Hepatitis C Virus Infection and the Rising Incidence of Hepatocellular Carcinoma

In 2012, more than half a million people worldwide will be diagnosed as having hepatocellular carcinoma (HCC), a primary cancer of the liver.[1] The incidence is rising globally at an alarming rate, making HCC the fifth most common cancer in men and the seventh most common cancer in women.[2-4] More than 80% of HCC cases occur in developing countries, but the impact of this disease is also seen in the United States. Southeast Asia and sub-Saharan Africa carry the heaviest burden of HCC largely owing to the widespread infection of hepatitis B virus (HBV). In the United States, the incidence of HCC has tripled in the last 3 years. The driving force behind this US epidemic is related to hepatitis C virus (HCV). The long-term prognosis of US patients diagnosed as having HCC remains grim, with a 5-year overall survival rate of 10% to 12%.[1,5] An even lower survival rate is seen in developing countries.

In the current issue of *Mayo Clinic Proceedings*, Yang et al[6] and Shire et al[7] report on the HCC incidence and etiologic trend in 2 widely contrasting patient populations in Minnesota. The study by Yang et al uses a community-wide medical record linkage system in Olmsted County, Minnesota. According to the authors, the incidence of HCC in this population (6.9 per 100,000 population) is higher than the reported national average (3.0 per 100,000 population) largely because of differences in establishing the HCC diagnosis. As the article points out, the requirement of histologic confirmation of HCC in many databases may substantially underestimate the incidences reported elsewhere because nationally and internationally established guidelines do not always require histologic confirmation to establish disease.[8,9] As stated by Yang et al, most patients diagnosed as having HCC from 1976 to 2000 had alcohol-related liver disease as their primary risk factor, but, following recent national trends, from 2001 to 2008 HCV infection was the most commonly identified risk factor for HCC.

Since 1990, immigration from sub-Saharan Africa to the United States has increased markedly, and according to US Census estimates, 25,000 to 50,000 Somalis currently live in Minnesota. Somalia, like all countries in sub-Saharan Africa, is in an area of high prevalence for HBV infection. Because few epidemiologic data have been available from Somalia since 1992, little is known about the incidence rates of HCV in this region.

The other article in the current issue of *Mayo Clinic Proceedings*, by Shire et al, states that Somalis in this part of Minnesota are more likely to be infected with HBV than with HCV. Surprisingly, the rate of chronic HCV infection was seen more often in patients diagnosed as having HCC than in those with hepatitis B infection. As the authors point out, the Centers for Disease Control and Prevention has published guidelines for screening individuals emigrating to the United States for HBV infection, but currently there are no guidelines that govern screening immigrants for HCV infection.

It is currently estimated that 170 million to 180 million people worldwide and 3 million to 4 million people in the United States are infected with HCV. Most individuals infected with the virus in the United States have now been infected for 10 to 30 years, and it is the progression of fibrosis in chronic HCV infection that places them at risk for HCC. The estimated risk of HCC is 15 to 20 times higher in persons infected with HCV than among those not infected with the virus. It has been projected that new cases of HCV-related HCC will continue to increase during the next 2 to 3 decades.

Chronic infection with HBV is responsible for approximately half of all cases of HCC worldwide. HBV infection is implicated in almost all cases of HCC occurring in childhood. In areas of endemic HBV infection, such as Southeast Asia and Africa, the most common transmission of the virus occurs from mother to newborn. Through this vertical route of transmission, up to 90% of infected individuals will develop a chronic disease course. The risk of HCC in these patients occurs even without significant fibrosis, so screening guidelines for HCC with early HBV acquisition recommend screening at a younger age (40 years for Asian men and 50 years for Asian women, as well as for Africans with hepatitis B or HBV carriers with a family history of HCC)[8,10] than that for the remainder of the at-risk population.

The primary risk factor for the development of HCC in patients with liver disease is progression to cirrhosis. More than 80% of patients with HCC will develop the disease in the setting of cirrhosis. Although there are patient populations, such as those described in these 2 studies with HBV and HCV infection, that are at higher risk for developing HCC, *any* patient with cirrhosis is at increased risk for developing HCC. The 5-year cumulative risk of the development of HCC in patients with cirrhosis ranges from 5% to 30%.[11] In several studies conducted in Western countries, 30% to 40% of patients with HCC were not infected with HBV or

HCV, suggesting causes and risk factors of liver disease other than viral hepatitis.[12,13]

Unlike many cancers, for which risk factors are not as clearly established and therefore targeted screening and surveillance of a limited population are made more difficult, in HCC the highest risk factors are plainly identifiable and the at-risk population is easily defined. The decision to enter a patient into a surveillance program is determined by the level of risk for HCC and the likelihood of early detection benefits. A single, randomized, controlled trial of surveillance vs no surveillance has shown a survival benefit in the strategy of ultrasonography and quantification of serum α-fetoprotein every 6 months.[14] In addition, although adherence to this surveillance was less than optimal, there was still a 37% reduction in HCC-related mortality in the surveillance arm.

The goal of surveillance is to find disease at a sufficiently early stage for treatment to be beneficial. Hepatocellular carcinoma detected after the onset of symptoms, for example, has a 5-year survival prognosis of 0% to 10%. In contrast, patients with smaller lesions at detection have a survival prognosis of 50% or greater when treated with resection or liver transplant.[15-17]

Studies continue to show that patients who are at risk and could benefit greatly from early disease detection are still not receiving adequate routine surveillance. In one study of US military veterans infected with hepatitis C, only 12.0% of patients with cirrhosis received routine surveillance, 58.5% received incomplete surveillance, and 29.5% received no surveillance of any kind.[18] Surveillance guidelines currently recommend an imaging study and α-fetoprotein serum testing every 6 months for patients at risk for HCC. The most common imaging modality used in surveillance is ultrasonography. The diagnosis of a suspicious lesion noted on ultrasonography then requires additional imaging with computed tomography with contrast or magnetic resonance imaging with contrast. As the articles in the current issue of *Mayo Clinic Proceedings* strongly suggest, greater attention to surveillance and screening of at-risk individuals will be increasingly important as we continue to treat patients with more advanced stages of fibrosis and liver disease.

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