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Hepatocellular carcinoma: a global view

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Abstract

Hepatocellular carcinoma (HCC) is a global health problem, although developing countries are disproportionally affected: over 80% of HCCs occur in such regions. About three-quarters of HCCs are attributed to chronic HBV and HCV infections. In areas endemic for HCV and HBV, viral transmission occurs at an early age, and infected individuals develop HCC in mid-adulthood. As these are their most productive years of life, HCC accounts for a substantial burden on the health-care system and drain of productive capacity in the low-income and middle-income countries most affected by HCV and HBV infections. Environments with disparate resource levels require different strategies for the optimal management of HCC. In high-resource environments, guidelines from the American Association for the Study of Liver Diseases or European Association for the Study of the Liver should be applied. In intermediate-resource or low-resource environments, the fundamental focus should be on primary prevention of HCC, through universal HBV vaccination, taking appropriate precautions and antiviral treatments. In intermediate-resource and low-resource environments, the infrastructure and capacity for abdominal ultrasonography, percutaneous ethanol injection, radiofrequency ablation and surgical resection should be established. Programs to provide targeted therapy at low cost, similar to the approach used for HIV therapy in the developing world, should be pursued.

Introduction

Hepatocellular carcinoma (HCC) is a major cause of morbidity and mortality: HCC is the seventh most common cancer worldwide, and the third leading cause of cancer-related deaths.[1] Over the past decade advances in population sciences, molecular and cellular biology and genomics have resulted in major progress in our understanding of the epidemiologic risk factors and molecular pathways driving liver carcinogenesis. Advances in treatment, imaging, medical device development, interventional radiology, surgical techniques and liver transplantation have also resulted in considerable improvements in local (that is, ablation techniques), locoregional (for example, radioembolization) and surgical therapy for HCC. These advances have resulted in substantial opportunities for HCC prevention, surveillance, early diagnosis, prediction of prognosis and therapy.

As with many other diseases, the burden of poor prevention, a lack of surveillance of individuals at risk of developing HCC, and inadequate (or completely absent) deployment of advances in imaging, hepatobiliary surgery, targeted therapies, and liver transplantation falls

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disproportionally on regions of the world with intermediate or low medical resources. These regions, however, are where the majority of individuals at risk or affected by HCC live. This Review considers HCC from the following perspectives: the global variation in HCC incidence and etiology; current knowledge about the prevention, screening, diagnosis, and treatment of this cancer; and global strategies for diagnosis and management of HCC.

Incidence

In 2008, an estimated 748,000 new cases of liver cancer occurred and approximately 696,000 people died of this cancer worldwide,[1] an increase from 626,000 new liver cancers and 598,000 deaths from liver cancer in 2002.[2] The numbers of incident cases and liver cancer deaths are similar because most HCCs are detected at an advanced stage in patients with underlying liver dysfunction, making this a highly lethal cancer. The incidence of liver cancer varies around the world (Table 1), and is highest in Mongolia (116.6 cases per 100,000 person-years for men; 74.8 cases per 100,000 person-years for women).[1] Over 80% of HCCs occur in developing countries in sub-Saharan Africa, southeast Asia, and East Asia (including Mongolia). By contrast, the incidence of HCC is much lower in developed countries in North America (6.8 cases per 100,000 person-years for men; 2.2 cases per 100,000 person-years for women), Europe (except for southern Europe), Central and South America, Australia and New Zealand.[1] Global variations in incidence rates of this cancer closely reflect the variation in risk factors for HCC; thus, countries with a high prevalence of HBV or HCV infections usually have a high incidence of HCC (Figure 1). This finding is consistent with the fact that about three-quarters of HCCs are attributed to chronic HBV and HCV infections.

During 1978–1992, the incidence of liver cancer increased in developed countries and decreased in developing countries.[3] For example, in the USA, the incidence of HCC tripled over the 30 years from 1975 to 2005 (from 1.6 cases to 4.9 cases per 100,000 of the population).[4] The increase in number of patients with chronic hepatitis C who became infected between 1960 and 1990 in developed countries is believed to drive this trend, which is expected to peak around 2015–2020 and then gradually decline.[5,6] As HCV is the most common risk factor for HCC in the USA, if HCV-related HCCs decrease, HCCs overall are expected to decrease as well. In contrast to the decreasing contribution of chronic hepatitis C, the increasing prevalence of the metabolic syndrome, diabetes mellitus and nonalcoholic steatohepatitis (NASH) are all expected to continue to contribute to increased rates of HCC in the USA for the foreseeable future.[7] The increased immigration of people from populations at high risk of HCC into developed countries also contributes to the rising trend in incidence rates of HCC in the USA and European countries.

The age at which HCC develops in individuals infected with HBV or HCV is closely related to their age at acquisition of infection and the rate of active viral replication. In West Africa, HBV infection is generally acquired between the ages of 1 and 5 years, and viral replication declines rapidly after adolescence. In this region, the incidence of HCC stabilizes after age 45 years, although this observation might not take into account that some individuals infected with HBV die from other causes before they develop HCC. In East Asia, HBV infection is acquired before the age of 1 year in the majority of cases, and active HBV replication continues until an advanced age; therefore, the incidence of HCC continues to increase with age, without reaching a plateau (Figure 2).[8] The difference in the viral replication rates in West Africa compared with East Asia might be related to differences in host immunity or to differences in the viral genotypes found in these two regions. As a consequence of viral infection at an early age, affected individuals (especially in African countries) develop cancer in their mid-adulthood, during their most productive years of life. This situation results in a substantial burden on health-care resources, as well as a drain of

intellectual and productive capacity in the low-income and middle-income countries most affected by these diseases. Conversely, in countries where hepatitis B is not endemic, HBV and HCV infections are usually acquired in adulthood. In these countries, HCC rarely develops before the age of 50 years and the highest age-specific incidence rates are observed in people over age 75 years.[9]

The risk of HCC is 2–7 times higher in men than in women, although this ratio varies across the world.[3,10] The explanation for this sex difference might be threefold: firstly, men could have higher rates of environmental exposure to liver carcinogens (such as smoking or alcohol) and hepatitis virus infections; secondly, estrogen effects might suppress interleukin (IL)-6-mediated inflammation in women, reducing both liver injury and compensatory proliferation; thirdly, testosterone effects could increase androgen receptor signaling in men, promoting liver cell proliferation.[11,12]

Risk factors

Hepatitis B

Chronic hepatitis B is the most frequent etiology of HCC in countries with scarce medical resources (Figure 3).[13] In fact, more than half of all HCCs in the world are attributed to chronic hepatitis B.[14] In a population-based cohort study from the 1980s, which involved 22,708 Taiwanese men who were followed up for 8.9 years, the incidence of HCC was 98.4 times higher in HBV carriers than noncarriers.[15] A subsequent study conducted in Taiwan and published in 2010 showed that even inactive HBV carriers (asymptomatic individuals who have normal liver tests, minimal replication of HBV and undetectable or minimal levels of virus in their blood) have a fourfold increased risk of HCC compared with healthy controls.[16]

The risk and presentation of HCC in hepatitis B carriers seems to depend on ethnicity. White hepatitis B carriers tend to develop HCC at an advanced age after a period of progressive liver cirrhosis, whereas Asian and African individuals tend to develop HCC in young adulthood and middle age and might exhibit fewer signs of cirrhotic liver disease than white hepatitis B carriers. Genetic variation might underlie the differences between these ethnic groups. Alternatively, this disparity might be explained by differences in the age at which HBV infection is acquired in different populations: vertical transmission is the major route of HBV acquisition in Asia, whereas horizontal transmission in early life is the predominant route of transmission in Africa. By contrast, in Western countries HBV is mostly transmitted in adolescence and adulthood through high-risk behaviors, such as intravenous drug use, sexual exposure or iatrogenic causes including blood transfusion, unsafe needle practices, invasive procedures, hemodialysis or organ transplantation.

In the past few years, a calculator to predict HCC risk in patients with HBV has been developed.[17,18] Infection with specific HBV genotypes or HBV strains that carry common mutations (including the basal core promoter mutation and pre-S deletion mutation) increase the risk of HCC, as do a high HBV load, advanced age, male sex, persistent HBV replication and a long duration of infection.[19–23]

The class II cytokine receptor gene cluster on chromosome 21 includes *IFNAR2* (which encodes the type I interferon receptor) and *IL10RB* (which encodes the receptor for IL-10-related cytokines, including the interferon λ family).[24] This cluster is strongly implicated in hepatitis B persistence. Protective alleles at this locus occur more frequently in white European individuals than in West African people. Variations in the HBV genotype might also partly explain differences in the risk and presentation of HCC between different populations. HBV genotype C is most commonly found in Asian individuals and is

associated with the persistent presence in serum of hepatitis B e antigen (HBeAg), a decreased rate of spontaneous HBeAg clearance, increased rates of reversion to HBeAg seropositivity after HBeAg clearance, and a raised risk of HCC, independent of HBV DNA viral load levels.[20,25–27]

Hepatitis C

Hepatitis C is the leading cause of both chronic liver disease and HCC in most Western countries, including the USA (Figure 3).[28] In a large, population-based study of 12,008 Taiwanese men who were followed up for 9.2 years, individuals who were seropositive for anti-HCV antibodies had a 20-fold increased risk of HCC compared with seronegative individuals.[29] In contrast to HBV, vertical transmission of HCV is rare, although a high maternal level of viral RNA is associated with an increased frequency of mother to infant HCV transmission.[30,31] HCV is usually transmitted through direct exposure to blood, such as intravenous drug use or high-risk sexual behavior involving multiple sexual contacts.[32] Iatrogenic transmission of HCV via contaminated needles, syringes and other medical instruments and procedures is also common.[33–35] In a study from Spain published in 2002, hospital admission (67%) was the most common risk factor preceding the diagnosis of acute HCV infection (45% were for surgery, 33% were admissions to a medical ward, and 22% of the admissions were for invasive procedures) followed by intravenous drug use (8%), accidental needle-stick injury (5%), and sexual contact (6%).[36] Since the implementation of HCV screening programs for donated blood in 1992 in the majority of developed countries the risk of HCV transmission from a blood transfusion is now less than 0.03% per unit transfused.[37,38] Other potential routes of transmission include intranasal cocaine use, scarification, cupping, tattooing, and body piercing.[35] Concomitant heavy alcohol use, diabetes mellitus, latent HBV infection, increasing age, belonging to a black ethnic group, a low platelet count, high levels of alkaline phosphatase, presence of varices and smoking seem to increase the risk of HCC in patients with HCV.[39–43]

Comorbidities and environmental factors

Alcoholic liver disease is the second most common risk factor for HCC in the USA, after hepatitis C.[44] Women are more susceptible than men to liver injury from alcohol intake—women are more likely than men to develop cirrhosis at equivalent alcohol intakes—owing to sex differences in alcohol metabolism.[45] Coexisting viral hepatitis increases the effect of excessive alcohol intake on the risk of HCC.[39,46]

NASH is also emerging as a risk factor for HCC in many developed countries.[7,47] Obesity, a major risk factor for NASH, has increased in the USA; contemporary survey data suggest that one-third of US adults are obese.[48,49] Although the increased number of people with NASH (as a result of increases in the prevalence of both obesity and the metabolic syndrome) is believed to contribute to the rising incidence of HCC, few population-based data support this assumption, as the loss of liver steatosis with the development of cirrhosis makes it difficult to prove a history of NASH at the time of HCC diagnosis.

Aflatoxin B is a mycotoxin that acts synergistically with HBV in the pathogenesis of HCC.[50] Aflatoxin causes DNA mutations, particularly of the *TP53* gene, that attenuate the tumor suppressor function of p53. This mycotoxin frequently contaminates food in regions with low medical resources, such as sub-Saharan Africa and eastern Asia. Efforts to eliminate aflatoxin B exposure are ongoing in regions with particularly high exposure to this mycotoxin, including China and West Africa.[51,52]

Prevention

As chronic viral hepatitis and the resultant liver cirrhosis together constitute the most important cause of HCC, the most effective measure to avert HCC is the prevention of HBV and HCV infections. The gradual introduction of HBV vaccination began in 1984 and by 2006 universal HBV vaccination (that is, of all newborn babies regardless of maternal hepatitis B surface antigen status) had been implemented in 164 of 190 WHO member states. These vaccination programs have resulted in dramatic decreases in the incidence of HBV infection.[53] A study from Taiwan showed that, after adjustment for age and sex, the relative risk of HCC was 0.31 among children aged 6–19 years in the vaccinated cohort, compared with similar-aged children in unvaccinated cohorts (Figure 4).[54] Universal vaccination of newborn babies will lead to a substantial reduction in the global incidence of HCC, especially in regions where HBV has a high incidence.

Unfortunately, no vaccine against HCV is yet available, owing to difficulties related to the high mutation rate of HCV RNA during viral replication. A key need remains, therefore, for recognition and prevention of HCV transmission in the health-care setting as well as in other high-risk practices, such as individuals receiving treatment from unlicensed practitioners. Infection-control measures, such as screening potential blood donors and recipients for hepatitis before transfusion; the use of disposable needles and other incidental supplies (for example, intravenous tubing sets or lancets for checking blood glucose); and thorough sterilization of surgical instruments should be implemented. These measures should be the primary focus of HCC prevention, especially in low-resource countries where unsafe medical practices are not uncommon and resources for treatment of viral hepatitis and HCC are often inadequate. Encouraging avoidance of high-risk behaviors through public education and social awareness is an effective measure to prevent HCV-induced HCC. Avoidance or mitigation of modifiable risk factors for HCC, such as heavy alcohol use, diabetes mellitus, obesity and smoking, are also important, especially in patients with chronic viral hepatitis.[39,41–43]

Antiviral treatment decreases the risk of HCC in patients with viral hepatitis. Lamivudine treatment reduces the risk of progression from cirrhosis to HCC in patients with chronic HBV, and this preventive effect has also been seen in patients without liver cirrhosis.[55–57] A sustained virologic response (SVR) to antiviral treatment with interferon and ribavirin for HCV is associated with a decreased risk of progression to HCC; however, patients who do not achieve an SVR continue to have a high risk of progression to HCC.[58–60] In patients with HCV-related, compensated cirrhosis, an SVR to antiviral treatment also seems to decrease the risk of HCC.[58,59,61] Maintenance antiviral treatment of patients with HCV and advanced fibrosis who do not achieve an SVR to therapy, however, does not decrease the risk of disease progression (including HCC development).[28]

Surveillance

Surveillance ultrasonography is recommended every 6–12 months for individuals at high risk of developing HCC (Table 2). The serum tumor marker α-fetoprotein (AFP) is frequently used in combination with ultrasonography for HCC surveillance in clinical practice. A randomized, controlled trial in China reported improved overall survival (a reduction in mortality of 37%) in the group of patients who underwent surveillance with ultrasonography and measurement of AFP levels every 6 months, compared with the group of patients assigned to no surveillance.[62] Although annual surveillance with both AFP and ultrasonography is equivalent to surveillance every 6 months in terms of early detection of HCC and 5-year survival,[63] most hepatologists in developed countries recommend that such

surveillance should be conducted every 6 months, as this finding was the result of a retrospective study and was, therefore, not considered sufficient to change clinical practice.

Findings of a multicenter study in the US demonstrated that AFP levels had the best area under the receiver operating characteristic curve, followed by levels of des-γ-carboxyprothrombin and the percentage of AFP-L3, as a marker for detection of early-stage HCC. The researchers suggested that an AFP level of 10.9 ng/ml (which had a sensitivity of 66% and specificity of 82%) was optimal for detection of early-stage HCC.[64] However, AFP levels have a low sensitivity in populations with a low pretest probability of HCC (as in the surveillance setting); moreover, the cut-off value suggested in this study pertained to diagnosis rather than surveillance.

The combined use of AFP and ultrasonography might considerably increase the medical costs of HCC surveillance, particularly those resulting from work-up of false-positive results. Given the low sensitivity of AFP levels, some experts recommend that monitoring of levels of this marker should not be used for HCC surveillance unless high-quality ultrasonography is not available.[65] However, measurement of AFP levels is inexpensive, and many hepatologists consider this test of additive value in surveillance for HCC.

Diagnosis and staging

After surveillance ultrasonography reveals suspicious liver lesions in a patient with cirrhosis, contrast-enhanced CT or MRI is the next diagnostic step. According to the latest guidelines from the American Association for the Study of Liver Diseases (AASLD), a new liver lesion of >1 cm in diameter that shows arterial enhancement followed by portal venous washout on one dynamic imaging modality in a patient with cirrhosis is diagnostic for HCC. Lesions <1 cm in diameter should be monitored with ultrasonography at intervals of 3–6 months. If the lesion shows no change in size during a 2-year period of such close follow-up, patients can return to routine surveillance.[65]

Percutaneous liver biopsy is indicated when lesions >1 cm develop in a patient without underlying liver cirrhosis or if dynamic imaging modalities show inconclusive results. However, percutaneous biopsy should be used with caution, particularly in patients who are eligible for curative treatment (surgical resection or liver transplantation), because of the 2–3% risk of tumor seeding along the biopsy needle track.[66]

Multiple staging systems for HCC have been described, including the Barcelona Clinic Liver Cancer (BCLC),[67] Cancer of the Liver Italian Program (CLIP),[68] TNM (tumor, node and metastasis),[69] Okuda,[70] and Japanese Integrated Staging Score (JIS) systems.[71] The BCLC system is currently endorsed by the AASLD and European Association for the Study of the Liver (EASL), and is considered the standard staging system for use in both clinical trials and routine practice. The BCLC system has the advantage that tumor staging is linked with treatment recommendations, as described below.

Treatment

The following sections describe the currently recommended treatment options for HCC in resource-rich countries. The situations of intermediate-resource and low-resource regions are discussed later on in this article.

According to the BCLC staging system, curative treatment (resection, liver transplantation, or percutaneous local ablative treatment) is primarily appropriate for asymptomatic patients with very early and early (both stage A) HCCs. Transarterial chemoembolization (TACE) is primarily indicated for patients with asymptomatic, multinodular HCC (intermediate, or

stage B), whereas chemotherapy with sorafenib is the only recommended treatment for patients with advanced (stage C) HCC—those with invasive or extrahepatic tumors. The best supportive care is recommended for patients with terminal (stage D) HCC.[65,72] The stage-by-stage treatment plan included in BCLC staging is proven to offer a survival benefit, particularly for patients with early-stage HCC.[73]

Resection

Surgical resection is a potentially curative treatment for HCC. However, the patient's residual liver tissue continues to be at risk of developing cancer and the 5-year risk of recurrence exceeds 70%.[74] Candidates for surgical resection should be carefully selected by a thorough evaluation of their underlying liver function and tumor extent. Hepatic reserve is assessed by the indocyanin green retention test in Asian countries, and clinical signs of portal hypertension (namely, thrombocytopenia, splenomegaly and varices) and elevated bilirubin in Western countries.[75] A Model for End Stage Liver Disease score ≤8 also reflects well-preserved liver function and is a strong predictor of both low perioperative mortality and long-term survival.[76] Dynamic contrast CT or MRI is used for anatomic delineation of tumor extent. Surgical resection is not recommended for HCCs with associated vascular invasion or tumor metastasis. Although large sizes and increased numbers of tumors are associated with a high risk of recurrence after surgical resection, the presence of these characteristics should not preclude surgical resection in patients with resectable tumors and a reasonable hepatic reserve.

Transplantation

Orthotopic liver transplantation is considered the definitive treatment for HCC because it removes not only the malignancy but also the whole diseased liver, which would otherwise have a high risk of cancer recurrence; however, this treatment is highly resource-intensive. Candidates with HCC are considered eligible for liver transplantation if they fulfill the Milan criteria (a single tumor <5 cm in diameter or up to three lesions with the largest no more than 3 cm in diameter). In patients who undergo transplantation for HCC, use of these criteria results in similar long-term survival to that of patients who receive liver transplants for non-HCC indications.[77] The University of California San Francisco criteria for liver transplantation for HCC (a single nodule no larger than 6.5 cm, or up to three lesions, the largest of which is 4.5 cm or smaller with the sum of the diameters up to 8.0 cm), and more recently the 'up to seven' criteria (seven being the sum of the size and number of tumors) have been proposed as expanded selection criteria for liver transplantation in this setting.[78,79] These are both more inclusive transplantation criteria, compared with the Milan criteria, for patients with HCC without compromising the long-term outcome. These proposals are yet to be universally implemented by the United Network for Organ Sharing (UNOS). For patients with HCCs that do not meet the Milan criteria, local or locoregional therapy can be used to reduce tumor size and number, such 'down-staging' might enable successful liver transplantation.[80,81]

Living donor liver transplantation was pioneered in Asian countries, mainly owing to the shortage of livers from deceased donors. This strategy has been successfully replicated worldwide, despite the considerable risks of morbidity (5–20%) and mortality (0.28%) in the donor and an increased risk of HCC recurrence in the recipient (5–15% in deceased donor transplantation versus 20–30% in living donor transplantation), compared with deceased donor transplantation.[82,83] Currently, it is not clear why living donor transplantations are associated with high HCC recurrence. Recurrence risk seems to be higher in living donor transplantation recipients because a short waiting period enables patients to receive a transplantation even when the patient has an aggressive tumor, in which case the patient would not have been eligible to receive a deceased donor liver transplantation. Patients

undergoing living donor transplantation also tend to have more extensive tumors than patients undergoing deceased donor liver transplantation. In addition, the humoral environment of liver regeneration from a partial liver graft seems to increase the risk of recurrence in living donor transplantations. In spite of the higher risk of recurrence, living donor transplantation is often used, owing to the limited availability of deceased donors, particularly in Asian countries.

Radiofrequency and percutaneous ablation

Percutaneous ablation, which is usually performed with radiofrequency ablation or percutaneous alcohol injection, is a potentially curative treatment for small tumors, usually <3 cm in size, in patients who are ineligible for liver transplantation or resection owing to comorbidities, liver dysfunction or limited surgical resources.

Percutaneous ethanol injection (PEI) has an excellent outcome in patients with small tumors, as complete necrosis is achieved in most HCCs <2 cm in diameter.[84] However, radiofrequency ablation (RFA) is currently more frequently used than PEI in most high-resource countries. Randomized, controlled trials have demonstrated that several measures of treatment success are improved in patients treated with RFA versus those treated with PEI: the rate of complete tumor necrosis, 96% versus 88%; 3-year recurrence-free survival, 34–49% versus 12–43%; and overall survival, 62–78% versus 36–72%, respectively.[85] Subsequent studies, including two further randomized controlled trials, showed that RFA has similar efficacy to surgical resection in the treatment of early-stage HCCs, and is associated with lower complication rates and costs than resection (Table 3).[86–89]

Transarterial chemoembolization

As HCC is a highly vascular tumor, TACE—performed by infusion of a mixture of chemotherapeutic agents and gel-foam particles into the hepatic artery branch that supplies the tumor—is an effective treatment strategy for HCC. TACE is primarily indicated for patients with unresectable HCCs without vascular invasion or metastasis. This treatment improves these patients' overall survival in the intermediate time frame, when compared with symptomatic supportive care alone. In two randomized, controlled trials, 2-year overall survival was 31–63% in the TACE groups versus 11–27% in the control groups.[90,91] TACE is considered an alternative treatment option in patients with early-stage HCC when ablative treatment cannot be performed safely owing to the tumor location. TACE is also frequently used as a bridging treatment or to downsize tumors before liver transplantation.[80,92]

Patients with poor liver function or HCC invasion of the portal vein should not be treated with TACE owing to the high risk of acute liver decompensation after this treatment.[93] New evidence suggests that TACE with doxorubicin-eluting beads is superior to conventional TACE, in terms of reduced adverse event rates and improved survival.[94,95] These beads are impregnated with doxorubicin, which is slowly released after being infused into the tumor vessels allowing a delivery of high intratumoral concentrations with a low serum doxorubicin level.

Transarterial radioembolization

Transarterial radioembolization (TARE) with ^{90}Y-impregnated glass microspheres (TheraSphere®; MDS Nordion, Ottawa, Canada) or resin beads (Sir-Sphere®; Sirtex, Sydney, Australia) is increasingly being used to treat patients with unresectable, multi focal HCC, including tumors with portal-vein invasion. TARE seems to achieve equivalent clinical outcomes to those of TACE, with acceptable safety and improved tolerability.[96,97] Additional randomized studies are required to evaluate the long-term efficacy and adverse-effect profile of TARE.

Pharmacological and chemotherapeutic agents

Most HCCs are resistant to conventional chemotherapeutic agents. Moreover, patients with HCC usually have poor tolerance of systemic chemotherapy owing to underlying liver dysfunction. Several important molecules and pathways have, however, been implicated in liver carcinogenesis, including receptor tyrosine kinases, Wnt–β-catenin signaling, the ubiquitin–proteasome system, epigenetic DNA modification (promoter methylation and histone acetylation), the PI3K–AKT–mTOR pathway, proangiogenic molecules and telomerase.[98] Agents that target these pathways are under active investigation.

Sorafenib, an oral multikinase inhibitor that targets the Raf kinase, VEGFR and PDGFR signaling pathways, is approved for the treatment of patients with advanced HCC (BCLC stage C; Eastern Cooperative Oncology Group performance status 1–2, portal-vein invasion, lymph node or extrahepatic spread). In a phase III, randomized, placebo-controlled trial in 602 patients with advanced HCC, overall survival was 10.7 months in the sorafenib group versus 7.9 months in the placebo group. Sorafenib treatment was associated with acceptable profiles of adverse effects such as fatigue, diarrhea, and hand–foot skin reaction (a known treatment-related adverse effect of sorafenib).[99] Another trial conducted in the Asia-Pacific region also showed that sorafenib therapy was associated with improved overall survival and a tolerable adverse effect profile.[100] The use of sorafenib after potentially curative resection or RFA (in the STORM study),[101] and in combination with TACE (in the SPACE study)[102] are currently under investigation.

Global strategies for management of HCC

The World Gastroenterology Organization published global guidelines on HCC in November 2009.[103] These guidelines defined minimal (low) resource regions as those where barely any treatment options for HCC are available, medium (intermediate) resource regions as those where both resection and ablation are available but liver transplantation is not available, and high-resource regions as those where liver transplantation is available.

In high-resource environments, the suggested guidelines from AASLD or EASL for surveillance, diagnosis, and treatment should be applied for the management of HCC.[65,104] Unfortunately, however, most HCCs occur in developing countries that have few medical resources. Effective therapy is generally not available in these regions, in some of which HCC confers a substantial burden. For example, HCC is a major cause of both morbidity and mortality in Asia and sub-Saharan Africa. Improved identification and management of HCC, therefore, requires strategies tailored to the specific resource levels of the environment (Table 4).

In environments with intermediate resources (rural China, Alaska) or low resources (sub-Saharan Africa), implementation of universal vaccination against HBV, education of health-care providers in how to prevent iatrogenic infections, improving food storage to prevent aflatoxin B exposure and effective antiviral treatments should be the main focus of strategies to lower the disease burden of HCC. A family history of HCC and/or HBV and HCV testing should be used to identify individuals at increased risk of HCC. Screening with ultrasonography should be strongly considered for the early diagnosis of HCC, especially in intermediate-resource countries, since potentially curative treatment can usually be offered to patients with early stages of HCC. Building the infrastructure and capacity to provide ultrasonography, PEI, RFA and surgical resection is a crucially important step in intermediate-resource and low-resource environments, to enhance surveillance, diagnosis and therapy in these regions. Lastly, a major effort towards providing low-cost, targeted therapies (such as sorafenib) should be undertaken in intermediate-resource or low-resource environments, where most HCCs are detected at an advanced stage.

Conclusions

Substantial progress has been made in the understanding of HBV, HCV and HCC over the past four decades. However, global collaboration is now needed to develop a robust strategy for prevention and therapy that can be deployed in a cost-effective and sustainable manner to all individuals at risk of or affected by these diseases.

Clearly, these efforts will need to include population, biomedical, pharmaceutical, medical device and clinical research. These advances will further improve our understanding of the global burden of HCC and guide the implementation of measures to reduce it. However, research alone is not enough. For these advances to improve the outcomes of patients throughout the world, a global coalition of public and private partners is required. Such a coalition would ideally include the WHO, governmental and nongovernmental organizations, continental, regional, scientific and civil organizations and social entrepreneurs. This body could guide the implementation of concerted efforts to decrease the burden of chronic hepatitis and HCC in the low-income and middle-income countries most affected by these diseases.

We have deployed appropriate technologies around the world to control the HIV epidemic, and we can do the same for HBV, HCV, and HCC. The lesson of the global response to HIV, AIDS and the H1N1 influenza epidemic is that technological and therapeutic advances can be disseminated around the world within a brief period of time, and can have an astounding effect (for example, an estimated 1.2 million lives have been saved in Africa by the US President's Emergency Plan for AIDS Relief).[105] Currently, however, antiviral drugs that have been made available at reduced cost for treating HIV in developing countries can only be purchased at substantially higher prices if they are to be used for treating HBV. This situation must change, so that these medications are made available to those who need them. Training programs should be implemented to enable progressive development of regional, national, and local centers of excellence in cost-effective surveillance, diagnosis, and therapy for HCC. We in the gastroenterology and hepatology communities can have a critical role in this effort by bringing scientific and professional leadership and advocacy to bear on these issues.

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Key points

- Hepatocellular carcinoma (HCC) is the seventh most common cancer and the third leading cause of cancer-related deaths in the world
- Over 80% of HCCs occur in developing countries, which lack infrastructure for the management of this disease
- High-resource environments should utilize American Association for the Study of Liver Diseases or European Association for the Study of the Liver guidelines for HCC prevention, surveillance, diagnosis and treatment
- In intermediate-resource or low-resource environments, primary prevention of HCC through universal HBV vaccination, appropriate precautions and antiviral treatment should be the primary focus
- The infrastructure and capacity for high-quality ultrasonography, percutaneous ethanol injection, radiofrequency ablation and surgical resection are crucial
- Programs to provide targeted therapy at low cost, similar to those used for HIV therapy, should be pursued in resource-poor environments

Review criteria

Literature searches were primarily performed in the PubMed database. Full-text papers and abstracts written in English were identified using the following search terms: “hepatocellular carcinoma”, “HCC” and “liver cancer” in combination with “incidence”, “etiology”, “prevention”, “surveillance”, “diagnosis” and “treatment”. Further relevant articles were also identified from the reference lists of review articles.

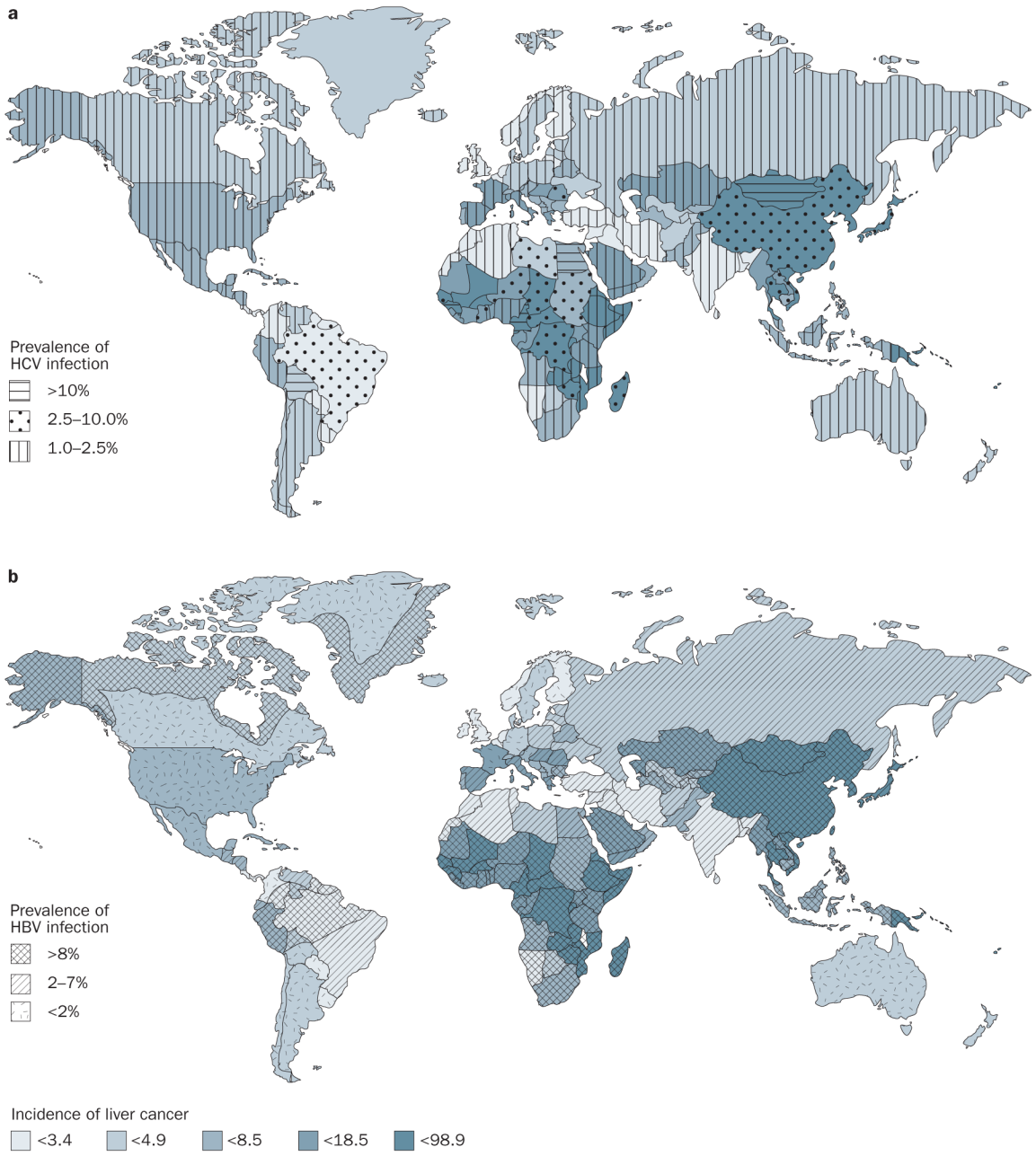

Figure 1.

Global variations in age-adjusted incidence rates of liver cancer, prevalence of chronic HCV infection and chronic HBV infection. Maps were generated using incidence rates of liver cancer from GLOBOCAN 2002;[2] prevalence of chronic HBV infection from US Centers for Disease Control and Prevention;[106] and prevalence of chronic HCV infection from WHO International Travel and Health.[107]

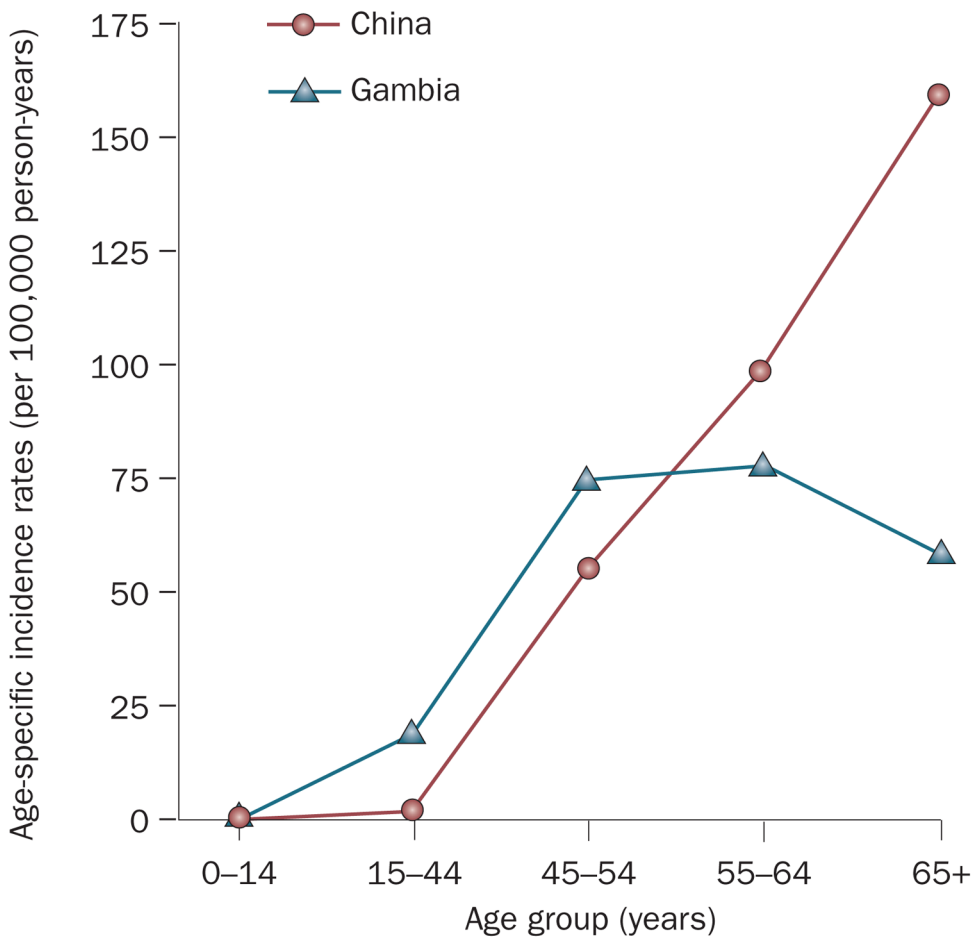

Figure 2.
Age-specific incidence rates of hepatocellular carcinoma among men in China and Gambia (West Africa). Data from GLOBOCAN, 2002.[2]

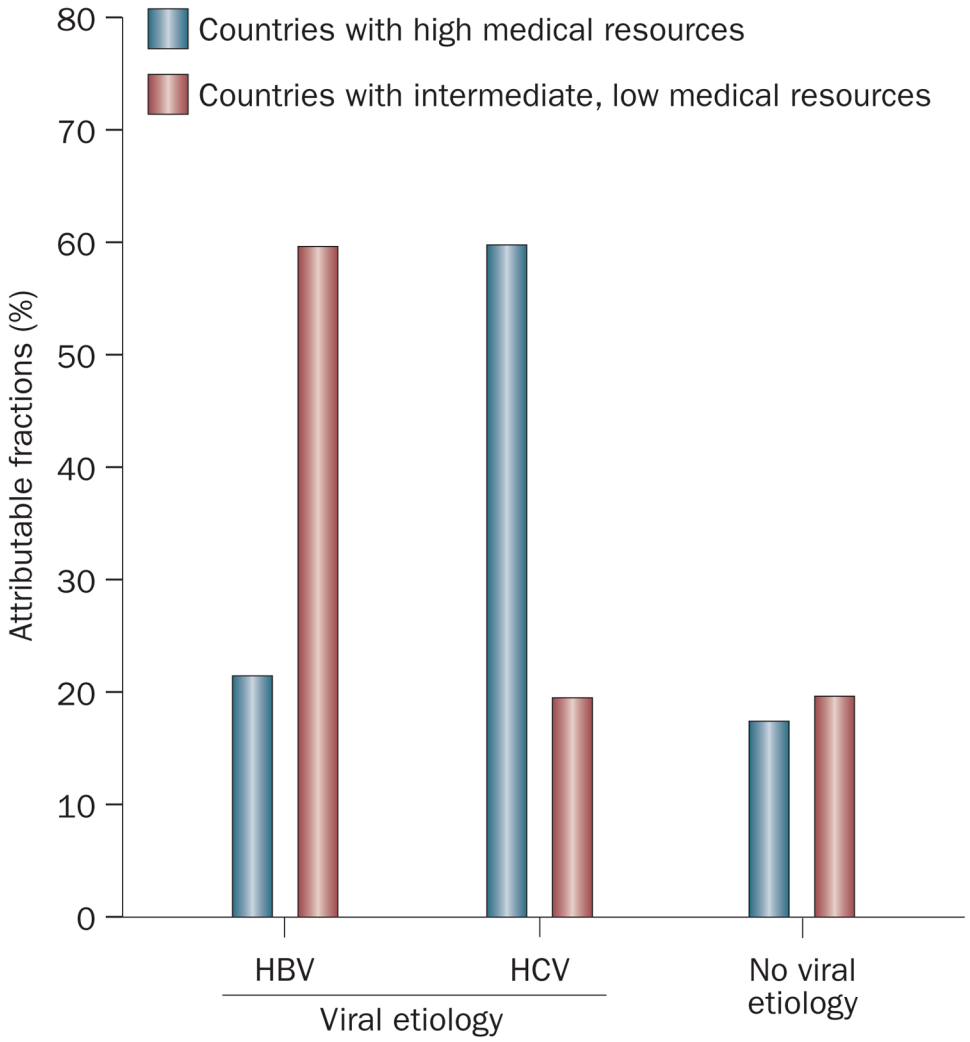

Figure 3.
Estimated attributable fractions of primary hepatocellular cancers with a viral etiology in countries with different levels of medical resources (data from Bosch *et al.* [2004]).[13] US and European countries were classified as having high-resource levels and Asian and African countries (except for Japan) were classified as having intermediate- or low-resource levels.

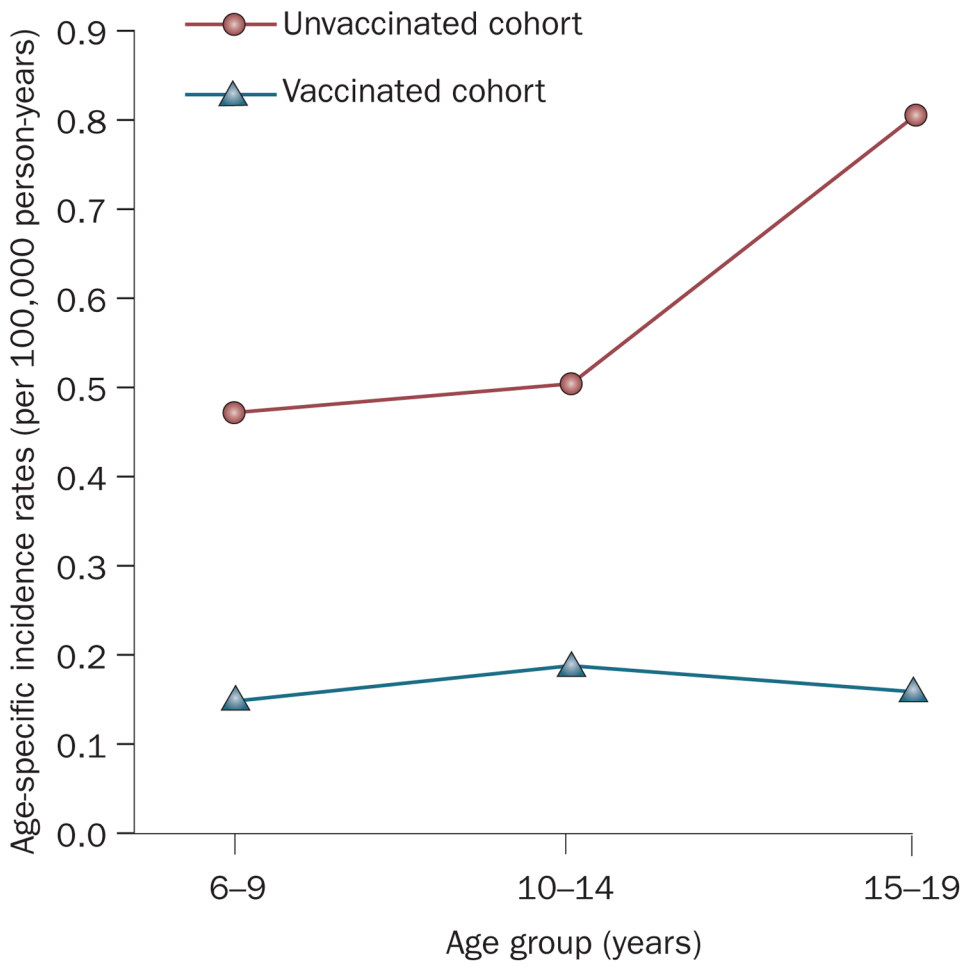

Figure 4.

Change in the incidence rates of hepatocellular carcinoma between 1983 and 2004. This period spans the introduction of universal HBV vaccination in Taiwan (data from Chang *et al.* [2009]).[54] The unvaccinated birth cohort consists of children born in Taiwan between July 1979 and June 1984. The vaccinated birth cohort consists of children born in Taiwan after July 1984.

Table 1

Age-standardized incidence rates for HCC*

Countries	Men	Women
Low resource		
Mongolia	116.6	74.8
Middle Africa	18.9	9.6
Eastern Africa	7.2	3.6
South-Eastern Asia	21.4	9.0
Melanesia	12.9	5.0
Western Africa	16.6	8.0
Polynesia	10.8	3.4
Intermediate resource		
China	37.4	13.7
Caribbean	6.3	4.4
South Africa	13.9	5.1
Central America	7.3	7.0
Western Asia	4.4	2.3
Northern Africa	7.5	2.5
South America	5.3	3.9
South Central Asia	3.4	1.6
High resource		
Korea	38.4	10.6
Southern Europe	9.8	3.2
Western Europe	7.2	2.1
Eastern Europe	4.6	1.9
Northern America	6.8	2.2
Australia/New Zealand	5.0	2.0
Northern Europe	3.8	1.6

* All values expressed per 100,000 of the population in 2008 (data from GLOBOCAN 2008[1]).

Abbreviation: HCC, hepatocellular carcinoma.

Table 2

Individuals for whom surveillance for HCC is recommended

Hepatitis B carriers	**Individuals with cirrhosis**
Those with a family history of HCC	Patients with hepatitis B
African individuals over age 20 years	Patients with hepatitis C
Asian men over age 40 years	Individuals with alcoholic liver disease
Asian women over age 50 years	Individuals with hereditary hemochromatosis
Patients with chronic hepatitis B and high viral load (HBV DNA >2,000 IU/ml)	Patients with primary biliary cirrhosis
Patients with persistently or intermittently increased alanine transaminase levels	Patients with cirrhosis of any other cause (prospective data to support this practice are still lacking)

Abbreviation: HCC, hepatocellular carcinoma.

Table 3

Comparison of efficacy and safety of RFA and surgical resection for HCC

Parameter	Chen *et al.*[86] (2006); single tumor of ≤5 cm diameter*			Lü *et al.*[89] (2006); single tumor ≤5 cm in diameter or up to 3 nodules (all ≤3 cm diameter)*		
	RFA	**Resection**	***P* value**	**RFA**	**Resection**	***P* value**
Number of patients	71	90	–	51	54	–
Overall survival (%)	67.9 (4 year)	64 (4 year)	NS	87.1 (3 year)	86.4 (3 year)	0.81
Disease-free survival (%)	46.4 (4 year)	51.6 (4 year)	NS	51.3 (3 year)	82.4 (3 year)	0.13
Treatment-related mortality (%)	0	1.1	NS	0	0	–
Treatment-related morbidity (%)‡	4.2	55.6	<0.05	7.8	11.1	0.74

*In these two randomized controlled trials, neither overall survival nor disease-free survival differed statistically between the two treatment groups.

‡Treatment-related morbidity was more common in the resection group in both trials, although the difference was statistically significant only in Chen and colleagues' study.

Abbreviations: HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; NS, not significant.

Table 4

Strategies for the management of HCC that differ by resource setting*

Resource setting	Strategy	
	Diagnosis	**Treatment**
Low	Ultrasound, AFP ± biopsy	PEI ± resection
Intermediate	CT, AFP, biopsy	Resection, PEI ± RFA, TACE ± sorafenib
High	CT and/or MRI, AFP, biopsy	OLT or resection, PEI or RFA, TACE or TARE, sorafenib, targeted treatment trials

* In all resource settings, prevention should consist of HBV vaccination, prevention of transmission via percutaneous, intravenous or sexual routes, and effective HBV and HCV therapy. Surveillance in all areas should comprise ultrasound and measurement of AFP levels.

Abbreviations: AFP, α-fetoprotein; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.