# Epidemiology and Risk Factors of Biliary Tract and Primary Liver Tumors

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**KEYWORDS**

• Hepatocelluar cancer • Gallbladder cancer • Cholangiocarcinoma • Viral hepatitis
• Benign liver tumor

**KEY POINTS**

- Primary liver and biliary tumors are a significant health threat globally.
- These tumors have wide geographic, ethnic, and gender variation.
- Research investigating the epidemiology and risk factors associated with these tumors has resulted in significant global public health measures to reduce incidence rates.
- Recently identified risk factors, such as metabolic disorders, show the important role that epidemiology will continue to have in the understanding and treatment of these tumors.

## HEPATOCELLULAR CANCER

Hepatocellular cancer (HCC) is the most common form of primary liver cancer, accounting for 85% to 90% of all primary liver cancers, with the burden of disease expected to increase in coming years, especially in the developing world.[1] It is the fifth most common cancer worldwide and the third most common cause of cancer mortality, accounting for more than 600,000 deaths annually.[2] HCC was one of the first cancers to be linked epidemiologically to a defined risk factor (hepatitis B virus [HBV] in Taiwan). Approximately 80% of HCC worldwide is caused by chronic infection with HBV or hepatitis C virus (HCV). Chronic hepatitis B infection remains the most common risk factor for HCC worldwide. There are an estimated 450 million carriers of HBV worldwide. However, chronic hepatitis C has become an important cause of chronic liver disease around the world, with an estimated 200 million people infected with HCV. HCC has several interesting epidemiologic features, including dynamic temporal trends; marked variations among geographic regions and racial, ethnic,

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and gender groups; and the presence of several well-documented, preventable environmental risk factors.

### *Global Incidence of HCC*

The incidence of HCC is not evenly distributed throughout the world. It is broadly divided into 3 major geographic subgroups: (1) sub-Saharan Africa; (2) eastern Asia; and (3) North and South America, northern Europe, and Oceania. Most cases occur in sub-Saharan Africa or in eastern Asia. Recent estimates published in the GLOBOCAN analysis indicate that 82% of liver cancer cases occur in developing countries, with more than 50% of cases in China (male, 35.2 per 100,000; female, 13.3 per 100,000). Other areas of high incidence include South Korea (male, 48.8 per 100,000; female, 11.6 per 100,000), Gambia (male, 39.7 per 100,000; female, 14.6 per 100,000), and Senegal (male, 28.5 per 100,000; female, 12.2 per 100,000). The rates of HCC in North America, South America, and northern Europe are lower compared with the geographic regions mentioned earlier, typically with incidence rates of less than 5 per 100,000. Southern European countries tend to have incidence levels between these 2 geographic extremes.

Although the incidence of HCC remains high, several regions are experiencing a decrease in overall rate, accounted for by public health measures including vaccination and environmental exposure restriction. The world's first nationwide hepatitis B vaccination program was implemented in Taiwan in 1984 and resulted in a decrease in the average annual incidence of hepatocellular carcinoma from 0.7 per 100,000 children between 1981 and 1986 to 0.36 per 100,000 children between 1990 and 1994.[3–5] The mortality from HCC also decreased during this period. Aflatoxin contaminants in corn and peanuts infected with *Aspergillus flavus* correlated with HCC mortality and the presence of aflatoxin-albumin adducts is higher in hyperendemic HCC areas.[6] A Chinese government program started in the late 1980s to shift the diet of the Jiangsu Province from corn to rice may have limited exposure to known hepatocarcinogen aflatoxin B1 in this area.[6] However, registries in several low-rate areas, including the United States, United Kingdom, and Australia, have shown an increase in HCC incidence. It is thought that the increased incidence in low-rate areas has resulted from the later introduction of HCV infection through intravenous drug abuse within these areas.

HCC is the fastest growing cause of cancer-related mortality in the United States. Between 1985 and 2002, age-adjusted HCC incidence doubled.[7,8] The increase in HCC started in the mid-1980s, with the greatest proportional increase occurring in Hispanic and non-Hispanic white people.[9] In the United States, the mean age of diagnosis is approximately 65 years, with 75% of cases in men. The racial distribution is 48% white, 15% Hispanic, 13% African American, and 24% other (predominantly Asian).[1] The greatest proportional increase occurred in HCV-related HCC, whereas HBV-related HCC had the lowest rate.

### *Gender*

Liver cancer is the fifth most common cancer in men worldwide and the seventh most common cancer in women. In almost all populations, the rate of HCC is higher among men than among women, with the male/female ratio usually averaging between 2:1 and 4:1. According to GLOBOCAN estimates for 2002, the overall male/female incidence ratio was 2.4.[2] The most discrepant ratios are found in Europe where registries have reported male/female ratios of greater than 5:1. Some of the lowest differences are found in Central and South America. In Colombia and Costa Rica, male/female ratios have been as low as 1.2:1.[1] It is thought that the discrepancy in the ratio of