

Viral Hepatitis and Hepatocellular Carcinoma in African Americans

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Introduction

HCC² is the eighth most common cancer worldwide. It is a diagnosis with very poor prognosis, causing about 1 million deaths each year. Chronic infection with HBV and HCV is a major risk factor for HCC.

For patients with active chronic hepatitis B, there is a 10–100-fold increase in the risk of hepatocellular cancer. Unlike many other forms of chronic liver diseases, hepatitis B can cause hepatocellular cancer in the absence of cirrhosis. Because recurrent inflammation is the major culprit in these cases, efforts geared toward the reduction of inflammation should be offered to all patients. Although hepatitis B is more prevalent among African Americans than Caucasian Americans, few trials have examined the response of African Americans to currently available therapies.

Hepatitis C is one of the most common chronic blood-borne viral infections in the United States. Recurrent bouts of inflammation lead to progressive fibrosis, cirrhosis, and HCC in some patients. Although enormous strides have been made in the treatment of chronic hepatitis C infection over the last two decades, lesser gains have accrued in the management of African Americans with this disease. African-American men have the highest rate of infection among groups in the United States; they also have lower rates of response to treatment in comparison with Caucasians. This poor response to treatment for hepatitis C among African Americans is not well understood, and studies on the efficacy of antiviral medications have included only a few African-American participants.

Viral Hepatitis and HCC in African Americans

The major risk factors associated with the development of cirrhosis and HCC in the United States include chronic infection with HBV, HCV, and alcoholic cirrhosis. Recent epidemiological studies as well as the results of treatment trials for viral hepatitis suggest that African Americans have a higher prevalence of hepatitis C infection, a lower rate of sustained virologic response in clinical trials, and a higher risk of HCC. In this paper, we review the problem of viral hepatitis and HCC in the African-American population.

HCC is the eighth most frequent cancer worldwide, sixth among men and eleventh among women (1). Although it is predominant in the sub-Saharan regions of Africa and parts of Eastern

Asia, it has been relatively uncommon in the United States. The incidence of HCC in the United States rose from 1.4 per 100,000 persons in 1976 to 2.4 per 100,000 persons by 1995. During this time, the mortality from HCC increased by 45% (2). The increase in HCC is most likely the result of a greater prevalence of chronic hepatitis C infection. Other factors that may contribute to the increase in HCC include enhanced immigration of people from regions where hepatitis B is endemic and improved imaging techniques that facilitate the diagnosis of HCC.

Cirrhosis and chronic liver disease are significant risk factors for the development of liver cancer. Various types of chronic liver disease can result in cirrhosis, which is characterized pathologically by diffuse fibrosis and nodular regeneration. Autopsy studies performed on patients with cirrhosis reveal that 7–23% of necropsy liver specimens reveal the presence of occult HCC (3). In patients with cirrhosis, risk factors for development of HCC include male sex, age, and degree of hepatic decompensation. Chronic hepatitis B infection alone, even in the absence of fibrosis or cirrhosis, elevates the risk of HCC.

Despite improved imaging techniques for screening and diagnosis, HCC continues to have a very poor prognosis, with a 5-year survival rate of 6% (4). Other than surgical resection and liver transplantation, which are curative for small lesions, other available treatments such as radiofrequency ablation, chemoembolization, and percutaneous ethanol injection only provide palliation (5, 6). Therefore, strategies to combat HCC should include screening of populations at risk for HBV and HCV infections as well as treatment.

For reasons that are not entirely clear, the incidence of HCC is significantly higher in African Americans than in Caucasian Americans. Between 1991 and 1995, the incidence of HCC among African-American men in the United States was 6.1 per 100,000 persons, whereas the incidence among Caucasian men during this same period was 2.8 per 100,000 persons. African-American men have a mortality rate from HCC that is twice the rate observed among Caucasian men (2). Many investigators attribute the racial difference in HCC incidence to higher prevalence of infection with HBV and especially HCV in African Americans. Nevertheless, these findings are difficult to reconcile with histological studies that suggest that HCV-infected African Americans progress to end-stage liver disease at a slower rate compared with Caucasians (7).

Chronic Hepatitis B Infection

The WHO estimates that 350 million people worldwide have chronic hepatitis B infection (8). In some parts of Africa and Asia, 15% of populations can be chronic carriers of HBV and are at risk of developing cirrhosis. As many as 25% of these patients will die prematurely as a result of complications of cirrhosis or of HCC. Chronic hepatitis B infection may increase the risk of developing HCC by 10–100 times, depending on the population studied (9, 10). In the United States, an estimated 1.25 million people have chronic HBV infection. Whereas the prevalence remains higher among African Americans (0.9%) than Caucasians (0.2%; Ref. 2), the incidence of acute hepatitis

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² The abbreviations used are: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; NHANES, National Health and Nutrition Evaluation Survey.

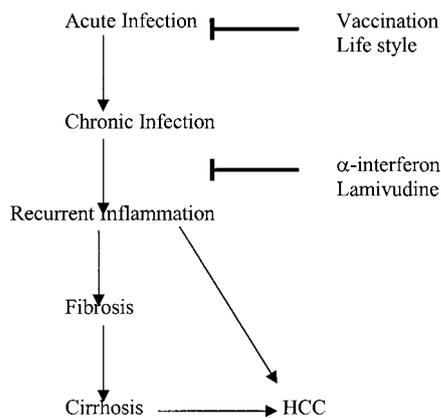


Fig. 1. Intercepting the natural history of hepatitis B infection. Vaccinations and lifestyle changes prevent acute infection. For patients who are chronically infected, treatment with lamivudine and α -IFN can reduce hepatic inflammation and consequently reduce the risk of hepatocellular cancer.

B infection in the United States has decreased significantly among Caucasians, African Americans, and Hispanics over the past two decades (11).

Hepatitis B infection may cause HCC by several mechanisms including chronic infection and development of cirrhosis, integration of HBV DNA into host cells, and through the activity of a HBV-associated protein (3). Studies of HCC in patients with chronic hepatitis B infection reveal that the severity of liver disease is the most important predictor of HCC risk in chronic carriers. Whereas the annual risk of developing HCC is less than 0.8% in patients with recurrent inflammation in the setting of chronic hepatitis B infection, the risk increases to between 1.5% and 6.6% in patients with cirrhosis (12).

A critical factor in the pathogenesis of chronic hepatitis B infection is the age of acquisition. Early age of infection increases the likelihood of chronic infection and thereby increases the risk of cirrhosis and HCC. In areas where chronic hepatitis B infection is endemic, the most common route of disease acquisition is vertically from mother to child at the time of birth. This mode of transmission is especially common in Asian populations. A second route, known as horizontal transmission, occurs when the disease is passed to a young child by contact with infected body fluids. Regardless of the route, early acquisition confers an increased likelihood of chronicity (13, 14).

In the United States, hepatitis B is most commonly acquired during adult life either by sexual transmission or through i.v. drug use. Health care workers also have a risk of acquiring hepatitis B through needle sticks and cuts sustained during the care of patients. Because health care institutions require that health workers receive vaccination for hepatitis B, this mode of transmission is becoming less common (13). Infection through blood product transfusion is now rare because blood banks effectively screen blood donors for hepatitis B, hepatitis C, and HIV. Immunocompetent adults who acquire the infection have approximately a 95% chance of mounting protective immunity and eliminating the virus. However, in immunocompromised patients such as those with concomitant HIV infection, the likelihood of chronic infection increases.

An effective campaign against hepatitis B must focus on various points in the natural history of the virus (Fig. 1). Perhaps the most important intervention is the prevention of chronic infection. Through childhood vaccination programs, the public health system in the United States has been success-

ful in preventing early infection. Every pregnant woman is tested for hepatitis B infection. If a mother tests positive, the child receives hepatitis B immunoglobulin at the time of birth in conjunction with vaccination. Vaccination of adolescents who were born before the institution of childhood vaccination for hepatitis B will also help to lower the incidence of hepatitis B infection (9). As adults, patients who belong to high-risk groups can be targeted for hepatitis B vaccination. Physicians and other health care workers can also counsel patients about changes in their lifestyles that may reduce the risk of infection with hepatitis B.

Vaccination against hepatitis B at birth decreases the risk of HCC. Data from Taiwan reveal that a policy of vaccination for hepatitis B at birth, which began in 1984, decreased the incidence of HCC in children between ages 6 and 14 years from 0.7 per 100,000 persons to 0.35 per 100,000 persons in the 10-year interval from 1981 to 1991. Therefore, universal vaccination for hepatitis B is an effective intervention to prevent childhood hepatitis B infection and HCC (15).

In patients who have already acquired chronic infection, the therapeutic goal is to prevent recurrent inflammation. People who are infected with hepatitis B but do not have hepatic inflammation are unlikely to progress to cirrhosis or to develop HCC (12). If infection cannot be prevented, it is appropriate to consider the use of antiviral therapies to reduce hepatic inflammation. The two medications available for treatment of hepatitis B are α -IFN by s.c. injection and oral lamivudine (16). Whereas neither medicine effectively eradicates the virus, both work in selected patients to reduce inflammation, even though the virus is still present (13).

Data from three controlled trials on the use of α -IFN in the treatment of hepatitis B suggest that 30% of patients will have a treatment response, defined as absence of viral envelope antigen and sustained loss of HBV DNA within 1 year of starting therapy. Whereas these studies enrolled only a few African-American subjects, the response rate was higher in these African Americans subjects (83%) compared with the Caucasian subjects (27%; Ref. 17). The reasons for this comparatively better response are not clear.

Similarly, lamivudine has proven effective in the treatment of chronic hepatitis B infection. A randomized trial of lamivudine *versus* placebo in patients with chronic hepatitis B found that after 52 weeks of therapy, patients treated with lamivudine were more likely to have a histological improvement and to exhibit treatment effect characterized by hepatitis B envelope antigen seroconversion, normalization of transaminases, and sustained suppression of HBV DNA (14). In this study, 33 of the 137 patients were African American, but unfortunately, the rates of response to lamivudine were not reported by race.

Additional studies are required to investigate the natural history of chronic hepatitis B in the African-American population and response to IFN and lamivudine therapy. The available data suggest that treatment with lamivudine or IFN should be offered to patients with chronic hepatitis B, particularly for immigrants from Africa and Asia, where hepatitis B is endemic. These patients most likely have had chronic hepatitis B infection since childhood and are at greater risk of cirrhosis and subsequent development of HCC.

Chronic Hepatitis C Infection

It is estimated that 4 million Americans have been exposed to the HCV. Of these, approximately 2.7 million carry a chronic infection, and fewer than 30% are aware that they carry the

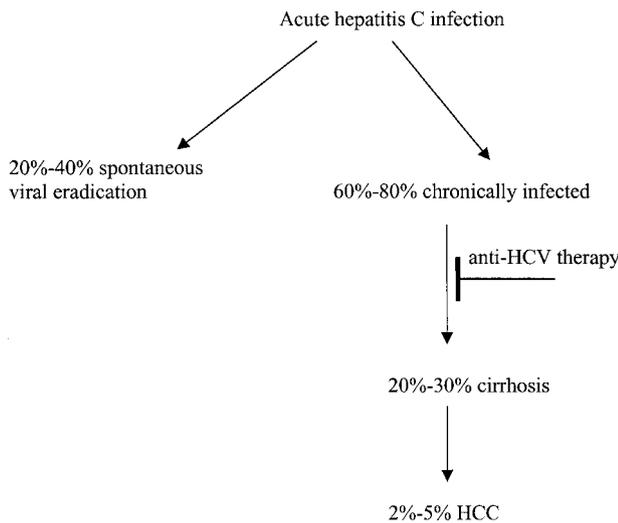


Fig. 2. Natural history of hepatitis C infection. Because the cirrhotic liver is a precursor of HCC, prevention of extensive fibrosis by viral eradication prevents cirrhosis and subsequent hepatocellular cancer.

infection. At present, hepatitis C is the most common etiology of end-stage liver disease in the United States and is the most common reason for liver transplantation (18).

Approximately 20–40% of patients acutely infected with the HCV eradicate the virus, whereas the remaining patients develop a persistent infection. Chronic hepatitis C infection can result in chronic hepatic inflammation and ultimately lead to fibrosis and cirrhosis (Refs. 19 and 20; Fig. 2). The factors that influence spontaneous viral clearance are not completely understood. The presence of cirrhosis is the primary predictor of HCC in patients with chronic hepatitis infection. Concurrent infection with HBV further increases risk for HCC (21, 22). Additional risk factors for progression to cirrhosis include male sex, late age of onset of hepatitis C infection, alcohol consumption, and HIV coinfection (21–23). If liver injury can be halted before the development of extensive fibrosis, then cirrhosis and ultimately liver cancer may be prevented.

In the late 1980s, α -IFNs were shown to be effective in the treatment of patients with hepatitis C. Patients treated with IFN were able to clear the virus, and long-term follow-up revealed a sustained viral response, defined as lack of detectable virus 6 months after cessation of therapy. Regimens to treat hepatitis C infection have evolved to include combination therapy with ribavirin (18). Within the past year, IFN linked with polyethylene glycol has become available. In combination with ribavirin, this “pegylated” IFN is superior to other available therapeutic modalities (24). These improvements in therapy for hepatitis C have resulted in rates of sustained viral eradication increasing from 7–10% of treated patients in the early 1990s to >50% in 2001. A number of factors including degree of fibrosis, advanced age, male sex, genotype, and pretreatment HCV viral load influence treatment outcome (25).

African Americans and Hepatitis C Infection

The NHANES III study conducted between 1989 and 1994 provides the most current estimate of the disease burden of HCV in the United States. Blood samples were collected from over 22,000 Americans between the ages of 5 and 70 years and analyzed for the presence of antibodies to HCV and for the presence of viral RNA.

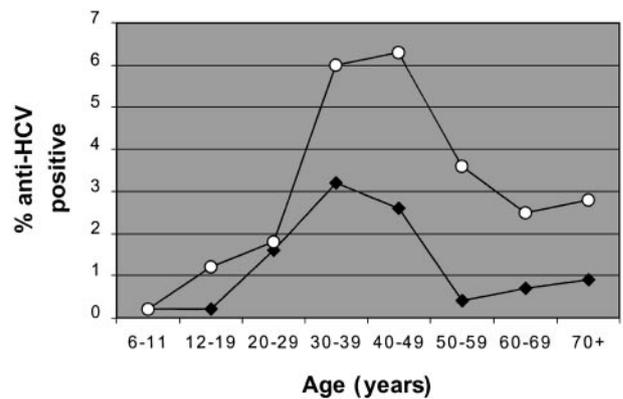


Fig. 3. Prevalence of anti-HCV antibodies by race, NHANES III, 1989–1994. Adapted from data by Alter *et al.* (Ref. 26). Circles represent African Americans, whereas squares represent Caucasians. Note the higher prevalence of anti-HCV antibodies among African Americans.

In this study, antibodies to HCV were found in 3.2% of African Americans and in 1.8% of Caucasians. Interestingly, the racial differences were not significant after adjustment for socioeconomic status and high-risk behaviors. Furthermore, 76% of people with antibodies to HCV had detectable HCV RNA. Therefore up to one-fourth of people with evidence of past infection had no evidence of current infection. However, the rate of viremia among African Americans was 86%, whereas the rate among Caucasians was 68%, suggesting that African Americans have a lower rate of spontaneous viral clearance (26).

The NHANES III data also revealed other important differences between African Americans and Caucasians infected with HCV, which may partly explain observed differences in treatment response and mortality between these groups. In African Americans, the highest prevalence of antibody to HCV was found in the 40–49-year age group, whereas the peak prevalence among whites occurred in the fourth decade of life (Fig. 3; Ref. 26). This observation is significant because older age predicts further progression of fibrosis at the time of diagnosis as well as poorer response to therapy. Moreover, African Americans were found to have a higher prevalence of genotype 1, which has been associated with lower rates of sustained viral response in several studies of therapy for HCV. Whereas genotype 1 accounted for 91% of HCV cases in African Americans, it accounted for 67% of infections among Caucasians (26, 27).

Unfortunately, the improvement in available therapies has not translated into better treatment outcomes among African Americans infected with HCV. In 1989, two landmark studies on the treatment of hepatitis C infection with α -IFN alone were published. Approximately 12% of treated subjects eradicated the virus and achieved a sustained virologic response. However, only 1% of African Americans achieved sustained response (28, 29). In 1998, studies showed that the combination of ribavirin with α -IFN resulted in better response rates. Sustained virologic response rates of around 35–40% were now reported after treatment, yet the sustained virologic response among African-Americans was only 11% (25, 30, 31). In the year 2000, results were published on the use of pegylated forms of IFN as monotherapy. A sustained virologic response rate of around 40% was reported, but the response rate for African Americans remained below 10% (27). In 2001, Manns *et al.* (32) reported on the use of pegylated IFN and ribavirin as combination therapy for hepatitis C. Sustained virologic response rates of approximately 55% were reported. There is as

yet no breakdown of this response by race (32). The above data, in conjunction with several smaller reports, suggest that African Americans have a poorer rate of response to the presently available therapies for hepatitis C than Caucasians.

A number of factors may contribute to the poor rates of response to therapies for hepatitis C among African Americans: (a) genotype (the prevalence of genotype 1 in this population is an important determinant of lower response to HCV therapeutic regimens); (b) inappropriate dosing of medication (the higher average weight among African Americans in the above studies suggests that the absence of weight-based regimens may place African Americans at a disadvantage in assessing response rates to therapy); and (c) compliance [whereas some investigators have suggested that poorer compliance may play a role, at least one study reported that African Americans have similar compliance as Caucasians (25)].

There are some fundamental problems with drawing conclusions from the available clinical literature on hepatitis C in African Americans. African Americans are underrepresented in drug trials to evaluate the efficacy of available therapies. In all of the major treatment trials for hepatitis C over the last 10 years, the participation of African Americans has been low. Generally, whereas 22% of patients with HCV are African American, they have comprised less than 5% of patients enrolled in several large clinical trials (27). In a large trial comparing IFN monotherapy with IFN and ribavirin combination therapy, African Americans represented only 3% (53 subjects) of the 1744 subjects, whereas 92% (1600 subjects) were Caucasian (25). Ultimately, the lower response rates of African Americans to HCV therapy can be adequately assessed only if there are enough patients enrolled in prospective studies to permit an analysis of important clinical and biological factors that may influence clinical response.

In summary, chronic infections with hepatitis B and C are risk factors for HCC. Because hepatic inflammation and fibrosis precede HCC, therapies that arrest histological progression of disease by suppressing viral replication are likely to decrease the subsequent risk of HCC. Such therapies include α -IFN and lamivudine for hepatitis B and α -IFN and ribavirin for hepatitis C. Despite these advances in therapeutic management, significant disparities continue to exist between African Americans and Caucasians in terms of the response to therapy and development of HCC. Ultimately, the increased participation of African-American patients in research studies will represent an important step in understanding the natural history of HBV and HCV infections and finding more effective treatment strategies.

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