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Screening for and surveillance of high-risk patients with HBV-related chronic liver disease: Promoting the early detection of hepatocellular carcinoma in China

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Summary **In China, hepatocellular carcinoma (HCC) is the second most common cancer in urban areas and first most common in rural areas. It ranks as the second leading cause of cancer-related deaths in males and the third leading cause of cancer-related deaths in females, with the total mortality rate of 26.26 per 100,000. Currently, people with hepatitis B virus (HBV) infection are a major population at risk of developing HCC in China. In fact, there are 93 million Chinese who are HBV carriers, and about 20 million of them have chronic HBV infection. Several cohort studies have shown that screening high-risk patients with HBV- or HCV-related chronic liver disease may improve the rate of early HCC detection and the rate of curative treatment. However, a government-funded national program to screen for high-risk patients with HBV-related chronic liver disease has yet to be established in China. Although several remarkable advances in HCC management have been made during the past few decades, most patients with HCC still present with advanced-stage disease, thus reducing the chance of curative treatment. Based on firsthand experience in Japan and other countries or areas, this work examined the current status, challenges, and prospects for the future of early detection of HCC in China. Findings suggested the need for a systematic guideline for the standardized management of HCC, a government-funded nationwide screening and surveillance program for high-risk patients with HBV-related chronic liver disease, and extensive use of des-γ-carboxyprothrombin (DCP) as a screening tool in China in order to facilitate the early detection of HCC in China.**

Keywords: Hepatitis B virus (HBV), hepatitis B (hepB) immunization, guideline, α-fetoprotein (AFP), des-γ-carboxyprothrombin (DCP)

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related deaths around the world. Asian countries account for 75-80% of the roughly 650,000 HCC cases reported globally each year. Of particular note is the fact that China alone accounts for 55% of HCC cases worldwide (*1*). Currently, the overall prevalence of HCC in China is 26-32 per 100,000 persons, and in some areas prevalence can be as high as 70-80 per 100,000 (*2*). HCC is now the second most common cancer in urban areas and the first most common in rural areas (*3*), and it ranks as the second leading cause of cancer-related deaths in males and the third leading cause of cancer-related deaths in females, with a total

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mortality rate of 26.26 per 100,000 in China (*4*).

The present work summarizes the current status of early detection of HCC in China. As shown in Table 1, several remarkable advances in HCC management have been made during the past few decades, such as the implementation of hepatitis B (hepB) immunization for susceptible and high-risk populations to prevent hepatitis B virus (HBV) infection and the publication of the "Expert Consensus on Treatment Standards for Hepatology Carcinoma (Chinese HCC Guideline)" (*5*) to guide clinical practice. However, most patients with HCC in China still present with advanced-stage disease (*6*). Currently, surgical resection and liver transplantation offer the best potential chances for treating HCC (*7*) but are only available to patients whose tumors are detected early. The overall 5-year survival rate for patients with HCC is about 40%, but liver resection of early HCC could result in a 5-year survival rate of 60-70% (*8*). In China, the challenge is that the majority of patients with HCC present with advanced disease, thus reducing the chance of curative treatment. Accordingly, early detection is crucial to achieving long-term disease-free survival for patients with HCC in China.

In order to determine how HCC is detected in its early stages worldwide, the literature was systematically reviewed. The reviewed literature consisted of 3,008 papers included in the PubMed database from 2001 to 2011. Also analyzed were 17 current guidelines for HCC management worldwide, including 5 guidelines from the United States of America (USA), 7 from Asia, and 5 from Europe (*9*). Several cohort studies have shown that screening high-risk patients with HBV- or HCV-related chronic liver disease may improve the rate of early HCC detection and the rate of curative treatment (*10-12*).

According to reports from the World Health Organization (WHO), approximately 2 billion people are HBV carriers, and 350 million of them have chronic HBV infection; about 1 million died due to hepatic failure, liver cirrhosis, or HCC caused by chronic HBV infection (*13*). In China, HBV is the biggest factor for developing HCC; approximately 85% of Chinese HCC cases are HBV-related, 10% of cases are HCV-related, and some cases involve HBV and HCV super-infection (*3*). Currently, people with HBV infection are a major population at risk of developing HCC in China. In fact, there are 93 million Chinese who are HBV carriers, and about 20 million of them have chronic HBV infection (*8,14*). A well-considered strategy of screening and surveillance for high-risk patients with HBV-related chronic liver disease is urgently needed in China to promote the early detection of HCC.

2. Early detection of HCC in China: Current status, challenges, and prospects for the future

2.1. *HCC guideline for the standardized management of HCC*

With the development of evidence-based medicine (EBM), the concept of "transfer of current best evidence into clinical decision-making" has garnered substantial attention worldwide. Guided by current best evidence, many clinical practice guidelines (CPGs) for HCC have been published worldwide (*15*). During the past few decades, a series of measures for standardized management of HCC have been published by the Chinese Government, and the Chinese HCC Guideline was also published in 2009 (*5*). Guidelines established by a systematic literature analysis include the guidelines established by American Association for the Study of Liver Disease (AASLD Guideline) (*16*), those of the British Society of Gastroenterology (BSG Guideline) (*17*), and the guideline established with the support of Japanese Ministry of Health, Labor, and Welfare (J-HCC Guideline) (*18*), all of which provide recommendations for the management of HCC supported by data. In contrast, the Chinese HCC Guideline was established based on a consensus of experts and not supporting

Table 1. The current status of early detection of HCC in China

Items	Current status in China
Prevalence	Overall prevalence of 26-32/100,000 (*2*).
Mortality	Total mortality rate of 26.26/100,000 (*4*).
Etiological factors	Eighty-five percent of patients with HBV infection, 10% of patients with HCV infection (*3*).
Major at-risk population	People with HBV infection; 93 million HBV carriers, 20 million people with chronic HBV infection (*13*).
Guideline	Expert Consensus on Treatment Standards for Hepatology Carcinoma (Chinese HCC Guideline) published in 2009 (*5*).
Prevention	HepB immunization for susceptible and high-risk populations.
Screening and surveillance	No government-funded nationwide screening program.
Screening tool	Ultrasonography and AFP.
Surveillance period	Six-month interval for HCC high-risk populations ages 35-40 (*5*).
Early detection	Most patients with HCC present with advanced-stage disease (*6*).

data. The Chinese HCC Guideline also covers only diagnosis and treatment, so other important aspects such as epidemiology, prevention, screening, surveillance, and follow-up are absent. This is particularly true of recommended strategies for screening and surveillance of high-risk patients with HBV-related chronic liver disease.

In Japan, there are two kinds of guidelines for HCC management. The J-HCC Guideline was established through a systematic analysis of 7,192 publications (*19*) with the support of Japanese Ministry of Health, Labor, and Welfare to guide clinical practice with recommendations supported by data. The JSH Guideline was established through a consensus of experts with the support of Japan Society of Hepatology (*20*) to provide experience-based recommendations for HCC management. The two guidelines do not contradict since they play different roles in Japan. In fact, the JSH Guideline may provide additional information based on experts' experience and up-to-date information on the management of HCC in Japan (*21*). Over the past ten years, HCC management in Japan has made remarkable progress due to the widespread acceptance and implementation of the J-HCC Guideline and JSH Guideline (*9,15,21*). More importantly, the guidelines in Japan have been systematically incorporated. The J-HCC Guideline was first published in 2005 and then revised in 2009, and the next version will be published in the near future with the incorporation of new evidence (*22*). The JSH Guideline was first published in 2007 and also be revised in 2010 (*23*).

According to the J-HCC Guideline and JSH Guideline, ultrasonography and measurement of α-fetoprotein (AFP), the lens culinaris agglutinin-reactive fraction of AFP (AFP-L3), or des-γ-carboxyprothrombin (DCP) should be performed at intervals of 3-4 months in the very-high-risk group (patients with HBV- or HCV-related liver cirrhosis) and at 6-month intervals in the high-risk group (patients with HBV- or HCV-related chronic liver disease or liver cirrhosis due to other causes) (*19,20,22,23*). Awareness of the J-HCC Guideline and its influence was studied in 2006, a survey showed that more than 70% of clinicians were aware of the guideline, and some clinicians changed their practices in line with the guideline (*24*). A survey of 200 Japanese experts was conducted in 2009 to determine the nature of HCC screening in Japan. The survey found that 72% of experts simultaneously measured the tumor markers of AFP, APF-L3, and DCP, and 44% of experts combined this measurement with ultrasonography (*25*).

The establishment and effectiveness of standardized management of HCC in Japan, and especially the periodic and simultaneous conduct of ultrasonography and measurement of AFP, AFP-L3, and DCP, may provide a good guide to HCC screening and surveillance for high-risk patients with HBV- or HCV-related chronic liver disease for other countries and areas, and especially for China.

2.2. *Nationwide screening and surveillance program for high-risk patients with HBV-related chronic liver disease*

In Asia, Japan and South Korea have implemented a nationwide screening and surveillance program for HBV and HCV infection. Similarly, Taiwan also established a screening and surveillance program to screen patients with cirrhosis every 3-6 months and patients with no cirrhosis every 6-12 months (*6,26*). However, there is no government-funded screening and surveillance program for HBV and HCV infection in Hong Kong or other parts of China. In 2002, the Japanese Ministry of Health, Labor, and Welfare started a national 5-year program to screen for HCV and HBV infection among people over 40 given the high prevalence of HCV infection in this age group (*27*). By the end of 2006, 9 million people had been screened. Of these, 112,000 were found to have HCV infection and 110,000 were found to have HBV infection (*28*). Since most high-risk patients were closely followed before developing HCC, HCC nodules was detected in the early stage in more than 60% of patients in Japan (*29*).

During the past few decades, a series of strategies have been implemented in China to control HBV infection. The "Nationwide Hepatitis B Virus Seroepidemiological Survey" was conducted in 1992 and in 2006 to ascertain epidemiological data on HBV in China (*30*). The "Chinese Chronic Hepatitis B Prevention and Cure Guideline" published in 2005 (revised version published in 2010) and the "2006-2010 National Hepatitis B Prevention and Control Plan" published in 2006 serve to guide clinical practice (*31,32*). In addition, enactment of "Blood Donation Law" and "Law for Licensing Medical Practitioners" and implementation of the "Regulations on Medical Waste Management" and "Administrative Regulations on Medical Institutions" led to further regulation of medical care. Specially, hepB immunization for infants and young children has been widely implemented in China. In 1992, hepB vaccination for infants and young children was included in the "National Hepatitis B Immunization Plan"; since 2002, the hepB vaccine for infants and young children has been subsidized by the Chinese Government; and since 2005, both the hepB vaccine and injection fee have been borne by public health insurance. Due to these efforts, the number of hepatitis B surface antigen (HBsAg) carriers among infants and young children decreased by 19 million from 1992 to 2006 and resulted in a HBsAg prevalence of 0.96% among children under 5 (*30*).

An important point to remember is that most of the implemented strategies focused on prevention, control, and curing of HBV infection in susceptible and high-risk populations. The "2006-2010 National Hepatitis B Prevention and Control Plan" seeks to establish

a national hepB conventional epidemic monitoring system, which includes revising the criteria for hepB diagnosis, to establish a national hepB laboratory testing network, and to conduct periodic evaluations of hepB diagnosis and the hepB laboratory testing network. However, a government-funded nationwide screening and surveillance program for high-risk patients with HBV-related chronic liver disease to promote early detection of HCC has yet to be established in China.

In Japan, the national 5-year program to screen people over 40 for HCV and HBV infection and the routine practice of surveillance of patients at risk of developing HCC resulted in the detection of HCC in its early stages in 60% of patients. Furthermore, the screening tools of ultrasonography, AFP, AFP-L3, and DCP are widely and routinely used to screen for HCC in Japan, and these tests are covered by Japanese national health insurance as serological biomarkers to screen for HCC in clinical settings (*14*). China needs to promptly establish a government-funded nationwide screening and surveillance program for high-risk patients with HBV-related chronic liver disease to promote early detection of HCC.

2.3. *Screening tools and surveillance period for high-risk patients with HBV-related chronic liver disease*

As mentioned before, a government-funded nationwide screening and surveillance program for high-risk patients with HBV-related chronic liver disease to promote early detection of HCC has yet to be established in China. According to the Chinese HCC guideline, AFP should be measured and ultrasound should be performed every 6 months for the HCC high-risk population ages 35-40 (*5*). In terms of cost-effectiveness, a surveillance interval of 6 months has been widely accepted worldwide. In some developed countries with advanced health insurance systems, very high-risk populations are also screened at an interval of every 3-4 months.

Imaging tools and serum tumor markers have been widely used in screening worldwide. Ultrasound is the imaging tool most often used to screen for HCC because it is simple, inexpensive, non-invasive, and allows real-time observation. However, the success of ultrasound depends on the expertise of the physician, the ultrasound equipment available, and the echo texture of the liver, so the actual sensitivity of ultrasound is difficult to assess due to the lack of a definitive standard for HCC (*33,34*). The serum tumor marker AFP is considered a useful and feasible tool for HCC screening and early diagnosis in China. The clinical usefulness of AFP in China has been confirmed by a randomized controlled trial in 2004 that involved 18,816 Chinese patients (*35*). A point to remember is that the sensitivity and specificity of AFP vary widely, and the total AFP is not always specific, especially when HCC is in its early stages (*36,37*). AFP has been found to have a sensitivity of 41-65% and specificity of 80-90% when detecting HCC given an AFP cut-off of 20 ng/mL (*38*). However, up to 50% of patients with HCC have an AFP level below 20 ng/mL (*39*), and elevated levels of AFP are also found in patients with liver diseases other than HCC, including viral hepatitis, at a rate of 10-42% (*40*). Thus, AFP cannot be used as the sole tool to screen for HCC.

Worldwide, a number of studies have looked at DCP. These studies showed that combined measurement of DCP and AFP have a sensitivity of 70-94% and specificity of 62-90%, while combined measurement of DCP and AFP-L3 have a sensitivity of 70-84% and specificity of 62-80% when detecting HCC in the early stage (*41-43*). However, DCP testing is currently approved only in Japan, South Korea, and Indonesia and has not been approved in China. In order to promote the clinical use of DCP in early detection of HCC in China, large-scale, multi-center studies of Chinese patients must be conducted to provide more data and corroborate earlier findings. Accordingly, a program involving 1,500 Chinese patients with HCC and 1,000 Chinese patients without HCC was launched by the Japan-China Joint Team for Medical Research and Cooperation on HCC in 2012 to assess the clinical usefulness of DCP in Chinese patients through a large-scale, multi-center study. Of these patients with HCC, more than 80% had HBV infection. The program found that there was no significant correlation between serum levels of DCP and AFP; DCP has a total sensitivity of 74% while the combined measurement of DCP and AFP could result in a sensitivity of 83%, which is higher than DCP or AFP alone. DCP could result in a specificity of 56% with a cut-off value of 40 mAU/mL and a specificity of 94% with a cut-off value of 100 mAU/mL (*8,14,44*). These findings provide a better perspective on the use of DCP to detect Chinese cases of HCC in their early stages. Moreover, many studies recommend that DCP be used to assess HCC progression, potentially indicating HCC recurrence after curative therapy, predicting the presence of vascular invasion and allowing the identification of recipients of liver transplants, and facilitating the development of new chemotherapeutic strategies for treating HCC (*45-48*). Thus, extensive use of DCP is expected, especially given the fact that China accounts for 55% of HCC cases worldwide.

3. Conclusion

China accounts for 55% of all HCC cases worldwide. Approximately 85% of these cases are HBV-related, and most patients with HCC present with advanced-stage disease, thus reducing the chance for curative treatment. In Japan, the establishment of standardized HCC management, implementation of a nationally

funded 5-year program to screen people over 40 for HCV and HBV infection and the routine practice of surveilling high-risk patients for HCC using ultrasound, AFP, AFP-L3, and DCP resulted in detection of HCC in its early stages in 60% of patients. In China, the established Chinese HCC Guideline lacks recommendations supported by data. This is particularly true of recommended strategies for the screening and surveillance of high-risk patients with HBV-related chronic liver disease. A government-funded national program to screen for high-risk patients with HBV-related chronic liver disease has yet to be established. In addition, AFP is the only serum biomarker that has been widely used to screen for and diagnose HCC in China. In the current work, analysis of the current status, challenges, and prospects for the future of early detection of HCC in China indicated the need for a systematic HCC guideline for the standardized management of HCC, implementation of a government-funded nationwide screening and surveillance program for high-risk patients with HBV-related chronic liver disease, and the extensive use of DCP as a screening tool in China in order to facilitate the early detection of HCC in China.

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