The Epidemiology of Hepatocellular Carcinoma in HCV

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Introduction
Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer death in the world. It accounts for up to 75% to 85% of primary liver cancer in the United States (U.S.) and for over 90% in high-risk areas [1•,2]. It has predominantly affected those in developing countries, such as sub-Saharan Africa, China, Taiwan, Korea, or Vietnam, where the hepatitis B virus (HBV) is endemic [3,4]. In the U.S., the incidence of HCC has reflected ethnic and regional variations (occurring most commonly in Alaskan Natives and immigrants from the Far East and their descendants). The incidence and mortality rates of HCC have been rising—a trend positively associated with the current hepatitis C virus (HCV) epidemic. This article explores the epidemiology of HCC in the setting of HCV.

Independent Risk Factors for HCC

In western society, viral infections account for over 80% of primary HCC [5–8]. Worldwide, 25% to 73% of HCC occurs in the setting of HCV and 12% to 60% with HBV; the remainder is associated with alcohol (4% to 38%) and other causes (2% to 6%). Advanced age, male gender, and severity of liver disease are almost universally reported to increase the risk of HCC (Table 1) [9–23]. HCC develops in the setting of cirrhosis in over 90% of cases. Noncirrhotic patients can also be affected, especially in developing countries where HBV and aflatoxin predominate [6]. Race, heavy alcohol use, cigarette smoking, obesity, and diabetes mellitus (DM) have also been associated with an increased risk of developing HCC [8,13,15,19,20,24]. HCC is now more often associated with HCV, particularly in developed countries.

Rising Incidence of HCC

Worldwide, between 350,000 and 1 million new cases of HCC are diagnosed annually, approximately 5.6% of all cancers [2]. The age-adjusted global incidence ranges from two to four per 100,000 in the western world to as high as 100 to 150 per 100,000 in areas of high incidence, where most cases (40% to 90%) are attributed to HBV [6]. In the U.S., cumulative lifetime risk for primary liver cancer (HCC and cholangiocarcinoma) is 0.88% in men and 0.42% in women [6]. HCC has a high case fatality rate, with similar incidence and mortality rates; thus, there are at least 250,000 to 1 million deaths reported each year [2]. Recently, the age at initial HCC diagnosis has shifted to younger cohorts (45 to 60 years), regardless of race or gender [25]. The age-adjusted HCC incidence rates in the U.S. have doubled from 1.3 (1978–1980) to three per 100,000 (1996–1998) [3,26]. This trend began in the mid-1980s, with the largest increase in the 1990s—a 25% increase between 1993 to 1995, to 1996 to 1998 [1]. Consequently, the number of hospitalizations and deaths from HCC has risen (from 2.9 to 4.1 per 10,000 hospitalizations and from 1.8 to 3.1 per 100,000 deaths) [26–28]. The current number of HCC cases in the U.S. ranges between 8500 to 15,000 per year [1,3].

Similar increases have been reported elsewhere. Italian surveillance studies indicate that in cirrhotic patients HCC progression as the cause of death has increased from 63% (1987–1991) to 69% (1992–1996) to 83% (1997–2001) [7]. In Canada, the incidence rates have increased from 1.97 (1969) to 4.0 (1984) to 4.43 (1997) to 5.5 per 100,000 (2000) in men, and 0.99 to 1.6 to 1.26 to 2.2 per 100,000 in women [29,30].

The epidemiologic patterns of HCC vary geographically. The greatest HCC burden has been seen in Asia and Africa where it is the most frequent cause of cancer death.
Similar increases in HCC were not seen in HCV-negative subjects that was greater than HCV-negative subjects [32] reported a 10-year liver disease mortality in HCV-positive subjects that was greater than HCV-negative subjects [32,35,39]. More HCV-induced cirrhotic patients in Japan (1960) to 27.1 per 100,000 (2000); over 40,000 annually reported in the United Kingdom, Italy, Australia, Switzerland, and to a lesser extent Greece. Development of HCV-HCC in the setting of noncirrhotic disease is rare, but has been reported. Overall, the annual incidence rate of HCV-HCC is 0.7 and 0 (immune globulins).

The first studies linking HCV to HCC were published as early as 1989. These and others reported that nearly all cases of HCV-associated HCC (HCV-HCC) occur in the setting of chronic hepatitis C (presence of cirrhosis was not specified) compared with HCV-negative subjects [22].

The incidence of HCC has also risen in Japan over the past 20 years [3,26]. Similar increases have been found in a hospital-based population, from 14.2 (1993) to 18.1 per 100,000 (1999). Thus, in developed countries HCV is responsible for a sizable portion of all HCC. The risk of developing HCV-HCC ranges from 0% to 90% [28,35,36].

Most countries experienced peak HCV infection rates during the past 40 years, and HCV-HCC has more than tripled over the past 15 years after development of cirrhosis is 12.5%, 19.4%, and 58.2%, respectively. This is significantly higher than the increase in incidence and mortality from HCC.

From 1993 to 1995, the prevalence of hepatitis B core antibody–positive HCC (18% vs 10%), whereas the prevalence of hepatitis B surface antigen–positive HCC (18% vs 10%), hepatitis B core antibody–negative HCC (15% vs 19%), and HCC without viral markers (14% vs 15%) all increased significantly from 1989 to 1998 in patients with chronic HCV infection. The risk of HCC increases with duration of HCV infection, and HCV viral levels or viral quasispecies are associated with the risk of HCC development. However, HCV viral genotype may not necessarily increase the risk. Genotype 1b is seen in 50% of HCV-HCC patients, and 1% to 4% in non-Asian populations [3,15,31]. The 5- to 15-year cumulative risk for developing HCV-HCC is 44.3%, and 58.2%, respectively. This is significantly higher than the risk of developing HCV-HCC in the United States and in 70% to 90% in Spain and Italy, but this association remains controversial. The mode of acquisition may also be an independent predictor of cirrhosis and HCC, respectively, were 1.9 and 0 per 1000 per-year studies and found that the weighted incidence rates for cirrhosis and HCV-HCC. Games Good et al. [31] reviewed 21 studies and found that the weighted incidence rates for cirrhosis and HCV-HCC. Goodgame et al. [31] reviewed 21 studies and found that the weighted incidence rates for cirrhosis and HCV-HCC. Goodgame et al. [31] reviewed 21 studies and found that the weighted incidence rates for cirrhosis and HCV-HCC. Goodgame et al. [31] reviewed 21 studies and found that the weighted incidence rates for cirrhosis and HCV-HCC.