2557–2576.
3. Bosch FX, Ribes J, Cleries R, et al. Epidemiology of hepatocellular carcinoma. *Clin Liver Dis* 2005; 9(2):191–211, v.
4. McGlynn KA, Tsao L, Hsing AW, et al. International trends and patterns of primary liver cancer. *Int J Cancer* 2001; 94(2):290–296.
5. Bosetti C, Bianchi C, Negri E, et al. Estimates of the incidence and prevalence of hepatocellular carcinoma in Italy in 2002 and projections for the years 2007 and 2012. *Tumori* 2009; 95(1):23–27.
6. Jepsen P, Vilstrup H, Tarone RE, et al. Incidence rates of hepatocellular carcinoma in the US and Denmark: recent trends. *Int J Cancer* 2007; 121(7):1624–1626.
7. El-Serag HB. Hepatocellular carcinoma: recent trends in the United States. *Gastroenterology* 2004; 127(5 suppl 1):S27–S34.
8. Ries L, Melbert D, Krapcho M, et al. *SEER Cancer Statistics Review, 1975–2004.* National Cancer Institute, Bethesda, MD; 2007.
9. Nguyen VT, Law MG, Dore GJ. Hepatitis B-related hepatocellular carcinoma: epidemiological characteristics and disease burden. *J Viral Hepat* 2009; 16(7):453–463.
10. Yu MW, Chang HC, Chang SC, et al. Role of reproductive factors in hepatocellular carcinoma: Impact on hepatitis B- and C-related risk. *Hepatology* 2003; 38(6):1393–1400.
11. Yuan JM, Ross RK, Stanczyk FZ, et al. A cohort study of serum testosterone and hepatocellular carcinoma in Shanghai, China. *Int J Cancer* 1995; 63(4):491–493.
12. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. *Cancer Incidence in Five Continents*, Vol. VIII. IARC Scientific Publications No. 155. IARC Press, Lyon; 2002.
13. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol* 2009; 27(9):1485–1491.
14. Colombo M, de FR, Del NE, et al. Hepatocellular carcinoma in Italian patients with cirrhosis. *N Engl J Med* 1991; 325(10):675–680.
15. Tiribelli C, Melato M, Croce LS, et al. Prevalence of hepatocellular carcinoma and relation to cirrhosis: comparison of two different cities of the world – Trieste, Italy, and Chiba, Japan. *Hepatology* 1989; 10(6):998–1002.
16. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997; 112(2): 463–472.
17. Fattovich G, Stroffolini T, Zagni I, et al. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; 127(5 suppl 1):S35–S50.
18. WHO. Hepatitis B. 2008 (Fact Sheet No. 204). 2010. 11-10-2009.
19. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 2006; 118(12): 3030–3044.
20. Kim SR, Kudo M, Hino O, et al. Epidemiology of hepatocellular carcinoma in Japan and Korea. A review. *Oncology* 2008; 75(suppl 1):13–16.
21. Raza SA, Clifford GM, Franceschi S. Worldwide variation in the relative importance of hepatitis B and hepatitis C viruses in hepatocellular carcinoma: a systematic review. *Br J Cancer* 2007; 96(7):1127–1134.
22. Seeger C, Mason WS. Hepatitis B virus biology. *Microbiol Mol Biol Rev* 2000; 64(1):51–68.
23. Donato F, Boffetta P, Puoti M. A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. *Int J Cancer* 1998; 75(3):347–354.
24. Shi J, Zhu L, Liu S, et al. A meta-analysis of case-control studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma in China. *Br J Cancer* 2005; 92(3):607–612.
25. McMahon BJ, Alberts SR, Wainwright RB, et al. Hepatitis B-related sequelae. Prospective study in 1400 hepatitis B surface antigen-positive Alaska native carriers. *Arch Intern Med* 1990; 150(5):1051–1054.

26. Chen CJ, Yang HI, Iloeje UH, REVEAL-HBV Study Group. Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. *Hepatology* 2009; 49(5 suppl):S72–S84.
27. Yang HI, Yeh SH, Chen PJ, et al. Associations between hepatitis B virus genotype and mutants and the risk of hepatocellular carcinoma. *J Natl Cancer Inst* 2008; 100(16):1134–1143.
28. Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004; 351(15):1521–1531.
29. Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. *Cancer* 1988; 61(10):1942–1956.
30. Torbenson M, Thomas DL. Occult hepatitis B. *Lancet Infect Dis* 2002; 2(8):479–486.
31. Chang MH, Chen CJ, Lai MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med* 1997; 336(26):1855–1859.
32. IARC Monographs. *Overall evaluations of carcinogenicity: An updating of IARC monographs volumes 1–42.* Suppl. 7. Lyon: IARC Press 1987; 83–87.
33. Garner RC, Miller EC, Miller JA. Liver microsomal metabolism of aflatoxin B 1 to a reactive derivative toxic to Salmonella typhimurium TA 1530. *Cancer Res* 1972; 32(10):2058–2066.
34. Bressac B, Kew M, Wands J, et al. Selective G to T mutations of p53 gene in hepatocellular carcinoma from southern Africa. *Nature* 1991; 350(6317):429–431.
35. Turner PC, Sylla A, Diallo MS, Castegnaro JJ, Hall AJ, Wild CP. The role of aflatoxins and hepatitis viruses in the etiopathogenesis of hepatocellular carcinoma: a basis for primary prevention in Guinea-Conakry, West Africa. *J Gastroenterol Hepatol* 2002; 17(suppl):S441–S448.
36. Qian GS, Ross RK, Yu MC, et al. A follow-up study of urinary markers of aflatoxin exposure and liver cancer risk in Shanghai, People's Republic of China. *Cancer Epidemiol Biomarkers Prev* 1994; 3(1):3–10.
37. Yu S. Primary prevention of hepatocellular carcinoma. *J Gastoenterol Hepatol* 1995; 10:674–682.
38. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis* 2005; 5(9):558–567.
39. Armstrong GL, Alter MJ, McQuillan GM, et al. The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. *Hepatology* 2000; 31(3):777–782.
40. Fasani P, Sangiovanni A, De FC, et al. High prevalence of multinodular hepatocellular carcinoma in patients with cirrhosis attributable to multiple risk factors. *Hepatology* 1999; 29(6):1704–1707.
41. Stroffolini T, Andreone P, Andriulli A, et al. Gross pathologic types of hepatocellular carcinoma in Italy. *Oncology* 1999; 56(3):189–192.
42. Yoshizawa H. Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future. *Oncology* 2002; 62(suppl 1): 8–17.
43. Donato F, Tagger A, Gelatti U, et al. Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. *Am J Epidemiol* 2002; 155(4):323–331.
44. Hassan MM, Frome A, Patt YZ, et al. Rising prevalence of hepatitis C virus infection among patients recently diagnosed with hepatocellular carcinoma in the United States. *J Clin Gastroenterol* 2002; 35(3):266–269.
45. Cramp ME. HBV + HCV = HCC? *Gut* 1999; 45(2):168–169.
46. Ong JP, Pitts A, Younossi ZM. Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease. *J Hepatol* 2008; 49(4):608–612.
47. Younossi ZM, Stepanova M. Hepatitis C virus infection, age, and Hispanic ethnicity increase mortality from liver cancer in the United States. *Clin Gastroenterol Hepatol* 2010; 8(8):718–723.
48. Abe H, Yoshizawa K, Kitahara T, et al. Etiology of non-B non-C hepatocellular carcinoma in the eastern district of Tokyo. *J Gastroenterol* 2008; 43(12):967–974.
49. Bugianesi E, Leone N, Vanni E, et al. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. *Gastroenterology* 2002; 123(1):134–140.
50. Marrero JA, Fontana RJ, Su GL, et al. NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. *Hepatology* 2002; 36(6):1349–1354.
51. Regimbeau JM, Colombat M, Mognol P, et al. Obesity and diabetes as a risk factor for hepatocellular carcinoma. *Liver Transpl* 2004; 10(2 suppl 1):S69–S73.
52. Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. *Hepatology* 2003; 37(5):1202–1219.
53. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003; 348(17):1625–1638.
54. Moller H, Mellemgaard A, Lindvig K, et al. Obesity and cancer risk: a Danish record-linkage study. *Eur J Cancer* 1994; 30A(3):344–350.
55. Wolk A, Gridley G, Svensson M, et al. A prospective study of obesity and cancer risk (Sweden). *Cancer Causes Control* 2001; 12(1):13–21.
56. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 2004; 126(2):460–468.

57. El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. *Clin Gastroenterol Hepatol* 2006; 4(3):369–380.
58. Bravi F, Bosetti C, Tavani A, et al. Coffee drinking and hepatocellular carcinoma risk: a meta-analysis. *Hepatology* 2007; 46(2):430–435.
59. Montella M, Polesel J, La VC, et al. Coffee and tea consumption and risk of hepatocellular carcinoma in Italy. *Int J Cancer* 2007; 120(7):1555–1559.
60. Shimazu T, Tsubono Y, Kuriyama S, et al. Coffee consumption and the risk of primary liver cancer: pooled analysis of two prospective studies in Japan. *Int J Cancer* 2005; 116(1):150–154.