Chapter 2
Etiology

HCC is a heterogeneous cancer caused by a variety of risk factors including alcohol and more recently, the metabolic syndrome (Aravalli et al. 2008). The myriad of factors varies according to the geographical region, thereby complicating the diagnosis, prognosis and treatment recommendations (Marrero et al. 2010). Even though most of the 600,000 new HCC cases that occur each year are from developing countries, the incidence of HCC is rising rapidly in Western countries. This is due in large part to hepatitis C, alcoholism, and obesity (Fletcher and Powell 2003; El-Serag 2012). Although screening blood for HCV began in the 1990s, those patients infected beforehand are now presenting with HCC and therefore, many individuals remain undiagnosed. The Centers for Disease Control recently recommended one-time screening for the entire generation born between 1945 and 1965. The growing incidence of HCC has generated intense research efforts to understand physiological, cellular, and molecular mechanisms of the disease with the hope of developing new treatment strategies.

Risk Factors

A variety of factors have been firmly identified in the development of liver cancer (Fig. 2.1). Such factors include infection with viruses (Cramp 1999; Blum 2005; El-Serag and Rudolph 2007), exposure to foodstuffs contaminated with aflatoxin B1 (AFB1) (Soini et al. 1996), and vinyl chloride (Boffetta et al. 2003), tobacco (Tsukuma et al. 1995), heavy alcohol intake (Donato et al. 2002), non-alcoholic fatty liver disease (Hashimoto et al. 2004), diabetes (Wideroff et al. 1997; Regimbeau et al. 2004), obesity (Regimbeau et al. 2004), diet (Yu et al. 1995), coffee (Kurozawa et al. 2005), oral contraceptives (Maheshwari et al. 2007), and hemochromatosis, to name a few (Hellerbrand et al. 2003). In general, these factors vary according to the geographical region. For instance, chronic hepatitis B virus (HBV) infection

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is common in many countries in Asia and sub-Saharan Africa, whereas HCV is prevalent in Japan, Western Europe, and the United States (El-Serag and Rudolph 2007). Such differences in infectivity add complexity to the extrapolation of data obtained from one geographical region and applying it to others.

### Demographics

The prognosis for liver cancer is very poor and the geographical patterns of incidence and mortality are similar. Analysis of the data compiled by the International Agency for Research on Cancer (IARC) has shown that 83% of the estimated 782,000 new liver cancer cases that occurred in 2012 were from developing countries, with China alone accounting for 50% (IARC 2012). While liver cancer is the fifth most common cancer in men and the ninth in women, it is the second most common cause of death from cancer worldwide (IARC 2012). Due to the prevalence of infection with hepatitis viruses, HCC has become one of the top three cancers in the Asia-Pacific region. Whereas HBV is predominant in most Asian countries, HCV is far more prevalent in Japan, Australia, and New Zealand (Yuen et al. 2009).

Age-standardized incidence rates, have shown that HCC occurrence worldwide is considerably higher in men than in women (Nordenstedt et al. 2010). The incidence of HCC in Asian patients was found to be 31% in males and 18% in females, while there was no difference in patients with HCV (Miyakawa et al. 1996). HCC among HBV carriers in Asia exceeds 0.2% by the age of 40; and therefore, surveillance was recommended in males older than 40 years and females older than age 50, even in the absence of cirrhosis (Yu et al. 2000). In a cohort of 391 HCC patients from South Africa, serum levels of HBV were significantly higher in 171 out of 173 individuals below the age of 30, potentially due to aflatoxin exposure and synergy with HBV, prompting the authors to suggest surveillance at any early age (Kew and
Macerollo (1988). Interestingly, HBV-infected individuals exposed to aflatoxin are 60 times more likely to develop HCC than those with no exposure (Qian et al. 1994). As shown in a recent study from Taiwan, heavy alcohol consumption significantly increased the incidence of HCC in patients with HBV-associated cirrhosis (Lin et al. 2013). In North America and Europe, HCV is the major etiological factor of HCC. However, HCV infection is primarily limited to patients with cirrhosis (Fattovich et al. 1997), and cirrhosis amplifies the risk of HCC among patients with chronic viral hepatitis (Kuper et al. 2001). In these geographical locations, alcoholic cirrhosis and nonalcoholic steatohepatitis (NASH) are also major risk factors for HCC development. Diabetes mellitus may also increase the risk of developing liver cancer (Adami et al. 1996). This was highlighted in a recent study with US veterans, where HCC was found to be overwhelmingly associated with HBV, HCV and alcohol consumption, as well as diabetes with no evidence of cirrhosis (Karagozian et al. 2013). Collectively, these studies demonstrated key differences in age, gender, and the nature and synergy of risk factors, and underscore the importance of early detection for the treatment of HCC.

References

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