Chen *et al. Hepatoma Res* 2019;5:12
DOI: 10.20517/2394-5079.2019.03

Hepatoma Research

Review

Open Access

Liver cancer screening in China: practices and its extended questions

Jian-Guo Chen[1,2], Yong-Hui Zhang[1], Ling-Ling Lu[1], Hai-Zhen Chen[2], Ai-Guo Shen[2], Yuan-Rong Zhu[1]

[1]Department of Epidemiology, Qidong Liver Cancer Institute, Qidong 226200, China.
[2]Department of Epidemiology, Cancer Hospital/Institute, Nantong University, Nantong 226361, China.

Correspondence to: Prof. Jian-Guo Chen, Department of Epidemiology, Qidong Liver Cancer Institute, Qidong 226200, China; Cancer Hospital/Institute, Nantong University, Nantong 226361, China. E-mail: chenjg@ntu.edu.cn

How to cite this article: Chen JG, Zhang YH, Lu LL, Chen HZ, Shen AG, Zhu YR. Liver cancer screening in China: practices and its extended questions. *Hepatoma Res* 2019;5:12. http://dx.doi.org/10.20517/2394-5079.2019.03

Received: 7 Jan 2019 **First Decision:** 6 Mar 2019 **Revised:** 3 Apr 2019 **Accepted:** 3 Apr 2019 **Published:** 26 Apr 2019

Science Editor: Guang-Wen Cao **Copy Editor:** Cai-Hong Wang **Production Editor:** Huan-Liang Wu

Abstract

Screening for liver cancer (hepatocellular carcinoma) in China started in early 1970s with the application of alpha-fetoprotein (AFP) in high-incidence regions. It has been extended to nationwide areas, emerging from the concepts of conducting screening in populations at-risk with positive hepatitis B surface antigen to the practice programs in rural and urban areas, and finally to the development of recommendations to guide medical practice for health care providers. The implementation of screening for liver cancer has resulted in earlier detection and hence the early curable treatment for patients who have gained short- or long-term survival, and even reduction in mortality rates, although these outcomes are more anecdotal than rigorously evidence-based. AFP or ultrasound examination has been considered as sensitive and specific methods for early detection but are with limitations. The combined use of these two modalities for screening populations at-risk every six months seems to have been reached consensus. The feasibility of screening for liver cancer is still debated because of differing opinions and even opposition to the choice of targeted sub-populations, the intrinsic necessity, and the contributions of the main risk factors among Western countries and China/Asian areas. Yet, the over 51% of global burden of liver cancer is in China, the solution to the early detection and treatment of liver cancer should fully consider the actual situation in China. The effectiveness of screening for liver cancer is worthy of anticipation.

Keywords: Hepatocellular carcinoma, screening, alpha-fetoprotein, ultrasound, early detection, high risk population

INTRODUCTION

Liver cancer [hepatocellular carcinoma (HCC)] is currently the second leading cause of cancer deaths worldwide, accounting for about 8.2% of the global burden of cancer[1]. China has the most patients with

this disease. Based upon the Chinese Cancer Registry Annual Report 2016, the incidence and mortality rates of liver cancer were 28.17 and 24.70 per 100,000, respectively, thereby contributing to total incident cases of 394 thousand, and total death cases of 346 thousand a year in mainland China[2]. Liver cancer has long been a public health challenge in China. While improvements in therapies for this cancer have been developed widely, and have achieved some progress in the past decades[3-6], the overall survival from liver cancer remains unsatisfactory[5-7]. This outcome is because the choice of treatment is driven by the cancer stage, the resources available, and the level of practitioner expertise[5]. Liver cancer often has no obvious clinical symptoms and signs in its early stages, and the tumor lumps grow quietly and rapidly. Most patients have been detected only in an advanced stage, resulting in limited treatment options and a very poor prognosis. A United States population-based study, for instance, reported that, in 2963 HCC patients diagnosed between 1992 and 1999, only 13% of the patients received a potentially curative therapy[8].

Recent survival rate data show that the 5-year survival rates of liver cancer from population-based cancer registries in China were around 9.8%-12.1%[9], and that the 5-year survival rate of liver cancer from a hospital-based cancer registry was 11.69%[7]. Furthermore, the 5-year survival rate from clinical series of data was 4.8% in 1958-1970, 11.2% in 1971-1982, and 45.4% in 1983-1994 for patients who received surgical resection[10]; and 63.8% for patients who had resection of small liver cancer[11]. The 5-year relative survival rates for liver cancer during 2002-2012 in Taiwan were 52.0% for stage I, 2.9% for stage IV and 28.9% for all stages[12]. A recent Australia report based on cancer registration shows that the 5-year survival was 5% during the years 1984-1993, and 16% during 2004-2013[13]. A current multicenter retrospective investigation shows that the overall survival is 19.6%, and is derived from 18,275 liver resection patients with HCC in China[14].

The fact that small or early stage liver cancer had better outcomes for survival has long been recognized[11], and attracted great efforts for the early detection of liver cancer by mass screening in the general population since the 1970s. In the Qidong area, for instance, population-based mass screening programs were first applied to field practice[15,16] when alpha-fetoprotein (AFP) was established to be synthesized in cancer of the liver, and had been proven to be a serological test for this cancer[17,18].

In the past 4 to 5 decades, the application value of AFP and the screening benefit for early detection has demonstrated the mixed results[15-23]. So far, there is no internationally recognized program of screening for the cancer of the liver, nor has a scientific consensus been formed in the academic world. Yet, case reports and research reports have provided evidence that screening is an effective way to achieve early detection, early diagnosis and opportunity for early treatment for liver cancer. Screening may have positive and important significance to improving prognosis and reducing mortality, especially in epidemic areas of hepatitis B/liver cancer. Here we describe and review the practice of the screening for liver cancer and discuss the problems arising from this approach.

DISCOVERY OF AFP AND ITS CLINICAL APPLICATION

After Bergstrandh and Czan discovered alpha-fetoprotein (AFP) in human fetal serum in the 1950s, former Soviet scholar Abelev discovered that AFP was mainly synthesized from placenta and yolk sac, and correspondingly AFP could be detected in both human and mammalian embryo serum[17,18]. AFP begins to be synthesized at 6 weeks of gestation and peaks at 12-15 weeks (AFP in fetal plasma can reach 3 μg/L). After birth, AFP synthesis is inhibited (content reduced to 50 μg/L); at the end of 12 months, the concentration is close to the adult level. Plasma AFP concentration in healthy adults is lower than 20 μg/L[24]. However, AFP would be re-expressed when hepatocytes become cancerous or have severe injury or other forms of diseases[17,25]. Human hepatic stem cells (*hHpSCs*) are currently considered to express AFP[26].

The probable association of AFP with liver diseases and liver cancer was noted in the 1960s. Tatarinov *et al.*[27] and O'Conor *et al.*[28] found that AFP was detected in the serum of patients with liver cancer; and a human

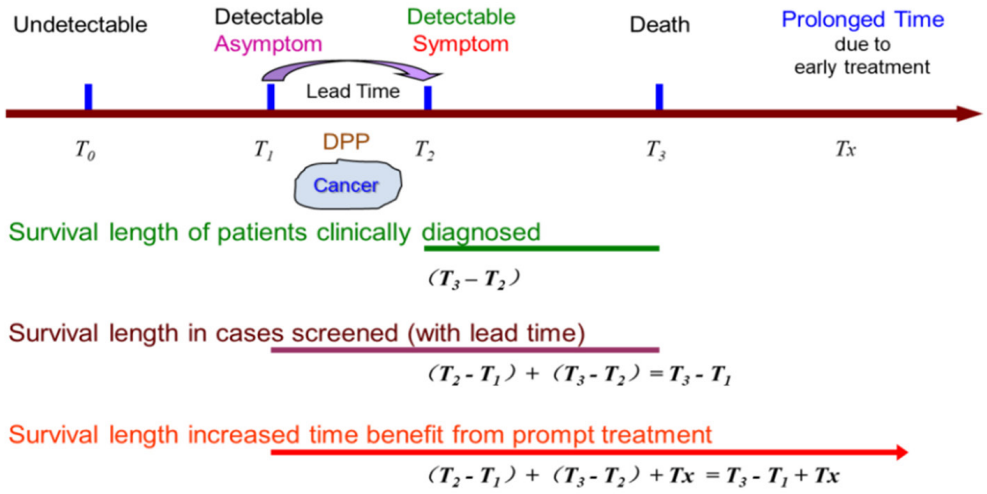

Figure 1. Schema for cancer detection and survival time

AFP variant was isolated in 1970[29]. However, since the relationship between AFP and liver diseases was not very clear, and the incidence of liver cancer in some developed countries was not high, the value of applying measures of AFP in the clinical diagnosis of liver cancer was totally ignored for a long time.

Fortunately, AFP detection technology was quickly introduced to China, and applied in high-risk areas of liver cancer, such as in Jiangsu (Qidong), Guangxi (Fusui), and Shanghai. From 1971-1976, 1,967,511 people were screened for serum AFP in the Shanghai general population: 300 patients with liver cancer were detected, of them, 134 (44.7%) cases were diagnosed as subclinical HCC[30]. During the period of 1974-1980 in Qidong, 1,310,871 people were screened for serum AFP, 499 patients with liver cancer were found, 177 (35.5%) patients being at early stage[15]. These results and subsequent studies have shown that AFP is a useful marker for the early detection of liver cancer[16].

RATIONALE FOR SCREENING

The overarching principles for screening are prevention and early detection. A detectable early cancer stage must exist for reasonable duration of time to allow the screening test to pick it up[31]. Hence screening trials must be based on an understanding of the natural history of the disease. From the view of clinical observation, any disease will have two states: an undetectable disease (normal) state, and a detectable disease state with symptoms or asymptom. Asymptomatically detectable, also known as the "detectable preclinical phase" (DPP)[32], detectable and curable preclinical phase (DCPP)[33], or "pre-clinical detectable phase (PCDP)"[34,35], is the ideal stage for early diagnosis. At this stage, it is possible to detect the disease and even reverse the disease through active and curable treatments. When the cancer was detected in the symptomatic stage, the disease was often developed fully, and showed the medium- or late-stage clinical manifestations. As to screening, a disease that can be detected asymptomatically is a disease suitable for screening. Liver cancer could have abnormal changes of AFP at early phase, vary from several months to several years before the appearance of subjective symptoms, thus providing a possibility for early detection of liver cancer.

In the debate about whether screening can prolong the survival rate of liver cancer, lead time is a key word that cannot be circumvented. Lead time is the time by which diagnosis is anticipated by screening with respect to the symptomatic detection of a disease, or is the time by which the diagnosis has been made in advance by screening[36]. Any screening program, including surveillance for liver cancer, is subject to lead time bias[23,31,35,37-40]. The relation of the lead time, natural survival length, and the prolonged time due to prompt treatment after screening may be expressed as Figure 1.

Assuming that any disease or the carcinogenic process started at T_0, and developed before the time T_1, this evolution process (T_1 - T_0) is undetectable. After the point T_1, the disease (cancer) is asymptomatic but can be detected, until the point T_2, when symptoms occur. This length of time (T_2 - T_1) is called lead time, or "detectable preclinical phase" (DPP), and also "sojourn time". In the absence of any screening test, a patient may be diagnosed as an outpatient due to symptoms and/or signs, and then experiences a natural disease course accompanying the process of healing and rehabilitation until the end of life (T_3 - T_2). Obviously, screening cases will survive with "cancer" for an additional time (lead time: T_2 - T_1); therefore, their full survival time will be (T_3 - T_2) + (T_2 - T_1) = T_3 - T_1, which is "longer" than the survival time (T_2 - T_1) of the outpatient cases. This "increase" in time essentially has no clinical significance for the patient, but it is artificially diagnosed earlier as a cancer. However, the real purpose of screening is to enable timely treatment of cases that are diagnosed early, and hence to prolong the time (T_3 - T_2) benefit from the prompt treatment, whose increment is assumed to be *Tx*. Thus, the survival time of the cases after actual screening is (T_3 - T_2) + (T_2 - T_1) + *Tx*, or, T_3 - T_1 + *Tx*, where *Tx* is the patient's real extension of survival length due to early detection and treatment.

MEANS OF SCREENING IMPLEMENTATION

It is possible to achieve the intended purpose of screening by mastering the principles of screening, identifying the target population for screening, using appropriate tests/examination or diagnostic tools, and relying on reliable and effective treatment. In terms of liver cancer screening, the evidence supporting feasible means of screening in populations at-risk or of specific individuals are summarized as follows.

Major risk factors should be point of focus

Epidemiological studies have confirmed the main risk factors for liver cancer in China, and high-risk areas as well as high-risk groups (populations) of liver cancer can be defined scientifically[5,16,19,41-44]. In accord with recent understanding, the risk factors for primary liver cancer may be categorized into 3 groups[41,45]: (1) established factors: chronic HBV infection, chronic HCV infection, alcoholic cirrhosis, dietary aflatoxins, tobacco smoking; (2) likely factors: diabetes mellitus, inherited metabolic disorders-α-antitrypsin deficiency, hemochromatosis, porphyria cutanea tarda, cirrhosis of any etiology, obesity; and (3) possible factors: decreased consumption of vegetables, oral contraceptives, high parity, ionizing radiation, organic trichloroethylene solvent, clonorchis sinensis infection. However, as a population screening strategy, it is impossible to consider all of these etiological factors or risk factors. Moreover, some characteristics of disease or risk factors need to be confirmed in advance by specific test methods; in addition, factors that are considered "established" and "likely" in some areas may only be "possible", or even "not possible" in other regions. For instance, liver fluke infection may be a "very likely" important risk factor for cholangiocarcinoma (CC) in Southeast Asia and Guangdong-Guangxi regions[46,47]; Hepatitis C virus (HCV) is considered to be the established factors in many countries[48-50], but these factors seem "impossible" in the etiology of liver cancer in some regions such in Qidong, Jiangsu[41,51]. The other example is the nonalcoholic fatty liver disease (NAFLD), which is becoming an increasingly important health issue nowadays in China, with an overall pooled prevalence of 20.09% (17.95%-22.31%)[52]. It is considered as an alarming important risk factor of HCC development[53]. Therefore, population screening in high-incidence areas should be implemented in conjunction with the major local risk factors that can be easily identified within the general population.

AFP could be used as a useful marker

AFP has been shown to be a sensitive and specific marker for screening[17,18,54-57]. In the early stage of liver cancer, abnormal levels (> 20 μg/L) can be detected in serum, which can ensure that most patients with liver cancer have a long enough DPP characterized with positive AFP even 2 years before the clinical presentation of liver cancer[58]. When an AFP cut-off of 20 μg/L is used, the sensitivity and specificity of AFP for HCC were in the range of 41%-65% and 80%-95%, respectively[56,59-61]; and the sensitivity and specificity of AFP would be changed if the cut-off value is modified[56,62]. In Qidong's screening program the sensitivity and

specificity were 55.3% and 86.5%, respectively[19]. A systematic review evaluating AFP in cirrhotic patients with HCV infection showed sensitivities and specificities of 41%-65% and 80%-94%, respectively, for HCC diagnosis[63]. In a Taiwan study, screening with AFP was reported to be feasible screening marker of risk identification, and could result in good prognosis in an aged population[64]. A recent report in a South East Scotland HCC Surveillance Study (January 2009 and December 2014)[65] showed that AFP as an HCC surveillance tool detects a significant number of treatable HCC in patients with satisfactory outcomes. They also found that the use of serum AFP in HCC surveillance has facilitated the early diagnosis of HCC in a large proportion of the patients undergoing HCC surveillance in whom the HCC was otherwise not detected by ultrasound (US) alone, and that AFP should be included in the liver cancer surveillance[66].

US could be used for early detection

The application of US and other imaging modalities facilitate localized diagnosis for liver cancer. In the 1980s, US examination began to be used widely in the clinical detection of liver diseases in China. The advantages of US are manyfold. It is non-invasive, produces no radioactive damage, is easy to repeat, has high sensitivity and at a relatively low cost. US is considered as the preferred method for liver cancer localization in screening[6,67,68]. US has a sensitivity of 60%-80% and a specificity of over 90% when it is done expertly[69]. An early prospective study reported in the United States in 1985[70] showed that in the initial screening for 528 patients, 17 liver cancer patients were found after an average follow-up of 1.4 years. In tumors < 5 cm, AFP levels were normal in 46.2%, 20-400 μg/L in another 46.2%, and only 7.6% were over 400 μg/L. Another 7 patients were found by further follow-up to have cancer varying from 1.6 to 4.7 cm, with normal serum AFP levels in 3 cases. Hence the authors concluded that real-time ultrasonography is more sensitive than AFP assay for the early detection of HCC, and that high-risk subjects should receive this procedure at regular intervals. A randomized trial[71] compared two US periodicities: 3 months *vs* 6 months, in a surveillance of HCC in cirrhotic patients. The results showed that 3-month US detection may find more small focal lesions than 6-months US detection, but does not improve detection rate of small HCC, nor improve the 5-year survival. The efficacy of US screening every 6 months for HCC or CC in a selective high risk group in endemic areas of hepatitis B such as in Thailand, Taiwan have been reported[72-74].

The combined application of AFP and US

AFP or US detection have their limitations. It is a common practice to combine these two methods for HCC surveillance. Many studies using a combined AFP and US surveillance/screening have proven survival benefit to patients by detecting smaller and curable liver cancers[20,55,61,75-78], US combined with AFP for screening for liver cancer is believed to be superior to AFP alone, but periodic US examination would be expensive, while AFP testing is relatively inexpensive[79,80]. At present, computed tomography (CT) and dynamic magnetic resonance imaging (MRI) as robust imaging location techniques for the diagnosis of liver cancer are used widely in clinical practice[81,82]. A prospective randomized study comparing two different HCC screening procedures (biannual ultrasonography vs. annual triphasic CT) with biannual AFP has suggested that biannual US is comparable to annual CT in detecting early-stage HCC, with lower costs[83]. So there is no evidence to support the use of CT or MRI for routine liver cancer surveillance/screening; while its disadvantages are obvious: significant cost and radiation exposure[81,82,84]. Furthermore, findings are frequently discordant even on both CT and MRI[85]. In an Alaskan Native screening cohort study during 1983-2012, the cost-effectiveness of two HCC screening methods (by US-alone, or screening by AFP initially and switching to US) was evaluated[86]. The sensitivity analysis demonstrated that AFP⟶US was more cost-effective than US-alone over a broad range of differences in sensitivity between the two HCC screening methods. It was also pointed out that for many of the patients in rural Alaska, AFP is the only locally available option for HCC screening, and it could potentially identify patients at high risk for HCC who could benefit from referral for a liver US or CT. Thus, public health officials should evaluate the cost-effectiveness of AFP⟶US to increase access to HCC screening for persons living in remote communities

without access to US. A balance between the application of AFP test with or without US in screening should be considered. General speaking, the combination of AFP and US can ensure early detection and improve detection rates, thus enabling early diagnosis for liver cancer[20]. As such, the combined use of US and AFP is recommended[5].

Early detection could lead to curable treatment

Early detection of liver cancer has led to effective early treatment, especially by means of surgical resection, and has led to long-term survival for those treatable patients[11,21,30,76,87], although the lead time due to screening may range from 2 to 6 months (70 to 200 days)[23,37,39]. Based upon a study of surveillance in cirrhotic patients, semiannual surveillance maintained a survival benefit over symptomatic diagnosis after lead time adjustment, and this benefit became durable in a long-term perspective[39]. In a community-based surveillance program[88], significantly improved survival rates were noted in HCC patients detected by surveillance, and in those who received surgical and loco-regional therapies, indicating that HCC patients identified by surveillance were more suitable for surgical and local regional therapies, and would improve survival and should be included as standard of care for patients with hepatitis B. A recent prospective population-based study in Australia[89] showed that increased survival was associated with participation in surveillance programs and curative treatment. The 1-, and 2-year survival rates for surveillance participants were 79% and 66%, compared with 49% and 33%, respectively, for non-participants.

HISTORY OF LIVER CANCER SCREENING IN CHINA

Pioneering start of screening in high-incidence area

The most representative region for liver cancer screening was in Qidong[16,19,90]: from the early 1970s to the early 1980s, a sensitive AFP test was used to detect more than 2 million person-times in the general population from Qidong, including about 1.8 million persons who joined the screening program. More than 1000 cases of liver cancer confirmed by screening, of which early (stage I) cases represented 35%[15]. The practice of screening in this period helped to answer a question of primary importance: could liver cancer be detected at in early stage? - it could be. The application of AFP in population-based screening in the field has demonstrated that it is a simple, easy, sensitive and specific way of detection for liver cancer. A large number of patients with liver cancer at early stage in that period has resulted in the improvement of the overall survival rate[15,16,30].

Formation of concepts of screening for high-risk populations

The large requirements in human resources and financial resources for the mass screening of liver cancer impeded further implementation of screening. Screening in the general population was halted in the 1980s in Qidong and other areas in China. Based on strategic considerations for early detection and early treatment in the high-incidence area, the role of AFP screening were reevaluated, recognizing that the economic benefits of screening through AFP detection are determined by the preferred choice of the target population at high-risk. The specific age (with high incidence rate), gender (males) and risk factors (such as infection with HBV) of liver cancer should be given prioritized consideration for screening[42]. Hence, men aged 30-59 who were positive for hepatitis B surface antigen (HBsAg) were identified as high-risk population of liver cancer in Qidong[90,91]. In the same time, a Shanghai report suggested that screening should be focused on those aged over 35 or 40 with hepatic diseases for more than 5 years and who are positive HBsAg[92].

Practice of screening in high-risk populations

From late 1980s to early 1990s, a selected population of 36,381 males at the ages of 30-59 were screened[19,90,93]. 5581 HBsAg carriers were identified, enrolled and then randomly assigned to a periodical screening group (once every six months) or a control group to investigate the effectiveness of screening for liver cancer. This research program and practice has helped to confirm and optimize a scheme of screening in populations at high risk that includes such indicators for periodic screening as the subclinical mean sojourn time, sensitivity and predicted values, the lead time (DPP) and the best interval of screening for liver cancer[19,93,94].

Table 1. Status of national screening for liver cancer in rural areas (2011-2018)

	No. of screened (areas)	No. of cases detected	Detection rate (%)	No. of early cases	Early detection* rate (%)	No. of treated	Treatment rate (%)
2011.7-2012.6	7,732 (6)	65	0.84	44	67.69	58	89.23
2012.7-2013.6	14,972 (11)	119	0.79	64	53.78	110	92.44
2013.7-2014.6	19,441 (13)	100	0.51	59	59.00	96	96.00
2014.7-2015.6	21,603 (13)	123	0.57	75	60.98	115	93.50
2015.7-2016.6	22,460 (13)	119	0.53	78	65.55	108	90.76
2016.7-2017.6	21,024 (13)	115	0.55	66	57.39	113	98.26
2017.7-2018.6	20,194 (13)	127	0.63	92	72.44	122	96.06
Total	127,426	768	0.60	478	62.24	722	94.01

Data from Ref.[98]. *The diameter of the tumor is less than 5 cm[96]

In the Qidong screening program, the lead time for screened patients with liver cancer was estimated to be 12 months[94]. In an Italian study, after 10-year follow-up, they found that the median lead-time calculated for all surveilled patients was 6.5 months (7.2 for semiannual and 4.1 for annual surveillance). Lead time bias accounted for most of the surveillance benefit until the third year of follow-up after HCC diagnosis[39].

Implementation of the national project on cancer early diagnosis and treatment

In 2004, the China Cancer Foundation launched a project for early diagnosis and treatment of cancer, subsidized by central financial transfer payment program[95], and in 2006, the demonstration project of early detection and early treatment of liver cancer was officially launched in Qidong, Jiangsu Province and in Fusui, Guangxi Zhuang Autonomous Region where screening was carried out in high risk populations, i.e., male residents aged 35-64 and female residents aged 45-64 with positive HBsAg, who should be followed up every 6 months by using repeat monitoring examinations of combined AFP and US. This project has been described in the "Chinese Technical Scheme for Early Diagnosis and Early Treatment of Cancer"[96,97].

CURRENT STATUS AND PROGRESS IN CHINA

Extensions of the screening program

After 2010, in order to meet the requirements for expanding the scale of liver cancer screening, two areas of Haimen, Jiangsu Province, and Tong'an, Fujian Province were included into the National screening project. Later on, Gong'an, Yidu, Yingshan, Dangyang, Honghu, Huangzhou, Jiayu of Hubei Province, Zherong of Fujian Province, Chongzuo, Guigang, Cenxi, Wuming of Guangxi Zhuang Autonomous Region, Zhongshan of Guangdong Province, and Huanchi, Shangdan of Gansu Province, were included into the program as well. At that time there were 19 areas included in the program, but some of them withdrew after one or more years, with 13 counties (cities) remaining nowadays. From 2007 to 2018, individuals with positive HBsAg have been repeatedly screened 146,637 times; 965 liver cancer patients were found/detected. The annual detection rate was 0.66%, the early detection rate was 62.38%, and the treatment rate was 91.09%. Among them, 127,426 high-risk individual-times were screened during the period of 2011-2018, and 768 liver cancer patients were found/detected. The detection rate was 0.60%, the early detection rate was 62.24%, and the treatment rate was 94.01% [Table 1][98].

Cancer Screening Project in Huaihe River Region

A cancer screening program (include liver cancer) was issued by the Bureau of Disease Control of the National Health Commission of the PR China in 2008 which has included Sheyang of Jiangsu Province, Fuyang, Suzhou of Anhui Province, Wenshang of Shandong Province, and Xiping, ShenQiu of Henan Province[99]. Now this program has been increased to 32 counties (cities) in four Provinces, and has screened more than 53,400 person-times. The results on the screening of liver cancer have not been reported.

Cancer Screening Program in Urban China

In 2012, the National Cancer Center of China proposed a Cancer Screening Program in Urban China (CanSPUC), which is also a National Major Medical Reform Project that includes screening for cancers of

the lung, colon-rectum, upper digestive tract (esophagus and stomach), and liver. Residents at ages of 40-69 were enrolled into the screening groups. About one to two medium-sized or more cities in each of 14 Provinces/Municipalities across the country joined the project. During the first 5-year round (2012-2016) of screening, it aimed to cover areas of some 3,500,000 of the population, and to screen about 700,000 individuals at high risk[100]. So far, 42 cities of 20 provinces were included into CanSPUC. However, there have not been any reports to show the findings of the detection rate or the effectiveness of screening for liver cancer, except on medical expenditures for liver cancer in urban China. The CanSPUC program analyzed the medical expenditure for liver cancer during 2002-2011 in urban areas of China[101] and found that the medical expenditure per case for liver cancer diagnosis and treatment was ¥31,020 ($4,528) from the year 2002 to 2011 and ¥35,248 ($5,146) from the year 2009 to 2011, indicating that the economic burden of liver cancer is high in China and the related medical expenditures are increasing.

Recent advances in screening from 2 rural areas

As one of the bases for demonstration of early detection and early treatment of liver cancer, Qidong launched its Special Fiscal Transfer Payment Project of the Central Government in 2006[97]. The screening scheme followed the recommendations of the Expert Committee of Early Detection and Early Treatment by China Cancer Foundation[96,98]. The high risk population screened was defined as those with positive HBsAg at ages of 35-64 for men and of 40-64 for women. Periodically diagnostic screening by using combined methods of AFP and US monitoring were recommended. Since 2007, a target population of 38,016 has been screened in the Qidong area: 3,703 (9.74%) individuals with positive HBsAg were found. Excluding for 29 patients with liver cancer at the initial screening, 3,674 persons in the cohort were followed up until the 31st of March, 2016. The 268 patients with liver cancer were detected from the 33,199 person-times screened, with an annual detection rate of 1.12%. Of them, 186 patients were found via repeated periodic screening (Group A), in which 149 patients were the early cases, with an early detection rate of 80.11%. Some participants with positive HBsAg were not followed by the suggested periodical screening schedule, but they (82 cases) were diagnosed as outpatients within the intervals of screening points (Group B). Calculated by the life-table method, the 1-, 3-, 5-, and 8-year survival of all patients with liver cancer in Group A were 77.16%, 49.04%, 38.53%, and 24.25%, and in Group B were 36.25%, 21.21%, 21.21%, and 0%, respectively, with significant differences between two groups ($P < 0.01$). This finding shows that the screening of individuals at high-risk with semiannual AFP and US detection is effective not only in increasing detection rate of early stage liver cancer but also in improving patients' survival. Ji *et al.*[102] reported another example from Zhongshan, Guangdong Province that started in 2012. The biannual screening also used serum AFP and US examination for subjects positive for HBsAg. Of the 68,510 eligible residents, 17,966 were screened for HBsAg. Within the first 4 years of follow-up, 57 incident cases of liver cancer (43 from 2,848 HBsAg-positive participants, 14 from 15,118 HBsAg-negative participants) were found. Compared with cases (104) identified from non-participants (50,544), the cases detected among screening participants were more likely to be at early stage and had better survival than those among non-participants. The 1-, 3-year overall survival rates for liver cancer cases in the screened group were 48.7% and 29.1%; and in non-screened group were 36.9% and 15.5%, respectively, showing better prognosis in screened group (HR = 0.64, 95%CI: 0.42-0.98, after adjustment for gender and age). However, this screening study did not show a reduction in liver cancer mortality within the first 4 years of follow-up by comparison of the two groups (RR = 1.04, 95%CI: 0.68-1.58).

GLOBAL DISPUTES AND CONSENSUS ON LIVER CANCER SCREENING

Notable randomized trials of screening from China

Whether liver cancer is suitable for screening, or whether screening has a significant effect, has caused much controversy globally. As one of the methods of cancer control, the values of population screening are often disputed because of differences in understanding of goals, benefits, disadvantage, costs, and potential adverse effects of screening, and of disagreements in assessing the effectiveness of screening[103]. Two randomized trials of screening for liver cancer were published in early this century: one from Qidong

in 2003[19], one from Shanghai in 2004[20], in which both screened carriers of HBsAg every 6 months. In the Qidong study, the percentage of cases in stage I were significantly higher in the screening group (29.6%) than in control group (6.0%), showing short survival benefit from screening, but no difference in 5-year survival between the groups. The mortality rate in the screened group (1,138 per 100,000 person-years) was not significantly different from that in the controls (1,114 per 100,000). This trial concluded that screening with AFP resulted in earlier diagnosis of liver cancer, but the gain in lead time did not result in overall reduction in mortality in this reported period. In the Shanghai study, the authors reported that the HCC mortality rate was significantly lower in the screened group (83.2 per 100,000) than in controls (31.5 per 100,000), with a mortality rate ratio of 0.63 (95%CI: 0.41-0.98). It concluded that the biannual screening with combined AFP and US in individuals aged 35-59 years reduced HCC mortality after 5-year follow-up. These two trials have been noticed and/or cited by over a hundred reports or guidelines, irregardless of whether they were in support or opposition to screening[5,8,21,57,68,103-108].

Screening recommendation in Western countries

After China's randomized trials were published, the benefit from screening in people at high risk was noted by professional societies, such as AASLD[21,105,108], simply because of the surveillance/screening for liver cancer had become widely applied, but, there was no evidence of benefit from it worldwide. In these guidelines on management of HCC, the two randomized trials performed in China mentioned above were evaluated. The guideline authors were interesting in the result of HCC related mortality that was reduced by 37% throughout the screening for 18,816 individuals with HBV infection in Shanghai, and added positive comments that these results probably represent the minimum benefit that can be expected from surveillance, because of poor compliance of less than 60%[20]. They also cited the earlier study conducted in Qidong[19] that failed to show long term survival/mortality-reduction benefit due to patients who were diagnosed with liver cancer did not undergo appropriate treatment, and suggested that these results should be validated in other geographical areas, and that assessing the benefits of surveillance by RCT are still considered necessary[21]. Since the recommendation was issued, other guidelines or suggestions have been published[106-110], and various studies have examined physicians' knowledge of or adherence to the guidelines and reported deficiencies and need for improvement[81]. Most gastroenterologists correctly identified the common high-risk scenarios, methods, and interval of HCC screening as recommended by AASLD[111]. A recent systematic review on surveillance detection demonstrated improved survival and increased detection rate of early stage HCC[68]. Forty-seven studies from January 1990 through January 2014 with 15,158 patients were identified, of whom 6,284 (41.4%) had HCC detected by surveillance, being associated with improved early stage detection (OR: 2.08, 95%CI: 1.80-2.37) and curative treatment rates (OR:2.24, 95%CI:1.99-2.52). HCC surveillance was associated with significantly prolonged survival (OR: 1.90, 95%CI: 1.67-2.17), even after adjusting for lead-time bias. It is believed that HCC surveillance is associated with significant improvements in early tumor detection, receipt of curative therapy, and overall survival in patients with cirrhosis[75], and may also reduce the mortality of HCC[20,74].

Debates on screening effectiveness

Although the effectiveness of liver cancer screening has been recognized in the literature and is also included in the AASLD surveillance guidelines for liver cancer[55,21], there have been different opinions and even opposition to the choice of at-risk populations, the necessity, and the effectiveness of screening. Lederle and Pocha[112] were opposed to the existing screening programs by criticizing the 2005 AASLD recommendations for HCC screening[21], arguing that the recommendations were based upon trials from China[19,20], which failed to account for clustering in the analysis (a cluster randomized trial cannot be analyzed at the patient level), hence they state "Ignoring the clustering results in confidence intervals which are too narrow and *P* values which are too small; hence it is likely to produce spuriously significant differences"[57,113]. Furthermore, they questioned the evidence obtained from the study that is not a level I evidence to support the liver cancer screening, and is not necessarily applicable to Western populations because it was conducted in a hepatitis B population in China, and most HCC in West countries and North America is caused by hepatitis

C[21,114]. In an editorial comment in the BMJ[115], Law points out that screening of unproved value should not be advocated, and that before any screening for cancer is introduced, large randomized trials with mortality end points should be conducted to establish and quantify any benefit. Evaluation of mortality of liver cancer in a screening population is a point of concern. A recent matched case-control study within the American Veterans Affairs (VA) health care system found that screening patients with cirrhosis for HCC by US or AFP alone, or both tests was not associated with decreased HCC-related mortality[116]. Some authors thought that randomized screening trials are bothersome, but there is no second-best option[103,112]; others illustrated that RCTs of screening for HCC is difficult and ethically questionable[40], is now not ethically feasible in clinical practice because screening for liver cancer in cirrhotic patients is routine practice for the majority of clinicians[117], even if patients show no interest in such a program[118]. In addition, the AFP use in screening has long been criticized because of its lower sensitivity and specificity than imaging modalities[60,119]. In the European clinical practice guidelines for HCC, US was seen as the most appropriate test to perform surveillance, but the combination with AFP is not recommended[108]. A meta analyses showed that AFP provided no additional benefit to US[69], while others concluded that there is not enough evidence to support or refute the value of AFP or US screening, or both, of HBsAg positive patients for HCC[120]. More emphatically, early in this century, it has been stated that "the time has come to bid a fond adieu to AFP"[121,122], or it is "the demise of a brilliant star"[123], as a test for HCC diagnosis and particularly for HCC surveillance.

Consensus on liver cancer screening

Despite the large debate over liver cancer screening, there is still much consensus on many of the relevant aspects of screening. For example, it is emphasized that the cancer screened must have DPP, or the cancer should be detected early by better sensitive and specific methods; moreover, the appropriate effects of the screening results can be evaluated, and could prolong the survival and may reduce mortality[20,124,125]. Many guidelines for the management and monitoring of liver cancer have been issued around the world; for example, they are available in the United States, Europe, and Asia[105-110]. However, evaluation of current liver cancer screening has not been carried out in a large scale because there is no consensus on the best strategy for liver cancer screening. On the other hand, it also believed that there is an urgent need to improve the strategies of screening and monitoring for liver cancer, in order to detect early stage liver cancer and improve the survival rate of patients[37,57]. The current problem is that, compared to other cancers, the development of globally accepted guidelines seems to be less relevant due to the existence of regional differences in etiologies underlyhing the resultant tumor biology as well as the resources available for management of liver cancer[126]. However, in recent years, research and practice of targeted liver cancer screening, screening methods and time intervals have become consistent and reached a point of consensus. For example, screening should be performed in high-risk populations[19,20,22,43,44,72,87,93,108,127]; chronic hepatitis B is a high-risk population of liver cancer[128]. The cost effectiveness of screening will be principally related to the sensitivity and specificity of the surveillance tools, as well as the efficacy of treatment[123], and surveillance is deemed cost-effective if the expected HCC risk exceeds 1.5% per year in patients with hepatitis C and 0.2% per year in patients with hepatitis B[105]; The screening methods used included AFP and US, with a recommended interval of 6 months[5,19,20,54,55,59,66,75,76,86,108,129-131]. In a two-stage screening intervention in Taiwan, potential cost-effectiveness compared with opportunistic screening in the target population of an HCC endemic area is reported[132].

PROSPECTS FOR LIVER CANCER SCREENING

Although there is currently no internationally recognized program for the screening for liver cancer, except for some aspects of the consensus, in the past decades China has experienced many screening trials[15,19,20,90,93,97,100,102], which have fully demonstrated the Chinese characteristics (most patients are HBV-related liver cancer) and the need for the management and control for the one of its most common malignancies. Professional societies in Western countries had proposed recommendations and guidelines

on this special issue[108], although in the recent American Cancer Society Guidelines, the screening for liver cancer is not mentioned[133]. Even in China, there are several clinical practice guidelines for liver cancer[134]. Therefore, any users of these guidelines should be aware that the recommendations are intended to guide clinical practice in circumstances where all possible resources and therapies are available; hence, they should adopt the recommendations in the context of their local regulations and/or team capacities, infrastructure and cost-benefit strategies[108,129]. Liver cancer nowadays is the second leading cause of cancer deaths worldwide, accounting for about 8.1% of the global burden of cancer, in which China represents its 51% of this burden[1]. The global solution to the early diagnosis and treatment of liver cancer should fully consider the actual situation in China. We present some suggestions in summary for liver cancer screening/surveillance.

Combined use of US and AFP are recommended

So far, AFP remains an effictive screening tool or marker for liver cancer detection, especially in undeveloped countries/areas, on Asia, and even in some areas in developed countries[55-57,65,80,86], because there is no a single "all-in-one" biomarker that fits all-surveillance, diagnosis, or prediction of prognosis[62]. In order to improve the sensitivity and specificity of screening and prevent missed diagnosis, the combination use of US and AFP test are strongly recommended. Since about 30% of liver cancers are negative for serum AFP, novel diagnostic markers need to be established[56]. There are no data to support the use of multidetector CT or dynamic MRI for surveillance[108], but one report[133] showed that the sensitivity estimates of CT and MRI for liver cancer detection were 0.70 and 0.86, respectively, and the combined use was 0.94. CT or MRI could be used for patients with cirrhosis and those suspected cases (such as with AFP positivity) requiring further clinical ascertainment[57,130,135].

Novel diagnostic markers are urgently needed

In addition to AFP (AFP-L3), DCP, GPC3, GP73, AFU, GGT and others are still recommended as markers for monitoring and diagnosis of liver cancer; DKK1, MDK, and microRNA are also being used as new markers[55,56,62,61,136-141]. For instance, a European study found that osteopontin (OPN) is a promising marker for early detection of HCC[142]. In this study, each of 100 HCC cases was matched with 2 controls. Conditional logistic regression model was used to calculate the multivariate OR and 95%CI for OPN levels in relation to HCC. The results showed that OPN levels were positively correlated with HCC risk: the multivariate OR was 1.30 (1.14-1.48) for every 10% increase. For cases diagnosed within 2 years, the combination of OPN and AFP was best able to predict the risk of HCC, indicating that the measurement of OPN and AFP could independently identify high-risk groups in liver diseases. In order to make up for the deficiency of sensitivity and specificity of diagnostic markers such as AFP, novel early diagnosis and early precursory (predictive) markers are urgently needed for research-development and verification.

Translating early detection to effective curable treatment

According to the current economic conditions and medical conditions (especially in undeveloped countries/areas), screening in high-risk groups of liver cancer every 6 months is particularly appropriate and acceptable. The key for a successful screening program should be a focus on individuals at high risk, conducting repeated or periodical screening and follow-up. Some authors may suggest patients with HCV, NAFLD or with cirrhosis should be screened, but so far there are no data from randomized trials of surveillance to evaluate effectiveness[5]. Liver cancer patients found in screening who fail to receive timely treatment will not improve survival and mortality. Any guidelines for screening on liver cancer should emphasize not only the early detection of liver cancer but also access and uptake of early curable or life-extending treatment.

Effectiveness of screening is in anticipation

For evaluating the efficacy of population-based cancer screening modalities, the reduction of mortality rate within the screened population is the gold-standard indicator[20,72], but it should not be a mandatory

requirement, since these outcomes will not be observable for many years[143]; survival rate change is indeed a necessary indicator. Any benefits and risks should be compared and reviewed before adopting a certain method of screening[57,117,144]. If the risks outweigh the benefits, it cannot be regarded as effective and is therefore not recommended. The surveillance adherence rates should be increased and improved[40,145], and should be supported by patients, providers, and health care systems/governments[37]. From the perspective of public health, cost-effective evaluation should be considered, and the benefits and risks of screening should be compared, as well[31,86,144,146]. Obviously, benefits of liver cancer screening, at least in terms of greater benefits than harms from the surveillance, have been evident so far.

CONCLUSION

The success of screening depends on having sufficient numbers of personnel to perform the screening tests by using the technology appropriately or to achieve adequate coverage of the population, and on the availability of facilities that can undertake subsequent diagnosis, treatment, and follow-up, as has been addressed by the WHO[147]. The bulk of available evidence suggests that screening for liver cancer is beneficial, certainly benefits outweigh harms. Inasmuch as symptomatic presentation of liver cancer has an almost universally fatal outcome, screening for liver cancer is an appropriate method that could be used to detect early stage liver cancer in China and other endemic countries/areas where liver cancer burden is substantial. The combined use of AFP and US for liver cancer screening, in the view of its relative cost-effective or applicability in community/population-based screening, are recommended while other novel markers or techniques remain to be developed. High risk individuals with established risk factors (etiological) and or characteristics (clinically identified) are the target populations; and opportunities for screening at-risk persons is to be encouraged even in regions with financial and medical limitations. Only in this way will it be possible to find more early and curable liver cancers.

DECLARATIONS

Acknowledgments

The authors would like to thank Prof. Thomas W. Kensler at Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington for his useful comments and language editing.

Authors' contributions

Design of the work, data analysis and interpretation: Chen JG
Data acquisition, material support: Chen JG, Zhang YH, Lu LL, Chen HZ
Provided administrative, technical support: Shen AG, Zhu YR
Wrote the manuscript: Chen JG, Shen AG

Availability of data and materials

Not applicable.

Financial support and sponsorship

This work was supported partially by the China Cancer Foundation Program, and by Chinese National Key Projects (2012ZX10002009, 2018ZX10732202-001).

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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