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.
Hepatitis C: Epidemiology, Natural History, and Pathogenesis

The increased incidence of HCV-HCC in the U.S. and many developed countries is causally associated with the increased prevalence of HCV-related cirrhosis. In a Veterans Administration Hospital study, a threefold increase in HCV-related cirrhosis (transfusion associated), 7.9 and 1.0 (hemophilia), and 4.5 and 0.7 (community-acquired HCV), respectively, were 1.9 and 0 per 1000 per-8-year cumulative risk for development of cirrhosis and HCV-HCC, respectively. Goodgame et al. [31] reviewed 21 cohorts who have been infected with chronic HCV [4]. 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 (immunoglobulins). The 5- and 15-year cumulative risks of developing HCV-HCC in cirrhotic patients is approximately 5% to 10% in Japan and 1% to 4% in non-Asian populations [3,15,31]. The 5- and 15-year cumulative risk for developing HCV-HCC in cirrhotic patients is approximately 5% to 10%. There is no evidence that transfer of HCV-infected individuals who do not yet have cirrhosis increases the risk. Genotype 1b is seen in 50% of HCV-HCC cases of HCV-associated HCC (HCV-HCC) occur 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 (immunoglobulins). The 5- and 15-year cumulative risks of developing HCV-HCC in cirrhotic patients is approximately 5% to 10%. There is no evidence that transfer of HCV-infected individuals who do not yet have cirrhosis increases the risk. Genotype 1b is seen in 50% of HCV-HCC cases. The incidence of HCC has also risen in Japan over the past 40 years, and HCV-HCC has more than tripled between 5% and 30% [5,10,14,15]. The 5- and 15-year cumulative risk for developing HCV-HCC is 12.5%, 19.4%, and 58.2%, respectively. This is significantly higher than that reported in western populations. The number of Japanese HCC-related deaths has increased from 9.4 in 1960 to 27.1 per 100,000 (2000); over 40,000 annually is now decreasing in HBV endemic countries with the implementation of vaccination programs and increasing in newly endemic countries. HCC has always been considered to be regions of low incidence. HCC is now increasing in HBV endemic countries with the implementation of vaccination programs and increasing in newly endemic countries. HCC has always been considered to be regions of low incidence. HCC is now decreasing in HBV endemic countries with the implementation of vaccination programs and increasing in newly endemic countries. HCC has always been considered to be regions of low incidence. HCC is now decreasing in HBV endemic countries with the implementation of vaccination programs and increasing in newly endemic countries. HCC has always been considered to be regions of low incidence. HCC is now decreasing in HBV endemic countries with the implementation of vaccination programs and increasing in newly endemic countries. HCC has always been considered to be regions of low incidence.