Chapter 8

# Liver Cancer

Hellen Gelband, Chien-Jen Chen, Wendong Chen, Silvia Franceschi, Sir Andrew Hall, W. Thomas London, Katherine A. McGlynn, and Christopher P. Wild

## INTRODUCTION

Deaths from liver cancer are common, especially in East Asia and Pacific, South Asia, and parts of Sub-Saharan Africa, largely as a result of infection decades ago. As the toll from other cancers is likely to climb in the coming decades, however, liver cancer incidence and mortality rates should fall, as generations vaccinated against the hepatitis B virus (HBV)—the cause of most liver cancers globally—reach middle and old age. Much still needs to be done and it is feasible and affordable to hasten the decline. Much can also be done to address other causes of liver cancer—including some on the rise, in particular, obesity-related non-alcoholic fatty liver disease (NAFD)—in the coming years and decades. The latter half of the twentieth century witnessed the identification of the main causes of liver cancer and deployment of the first cancer prevention vaccine for humans. All of the risk factors that lead to cirrhosis cause at least as many noncancer deaths as cancer deaths. Controlling these risk factors would not only reduce the incidence of liver cancer; it would also reduce the incidence of cirrhosis and its other complications, notably, end-stage liver disease and portal hypertension.

## GLOBAL BURDEN OF LIVER CANCER

Primary liver cancer—cancer originating in the liver—is the sixth most commonly occurring cancer in the world (782,000 cases in 2012) and the second largest cause of cancer mortality (746,000 deaths in 2012) (Ferlay and others 2013). Incidence and mortality rates vary greatly, mirroring the uneven distribution of major risk factors. In most high-rate liver cancer areas, the dominant risk factors are chronic infection with HBV and consumption of foods contaminated with the mycotoxin aflatoxin B1. In contrast, in most low-rate areas, the major risk factors are infection with the hepatitis C virus (HCV), excessive alcohol consumption, obesity, and diabetes. HBV and HCV have been classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (Group 1).

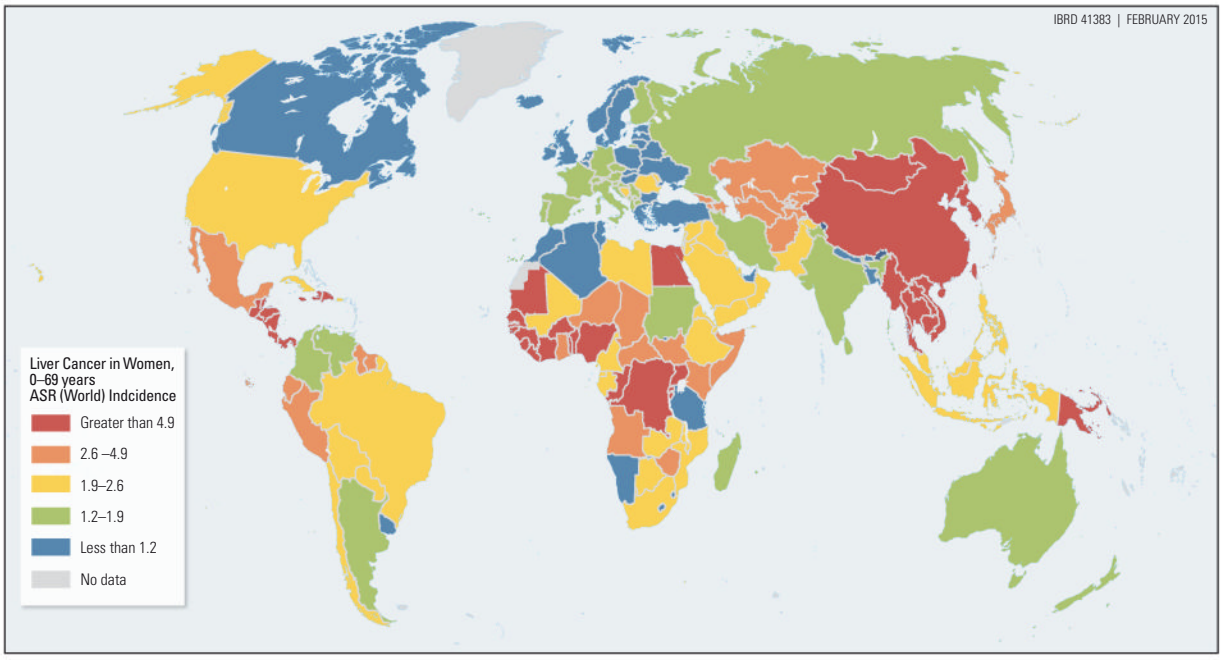
The most common histologic type of primary liver cancer, hepatocellular carcinoma (HCC), arises from the epithelial liver cells known as *hepatocytes*. Globally, approximately 80–85 percent of primary liver cancers are HCCs; the rates of primary liver cancer and rates of HCC are roughly equivalent. Intrahepatic cholangiocarcinoma, which arises from *cholangiocytes*—epithelial cells that line the bile duct—is the second most common type of primary liver cancer, but it accounts for only 10–12 percent of primary liver cancer worldwide. Infection with liver flukes (flatworms) is a major cause of cholangiocarcinoma in high-incidence regions.

### Incidence and Mortality Rates[1]

The highest national liver cancer incidence rates in the world are found in East Asia and Pacific and Sub-Saharan Africa (maps 8.1 and 8.2). Approximately

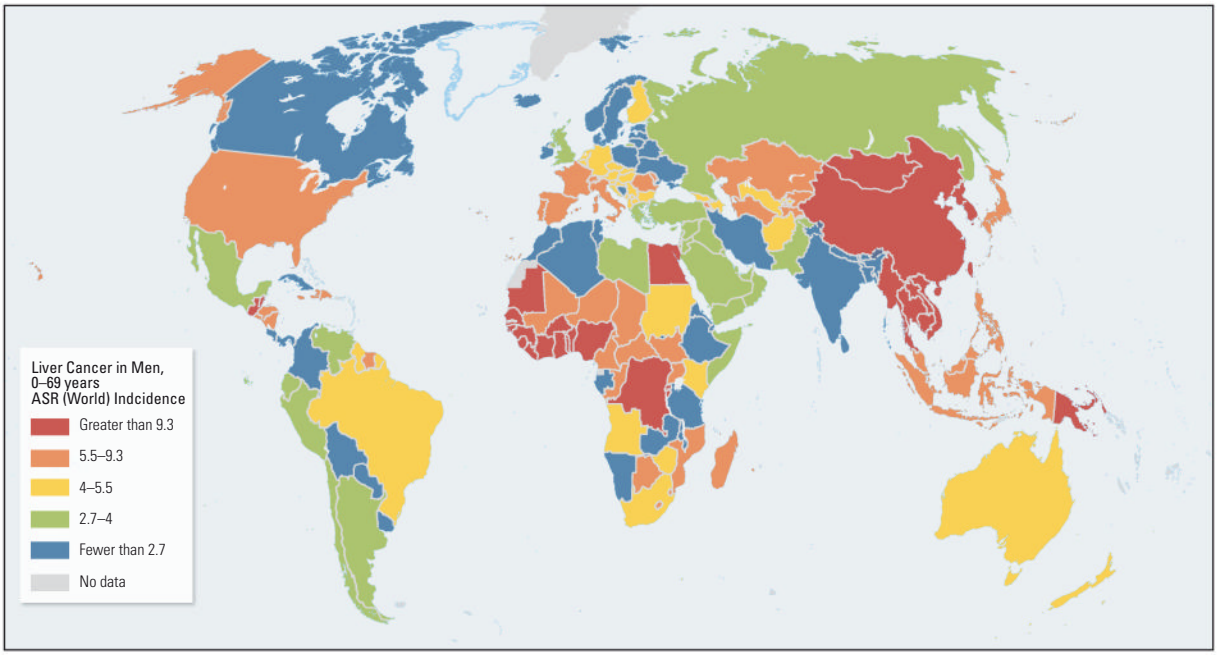
Corresponding author: Hellen Gelband, gelband@cddep.org

**Map 8.1** Age-Standardized Liver Cancer Incidence Rates for Women, 2012




*Source:* Ferlay and others 2013.
*Note:* ASR = age-standardized rate.

**Map 8.2** Age-Standardized Liver Cancer Incidence Rates for Men, 2012




*Source:* Ferlay and others 2013.
*Note:* ASR = age-standardized rate.

85 percent of the total liver cancer burden is concentrated in these areas; China alone—because of high rates and a very large population—bears over half of the global burden (Ferlay and others 2013). Although more liver cancers occur in China than any other country, the country with the highest liver cancer incidence rate in the world is Mongolia (78.1 per 100,000 population), with an incidence rate more than three times as high as that of China (22.3 per 100,000) (Ferlay and others 2013). These exceedingly high rates are reportedly the result of high rates of infection with HBV, HCV, or both, as well as co-infection of HBV carriers with hepatitis D virus (HDV) (Oyunsuren and others 2006).

The prevalence of HBV infection in Mongolia is likely to decline as the results of a childhood HBV vaccination program that began in 1991 decrease the prevalence of new infections. However, the continued high rate of HCV infection may result in liver cancer incidence rates increasing for some years (Dondog and others 2011). Alcohol consumption rates are reportedly higher in Mongolia than in many Asian populations, a factor that may contribute to the liver cancer burden (Alcorn 2011).

In addition to China, other East Asian and Pacific countries and economies with incidence rates greater than 20 per 100,000 include Taiwan, China; the Republic of Korea; the Lao People's Democratic Republic; Thailand; and Vietnam. Thailand has high rates of both HCC and intrahepatic cholangiocarcinoma in the northeastern part of the country, where liver fluke infection is common. Countries in Sub-Saharan Africa with incidence rates greater than 20 per 100,000 include The Gambia and Guinea; rates in the Democratic Republic of Congo (10.6 per 100,000), Ghana (11.1 per 100,000), and Guinea-Bissau (13.4 per 100,000) are almost as high (Ferlay and others 2013). Although the reported incidence of liver cancer in Sub-Saharan Africa is lower than the incidence in East Asia and Pacific, at least some of the difference arises from underdiagnosis and the historic paucity of well-functioning, reliable cancer registries. Another reason for the lower incidence in Sub-Saharan Africa is that babies are less likely to become infected with HBV in the perinatal period compared with babies in Asia (Marinier and others 1985). The later age at infection results in lower HBV replication rates in Sub-Saharan Africa than in East Asia and Pacific (Evans and others 1998). Nevertheless, in both East Asia and Pacific and Sub-Saharan Africa, the major risk factor for liver cancer is chronic HBV infection. Notable exceptions are the Arab Republic of Egypt and Japan, in which HCV is the dominant risk factor.

In contrast to these high-rate areas, rates are low in North and South America and northern Europe. Incidence rates in these areas are generally less than 5 per 100,000. Rates are intermediate—typically between 5 per 100,000 and 10 per 100,000—in some countries of central Europe (for example, Greece and Italy) and central Asia (for example, Kazakhstan, the Kyrgyz Republic, Pakistan, and Turkmenistan). Not all low- and middle-income countries (LMICs) have high HBV infection rates. A prime example is India, which has historically had low HBV infection rates and, as a result, low liver cancer incidence rates.

At all incidence levels, almost all countries report rates in men that are twofold to threefold higher than rates in women. The greatest gender disparity in incidence, however, is not reported by countries with the highest liver cancer rates, such as Mongolia (where the ratio in men to women is 1.6) (men, 97.8; women, 61.1), but by countries with intermediate rates, such as France (men, 11.3; women, 2.5) and Spain (men, 9.9; women, 2.4). An exception to the general predominance in men occurs in Central America and Mexico, where the rates of both genders are low and not very different. Although the reasons for higher rates in men in most regions are not completely understood, the differences may be partly explained by the sex-specific prevalence of risk factors. Men are more likely to be chronically infected with HBV and HCV, consume alcohol, and smoke cigarettes. Whether androgenic hormones or increased genetic susceptibility also predispose men to the development of liver cancer is unclear (Hsieh and others 2007).

### Age-Specific Incidence

Liver cancer incidence rates increase with age in all populations, with the highest rates in those ages 75 years and older. The age-specific curves look somewhat different in various regions, but in no area do the rates decline among older persons (men and women combined). In a low-rate area, such as northern Europe, rates are generally very low before age 40 and then rise exponentially with age. In high-rate areas of East Asia and Pacific, rates become elevated in childhood and continue to rise with age. In contrast, in the high-rate area of Sub-Saharan Africa, rates increase until age 55 years and then plateau until age 70 years. The reasons for the slightly different patterns in Asia and Sub-Saharan Africa may be related to competing causes of mortality and differences in mean ages at HBV infection and/or differences in HBV viral replication patterns (Evans and others 1998).

### Incidence by World Bank Economic Group

Globally, the single greatest determinant of liver cancer prevalence in any country is the prevalence of chronic HBV infection. As chronic HBV infection has historically

**Figure 8.1** Age-Standardized Liver Cancer Incidence and Mortality Rates in Men and Women, by World Bank Income Classification, 2012


*Source:* Ferlay and others 2013.

been much more common in LMICs, liver cancer has been more prevalent in these countries (figure 8.1). In general, the incidence rates decrease as a country's per capita gross domestic product (GDP) increases. Among the low-income countries (LICs), 13 of the 34 (38 percent) have rates of 10 per 100,000 or greater. In the lower-middle-income group, excluding India, 18 of 49 countries (37 percent) have rates of 10 per 100,000 or higher. In the upper-middle-income group, excluding China, only 2 of 55 countries (4 percent) have rates of this magnitude; in the high-income countries (HICs), only 2 of 75 countries (3 percent) have rates of 10 per 100,000 or higher.

A rapidly expanding economy does not have an immediate effect on a country's HBV carrier rate and does not greatly alter its liver cancer incidence in the short term. For example, although China has undergone rapid economic development in the late twentieth century, it still has a high liver cancer rate. With economic growth, however, comes the ability to reduce future liver cancer rates by funding universal HBV vaccination of newborns and aflatoxin abatement programs, ensuring that the blood supply is free of HCV, and possibly treating HCV infection.

## Trends

From 1983–87 through 1998–2002, liver cancer incidence increased in many areas of the world. Increases were notable in northern Europe, India, Israel, North and South America, Oceania, and most countries in southern Europe. In contrast, incidence rates declined in most eastern Asian countries. Increases in incidence in HICs and India have been linked to HCV infection, increasing rates of obesity and diabetes, and improved treatment of cirrhosis (which reduces the risk of death from cirrhosis, leaving individuals at persistent risk of HCC).

Rates have been declining in some eastern Asian countries for several reasons. In Japan, the large cohort of individuals infected with HCV in the 1930s and 1940s is dying off, and the rate of HCV-related HCC is declining accordingly (Tanaka and others 2002). In China, where HBV is the dominant risk factor, HBV vaccination of newborns was introduced in the mid-1980s but ramped up only after 2000. Vaccine recipients are still too young to have their rates greatly affect the rates in the overall population. It is more likely that the rates in China have declined because exposure to aflatoxin B1 in the diet has decreased as a result of shifting from a corn-based to a rice-based diet (Sun and others 2013). The declining rates of HCC in younger age groups reported in Jiangsu Province, a high aflatoxin B1 area, support this hypothesis (Chen and others 2006; Wang and others 2010).

## Prognosis and DALYs

The prognosis for liver cancer, even in HICs, is unfavorable. In the United States, the one-year survival rate is less than 50 percent; the five-year survival rate is only 16 percent (NCI 2013). As with all cancers, survival is best when detected early—for localized liver cancer, five-year survival is 29 percent, but it falls to 3 percent for cancers detected late (NCI 2013). Survival is even less favorable in LMICs. Mortality rates in all locations are roughly equivalent to incidence rates, and the number of years lived with disability is very small. Accordingly, disability-adjusted life years (DALYs) caused by ill health, disability, or early death from liver cancer are almost identical to the years of life lost (YLLs) because of liver cancer. The age-standardized rate of DALYs is highest in the high-incidence areas of eastern Asia (744 per 100,000 for men; 277 per 100,000 for women) and western Africa (451 per 100,000 for men; 213 per 100,000 for women); it is lowest in the low-incidence areas of Europe (110 per 100,000 for men; 45 per 100,000 for women) and North America (109 per 100,000 for men; 39 per 100,000 for women).

## Major Risk Factors

### Hepatitis B Virus

An estimated two billion people alive today have been infected with HBV; about 360 million of these are chronically infected (carriers) (Dienstag 2008). Routes of transmission vary by life stage, but HBV is never spread by air, food, or water. Neonates may be infected by their mothers, if the mothers are infectious carriers. During childhood, transmission can occur among children living in close proximity, although the precise route is unclear. The virus is found in the blood and in most body secretions. In adult life, the virus can be spread sexually via semen and vaginal fluid or by contaminated needles, frequently the result of intravenous drug

misuse. Blood transfusion was an important source of infection before the introduction of donor selection and serological screening of donated blood.

The natural history of chronic infection is the development of chronic hepatitis, then cirrhosis, and finally, liver cancer. However, especially in Sub-Saharan Africa, cancer can develop without underlying cirrhosis. Aflatoxin exposure multiplies the risk of liver cancer in chronic carriers by a factor of twofold to tenfold. The interval from the initial HBV infection to the development of cancer is in the range of 5–75 years, with most cases manifesting after several decades. In 1994, IARC declared HBV a human carcinogen (Group 1).

The age of infection is critically important in determining whether the infection becomes chronic. Newborns infected by their mothers have an 80–90 percent probability of becoming carriers. Those infected in the first five years of life beyond the perinatal period have a 20–50 percent probability; those infected in adult life have a probability of less than 10 percent. This is the inverse of the risk of developing acute hepatitis, which manifests in one-third of adult infections with the characteristic fever, jaundice, and lethargy, whereas it is very unusual following infection in children under age five years.

Acute hepatitis carries a risk of death of 1 percent or less. Chronic infection increases the risk of primary liver cancer by tenfold to fiftyfold.

In some populations in the pre-vaccination era, the prevalence of chronic HBV infection was 10–15 percent of the adult population. This was the case in China and surrounding East Asian countries, much of Sub-Saharan Africa, and the Amazon forest. These high carriage rates resulted from very high rates of infection in the early years of life, either perinatally from mothers or in early childhood from other children (WHO 2004). In China, some 40 percent of carriers were infected perinatally by their mothers. In contrast, in Sub-Saharan Africa, only 10 percent of carriers were infected perinatally and 90 percent were infected through child-to-child transmission during the first few years of life, but overall, rates were very high. These differences resulted from the fact that about half of Chinese women who were HBV-positive remained infectious into adult life, whereas only 10 percent of HBV-positive African women did so (Marinier and others 1985).

Rates of liver cancer in Chinese carriers are higher than in Sub-Saharan African carriers. The reasons for this are unclear but may be related to the differences in age at infection.

**Hepatitis C Virus**

HCV, a blood-borne RNA virus identified in 1988, was declared a definite human carcinogen by IARC in 1994. The World Health Organization (WHO) estimates that about 180 million people, some 3 percent of the world's population, are infected with HCV, of which 130 million are chronic carriers. At least three million to four million people are newly infected each year; this compares with the approximately 360 million people chronically infected with HBV. HCV prevalence is highest (10 percent or more) in Pakistan (Ahmad 2004), Egypt (Attia 1998), Mongolia (Dondog and others 2011), and some parts of China (Gao and others 2011). Prevalence is also high in some parts of Italy (Fusco and others 2008) and Japan (Tanaka and others 2002). Globally, 10 million intravenous drug users are HCV-positive, with prevalence in this group exceeding 60 percent in most countries (Nelson and others 2011).

HCV transmission is primarily from contaminated blood or blood products; however, HCV can be acquired from sexual and household contacts. Acute infection with HCV is usually asymptomatic; in approximately 75 percent of people, HCV persists as a chronic infection, in which HCV RNA and serum HCV antibodies (anti-HCV) can be detected in the blood (Alter and Seeff 2000). Approximately 20 percent of individuals with chronic HCV will develop HCC by age 75 (Huang and others 2011).

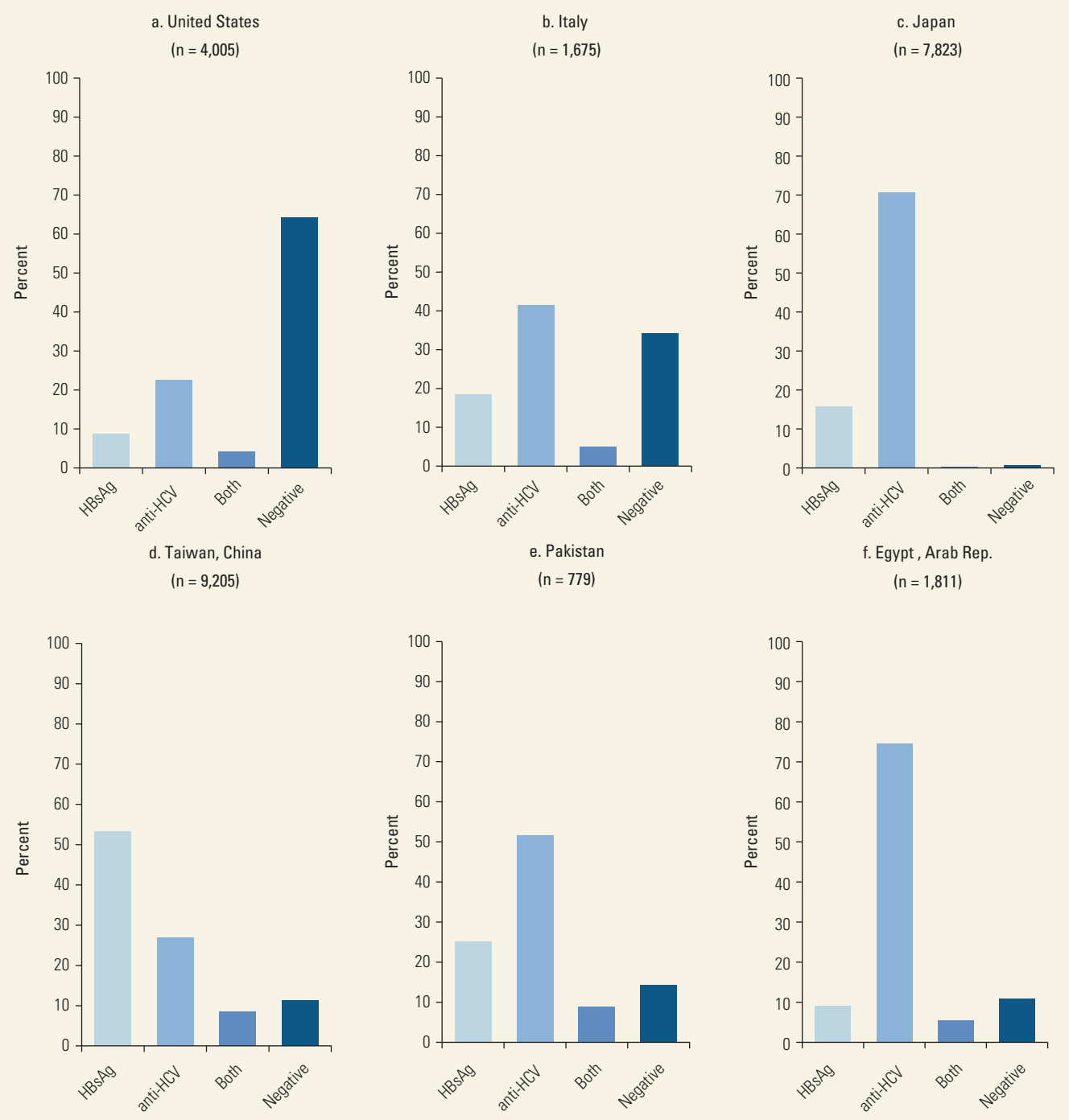
Evidence suggests that HCV prevalence is substantially underestimated for several reasons:

- Country-specific data are absent, notably in LICs.
- Surveillance systems that focus on acute HCV infection are insensitive because the infection is rarely symptomatic.
- Prevalence surveys tend to include mainly young adults (for example, blood donors or pregnant women), while transmission of HCV through contaminated blood and needles is more probable in adulthood and old age than in childhood (Dondog and others 2011).

The seroprevalence of HCV and HBV in cases of HCC can be used to estimate HCV and HBV prevalence where accurate population-based data are lacking. In a large meta-analysis of seroprevalence (Raza and others 2007), a higher proportion of cases had HBV than HCV in most countries in East Asia and Pacific, Latin America and the Caribbean, South Asia, and Sub-Saharan Africa. In contrast, in most European countries, Japan, the United States, and, among low-resource countries, Egypt and Pakistan, HCV was more frequent than HBV (figure 8.2). The proportion of HCV-associated HCC cases is growing steadily in other countries and economies, for example, Taiwan, China (Lu and others 2006).

HCV epidemics have accompanied the increase in the availability of injections and blood transfusions in several countries (Prati 2006). Massive and unsafe injection campaigns have occurred in many countries, for example, the anti-schistosomal treatments in Japan

**Figure 8.2** HCV and HBV Presence in HCC Cases: Countries and Economies Where HCV Predominates or Is Increasing




*Source:* Adapted from Raza and others 2007.
*Note:* Includes studies that reported seroprevalence of both hepatitis B surface antigen (HBsAg) and anti-HCV, alone and in combination, for at least 20 hepatocellular carcinoma cases; updated through 2010. HBV = hepatitis B virus; HCV = hepatitis C virus; HCC = hepatocellular carcinoma.

starting in the 1920s and in Egypt in the 1960s, and the use of intravenous stimulants starting in Japan in the 1940s (Tanaka and others 2002). Unsafe blood transfusions and medical procedures have tended to increase in times of military conflicts. By the end of the 1980s, most chronic transfusion recipients, and virtually all patients receiving clotting factor concentrates, had been infected by HCV (Prati 2006). New cases of HCV infection greatly decreased in high-resource countries in the 1990s after the introduction of HCV testing for blood donors, inactivation procedures for blood derivatives, and disposable needles and syringes.

However, HCV-related HCC continued to increase as those people who were infected decades ago aged. Trends in HCV prevalence were generally dominated by cohort effects: an estimated 73 percent of HCV infections in the United States, for example, involve individuals born between 1945 and 1965 (Smith and others 2012). In some low-resource countries, the spread of HCV has continued and may undermine the future benefits of HBV immunization (Dondog and others 2011).

**Aflatoxins**

Aflatoxins are secondary metabolites of the fungal species *Aspergillus flavus* and *A. parasiticus*. These toxins contaminate many staple cereals and oilseeds, with particularly high levels found on maize (corn) and groundnuts (peanuts) (IARC 2002). Contamination occurs during crop cultivation and increases postharvest under poor storage conditions, in which high humidity and temperature promote fungal growth and toxin production. An estimated 4.5 billion people worldwide are exposed to aflatoxins (Williams and others 2004); the highest exposures are in LICs in East and Southeast Asia and Sub-Saharan Africa, where regulatory control is weak.

The naturally occurring aflatoxins are aflatoxins B1, B2, G1, and G2 (AFB1, AFB2, AFG1, and AFG2, respectively). AFB1 is the most abundant, toxic, and carcinogenic. Aflatoxins M1 and M2 (AFM1 and AFM2, respectively), the hydroxylation products of AFB1 and AFB2, respectively, are found in milk and milk products (IARC 2002).

Aflatoxins induce toxicity and tumors in the liver in a wide range of animal species. Epidemiological studies in different populations have established aflatoxins as a risk factor for HCC (IARC 2002, 2012a). Prospective cohorts have provided the most convincing evidence, with the increased risk highest among individuals who were also chronically infected with HBV (Qian and others 2013; Wang and others 1996; Wu and others 2009). The effect of aflatoxins in the absence of chronic HBV infection is more difficult to assess because of their common co-occurrence in many populations. Nevertheless, some studies have reported an increased risk with aflatoxin exposure among individuals not chronically infected with HBV (Omer and others 2004; Wu and others 2009). In contrast to aflatoxins and HBV, there has been little focus on the potential for interaction with HCV. Knowledge about aflatoxin and risk of liver cirrhosis is also limited (Kuniholm and others 2008). However, exposure to aflatoxins in childhood has been linked to hepatomegaly (enlarged liver) (Gong and others 2012).

Improved understanding of the biochemistry of aflatoxin-cell interactions strongly supports the association between aflatoxin exposure and liver cancer. Following bioactivation, AFB1 binds predominantly to guanine in DNA, leading to a mutation from guanine to thymine. In HCCs collected from areas where aflatoxin exposure is high, up to half have been shown to harbor this type of mutational change in one specific location within the tumor suppressor gene TP53. This same mutation is extremely rare in liver tumors from regions where aflatoxin exposure is low (Wild and Gong 2010).

Based on animal, epidemiological, and mechanistic data, IARC has classified mixtures of naturally occurring aflatoxins as carcinogenic to humans (Group 1) (IARC 2002, 2012a). An association between early life exposure to aflatoxins and impaired child growth has been reported and may represent a significant additional disease burden globally (Gong and others 2002, 2004).

Aflatoxin exposure is ubiquitous in many of the poorest populations worldwide and is a cause of human liver cancer. Aflatoxins appear to be more potent among HBV chronic carriers than among noncarriers, but there may also be an increased risk in the absence of HBV. Given more than 350 million chronic HBV carriers worldwide, many in areas with endemic aflatoxin consumption, the need for reduction of aflatoxin exposure is highly relevant for liver cancer prevention. Adverse effects of early life exposure to aflatoxins add to the public health concerns related to these potent, naturally occurring toxins.

**Alcohol**

In 1988, IARC classified alcohol as a Group 1 human carcinogen of the liver, causing HCC (IARC 2012a). The National Institute of Alcohol Abuse and Alcoholism (NIAAA) has also documented that prolonged heavy drinking is associated with primary liver cancer (NIAAA 1993), mainly through cirrhosis (Corrao and Arico 2000). The dose-response relationship for the amount of alcohol consumed and the risk of HCC has been explored in a meta-analysis (Corrao and others 2004), which produced a relative risk of liver cirrhosis of 27 and of HCC of 1.8 for the heaviest drinkers (100 grams daily) compared with non-drinkers. The incidence of liver cancer increases by 0.7 per 1,000 for every additional drink, defined as 14.0 grams (0.6 ounces) of pure alcohol by

NIAAA, regularly consumed per day (Allen and others 2009). Alcohol-associated liver cirrhosis is the most important risk factor for HCC in populations with low prevalence of HBV and HCV, as in the United States and northern Europe (Boffetta and Hashibe 2006). Alcohol-related HCC without preexisting cirrhosis is rare.

Alcohol is synergistic with tobacco consumption and chronic viral hepatitis (either HBV or HCV) in causing HCC (Haenel 1989). Alcohol as a solvent increases the exposure of hepatocytes to carcinogens such as 4-aminobiphenyl and polycyclic aromatic hydrocarbons in tobacco smoke (IARC 2012a). However, alcohol consumption remains an independent risk factor for HCC after adjustment for multiple host and viral factors (Chen, Yu, and Liaw 1997). The risk of developing HBV/HCV-related HCC is about twice as high for habitual alcohol drinkers as for non-drinkers (Chen and Chen 2002).

The carcinogenicity of alcoholic beverages does not seem to vary with the type of beverage; the effect appears to be caused by ethanol itself. After ingestion, ethanol is converted by the enzymes alcohol dehydrogenase and cytochrome P450 2E1 into acetaldehyde, which is oxidized by aldehyde dehydrogenase (ALDH) to acetate (IARC 2012b). Acetaldehyde is a plausible candidate for the carcinogenic effects of alcoholic drinks through two mechanisms. It forms adducts (bonds) with DNA, leading to mutations, and it can increase cell proliferation (Boffetta and Hashibe 2006). Ethanol-caused hepatocellular injury can result in enhanced fibrogenesis and, finally, cirrhosis. A deficiency of ALDH—and subsequent inefficient oxidation of acetaldehyde to acetate—substantially increases the risk of alcohol-related liver cancer.

**Liver Flukes**

*Opisthorchis viverrini* and *Clonorchis sinensis*—liver flukes—are the strongest risk factors for cholangiocarcinoma, accounting for about 15 percent of liver cancers globally. *O. viverrini* was classified by IARC as a human carcinogen in 1994, and *C. sinensis* was so classified in 2009. These small, but not microscopic (1–2.5 centimeters by 0.3–0.5 centimeter), worms are prevalent only in parts of eastern Asia, but infection in some places is extraordinarily common—historically reaching virtually entire populations in some areas—and possibly one-sixth of those with chronic infection develop cholangiocarcinoma, starting in middle age. The worms, protected in the bile duct, live surprisingly long lives—up to two decades or more for *C. sinensis* but possibly less than 10 years for *O. viverrini* if untreated (Sithithaworn and Haswell-Elkins 2003).

*O. viverrini* infects at least 10 million people in Lao PDR and Thailand and an unknown number in Cambodia and Vietnam (Sripa and others 2011). The prevalence of infection varies greatly. In Thailand in 1980–81, approximately 35 percent of the population in the northeast was infected; prevalence in the south was close to zero. The national average was 14 percent. By 2001, presumably as a result of treatment and control, prevalence in the northeast had fallen to 15 percent and the national average to 10 percent.

The variation in *O. viverrini* infection in Thailand is echoed in the variation in mortality rates from cholangiocarcinoma, which varies more than 12-fold from a low in Prachuap province in the south to a high in Nakhon Phanom province in the northeast (Sripa and others 2011).

In 2009, IARC estimated that 35 million people were infected with *C. sinensis* in China, Korea, Lao PDR, Thailand, the Russian Federation, and Vietnam (IARC 2009). Infections are occasionally reported in Malaysia and Singapore. In China, prevalence varies, with the highest rates in Guangdong (16.4 percent) and Guangxi (9.8 percent) in southern China and in Korean ethnic communities in northeastern Heilongjiang province (4.7 percent) (Shin and others 2010).

The spread of these liver flukes is restricted by the distribution of the two definitive hosts other than humans—particular species of snail (mainly of the genus *Bothynia*) and cyprinid fish—and the cultural practice of eating raw fish (either fresh or fermented fish can harbor fluke metacercariae that infect humans after ingestion). The transmission cycle also requires eggs from fish-eating hosts, which emerge in feces, to contaminate the freshwater bodies inhabited by the snails and fish—the consequences of the poor sanitation that is synonymous with poverty. Other fish-eating mammals, notably dogs and cats, play some role in maintaining the cycle, but their part is thought to be relatively unimportant.

**Obesity**

Obesity is discussed last because it currently is not an important risk factor in LMICs. However, like other obesity-related health problems, cirrhosis from NAFD is on the rise in HICs (Baffy, Brunt, and Caldwell 2012; Michelotti, Machado, and Diehl 2013; Vanni and Bugianesi 2014). All expectations are that in the coming decades it will have a similar impact in LMICs. HCC is the cancer most strongly affected by NAFD.

## INTERVENTIONS

### Hepatitis B Virus

The major intervention is primary prevention of chronic infection by vaccination (vaccination has no impact on established chronic infection). The vaccine consists of the surface antigen of the virus, an antigen that circulates in the blood of carriers. The first vaccine was made by

separating this antigen from the blood of carriers and sterilizing it. Although this plasma-derived vaccine is still used in some parts of the world, in most places it has been replaced by recombinant hepatitis B vaccine, which uses a manufactured surface antigen.

The plasma-derived vaccine first became available in 1982 and initial trials in high-risk populations showed it to be safe and effective. It has subsequently been introduced in 168 countries as part of the routine childhood vaccination program. However, this has been a gradual process over the intervening 30 years. Three doses of the vaccine are required to ensure protection against acute hepatitis and chronic infection. These can be given at intervals of one month. Most countries use a schedule of doses at two, three, and four months of age, either as a separate injection or as part of a combination vaccine with diphtheria, pertussis, and tetanus. Early studies showed that administration of the vaccine in the first 24 hours of life could prevent transmission from a highly infectious mother. The recommended WHO schedule is three or four doses of vaccine, with the initial dose within 24 hours of birth (WHO 2009).

The HBV vaccine is supported by The Vaccine Aliance (Gavi) in countries eligible because of low income levels. By the end of 2011, Gavi estimated that the vaccines it has supported would save 5.5 million lives, 3.7 million of them attributable to the HBV vaccine.

Dramatic reductions in the prevalence of HBV carriage have been demonstrated in early adopters of universal vaccination. In China, for example, vaccination has reduced the prevalence of carriage from greater than 10 percent to less than 1 percent (Cui and others 2010). In Taiwan, China, mortality rates from infant fulminant hepatitis, chronic liver disease, and HCC have declined more than 90 percent among those vaccinated since a nationwide HBV immunization began (Chiang and others 2013).

### Screening for and Treating HBV

In addition to vaccination, testing blood donors for chronic infection and excluding positive blood has eliminated this relatively small but important source of infection. A global program to reduce needle reuse and to ensure the safe disposal of used needles has also reduced the risk of infection.

More recently, antiviral treatment of those chronically infected has been shown to reduce the risk of liver cancer. Studies are underway in countries with a high prevalence of HBV in adults to screen for carriage, evaluate those found infected, and treat those with significant disease.

## Hepatitis C Virus

Although no vaccines against HCV are available, most HCV transmission could be avoided. Needle sharing by intravenous drug users has become the predominant source of HCV acquisition in high-resource countries (Nelson and others 2011). In contrast, most infections in low-resource countries are iatrogenic, acquired through contaminated blood and contaminated injections of medications. Many low-resource countries, mostly in East Asia and Pacific, South Asia, and Sub-Saharan Africa, do not systematically screen blood donations for HCV, although screening for HBV and human immunodeficiency virus (HIV) is common (Prati 2006). Blood safety in low-resource countries is additionally threatened by lack of voluntary, nonpaid blood donors; inadequate supplies of medical instruments and laboratory reagents; and lack of infrastructure. Many transfusions could be avoided with the use of appropriate measures to optimize the patient's own blood volume before surgery and to minimize blood loss during surgery (Goodnough 2013).

More than 16 billion injections are administered annually in low-resource countries (Prati 2006). Especially high rates of injections have been reported in Mongolia and some countries of the former Soviet Union; they have also been reported in Pakistan (Ahmad 2004) and some Sub-Saharan African countries (Attia 1998). The most frequently injected medications, nearly all of which could be taken orally, include antibiotics, vitamins, iron, and analgesics, as well as treatments for nonspecific symptoms such as headache, fatigue, or fever. Injections represent an important source of revenue for providers and are encouraged by the popular belief that injections are more effective than oral administration. Insufficient hygiene, inappropriate use of multiple-dose medication vials, and sharing bottles of intravenous solution also contribute to the spread of HCV. Finally, HCV transmission can occur through traditional medicine (for example, acupuncture and scarring) and outside health care settings (for example, tattooing). Preventing infection is the most affordable option to reduce HCV-related diseases in low-resource countries (box 8.1).

### Screening and Treating Chronic HCV

Much progress has been made in the management of chronic hepatitis C, in terms of eradicating the virus and reducing hepatic and extrahepatic complications and HCV-related deaths. Increasingly efficacious regimens have been developed to eradicate the virus. The first was interferon monotherapy, which was introduced in 1990; a combination of ribavirin and pegylated interferon was introduced in 2002; and in 2011, a protease inhibitor (telaprevir or boceprevir) was added to ribavirin and pegylated interferon (Morgan and others 2013).

A new generation of direct-acting antiviral drugs, the first two of which entered the market in late 2013—sofosbuvir and simeprevir—is promising. Compared with the best previous regimens, they are significantly

**Box 8.1**

### Interventions to Prevent Blood-Borne Infections, Including HCV

- Increase awareness of the importance of HCV and other blood-borne infections and the means of preventing them, among the population, health care workers, and traditional healers.
- Use oral treatments instead of injections and use alternatives to blood transfusions whenever possible.
- Use safe injection practices in the management of sharp waste.
- Provide services to intravenous drug users, including access to sterile needles and syringes.
- Make blood supplies safe by recruiting voluntary donors and screening all donated blood for markers of HCV, HBV, and HIV.

*Note:* HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus.

more effective in clearing the virus (in trials, up to 100 percent of patients cleared, including multiple viral genotypes), are taken for half the treatment period of previous regimens (12 versus 24 weeks), have few side effects, and are taken orally (with another oral antiviral drug, ribavirin) rather than having an injectable component. At least two other similar drugs are in late-stage development. Hepatitis C medications were put on the WHO Essential Medicines List in 2015. They are all, however, priced well above what is affordable in LMICs; they would have serious budgetary implications, even in HICs. In the United States in 2014, sofosbuvir is priced at US$84,000 for a course of treatment, and simeprivir at US$66,000. Because the previous regimens are also expensive (US$25,000–US$45,000), relatively few HCV-infected people anywhere have been treated. In 2010, an estimated 7 percent of those with chronic infection in France were treated, 3 percent in the United Kingdom, and 0.3 percent in Russia (Razavi and others 2013).

The only way the new anti-HCV drugs can benefit most infected individuals is if they can be made affordable, particularly in LMICs. Patents on these drugs will not begin to expire until 2025. In the meantime, several hundred thousand deaths per year could be averted by finding an acceptable means of setting lower prices, at least for LMICs, similar to the success story of low-priced antiretrovirals for HIV.

One of the factors allowing for low-priced antiretrovirals for HIV has been the economies of scale that come with a hugely expanded market. Hill and others (2014) estimate the minimum production costs of the two available HCV drugs, the two in late-stage development, and ribavirin, using the history of HIV drugs as a guide. Using these costs, they estimate the costs of complete combination 12-week regimens at from US$78 to US$166 for the least expensive, to US$232 to US$454 for the most expensive. Recognizing that companies require compensation for their investment and profit, these are not suggested as realistic sales prices; however, with tiered pricing (charging higher prices in richer countries) and high volumes, affordable prices can be envisioned and should be pursued by the global community for this now highly curable infection.

Widespread treatment implies screening, as well, which currently is recommended for relatively few individuals. Should treatment be made affordable, the recommended populations should be expanded.

## Aflatoxins

Human exposure to aflatoxins can be reduced in several ways. *Aspergillus spp.* infects crops during cultivation, but toxins accumulate postharvest under poor storage conditions. Accordingly, preharvest and postharvest interventions can contribute to controlling aflatoxins (Groopman, Kensler, and Wild 2008; Wild and Hall 2000). Aflatoxin control measures are applied to commercial crops to meet the stringent regulatory demands to limit exposure in HICs. Industrial-scale sorting, optimal storage, and extensive aflatoxin testing programs combine to limit exposure in wealthier nations. In contrast, little is done to reduce the exposure of the populations in LICs, where aflatoxin levels are high (Pitt and others 2012).

The most effective measure to reduce exposure is to avoid consumption of contaminated foods or to reduce dependence on them. In China, for example, economic development led to a shift from consumption of maize to rice, which is far less susceptible to aflatoxin contamination. This dietary shift has been linked to reduced exposure to aflatoxins and falling HCC rates (Chen and others 2013). However, many of the poorest populations remain trapped by poverty and the lack of dietary alternatives.

Preharvest mycotoxin control includes a wide range of good agricultural practices to reduce crop stress—such as irrigation; early sowing; low plant density; and the use of fungicides, pesticides, and insecticides—as well as the identification of fungus-resistant strains, genetic engineering of crop resistance, and biocontrol (Pitt and others 2012). Biocontrol is one of the most

vigorously investigated approaches (Mehl and others 2012), although it is too early to know whether it will produce usable interventions (Atehnkeng and others 2008). The approach relies on competitive exclusion: strains of *Aspergillus* that do not produce aflatoxin (atoxigenic strains) are introduced into the soil, and they compete with native aflatoxin-producing spores for colonization of crops. The cost can be high; ensuring access and sustainability at the subsistence or small-farm level is critical.

Increased aflatoxin during storage is a major problem with dietary staples, such as maize and groundnuts in LMICs. Improved storage presents the simplest and most affordable opportunity for limiting exposure in such settings. In studies in West Africa, basic improvements in sorting, drying, and storing the groundnut crop in West Africa resulted in marked reductions in aflatoxin contamination, feasibly and cost-effectively (Turner and others 2013; Wu and Khlangwiset 2010a, 2010b), suggesting that simple, inexpensive approaches can offer significant benefits. Nevertheless, challenges remain in scaling up and implementing such approaches.

Once present in a food commodity, the toxins are relatively resistant to destruction during preparation and cooking. An exception is the use of alkaline methods (nixtimalization), for example, using lime for maize tortilla preparation, as is done by some populations in Latin America and the Caribbean (Pitt and others 2012).

An alternative to primary prevention is to modify the effects of toxins once ingested, either by preventing absorption or by modifying metabolism (Groopman, Kensler, and Wild 2008). Reduced absorption has been achieved in animal feeds by the incorporation of clays into feeds to bind aflatoxin in the gastrointestinal tract; this process remains at the pilot phase in humans (Wang and others 2008) and may be limited to emergency situations of high contamination and food insufficiency. In terms of altered metabolism, several compounds have been explored—including chlorophyllin, oltipraz, and broccoli sprout extract (Groopman, Kensler, and Wild 2008)—but these have not been translated to widespread application.

## Alcohol

Alcohol is found in beer, wine, and liquor, as well as in some medicines, mouthwashes, household products, and essential oils (for example, scented liquids taken from plants). The alcohol content of various alcoholic beverages varies: 3–7 percent for beers and hard ciders; 9–15 percent for wines and sake; 16–20 percent for wines fortified with liquors, such as port; and 35–40 percent for liquor or distilled spirits, such as gin, rum, vodka, and whiskey (IARC 2012b). Alcohol consumption varies among adults over age 15 years in different parts of the world. From 2003 to 2005, average annual alcohol consumption per adult (over age 15) was highest in Europe and Central Asia (12.2 liters of pure alcohol); followed by North and South America (8.7 liters), the western Pacific (6.3 liters), Sub-Saharan Africa (6.2 liters), and southeast Asia (2.2 liters); it was lowest in the eastern Mediterranean (0.7 liters) (WHO 2008).

Excessive alcohol consumption can take the form of heavy drinking, binge drinking, or any drinking by pregnant women or underage youth (CPSTF 2013). Heavy drinking is defined as more than two drinks per day on average for men or more than one drink per day on average for women. Binge drinking is defined as five or more drinks during a single occasion for men, or four or more drinks during a single occasion for women.

Several interventions have been developed to reduce excessive alcohol consumption. The U.S. Community Preventive Services Task Force has reviewed the effectiveness of current intervention strategies, although not commenting on the use of interventions outside the United States. The recommended effective interventions that are most likely to be applicable in LMICs include the following:

- Increase alcohol taxes.
- Maintain limits on days of sale.
- Maintain limits on hours of sale.
- Enforce laws against privatizing retail alcohol sales.
- Regulate alcohol outlet density.
- Enhance enforcement of laws prohibiting sales to minors.

The effectiveness of other interventions, such as overservice law enforcement initiatives—efforts to increase enforcement of laws against serving intoxicated individuals—and responsible beverage service training, is not supported by sufficient evidence to recommend them. Unfortunately, very little information is available about the effects of these and alternative interventions in LMICs.

## Liver Flukes

Infection with liver flukes can be prevented, and infections can be treated with a single dose of praziquantel, an inexpensive and relatively safe drug. Infections are detected by the presence of eggs excreted in stool, a standard laboratory procedure. Once cholangiocarcinoma develops, like HCC, treatment of the cancer is almost always futile.

The simplest means of preventing infection appears to be stopping the consumption of raw fish. This approach, however, has not been simple, because raw fish dishes are well-established components of the cuisine of certain cultures.

Control programs in Thailand started in the 1950s. In the late 1980s, the Thai government initiated a new three-pronged control strategy that includes screening and treatment with single-dose praziquantel (which has a cure rate of 95 percent or higher), education programs to encourage cooking fish before eating, and practicing hygienic defecation (Jongsuksuntigul and Imsomboon 2003). The large decreases in infection prevalence in Thailand are attributed to these combined efforts.

Finally, work is proceeding on a vaccine against *O. viverrini* and is considered a feasible development (Sripa and others 2011).

### Treatment of HCC

Liver resection and liver transplantation are the gold standards for treating HCC, but even with the best treatment, survival is poor. In the United States, five-year relative survival from liver cancer was 16 percent during the 2000s, with a plurality of patients diagnosed with early-stage disease. Survival from late-stage disease was less than 5 percent (NCI 2013).

Some new loco-regional ablative methods, notably, percutaneous radiofrequency ablation, may represent safer and cheaper alternatives for small lesions (less than 5.0 centimeters) (Zhang and Chen 2010) and may eventually be commonly used in LMICs.

## COSTS AND COST-EFFECTIVENESS OF INTERVENTIONS

Fortunately—and unlike most other major cancers—preventive interventions for all of the major risk factors are feasible. However, as is the case for other cancers and many other conditions, costs and cost-effectiveness are not well studied in LMICs. We present the evidence as documented in the literature, focusing first on prevention and then on treatment of liver cancer. We could find no economic analysis of liver fluke control. (Discussion of excessive alcohol consumption prevention is covered in *DCP3* volume 4, Mental, Neurological, and Substance Use Disorders.)

### HBV Control

Vaccination against HBV is highly cost-effective in HBV-endemic countries. The economic evidence from China suggests that universal HBV vaccination is cost-saving compared with not vaccinating (Hutton, So, and Brandeau 2010). Even in India, a low HBV-endemic country, universal HBV vaccination is also highly cost-effective at US$13.22 per quality-adjusted life year (QALY) gained (Aggarwal, Ghoshal, and Naik 2003). Since the introduction of vaccines in the 1980s, more and more countries have begun vaccinating; now, 168 of 190 WHO member countries have implemented universal hepatitis B vaccination in newborns and infants.

Chronic HBV can be treated with medications, although current therapy seldom results in a cure (Aman and others 2012). The antiviral agents currently used include lamivudine, adefovir, tenofovir, telbivudine, entecavir, and the two immune system modulators, interferon alpha-2a and pegylated interferon alpha-2a. Lifetime treatment inhibits virus replication, minimizing liver damage and reducing the risk of HCC (Matsumoto and others 2005). In an Indian study, the incremental cost-effectiveness ratio (ICER) per QALY gained associated with interferon use compared with usual care was six times the per capita GDP of India (Aggarwal, Ghoshal, and Naik 2002); this cost is not considered cost-effective according to the WHO definition of cost-effectiveness, as an ICER less than three times the per capita GDP of the country. Even if drug therapy were cost-effective in HICs, it may be unaffordable in LMICs. For example, the ICER per QALY gained for lamivudine in HICs ranged from 0.024 per capita GDP in Australia (Crowley and others 2000) to 0.819 per capita GDP in the United States (Yuan and others 2008). In LMICs, the ICER per QALY gained for lamivudine could be as high as three times the per capita GDP (Lui and others 2010). Therefore, the current strategy of treating patients from a young age is very expensive for LMICs, although this could change when the price of these drugs declines. Future studies should explore the cost-effectiveness of treating older patients before the onset of cirrhosis, possibly using on-off treatment that may be significantly less costly but have similar long-term clinical benefits.

### HCV Control

There is no effective vaccine for HCV, but viral transmission can be prevented by reducing exposure to infected blood products and unsafe medical procedures, the main routes of infection in LMICs (Kermode 2004). Screening blood donors and improving the safety of medical procedures can significantly reduce HCV infection (Chanzy and others 1999; Wang and others 2013). The main laboratory test for detecting HCV in blood donations is the third-generation HCV antibody enzyme-linked immunosorbent assay, which has high sensitivity and specificity (Colin and others 2001).

Unsafe injections, which could be eliminated by single-use needles and syringes, are another important route for HCV transmission in LMICs. A recent cost-benefit analysis reported that introducing auto-disable syringes (which prevent reuse by locking mechanisms or other mechanical means) for all medical

injections in India would be highly cost-effective, costing US$46–US$48 per DALY (Reid 2012).

Standard antiviral therapy for HCV before the new generation of drugs—pegylated interferon plus ribavirin—cures more than half of all patients (Hartwell and Shepherd 2009). However, the treatment takes months and is expensive, making it cost-effective only in patients in HICs who have progressive liver disease placing them at high risk of HCC (Shepherd and others 2004). The new drugs discussed earlier in this chapter are currently even more expensive, but more effective, are all oral, and are taken for a shorter duration. If costs can be brought down, they could become affordable in LMICs.

### Aflatoxin Control

The economic burden of HCC in LMICs can be reduced by controlling the risk of food contamination by aflatoxin. Preharvest and postharvest interventions are possible.

Good farming practices to reduce crop stress (for example, irrigation; early sowing; low plant density; use of fungicides, pesticides, and insecticides) reduce aflatoxin production in addition to providing other more direct benefits, but the practices may be costly. For example, advanced irrigation systems cost US$740–US$940 per acre in the United States (Burt 2000).

Introducing atoxigenic strains of *Aspergillus* is potentially cost-effective in LMICs (Khlangwiset and Wu 2010; Wu and Khlangwiset 2010a, 2010b). In Nigeria, local atoxigenic strains of *A. flavus* were inoculated on maize and substantial reductions in aflatoxin levels were achieved (Atehnkeng and others 2008); data from additional field trials are awaited. Sun drying and hand sorting, together with other postharvest measures, were effective in reducing aflatoxins in the groundnut crop in Guinea and were considered cost-effective (Wu and Khlangwiset 2010b).

Postharvest interventions include sorting, adequate drying, and good storage conditions for grains. In large-scale commercial farming, mechanical blanching and sorting is highly cost-effective in the United States, completely eliminating aflatoxin at a cost of US$150–US$170 per ton (Dorner and Lamb 2006). However, their reliance on electricity and technical support puts them out of reach in many LMICs. The cost-effectiveness of artificial drying to reduce aflatoxin is highly correlated with the costs of fuel and electricity and moisture content in harvested crops.

### Costs of Treating HCC

The clinical burden of HCC in LMICs is relatively well understood, but analyses of health expenditures for treating HCC are almost entirely lacking. A thorough search of the medical literature identified just three studies of health expenditures for HCC treatment, all in HICs. The average treatment cost in Russia for an HCC patient in 2008 was US$10,400, almost equal to the per capita GDP in that year. Inpatient care accounted for 90 percent of the total. The average indirect cost associated with HCC was US$707, in which productivity loss accounted for 26 percent and social welfare for disability accounted for 74 percent (Omelyanovsky and others 2010).

The second study is from Taiwan, China, and reports on national insurance claims data for 2,873 patients diagnosed between 1996 and 2002 (Lang and others 2008). More than 30 percent of the patients had died within one year of diagnosis. The highest expenditures accrued during the six months before death, equaling US$7,183, or half of Taiwan, China's per capita GDP in 2002. The projected 10-year costs were the equivalent of the per capita GDP.

A recent Canadian study investigated the health care costs of 2,341 HCC patients in Ontario, Canada, from 2002 to 2008. Average five-year net costs were US$77,509, or US$15,502 annually, about 30 percent of Canada's 2008 per capita GDP.

Without studies from LMICs, it is impossible to know what the economic burden of treating HCC would be, but we can make some inferences. First, we know that patients in LMICs are much less likely to receive treatment than patients in HICs. Most HCCs, even in HICs, are diagnosed at late stages. Second, for those who are treated, the dollar costs might be somewhat lower than in the studies cited, assuming lower input prices. However, it is likely to be an even larger fraction of per capita GDP—possibly many multiples—making the burden even heavier for what is, in most cases, treatment that does not save the patient's life.

### Summary of Costs

The direct and indirect costs of HCC in LMICs are higher compared with costs in HICs because the disease is more frequent, it occurs at younger ages, and diagnosis is often delayed.

The most cost-effective approaches to preventing HCC are the following:

- Reducing the prevalence of HBV through vaccination of infants, including a birth dose, and uninfected adolescents.
- Preventing HCV transmission by blood donor screening and safe injection practices, including autodisable syringes.

- Controlling aflatoxin through postharvest and possibly some preharvest (genetically resistant maize and/or atoxigenic strains of *Aspergillus*) practices.
- Educating people to eat fully cooked food in areas with high prevalence of liver fluke infection to prevent cholangiocarcinoma.
- Treating liver fluke infection with single-dose praziquantel.

Approaches that are not currently cost-effective are the following:

- Antiviral therapies for HBV and HCV, which are very expensive and require extended periods of treatment (HBV requires lifetime treatment). They are used by only a small fraction of infected individuals in HICs and unlikely to be cost-effective in LMICs. However, as treatment efficacy improves and prices moderate, these interventions could become more attractive, especially if preventive measures have reduced transmission.
- HCC and cholangiocarcinoma treatments, which are usually unsuccessful for long-term survival in any country, particularly because the diseases are not usually diagnosed until late stages. Liver cancer treatment cannot be recommended as an important control strategy for LMICs.

The economic attractiveness of these interventions may change, however, as new technologies are introduced and the prices of existing effective technologies fall.

**Table 8.1** Liver Cancer Risk Factors and Feasible Interventions

| Risk factor | Intervention | Cost-effectiveness |
|---|---|---|
| HBV | HBV vaccine | +++ |
| | HBV treatment | –/+ |
| | Blood supply protection | +++ |
| HCV | Blood supply protection | +++ |
| | Safe medical injection | +++ |
| | Programs to provide clean needles for injected-drug users | ++ |
| | HCV treatment | –/+ |
| Aflatoxin | Preharvest good agricultural practices to reduce crop stress | ++ |
| | Fungus-resistant strains | ++ |
| | Biocontrol | Not yet known |
| | Postharvest sorting, storing, drying | +++ |
| | Improved grain storage | +++ |
| | Postharvest treatment of grain | + |
| | Postingestion effect modification | – |
| Alcohol | Taxation | +++ |
| | Legal/regulatory interventions | +++ |
| | Behavioral interventions | ++ |
| Liver flukes | Public education to avoid raw fish | ++ |
| | Screen for infection and treat with praziquantel | ++ |

*Note:* Scale from not cost-effective (–) to highly cost-effective (+++) in low- and middle-income countries. HBV = hepatitis B virus; HCV = hepatitis C virus.

## CONCLUSIONS

Liver cancer is among the least successfully treated of all cancers but among the most readily prevented. Each major risk factor is amenable to modification by feasible and cost-effective (and some effective but expensive) interventions. Some of these should become more affordable in LMICs in the medium term; for example, drugs that are currently expensive will eventually be much less expensive. All of these interventions will prevent morbidity and mortality from other liver diseases and, in the case of alcohol, from a number of other conditions. The risk factors and interventions are summarized in table 8.1.

## NOTES

World Bank income classifications as of July 2014 are as follows, based on estimates of gross national income per capita for 2013:

- Low-income countries: US$1,045 or less
- Middle-income countries:
  - Lower-middle-income: US$1,046–US$4,125
  - Upper-middle-income: US$4,126–US$12,745
- High-income countries: US$12,746 or more

1. Maps and figures in this chapter are based on incidence and mortality estimates for ages 0 to 69, consistent with reporting in all *Disease Control Priorities* volumes. Global cancer statistics are estimates for the year 2012 and have been provided by the International Agency for Research on Cancer from its GLOBOCAN 2012 database. Observable population-based data were derived from *Cancer Incidence in Five Continents, 10th edition* (Forman and others 2013) and for trends over time from *CI5 Plus* (http://ci5.iarc.fr/CI5plus/Default.aspx). The discussion of burden (including risk factors), however, includes all ages unless otherwise noted. Interventions also apply to all age groups, except where age ranges or cutoffs are specified.

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