

Hepatocellular Carcinoma

Epidemiology, Prevention, and Screening

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world. Approximately half a million new cases of HCC are diagnosed annually, making it the 5th most common cancer for men, and 9th for women worldwide. In areas where the incidence of HCC is high, such as Asia and sub-Saharan Africa, patients are generally 1-2 decades younger than those from low incidence regions. In the United States and other developed nations, HCC was relatively uncommon until recently.⁵

The clinical presentation of HCC can be variable. The vast majority of HCC occur in patients with underlying cirrhosis. Therefore, liver tumors in the absence of cirrhosis may indicate secondary metastases rather than HCC. One important aspect of diagnosing HCC involves recognizing the wide range of paraneoplastic syndromes that rivals with that of bronchogenic carcinoma. Severe hypoglycemia mediated through insulin like growth factors, erythrocytosis caused by malignant hepatic production of erythropoietin, and new onset hypertension from synthesis of excessive angiotensinogen and renin, are only few of the better-recognized syndromes that should raise one's clinical suspicion. While one hundred years ago physicians often diagnosed HCC with palpation and the presence of a hepatic bruit, the modern day diagnosis of HCC is made via a combination of tumor markers, imaging, and biopsy.¹²

Currently, treatment of HCC combines chemotherapy, radiation, embolization and surgery. However, survival of HCC remains dismal. The most recent analysis in the United States shows a 5-year survival of less than 5%, far below that of breast, prostate, colon and the majority of lung cancers. More importantly, for the past 20 years in the United States and other developed nations, there is now a rising incidence of HCC, with a projected further increase in the next 5-10 years.^{4,7,8} Therefore, prevention of HCC is at least as important, if no more, than finding a cure. The purpose of this report is to summarize current knowledge on the epidemiology, prevention strategies, as well as potential screening methods to identify HCC at a more treatable stage.

Epidemiology

In 1998, a landmark study examined 3 national databases in the United States: the Surveillance, Epidemiology, and End Results (SEER) from the National Cancer Institute (NCI), the Department of Veterans Affairs patient treatment files (VA-PTA), and the National Center for Health Statistics. It showed that during the period of 1975 to 1995, the incidence of HCC rose from 1.4 to 2.4 cases per 100,000 populations. The incidence was highest among Asian Americans, Pacific Islanders and Native Americans, who were at least 2 times more affected than African Americans, who in turn were 2 times more affected than Caucasian Americans. The incidence among men was 3 times higher than women. More importantly, HCC cases in recent years are shifting significantly towards younger ages. A follow-up study from 2003 by the same authors using the SEER database showed the incidence of HCC continued to rise as of 1998.^{4,8}

During the same time period, mortality and hospitalization rate for HCC rose correspondingly. On the other hand, survival of HCC has improved only minimally. Because HCC is rapidly fatal, the incidence to mortality ratio is close to one. Median survival of HCC increased from 0.57 years in 1977-1981, to 0.64 years in 1992-96. This likely reflects lead-time bias because most of the improvement was observed within the first year after diagnosis, and the difference disappeared after 4-5 years. It appears that patients who underwent surgery survived longer than those who did not. However, only 8% of HCC underwent any form of surgery during the 20-year study period. While significant difference exists in HCC incidence and mortality among genders and ethnicities, there is no difference in terms of HCC survival.⁷

Globally, Asia has the highest incidence of HCC, accounting for more than 75% of all HCC. While Taiwan and parts of China have recently had decreasing numbers of new tumors, many countries previously categorized as low incidence areas, such as the United Kingdom, Italy, Canada, and Australia, have now observed an increasing incidence of HCC similar to that of the United States. To best devise strategies to halt the rising trend, one needs a thorough understanding of the risk factors leading to the development of HCC.¹⁴

Risk Factors

Identifying risk factors is important for prevention of most diseases. In the case of HCC, cirrhosis is the single most important disease state for HCC development. Viral hepatitis, alcohol, autoimmune liver diseases and various metabolic liver diseases have all been shown to cause cirrhosis. While HBV remains the most common risk factor worldwide, in developed nations, HCV has emerged as the predominant cause of chronic liver disease and HCC. In the United States, HCV, alcohol, and cryptogenic cirrhosis (cirrhosis of unknown etiology) are the three major causes of HCC. Fatty liver disease has become increasingly recognized as the underlying disease for “cryptogenic” cirrhosis.

Cirrhosis

Cirrhosis leads to the development of HCC through continuous or recurring cycles of repair of damaged liver cells followed by regeneration. While various etiologies induce liver inflammation through different mechanisms, there exists a common molecular pathway that leads to fibrosis formation, and finally cirrhosis. Chronic inflammatory changes in cirrhosis provide a highly carcinogenic environment – the active cytokines and reactive oxygen species increases the chance of spontaneous chromosomal mutations within hepatocytes, predisposing them to tumor formation. Different etiologies of cirrhosis carry different risk of HCC. For example, macro-nodular cirrhosis associated with viral hepatitis carries a significantly greater risk for HCC than micro-nodular cirrhosis related to alcohol, and even greater comparing to primary biliary cirrhosis. The exact explanation for this observation is unclear.⁵

HBV

Worldwide, HBV is the most common risk factor for HCC. In the United States, it accounts for less than 10% of overall HCC cases. However, it comprises as high as 20% of HCC cases among Black Americans. In areas of high incidence such as Asia and Africa, HBV are transmitted vertically and the majority of patients become chronic carriers. In the United States and other developed nations, HBV is transmitted in adulthood, and patients are much more likely to clear the virus.^{2,5}

Numerous studies have examined the various stages of HBV, including chronic carrier, chronic active infection, past infection and their effect on the development of HCC. There is some evidence demonstrating the association between past HBV infection and HCC. One case control study in the United States showed the presence of HBV core antibody or HBV surface antibody increased risk of HCC 2.6 fold. But this result has not been reproduced in prospective studies. In terms of chronic HBV, one of the first pieces of evidence came from a landmark prospective study of more than 20,000 men in Taiwan published in 1981, where chronic HBV carriers with positive HBV surface antigen (regardless of e antigen status) was associated with a 223 fold increase risk of HCC comparing to controls.¹⁴ Later in 1995, a similar risk was found in a North American population. Active HBV replication, associated with positive e antigen, has long been suspected to have a worse clinical outcome. One of the first few studies, conducted in more than 300 HBV related cirrhotic patients, found HBV e antigen was not an independent risk factor for HCC development. More recently in 2003 however, more

convincing evidence came from a prospective study of 10,000 patients in Taiwan. It suggested while the presence of HBV surface antigen increased risk of HCC by a factor of 10, the presence of both surface antigen and e-antigen, increased risk of HCC by a factor of 60.¹⁵

While roughly 80% of HBV-related HCC occur in cirrhotic livers, the rest of HBV associated HCC occur in non-cirrhotic livers. This observation fits well with the current theory on how HBV induces tumor formation. Most evidence suggests that the carcinogenic effect of HBV in part is related to its causing inflammation and eventual cirrhosis. But more importantly, it integrates into the host chromosome causing mutations, predisposing hepatocytes to carcinogenesis even before the onset of cirrhosis. Comparing to HCC stemming from other liver disease etiologies, HBV related tumors occur 1-2 decades earlier. Part of the reason is that HBV related HCC patients often contracted the virus since birth; the other is probably related to the direct carcinogenic effect of HBV. Children with HBV related HCC are well documented.¹⁴

HCV

In contrast to HBV, HCV is the most common risk factor for HCC in the United States and other developed nations, such as France, United Kingdom, and Japan.⁹ It accounts for more than 50% of cases in the U.S. Interestingly, while the prevalence of HCV is at least twice as high among Black Americans than White Americans, HCV related HCC is equally common in the two races³. While most experts in the field have attributed the rising incidence of HCC to HCV in the past decade, very few studies have tried to prove this relationship. One retrospective study examining the VA Hospital database showed a 3 fold increase in HCV related HCC from 1993-1998. During the same period, hospitalization rates for HBV or alcohol related HCC remained stable.⁶ Another single center experience reported an increase of HCV related HCC from 18% during 1993-1995 to 31% during 1996-1998 ($p = 0.01$).¹⁰ In the United States, the peak age of HCV related HCC ranges from 40-60. Combining with the data that recent HCC incidence in the U.S. is shifting significantly towards younger patients, this suggests more HCV related tumors may be responsible for the shift towards younger age of patients.

HCV does not integrate into the host genome as HBV does, but the viral RNA can be found in the serum, liver and tumor tissues. The vast majority, or greater than 98% of HCV related HCC occurs in cirrhotic livers. Therefore, the carcinogenic effect of HCV is more likely mediated through inducing fibrosis – the end result of chronic infection, in contrast to genome integration with HBV. The risk of HCC is indeed directly related to the degree of fibrosis: HCC incidence was about 0.5% per year with low-grade fibrosis, and almost 8% in those with severe fibrosis. There are currently at least 6 genotypes of HCV. The most common genotype in the United States, 1, carries a higher risk for HCC than other genotypes.⁹

The magnitude of HCV infection was demonstrated in the landmark study in 1997, estimating at least 4 million infected Americans. Worldwide, HCV is estimated to affect 70 million people.¹² The infection reached its current epidemic proportion largely

through blood transfusions, and the culture of drug use during the 1960-70s. Among the infected, 80% never clears the virus. Of these 80%, 20% develops cirrhosis. Once cirrhosis develops, one has a 2-3% chance of developing HCC per year, all of which takes on average 20-30 years.⁹

Viral Co-Infection

HBV/HCV co-infection carries a higher risk of HCC than either infection alone. As both HBV and HCV, at least in developed nations such as the United States, share similar risk factors of contracting the virus, it is not rare to see them presenting together in a patient. One recent case series in U.S. transplant centers showed HBV/HCV co-infection accounting for 3.4% and 8.4% of White and Black American HCC patients, respectively.³ In 1997, Kew et al showed that in cirrhotic HIV negative patients, HBV/HCV co-infection had an odds ratio of 82 for developing HCC, while HBV and HCV alone had odds ratios of 23.3 and 6.6, respectively. Since then, many studies have confirmed this association, but there are few prospective studies estimating the true incidence of HCC development in these co-infected patients. In addition to active HBV, it has been demonstrated, prospectively, that prior HBV infection with the presence of HBV core antibody alone, was also an independent risk factor for HCC among HCV patients.¹⁴

Similarly, HIV/HCV co-infection also increases the risk of HCC when compared to HCV infection alone. It has been estimated the prevalence of HCV is as high as 50% among HIV infected individuals. In fact, as HIV patients live longer with advances in anti-retroviral therapy, end stage liver disease, including HCC, has become one of the major causes of mortality in patients with AIDS.

Fatty Liver Disease and Cryptogenic Cirrhosis

Twenty to forty percent of HCC in the United States are attributed to cirrhosis of unknown etiology, or cryptogenic cirrhosis (CC). There is now cumulating evidence that a high percentage of these patients have developed cirrhosis secondary to the clinical spectrum of fatty liver disease, ranging from non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH).²¹ However, it is difficult to prove the causal relationship between fatty liver disease and cryptogenic cirrhosis because the pathology of cryptogenic cirrhosis often lacks prominent fat infiltration characteristic in NAFLD or NASH, and is virtually indistinguishable from cirrhosis related to alcohol. The diagnosis of CC is most often made retrospectively in the absence of heavy alcohol history and other common liver disease etiologies. Therefore, the epidemiological evidence linking NAFLD to CC to HCC, has mostly come from the observation that HCC patients with underlying CC share similar clinical characteristics with NAFLD or NASH patients. One recent Italian case control study of 46 HCC patients with underlying CC showed diabetes, obesity and hyper-triglyceridemia, were significantly more common among their cases than HCC patients with other underlying liver diseases.²⁰ While the exact natural history of NASH to HCC is unclear, this study also showed CC related HCC occur in much older patients comparing to viral related tumors. Marrero et al, showed CC to be the second most common cause of HCC in a Midwest US population. Seventy percent of these patients had characteristics of NAFLD or NASH.²⁵ One of the few prospective cohort

studies showed that in a series of 42 Australian patients with fatty liver disease, HCC developed in 2% of the patients who progressed to cirrhosis.²¹

The importance of fatty liver disease cannot be underestimated because of the current epidemic of obesity. The prevalence of NAFLD is about 20%, and NASH about 3% in the general population. Among individuals with type 2 diabetes or morbid obesity, the prevalence is likely much higher. The exact clinical course varies depending on the individual histology. Patients with simple steatosis and minimal inflammation generally do not progress to cirrhosis. Patients with significant steatosis and lobular inflammation are much more likely to progress to cirrhosis. Several cohort studies following NASH patients for 10 years showed at least one quarter of NASH patients progress to cirrhosis. Currently, the exact incidence of HCC among patients with fatty liver disease is unknown.²¹

Alcohol

Alcohol has not been shown to have a direct carcinogenic effect on the liver. Moderate amount of drinking does not appear to increase one's risk of HCC. However, heavy alcohol intake, > 50 g/day for a prolonged period of time increases the risk of HCC by predisposing one to cirrhosis. Similar to HCC related to cryptogenic cirrhosis, HCC related to alcohol develop in patients 1-2 decades older than those with viral related tumors. Some experts believe in the absence of viral etiologies, alcohol poses a relative small risk to tumor development.⁵ In the presence of viral etiologies, heavy consumption of alcohol had an odds ratio of 54 for developing HCC, versus 4.5 with alcohol alone.²⁴

Despite its relatively low risk, alcohol consumption is very common in the United States. Sixty seven percent of adults drink alcohol. However, more than 25% of alcohol is consumed by top 2.5% of drinkers. Among the heavy drinkers, not all develop alcohol related liver disease. Many suspect genetic susceptibility plays role, but it is largely unclear what predisposes one to cirrhosis. To date, there is no exact data on the incidence and prevalence of alcohol related cirrhosis or HCC mainly because most surveys do not ask questions detail enough regarding one's drinking history.⁵

Iron

Excessive iron has been postulated to induce carcinogenesis by generating reactive oxygen species. Genetic hemochromatosis and dietary iron overload are two recognized states that predispose patients to progressive hepatic iron accumulation. Genetic hemochromatosis is the most commonly recognized genetic disorder in the Caucasian population. The prevalence is as high as 1/200 in patients of Nordic or Celtic ancestry. The majority of 90% of patients exhibit the C282Y/C282Y mutation on chromosome 6 leading to a gene product that promotes excessive iron absorption. Once cirrhosis develops, HCC accounts for as high as 30% of all deaths in these patients. Dietary iron overload appears to be very common among sub-Saharan countries. Independent of viral hepatitis status, excessive dietary iron was shown to be an independent risk factor for HCC. Other disease states where there is significant secondary iron overload, such as sickle cell anemia has a theoretical increased risk of HCC. However, it has not been shown in any well-controlled studies.^{12,29}

Aflatoxin

In certain regions of the world, dietary aflatoxin is an important risk factor for HCC. It is a fungal toxin of *Aspergillus Flavus*, which can be found in contaminated food products especially in damp conditions. While many of these regions also has a high prevalence of HBV, well-designed prospective studies have demonstrated a clear causal role of aflatoxin in HCC development even after adjustment for HBV infection. One ten-year prospective study found aflatoxin had a 3.3 fold higher risk for HCC.⁵

Others

Other well-documented etiologies for HCC increase the risk for HCC by predisposing cirrhosis. These etiologies include autoimmune hepatitis, and metabolic conditions such as Wilson's disease, alpha-1-antitrypsin deficiency, tyrosinemia, and porphyria. Hepatitis A virus virtually never causes chronic hepatitis and therefore does not lead to cirrhosis. Hepatitis D virus occurs in conjunction with HBV, and one study from Europe found HBV along with HDV had a 27-fold increased risk of HCC comparing to HBV alone. Obesity was recently studied retrospectively among transplant patients, where it was found to be an independent risk of HCC in alcoholic and cryptogenic cirrhotic patients.²⁷ Diabetes appears not to be an independent risk factor, but rather increases the risk of HCC development among HCV patients.^{6,24}

Prevention

Prevention of HCC should target identifiable risk factors. Public health effort to provide clean drinking water, advocate safe sex practice and use of clean needles make sense, although its efficacy in decreasing the incidence of HCC has not been fully evaluated. Avoiding additional hepatotoxic agents such as alcohol should be recommended to all patients with other concurrent liver diseases. HBV vaccination has been available since the 1980s, its utility in decreasing HCC in high incidence area has been proved. The current epidemic of obesity likely contributes to NASH or cryptogenic cirrhosis related HCC. Weight loss of 10% of baseline body weight has been shown to improve steatohepatitis and histology.²¹ This report will not belabor the importance of these strategies, but rather focusing on current evidence of pharmacological therapies to prevent HCC development after the presence of primary risk factors. As the vast majority of HCC occur in cirrhotic livers, delaying the progression of fibrosis to eventual cirrhosis is the main goal of therapy. Among viral etiologies, removing the virus, should in theory, translate into cure of the liver disease. However, it has been very difficult to achieve viral clearance in high percentage of patients. Therefore, in addition to anti-viral drugs, there is also considerable interest in developing new anti-fibrosis medications in patients who cannot tolerate therapy or clear the virus. Several other theoretically useful therapies for HCC prevention will also be discussed.

HBV

Treatment of HBV is a complicated decision for several reasons: 1. treatment such as interferon has significant toxicity, 2. efficacy of treatment is low, 3. the natural course of HBV infection is unpredictable therefore treatments may not be warranted. The current recommendations on chronic HBV are based on clinical trials that evaluate the efficacy of viral clearance, rather than long-term morbidity, mortality, and survival of HBV infection. Very few studies evaluated the development of HCC as an end point of treatment. It is in deed difficult to conduct such long-term studies because HBV is an insidious disease, and patients who were randomized to placebo initially were often offered treatment after study completion.²⁸

Interferon alpha has been the main stay of therapy for HBV. Viral DNA clearance and conversion to e antigen negativity is found in roughly 30% of patients who have chronic active HBV or compensated HBV cirrhosis. Virus remains cleared in 80-90% of patients who responded after up to 8 years of follow up. To date, there are 3 published trials evaluating the effect of therapy on HCC development. In 1999, an 8-year follow-up of more than 100 Taiwanese HBV patients treated by interferon showed HCC developed in 1.5% of treated patients vs. 12% in untreated patients ($p = 0.04$). Similarly in Italy, treatment with interferon alpha resulted in significantly lower incidence of HCC in HBV cirrhotic patients. In contrast, HCC incidence was not decreased in one trial conducted in the United States.²¹

Lamivudine inhibits HBV viral replication by incorporating into the growing DNA chains of the virus causing premature termination. Viral clearance and e antigen seroconversion can be achieved in 16-18% of patients after one year of treatment, vs. 6-

8% with placebo. However, compared to interferon alpha, the rate of relapse is significantly higher: 40-70% after 1-2 years of stopping treatment. To date, there is only one trial addressing lamivudine's effect on HCC development. A 5-year double blind randomized control trial on 651 HBV patients showed a statistically significant decrease in the incidence of HCC among those receiving the drug. The study was in fact terminated early due to this observed difference and all patients were offered open label lamivudine. This final study results have not been published since the presentation of the abstract.²¹

Overall, data on the efficacy of HBV treatments in HCC prevention are scarce and equivocal. Viral clearance, especially with lamivudine's high relapse rate, does not necessarily equal to improvement in HBV associated complications, including HCC. Chronic HBV should be treated following the most recent guidelines. Reproducible studies on the long-term effects of both interferon and lamivudine are needed before a firm recommendation can be made on their chemopreventive effects. Other areas of uncertainty include the optimal duration of lamivudine and interferon therapy. Lamivudine resistance and HBV mutants are emerging problems questioning the benefit of long-term therapy. Whether adult immunization against HBV affects HCC incidence is also unclear.

HCV

Treatment of HCV infected patients involves complicated decision making for reasons similar to that of HBV. The standard treatment includes interferon as in HBV, plus ribavirin, which is especially toxic to the hematological and cardiovascular system. HCV genotype 1, the most common genotype in the United States, has a response rate to peg-interferon and ribavirin of less than 50% in large randomized studies. Their effect in the general population is likely lower. There are currently no long-term data on the relapse rate of patients who were able to clear the virus. Several large trials in the late 1990s showed the incidence of HCC is less in patients who received interferon treatments regardless of whether they achieved viral clearance. One meta-analysis pooling 11 studies with more than 2,000 patients showed interferon therapy decreased HCC incidence in sustained virological responders; more importantly, the effect was slightly less, but still statistically significant among non-responders. Currently, several large-scale, multi-center U.S. trials are evaluating the role of low dose, maintenance interferon therapy in preventing liver disease progression. Until these results are finalized, the American Association for the Study of Liver Disease does not recommend low dose interferon in chronic HCV patients except under experimental conditions.⁹

Anti-Fibrotic Therapy in Viral Non-responders

Given the low rate of viral clearance of both HBV and HCV, therapy aiming specifically at slowing the rate of fibrosis formation and delaying cirrhosis has been widely discussed. These discussions came with the recent dramatic increase in understanding of liver fibrosis. Central to the molecular mechanism of fibrogenesis are stellate cells, which are part of the liver extra cellular matrix lining the sinusoids. In response to injury, stellate cells become activated through a series of cytokine-mediated actions. They proliferate and deposit collagen leading to extracellular matrix production

or fibrosis. While cirrhosis is often irreversible, fibrosis before reaching the stage of cirrhosis, is a dynamic process and CAN be reversed.⁴¹

Potential anti-fibrosis targets include major cytokines involved in stellate cell activation: TGF-beta, angiotensinogen-II, interleukin-10 and 13. Targets against all four cytokines have been shown to effectively reverse fibrosis in vitro. However, there are currently no published clinical trials in humans. Colchicine is an anti-inflammatory drug that has been in existence for treatment of acute gout. Multiple small studies in humans have shown its effectiveness in reversing fibrosis. Unfortunately, the largest trial to date conducted among more than 500 U.S. veterans over at least 3 years, showed it not to be more effective than placebo.⁴¹

Several formulas of Traditional Chinese medicine have been shown to reverse liver fibrosis. The best studied, TJ-9, a Chinese formula that is widely used in Japan, was shown to significantly decrease the incidence of HCC among HBV surface antigen negative patients. The active ingredients of TJ-9, including glycyrrhiza, or licorice, and scutellaria, reverse hepatic fibrosis via modulating interleukin 10 in vivo. To date, TJ-9 is the only formula that has been studied in a well-conducted prospective fashion.⁴⁰ Unfortunately, there has been several case reports of TJ-9 related hepatic toxicity. Its use and further study has since curtailed.

In summary, while reversing fibrosis appears to be a logical and attractive strategy of preventing end stage liver disease including HCC, there is currently no approved therapy.

Fatty Liver Disease

Insulin resistance and insulin resistance related metabolic changes appear to induce hepatocyte damage in fatty liver disease. In patients with insulin resistance, there is a suppression of insulin-mediated lipolysis. The resultant high serum fatty acid levels increases hepatic fatty acid uptake and oxidation. The cumulative damage of these processes lead to inflammation and cirrhosis.²¹

Insulin sensitizers, such as biguanides and thiazolidinediones, should then have a theoretical benefit in NAFLD or NASH. In the early 2000s, two small uncontrolled trials evaluated these therapies. Metformin showed improved serum aminotransferase activities but the study did not provide histological data. The trioglitzazone study treated 10 patients for 6 months. ALT improved in 9/10 patients, biopsy inflammatory score improved in 5 patients.²¹ Most recently in January of 2004, an uncontrolled pilot study of pioglitazone was published. With 18 non-diabetic biopsy proven NASH patients, 30 mg each day of the drug was given for 48 weeks. There was significant improvement in histology assessed by less inflammation, injury, and steatosis in 2/3 of patients ($p < 0.05$).³⁵

In summary, preliminary study showed promise of thiazolidinediones in improving liver histology in patients with fatty liver disease. Currently, there is no long-term data on their effect on the development of end stage liver disease or HCC.²¹

Hemochromatosis

Patients with hemochromatosis, as mentioned prior, have a high incidence of HCC once cirrhosis develops. However, it appears HCC is exceedingly rare in patients without cirrhosis. While there is no prospective data on the effects of treatment on HCC incidence, patients who begin treatment before the onset of cirrhosis or diabetes, have essentially a normal life expectancy. Treatment includes periodic phlebotomy with a serum ferritin goal between 25-50.²⁹

Aflatoxin

In areas of the world where it is difficult to avoid contaminated stream, there are several pharmacotherapies that may be effective in preventing aflatoxin related HCC. Oltipraz, an anti-schistosomal agent, inhibits carcinogenesis by decreasing aflatoxin-DNA adduct formation. Phase I trial in the U.S. showed the drug to be fairly well tolerated. To date, larger randomized placebo-controlled trial is being planned. Another agent, chlorophyllin, a water soluble form of chlorophyll, reduces intestinal absorption of aflatoxin by forming molecular complex with the toxin. Three times a day dosing of chlorophyllin was able to decrease urinary excretion of metabolite of aflatoxin by 50%. No clinical significant toxicity was observed. While both of these agents are promising, there are currently no long-term data to observe the occurrence of HCC as an end point of clinical trials.^{36,37}

Others

Several other less well-known HCC prevention therapies exist. Their aim is to prevent recurrence of HCC after initial treatments, or halt tumor progression for patients who are not candidates for therapy.

One of them is cyclooxygenase (COX)-2 inhibitor. COX-2 is over-expressed in several HCC cell lines, and it promotes tumor progression via angiogenesis and cell proliferation. There are many current discussions on using the agent in HCC prevention.³⁴

The other agent is acyclic retinoids. It induces apoptosis or death of malignant hepatic cells and preferentially targets malignant clones. Muto, et al demonstrated a significantly less recurrence rate among Japanese HCV related HCC patients. But there has not been any further studies published.³²

Screening

The previous section dealt with prevention of HCC, which aims to lower the disease incidence. HCC screening, on the other hand, aims to cure or prolong survival from the disease by detecting it at an earlier stage. While the target population is easily identifiable given the majority of HCC occur in cirrhotic patients, screening for HCC is controversial. The uncertainty is due to three main reasons: 1. lack of ideal screening tests that have high sensitivity and specificity, 2. current screening strategy has not been shown to improve survival, 3. the cost effectiveness of screening has not been analyzed.⁴²

Screening Tests

There have been many studies examining the performance characteristics of HCC screening tests. Alpha fetoprotein (AFP), depending of the cut-off value and the study, has a sensitivity range of 40-100%, and specificity of 70-100%. Most experts agree that AFP level > 400 ng/ml indicates HCC. The problem is that it can be elevated to as high as 200 ng/ml, if the patient is either cirrhotic or has active hepatitis, especially HBV. More importantly, up to 30% of HCC has AFP < 10 ng/ml. This is especially true among African Americans with HCC.⁴³ Several other serum markers may have somewhat higher sensitivity and specificity, but none are currently available in the United States.

Ultrasound is the most common imaging study used in HCC screening. It has a better sensitivity than AFP. One can detect most tumors > 1 cm. The specificity is similar but more consistent than AFP of > 90%. The drawback of ultrasound is that it also detects simple dysplastic nodules, which can be quite common in cirrhosis. These nodules are now evaluated by contrast CT or MRI. In the past however, it often lead to biopsies that carry a small but significant morbidity. One study evaluated the sensitivity and specificity of combination of ultrasound and AFP. It showed a sensitivity of 100% vs. 75% (> 10 ng/ml) or 87% if using AFP or US alone, respectively. One study reported CT scan had a sensitivity of almost 100% in detecting HCC, however, the study was not designed to measure the performance status of CT scan. Currently, MRI is considered too expensive for screening purposes.⁴²

Survival

There is no randomized control study, and very few prospective studies that evaluated the efficacy of screening, meaning whether active screening prolongs survival of patients with HCC. However, there is indirect evidence to suggest screening is helpful. Indirect evidence implies rather than following patients' survival longitudinally, detecting HCC that are smaller is interpreted as significant because they can be treated surgically. There has been consistent evidence showing tumors detected by screening using AFP alone or combination of AFP and U/S were significantly smaller than those not detected by screening. These smaller tumors were more likely than larger tumors to receive definitive treatment, as well as tumor-free survival of > 5 years.⁴²

Cost-effectiveness

One study evaluated the cost-effectiveness of screening using ultrasound and AFP every 6 months. The study population included 113 patients diagnosed with incidental

HCC as controls, and 104 consecutive cirrhotic patients under the screening protocol. Mean follow-up for the screened patients were 56 months. It showed that the cost for treatable HCC was nearly identical between screened and unscreened groups, \$17,934 vs. \$14,555, respectively. The calculated cost per year life saved was \$112,993. The author concluded that HCC screening was not cost-effective.⁴⁴

Recommendations

There are few specific recommendations aiming at specific liver diseases. For high risk HBV patients, including men age > 45 year-old, family history of HCC, cirrhotic, AFP and US very 6 month is recommended; for low risk HBV patients, who do not have the above characteristics, AFP alone may be considered. In chronic HCV patients, as of 2002, NIH consensus conference recommended that HCV patients without cirrhosis should not be screened, and no specific screening strategy for cirrhotic HCV patients. Currently, there is no HCC screening recommendation for other chronic liver diseases. While the combination of AFP and ultrasound appears to detect tumors at an earlier stage, specific trials comparing the survival benefit of screened vs. non-screened patients are needed before such strategy can be firmly recommended. The lack of cost-effectiveness of screening needs to be reproduced, given smaller or resectable tumors found on screening.^{9,28,45}

Summary

Experts have projected continued increase of HCC incidence in the United States in the near future. HCV and fatty liver disease are likely the two major culprits responsible for this increase. Patients infected with HCV in the 1980s will likely develop HCC into the 2nd decade of the 21st century. The good news is that current understanding of the virus has curtailed the spread of HCV dramatically. The newest estimate shows the annual incidence of HCV has decreased from its peak of 100 per 100,000 populations in the mid 1980s to less than 20 per 100,000 populations in the late 1990s (Kim, Alter). On the other hand, our understanding of fatty liver disease is only in its beginning. Even fewer pharmacological therapies exist for NAFLD or NASH than HCV. The socioeconomic cause that is part of the obesity epidemic will provide bigger challenges than preventing the spread of HCV. Finally, HBV remains the biggest environmental carcinogen worldwide. Continued monitoring on the global epidemiology of HCC should correlate with the use of HBV vaccine. As outlined in this report, in addition to primary prevention, the most obvious strategy to decrease the mortality associated with HCC would be to slow the development of cirrhosis, either through direct anti-viral therapy, or controlling the pathway of fibrogenesis. The benefits of screening need to be confirmed in well-designed studies before it can be firmly recommended.

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