Review

HCC prevention and surveillance

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Prevention of hepatocellular carcinoma and monitoring of high-risk patients

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Abstract

Hepatocellular carcinoma (HCC) accounts for some 80% of primary liver tumors. According to recent data, HCC is the sixth most common type of cancer and the third leading cause of cancer-related mortality worldwide. Risk factors for HCC include the presence of the hepatitis B virus, hepatitis C virus, non-alcoholic fatty liver disease, and exposure to noxious agents, such as alcohol, or toxins, such as aflatoxin, which are considered preventable etiologies of HCC. Monitoring strategies are needed for patients at risk of developing HCC. There is a consensus on routine monitoring of cirrhotic patients due to definitive evidence of a significantly high rate of progression to HCC; however, the appropriate surveillance of patients with advanced fibrosis remains a topic of discussion. Nevertheless, adherence to a strict observation protocol is the cornerstone of early detection and treatment with curative options for patients with a high risk of developing HCC. This review examines prevention strategies, risk factors, and surveillance based on current guidelines.

Keywords: Hepatitis B; hepatitis C; hepatocellular carcinoma; non-alcoholic fatty liver disease; prevention; surveillance.

Introduction

According to 2020 data provided by the Global Cancer Observatory: CANCER TODAY (GLOBOCAN), primary liver cancer is the sixth common cancer type, and the third leading cause of cancer-related mortality worldwide, with approximately 830,000 deaths per year. Hepatocellular carcinoma (HCC) accounts for approximately 80% of primary liver cancer cases, followed by intrahepatic cholangiocarcinoma, and other rare types.[1] Mongolia has the highest HCC incidence in the world, with 78.1 per 100,000.[2] The primary etiology for this high incidence rate is thought to be the high seroprevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV), rather than aflatoxin exposure.[3] Fortunately, the HCC incidence rate has been decreasing in many high-risk regions, including Eastern and South Eastern Asia, with decreased HBV and HCV seroprevalence and aflatoxin exposure.[4] On the other hand, the increasing prevalence of obesity, diabetes, metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD) counteract the gains achieved with a reduction in viral- and toxin-related HCC.[5]

Despite efforts to reduce the burden of cancer, the prevalence of primary liver cancer has doubled in recent decades.[6] It has been estimated to rise further by 2030. According to a Bayesian model, HBV-related HCC is predicted to decrease, whereas HCC related to HCV, alcohol use, and non-alcoholic steatohepatitis (NASH) is expected to increase.[4] Among those etiologies, the incidence of NASH, which is closely associated with obesity, has been projected to demonstrate the greatest increase.[6] A worldwide rise in obesity has been observed with economic growth and industrialization, which has led to greater availability of foods high in sugar and fat, and changes in behavior, such as a more sedentary life style.[7] Given that the disease burden is growing despite a decrease in HBV-related cases, an etiology-specific prevention and monitoring strategy is of clinical importance. This review provides a summary of some of the most important aspects related to prevention and surveillance strategies in the current guidelines.

HCC Risk Factors and Prevention Strategies

Viral Hepatitis

Viral hepatitis is the most important cause of HCC. Chronic HBV and HCV infection account for an estimated 75% to 80% and 10% to 20%, respectively, of cases of virus-associated HCC.[8] HBV-related HCC represents some 56% of liver cancer deaths worldwide, and some 20% are HCV-related.[9]

The foundation for HBV eradication is an appropriate vaccination strategy. Results from a Taiwanese study of 30 years of neonatal vaccination revealed a decrease in the incidence of HCC of 80% and 90% for HCC-associated mortality.[10] Similar results have also been reported from China[11] and Singapore.[12] Global coverage with 3 doses of the HBV vaccine has been reported to be 83%, largely due to the success of vaccination programs.[13] Although neonatal vaccination has been introduced in many countries, and important progress has been made, in African countries, where the HBV-related HCC is still a major clinical is-

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sue, a need to improve the vaccination strategy remains.[14] For example, only 1% of the children in Gambia were reported to have their first dose of the HBV vaccination at birth.[15] Unfortunately, the ongoing coronavirus 2019 (COVID-19) pandemic has created disruptions in HBV vaccination programs. This will have an impact on the goal to eliminate HBV by 2030, particularly in vulnerable low- and middle-income countries.[16] In addition to vaccination, antiviral treatment during pregnancy has also been shown to reduce the risk of vertical transmission.[17]

There are also ongoing efforts to eliminate HCV. A World Health Organization (WHO) global campaign targets HCV elimination by 2030. However, according to a recent analysis, only a limited number of countries (Australia, Canada, France, Germany, Iceland, Italy, Japan, Spain, Sweden, Switzerland and the United Kingdom) are expected to reach this goal.[18] In fact, other researchers have reported that only 9 of 45 nations analyzed were likely to meet goals of an 80% reduction in incidence and a 65% reduction in mortality, and most were not anticipated to eliminate HCV before 2050.[19] Moreover, this analysis did not foresee the impact of the COVID-19 pandemic, which can be expected to prolong the time to achieve eradication goals.[20] There are considerable efforts in the field of HCV vaccine development.[21] Direct-acting antivirals that can provide a sustained virologic response are the latest form of HCV treatment, and have proven to be efficacious.[22] However, an effective vaccine against HCV remains a great challenge for the scientific community.

Factors such as alcohol use (hazard ratio [HR]: 1.24; 95% confidence interval [CI]: 1.03-1.50), older age (HR: 1.03; 95% CI: 1.02-1.05), HCV genotype 3 (HR: 1.60; 95% CI: 1.08-2.38), and consistently high scores suggesting advanced fibrosis (HR: 6.69; 95% CI: 4.98-9.81) significantly contribute to HCC progression. Patients who receive treatment in the early stages of fibrosis have a lower risk for HCC. Therefore, elimination of these factors or supervision based on these characteristics and timely treatment of HCV may be considered primary elements of a prevention strategy for HCV-related HCC.[23] Many individuals living with chronic viral hepatitis are unaware of their status. The WHO has targeted increasing the diagnosis rate, setting a goal of 30% of people infected knowing their status by 2020 and 90% by 2030,[24] as well as the establishment of routine, targeted screening for patients with specific characteristics.[25] One-time opt-out HCV screening has also been recommended for all individuals over the age of 18 years as a means of early detection.[26] Infants of high-risk mothers should also be included in screening programs to promote early diagnosis and treatment.[27]

Aflatoxin B

Aflatoxins are one of the most potent hepatocarcinogens known. These toxins are produced by fungi, such as Aspergillus flavus and Aspergillus parasiticus, which are common in warm, humid environments, and are often seen in maize, nuts, and other agricultural crops. Aflatoxins are most often observed in Sub-Saharan Africa, China, and Southeast Asia.[28] Basic prevention strategies, such as drying crops before storage, are helpful to efforts to eliminate aflatoxins.[29] In China, public health policies designed to reduce exposure to aflatoxins and increase the HBV vaccination rate resulted in dramatic reductions in primary liver cancer risk and mortality.[30]

Non-alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is currently the most common chronic liver disease in the world, with an estimated global prevalence of 25%.[31] Obesity and type 2 diabetes mellitus (T2DM) are important risk factors for the development of NAFLD. The growing prevalence of NAFLD has occurred alongside a growing worldwide prevalence of obesity and T2DM.[7,32-35] The annual incidence of HCC among NAFLD patients has been reported to be 0.44 per 1000 person-years (95% CI: 0.29-0.66) and 5.29 per 1000 person-years for NASH patients (95% CI: 0.75-37.56).[36] Cases of NASH-related HCC have already been reported to be a more rapidly growing proportion of liver transplantation patients than HCV-related HCC in the USA.[37] It is likely that there will be more NASH-related HCC patients than HCV-related HCC patients on the liver transplant waiting list in the near future.[38] Notably, development of HCC has been reported in non-cirrhotic NAFLD patients. When compared with NASH-induced HCC, alcohol-induced HCC was more likely to be associated with the presence of cirrhosis. This highlights the importance of considering screening for HCC in early-stage NAFLD patients.[39] According to a study of a German database of 4,580,434 patients, 4.7% were NAFLD cases. In that group, 36.8% were non-progressors, 0.2% compensated cirrhosis, 9.6% decompensated cirrhosis, 0.0005% liver transplant, and 0.2% HCC. The mortality rate was 3.6%, 18.7%, 28.8%, and 68% for the non-progressor, compensated cirrhosis, decompensated cirrhosis, and HCC groups, respectively. The economic burden of NAFLD increased with disease severity, which reinforces the significance of early detection.[40]

Unfortunately, there is currently no approved pharmacological therapy for NAFLD or NASH. A hypocaloric diet and exercise targeting a weight loss of 7% to 10% remains the cornerstone of most NAFLD therapy.[41] There is no direct evidence linking weight loss to less risk of HCC, however, a study that used 52 weeks of follow-up data of a cohort of 261 NAFLD patients who were encouraged to adopt lifestyle changes demonstrated that a large proportion of those who achieved a weight loss of >5% had NASH resolution or a reduction in the NAFLD activity score (NAS), and that all of those who lost >10% of their weight had a reduction in the NAS measurement, 90% had resolution of NASH and 45% saw a regression in fibrosis.[42] The association between progressive NASH and HCC suggests that lifestyle modifications are helpful to reducing the risk of HCC in NAFLD patients.[36] Bariatric surgery has also been reported to be valuable.[43] In addition, coffee consumption has been demonstrated to decrease the risk of HCC.[44]

The presence of T2DM significantly contributes to the risk of HCC development. In a real-world study conducted with a European cohort consisting of 18 million adults, T2DM was the strongest independent predictor of HCC or cirrhosis in NAFLD cases (HR: 3.51; 95% CI: 1.72-7.16).[45] Moreover, evidence from a large German study of 4,580,434 patients indicated that the presence of T2DM was an independent predictor of mortality in NAFLD patients.[46] Similarly, in a NASH cirrhosis study, it was demonstrated that the development of HCC was significantly greater in T2DM patients (HR: 4.2; 95% CI: 1.2–14.2).[47] Accumulating evidence suggests that use of metformin has been beneficial in decreasing the risk of HCC development.[48-50] Similarly, statins have been reported to be beneficial in the prevention of HCC.[51] In a meta-analysis of 1,925,964 patients that compared statin users and non-users, the crude odds ratio (OR) for HCC incidence was 0.59 (95% CI: 0.47-0.74), and was confirmed in adjusted analysis (OR: 0.74; 95% CI: 0.70-0.78). This indicates a beneficial effect of statin use. Furthermore, lipophilic statins have been associated with a reduced incidence of HCC (HR: 0.49; 95% CI: 0.39-0.62).[52] Aspirin has also been presented as a primary prevention option. It was found that aspirin use for >5 years was associated with a lower HCC risk; nonaspirin nonsteroidal anti-inflammatory drug use did not produce similar results.[53]

Table 1. Summary of guideline surveillance recommendations

	AASLD (2018)	EASL (2018)	APASL (2017)	ESMO (2019)	ESMO (Pan-Asia adapted) (2020)
Target population	Cirrhosis of any etiology	Cirrhosis of any etiology	Cirrhosis of any etiology	Cirrhosis of any etiology	Cirrhosis of any etiology
	Chronic HBV carriers Asian men >40 y Asian women >50 y African, African-American, or family history of HCC	Chronic HBV carriers at intermediate or high risk of HCC according to PAGE-B score Patients with advanced fibrosis regardless of etiology	Chronic HBV carriers Asian men >40 y Asian female >50 y African >20 y Family history of HCC	HBV carriers with serum viral load >10,000 copies/mL HCV-infected patients advanced fibrosis	HBV carriers with serum viral load > 10,000 copies/mL HCV-infected patients advanced fibrosis
Screening modality	4-8 months	6 months	6 months	6 months	6 months
Screening interval	USG with or without AFP	USG	USG and AFP	USG with or without AFP	USG with or without AFP

AASLD: American Association for the Study of Liver Diseases; AFP: alpha-fetoprotein; APASL: Asia Pacific Association for the Study of the Liver; EASL: European Association for the Study of the Liver; ESMO: European Society for Medical Oncology; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; PAGE-B: Platelet, Age, Gender, hepatitis B; USG: Ultrasonography.

Use of Noxious Agents

Exposure to either alcohol or tobacco has been reported to be associated with increased HCC risk.[54] Although alcohol-related cirrhosis is less frequently associated with HCC development than viral-associated hepatitis,[55] avoiding alcohol consumption is strongly recommended.[56] Heavy alcohol consumption has been established to be significantly associated with increased HCC risk.[57,58] A synergistic relationship between obesity and alcohol use has been reported. In 1 study, the cumulative risk for HCC development was 1.2% for non-obese individuals and 1.3% for obese individuals who did not consume alcohol, while the percentage was 2.7% for non-obese and 8.7% for obese individuals known to consume alcohol.[59] Current smokers have also shown to be at increased risk for HCC (HR: 1.86; 95% CI: 1.57-2.20). However, having quit for >30 years nearly equalized the risk to that of those who never smoked (HR: 1.09, 95% CI: 0.74-1.61).[57] Smoking cessation would appear to contribute to HCC prevention.

Coffee Consumption

Evidence seems to indicate that coffee consumption may be significantly associated with reduced risk of HCC.[60-63] Participants in 1 study that included 16 years of follow-up data who consumed 2 servings of coffee per day were reported to have a significantly lower HCC risk (HR: 0.4; 95% CI: 0.20-0.79) than those who did not drink coffee. A similar relationship could not be confirmed for tea consumption.[60] A dose-dependent relationship between the quantity of coffee consumed and HCC development risk has also been reported. According to a meta-analysis performed by Kennedy et al.,[61] an extra 2 cups of coffee daily was associated with a 35% reduction in the risk of HCC (relative risk [RR]: 0.65; 95% CI: 0.59-0.72). The HCC risk decreased by 50% with consumption of 5 cups of coffee per day.[61] Conflicting results have also been reported. In the recent meta-analysis reported by Di Maso et al.,[62] coffee consumption was found to reduce HCC risk (RR: 0.93; 95% CI: 0.80-1.08), but the association did not reach the level of statistical significance. The European Association for the Study of the Liver (EASL) guidelines encourage coffee consumption as a means to prevent HCC.[64]

Guideline-based HCC Surveillance in High-risk Populations

HCC monitoring is a cost-effective secondary prevention strategy for patients at high risk of developing HCC. The professional guidelines recommend that a surveillance program should be implemented for all cirrhotic and HBV-infected patients at high risk. Generally, the screening strategy includes a semi-annual ultrasonography examination, with or without alpha-fetoprotein (AFP) measurement.[64-68] Several leading guideline recommendations, including details of the target population, screening methodology, and observation interval are summarized in Table 1.

Guidelines recommend regular screening for cirrhosis patients regardless of the etiology.[64-68] However, the surveillance recommendation has been limited to those patients with a Child-Pugh class A or B categorization unless the patient is listed for liver transplantation.[64,65] This strategy was based on the evidence that 80% of HCC patients had pre-existing cirrhosis.[69] Recently, a new definition for NAFLD was recommended that includes the presence of positive metabolic dysfunction criteria in addition to evidence of hepatic steatosis and a new name was proposed: metabolic (dysfunction) associated fatty liver disease (MAFLD).[70] The guideline of the Asian Pacific Association for the Study of the Liver (APASL) recommends HCC surveillance for cases of MAFLD cirrhosis. Monitoring is also recommended for patients with a liver stiffness measurement (LSM) >15 kPa. As in the HCC guideline, semi-annual ultrasonography examinations with AFP determination are recommended.[71]

The guidelines differ in recommendations related to the surveillance of HBV-infected patients. The American Association for the Study of the Liver Diseases (AASLD) and the APASL recommend surveillance for Asian men >40 years of age, Asian women >50 years of age, and patients with a positive family history of HCC.[65,66] The AASLD defined a specific age cut-off for patients for patients of African ancestry of >20 years, while the APASL guideline African ancestry was a sufficient characteristic for surveillance regardless of age.[65,66] The EASL guideline provides a specific risk stratification score for HBV patients, the Platelet, Age, Gender, hepatitis B (PAGE-B) score, which uses decades of age (16-29=0, 30-39=2, 40-49=4, 50-59=6, 60-69=8, ≥70=10), gender (male=6, female=0), and platelet count (≥200,000/μL=0, 100,000-199,999/μL=1, <100,000/μL=2). A score of ≤9 points

is defined as a low risk of HCC (almost 0% HCC at 5 years), 10-17 indicates an intermediate risk level (3% incidence HCC at 5 years), and ≥18 is considered high (17% HCC at 5 years). Monitoring is recommended for HBV-infected patients with an indeterminate or high risk.[64,72] Alternatively, the European Society for Medical Oncology (ESMO) based their surveillance strategy for HBV-infected patients on viral load.[67,68]

Although there is broad agreement about the screening of cirrhotic patients, there is still no consensus on how to conduct monitoring of non-cirrhotic patients. The AASLD does not recommend surveillance for non-cirrhotic NAFLD and HCV patients due to the significantly lower risk of developing HCC.[65] In the APASL guideline, due to uncertainty of the benefits, a strict recommendation was not made for these groups.[66] The EASL guideline for screening, however, includes advanced fibrosis patients, regardless of the etiology.[64] The ESMO clinical practice guidelines consider only patients with advanced fibrosis due to HCV to be at high risk for advanced fibrosis, and therefore, surveillance was recommended only for those patients.[67,68]

Generally, a semi-annual HCC ultrasonography screening seems to be effective, given the tumor volume doubling time.[73,74] Importantly though, ultrasonography seems to have insufficient sensitivity in the detection of HCC. Therefore, use in combination with AFP has been recommended in an effort to improve the sensitivity, although this is not a uniform view. In a meta-analysis of 13,367 individuals, the combined use of AFP and ultrasonography was reported to increase the sensitivity for the detection the early-stage HCC from 45% to 63% (p=0.002).[75] Nonetheless, the performance may still be considered inadequate. The GALAD score, which consists of gender, age, AFP-L3, AFP, and des-gamma carboxyprothrombin measures, was developed to address this issue.[76] The score was validated in a cohort consisting of non-HCC and early-stage HCC patients. The GALAD score demonstrated a sensitivity of 68% and specificity of 95% in the detection of early-stage HCC, and appears to be promising.[77] Subsequently, the GALAD score was shown to accurately detect early-stage HCC in viral hepatitis patients as well.[78] Considering current challenges, such as the pandemic, and other changes related to etiology, the GALAD score seems to be a useful tool to help improve early detection.[79]

Although still not recommended in the guidelines, accumulating data also suggest that liver stiffness measurement (LSM) with transient elastography may have a beneficial role in clinical practice in the prediction of liver-related outcomes. The analysis of 1039 NAFLD patients with a histologic diagnosis of F3-F4 fibrosis and/or an LSM >10 kPa showed that the change in LSM over time predicted the occurrence of HCC (HR: 1.72; 95% CI 1.01-3.02).[80] The clinical benefit appears to be more pronounced for patients with non-viral hepatitis rather than viral hepatitis.[81] LSM values achieved with magnetic resonance elastography have emerged as a useful indicator of HCC recurrence.[82,83]

Despite the recognized importance of regular surveillance for high-risk patients, the measures implemented to manage the COVID-19 pandemic have had an impact on HCC surveillance because elective imaging, such as ultrasonography, has generally been postponed. Prioritizing surveillance of patients at high risk for HCC is of paramount importance. In addition, blood examinations including AFP and use of the GALAD score are valuable, given the impossibility of maintaining personal distance and the prolonged contact time required for an ultrasonography examination. Magnetic resonance imaging has been presented as an alternative method, however, an expectation of routine use is not realistic due to limited availability.[78]

Conclusion

In conclusion, HCC prevention strategies include HBV vaccination, early detection and treatment of HCV, and lifestyle changes targeting weight loss for NAFLD patients. Minimizing aflatoxin exposure has also been useful in high-risk regions. Due to the significant contribution of alcohol in hepatocarcinogenesis, strict abstinence is recommended. Although there is still a lack of strong evidence, avoiding smoking and cessation of smoking would also decrease HCC development. Coffee consumption has been recommended due to its beneficial effects in reducing the HCC risk. Cirrhotic patients and HBV-infected patients, regardless of the presence of cirrhosis, are considered high-risk patients who need to be included in surveillance programs. However, recommendations for non-cirrhotic patients remain unclear. Currently, the preferred surveillance modality seems to be semi-annual ultrasonographic follow-up with or without AFP detection. Although there are no definitive data on the impact of COVID-19 in HCC surveillance, the COVID-19 pandemic has had a negative impact on regular patient follow-up. The effects of the pandemic on HCC will be evident in the upcoming decade.

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