Section 1

Introduction to hepatocellular carcinoma: A tale of two diseases

Introduction

Primary liver cancer or hepatocellular carcinoma (HCC) is a tumor of the hepatocyte, the specialized liver epithelial cell that is responsible for most liver function. It is the most common cancer that originates in the liver (primary cancer). By contrast, liver metastases have spread to the liver from cancers arising in other organs and are not further considered here.

Key point

The prognosis and management of HCC are colored and influenced in most patients by the concurrence of two separate but related and interacting liver diseases: hepatitis or cirrhosis from any course on the one hand and HCC on the other hand. It is likely that each influences the other (ie, cirrhosis is a precursor to most HCC and growing HCC can worsen liver function) and the selection of HCC therapy cannot take place without considering the limitations imposed by the concurrent liver disease; thus, it is "a tale of two diseases".

The grading of the degree of HCC differentiation into more or less "hepatocyte-like" features has prognostic significance. On biopsy, the microscopic appearance of poorly differentiated HCCs can look like cancer, while very well-differentiated HCCs may appear more like normal liver cells. Well-differentiated HCCs usually are surrounded by a capsule, but more aggressive HCCs often do not have one and are labeled as "diffuse". HCCs also have a characteristic propensity to invade local blood vessels within the liver (ie, portal vascular invasion or thrombosis [PVT]). A characteristic pattern of reticulin staining is often helpful in pathological diagnosis. The underlying liver is often abnormal, and has varying degrees of necrosis and inflammation, regenerating nodules, and fibrosis, which are the result of chronic injury, usually from hepatitis, and cause cirrhosis. Variant patterns of primary liver tumors, which have quite different behavior, include fibrolamellar HCC of young adults and hepatoblastoma of childhood.

Summary for patients, families, and caregivers

Cancer that starts in the liver is called primary liver cancer, also known as hepatocellular carcinoma or HCC. HCC is closely linked to several other types of inflammatory liver disease. This is because liver diseases can cause HCC and HCC can worsen liver disease. When caring for a patient, healthcare teams must manage the patient's HCC as well as their liver disease. It is a tale of two diseases.

Two types of liver diseases are hepatitis and cirrhosis:

- Hepatitis is an inflammation of the liver. Hepatitis can be caused by a number of factors, including hepatitis viral infections and alcoholism.
- Cirrhosis occurs when scarred or damaged liver tissue from chronic hepatitis replaces healthy liver tissue.

The patient's healthcare team grades and evaluates the patient's HCC and the underlying liver to determine how the cancer might develop and the treatment plan for the patient. Grading is based on analyzing the liver cells under a microscope after a piece of the liver tissue is removed, which is called a needle biopsy.

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Incidence and geography

HCC is the sixth most common cancer worldwide and the third most common cause of death from cancer; the reason for this discrepancy is due to the fact that a high proportion of patients die from this disease (overall ratio of mortality to incidence is about 0.9). There are about 750,000 new global cases annually; it is the fifth most common cancer in males and the seventh most common in females. There is a male predominance in incidence, varying from 9:1 male: female to 2:1 male: female cases, depending on the country, except in low-cirrhosis Western countries where the ratio approaches 1:1 (Figure 1). Possible contributors to the high male incidence include tobacco smoking and alcohol consumption, which are known contributory factors to risk of HCC development.

Most HCC cases worldwide occur in developing countries (Figure 1). The world's highest incidence rates are found in Eastern Asia, followed by Southeast Asia then Central Africa. Southern

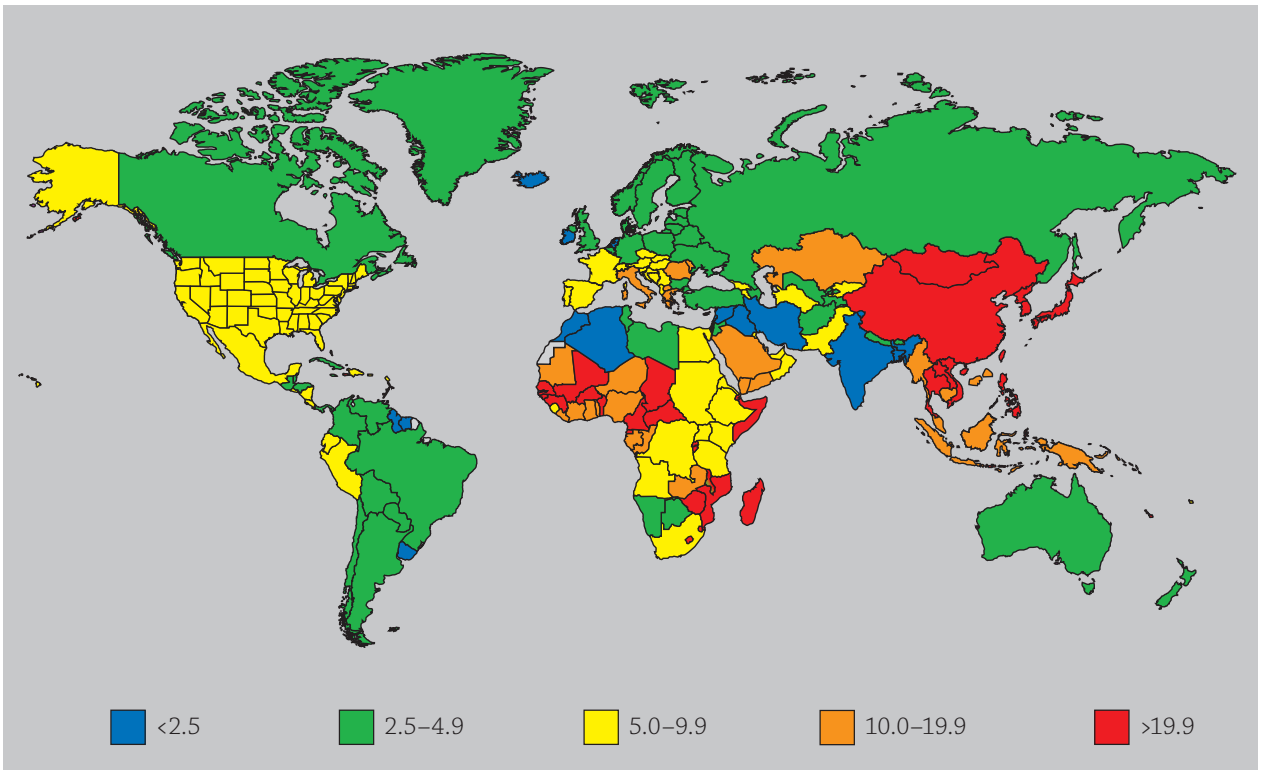

Figure 1 Age-standardized incidence rates of primary liver cancer worldwide, 2002. Reproduced with permission from © GLOBOCAN, 2014; International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidence Mortality and Prevalence Worldwide in 2012. Liver. globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed January 10, 2014; © Elsevier Limited, 2014; Nordenstedt H, White DL, El-Serag HB. The changing pattern of epidemiology in hepatocellular carcinoma. *Dig Liver Dis*. 2010;42 Suppl 3:S206-S214.

Europe has moderately high rates, as does Central America and Polynesia. Low rates occur in Western Europe, the USA, and South America, with the lowest being in Northern Europe, Australia/New Zealand, and South Central Asia (Figure 2). The large global variation is thought to be due to differences in exposure to causative factors, such as hepatitis virus or carcinogen contamination of foodstuffs, but not to ethnicity. Supporting this, studies of migrant populations, such as Japanese or Jews living in various locales, show changes in HCC incidence in the same ethnic group, but living in different locations.

In the USA, HCC is the fifth most common cancer in men after lung, prostate, colon, and pancreas cancers. It was recently estimated that there were approximately 31,000 new annual cases of HCC in the USA in 2013 (23,000 male, 8000 female). In the last 30 years there has been a steady increase in incidence of HCC in the USA, especially among Hispanics, Blacks, and White middle-age people, likely attributable to the hepatitis C (HCV) epidemic, as well as the rising levels of obesity and diabetes. There are clear differences in incidence within the USA population (Table 1) but the differences between males and females in both incidence and mortality are preserved. In Japan, the incidence is thought to have peaked due to the increased screening of blood in blood banks for hepatitis viruses, while in Taiwan and China it is set to decrease due to widespread hepatitis B (HBV) neonatal vaccination.

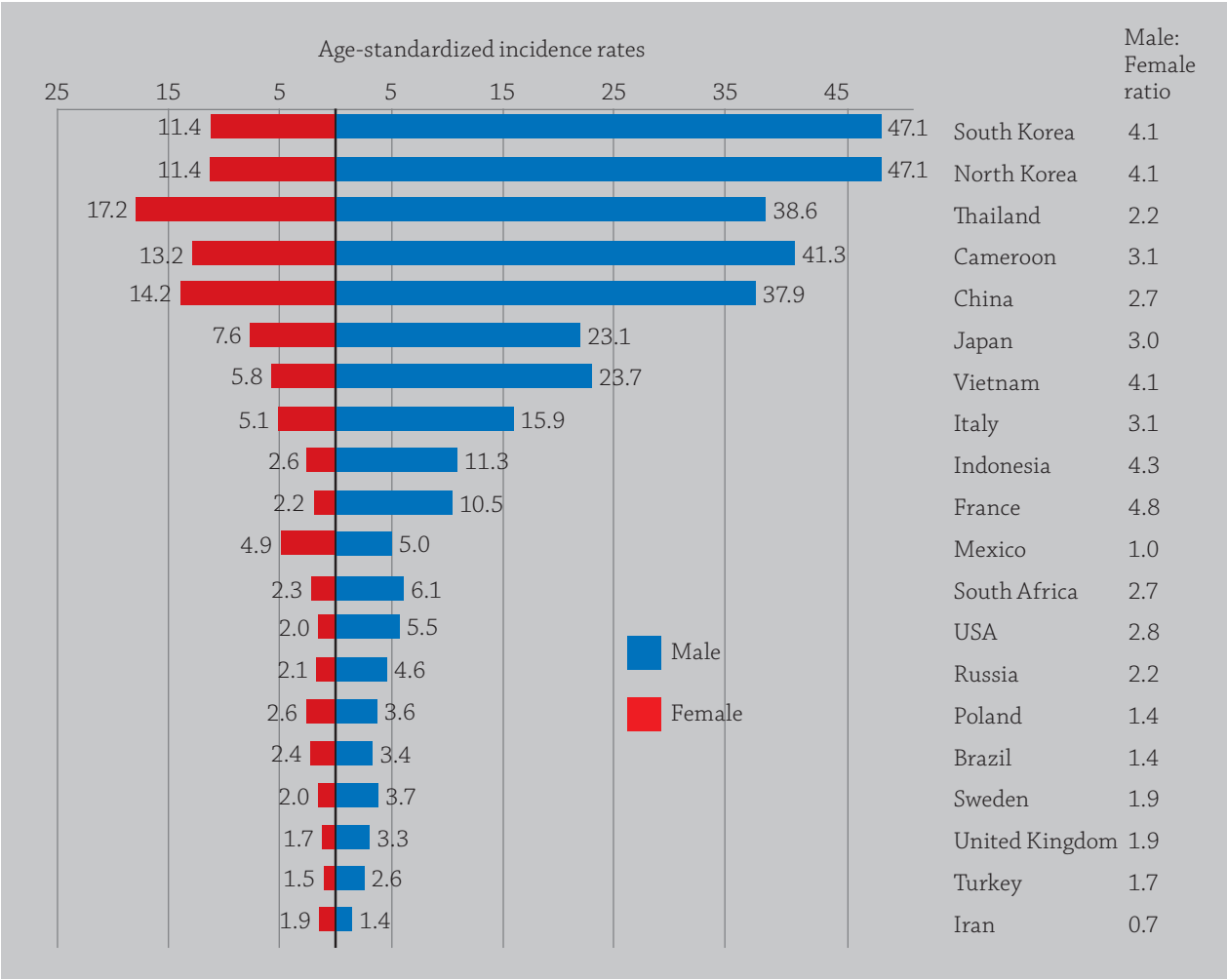

Figure 2 Age-standardized incidence rates of primary liver cancer, per 100,000 population at risk.
Reproduced with permission from © GLOBOCAN, 2014; International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidence Mortality and Prevalence Worldwide in 2012. Liver. globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed January 10, 2014; © Elsevier Limited, 2014; Nordenstedt H, White DL, El-Serag HB. The changing pattern of epidemiology in hepatocellular carcinoma. *Dig Liver Dis*. 2010;42 Suppl 3:S206-S214.

	White	African American	Asian American	American Indian and Alaskan	Hispanic/ Latino
Incidence, all cancers					
Male	543	619	328	423	419
Female	424	397	286	360	333
Incidence, liver and bile duct cancers					
Male	**9.1**	**15**	**21.6**	**16**	**17.5**
Female	**3.1**	**4.2**	**8.1**	**7.6**	**6.6**
Mortality, all cancers					
Male	217	288	133	185	146
Female	151	175	93	136	101
Mortality, liver and bile duct cancers					
Male	**7.4**	**12**	**14.5**	**13**	**12**
Female	**3.1**	**4**	**6.1**	**6**	**5**

Table 1 Incidence and death rate per 100,000, United States, 2005–2009. Population by site, race, and ethnicity. Per 100,000 population, age adjusted to the 2000 US standard population. Adapted with permission from © John Wiley and Sons, 2014; Siegel R, Naishadham D, Jemal A. Cancer Statistics, 2013. *CA Cancer J Clin*. 2013;63:11-30.

The cause of the gender discrepancy in HCC arising from cirrhosis (>80% of HCC cases) is unclear for viral causes. However, for chemical causes, such as aflatoxin B_1 contamination of foods, animal studies have shown that male rodent livers are better able to metabolize the carcinogen to its DNA reactive and thus carcinogenic form.

Summary for patients, families, and caregivers

Globally, HCC is the sixth most common type of cancer and the third most common cause of death from cancer. The number of new HCC cases varies from country to country. Asian and sub-Saharan African countries have more new cases of HCC than Western countries. This difference is probably due to how each population is exposed to different risk factors. Examples of these risk factors include having hepatitis or eating food that is contaminated by fungal toxins. Generally, men have a higher rate of HCC than women. This may be due increased tobacco smoking and alcohol consumption. Both smoking and drinking are risk factors for developing HCC.

Further reading

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Causes of hepatocellular carcinoma

Risk factors for developing HCC in patients with cirrhosis include older age, male gender, and severity of compensated cirrhosis, independent of etiology or cause of the cirrhosis (most commonly from hepatitis B virus [HBV], hepatitis C virus [HCV] or alcoholism). Mixed infection with HBV and HCV,

HCV and HIV, or HBV plus alcohol greatly increase the HCC risk as well; common factors associated with an increased risk for developing HCC are:

- Cirrhosis from any cause
- HBV or HCV chronic infection
- Alcohol chronic consumption
- NASH/NAFLD (nonalcoholic steatohepatitis, typically from obesity)
- Aflatoxin B_1 or other mycotoxin contaminated foods

Less common factors associated with an increased risk for developing HCC are:

- Primary biliary cirrhosis
- Hemochromatosis (increased iron)
- α_1 Antitrypsin deficiency
- Glycogen storage diseases (rare metabolic diseases)
- Citrullinemia (rare metabolic disease)
- Porphyria cutanea tarda (rare metabolic disease)
- Hereditary tyrosinemia (rare metabolic disease)
- Tyrosinemia type I (rare metabolic disease)
- Wilson's disease (increased copper)
- Autoimmune hepatitis
- Alagille syndrome of infants

Patients with any of the diseases that predispose them to HCC can be exposed to a variety of additional factors that increase their risk for HCC, including diet, alcohol and possibly obesity.

In addition, a wide range of factors in the human diet can cause HCC in experimental animals, as well as many industrial compounds. Several dietary factors, such as coffee and flavonoids, are also thought to be protective against cancer development (carcinogenesis) (Table 2).

Cirrhosis from any cause predisposes patients to a higher risk of developing HCC. Cirrhosis can typically take 10–15 years to develop after hepatitis viral infection, and HCC typically develops after an additional 10 years or more of chronic infection; cirrhosis is thus a pre-malignant disease. Many patients may die of liver failure from their cirrhosis without developing HCC. Conversely, many patients with cirrhosis can receive curative liver transplants without developing HCC. Cirrhosis occurs in about 10–15% of alcoholics, of whom about 15–20% develop HCC at a rate of 3–4% per annum. Alcohol is not a direct carcinogen, but HCC likely develops as a consequence of alcohol-induced oxidative stress (reactive oxygen species), which then affects downstream cellular lipids, proteins, DNA, and cell signaling pathways. Reactive oxygen species are also thought to be important in iron and copper accumulation disorders as well as in nonalcoholic steatohepatitis (NASH), resulting from fatty liver disease.

The emerging obesity epidemic is associated with NASH, which requires liver biopsy for diagnosis and may also lead to a symptomless form of cirrhosis. NASH is distinct from the usually harmless fatty liver by being associated with liver inflammation. Nonalcoholic fatty liver disease (NAFLD) may or may not be associated with NASH. NAFLD is associated with metabolic syndrome and diabetes mellitus type 2, which in turn can be associated with HCC.

The major cause of HCC in Asia (where HCC is globally most prevalent) and sub-Saharan Africa is chronic HBV. There are over 300 million HBV carriers worldwide who may develop HCC with or without the development of the intermediate step of cirrhosis, unlike HCV in Western countries, where cirrhosis is an intermediate step. The conversion rate for chronic HBV carriers to HCC is thought to be approximately 2–3% per annum. HBV is a DNA-binding virus and may directly influence gene function. The incidence of HCC is lower in alcoholic cirrhosis, NASH and hereditary hemochromatosis. In China, Southeast Asia, and sub-Saharan Africa, aflatoxin B_1 is the most potent naturally occurring liver chemical carcinogen known (a group 1 carcinogen) and is a fungal product that contaminates stored rice, peanuts, ground nuts, and maize, and is an important cause of HCC. The carcinogen is produced by the carcinogenic fungi *Aspergillus flavus* and *Aspergillus parasiticus*. Concomitant HBV plus alcohol as well as HBV plus aflatoxin B_1 exposure are thought to substantially increase the HCC risk; less is known of aflatoxin B_1 combinations with HCV.

A	Complete carcinogens
1	*Aflatoxins – fungal contamination of stored rice and grains; Ochratoxin A
2	Nitrosamines – fried bacon, cured meats
3	Hydrazines – found in edible mushrooms (false morel)
4	Safrole – found in sassafras plant and black pepper. Oil of sassafras in "natural" sarsaparilla root beer is 75% safrole
5	Pyrrolizidine alkaloids – found in herbs, herbal teas, and occasionally in honey (eg, senkirkine [coltsfoot], symphyline [comfrey])
6	Estrogens – from wheat germ, unpolished rice, forage crops
7	Bracken fern carcinogen
8	Methylazoxymethanol or cycasin (cycad plants)
9	Carrageenan – from red seaweeds
10	Tannins – from tea, wine, and plants
11	Ethyl carbamate in some wines, beers
B	**Carcinogens from food containing molds and bacteria**
1	Aflatoxins (*Aspergillus*)
2	Sterigmatocystin (*Aspergillus versicolor*)
3	Microcystins – from Cyanobacteria in drinking water in China
C	**Tumor antagonists**
1	Selenium
2	Coffee
3	Antioxidants
4	Phytochemicals, including polyphenols (curcumin from turmeric; resveratrol from red wine)
5	Vitamins A, K, and D. Vitamin A analog (polyprenoic acid, an acyclic retinoid)
6	Flavonols
7	Fish consumption
8	Vitamin K_2 or with polyprenoic acid (an acyclic retinoid)

Table 2 Compounds of natural origin in the human diet that are carcinogenic to experimental animals.
*Only aflatoxins have strong epidemiologic evidence of association with human HCC. Reproduced with permission from © John Wiley and Sons, 2014; Carr BI. Chemical carcinogens and inhibitors of carcinogenesis in the human diet. *Cancer.* 1985;55:218-224.

The major risk factor for developing HCC in Japan, Western Europe, and the USA is by contracting HCV-mediated cirrhosis, mainly from transfusion with contaminated blood or use of contaminated syringes or needles through medical or recreational drug use. The mechanism of HCV-mediated carcinogenesis is complex and it does not bind to DNA like HBV. It is thought that the risk for HCC development in HCV-based cirrhosis is approximately 3–5% per year. HCV seems to relate to HCC mainly via the development of cirrhosis and the risk seems proportional to the severity and duration of the HCV-induced hepatic inflammation and fibrosis that are part of the resulting cirrhosis. Studies involving outbreaks of HCV from contaminated blood transfusions have indicated that it takes decades to develop HCC. However, now that donors and their blood in blood banks can be screened for HCV, it is thought that HCV infections will sharply decrease over the next 30 years. Evidence of this trend is already clearly available in Japan.

Given that the severity of cirrhosis is both an HCC risk factor for patients with HCV and also limits the liver tolerance to surgery or chemotherapy, it is necessary to know the severity of a patient's cirrhosis as graded by the Child-Pugh (CP) score (Table 3). The CP score is categorized as:

- CP A: normal liver function
- CP B: intermediate liver dysfunction
- CP C: severe liver dysfunction

In CP C, the only treatment that the liver can tolerate is complete replacement by transplantation. The 1-year survival with a CP C score, with or without HCC, is only 45% on average, without liver

A	**Child-Pugh score for cirrhosis grade**							
	Factor		1 point		2 points		3 points	
	Total bilirubin (μmol/L)		<35		35–50		>50	
	Serum albumin (g/L)		>35		28–35		<28	
	PT INR		<1.7		1.71–2.30		>2.30	
	Ascites		none		mild		moderate/severe	
	Encephalopathy		none		mild		severe	
	Scores		**Class A**		**Class B**		**Class C**	
			5–6 points		7–9 points		10–15 points	
			100% 1-year survival		80% 1-year survival		45% 1-year survival	
B	**Some staging systems for hepatocellular carcinoma**							
	CLIP classification*							
	Variables		0 points		1 point		2 points	
i	Tumor number		Single		Multiple		–	
	Hepatic replacement by tumor		<50%		<50%		>50%	
ii	Child-Pugh score		A		B		C	
iii	α Fetoprotein level (ng/mL)		<400		≥400		–	
iv	Portal vein thrombosis (CT)		No		Yes		–	
	Okuda classification†							
	Tumor extent‡		Ascites		Albumin (g/L)		Bilirubin (mg/dL)	
	≥50%	<50	+	–	≤3	>3	≥3	<3
	(+)	(–)	(+)	(–)	(+)	(–)	(+)	(–)

Table 3 Staging of cirrhosis and hepatocellular carcinoma. A, Child-Pugh score for cirrhosis grade; **B,** staging systems for hepatocellular carcinoma. *CLIP stages (score = sum of points): CLIP 0, 0 points; CLIP 1, 1 point; CLIP 2, 2 points; CLIP 3, 3 points; †Okuda stages: stage 1, all (–); stage 2, 1 or 2 (+); stage 3, 3 or 4 (+); ‡Extent of liver occupied by tumor. CLIP, Cancer of the Liver Italian Program; CT, computed tomography scan; PT INR, prothrombin time international normalized ratio.

transplantation. Thus, to make treatment decisions and survival estimations, both the patient's tumor characteristics and the severity of liver damage need to be taken into account (see page 25). In this respect, HCC differs from most other cancers, such as breast or colon cancer, for which only tumor factors are the primary treatment and prognostic concern.

Macroenvironmental factors appear to influence the incidence and prognosis of HCC. It is a male dominant disease in its incidence, and males with HCC also tend to have more aggressive disease and shorter survival rates than females. This has given rise to past attempts to use hormonal therapies, such as tamoxifen (a breast cancer drug). A large number of trials led to a meta-analysis showing tamoxifen actually had little impact on survival. A similar negative result was obtained for anti-androgen therapy (ie, anandrone plus/minus goserelin). Age is also an important macroenvironmental risk factor. As with most other cancers, HCC has a peak incidence in the 60-year age group. However, very old people tend to have slower growing tumors with a better prognosis, while young people (<35 years) tend to have a quite aggressive tumor biology.

Summary for patients, families, and caregivers

The most common risk factors for developing HCC include: scarring of the liver (cirrhosis), chronic hepatitis B or C viral infection, heavy drinking, fatty liver disease caused by obesity, and eating foods that have been contaminated by cancer-causing fungal toxins.

Continues over

Summary for patients, families, and caregivers (continued)

Cirrhosis is a leading cause of HCC. Cirrhosis is often caused by a hepatitis C infection or alcoholism. Cirrhosis happens when the liver cells become damaged and scar tissue replaces healthy tissue. This stops the liver from working properly. Cirrhosis-associated inflammation increases the risk of developing HCC. The healthcare team must know how severe a patient's cirrhosis is to determine if they can tolerate surgery or chemotherapy to treat their HCC. However, liver transplantation can be safely performed in presence of any degree of cirrhosis severity.

The leading cause of HCC in Asia and sub-Saharan Africa is hepatitis B infection. Patients have a higher risk for developing HCC if they have hepatitis B infection and are alcoholics or have hepatitis B infection and are exposed to fungal toxins.

The leading cause of HCC in Japan, Western Europe, and the USA is cirrhosis that is caused by hepatitis C. People can get hepatitis C through contaminated blood transfusions, syringes, needles, or drug abuse.

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Prevention

Prevention and early detection can critically affect outcomes for any disease, especially cancer. Prevention can only be rationally planned when the causes or predisposing factors for a disease are known or determined to be highly likely. As previously mentioned, the most common causes of HCC are chronic HBV infection, chronic HCV infection-associated cirrhosis, mycotoxin (ie, aflatoxin B_1) contamination of foodstuffs, such as peanuts and maize, chronic alcohol-associated cirrhosis, and obesity-associated fatty liver. These are all preventable risk factors.

Primary prevention

Destroying aflatoxin B_1-contaminated, spoiled foodstuffs is simple in theory, but can result in a major financial burden to farmers in impoverished regions in rural China or Africa where it is most

common. Prevention of the *Aspergillus* mold from growing in the first place, by storing grains, such as peanuts in refrigerated silos, is likely the most effective preventive measure in these areas, but requires capital outlay for refrigeration in these farming communities.

The near-universal neonatal vaccination against HBV is already showing dramatic decreases in both HBV and the resulting HCC in children and adolescents in those areas with a high incidence of HBV. This approach is likely to cause a huge decrease in Asian HCC in the coming decades.

The elimination of HCV-contaminated blood in blood banks in Europe and Asia is expected to contribute to a major decrease in HCV infection, although recreational drug abuse remains a problem.

Secondary prevention

Once HBV infection has taken place, viral treatment strategies are needed and have become increasingly effective in recent years in decreasing the blood-viral load (sustained virological response). It is expected that this will interfere with the development of cirrhosis and minimize the development of HCC. Although the data are preliminary, some suggestive evidence has been published from meta-analyses of the effectiveness of HBV therapy. The treatment of chronic HCV infection has so far been less effective than that for HBV, but new and more potent therapies have been recently announced and have received US Food and Drug Administration (FDA) approval. Their treatment effects on subsequent HCC development are not yet known, but sustained virological responses in patients with HCV following treatment with these new antiviral therapies may translate into a lower incidence of subsequent HCC development. For both patients with chronic HBV and chronic HCV, a treatment-induced sustained virological response has been found in several studies to reduce the HCC incidence rate by >50%. It remains to be determined if this will be true of patients with HCV who also have cirrhosis.

Since alcohol consumption is a lifestyle choice and a contributor to HCC development, it would seem that alcohol counseling might be effective in either alcohol consumers or for alcohol consumers who are also HBV or HCV carriers, but the effects of an intervention are likely to be greater when undertaken at younger age or at earlier phases of the hepatitis.

Summary for patients, families, and caregivers

Many risk factors for developing HCC can be prevented. There are two methods of prevention: primary and secondary prevention.

- Primary prevention is a method for reducing the chance of developing HCC before it begins. For example, primary prevention includes: destroying contaminated food, vaccinating women (and thus protecting their unborn babies) against hepatitis B, and screening blood at blood banks for hepatitis C. Currently, the most important is vaccinating newborns (neonates) against hepatitis B.
- Secondary prevention means the patient has risk factors, and their healthcare team is trying to prevent HCC from developing. Examples of secondary prevention include: treating patients who have chronic hepatitis B or C infections with antiviral therapy and reducing alcohol consumption. Note: hepatitis A infections do not cause HCC development.

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Surveillance screening

As HCC is one of the few human cancers with mostly known causes (particularly from chronic HBV or HCV infection or alcoholism), surveillance or screening is useful in those patients who are known to be at risk, in order to diagnose the disease at an earlier and potentially curable stage.

There are two aims of surveillance screening:

1. To diagnose HCC at early stages of its growth and at a small size, when curative therapies are more feasible and more effective. These therapies include resection, radiofrequency ablation (RFA) and transplantation. Several studies have shown the benefits of this for HBV carriers, but less so for HCV carriers who have developed cirrhosis.
2. To begin these therapies earlier in the tumor growth trajectory, with the assumption that they will result in longer survival rates for patients. Until recently, the evidence for this aim was not available. However, recent preliminary evidence strongly suggests that there may also be a survival benefit, especially amongst HBV carriers. Performing randomized studies are difficult for screening, as most patients with chronic hepatitis will not willingly agree to not be screened, and thus to not have their tumor diagnosed at earlier and thus treatable stages.

Consensus screening recommendations advise that abdominal ultrasound examinations should be performed every 6–12 months for patients with diseases that put them at risk for developing HCC; however, a recent study showed there was no survival difference between 6- and 12-monthly screenings. Screening and surveillance guidance based on tumor size is explained in Table 4.

There has been much debate as to whether screening should also include the blood alpha-fetoprotein (AFP) test. In the absence of ultrasound availability in poor or rural areas of the third world, there is consensus that AFP tests should be used. In this author's view, AFP is inexpensive and easy to measure in routine clinical laboratories and thus should be included with ultrasound testing. Elevated levels can also occur in association with hepatitis without HCC, but levels >400 ng/ml are accepted as suspicious for presence of HCC. Around 50% of patients with HCC do not have elevations of AFP levels, so normal values do not exclude the presence of HCC. Whereas AFP can be increased in hepatitis as well as HCC, the two newer markers (both FDA-approved for clinical use in diagnosis) AFP-L3 and des-gamma carboxy prothrombin are HCC-specific; in Japan, the consensus is to measure all three markers (there is a combination kit) in patients at risk for developing HCC.

Summary for patients, families, and caregivers

Screening for HCC is possible because it has several known risk factors. The earlier the cancer is detected by screening, the sooner it can be treated. Furthermore, preliminary evidence shows that patients who are treated early have longer survival rates.

Screening for HCC involves an abdominal ultrasound scan. This ultrasound scan can determine if there is a tumor, its potential size, and possibly its growth after repeated scans. Abdominal ultrasound scans should be performed every 6–12 months for patients at risk for developing HCC. Screening can also include a cheap blood test that is called an alpha-fetoprotein (AFP) test.

1	≤1 cm diameter nodule	Repeat scan every 3–6 months for 2 years, if stable
		If growing, evaluate with contrast CT or MRI, looking for lesion hypervascularity on the arterial phase followed by venous or delayed phase washout. If typical, treat as HCC. If atypical, biopsy needed
2	1–2 cm diameter nodule	Evaluate as per growing lesion above
3	>2 cm diameter lesion	CT or MRI as above plus serum AFP measurement. If AFP >200 ng/ml, high probability of HCC

Table 4 Evaluation of a suspicious liver nodule found on surveillance ultrasound scan in patients with cirrhosis or chronic hepatitis B infection. AFP, alpha-fetoprotein; CT, computed tomography scan; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging scan.

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Biology of human hepatocellular carcinoma

Important principles of the biology of HCC will be presented in this section, which may help when evaluating an individual patient and determining a management approach.

Primary drug resistance

For most other cancers that have been studied, after a given number of chemotherapy treatments, the tumors can adapt and become resistant to the cell-killing effects of the chemotherapy. This is called secondary or acquired resistance, and is similar to the resistance seen in bacteria after exposure to antibiotics or in insects to insecticides. HCC is different in that it has primary resistance to a huge array of toxins and most chemotherapeutics. Work done decades ago showed that cells that develop in a chronic toxic/carcinogenic milieu acquire a pan-drug resistance phenotype when they become cancers. This is called primary resistance. Thus, trying to overcome this resistance with high doses of chemotherapeutic agents, especially in the presence of chronic liver damage, is often futile at best and dangerous for the liver at worst. Perhaps this is why such a large number of chemotherapy clinical trials failed to produce any meaningful survival advantage for patients with HCC, and could be usually only done in selected patients.

Vascular characteristics

There are two different vascular characteristics of HCC. First, it is one of the most vascular of tumors, and HCC has distinctive features on computed tomography (CT) and magnetic resonance imaging (MRI) scans. Unlike other organs, most of the liver's oxygenated blood, approximately 95%, comes from the portal vein and not from a feeding artery. In contrast, around 80% of oxygenated blood for HCCs comes from arterial outgrowths from hepatic arterial branches. This was noted 30 years ago in Japan to offer a potential means for delivering drugs/chemotherapy moderately selectively to the tumor by injecting them into the hepatic artery and thus minimizing the exposure of the underlying

diseased liver to the drug toxicities; however, the liver is only partially protected because in cirrhosis there is hepatic arterial blood shunting and direct intrahepatic arteriovenous connections open up.

A second characteristic of HCC is the propensity of HCC cells to invade the portal vein and grow in its lumen. When the portal vein is occluded, a characteristic enlargement and vascular enhancement is seen on CT. This is called macrovascular venous invasion (PVT) as shown in Figure 3, in contrast to microvascular venous invasion that is only seen on biopsy or in pathology liver specimens. Because the tumor cells are now in a vein, they can/do get carried by the blood stream around the circulation, with the possibility of forming distant metastases. Macrovascular invasion very often results in post-liver transplant recurrences and is thus considered a contraindication to this surgery. Microvascular invasion does not seem to carry such a great risk. The reasons are unclear, as the cells are also within the venous lumen (inside the vein). Main branch PVT is considered to be a contraindication to transarterial chemoembolization (TACE)/chemoembolization, as disease has blocked the portal vein and the TACE/chemoembolization therapy blocks the artery, so the affected liver lobe loses its blood supply and can be severely damaged. Often, if only one of the two major portal vein branches is blocked by the tumor (branch PVT), then the therapy can still be safely given to the other side of the liver.

Hepatocellular carcinoma growth rates

HCCs have been reported to have a wide range of doubling times (growth rates) from one month to a year. Without repeated scans over several months or more, it is impossible to calculate the tumor growth rate of HCC in an individual patient. A newly diagnosed patient could have had a slow growing 5 cm HCC for 3 years (Figure 4, red line); another patient with the same size tumor on the first clinic visit might have had only a 2 cm tumor 6 months ago and will thus have an aggressively behaving tumor (Figure 4, blue line). On that first visit without the knowledge of prior scans, it would have been impossible to know the growth rate of the tumor. Thus, patients are quite heterogeneous with respect to their tumor biology and characteristics.

Size alone may not be so important, as many large HCCs with >8 cm diameter can arise in noncirrhotic liver and are thus quite resectable. Fast growing tumors are often associated with several "satellite" lesions likely because they "seed" the surrounding liver. However, there is another mechanism for multifocality, as the presence of PVT is also a means of tumor spread within the liver (more common than distant metastases). This has significance for resection surgery, where up to 40% of patients have recurrence within 5 years after supposedly curative surgery. Such recurrences are observed to be "early" within a few months or "late" after a year or more, which have different causes. Early recurrence tends to be near the resection site and close to where the removed tumor was located; it is thought to be direct tumor extension from cells that could not have been seen at surgery or on the preresection scan. The late recurrences are often in other parts of the liver and may be new primary HCCs. In cirrhosis this may occur because there are hundreds of millions of proliferating cirrhotic nodules, all being potentially pre-malignant, and eventually one or more of the nodules develop new HCCs.

The inflammatory background

More than 80% of patients with HCC also have separate liver disease(s) that often profoundly affects future management options. Most commonly this disease is associated with chronic inflammation (from HBV, HCV, or alcoholism, for example), which may lead to cirrhosis, depending on the duration and intensity of the inflammation. Such inflammation may also lead to complete liver failure, for which only liver transplantation is an effective treatment. Depending on the severity of the underlying liver damage (inflammation/fibrosis/cirrhosis), the ability to do resection or perform any ablation beyond that is needed for a minimal size tumor could be compromised by the risk of subsequent liver failure after the contemplated intervention. This can also be true for any potentially hepatotoxic medical therapy, such as systemic chemotherapy or TACE, also called chemoembolization. Since many chemotherapeutics also damage the bone marrow where granulocytes and platelets are produced, this combination can produce clinical toxicities. Furthermore, cirrhosis is often associated with

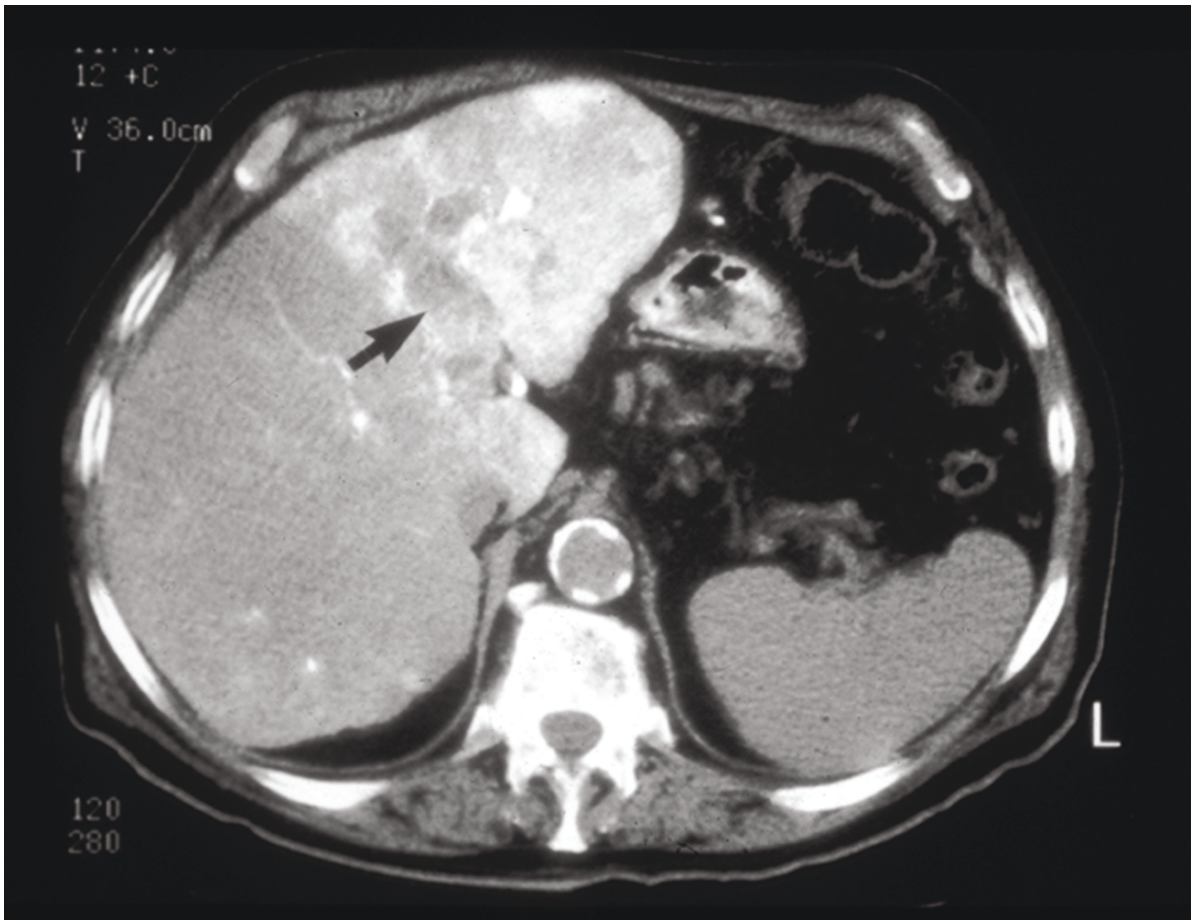

Figure 3 CAT scan showing vascularity and portal vein thrombosis (arrow) of hepatocellular carcinoma. Reproduced with permission from © Springer Science+Business Media, 2014; Carr BI. *Hepatocellular Carcinoma.* 2nd ed. New York, NY: Springer Science+Business Media; 2010.

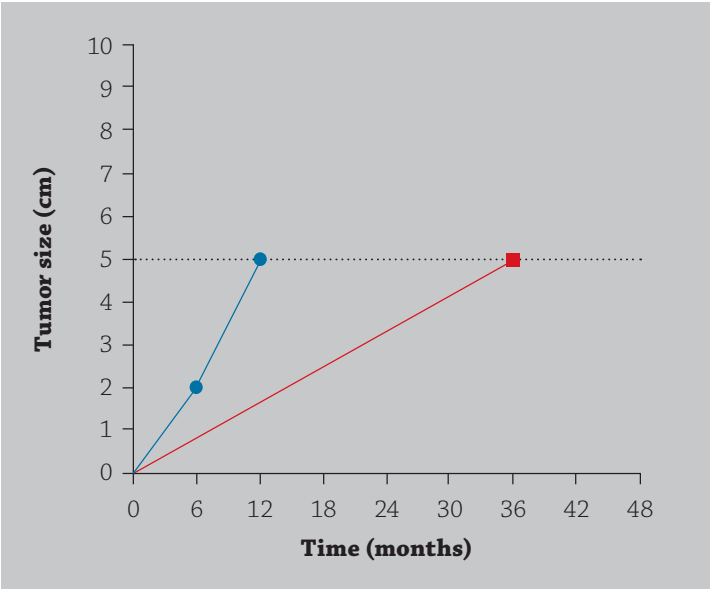

Figure 4 Varying growth rates of hepatocellular carcinoma.

bleeding tendencies from failure of the liver to produce sufficient coagulation proteins, in addition to low blood platelet counts thought to be due to splenic destruction of platelets from the back-pressure resulting from liver fibrosis. In summary, the fragility of the underlying liver can limit the safety of any therapy except liver transplantation.

Microenvironment

For several decades, it has been thought that tumors arise because one or more growth pathway genes become mutated and are expressed or otherwise activated in a way that leads to excessive stimulation of the growth control pathways of the cell; this is known as the oncogene hypothesis. There is much experimental support for this hypothesis; however, in recent years it has become clear that the activity of genes is often affected by other factors, either chemical controls on the gene involved, such as methylation, or by not yet well understood factors in their microenvironment (Table 5). Thus, both oxygenation and nutrients can affect how a given gene might behave within a cell, including oncogenes. Recent support for this "seed" (gene) and "soil" (cell environment) idea (a hypothesis originally developed for metastases by Stephen Paget) has come from molecular/clinical studies in which it has been found that the behavior of an HCC can be predicted from knowledge of the pattern of genetic changes (molecular signature) to be found in the nontumorous part of the liver. This environmental influence will have relevance in at least two HCC circumstances:

1. prediction of the behavior of an individual's tumor, such as the likelihood of recurrence after resection; and
2. the reason for the benefit of virus hepatitis therapy as part of HCC therapy in chronic virus carriers.

It has recently been shown that the high rates of recurrence after HCC resection can be significantly reduced, not by cancer therapeutics, but by antiviral therapy. Thus, the viral-mediated inflammation

1	**Pathophysiological processes: inflammation, fibrosis, angiogenesis**	
2	**Stromal cells: stellate cells (produce collagen and fibrosis), fibroblasts (involved in matrix), immune cells (lymphocytes and macrophages), angiogenic endothelial cells, platelets, gut bacteria/microbiota, stem cells/progenitor cells**	
3	**Stroma-derived growth and signaling molecules**	
a	Extracellular matrix proteins: fibronectin, collagen IV, tenascin C, matrix metalloproteinases (tissue remodeling, tumor cell invasion)	
b	Vascularization/angiogenesis factors: VEGF, PDGF, FGF, TGFα	
c	Immune and inflammatory mediators: interleukins, chemokines, reactive oxygen molecules, PDL-1	
d	Platelets: VEGF, PDGF, FGF, serotonin	
4	**Some drugs being tested that inhibit some of these targets**	
	Drug	**Target**
	Brivanib	VEGFR2, FGFR1
	Linifanib	VEGFR1, PDGFR
	Ramucirumab	VEGFR2
	Cixutumumab	IGF-R1
	CT-011	PD 1 and 2
	PI-88	Heparanase, sulfatase
	Sirolimus	mTOR
	AMG386	Angiopoietin 1 and 2
	Tivantinib	c-Met

Table 5 Hepatocellular carcinoma microenvironment. FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; IGF-R, insulin-like growth factor receptor; mTOR, mammalian target of rapamycin; PD, programmed death; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PDL-1, programmed death ligand-1; TGFα, transforming growth factor alpha; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

must influence the HCC behavior. In summary, there are at least two types of molecular signatures (patterns of genetic changes) and clinical prognostic factors in HCC: those of the tumor and those of the underlying liver.

It has become increasingly clear in recent years that the behavior of a given HCC, and thus the treatment approaches for a patient with HCC, depend on more than just the clinically observed tumor characteristics. This was in a real sense anticipated in the 1985 staging system of the Japanese hepatologist Kunio Okuda, who brought attention to the need to consider both tumor and liver characteristics in prognosis and therapy. More recently, this approach has been greatly expanded by advances in HCC biology, biochemistry, and molecular understanding. As a result, a fuller understanding of HCC behavior needs to consider genes and gene alterations, tumor stroma (the underlying tissues), tumor neovasculature (the growth of new blood vessels that is necessary to support the increasing mass of the growing tumor), inflammation, supporting liver parenchyma (cells in the liver that support the specialized hepatocytes), and gene/molecular signatures (patterns of genes and their expression through proteins). Although much of this is still in the research realm (at least for the vasculature, inflammation, and molecular signatures), there is rapidly advancing clinical application. For example, new knowledge of the growth factors that encourage new blood vessel growth has led to the development of several new cancer drugs that target this vasculature, such as bevacizumab or sorafenib. Another example is the use of antihepatitis therapy to control HCC recurrences after successful resection.

Summary for patients, families, and caregivers

Understanding how HCC develops and progresses can help determine the best treatment options for the patient.

- Most people with HCC also have separate liver diseases, such as inflammation of the liver (hepatitis), scarred liver tissue (cirrhosis), or both. The severity of these diseases influences the patient's treatment choices. For example, a patient's diseased liver may be too fragile to safely treat the HCC with anticancer drugs. In this case, the patient's only option may be liver transplantation.
- Liver cancer cells can become resistant to the effects of anticancer drugs, such as chemotherapy. Giving these drugs, even at high doses, may have no effect for patients whose cells are resistant. The drugs can also be dangerous for their liver.
- The way blood travels in and out of the liver can also affect the development and treatment of a patient's HCC.
  - HCC tends to grow in the liver's blood vessels, and this may help cancerous cells enter the bloodstream and grow within other areas of the body.
  - Drugs and chemotherapy can sometimes be delivered directly into the cancer without affecting the rest of the liver.
- HCC cells grow at different rates: tumors that grow faster are associated with worse disease. Faster growing cancers can grow and spread around the surrounding liver, causing more lesions and tumors. It is important for patients to have repeated scans done to monitor how fast their tumors are growing.
- In recent years, there has been much progress in understanding HCC's structure, development, genetics, and how this relates to the patient's underlying liver disease. This has led to the development of new drugs and approaches for treating the disease.

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