Surveillance for Hepatocellular Carcinoma

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Module 2:	Evaluation, Staging, and Monitoring of Chronic Hepatitis C
Lesson 6:	Surveillance for Hepatocellular Carcinoma

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Epidemiology

Global Epidemiology of Liver Cancer

In 2020, hepatocellular carcinoma (HCC) was the seventh most common malignancy worldwide, with approximately 900,00 cases, and the second leading cause of cancer-related death (Figure 1).[1] The rates of liver cancer are highest in Asia and in Notherrn Africa.[1] Among all cases of liver cancer globally, the rates are much higher in males (14.1 per 100,000 people) than in females (5.2 per 100,000 people).[1]

Epidemiology of Liver Cancer in the United States

In the United States, the National Cancer Institute (NCI) data for “liver cancer” combines liver and intrahepatic bile duct carcinoma.[2] Liver cancer data for the United States, including trends and demographic features, are shown in (Figure 2) below.[2] The annual reported rate of liver cancer in the United States has changed significantly in the past 30 years. In 1992, the rate of new cases of liver and intrahepatic bile duct carcinoma was 4.46 per 100,000 persons, but this increased steadily to a peak of 9.38 cases per 100,000 persons in 2015, followed by a decrease in recent years.[2,3] In 2023, there were an estimated 41,210 new cases of liver and intrahepatic bile duct carcinoma reported in the United States, accounting for 2.1% of all new cancer cases.[2] The significant increase in HCC incidence in the United States over the past 30 years has been largely attributable to HCV-related HCC.[4] Rates of liver cancer in the United States show major differences based on sex, age, and race/ethnicity.[2] Data from 2000 to 2020 showed rates of liver and intrahepatic bile duct carcinoma in the United States are consistently higher in males than females.[2] Most of the cases of liver and intrahepatic bile duct carcinoma have occurred in persons 55 to 74 years of age, with a median age of 66 years for persons newly diagnosed with liver cancer.[2] There are significant differences in new liver cancer diagnoses based on race/ethnicity, with the highest rates among American Indian/Alaska Natives and Hispanic people.[2] From 2016-2020, liver and intrahepatic bile duct cancer was the sixth leading cause of cancer death in the United States, and the median age of those who died was 68 years.[2]

Risk Factors and Prognosis

Risk Factors

Cirrhosis from any cause is the primary risk factor for HCC: approximately 80% of cases of HCC occur in individuals with cirrhosis and the risk of developing HCC increases with fibrosis stage.[5,6] The most common underlying etiologies for HCC include chronic viral hepatitis (B or C), alcoholic liver disease, and metabolic-associated steatotic liver disease (MASLD).[7] Chronic hepatitis B or C accounted for more than two-thirds of the global deaths from primary liver cancer each year between 1990-2019. In recent years, the attributable risk of HCC incidence has been shifting in the era of antiviral therapy, with a slightly lower contribution of chronic HBV or HCV in higher-income countries in recent years.[7] Persons with chronic HCV infection and cirrhosis have a 1 to 4% annual risk of developing HCC.[8] The risk of developing HCC among persons with HCV increases with substantial alcohol intake in a dose-dependent linear fashion if daily alcohol intake is greater than 60 g (approximately 6 cans of beer, shots of liquor, or glasses of wine), for both men and women.[9] Diabetes has also been identified as a risk factor for HCV-associated HCC.[10] Less frequently cited risk factors for developing HCC include stage 4 primary biliary cirrhosis, hemochromatosis, glycogen storage disease, Wilson’s disease, alpha-1-antitrypsin deficiency, and acute intermittent porphyria.[11,12,13]

Prognosis of Persons Diagnosed with HCC

The overall prognosis for persons diagnosed with HCC in the United States has improved in the past 15 years, but it remains poor, with an overall 5-year survival of approximately 22%.[2] In general, persons who have HCC detected after the onset of symptoms have an even worse prognosis, with an overall 5-year relative survival of less than 10%.[2,6] Symptoms associated with HCC may include abdominal pain, anorexia, early satiety, weight loss, obstructive jaundice, fever, watery diarrhea, and bone pain (from metastases). In contrast, detection of very early-stage HCC can be cured with an excellent long-term prognosis.[12] Unfortunately, the vast majority of individuals diagnosed with HCC have cancer that is advanced beyond the stage where surgical cure with surgical resection or locoregional ablative therapy is an option.

Benefit of HCC Surveillance with HCV Infection

Rationale for HCC Surveillance

The rationale for conducting HCC surveillance is that regular screening of asymptomatic persons at risk for HCC may detect tumors at an early stage when potentially curative treatment can be offered.[6,12,14,15] Early detection of HCC is particularly important, given the very poor prognosis with lesions that are detected late.[6,12,16]

Definition of Screening and Surveillance

By definition, screening a person for HCC means they have no symptoms related to HCC. With screening, the person is asymptomatic but undergoes testing in order to detect HCC early and before the development of symptoms.[14] Surveillance is the process of serial application of the screening test to detect the presence of HCC before it becomes clinically suspected or evident.[14] In addition, the term surveillance has been used to describe regular clinical monitoring in individuals who already have cancer. For the purposes of this topic, we will refer to HCC surveillance as the activity of screening persons who do not have a known diagnosis of HCC.

Evidence Supporting Surveillance with Chronic Hepatitis

The main body of evidence to support HCC surveillance is a single-cluster, randomized, controlled trial that assessed the impact of HCC surveillance on HCC-related mortality; this study enrolled 18,816 individuals in urban Shanghai, China, 35 to 59 years of age, with HBV infection or chronic hepatitis from another cause.[17] The investigators randomized 300 units (factories, businesses, schools) 1:1 to undergo HCC surveillance (with serum alfa-fetoprotein (AFP), with cutoff value 20 ng/mL, and ultrasound every 6 months) versus usual care.[17] Overall, approximately two-thirds of the individuals enrolled had documented positive HBsAg; infection with hepatitis C virus was not assessed.[17] The screening group had only 58% compliance with screening, but notably had HCC diagnosed at an earlier stage and had a reduction in HCC-related mortality when compared with the control group (Figure 3).[17] Since most of the persons in this study had chronic hepatitis B virus (HBV) infection, it is not the ideal study to support screening in persons with chronic HCV; it is, however, the largest prospective study of HCC screening in any population and provides evidence for screening in the hepatitis B population. There are also multiple observational trials and systematic reviews involving persons with cirrhosis that have shown surveillance for HCC was associated with earlier-stage tumor detection and improved survival.[18,19,20] Unfortunately, in addition to these data not being specific for HCV-associated cirrhosis, many of these studies did not adjust for liver disease severity or lead-time or selection bias. One meta-analysis of 59 studies, however, demonstrated improved early-stage detection and overall survival with HCC surveillance even after adjusting for lead-time bias.[21]

HCC Surveillance with HCV Infection

To date, there have been no published randomized, controlled trials that have evaluated HCC screening specifically in persons with chronic HCV infection and cirrhosis. This is likely to remain the case given the established role of HCC surveillance in routine clinical care. Direct-acting antiviral (DAA) therapy has transformed the HCV treatment landscape, with a growing number of individuals achieving sustained virologic response (SVR). Treatment of HCV with DAAs can significantly reduce but not eliminate the risk of HCC in individuals with HCV-associated cirrhosis.[22] Research is evolving as to whether HCC surveillance can be further fine-tuned to risk-stratify the growing population of individuals with cured HCV who have a range of HCC risk, but until then, even those with cleared HCV and cirrhosis are recommended to undergo surveillance (as discussed further in this lesson).[23]

Indications for HCC Surveillance

Indication for HCC Surveillance

In 2023, the American Association for the Study of Liver Diseases (AASLD) issued updated Hepatocellular Carcinoma guidance.[24] The 2023 AASLD HCC Guidance recommends all adults with cirrhosis of any etiology should have surveillance for HCC because surveillance improves survival and increases the detection of early-stage HCC.[24] This guidance also emphasize the importance of antiviral therapy in the prevention of HCC, noting the reduced risk of HCC in patients with sustained HBV viral suppression and HCV clearance.[24] To this end, the updated guidance recommends against routine use of HCC surveillance in patients with HCV post-SVR with advanced fibrosis (without cirrhosis), but continues to recommend surveillance post-SVR in persons with cirrhosis.[24] Other guidelines, however, recommend performing HCC surveillance in persons with chronic HCV infection who have developed advanced fibrosis or cirrhosis (Metavir stage 3 or 4).[25] Persons with unknown cirrhosis status (or unknown stage of liver fibrosis), should undergo evaluation for liver fibrosis staging, especially given the availability of improved noninvasive options for evaluating hepatic fibrosis.[26,27] For persons with chronic HCV and cirrhosis, achievement of sustained virologic response (SVR) with direct-acting antiviral (DAA) therapy reduces the risk of HCC by 71 to 79%.[28] Although the risk of HCV-related HCC decreases following successful treatment and cure of HCV, the risk of HCC is not eliminated.[28,29,30,31,32] Accordingly, individuals with chronic HCV infection who are undergoing HCC surveillance should continue to do so, even if they achieve a sustained virologic response following treatment of HCV.[33]

Indications for HCC Surveillance in Persons with HBV and HCV Coinfection

Since a significant number of persons with chronic HCV also have coinfection with HBV, it is important to review current recommendations for HCC surveillance in persons with chronic HBV infection. In general, HBV has a significantly stronger oncogenic potential than HCV. The 2023 AASLD HCC Guidance recommends HCC surveillance for the following groups of HBsAg-positive persons:[24]

- All persons with cirrhosis
- Men from an endemic country who are older than 40 years of age
- Women from an endemic country who are older than 50 years of age
- Persons who are from Africa (can be initiated as early as third decade of life)
- Persons with a first-degree family member with a history of HCC
- Persons with a PAGE-B score >10 (requires use of PAGE-B calculator)

Surveillance Testing Methods

Biomarker Serologic Tests

- **Alpha-Fetoprotein (AFP)**: Alpha-fetoprotein (AFP) is the most widely used biomarker for HCC surveillance, but this test has a sensitivity of only 47 to 64% and a specificity of 82 to 95% for detecting HCC among persons with HCV infection. The test alone clearly performs suboptimally compared with hepatic ultrasound for HCC surveillance.[34] The poor sensitivity results primarily from the lack of uniform secretion of AFP by all HCC tumors.[35] The lower specificity occurs because AFP can often be elevated above the upper limit of normal in persons with advanced fibrotic liver disease but without HCC.[36] Some experts have suggested that AFP can be useful for the diagnosis of HCC if the level is elevated at a higher threshold, but very few individuals have markedly elevated AFP levels at screening, thereby reducing the sensitivity of this maker if a high threshold is used. There are, however, data to suggest that the addition of AFP to ultrasound has incremental benefit for improved sensitivity to ultrasound surveillance alone.[37,38]
- **Des-gamma-Carboxy Prothrombin (DCP)**: Des-gamma-carboxy prothrombin (DCP) has been used widely in Japan for HCC diagnosis and surveillance.[39] The protein DCP is an abnormal prothrombin molecule that forms in malignant cells as a result of an acquired defect in the posttranslational carboxylation of the prothrombin precursor; this prothrombin defect in malignant cells is similar to the deficit in vitamin K deficiency and DCP is also known as the Protein Induced by Vitamin K Absence (PIVKA).[40,41] Experience with DCP in Western countries, particularly the United States, remains limited. In a large study involving persons with chronic HCV infection and cirrhosis, investigators examined DCP, AFP, and the combination of DCP and AFP, but none of these strategies showed adequate sensitivity and specificity to justify the use of DCP (with or without AFP) as a routine surveillance test.[39]

Radiographic Imaging

- **Hepatic Ultrasound**: Hepatic ultrasound, when performed by an operator with expertise, has a sensitivity of 60 to 80% and specificity greater than 90% for overall detection of HCC at any stage.[6,38,42] The sensitivity for detecting early-stage HCC is significantly lower, in the range of 45 to 60%.[38,43,44] When using hepatic ultrasound for HCC surveillance in persons with cirrhosis, screening every 6 months increases the detection rate of very early hepatocellular carcinomas and reduces the number of advanced tumors when compared with screening every 12 months.[45] It does not appear that routine screening every 3 months with ultrasound provides a significant benefit over every 6-month screening.[46] The clinician’s order for the hepatic ultrasound should designate the purpose of the ultrasound as a screening test for HCC. The interpretation of ultrasound is operator-dependent and can be difficult in persons who are obese or have underlying cirrhosis, particularly those with nodular cirrhosis. If a nodule less than 1 cm is detected, the recommendation is to increase the frequency of surveillance to every 3 months; if the lesion remains unchanged for 2 years or longer, the surveillance frequency can return to every 6 months.[24] If a nodule larger than 1 cm is detected, further testing should be performed with either multiphasic computed tomography (CT) or multiphasic magnetic resonance imaging (MRI).[24]
- **Computed Tomographic Abdominal Scan**: No current evidence exists for the routine use of computed tomographic (CT) abdominal scanning as a routine surveillance test for HCC. For persons with a liver nodule greater than 1 cm detected on ultrasound, a 4-phase (unenhanced, arterial, venous, and delayed) contrast CT scan of the liver can be of diagnostic value.[24] During the arterial phase, HCC lesions enhance more intensely than the surrounding liver, but the opposite is observed during the venous and washout phases (where HCC lesions have little enhancement). The characteristic finding of HCC is the presence of arterial hypervascularity (uptake) in the lesion followed by venous or delayed phase washout. The role of a multiphasic CT scan in the diagnosis of HCC is particularly important since many experts rely on CT or magnetic resonance imaging findings to establish the diagnosis, without the need for liver biopsy, if characteristic radiographic findings for

HCC are present in a person at risk for HCC.

- **Magnetic Resonance Imaging (MRI)**: Similar to recommendations for abdominal CT scanning, no current evidence exists that supports a recommendation to use a hepatic MRI as a routine surveillance test. For persons with a nodule greater than 1 cm detected on ultrasound, a contrast-enhanced multiphasic MRI is recommended as a diagnostic test.[24] This should be distinguished from the use of MRI as a screening test since current guidelines do not recommend MRI as a screening test.

Guidance for HCC Surveillance

Slight differences exist between various practice guidelines for HCC surveillance recommendations, as described below, but the general approach for HCC surveillance is similar.

2023 AASLD Hepatocellular Carcinoma Guidance

The 2023 AASLD HCC Guidance recommend HCC surveillance in all adults with cirrhosis, using abdominal ultrasound and serum AFP at a frequency of approximately every 6 months.[24] This is a notable change from prior AASLD HCC guidelines, where the option of adding AFP was left to the provider's discretion, given limited data.[47] For adults with suspected HCC based on a screening test result, the guidance recommends further evaluation with either a multiphasic CT or multiphasic MRI.[24] The 2023 AASLD HCC Guidance recommends against screening persons with stage 3 fibrosis (without cirrhosis), following HCV clearance with DAA treatment, but do not provide guidance on whether to screen those with stage 3 fibrosis and untreated HCV infection.[24]

Implementation of HCC Surveillance

In the United States, several potential barriers exist for effective HCC surveillance in persons with chronic HCV, including unknown fibrosis stage of the individual, lack of clinician awareness of HCC screening guidelines, scheduling logistics, and cost of surveillance.[48,49,50] Since current guidelines for persons with chronic HCV recommend HCC surveillance only for those with cirrhosis, clinicians must first accurately identify which individuals meet these criteria. In one study of the implementation of HCC screening in the Veterans Health System that was conducted between 1998 and 2005, investigators identified 126,670 persons with HCV infection, 10.1% of whom had cirrhosis.[51] Among those with cirrhosis (with at least 2 years of follow-up), routine HCC surveillance occurred in 12.0%, inconsistent surveillance in 58.5%, and no surveillance in 29.5%.[51] A contemporary assessment of HCC screening practice in the DAA era has not yet been done, but it would clearly need to account for the growing population of individuals who have cleared their HCV yet still have cirrhosis and who are aging with their liver disease.[52]

Summary Points

- Cirrhosis (Metavir stage F4 fibrosis) is the most important risk factor for developing HCC in persons with chronic HCV infection.
- In the United States, the incidence of HCC has steadily increased, and this rise is primarily attributed to the expanding prevalence of HCV-related liver disease and aging of the population living with chronic HCV.
- Persons who develop HCC and live in the United States have a poor prognosis, with an estimated median 5-year survival duration of approximately 22%.
- Potentially curative therapies for early-stage HCC include locoregional ablative therapy, hepatic resection, or liver transplantation. The primary goal of HCC surveillance is to detect disease in an early stage and, therefore, increase the likelihood of potentially curative therapy.
- The AASLD HCC Guidance recommends surveillance for HCC in all adults with HCV and cirrhosis, using abdominal ultrasound and AFP at a frequency of approximately every 6 months.
- In persons with advanced fibrosis or cirrhosis, successful HCV treatment with DAA therapy can lower HCC risk by 71 to 79%.
- Despite the greatly reduced HCC risk from an SVR, the risk is not eliminated, and clinicians should not stop HCC screening in persons after SVR is achieved. For persons who qualify for HCC screening, the screening should continue after SVR is achieved, and this message should be emphasized to these individuals.

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Figures

Figure 1 (Image Series) - Global LIver Cancer Epidemiolgy (Image Series) - Figure 1 (Image Series) - Global LIver Cancer Epidemiolgy
Image 1A: 2020 Global Cancer Incidence Estimates

This graphic shows estimates for the number of global cases of cancer, by type of cancer in 2020. Globally, an estimated 905,677 persons had a diagnosis of liver cancer in 2020.

Source: Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71:209-49

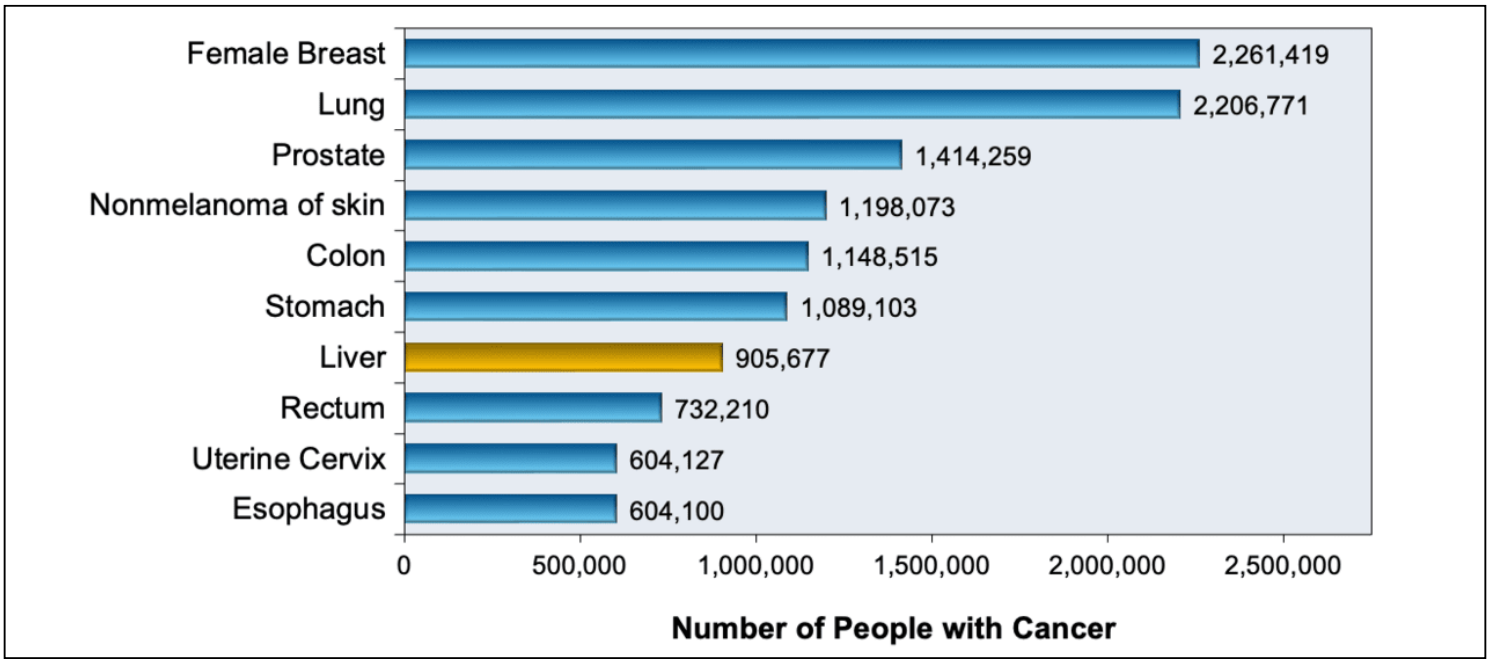


Figure 1 (Image Series) - Global LIver Cancer Epidemiolgy
Image 1B: 2020 Global Cancer Death Estimates

This graphic shows estimates for the number of global cancer-related deaths, by type of cancer in 2020. Globally, an estimated 830,180 persons died of liver cancer in 2020.

Source: Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71:209-49.

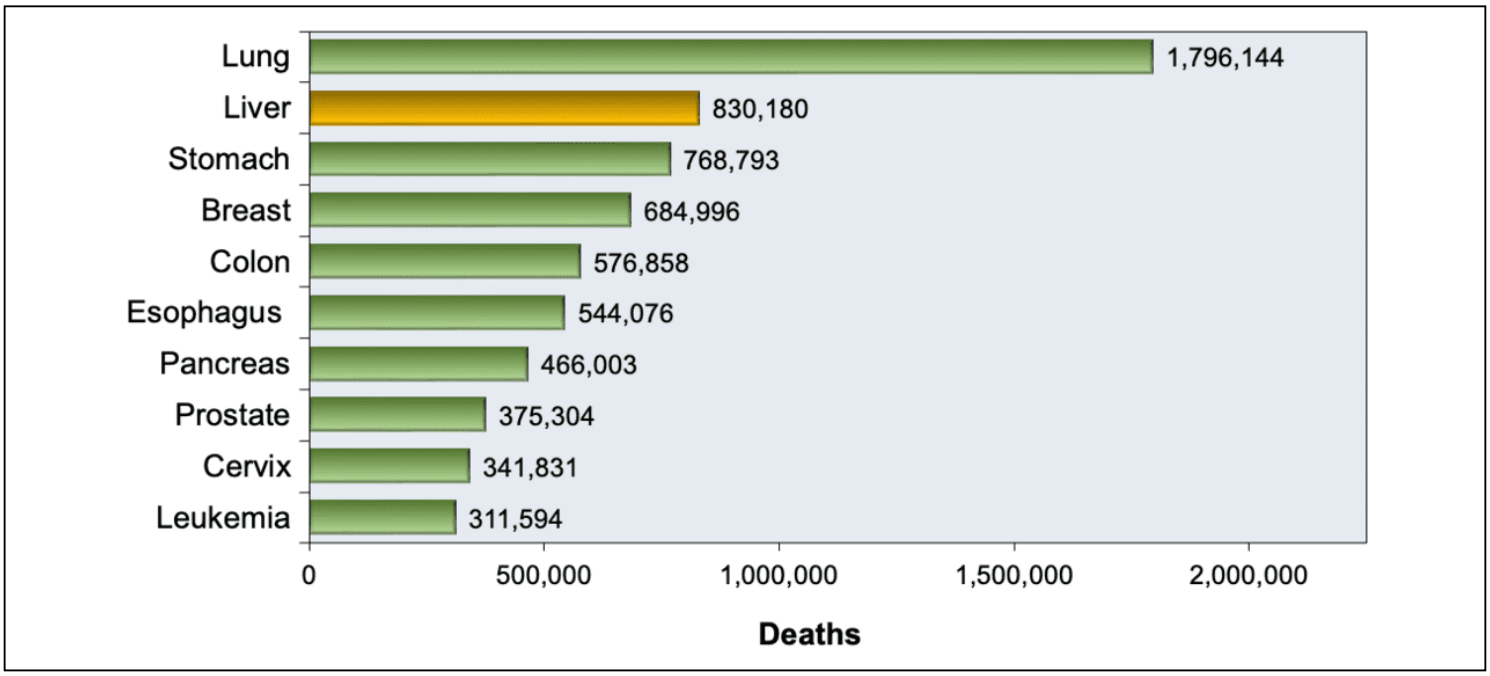


Figure 2 (Image Series) - Liver Cancer in the United States (Image Series) - Figure 2 (Image Series) - Liver Cancer in the United States
Image 2A: Rate of New Cases for Liver and Intrahepatic Bile Duct Cancer, 2000-2020

These data are from the National Cancer Institute Surveillance, Epidemiology, and End Results 22 Program (SEER22). Data from 2020 may not be reliable due to impact of COVID-19 on diagnosis and reporting.

Source: National Cancer Institute. Surveillance, Epidemiology, and End Results Program (SEER). Stat Facts: Liver and Intrahepatic Bile Duct Cancer.

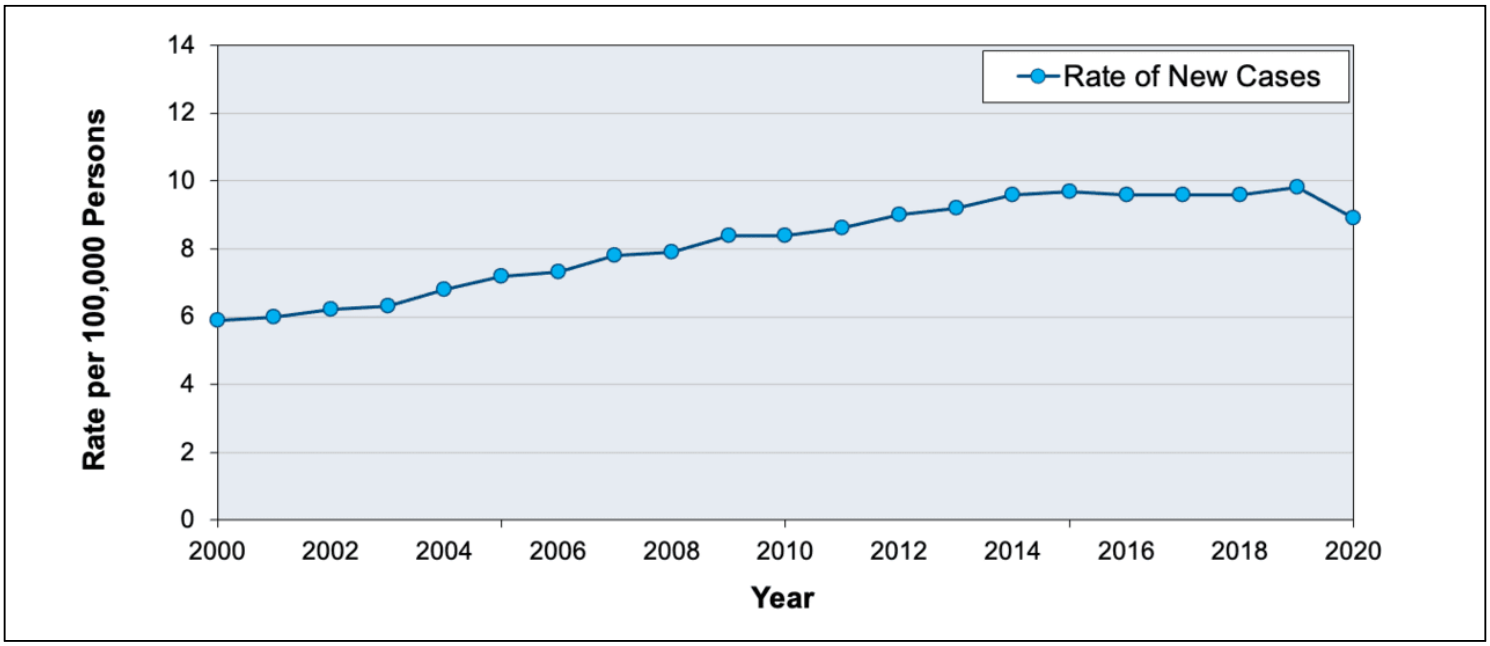


Figure 2 (Image Series) - Liver Cancer in the United States
Image 2B: Rates of New Liver Cancer, by Sex, 2016-2020

Data shown are the rate of new cases per 100,000 persons by sex for liver and intrahepatic bile cancers in the United States. Data from 2020 may not be reliable due to impact of COVID-19 on diagnosis and reporting.

Source: National Cancer Institute. Surveillance, Epidemiology, and End Results Program (SEER22). Stat Facts: Liver and Intrahepatic Bile Duct Cancer.

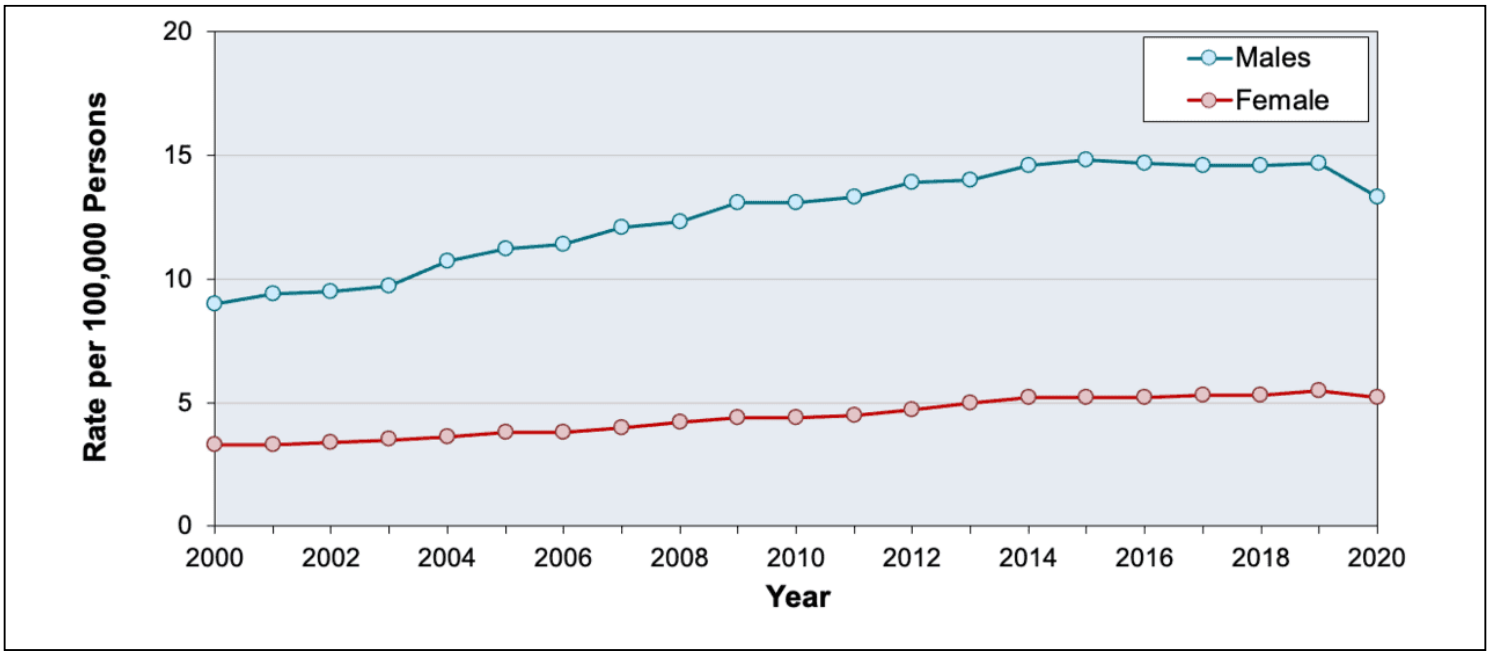


Figure 2 (Image Series) - Liver Cancer in the United States
Image 2C: Incidence of New Liver and Intrahepatic Bile Duct Cancer, by Age Group, 2016-2020

As shown, in the United States, the most new diagnoses of liver cancer occur in persons 55 to 64 years of age. Note that for these statistics, liver cancer includes liver and intrahepatic bile duct cancer. These data are from the National Cancer Institute Surveillance, Epidemiology, and End Results 22 Program (SEER22).

Source: National Cancer Institute. Surveillance, Epidemiology, and End Results Program (SEER). Stat Facts: Liver and Intrahepatic Bile Duct Cancer.

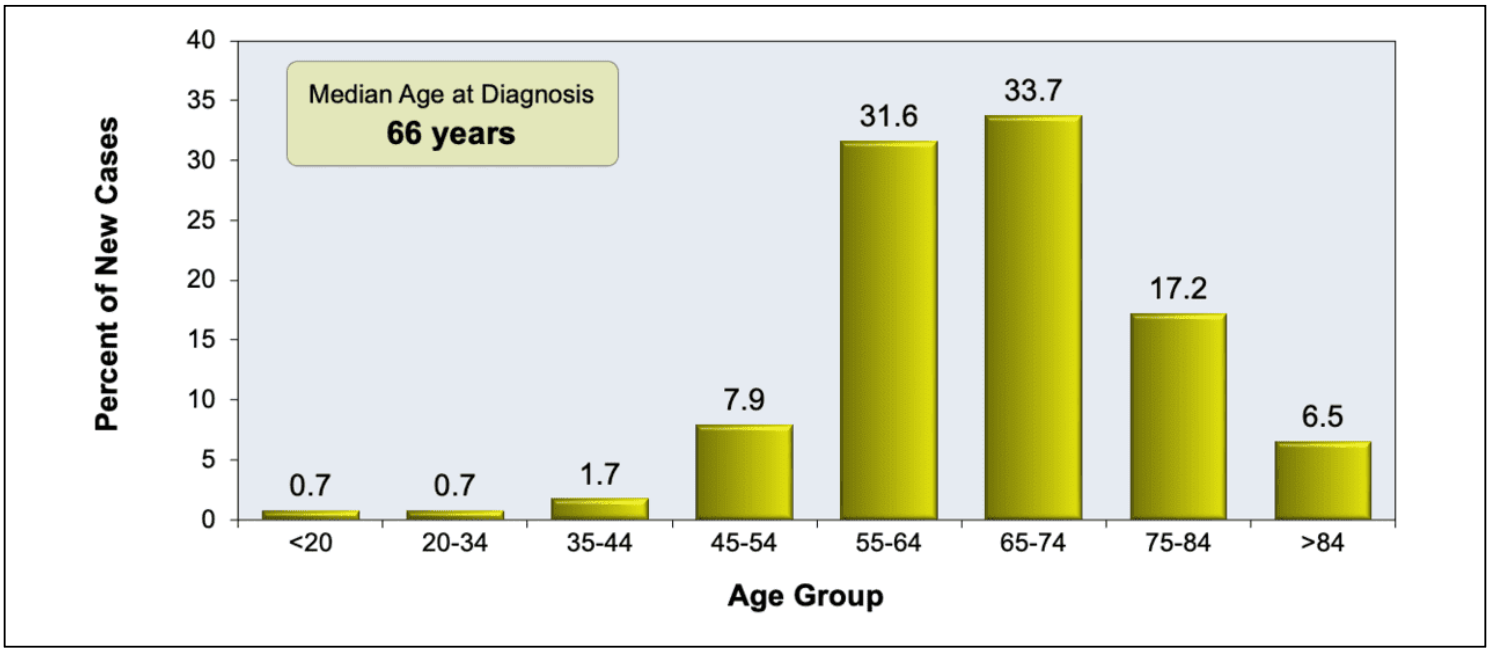


Figure 2 (Image Series) - Liver Cancer in the United States
Image 2D: Rates of New Liver Cancer, by Race/Ethnicity and Sex, 2016-2020

Source: National Cancer Institute. Surveillance, Epidemiology, and End Results Program (SEER22). Stat Facts: Liver and Intrahepatic Bile Duct Cancer.

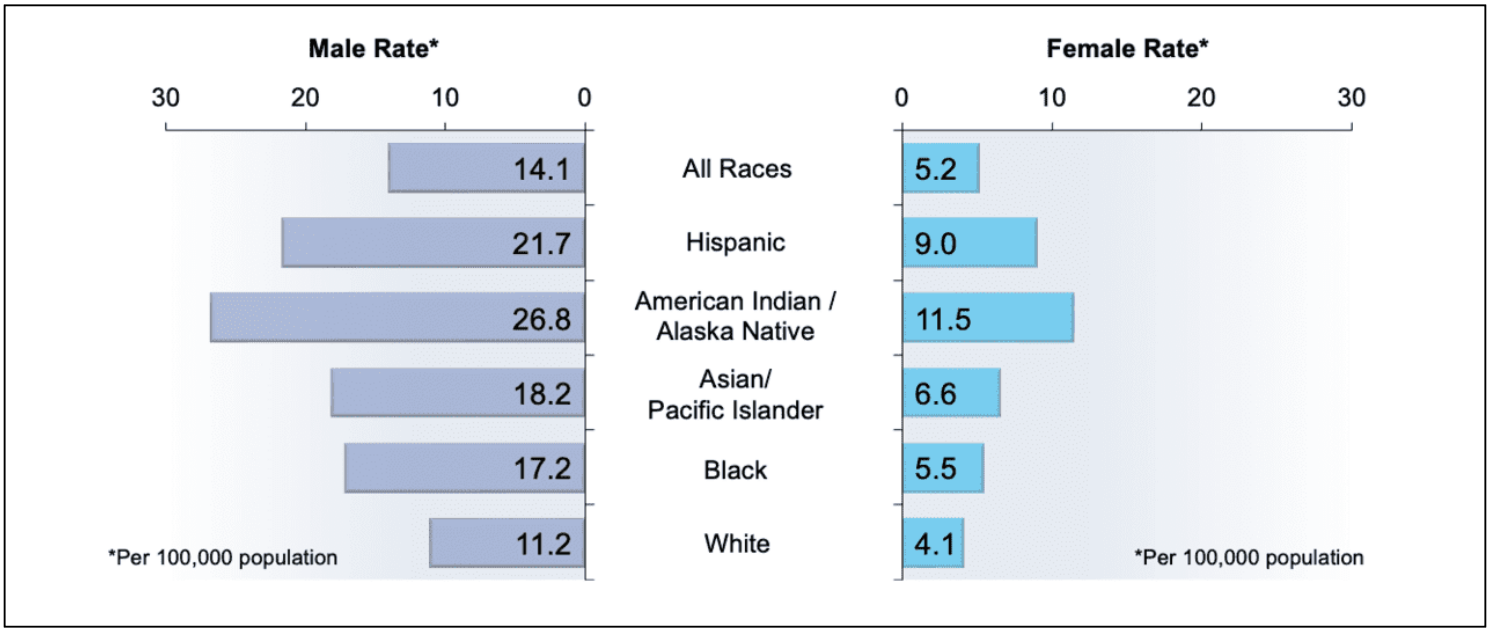


Figure 3 (Image Series) - Impact of Screening on HCC Outcomes (Image Series) - Figure 3 (Image Series) - Impact of Screening on HCC Outcomes
Image 3A: Impact of Screening on Stage of HCC at Time of Diagnosis

In a trial performed in Shanghai, China, more than 18,000 persons with chronic viral hepatitis (most of whom had chronic hepatitis B), were randomized to screening for HCC or no screening (control). As shown, individuals who received screening were more likely to have their HCC diagnosed at an earlier stage (Stage 1) than those who did not have screening.

Source: Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004;130:417-22.

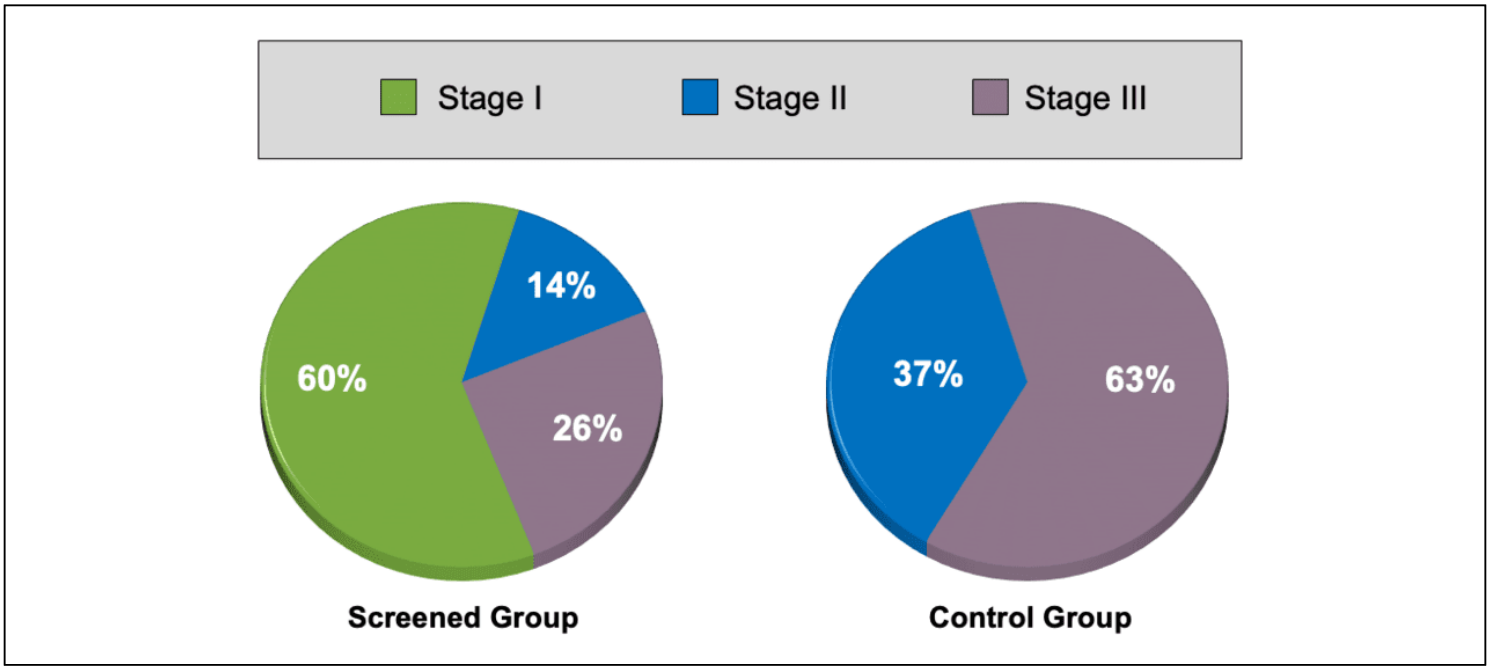
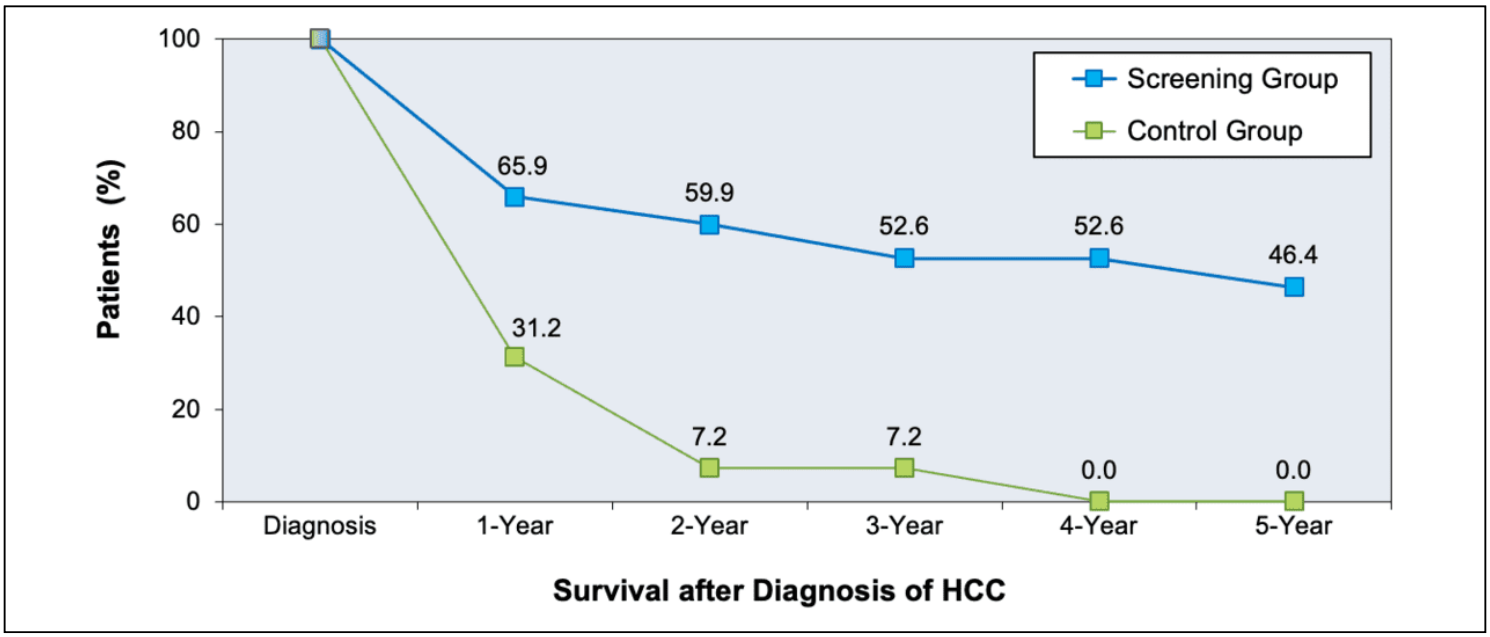


Figure 3 (Image Series) - Impact of Screening on HCC Outcomes
Image 3B: Impact of Screening on Survival after Diagnosis of HCC

In this trial, patients with chronic viral hepatitis who underwent screening for HCC had improved survival after the diagnosis of HCC when compared with the control group that did not receive screening for HCC.

Source: Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004;130:417-22.