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Current prevention approaches for hepatocellular carcinoma

Keywords: HCC, cancer, aflatoxin, HCC patients, diagnosis, hepatocellular carcinoma, AFB1

Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; AFB1, aflatoxin B1; IFNs, interferons

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Introduction

Liver is the largest internal organ that is responsible for indispensable vital functions. Affecting this critical organ, five-year survival rate for liver cancer is below 15 percent after diagnosis.[1] More than 80 percent of primary liver cancers are hepatocellular carcinoma (HCC), which is closely associated with liver cirrhosis. HCC is the fifth most common cancer type in men, eighth in women and it also has the third place of all cancers with highest mortality worldwide.[2] Every year, more than 700,000 people are diagnosed with HCC.[2,3] Liver cancer incidence, especially HCC cases are continuously increasing all over the world.[4,5] HCC is generally diagnosed late on its course, show poor prognosis and despite significant advances in medicine available diagnosis and treatment modalities for liver cancer are insufficient. Because of the detoxification function, liver is highly resistant to most of the chemo and radiotherapies and at early stages liver cancer does not show any particular symptoms.[1,6] Although recent advanced cancer therapies exist for most of the solid/solitary tumor cases, HCC treatments are very limited to patients with small nodules and full liver function. Combination of chemotherapeutic agents has been tried on HCC and some have been found to increase response.[7,8] However most of these combinations have not been clinically approved yet.

Currently the best treatment option for HCC is surgical resection, which is suitable only for less than 20 percent of HCC patients with over 50 percent risk of recurrence rate within a few years of surgery.[9] The other successful option for treatment of HCC is liver transplantation; however organ donation shortage greatly diminishes this alternative. Sorafenib is the only drug clinically approved by FDA for advanced stage HCC. Indeed, sorafenib increases median survival time in HCC patients. However it merely adds three months on average to median survival time with several adverse effects.[9] For the time being, there is no standard cure or regimen resulting in complete remission in all patients for HCCs. Consequently, prevention of HCC becomes an urgent perspective in populous low-income countries and high risk groups with any etiology of HCC. Current HCC prevention can be divided into three levels: the prevention based on its etiological risk factors (primary prevention), mechanisms of carcinogenicity causes (secondary prevention) or stopping cancer progression (tertiary prevention).[10]

Primary prevention

The most dominant risk factor for HCC is cirrhosis originating from any etiology. Primary prevention of HCC is preventing the risk factors includinghepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, aflatoxin B1 exposure, diabetes, obesity, tobacco use, and heavy alcohol consumption before development of cirrhosis.[11] Globally almost 80 percent of HCC has been caused by oncogenic hepatitis viruses. Therefore 181 countries have started "Expanded Program of Immunization" (EPI) against HBV and nearly 90 percent of their infants have been vaccinated since 1970s in eastern and south-eastern Asia and Pacific islands. This program accomplished more than 10 fold decrease of incidence for HCC in vaccinated chronic HBV carriers. Unfortunately, HCV related HCC remains a problem due to lack of a vaccine against HCV. HCV genomic structure is hypervariable and there are many mutated forms in the infected individuals. Consequently it is extremely difficult to design a universal effective vaccine against the HCV.[9,10] Foremost method of primary prevention against HBV and HCV is taking precautions to prevent these viruses spreading, especially through intravenous injection abuse and contaminated blood or blood products transfusion. The other prevention method is treating HCV or HBV infected individuals with anti-viral drugs such as interferon-alpha (IFN-α) that reduces the risk of, or delays the development of viral HCC.[9,10] Aflatoxin B1 (AFB1) exposure to crops is another etiology for HCC development and this problem occurs generally in low-income countries where foodstuff are not screened for aflatoxin content. As industrialized countries have regulations for AFB1 contamination screening, effected foodstuff never enters the market. Prevention of this problem can be solved by proper storage of crops or replacing them with low risk ones, such as rice. However replacement of crops is not feasible for most low-income countries. Fungicide usage or genetically-modified *Aspergillus* resistant crop lines might be an alternative solution for those countries. Other prevention method for AFB1 exposure might be the inoculation of crops by non-aflatoxigenic *Aspergillus* strains to compete with aflatoxin-producing *Aspergillus*. However this method is not cost-effective for low-income countries. To prevent AFB1 contamination, the crops should be protected from excessive moisture by sun-drying or keeping them in well-ventilated facilities. For crop storage, wooden containers should preferred rather than storing the crops in open-air mounds. These kind of preventions seem relatively simple, however training of farmers must be done by agricultural institutions or trading

associations to achieve success.[9,10] Like aflatoxin exposure, dietary iron overload must be controlled to prevent HCC development. In Africa, iron containing alcohol consumption is still a problem in rural areas, where iron containers are used for alcohol storage. Education for usage of aluminum or iron-free containers could solve this problem.

Secondary prevention

Secondary or chemoprevention of HCC is based on dietary consumption of fruits and vegetables. According to epidemiological studies, natural constituents from fruits, vegetables, nuts and spices are shown to suppress or reverse the hepatocellular carcinogenesis and even kill the neoplastic cells.[9,10–12] *Chlorophyllin* (*Natural Green 3, E141*) is one of them and it forms molecular complexes with chemical carcinogens such as aflatoxins to reduce their bioavailability, consequently decreasing their carcinogenicity.[13,14] Oltipraz (*4-methyl-5-(2-pyrazinyl)-3-dithiolethione*) could be used for secondary prevention of HCC because it was shown to block AFB1 induced HCC by inducing phase II detoxifying and anti-oxidative enzymes, such as glutathione-S-transferase.[15] Polyprenoic acid is an acyclic retinoid which could be used for restoration of retinoids during alcohol induced hepatic damage.[16] Furthermore, there are other chemo preventive compounds such as isothiocyanates, glycosinolates, terpenoids (isoprenoids) that are also useful for chemoprevention of HCC. As a result, biologically active phytochemical-containing vegetable consumption correlates with a decreased risk of HCC.[4]

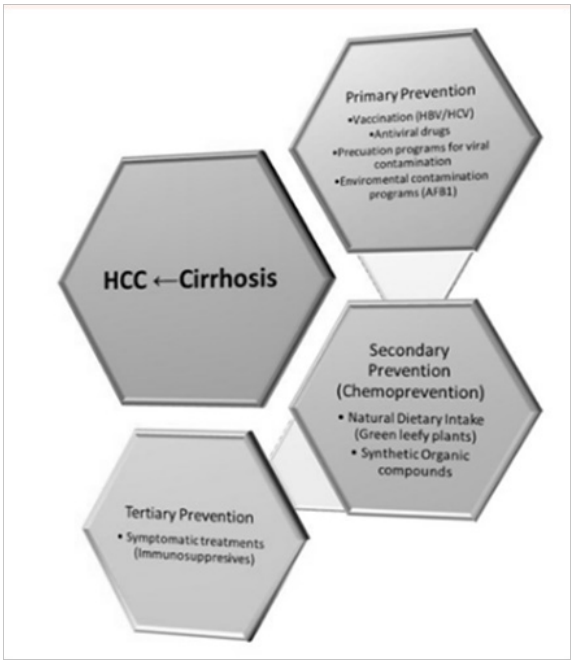

Figure 1 Prevention methods for targeting tumorigenesis of hepatocellular carcinoma through cirrhosis.

Tertiary prevention

Chronic necroinflammation is a common symptom in cirrhosis caused by HBV, HCV infections and alcohol abuse, resulting in development of HCC. Therefore, immunosuppressive agents like interferons (IFNs) and glucocorticoids have been used for suppressing the inflammation, thereby preventing HCC progression. Type-I IFN has been used for treating the patients with both HCV and HBV, while glycyrrhizin has been tested for HCV patients.[12] Progression of HCC is a long term process and tumorigenesis might take 20 to 30 years. Many etiological risk factors have roles during the progression steps of HCC. Cirrhosis is the most important early step of HCC, almost 80 percent of cirrhotic patients end up developing HCC. Therefore control of cirrhosis might readily mean preventing HCC. Furthermore, as the diagnosis of HCC generally occurs during its late course, prevention has become very important for individuals already infected with hepatitis viruses or affected by environmental contaminants (i.e. AFB1). In 1970s, most but not all governments realized that prevention of HCC is a public health problem and they started HBV vaccinations for newborns. Since then, HBV related HCC cases have decreased significantly. Currently, there is no effective vaccine for HCV due to its variable genomic properties; however patients with HCV have been treated with antiviral drugs or immunosuppressive agents as mentioned above. Environmental toxins in food remain a problem for HCC development in low-income countries, because of lacking regulations on agricultural crop storage. Taken all together, raising awareness for healthy food consumption, regulating obesity and diabetes that are secondary risk factors for HCC, and limiting alcohol intake are valid approaches for prevention of HCC (Figure 1).

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None.

Conflicts of interest

The authors declare that there is no conflict of interest.

References

1. El-Serag HB. Hepatocellular carcinoma. *N Engl J Med*. 2011;365(12):1118–1127.
2. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet*. 2012;379(9822):1245–1255.
3. Forner A, Gilabert M, Bruix J, et al. Treatment of intermediate-stage hepatocellular carcinoma. *Nat Rev Clin Oncol*. 2014;11(9):525–535.
4. Thoppil RJ, Bishayee A. Terpenoids as potential chemopreventive and therapeutic agents in liver cancer. *World J Hepatol*. 2011;3(9):228–249.
5. Villanueva A, Llovet JM. Impact of intra-individual molecular heterogeneity in personalized treatment of hepatocellular carcinoma. *Hepatology*. 2012;56(6):2416–2419.
6. Thun MJ, DeLancey JO, Center MM, et al. The global burden of cancer: priorities for prevention. *Carcinogenesis*. 2010;31(1):100–110.
7. Wörns MA, Galle PR. Novel inhibitors in development for hepatocellular carcinoma. *Expert Opin* Invest Drugs. 2010;19(5):615–629.
8. Zhu AX. Molecularly targeted therapy for advanced hepatocellular carcinoma in 2012: current status and future perspectives. *Semin Oncol*. 2012;39(4):493–502.
9. Bishayee A, Thoppil RJ, Waghray A, et al. Dietary phytochemicals in the chemoprevention and treatment of hepatocellular carcinoma: in vivo evidence, molecular targets, and clinical relevance. *Curr Cancer Drug Targets*. 2012;12(9):1191–1232.
10. Kew MC. Prevention of hepatocellular carcinoma. *HPB (Oxford)*. 2005;7(1):16–25.
11. Colombo M. Prevention of hepatocellular carcinoma and recommendations for surveillance in adults with chronic liver disease. 2015.
12. Singh S, Singh PP, Roberts LR, et al. Chemopreventive strategies in hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol*. 2014;11(1):45–54.

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13. Dashwood RH. The importance of using pure chemicals in (anti) mutagenicity studies: chlorophyllin as a case in point. *Mutat Res*. 1997;381(2):283–286.

14. Breinholt V, Schimerlik M, Dashwood R, et al. Mechanisms of chlorophyllin anticarcinogenesis against aflatoxin B1: complex formation with the carcinogen. *Chem Res Toxicol*. 1995;8(4):506–514.

15. Morel F, Fardel O, Meyer DJ, et al. Preferential increase of glutathione S-transferase class alpha transcripts in cultured human hepatocytes by phenobarbital, 3-methylcholanthrene, and dithiolethiones. *Cancer Res*. 1993;53(2):231–234.

16. Okuno M, Kojima S, Moriwaki H. Chemoprevention of hepatocellular carcinoma: concept, progress and perspectives. *J Gastroenterol Hepatol*. 2001;16(12):1329–1335.

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