GASTROENTEROLOGY 2012;142:1264–1273

Epidemiology of Viral Hepatitis and Hepatocellular Carcinoma

Hashem B. El–Serag

Section of Gastroenterology and Hepatology, Department of Medicine, Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, Houston, Texas

Most cases of hepatocellular carcinoma (HCC) are associated with cirrhosis related to chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Changes in the time trends of HCC and most variations in its age-, sex-, and race-specific rates among different regions are likely to be related to differences in hepatitis viruses that are most prevalent in a population, the timing of their spread, and the ages of the individuals the viruses infect. Environmental, host genetic, and viral factors can affect the risk of HCC in individuals with HBV or HCV infection. This review summarizes the risk factors for HCC among HBV- or HCV-infected individuals, based on findings from epidemiologic studies and meta-analyses, as well as determinants of patient outcome and the HCC disease burden, globally and in the United States.

Keywords: Liver Cancer; Association; Virology; Genetics.

According to the International Agency for Research on Cancer, liver cancer is the fifth most common cancer in men worldwide (523,000 cases/y, 7.9% of all cancers) and the seventh most common cancer in women (226,000 cases/y, 6.5% of all cancers). Liver cancer has a high mortality rate; the geographic distribution of mortality is similar to that of incidence. Most of the burden of liver cancer is in developing countries, where almost 85% of the cases occur. Hepatocellular carcinoma (HCC) is the most common form of liver cancer; most cases of HCC (approximately 80%) are associated with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections. Variations in the age-, sex-, and race-specific rates of HCC in different geographic regions are likely to be related to differences in the prevalence of hepatitis viruses in the populations, as well as the timing of the spread of the viral infection and the age of individuals at the time of the infection.

Global Epidemiology of HCC

Most cases of HCC (>80%) occur in sub-Saharan Africa and in Eastern Asia, with typical incidence rates of more than 20 per 100,000 individuals. Southern European countries (such as Spain, Italy, and Greece) tend to have mid-incidence levels (10.0–20.0 per 100,000 individuals), whereas North America, South America, Northern Europe, and Oceania have a low incidence of HCC (<5.0 per 100,000 individuals) (Figure 1). Recent decreases in the incidence of HCC were reported among Chinese populations in Hong Kong, Shanghai, and Singapore; the incidence in Japan also is decreasing. However, cases of HCC are increasing in low-incidence areas such as the United States and Canada.

HCC rarely is seen during the first 4 decades of life, except in populations in which HBV infection is hyperendemic. The mean ages of diagnosis with HCC were 55–59 years in China and 63–65 years in Europe and North America. In low-risk populations, the highest incidence of HCC is among individuals aged 75 or older. However, in Qidong, China, where HCC burden is among the world's highest, the age-specific incidence rates among men increases until age 45 years and then plateaus; among women, the incidence rate increases until age 60 years and then plateaus. HCC is predominant among men, with the highest male:female ratios in areas of high incidence (Figure 1).

The Role of HBV and HCV in HCC

HBV and HCV promote cirrhosis, which is found in 80%–90% of patients with HCC. The 5-year cumulative risk of developing HCC for patients with cirrhosis ranges between 5% and 30%, depending on etiology (it is highest in individuals with HCV infection), region or ethnicity (it

Abbreviations used in this paper: AFB_1, Aflatoxin B_1; ALT, alanine aminotransferase; GST, glutathione S-transferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IL, interleukin; REVEAL-HBV, Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer–Hepatitis B Virus; TNF, tumor necrosis factor.

0016-5085/$36.00
doi:10.1053/j.gastro.2011.12.061

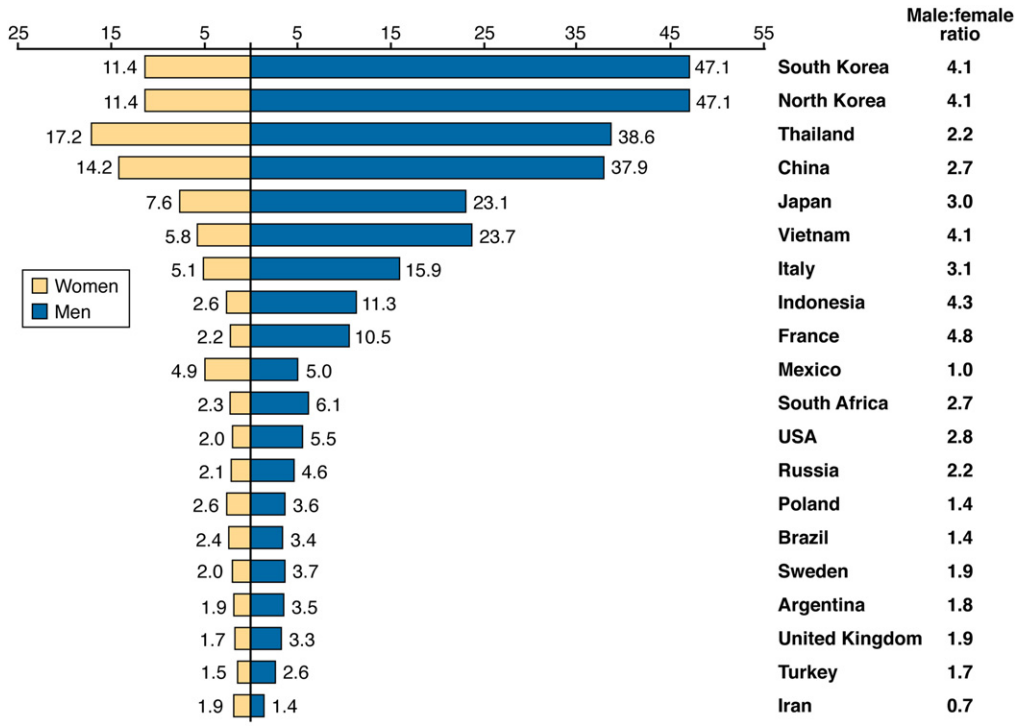

Figure 1. Age-standardized incidence rates of liver cancer per 100,000 person-years, shown for different regions of the world and for men and women (GLOBOCAN 2002).

is highest in Asians), and stage of cirrhosis (it is highest in individuals with decompensated disease).[1]

Approximately 5% of the world population (350–400 million people) is chronically infected with HBV; 75% of infected people are Asian,[2] with a lower prevalence (0.3%–1.5%) in Western countries. There is high ecologic correlation between areas of HBV prevalence and HCC incidence and mortality worldwide (Figure 2). Chronic HBV infection accounts for approximately 50% of the total cases and virtually all childhood HCC; it is the dominant risk factor in most areas of Asia and sub-Saharan Africa that have a high incidence of HCC, with the exception of Japan, where the major risk factor for HCC is chronic HCV infection. HB surface antigen (HBsAg) seroprevalence among persons with HCC varies widely: it is 3% in Sweden, 10% in the United States, 10%–15% in Japan, 19% in Italy, 55% in Greece, and 70% in South Korea.

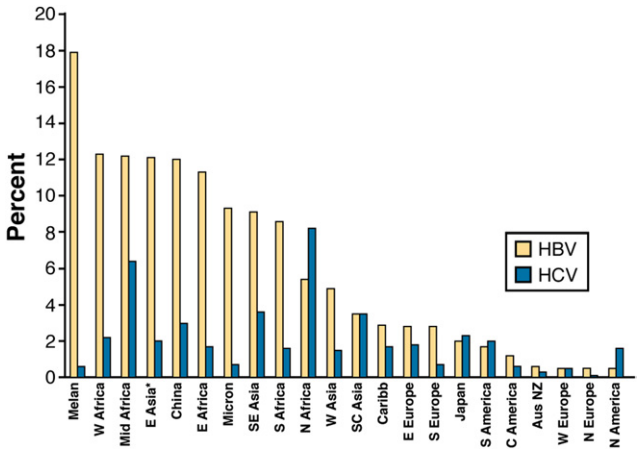

Figure 2. Prevalence of HBsAg carrier and chronic HCV status in different geographic regions.[71] Melanesia (includes the Amphlett Islands, Bismarck Archipelago, d'Entrecasteaux Islands, Fiji, Louisiade Archipelago, Maluku Islands, New Caledonia, New Guinea, Norfolk Island, Raja Ampat Islands, RotumaSchouten Islands, Santa Cruz Islands, and Solomon Islands) and Micronesia (Banaba, Gilbert Islands, Mariana Islands, Marshall Islands, Caroline Islands, Nauru, and Wake Island).

The global prevalence of HCV is estimated to be 2% (approximately 180 million people worldwide) and varies considerably among different regions (Figure 2). Phylogenetic studies of HCV diversity described the chronology of the spread of HCV epidemics in Japan, Europe, and the United States; these findings account for the geographic differences in the timing of the burden of HCV-related HCC.[3] Based on these studies, HCV began to infect large numbers of young adults in Japan in the 1920s, in southern Europe in the 1940s, and in North America in the 1960s and 1970s.[4] The HCV epidemic in the United States originated from contaminated needles and/or injection drug use. The virus spread into national blood supplies and circulated until the late 1980s; the rate of new infections was greatly reduced thereafter. Although the seroprevalence of HCV is similar among the general populations of Japan, southern Europe, and North America, markers of HCV infection are highest among individuals with HCC in Japan (80%–90%), followed by Italy (44%–66%), and then the United States (30%–50%).[5] The incidence of HCC is almost 3-fold higher in Japan than Italy and almost 6-fold higher than in the United States. The burden of HCC in the United States therefore eventually might equal that of Japan.

The age distribution of HCC in different regions is determined partly by type of virus and timing of infection. In areas that have a high incidence of HCC in Asia, HBV

infection largely is acquired by mother–child transmission, whereas transmission among siblings of young ages is more common in Africa. Therefore, individuals in these regions develop HCC at earlier ages than in low-incidence areas, where the main risk factors for HCV infection are encountered later in life. Differences in age-related prevalence of HCC might affect applicability and outcomes of therapies such as liver transplantation. The high male: female ratio of HCC might result, in part, from the higher prevalence of HBV and HCV infection among men than women.

It is estimated that more than 90% of countries routinely vaccinate newborns against HBV, and approximately 70% are now delivering 3 immunization doses. In 1984, Taiwan became the first country to vaccinate newborns against HBV, and give HB immunoglobulin to infants of high-risk (HBsAg-positive) and HB e antigen (HBeAg)-positive mothers. Since then, the number of HBV carriers in the juvenile population has been greatly reduced, and the incidence of HCC among children aged 6–14 years was reduced by 65%–75%.[6] However, the HBV-related incidence of HCC is projected to increase for several decades because of the high prevalence of chronic HBV infection and prolonged latency to HCC development.

Risk of HCC From HBV Infection

Prospective cohort studies showed a 5- to 100-fold increase in the risk of developing HCC among persons chronically infected with HBV. Meta-analyses of case-control and cross-sectional studies indicated that the lifetime relative risk for HCC was 15–20 among HBsAg-positive individuals, compared with HBsAg-negative individuals. A systematic review of longitudinal (cohort) studies published through June 2007, by Fattovich et al,[7] estimated the incidence rates of HCC in subjects with chronic HBV infection in East Asian countries to be 0.2 per 100 person-years in inactive carriers (HBsAg-positive but with normal levels of alanine aminotransferase [ALT]), 0.6 person-years for those with chronic HBV infection without cirrhosis, and 3.7 person-years for those with compensated cirrhosis. There have been few adequate studies in Europe or North America to determine the incidence of HCC in HBsAg-positive individuals—most studies included only small numbers of HBsAg-positive patients. Nevertheless, the summary HCC incidence rate was 0.02 per 100 person-years in inactive carriers, 0.3 in subjects with chronic HBV without cirrhosis, and 2.2 in subjects with compensated cirrhosis.

Most HBV-infected individuals who develop HCC have cirrhosis secondary to chronic necroinflammation. HBV can cause HCC in the absence of cirrhosis, although most cases of HBV-related HCC (70%–90%) occur in patients with cirrhosis.[8] Factors that have been reported to increase HCC risk among HBV carriers are demographic (male sex, older age, Asian or African ancestry, family history of HCC), viral (higher levels of HBV replication; HBV genotype; longer duration of infection; co-infection with HCV, human immunodeficiency virus [HIV], or hepatitis D virus), clinical (cirrhosis), and environmental (exposure to aflatoxin, heavy intake of alcohol or tobacco).

HBV Transmission and Replication

In many high-risk areas, particularly those in Asia, HBV is transmitted from mother to newborn (vertical transmission); as many as 90% of infected babies develop chronic infections. This pattern is different in areas that have a low incidence of HCC; HBV infection usually is acquired in adulthood, through sexual and parenteral routes (horizontal transmission). More than 90% of these cases of acute HBV infection resolve spontaneously. The higher frequency and longer period of chronic HBV infections contribute to a greater risk for HCC in areas where HBV infection is common.

The risk of HCC is increased in patients with higher levels of HBV replication, determined by tests for HBeAg and levels of HBV DNA. One large study evaluated the effect of HBV replication on the risk of HCC among 11,893 Taiwanese men who were followed up for a mean of 8.5 years. The incidence rate of HCC was 1169 per 100,000 person-years among men who were HBsAg-positive and HBeAg-positive, 324 per 100,000 person-years for those who were only HBsAg-positive, and 39 per 100,000 person-years for those who were HBsAg-negative. Similarly, the relative risks of HCC among men who were HBsAg-positive and HBeAg-positive were increased 60-fold, and 10-fold among those who were only HBsAg-positive.[9] A community-based Taiwanese prospective study, the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer–Hepatitis B Virus (REVEAL-HBV), reported that in a cohort of 3653 HBsAg-positive participants, the incidence of cirrhosis and HCC increased in proportion to the serum level of HBV DNA, from less than 300 (undetectable) to 1,000,000 or more copies/mL (Figure 3). These associations remained significant after adjustment for age, sex, smoking, alcohol consumption,

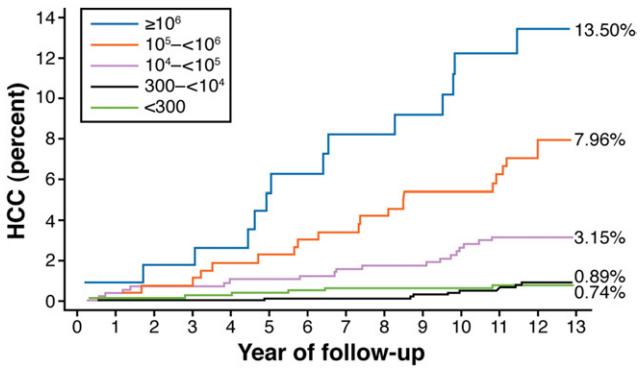

Figure 3. An association between baseline serum level of HBV DNA and future incidence of HCC. The cumulative incidence of HCC also was calculated for a subcohort of 2925 Taiwanese participants in the REVEAL-HBV study who were HBeAg-negative, had normal levels of ALT, and did not have cirrhosis when the study began. Modified from Chen CJ, et al. JAMA. 2006;295:65–73.[72]

and HBeAg serostatus.[10] The increased incidence in HCC in relation to HBV-DNA level also was observed in a study that showed that inactive carriers of HBV (seronegative for HBeAg, serum levels of HBV DNA <10,000 copies/mL, and normal liver enzyme levels) had an almost 5-fold greater risk for HCC than controls (HBsAg-negative).[11] It is not clear if the findings from REVEAL-HBV pertain to Western populations, who acquire HBV as adults and have different risk factors for disease (obesity, diabetes, and alcohol use).

Levels of viral replication also are affected by antiviral treatment. There is moderately strong evidence that effective antiviral therapy, which suppresses HBV infection in HBsAg-positive patients, substantially reduces but does not completely eliminate risk for HCC. In a large Asian study, patients with chronic HBV and cirrhosis or advanced fibrosis were given 100 mg/d of lamivudine or placebo for up to 5 years. A smaller percentage of patients given lamivudine developed HCC (3.9%), compared with those given placebo (7.4%), which mostly achieved a reduced level of HBV DNA.[12] Lower-quality evidence from nonrandomized trials and observational studies has indicated that therapy with interferon or lamivudine reduces the risk for HCC.[13]

HBV Genotypes

Several HBV genotypes (A–H) have been identified, based on differences of 8% or more in their whole-genome sequence. HBV genotypes have distinct geographic and ethnic distributions: genotypes A and D predominate in Africa, Europe, and India; genotypes B and C predominate in Asia; genotype E predominates in West Africa; and genotype F predominates in Central and South America. In the United States, HBV genotypes A and D are more common in black and white persons, whereas HBV genotypes B and C are more common among persons of Asian ancestry.

HBV genotypes seem to affect clinical outcomes. In studies performed in Asia, there was a greater association between genotype C infection and severe liver disease, cirrhosis, and HCC than genotype B; in Western Europe and North America, individuals with genotype D had a greater incidence of severe liver disease or HCC than those with genotype A. However, some data associate genotype B HBV with the development of HCC in young carriers without cirrhosis. A study from Taiwan showed that genotype B was significantly more common in patients with HCC younger than age 50 than in age-matched carriers with inactive infections (80% vs 52%).[14] Most of these participants did not have cirrhosis. A 15-year Taiwanese study of 460 carriers of HBV reported that genotype B was the most frequent genotype among 26 children with HBV-related HCC (found in 74%).[15] Mutations in the region of the HBV genome that encode the basal core promoter, such as T1762 and A1764,[16] have been associated with increased incidence of HCC, whereas those in the precore region (G1896A) have been associated with decreased incidence of HCC.[17]

Aflatoxin B_1

Aflatoxin B_1 (AFB_1) is a mycotoxin produced by fungi of the *Aspergillus* species (*A flavus* and *A parasiticus*) that grows readily on foods such as corn and peanuts stored in warm, damp conditions. In animals, AFB_1 is a powerful hepatocarcinogen, leading the International Agency for Research on Cancer to classify it as a carcinogen.

Once ingested, AFB_1 is metabolized to an active intermediate, AFB_1-*exo*-8,9-epoxide, which can bind to and damage DNA. AFB_1 causes a mutation at serine 249 in the tumor-suppressor p53[18] that was detected in 30%–60% of HCC tumor samples collected from individuals in aflatoxin-endemic areas, most of whom had HBV infections.[19,20] Assays have been developed to measure aflatoxin metabolites in urine and AFB_1–albumin adducts in serum, and to detect specific aflatoxin-associated DNA mutations in tissues.

Areas in which AFB_1 exposure is an environmental problem also have a high prevalence of chronic HBV infection. Although AFB_1 might contribute to hepatocarcinogenesis by other mechanisms, its role in the pathogenesis of HCC is mediated primarily by its effects on chronic HBV infection. For example, prospective studies in Shanghai, China, showed that urinary excretion of aflatoxin metabolites increased the risk of HCC up to 4-fold, and HBV infection increased the risk 7-fold. However, individuals who excreted AFB_1 metabolites and were carriers of HBV had as much as a 60-fold increase in risk of HCC.[21] Importantly, prevention of HBV-related HCC would reduce the effects of aflatoxin on HCC risk.

Occult HBV Infection

Studies with sensitive amplification assays have shown that HBV DNA persists in serum or liver, as an occult HBV infection, among persons who have serologic recovery from transient HBV infection (who are HBsAg-negative). In many instances, occult hepatitis B is associated with antibodies to hepatitis B core antigen and/or anti-HBs. A systematic review identified 16 studies of the association between occult HBV and HCC risk; 6 of these studies found no significant association. None of the studies included in this review was population-based—most had a small number of cases or controls, 11 were from Asia (only 1 was performed in the United States), and they had varied and few adjustments for confounders. A pooled adjusted estimate could be calculated for only 4 longitudinal studies (3 from Japan) that indicated a modest association between occult HBV infection and HCC (relative risk, 2.83).[22] A recent small case-control study from Hong Kong showed a high prevalence of occult HBV in patients with cryptogenic HCC.[23] However, there is no convincing evidence that occult HBV is an independent risk factor for HCC or a cofactor with HCV infection in most regions of the world.

Risk of HCC From HCV Infection

There is much evidence that HCV infection can cause HCC. Prospective studies have shown a significant increase in the incidence of HCC among HCV-infected

cohorts, compared with HCV-negative cohorts.[24] The rate of HCC among HCV-infected persons ranges from 1% to 3% over 30 years. Similarly, HCV infection is associated with a 15- to 20-fold increase in risk for HCC compared with HCV-negative subjects in cross-sectional and case-control studies.

HCV increases the risk for HCC by inducing fibrosis and, eventually, cirrhosis. Although HCC has been reported among individuals without or with low levels of fibrosis,[25–27] the risk of HCC increases with fibrosis stage; most cases of HCV-related HCC occur among patients with advanced fibrosis or cirrhosis, making it a condition listed for HCC surveillance in current recommendations. Once HCV-related cirrhosis is established, HCC develops at an annual rate of 1%–4%; although rates up to 8% have been reported in Japan. The incidence of cirrhosis (and consequently HCC) 25–30 years after HCV infection ranges from 15% to 35%,[28] and is highest among recipients of HCV-contaminated blood products and hemophiliac patients, and lowest among women who received a single dose of contaminated anti-D immunoglobulin. HCC risk also might vary based on the amount of virus in the contaminated product or repeated exposure. Other risk factors for HCC include the sex of the HCV-infected individual, comorbidities (co-infection with HBV or HIV, diabetes, obesity, steatosis), viral genotype (HCV 1b), level of alcohol consumption, and age. Among patients with HCV-related cirrhosis, low numbers of platelets or increased levels of α-fetoprotein are risk factors for HCC.

Viral Factors

HCV viremia of any level is a strong risk factor for HCC; conversely, treatment that eliminates the virus decreases risk for HCC. Evidence from randomized controlled studies and several nonrandomized studies of HCV-infected patients with and without cirrhosis indicates a 57% to 75% reduction in risk of HCC in patients who received interferon-based therapy and achieved a sustained viral response. There are at least 6 HCV genotypes, which differ in 30%–35% of nucleotides in the complete genome. There are also several subtypes; HCV subtypes 1a and 1b are the most common in the United States and Europe, whereas in Japan, 73% of HCV-infected individuals carry subtype 1b. Reports of the association between HCV genotype and HCC risk are inconsistent. However, a meta-analysis of 21 studies that calculated age-adjusted risk estimates reported that patients infected with HCV genotype 1b had an almost 2-fold greater risk of developing HCC than patients with other HCV genotypes (pooled relative risk, 1.78). The pooled risk estimate remained significant but lower in an analysis limited to 8 studies conducted in patients with cirrhosis (pooled relative risk, 1.60).[29] There is no consistent evidence that other viral factors, such as HCV load or quasispecies, affect the risk of progression to cirrhosis or HCC. A study performed in Taiwan reported a correlation between level of HCV RNA and the risk of HCC,[30] but studies from the United States and Europe have not made this association.

HIV

Many studies examined the effect of HIV infection on the progression of HCV-related liver disease, measured by fibrosis, cirrhosis, HCC, decompensated liver disease, and liver-related death. These studies mostly used the retrospective cohort or cross-sectional study design. Despite the limitations of these studies and some inconsistent results, it was evident that persons co-infected with HIV have faster progression to cirrhosis and decompensated liver disease, especially during immunosuppression. However, the effect of antiretroviral therapy on liver disease in patients co-infected with HCV and HIV is not clear. At least 4 studies included in a systematic review did not associate antiretroviral therapy with risk for HCC, although it is difficult to make general conclusions because of the small number of cases of HCC in these studies. Antiretroviral therapy might reduce the risk for HCC, given the association between HIV co-infection and accelerated liver disease.[31]

HBV infection persists in 25% of HIV-infected adults, compared with less than 5% of adults without HIV infection. Furthermore, individuals co-infected with HIV and HBV have an increased risk for liver-related mortality. However, there are few data on the effects of co-infection with HBV and HIV on risk for HCC.

Coffee

Population-based studies have associated high levels of coffee consumption (>2 cups/d) with reduced serum levels of ALT and γ-glutamyl transferase and reduced incidence of chronic liver disease. Consumption of high levels of caffeine was associated with milder fibrosis in patients with chronic HCV infection.[32] Coffee consumption also was associated inversely with progression of liver disease among participants in the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis trial who had hepatitis C–related bridging fibrosis or cirrhosis and did not have a sustained virologic response to peginterferon and ribavirin treatment.[33] In the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis study, consumption of caffeine from sources other than coffee or of decaffeinated coffee was not associated with reduced levels of liver enzymes or fibrosis.

Several studies have suggested an inverse relation between coffee drinking and risk of HCC. One meta-analysis of studies published through 2007 included 10 studies (2260 cases of HCC; 6 case-control studies from southern Europe and Japan and 4 cohort studies from Japan). Given the geographic location of these studies, most patients with HCC probably were infected with HCV, or possibly HBV. All the studies observed an inverse relation between coffee consumption and risk of HCC, and in 6 studies the association was statistically significant. The summary relative risk for coffee drinkers vs non–coffee drinkers was 0.54 from case-control studies and 0.64 from cohort studies. It was estimated that for an increase of 1 cup of coffee per day, the summary risk ratio was 0.77

from case-control studies and 0.75 from cohort studies.[34,35] The mechanisms by which coffee reduces the risk of liver disease, including HCC, are unclear, but could involve a reduced risk for cirrhosis. In addition to caffeine, coffee compounds such as cafestol and ditrepens are similar to enzymes involved in carcinogen detoxification. Coffee drinking also might protect against HCC by reducing levels of insulin and thereby the risk for type 2 diabetes,[36] a risk factor for fatty liver disease, cirrhosis, and HCC.

Risk Factors for HCC Common to HBV and HCV

Sex

Men are at increased risk for HCC partly because they have a greater incidence of viral hepatitis and alcoholic cirrhosis. However, their risk still is increased after adjusting for these confounders. Men have an increased risk of cirrhosis and HCC from different diseases, such as HBV and HCV infection. High serum levels of testosterone have been associated with HCC risk in nested case-control studies of HBV carriers in Taiwan and Shanghai.[37] Male carriers of HBV usually have higher viral loads. Studies of HBV infection in transgenic mice showed that the androgen pathway can increase the transcription of HBV genes; androgens bind directly to sites in the viral genome, and, conversely, the HBV protein HBx can increase the transcription of androgen receptors.[38,39] Other studies have reported that estrogen protects against progression of HBV infection. There have been fewer studies of the role of testosterone in HCV-related liver disease. There have been differing results from small, case-control studies of HCV-infected patients regarding total serum levels of testosterone and degree of HCV-related hepatic fibrosis. A cross-sectional study associated higher total serum levels of testosterone with risk of advanced hepatic fibrosis and inflammatory activity in male veterans with chronic HCV infections in the United States. However, the association with HCC was not examined.[40]

Co-Infection With HCV and HBV

There has been no single study large enough to adequately address the risk of HCC among patients with HBV and HCV co-infection. Two meta-analyses of studies from various countries (1998)[41] and China (2005)[42] reported the additive effects of HBV and HCV on risk for HCC. A meta-analysis of 32 case-control studies by Donato et al[41] found that infection with HBV and HCV had an odds ratio of 165 for HCC, compared with an odds ratio of 17 for HCV infection alone and an odds ratio of 23 for HBV infection alone. In a meta-analysis of Chinese studies that included 3201 cases and 4005 controls, the pooled odds ratio for HBsAg positivity was 14.1, for antibodies against HCV (anti-HCV) and HCV RNA the odds ratio was 4.6, and for HBsAg-positivity and anti-HCV and HCV RNA the odds ratio was 35.7.[42]

However, an updated meta-analysis that included 59 studies that assessed HBV and HCV co-infection reported a subadditive effect on HCC risk, based on more recent studies (2000–2009), cohort studies, and studies conducted in areas in which HBV and HCV infection were not common; it reported an additive effect in older studies, case-control studies, and studies conducted in areas where HCV infection was common.[43] A subadditive effect of HBV and HCV co-infection is possible because infection with one virus can inhibit infection with the other.

Alcohol

There is evidence of a synergistic effect between heavy ingestion of alcohol and HCV infection and, to a lesser extent, HBV infection; these factors presumably operate together to promote cirrhosis. A meta-analysis of 20 studies published between 1995 and 2004 that involved more than 15,000 persons with chronic HCV infection reported that the pooled relative risk of cirrhosis associated with heavy alcohol intake was 2.33, compared with no or low-quantity alcohol intake.[44] This synergistic effect also has been observed in the development of HCC. Donato et al[45] reported that, among alcohol drinkers, HCC risk increased in a linear fashion with daily intake greater than 60 g (6 cans of beer, glasses of wine, or shots of hard liquor). However, concomitant HCV infection increased this risk for HCC 2-fold (Figure 4).

Few cohort studies have investigated the association between HBV infection and alcohol drinking or intake of different amounts of alcohol. A Japanese study of patients with compensated, HBV-related cirrhosis showed that heavy alcohol intake increased the risk for HCC 3-fold.[46] A population-based cohort study performed in Korea found that among individuals with chronic HBV infection, the risk for HCC increased significantly among subjects with an alcohol intake of 50 g/d or more, with a relative risk of 1.2 for 50–99 g/d and of 1.5 for greater than 100 g/d.[47]

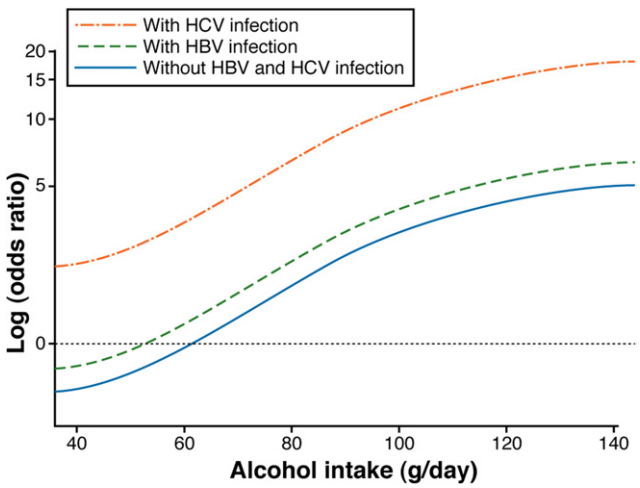

Figure 4. Odds ratios for hepatocellular carcinoma, according to alcohol intake and the presence of HBV or HCV infection. The plot was obtained by fitting spline regression models on data obtained in Brescia, Italy, 1995–2000. Modified from Donato et al.[45]

Tobacco Smoking

The relationship between cigarette smoking and HCC has been examined in more than 60 studies, in areas of high and low incidence of HCC; both positive associations and no associations have been reported in different studies. Among studies reporting positive associations, several found that effects were limited to subgroups defined by HBV or HCV status. In a meta-analysis of 16 publications that evaluated the epidemiologic interactions between HBV and HCV infection, cigarette smoking, and risk of HCC, there was a more than additive interaction between HBV infection and cigarette smoking and a more than multiplicative interaction between HCV infection and cigarette smoking.[48]

Metabolic Syndrome

Insulin resistance is associated with hepatic steatosis, advanced fibrosis, and HCC among patients with HCV infection. A meta-analysis of studies published through February 2005 reported that, of 13 case-control studies, diabetes was associated significantly with HCC in 9 studies (pooled odds ratio, 2.5), and that of 13 cohort studies, diabetes was associated significantly with HCC in 7 studies (pooled risk ratio, 2.5). The significant association between HCC and diabetes was independent of viral hepatitis or alcohol use in the 10 studies that examined these factors.[49] An updated review of studies published through February 2011 reported on a total of 17 case-control studies and 32 cohort studies. The pooled risk estimate of 17 case-control studies (odds ratio, 2.40) was slightly higher than that from 25 cohort studies (relative risk, 2.23).[50] Cirrhosis causes glucose intolerance and type 2 diabetes, and also leads to HCC, making it difficult to interpret the association between HCC and diabetes. This bias is less likely to be present in longitudinal studies that exclude patients with liver disease at baseline.

The association between diabetes and HCC might depend on the type of viral infection. There is a significant (68%) increase in diabetes among HCV-infected individuals, compared with noninfected individuals, based on retrospective and prospective studies. Individuals with HCV infection also have a greater risk of diabetes than HBV-infected individuals.[51] However, few studies found that HCV and diabetes synergize to increase the risk of HCC.[52,53]

The association between diabetes and HCC is less consistent in areas with a high incidence of HBV infection than in other regions. For example, although a large Korean cohort study reported a modest association between diabetes and risk for HCC,[54] several Taiwanese studies did not.[55] Compared with HCV infection, there are less data on insulin or steatosis and risk of advanced liver disease, including HCC, among individuals with HBV infection. A prospective case-cohort study from Taiwan (of 124 HCC cases and 1084 controls, and measured baseline levels of insulin) reported that insulin resistance increased the risk of HCC among men with chronic HBV infection, with a hazard ratio of 2.36 for those in the highest tertile of insulin levels and a hazard ratio of 1.57 for those with the lowest levels of insulin, after adjusting for body mass index.[56]

Host Genetic Factors

Most individuals with HCV or HBV never develop cirrhosis or HCC. Family history of liver cancer has been associated with increased risk for HCC among HBV carriers (in cohort and case-control studies) and possibly among HCV-infected persons (in case-control studies), irrespective of viral hepatitis.[57,58] Host genetic factors might account for some of the variation in the risk of developing cirrhosis or HCC. Individual genetic association studies frequently are underpowered and often report small or variable effects. Meta-analysis has been recognized as an important tool to precisely define the effect of selected polymorphisms on risk of disease.

Tumor Necrosis Factor-α Variants

Two meta-analyses investigated the association of common polymorphisms in tumor necrosis factor-α (TNFα), including −308 G >A, with risk for HCC. One meta-analysis analyzed 9 published studies that included 1362 cancer cases and 2426 controls and associated the TNFα−308 AA and AG variants (vs GG) with a significantly increased risk of HCC in different genetic models, including a dominant inheritance model that produced an odds ratio of 1.59.[59] The second meta-analysis summarized 10 case-control studies involving 1421 HCC cases and reported that patients with HCC had a significantly lower frequency of the TNFα polymorphism −308 GG than healthy controls, but not more than HBV-infected controls.[60]

A recent meta-analysis examined the relationship between polymorphisms in TNFα, interleukin (IL)-1B, and IL-10 and the risk for HCC in studies published through September 2010. Twenty studies were identified, involving 2763 patients with HCC and 4152 controls. This meta-analysis confirmed the significant association (odds ratio, 1.84) between a polymorphism at TNFα-308 and HCC in Asian subgroups. The polymorphisms TNFα-238 G/A, IL-1B 31 T/C and −511 C/T, and IL-10 1082 G/A were not associated with the risk for HCC.[61]

Glutathione S-Transferase *Variants*

Variants of *glutathione S-transferase* (*GST*) genes are among the most extensively studied genetic risk factors for HCC. GSTs are a broadly expressed family of phase II isoenzymes that protect against endogenous oxidative stress. A meta-analysis that evaluated the effect of polymorphisms that cause deletions in *GSTM1* and *GSTT1*[62] in 14 studies (2514 cases and 4416 controls) indicated that forms of *GSTM1* or *GSTT1* that do not produce a functional product (null genotypes) slightly increased the risk for HCC, although findings approached significance only for *GSTT1* (odds ratio, 1.16). An updated meta-analysis of studies published through November 2009 that analyzed 24 individual case-control studies involving 3349 HCC

cases and 5609 controls also showed a significant increase in risk for HCC among individuals with the null genotypes of *GSTM1* (odds ratio, 1.2) and *GSTT1* (odds ratio, 1.28). A subgroup analysis showed that the increase in risk for HCC was statistically significant in areas where HBV infection was common.[63]

Radiograph repair cross-complementing group 1 variants. A meta-analysis of 11 case-control studies, involving 2208 cases of HCC and 3265 controls, found no association between the *radiograph repair cross-complementing group 1* polymorphism that encodes Arg399Gln and the risk of HCC.[64]

Using Epidemiologic Findings to Determine HCC Risk in the Clinic

Investigators from Taiwan examined the potential use of noninvasive clinical and laboratory measures, which have been shown in epidemiologic studies to be associated with HCC risk, to construct clinically usable nomograms to predict HCC risk in patients with chronic HBV infection.[65] A number of risk factors, including sex, age, family history of HCC, heavy alcohol consumption, serum levels of ALT, HBeAg serostatus, serum levels of HBV DNA, and HBV genotype were used to create predictive models based on data from 2435 subjects in the REVEAL-HBV study; these were validated in an analysis of 1218 subjects. The models have shown very good to excellent predictive and discriminant abilities. However, it is not clear whether these can be applied to the clinical setting and to non-Taiwanese populations. There is no such model for predicting HCC among HCV-infected patients.

HCC and Viral Hepatitis in the United States

In the United States, the age-adjusted incidence rates for HCC have tripled since the early 1980s. Incidence rates are 2- to 3-fold lower among Caucasians than African Americans, and 2- to 3-fold lower among African Americans than Asians, Pacific Islanders, or Native Americans. Asian men (Chinese, Korean, Filipino, and Japanese) have the highest age-adjusted incidence rates (as high as 23 per 100,000). However, the largest proportional increases have occurred among whites (Hispanic and non-Hispanic), whereas the lowest proportional increases have occurred among Asians. In addition, the age distribution of HCC patients has shifted to younger ages, with the greatest proportional increases among individuals 45–60 years old.

Secular Trends of HBV and HCV in HCC in the United States

Among patients with HCC in the United States, 50%–60% are infected with HCV, 10%–15% are infected with HBV, less than 5% are infected with both viruses, and 30%–35% are infected with neither virus. HCV infection is the most frequently reported etiologic factors in Hispanics and African Americans with HCC, whereas HBV infection is the most frequently reported factor in Asians with HCC.

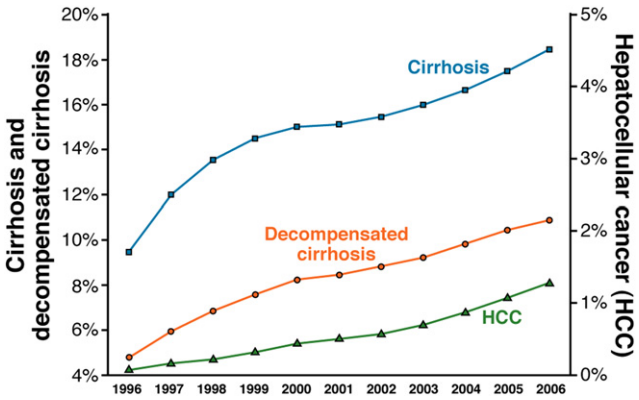

Figure 5. Secular trends in the prevalence of cirrhosis, decompensated cirrhosis (*left axis*), and HCC (*right axis*) between 1996 and 2006 among HCV-infected veterans. The annual prevalence rates of these conditions were calculated by dividing the number of HCV patients with either a new or prior diagnosis by the total number of HCV patients with 1 or more visits to a Veteran's Administration Hospital during that particular year. Modified from Kanwal F, et al. Gastroenterology 2011.[73]

Four studies have examined temporal variations in risk factors among patients with HCC in the United States; data used in 2 studies came from large, single centers where viral risk factors were determined based on serologic markers, and data used in the 2 other studies were collected from national administrative databases, in which risk factors were confirmed using International Classification of Disease codes in billing claims or discharge records. In all these studies, HCV-related HCC had the largest proportional increase, whereas the proportion of HCC associated with HBV infection remained stable in 3 studies and increased slightly in 1 study, among persons aged 65 years and older. The rate of HCC related to alcoholic liver disease was stable in all 4 studies. Similar national trends have been observed: increased HCV-related mortality and decreased or stabilized HBV-related mortality, based on data from liver transplant waitlist registration.

Future Burden of HBV- and HCV-Related HCC

In the United States, the incidence of HBV-related HCC is likely to remain steady. Although vaccination against HBV could prevent HCC, it does not prevent cancer in persons with chronic infections. The most recent (1999–2006) National Health and Nutrition Examination Survey estimated that only 0.27% of the US population, 6 years or older, had chronic HBV infection.[66] However, screening studies of Native Americans (particularly Eskimos) and of Asian Americans and foreign-born persons who immigrated from the Middle East and Africa revealed a much higher prevalence of chronic HBV infection (10%–15%).

The incidence of HCV-related cirrhosis and HCC in the United States has been progressively increasing (Figure 5)

and will continue to do so for a few more decades. The National Health and Nutrition Examination Survey also estimated that 1.3% of the noninstitutionalized, civilian US population had chronic HCV infection; approximately 66% of those infected were born between 1945 and 1964, and therefore have been living with the infection for several decades. This cohort also carries multiple risk factors for progression, such as alcohol drinking and obesity. It was estimated that approximately 50% of individuals with chronic HCV infections in the United States are undiagnosed. Projections estimate that, without effective treatment, the annual number of patients with cirrhosis or HCC will roughly double by 2020.[67]

World Health Organization data indicate a progressive increase in the total number of people diagnosed with primary liver cancer, mostly HCC, from 437,408 cases in 1990 to 714,600 in 2002.[68] In general, HCC incidence and mortality (to be distinguished from number of cases) have been decreasing slowly in areas of high and intermediate incidence, including China and Japan, and increasing in low-incidence areas, including the United States and Canada. The percentage of HCC cases associated with HBV has decreased progressively whereas the percentage associated with HCV has increased. However, each region or country can be its own case study. For example, World Health Organization mortality data from several European countries indicated that between 1980 and 2004, the overall mortality from HCC among men increased in Austria, Germany, and Switzerland, although it decreased significantly in France and Italy.[69]

HBV and HCV will remain the main risk factors for HCC. It has been estimated that there will be a 2.5-fold increase in HCV-related mortality worldwide between 2000 and 2020, which can be as high as a 3.5-fold increase in Egypt, the country with the highest prevalence of HCV infection.[70] The 2010 Institute of Medicine report on Hepatitis and Liver Cancer highlighted the lack of awareness about HBV and HCV infections and insufficient understanding about the extent and seriousness of their public health impact. HBV- and HCV-related HCC might be prevented by increasing screening and detection of infected patients, approaches to reduce viral transmission, global vaccination of infants and susceptible adults against HBV, reducing aflatoxin exposure, treating patients with chronic HBV and HCV infections, reducing cofactors for progression (alcohol intake and metabolic syndrome), and identifying high-risk groups for surveillance, early detection, and treatment.

Supplementary Material

Note: The first 50 references associated with this article are available below in print. The remaining references accompanying this article are available online only with the electronic version of this article. To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi:10.1053/j.gastro.2011.12.061.

References

1. Fattovich G, Stroffolini T, Zagni I, et al. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004; 127(Suppl 1):S35–S50.
2. 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;150:1051–1054.
3. Mizokami M, Orito E. Molecular evolution of hepatitis viruses. Intervirology 1999;42:159–165.
4. Tanaka Y, Kurbanov F, Mano S, et al. Molecular tracing of the global hepatitis C virus epidemic predicts regional patterns of hepatocellular carcinoma mortality. Gastroenterology 2006;130: 703–714.
5. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007;132: 2557–2576.
6. Chang MH. Hepatitis B virus and cancer prevention. Recent Results Cancer Res 2011;188:75–84.
7. Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. J Hepatol 2008;48:335–352.
8. Yang JD, Kim WR, Coelho R, et al. Cirrhosis is present in most patients with hepatitis B and hepatocellular carcinoma. Clin Gastroenterol Hepatol 2011;9:64–70.
9. Yang HI, Lu SN, Liaw YF, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002;347:168–174.
10. Chen CJ, Yang HI, Iloeje UH. Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. Hepatology 2009;49(Suppl): S72–S84.
11. Chen JD, Yang HI, Iloeje UH, et al. Carriers of inactive hepatitis B virus are still at risk for hepatocellular carcinoma and liver-related death. Gastroenterology 2010;138:1747–1754.
12. Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004;351:1521–1531.
13. Sung JJ, Tsoi KK, Wong VW, et al. Meta-analysis: treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. Aliment Pharmacol Ther 2008;28:1067–1077.
14. Kao JH, Chen PJ, Lai MY, et al. Basal core promoter mutations of hepatitis B virus increase the risk of hepatocellular carcinoma in hepatitis B carriers. Gastroenterology 2003;124:327–334.
15. Ni YH, Chang MH, Wang KJ, et al. Clinical relevance of hepatitis B virus genotype in children with chronic infection and hepatocellular carcinoma. Gastroenterology 2004;127:1733–1738.
16. Liu CJ, Chen BF, Chen PJ, et al. Role of hepatitis B viral load and basal core promoter mutation in hepatocellular carcinoma in hepatitis B carriers. J Infect Dis 2006;193:1258–1265.
17. 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;100:1134–1143.
18. 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;32:2058–2066.
19. Bressac B, Kew M, Wands J, et al. Selective G to T mutations of p53 gene in hepatocellular carcinoma from southern Africa. Nature 1991;350:429–431.
20. Turner PC, Sylla A, Diallo MS, et al. 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.
21. 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;3:3–10.
22. Shi Y, Wu YH, Wei W, et al. Association between occult hepatitis B infection and the risk of hepatocellular carcinoma: a meta-analysis. Liver Int 2012;32:231–240.

23. Wong DK, Huang FY, Lai CL, et al. Occult hepatitis B infection and HBV replicative activity in patients with cryptogenic cause of hepatocellular carcinoma. Hepatology 2011;54:829–836.
24. Goodgame B, Shaheen NJ, Galanko J, et al. The risk of end stage liver disease and hepatocellular carcinoma among persons infected with hepatitis C virus: publication bias? Am J Gastroenterol 2003;98:2535–2542.
25. De Mitri MS, Poussin K, Baccarini P, et al. HCV-associated liver cancer without cirrhosis. Lancet 1995;345:413–415.
26. Haydon GH, Jarvis LM, Simmonds P, et al. Association between chronic hepatitis C infection and hepatocellular carcinoma. Lancet 1995;345:928–929.
27. Tong MJ, Lai LP, Murakami-Mori K. Development of hepatocellular carcinoma after clearance of hepatitis C virus with interferon therapy. West J Med 1997;167:103–105.
28. Freeman AJ, Dore GJ, Law MG, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatology 2001; 34:809–816.
29. Raimondi S, Bruno S, Mondelli MU, et al. Hepatitis C virus genotype 1b as a risk factor for hepatocellular carcinoma development: a meta-analysis. J Hepatol 2009;50:1142–1154.
30. Lee MH, Yang HI, Lu SN, et al. Hepatitis C virus seromarkers and subsequent risk of hepatocellular carcinoma: long-term predictors from a community-based cohort study. J Clin Oncol 2010;28: 4587–4593.
31. Kramer JR, Giordano TP, El-Serag HB. Effect of human immunodeficiency virus and antiretrovirals on outcomes of hepatitis C: a systematic review from an epidemiologic perspective. Clin Gastroenterol Hepatol 2007;5:1321–1328.
32. Modi AA, Feld JJ, Park Y, et al. Increased caffeine consumption is associated with reduced hepatic fibrosis. Hepatology 2010;51: 201–209.
33. Freedman ND, Everhart JE, Lindsay KL, et al. Coffee intake is associated with lower rates of liver disease progression in chronic hepatitis C. Hepatology 2009;50:1360–1369.
34. Bravi F, Bosetti C, Tavani A, et al. Coffee drinking and hepatocellular carcinoma risk: a meta-analysis. Hepatology 2007;46:430–435.
35. Larsson SC, Wolk A. Coffee consumption and risk of liver cancer: a meta-analysis. Gastroenterology 2007;132:1740–1745.
36. Huxley R, Lee CM, Barzi F, et al. Coffee, decaffeinated coffee, and tea consumption in relation to incident type 2 diabetes mellitus: a systematic review with meta-analysis. Arch Intern Med 2009;169: 2053–2063.
37. Yuan JM, Ross RK, Stanczyk FZ, et al. A cohort study of serum testosterone and hepatocellular carcinoma in Shanghai, China. Int J Cancer 1995;63:491–493.
38. Chiu CM, Yeh SH, Chen PJ, et al. Hepatitis B virus X protein enhances androgen receptor-responsive gene expression depending on androgen level. Proc Natl Acad Sci U S A 2007;104:2571–2578.
39. Yeh SH, Chen PJ. Gender disparity of hepatocellular carcinoma: the roles of sex hormones. Oncology 2010;78(Suppl 1):172–179.
40. White DL, Tavakoli-Tabasi S, Kuzniarek J, et al. Higher serum testosterone is associated with increased risk of advanced hepatitis C-related liver disease in males. Hepatology 2012;55:759–768.
41. 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: 347–354.
42. 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: 607–612.
43. Cho LY, Yang JJ, Ko KP, et al. Coinfection of hepatitis B and C viruses and risk of hepatocellular carcinoma: systematic review and meta-analysis. Int J Cancer 2011;128:176–184.
44. Hutchinson SJ, Bird SM, Goldberg DJ. Influence of alcohol on the progression of hepatitis C virus infection: a meta-analysis. Clin Gastroenterol Hepatol 2005;3:1150–1159.
45. 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;155:323–331.
46. Ikeda K, Saitoh S, Suzuki Y, et al. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. J Hepatol 1998; 28:930–938.
47. Jee SH, Ohrr H, Sull JW, et al. Cigarette smoking, alcohol drinking, hepatitis B, and risk for hepatocellular carcinoma in Korea. J Natl Cancer Inst 2004;96:1851–1856.
48. Chuang SC, Lee YC, Hashibe M, et al. Interaction between cigarette smoking and hepatitis B and C virus infection on the risk of liver cancer: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2010;19:1261–1268.
49. El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol 2006;4:369–380.
50. Wang P, Kang D, Cao W, et al. Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. Diabetes Metab Res Rev 2012;28:109–122.

Received October 25, 2011. Accepted December 22, 2011.

Reprint requests

Address requests for reprints to: Hashem B. El-Serag, MD, MPH, Section of Gastroenterology and Hepatology, Department of Medicine, Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, Houston, Texas. e-mail: hasheme@bcm.edu; fax: (713) 748-7359.

Conflicts of interest

The authors disclose no conflicts.

Funding

This material is based on work supported in part by the Houston VA Health Services Research & Development Center of Excellence (HFP90-020) and support from NIH P30 DK58338.

Supplementary References (Online Only)

51. White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. J Hepatol 2008;49:831–844.
52. Hassan MM, Hwang LY, Hatten CJ, et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. Hepatology 2002;36:1206–1213.
53. El-Serag HB, Richardson PA, Everhart JE. The role of diabetes in hepatocellular carcinoma: a case-control study among United States veterans. Am J Gastroenterol 2001;96:2462–2467.
54. Jee SH, Ohrr H, Sull JW, et al. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005;293:194–202.
55. Lai MS, Hsieh MS, Chiu YH, et al. Type 2 diabetes and hepatocellular carcinoma: a cohort study in high prevalence area of hepatitis virus infection. Hepatology 2006;43:1295–1302.
56. Chao LT, Wu CF, Sung FY, et al. Insulin, glucose and hepatocellular carcinoma risk in male hepatitis B carriers: results from 17-year follow-up of a population-based cohort. Carcinogenesis 2011;32:876–881.
57. Hassan MM, Spitz MR, Thomas MB, et al. The association of family history of liver cancer with hepatocellular carcinoma: a case-control study in the United States. J Hepatol 2009;50:334–341.
58. Yu MW, Chang HC, Liaw YF, et al. Familial risk of hepatocellular carcinoma among chronic hepatitis B carriers and their relatives. J Natl Cancer Inst 2000;92:1159–1164.
59. Guo YM, Wei WY, Shen XZ. Tumour necrosis factor 308 polymorphisms and hepatocellular carcinoma risk: a meta-analysis. Hepatogastroenterology 2010;57:926–931.
60. Qin H, Liu B, Shi T, et al. Tumour necrosis factor-alpha polymorphisms and hepatocellular carcinoma: a meta-analysis. J Int Med Res 2010;38:760–768.
61. Yang Y, Luo C, Feng R, et al. The TNF-alpha, IL-1B and IL-10 polymorphisms and risk for hepatocellular carcinoma: a meta-analysis. J Cancer Res Clin Oncol 2011;137:947–952.
62. White DL, Li D, Nurgalieva Z, et al. Genetic variants of glutathione S-transferase as possible risk factors for hepatocellular carcinoma: a HuGE systematic review and meta-analysis. Am J Epidemiol 2008;167:377–389.
63. Wang B, Huang G, Wang D, et al. Null genotypes of GSTM1 and GSTT1 contribute to hepatocellular carcinoma risk: evidence from an updated meta-analysis. J Hepatol 2010;53:508–518.
64. Liu F, Li B, Wei Y, et al. XRCC1 genetic polymorphism Arg399Gln and hepatocellular carcinoma risk: a meta-analysis. Liver Int 2011;31:802–809.
65. Yang HI, Sherman M, Su J, et al. Nomograms for risk of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. J Clin Oncol 2010;28:2437–2444.
66. Coleman PJ, McQuillan GM, Moyer LA, et al. Incidence of hepatitis B virus infection in the United States, 1976-1994: estimates from the National Health and Nutrition Examination Surveys. J Infect Dis 1998;178:954–959.
67. Davis GL, Alter MJ, El-Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology 2010;138:513–521.
68. Gomaa AI, Khan SA, Toledano MB, et al. Hepatocellular carcinoma: epidemiology, risk factors and pathogenesis. World J Gastroenterol 2008;14:4300–4308.
69. Bosetti C, Levi F, Boffetta P, et al. Trends in mortality from hepatocellular carcinoma in Europe, 1980-2004. Hepatology 2008;48:137–145.
70. Deuffic-Burban S, Mohamed MK, Larouze B, et al. Expected increase in hepatitis C-related mortality in Egypt due to pre-2000 infections. J Hepatol 2006;44:455–461.
71. Custer B, Sullivan SD, Hazlet TK. Global epidemiology of hepatitis B virus. J Clin Gastroenterol 2004;38(10 Suppl 3):S158–S168.
72. Chen CJ, Yang HI, Su J, et al. Risk of hepatocelluar carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65–73.
73. Kanwal F, Hoang T, Kramer JR, et al. Increasing prevalence of HCC and cirrhosis in patients with chronic hepatitis C virus infection. Gastroenterology 2011;140:1182–1188.

Update

Gastroenterology
Volume 143, Issue 1, July 2012, Page 269

DOI: https://doi.org/10.1053/j.gastro.2012.06.002

dedicated to the identification and management of alcohol and drug abuse written by substance abuse experts is a thoughtful addition to the textbook, reflecting the importance of substance abuse issues to the outcome of liver disease among HIV-infected patients.

Bottom Line: *HIV and Liver Disease* is a welcomed reference for healthcare practitioners engaged in the management of patients with HIV or liver disease. It provides a succinct update on liver conditions frequently seen in persons living with HIV, as well as excellent supporting chapters on relevant virology, immunopathogenesis, and pathology. Given the importance of these intersecting chronic diseases—HIV and liver diseases caused by HBV, HCV, and alcohol—the availability of this textbook is timely. Those healthcare providers wanting to gain greater expertise in managing liver diseases in their HIV-infected patients will find this book to be a valuable resource.

JENNIFER A. FLEMMING
NORAH A. TERRAULT
University of California San Francisco
San Francisco, California

Correction

El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012;142: 1264–1273.

In figure 1 of the above article, the box labelled "Men," in the figure key, should correctly be shaded in the color blue. The box labelled "Women," in the figure key, should correctly be shaded in the color yellow.

The key for figure 1 has been corrected as shown below and in the online version of the article.