Review

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HCC prevention and surveillance

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Prevention of hepatocellular carcinoma and monitoring of high-risk patients

Eda Kaya[1,2], Guillermo Daniel Mazzolini[3], Yusuf Yilmaz[4,5], Ali Canbay[1,2]

[1]Section of Gastroenterology and Hepatology, University, Hospital Knappschaftskrankenhaus Bochum, Ruhr University Bochum, Bochum, Germany; [2]Department of Medicine, University Hospital, Knappschaftskrankenhaus Bochum, Ruhr University Bochum, Bochum, Germany; [3]Laboratory of Gene Therapy, Instituto de Investigaciones en Medicina Traslacional, CONICET-Universidad Austral, Buenos Aires, Argentina; Liver Unit, Hospital Universitario Austral, Universidad Austral, Argentina; [4]Department of Gastroenterology, School of Medicine, Marmara University, Istanbul, Turkey; [5]Institute of Gastroenterology, Marmara University, Istanbul, Turkey

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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Corresponding author: Ali Canbay; Ruhr-University Bochum, University Hospital, Knappschaftskrankenhaus Bochum, In der Schornau 23-25, 44892 Bochum, Germany

Phone: +49 234 299 3401; **e-mail:** ali.canbay@rub.de

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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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021 May;71(3):209-249. [CrossRef]
2. Baatarkhuu O, Gerelchimeg T, Munkh-Orshikh D, Batsukh B, Sarangua G, Amarsanaa J. Epidemiology, genotype distribution, prognosis, control, and management of viral hepatitis b, c, d, and hepatocellular carcinoma in mongolia. Euroasian J Hepatogastroenterol 2018;8(1):57-62. [CrossRef]
3. Popp W, Gantumur T, Ross B, Zorigt K, Davaadorj D, Rossburg M, et al. Aflatoxin exposure may not play a role in liver cancer development in Mongolia. Digestion 2014;89(4):268-71. [CrossRef]
4. Valery PC, Laversanne M, Clark PJ, Petrick JL, McGlynn KA, Bray F. Projections of primary liver cancer to 2030 in 30 countries worldwide. Hepatology 2018;67(2):600-611. [CrossRef]
5. Petrick JL, Florio AA, Znaor A, Ruggieri D, Laversanne M, Alvarez CS, et al. International trends in hepatocellular carcinoma incidence, 1978-2012. Int J Cancer. 2020;147(2):317-330. [CrossRef]
6. Liu Z, Xu K, Jiang Y, Cai N, Fan J, Mao X, et al. Global trend of aetiology-based primary liver cancer incidence from 1990 to 2030: a modelling study. Int J Epidemiol. 2021;50(1):128-142. [CrossRef]
7. Seyda Seydel G, Kucukoglu O, Demir OO, Yilmaz S, Akkiz H, et al. Economic growth leads to increase of obesity and associated hepatocellular carcinoma in developing countries. Ann Hepatol 2016;15(5):662-672.
8. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006;45(4):529-538. [CrossRef]
9. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health 2016;4(9):e609-e616. [CrossRef]

10. Chiang CJ, Yang YW, You SL, Lai MS, Chen CJ. Thirty-year outcomes of the national hepatitis B immunization program in Taiwan. JAMA 2013;310(9):974-976. [CrossRef]
11. Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, et al. Evaluation of the impact of hepatitis B vaccination among children born during 1992-2005 in China. J Infect Dis 2009;200(1):39-47. [CrossRef]
12. Ang LW, Cutter J, James L, Goh KT. Seroepidemiology of hepatitis B virus infection among adults in Singapore: a 12-year review. Vaccine 2013;32(1):103-110. [CrossRef]
13. World Health Organization. Immunization coverage. Available at: https://www.who.int/news-room/fact-sheets/detail/immunization-coverage. Accessed on July 31, 2021.
14. World Health Organization. WHO-UNICEF estimates of HepB3 coverage. In: World Health Organization. Available at: http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragehepb3.html. Accessed on July 31, 2021.
15. Miyahara R, Jasseh M, Gomez P, Shimakawa Y, Greenwood B, Keita K, et al. Barriers to timely administration of birth dose vaccines in The Gambia, West Africa. Vaccine 2016;34(29):3335-3341. [CrossRef]
16. Pley CM, McNaughton AL, Matthews PC, Lourenço J. The global impact of the COVID-19 pandemic on the prevention, diagnosis and treatment of hepatitis B virus (HBV) infection. BMJ Glob Health 2021;6(1):e004275. [CrossRef]
17. Jourdain G, Ngo-Giang-Huong N, Harrison L, Khamduang W, Tierney C, Salvadori N, et al. Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. N Engl J Med. 2018;378(10):911-923. [CrossRef]
18. Gamkrelidze I, Pawlotsky JM, Lazarus JV, Feld JJ, Zeuzem S, Bao Y, et al. Progress towards hepatitis C virus elimination in high-income countries: An updated analysis. Liver Int 2021;41(3):456-463. [CrossRef]
19. Razavi H, Gonzalez YS, Yuen C, Cornberg M. Global timing of hepatitis C virus elimination in high-income countries. Liver Int 2020;40(3):522-529.
20. Kondili LA, Craxì A, Aghemo A. Absolute targets for HCV elimination and national health policy paradigms: Foreseeing future requirements. Liver Int 2021;41(4):649-655. [CrossRef]
21. Kardani K, Sadat SM, Kardani M, Bolhassani A. The next generation of HCV vaccines: a focus on novel adjuvant development. Expert Rev Vaccines 2021;20(7):839-855. [CrossRef]
22. Chhatwal J, Kanwal F, Roberts MS, Dunn MA. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. Ann Intern Med 2015;162(6):397-406. [CrossRef]
23. Kanwal F, Kramer JR, Asch SM, Cao Y, Li L, El-Serag HB. Long-Term Risk of hepatocellular carcinoma in hcv patients treated with direct acting antiviral agents. Hepatology 2020;71(1):44-55. [CrossRef]
24. World Health Organization. Global Health Sector Strategy on Viral Hepatitis2016-2021. Towards Ending Viral Hepatitis. Available at: https://apps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf?sequence=1. Accessed on August 1, 2021.
25. Ghany MG, Morgan TR; AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Hepatology 2020;71(2):686-721. [CrossRef]
26. Sulkowski M, Cheng WH, Marx S, Sanchez Gonzalez Y, Strezewski J, Reau N. Estimating the year each state in the United States will achieve the world health organization's elimination targets for hepatitis C. Adv Ther 2021;38(1):423-440. [CrossRef]
27. Epstein RL, Sabharwal V, Wachman EM, Saia KA, Vellozzi C, Hariri S, et al. Perinatal transmission of hepatitis C virus: defining the cascade of care. J Pediatr. 2018;203:34-40.e1. [CrossRef]
28. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. Clin Liver Dis 2015;19(2):223-238. [CrossRef]
29. Strosnider H, Azziz-Baumgartner E, Banziger M, Bhat RV, Breiman R, Brune MN, et al. Workgroup report: public health strategies for reducing aflatoxin exposure in developing countries. Environ Health Perspect. 2006;114(12):1898-1903. [CrossRef]
30. Chen JG, Egner PA, Ng D, Jacobson LP, Muñoz A, Zhu YR, et al. Reduced aflatoxin exposure presages decline in liver cancer mortality in an endemic region of China. Cancer Prev Res (Phila) 2013;6(10):1038-1045. [CrossRef]
31. Younossi Z, Tacke F, Arrese M, Chander Sharma B, Mostafa I, Bugianesi E, et al. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology 2019;69(6):2672-2682. [CrossRef]
32. Dai W, Ye L, Liu A, Wen SW, Deng J, Wu X, et al. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: A meta-analysis. Medicine (Baltimore) 2017;96(39):e8179. [CrossRef]
33. Li L, Liu DW, Yan HY, Wang ZY, Zhao SH, Wang B. Obesity is an independent risk factor for non-alcoholic fatty liver disease: evidence from a meta-analysis of 21 cohort studies. Obes Rev 2016;17(6):510-519. [CrossRef]
34. Yilmaz Y, Younossi ZM. Obesity-associated nonalcoholic fatty liver disease. Clin Liver Dis 2014;18(1):19-31. [CrossRef]
35. Kaya E, Yilmaz Y. Non-alcoholic Fatty Liver Disease: A Global Public Health Issue. In: Faintuch J, Faintuch S, editors. Obesity and Diabetes. New York: Springer, Cham; 2020. pp. 321-333. [CrossRef]
36. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64(1):73-84. [CrossRef]
37. Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. Hepatology 2014;59(6):2188-2195. [CrossRef]
38. Goldberg D, Ditah IC, Saeian K, Lalehzari M, Aronsohn A, Gorospe EC, et al. Changes in the prevalence of hepatitis C virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. Gastroenterology 2017;152(5):1090-1099.e1. [CrossRef]
39. Ertle J, Dechêne A, Sowa JP, Penndorf V, Herzer K, Kaiser G, et al. Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. Int J Cancer 2011;128(10):2436-2443. [CrossRef]
40. Canbay A, Kachru N, Haas JS, Meise D, Ozbay AB, Sowa JP. Healthcare resource utilization and costs among nonalcoholic fatty liver disease patients in Germany. Ann Transl Med 2021;9:615. [CrossRef]
41. Brunner KT, Henneberg CJ, Wilechansky RM, Long MT. Nonalcoholic Fatty Liver Disease and Obesity Treatment. Curr Obes Rep 2019;8(3):220-228.
42. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015;149(2):367-378.e5; quiz e14-5. [CrossRef]
43. Ramai D, Singh J, Lester J, Khan SR, Chandan S, Tartaglia N, et al. Systematic review with meta-analysis: bariatric surgery reduces the incidence of hepatocellular carcinoma. Aliment Pharmacol Ther 2021;53(9):977-984.
44. Kennedy OJ, Roderick P, Buchanan R, Fallowfield JA, Hayes PC, Parkes J. Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic review and dose-response meta-analysis. BMJ Open 2017;7(5):e013739. [CrossRef]
45. Alexander M, Loomis AK, van der Lei J, Duarte-Salles T, Prieto-Alhambra D, Ansell D, et al. Risks and clinical predictors of cirrhosis and hepatocellular carcinoma diagnoses in adults with diagnosed NAFLD: real-world study of 18 million patients in four European cohorts. BMC Med 2019;17(1):95.
46. Canbay A, Kachru N, Haas JS, Sowa JP, Meise D, Ozbay AB. Patterns and predictors of mortality and disease progression among patients with non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2020;52(7):1185-1194.
47. Yang JD, Ahmed F, Mara KC, Addissie BD, Allen AM, Gores GJ, et al. Diabetes is associated with increased risk of hepatocellular carcinoma in patients with cirrhosis from nonalcoholic fatty liver disease. Hepatology 2020;71(3):907-916. [CrossRef]

48. Franciosi M, Lucisano G, Lapice E, Strippoli GF, Pellegrini F, Nicolucci A. Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. PloS One 2013;8(8):e71583. [CrossRef]
49. Singh S, Singh PP, Singh AG, Murad MH, McWilliams RR, Chari ST. Anti-diabetic medications and risk of pancreatic cancer in patients with diabetes mellitus: a systematic review and meta-analysis. Am J Gastroenterol 2013;108(4):510-519. quiz 520. [CrossRef]
50. Zhang H, Gao C, Fang L, Zhao HC, Yao SK. Metformin and reduced risk of hepatocellular carcinoma in diabetic patients: a meta-analysis. Scand J Gastroenterol 2013;48(1):78-87. [CrossRef]
51. Goh MJ, Sinn DH, Kim S, Woo SY, Cho H, Kang W, et al. Statin use and the risk of hepatocellular carcinoma in patients with chronic hepatitis B. Hepatology. 2020;71(6):2023-2032. [CrossRef]
52. Facciorusso A, Abd El Aziz MA, Singh S, Pusceddu S, Milione M, Giacomelli L, et al. Statin use decreases the incidence of hepatocellular carcinoma: an updated meta-analysis. Cancers (Basel). 2020;12(4):874. [CrossRef]
53. Simon TG, Ma Y, Ludvigsson JF, Chong DQ, Chong DQ, Giovannucci EL, et al. Association between aspirin use and risk of hepatocellular carcinoma. JAMA Oncol 2018;4(12):1683-1690. [CrossRef]
54. Purohit V, Rapaka R, Kwon OS, Song BJ. Roles of alcohol and tobacco exposure in the development of hepatocellular carcinoma. Life Sci. 2013;92(1):3-9. [CrossRef]
55. West J, Card TR, Aithal GP, Fleming KM. Risk of hepatocellular carcinoma among individuals with different aetiologies of cirrhosis: a population-based cohort study. Aliment Pharmacol Ther 2017;45(7):983-990. [CrossRef]
56. World Cancer Research Fund Network. Diet, nutrition, physical activity and liver cancer. Available at: https://www.wcrf.org/wp-content/uploads/2021/02/liver-cancer-report.pdf. Accessed on August 1, 2021.
57. Petrick JL, Campbell PT, Koshiol J, Thistle JE, Andreotti G, Beane-Freeman LE, et al. Tobacco, alcohol use and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: The Liver Cancer Pooling Project. Br J Cancer 2018;118(7):1005-1012. [CrossRef]
58. Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer 2015;112(3):580-593. [CrossRef]
59. Loomba R, Yang HI, Su J, Brenner D, Barrett-Connor E, Iloeje U, et al. Synergism between obesity and alcohol in increasing the risk of hepatocellular carcinoma: a prospective cohort study. Am J Epidemiol 2013;177(4):333-342.
60. Tamura T, Wada K, Konishi K, Goto Y, Mizuta F, Koda S, et al. Coffee, green tea, and caffeine intake and liver cancer risk: a prospective cohort study. Nutr Cancer 2018;70:1210-1216. [CrossRef]
61. Kennedy OJ, Roderick P, Buchanan R, Fallowfield JA, Hayes PC, Parkes J. Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic review and dose-response meta-analysis. BMJ Open 2017;7(5):e013739. [CrossRef]
62. Di Maso M, Boffetta P, Negri E, La Vecchia C, Bravi F. Caffeinated coffee consumption and health outcomes in the us population: a dose-response meta-analysis and estimation of disease cases and deaths avoided. Adv Nutr 2021;12(4):1160-1176. [CrossRef]
63. Bravi F, Tavani A, Bosetti C, Boffetta P, La Vecchia C. Coffee and the risk of hepatocellular carcinoma and chronic liver disease: a systematic review and meta-analysis of prospective studies. Eur J Cancer Prev 2017;26(5):368-377.
64. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69(1):182-236.
65. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53(3):1020-1022. [CrossRef]
66. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017;11(4):317-370. [CrossRef]
67. Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29(Suppl 4):iv238-iv255. [CrossRef]
68. Chen LT, Martinelli E, Cheng AL, Pentheroudakis G, Qin S, Bhattacharyya GS, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with intermediate and advanced/relapsed hepatocellular carcinoma: a TOS-ESMO initiative endorsed by CSCO, ISMPO, JSMO, KSMO, MOS and SSO. Ann Oncol 2020;31(3):334-351. [CrossRef]
69. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011;53(3):1020-1022. [CrossRef]
70. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol 2020;73(1):202-209. [CrossRef]
71. Eslam M, Sarin SK, Wong VW, Fan JG, Kawaguchi T, Ahn SH, et al. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Hepatol Int 2020;14(6):889-919. [CrossRef]
72. Kim JH, Kang SH, Lee M, Choi HS, Jun BG, Kim TS, et al. Individualized surveillance of chronic hepatitis B patients according to hepatocellular carcinoma risk based on PAGE-B scores. Eur J Gastroenterol Hepatol 2021;33(12):1564-1572. [CrossRef]
73. Santi V, Trevisani F, Gramenzi A, Grignaschi A, Mirici-Cappa F, Del Poggio P, et al. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. J Hepatol 2010;53(2):291-297. [CrossRef]
74. Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, et al. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009;30(1):37-47. [CrossRef]
75. Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, et al. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis. Gastroenterology 2018;154(6):1706-1718.e1. [CrossRef]
76. Johnson PJ, Pirrie SJ, Cox TF, Berhane S, Teng M, Palmer D, et al. The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. Cancer Epidemiol Biomarkers Prev 2014;23(1):144-153. [CrossRef]
77. Best J, Bechmann LP, Sowa JP, Sydor S, Dechêne A, Pflanz K, et al. GALAD score detects early hepatocellular carcinoma in an international cohort of patients with nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 2020;18(3):728-735.e4. [CrossRef]
78. Mehta N, Parikh ND, Kelley RK, Hameed B, Singal AG. Surveillance and Monitoring of Hepatocellular Carcinoma During the COVID-19 Pandemic. Clin Gastroenterol Hepatol 2021;19(8):1520-1530. [CrossRef]
79. Schotten C, Ostertag B, Sowa J-P, Manka P, Bechmann LP, Hilgard G, et al. GALAD score detects early-stage hepatocellular carcinoma in a european cohort of chronic hepatitis B and C patients. Pharmaceuticals (Basel) 2021;14(8):735. [CrossRef]
80. Petta S, Sebastiani G, Viganò M, Ampuero J, Wai-Sun Wong V, et al. Monitoring occurrence of liver-related events and survival by transient elastography in patients with nonalcoholic fatty liver disease and compensated advanced chronic liver disease. Clin Gastroenterol Hepatol 2021;19(4):806-815.e5. [CrossRef]
81. Oh JH, Goh MJ, Park Y, Kim J, Kang W, Sinn DH, et al. Different performance of liver stiffness measurement according to etiology and outcome for the prediction of liver-related events. Dig Dis Sci 2021;66(8):2816-2825.
82. Wang J, Shan Q, Liu Y, Yang H, Kuang S, He B, et al. 3D MR Elastography of hepatocellular carcinomas as a potential biomarker for predicting tumor recurrence. J Magn Reson Imaging 2019;49(3):719-730. [CrossRef]
83. Cho HJ, Kim B, Kim HJ, Huh J, Kim JK, Lee JH, et al. Liver stiffness measured by MR elastography is a predictor of early HCC recurrence after treatment. Eur Radiol 2020;30(8):4182-4192. [CrossRef]