Screening for Hepatocellular Carcinoma

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Module 4: Other Topics
Lesson 1: Screening for Hepatocellular Carcinoma

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Epidemiology of HBV-Associated Hepatocellular Carcinoma (HCC)

Global HCC Epidemiology

Liver cancer or hepatocellular carcinoma (HCC) is the sixth most common malignancy (Figure 1) and the third leading cause of cancer-related deaths worldwide (Figure 2).[1] In 2020, the age-standardized incidence rates for liver cancer were highest in Eastern Asia and Northern Africa, at 17.8 and 15.2 cases per 100,000 persons, respectively, whereas the United States fell into the higher intermediate category with an age-standardized rate of 6.9 cases per 100,000 persons.[1] This geographic disparity is likely attributable in large part to the higher prevalence of chronic hepatitis B virus (HBV) infection in Asia and Africa. Globally, chronic infection with hepatitis B virus (HBV) is the leading cause of liver cancer. Individuals with chronic HBV infection can carry a 20- to 60-fold increased risk of HCC compared to individuals without HBV infection.[2,3]

Incidence of HCC in the United States

In the United States, the Centers for Disease Control and Prevention (CDC) and the National Cancer Institute (NCI) combine liver cancer and intrahepatic bile duct cancer under "liver cancer", but HCC represents 75 to 90% of these total liver malignancies.[4,5]. The annual number and rate of new liver cancer cases have overall increased during the past 20 years, which is consistent with the advancing age of the United States population, though the number of cases and rate has leveled off since 2014 (Figure 3).[4] In 2019, there were an estimated 35,563 liver and intrahepatic bile duct cancer cases reported in the United States, according to the U.S. Cancer Statistics Working Group.[6] The rates of liver cancer and intrahepatic bile duct cancer in the United States vary significantly among different racial and ethnic groups (Figure 4).[4]

HCC-Related Deaths in the United States

In 2019, liver cancer was the sixth leading cause of cancer deaths in the United States (Figure 5). The number of liver cancer deaths in the United States has steadily increased from 1999 through 2019, with 27,958 liver cancer deaths in 2019 (Figure 6).[4] The age-adjusted death rates for liver cancer increased at an average of 0.8% per year in the United States from 2011-2020, with 88% of the deaths occurring among those older than 55 years of age.[7] In 2019, men had a much higher incidence of HCC than women, with an age-specific rate per 100,000 people of 12.6 among men versus 4.5 among women.[4] The liver cancer and intrahepatic bile duct cancer death rates in the United States varied significantly among different racial and ethnic groups (Figure 7).[4]

Factors that Impact HBV-Associated HCC

Factors that Increase Risk for HCC

Cirrhosis from any cause is an important risk factor for HBV-associated HCC and for HCC overall.[8,9,10,11] The reported HCC incidence in persons with cirrhosis is 2.2 to 4.3 per 100 person-years versus 0.1 to 0.8 per 100 person-years in those without cirrhosis.[12] The immune-mediated changes in the liver microenvironment and genetic damage induced by integration of HBV DNA into the host genome are thought to be contributing factors in hepatocarcinogenesis. In contrast to chronic hepatitis C virus (HCV)-related HCC, where cirrhosis is nearly ubiquitous, HBV is unique in its ability to promote tumorigenesis in the absence of cirrhosis through a variety of oncogenic mechanisms.[13,14] The integration of HBV DNA into the host cellular genome, which can induce genetic damage and stimulate HBV-associated immune-mediated changes in the liver microenvironment, is thought to be a contributing factor in hepatocarcinogenesis.[15] Most studies involving persons with HBV, however, have shown that the risk of HCC is orders of magnitude higher in the presence of cirrhosis in both treated and untreated individuals.[11,16] In addition to liver disease severity, a number of other factors have been associated with an increased risk of HCC:

- **Older Age**: Multiple studies from different regions of the world have shown that older persons with chronic HBV have a significantly higher risk of developing HCC than younger persons with chronic HBV.[16] Further, a study in the United States that utilized national Veterans Administration data showed that even in the absence of cirrhosis HCC risk was high among persons with chronic HBV who had high alanine aminotransferase (ALT) levels and were older than 40 years of age, irrespective of their race.[17]
- **Male Sex**: The risk of HCC is elevated in men, at an approximately 2- to 4-fold higher risk compared with women.[18]
- **Heavy Alcohol Use**: Heavy alcohol use (definitions for this vary by study) has also been shown to correlate with HCC risk.[19] In an Italian case-control study, investigators reported that persons with chronic HBV increased their risk of developing HCC if they were drinking more than 60 grams of alcohol per day.[20]
- **Smoking**: There have also been many studies showing evidence to support an association between tobacco smoking and the risk of HCC.[21] A large study using pooled data from 14 United States-based cohort studies showed that smoking more than 25 cigarettes per day was associated with a 55% increased risk of HCC.[22]
- **Obesity and/or Diabetes Mellitus**: Other key host factors include the presence of obesity and/or diabetes mellitus, which may serve as a surrogate for nonalcoholic fatty liver disease, an increasingly important driver of HCC in the United States and Asia.[23,24]
- **Family History of HCC**: A family history of HCC is also associated with a moderately increased risk of HCC, particularly among persons from Asia who have a first-degree relative with HCC.[14,25,26]
- **Aflatoxin Exposure**: Dietary exposure to aflatoxin is probably the strongest single environmental risk factor for HCC development that has been identified. Aflatoxin is a mycotoxin that originates from fungal contamination of staple foods (typically grains) in tropical and subtropical regions, particularly in sub-Saharan Africa and Southeast Asia. Epidemiologic data have shown a strong association between such exposure and DNA mutations of the tumor suppressor gene TP53 in chronic hepatitis B-associated HCC.[27]
- **High HBV DNA Levels**: Among the virologic factors that may be unfavorable for HCC, active viral replication and higher HBV DNA levels have been shown to be associated, in a dose-dependent manner, with greater risk of HCC.[28]
- **Hepatitis B e Antigen (HBeAg)-Positive Status**: Several studies have shown a correlation between positive HBeAg status and increased risk for HCC.[29,30,31] The presence of HBeAg serves as a marker for active viral replication.
- **HBV Genotype C**: Multiple population studies have shown an increased risk of developing HCC in persons with HBV genotype C, but infection with this genotype has not been well established outside of Asia.[25] In a study that evaluated Taiwanese men with HBV, infection with HBV genotype C was

associated with an estimated 5-fold greater risk for HCC compared with other HBV genotypes.[25,32] The presence of HBV genotype C is also associated with higher HBV DNA levels. In Asia, HBV genotypes B and C are the predominant genotypes.[32]

- **Hepatitis Delta Virus (HDV) Coinfection**: Hepatitis delta virus is a defective single-stranded RNA virus that requires HBV to invade the host cell and complete its life cycle. Coinfection with HDV can exacerbate disease progression and increase the risk of cirrhosis, liver decompensation, and death. Its role in hepatocarcinogenesis is less clear given confounding factors, but one meta-analysis noted an increased risk compared with individuals with HBV monoinfection.[33] The association was more pronounced when heterogeneity of studies was removed, and prospective cohort studies were examined.[33]
- **Hepatitis C Virus (HCV) Coinfection**: Individuals with HBV and HCV coinfection have also been reported to be associated with an excess risk of HCC, which is consistent with the greater incidence of hepatic inflammation and cirrhosis that has been observed with HBV and HCV dual infection.

Protective Factors

There are a few factors that have been shown to reduce the risk of HCC.

- **Primary Prevention of HBV**: Primary prevention of HCC can also be accomplished through HBV vaccination. By blocking HBV perinatal transmission, HBV immunization was the first vaccine shown to have a population-level impact on cancer prevention and shown by convincingly reducing the cumulative risk of HCC.[34]
- **Treatment of Chronic HBV**: The process of hepatitis e seroconversion (change from positive HBeAg to negative HBeAg in conjunction with change from negative anti-HBe to positive anti-HBe) and sustained HBV viral suppression with antiviral therapy have been shown to reduce but not eliminate the risk of HCC.[11,15,35,36] The HBV treatment-related risk reduction for HCC has been best shown with the oral antivirals entecavir and tenofovir DF.[35,37,38,39] Because treatment reduces but does not eliminate risk for HCC, screening should continue for HCC in treated patients.

Prognosis of Persons Diagnosed with HCC

The overall prognosis for persons diagnosed with HCC in the United States has improved some in the past 15 years, but it remains poor, with an overall 5-year survival of only approximately 21%.[6,10,40,41] This continued poor outcome is largely because individuals with HCC often present at advanced stages of disease.[6,10] The earlier the cancer is identified, when it is localized to the liver only, the more amenable it is to local ablative therapies and the better the odds of survival. The 5-year survival rate drops considerably once regional (extension to lymph nodes) or metastatic cancer to distant sites occurs (Figure 8).[6,9,10] Symptoms associated with HCC, which may include abdominal pain, anorexia, early satiety, weight loss, obstructive jaundice, fever, ascites, and bone pain (from metastases), usually suggest the presence of advanced disease.[10]

Benefit of HCC Screening in Persons with HBV

Rationale for HCC Screening

The rationale for HCC screening of asymptomatic patients is that this practice may detect tumors at an early stage when potentially curative treatment, either surgical or locoregional, can be offered.[9,10,41,42] Early detection of HCC is particularly important, given the very poor prognosis associated with advanced or metastatic disease.[9,10,43,44]

Definition of Screening and Surveillance

By definition, screening a patient for HCC means that the patient has no symptoms, and the clinician does not have a reason to suspect the patient has HCC. With screening, the patient is asymptomatic but undergoes testing in order to detect HCC early and before the development of symptoms.[41] Surveillance is the process of serial application of the screening test to detect the presence of HCC before it becomes clinically suspected or evident.[41] These terms have been used interchangeably, but the term surveillance can also be used to describe monitoring and follow-up of HCC after treatment. Therefore, to minimize ambiguity, the term screening will be used henceforth except in the context of specific recommendations from professional organizations.

Evidence Supporting HCC Screening in Chronic Hepatitis B

The most well-known clinical study to support HCC screening is a cluster-randomized, controlled trial conducted in China that assessed the impact of HCC screening on HCC-related mortality.[45] This study enrolled 18,816 individuals with chronic HBV aged 35 to 59 from 300 factories, businesses and schools in urban Shanghai. Half of these 300 units (n = 9,373 individuals) were randomized to screening using serum alfa-fetoprotein (AFP), with cutoff value 20 ng/mL, and ultrasound every 6 months; the other arm (n=9,443) underwent usual care without screening and were not actively followed.[45] The screening group had only a 58% compliance with screening but notably had HCC diagnosed at an earlier stage (Figure 9) and this group had a lower HCC-related 5-year mortality rate compared with the control group (83.2 versus 131.5 per 100,000 person-years; rate ratio 0.63, 95% CI 0.41-0.98) (Figure 10).[45] This study, however, had some methodologic limitations, conferring a high risk for bias.[46] A number of observational cohort studies have since suggested a survival benefit with screening, but the quality of this evidence is limited by selection, lead time and length-time biases.[47] There are also several observational trials and reviews involving patients with cirrhosis that have shown surveillance for HCC was associated with early-stage tumor detection and improved survival.[45,47,48] Despite the suboptimal quality of evidence supporting HCC screening, it is currently the standard of practice, and it is unlikely that a rigorously conducted randomized study would take place given the widespread acceptance of screening at this time.

Implementation of HCC Screening

In the United States, several potential barriers have been identified for effective HCC screening in patients with chronic HBV infection have been identified, including undiagnosed chronic HBV infection, unknown hepatic fibrosis stage, lack of clinician awareness of HCC screening guidelines, scheduling logistics, and cost of screening.[49,50,51] Current guidelines recommend HCC screening in the context of chronic hepatitis B for patients with a variety of risk factors that include but are not exclusive to cirrhosis. It is up to the clinician to first identify these patients and then assess their risk based on these multiple features that can be challenging in non-expert settings.

HCC Surveillance Testing Methods

Serum Biomarker Tests

In general, existing serum biomarkers have a limited role in surveillance or diagnosis of HCC due to some inherent limitations in accurate early detection. The following discussion highlights currently available assays.

- **Alpha-Fetoprotein (AFP)**: Serum alpha-fetoprotein (AFP) is the most widely evaluated biomarker for HCC surveillance, but this test has some significant drawbacks that limit it as an effective HCC screening test and high-specificity tumor marker. Using a threshold value of greater than 20 ng/mL for detecting HCC, this test has a sensitivity of only 60% and a specificity of 90%.[14,52] The AFP test on its own performs suboptimally compared to hepatic ultrasound for HCC screening.[53] The poor sensitivity is in part due to (1) the lack of uniform secretion of AFP by HCC tumors, particularly tumors less than 3 cm^2, (2) the limited specificity due to fluctuating AFP levels in patients with viral hepatitis, and (3) elevated AFP levels in patients with advanced fibrotic liver disease without HCC.[54] Some experts have suggested that AFP can be useful for the diagnosis of HCC if the level is extremely elevated, but very few patients with HCC have extremely elevated AFP levels at screening. For these reasons, AFP is no longer recommended as the only routine surveillance test.[47,53,55] In contrast to a single threshold AFP, longitudinal changes in AFP or serial testing of AFP have been reported to increase sensitivity and specificity for detecting HCC, although this approach is not yet recommended as routine clinical practice.[56,57]
- **Des-Gamma-Carboxy Prothrombin (DCP)**: Des-gamma-carboxy prothrombin (DCP) has been used widely in Japan for HCC diagnosis and surveillance.[58] The protein DCP is an abnormal prothrombin molecule that forms in malignant hepatocytes as a result of an acquired defect in the post-translational carboxylation of the prothrombin precursor, similar to the deficit in vitamin K deficiency; DCP is also known as the Protein Induced by Vitamin K Absence-II (PIVKA-II).[59] Experience with DCP in other countries, specifically the United States, remains limited.[60]
- **Lens Culinaris Lectin-Binding Subfraction of AFP (AFP-L3%)**: The AFP-L3% assay measures a subfraction of the AFP which has been shown to be more specific though less sensitive than AFP.[14] Both of these biomarkers are approved by the United States Food and Drug Administration for HCC risk stratification but not for HCC screening or surveillance.
- **Liquid Biopsy**: Given the low sensitivity of currently available biomarkers, there is active development of novel assays to identify circulating cell-free tumor DNA, circulating tumor cells and circulating exosomes that can aid in the early detection of HCC, but “liquid biopsy” for HCC detection remains investigational at this time.[61]

Radiographic Imaging

At this time, ultrasound remains the cornerstone method for HCC surveillance. The following discussion reviews why this, as opposed to other imaging, remains the main recommended modality.

- **Hepatic Ultrasound (US)**: 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.[58,62,63] Screening with ultrasound every 6 months has been shown to be the optimal interval both from the standpoint of cost-effectiveness and sensitivity for early-stage tumors (determined by mean HCC doubling time).[59,64,65] The interpretation of hepatic ultrasound is operator-dependent and can, at times, be difficult. For example, it can be challenging to detect a new lesion in patients with significant truncal obesity or in those who have a markedly echogenic (bright-looking) and/or heterogeneous liver, such as in those with significant fatty liver or nodular cirrhosis.[66] Guidelines have been developed to standardize the interpretation and reporting in the context of HCC screening.[67] A 1 cm size threshold is used to determine whether a lesion is considered potentially positive, as those under 1 cm are rarely malignant, whereas lesions 1 cm or larger are easier to diagnose reliably and have greater risk of representing HCC.

- **Computed Tomographic (CT) Abdominal Scan**: CT scanning of the abdomen (either with standard or multiphase contrast) is not recommended for use as a routine HCC surveillance test, given the paucity of data to support its use for screening and the potential harms associated with recurrent radiation exposure and false-positive results.[68,69] For patients who have a liver nodule greater than 1 cm detected on ultrasound, a dynamic 4-phase (not enhanced, arterial, venous, and delayed) contrast-enhanced CT scan of the liver can have diagnostic value.[47,52,69] 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). This characteristic feature of HCC—the presence of arterial hypervascularity (uptake) in the lesion followed by venous or delayed phase washout—is why multiphasic cross-sectional imaging (by CT or magnetic resonance imaging [MRI]) plays an important role in the diagnosis of HCC. In persons at risk for HCC, multiphase contrast CT or MRI can establish the diagnosis of HCC without the need for liver biopsy, if characteristic radiographic findings for HCC are present.
- **Magnetic Resonance Imaging (MRI)**: Similar to recommendations for abdominal CT scanning, a hepatic MRI is not recommended as a routine surveillance test. Apart from the high cost and necessity of contrast enhancement, false-positive results can occur with MRI that may trigger further diagnostic work-up and associated harms (e.g., in increased time and anxiety for the patient). For patients who have a nodule greater than 1 cm detected on ultrasound, a contrast-enhanced multiphasic MRI is recommended as a diagnostic (as opposed to surveillance) test.[47] Further research needs to be done to evaluate the cost-effectiveness of safer modalities of MRI (such as abbreviated MRI protocols) for screening, which may be necessary for those patients in whom ultrasound performs poorly due to significant truncal obesity or marked parenchymal heterogeneity in the liver.[69]

Risk Scores to Guide Selection of Patients for HCC Surveillance

A variety of risk scores have been developed to predict the risk of HCC in patients with chronic hepatitis B, such as the REACH-B, GAG-HCC, and PAGE-B.[70,71,72] Many of these scoring systems were derived from individuals who were not being treated for their chronic hepatitis B and/or from Asian populations, which comprise only a subset of HBV patients in care today, thus limiting the generalizability and applicability of these risk calculators.[13] In addition to the need for further external validation in different ethnicities and populations, the determination of the appropriate risk cutoffs and associated management strategies based on these cutoffs also remains an issue at this time. Current guidelines do not endorse these scoring systems for widespread adoption and use.

AASLD Guidance for HCC Surveillance

HCC Screening Indications

Although there are no experimental data that would indicate the exact threshold incidence of HCC to trigger screening, decision analysis/cost-effectiveness models for HCC surveillance have shown that effectiveness of screening depends on the incidence of HCC, with surveillance becoming cost-effective if the HCC incidence is at least 0.2% per year.[14,46,69,73] For persons with chronic HBV infection, the 2023 AASLD HCC Guidance recommends HCC surveillance in all adults with cirrhosis of any etiology, including cirrhosis due to chronic HBV infection.[73] The exception, however, is patients with severely decompensated disease, specifically Child-Turcotte-Pugh class C cirrhosis, unless they are considered a liver transplantation candidate.[73] The following summarizes the 2023 AASLD HCC Guidance specific indications for HCC surveillance in HBsAg-positive adults.[73]

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

HCC Surveillance Method

The HCC surveillance method recommended in the 2023 AASLD HCC Guidance is ultrasonography and serum AFP approximately every 6 months.[73] 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.[14]

Follow-Up Based on HCC Screening Results

The 2023 AASLD HCC Guidance recommends follow-up, as outlined below, based on the results of the surveillance ultrasound and the AFP test.[73]

- Vis score A with no lesions on ultrasound and AFP normal: repeat ultrasound and AFP in 6 months
- Vis score B or lesion less than 1 cm on ultrasound and AFP normal: repeat ultrasound and AFP in 3-6 months and AFP in 6 months. If stable, continue to repeat ultrasound every 3-6 months and AFP every 6 months. If there is growth of the lesion, perform diagnostic contrast-enhanced multiphasic MRI or CT. Subsequent follow-up is based on the MRI/CT results.
- Vis score C (with no lesion or lesion less than 1 cm on ultrasound: perform screening contrast-enhanced MRI or multi-phasic CT; repeat ultrasound can be considered in some patients. Subsequent follow-up is based on the results of this imaging test.
- Lesion greater than 1 cm on ultrasound, AFP greater than 20 ng/mL, or AFP increasing; perform diagnostic contrast-enhanced multiphasic MRI or CT. Subsequent follow-up is based on the MRI/CT results.

Summary Points

- Cirrhosis is an important risk factor for developing HCC in persons with chronic HBV infection. Other risk factors include older age, male sex, family history of HCC, heavy alcohol use, aflatoxin exposure, high HBV DNA levels, HBeAg-positive status, and HBV genotype C.
- The incidence of HBV-associated HCC can be reduced by hepatitis B vaccine. Treatment of chronic HBV with antiviral therapy has also been shown to be associated with reduced HCC risk.
- The overall 5-year survival of HCC in the United States is approximately 20%. Survival depends on the stage of HCC at the time of diagnosis, with a very poor prognosis for those with advanced or metastatic HCC.
- 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 recommends HCC surveillance in all adults with chronic HBV infection and cirrhosis. For HBsAg-positive adults without cirrhosis, surveillance is based primarily on age and country of origin.
- The recommended HCC screening method is hepatic ultrasound and serum AFP every 6 months, with subsequent follow-up based on these results.

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Figures

Figure 1 Global Number of New Cases of Cancer, 2020

Source: World Health Organization. Liver Fact Sheet: Globocan, 2020. WHO's International Agency for Research on Cancer.

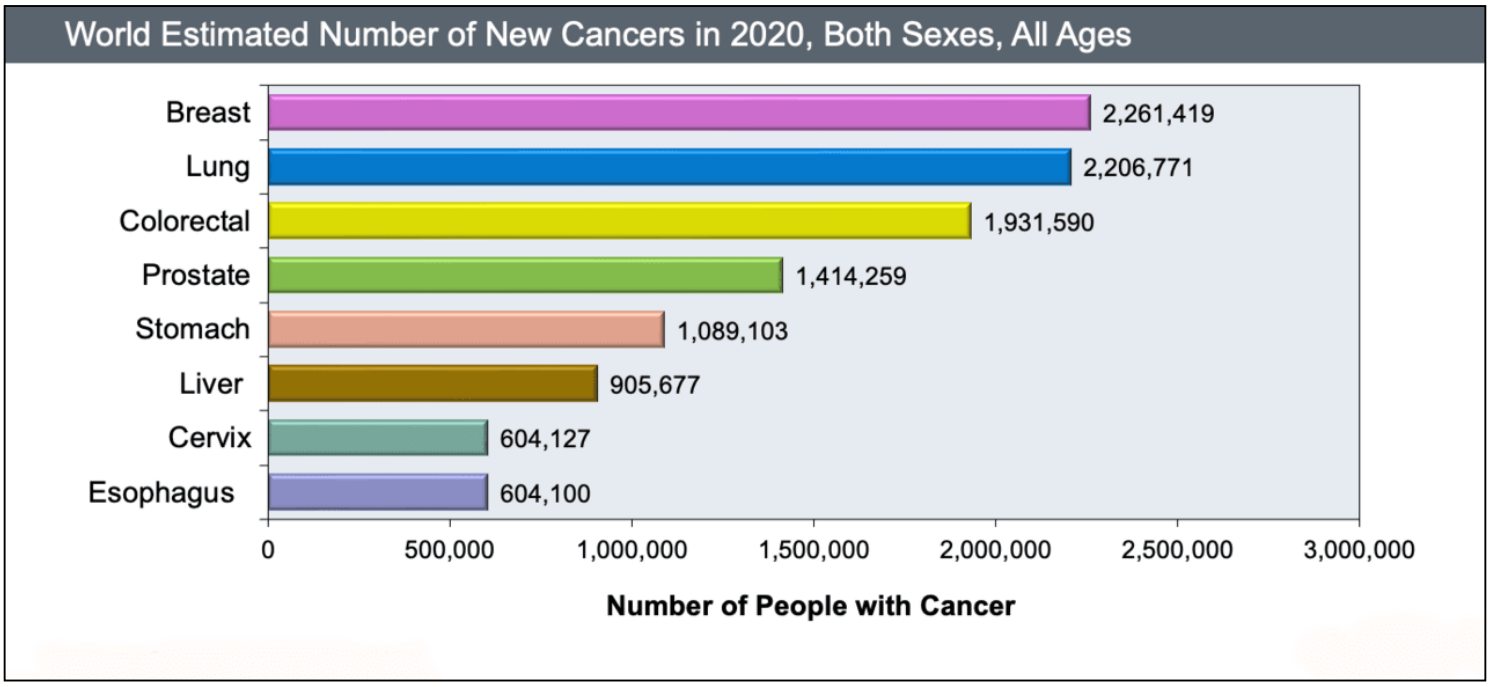

Figure 2 Global Cancer-Related Deaths, 2020

Source: World Health Organization. Liver Fact Sheet: Globocan, 2020. WHO's International Agency for Research on Cancer.

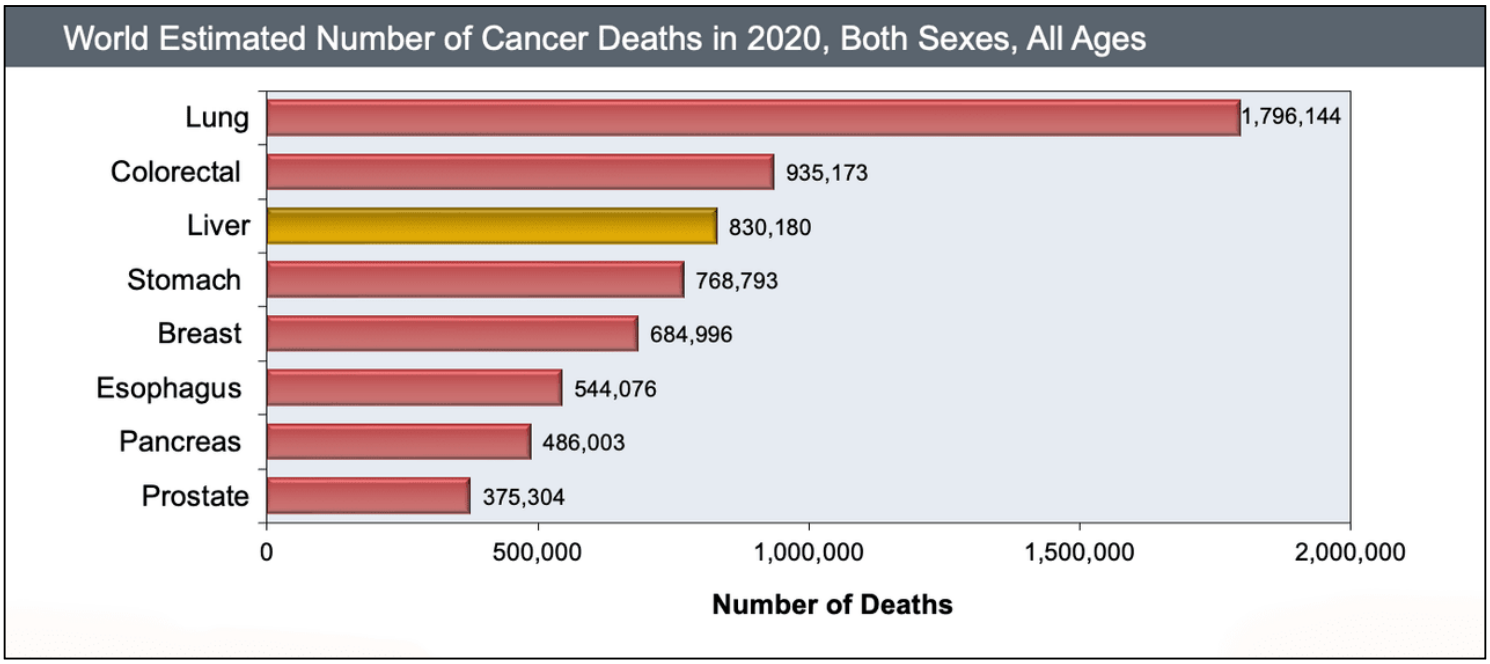

Figure 3 Liver and Hepatic Duct Cancers in United States—Annual Number of New Cancers, 1999-2019

Source: U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2021 submission data (1999-2019): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. Released in June 2022.

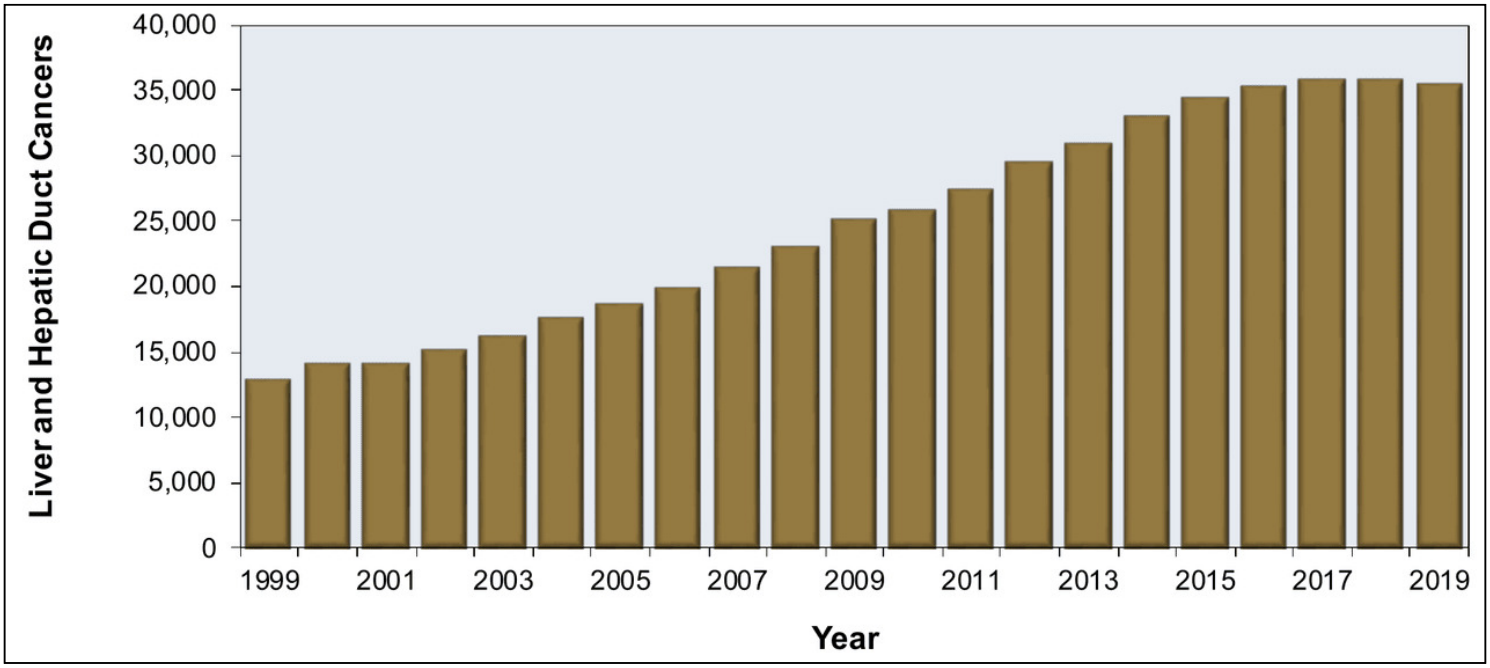

Figure 4 Liver and Intrahepatic Bile Duct Cancers and Rate by Race/Ethnicity, United States, 2019

Source: U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2021 submission data (1999-2019): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. Released in June 2022.

Age-Adjusted Liver and Intrahepatic Bile Duct Cancer Incidence Rates, United States, 2019	
Race/Ethnicity	**Incidence Rate** (per 100,000 persons)
All Racial/Ethnic Groups	8.4
Black	9.6
Hispanic	13.2
Asian/Pacific Islander	11.4
White	7.8
American Indian/Alaska Native	10.5

Figure 5 Cancer-Related Deaths in United States 2019

Abbreviations: NOS = not otherwise specified

Source: U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2021 submission data (1999-2019): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. Released in June 2022.

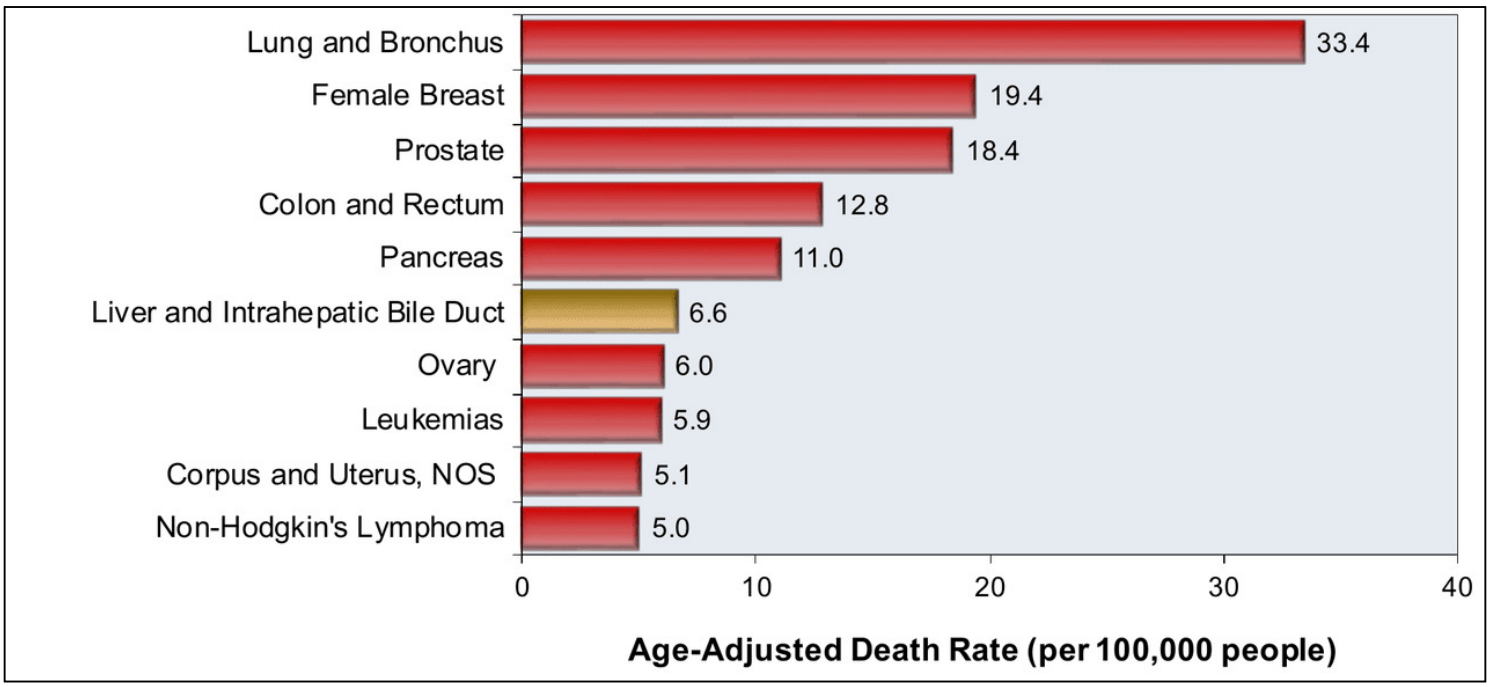

Figure 6 Liver and Intrahepatic Bile Duct Cancer-Related Deaths, United States, 1999-2019

Source: U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2021 submission data (1999-2019): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. Released in June 2022.

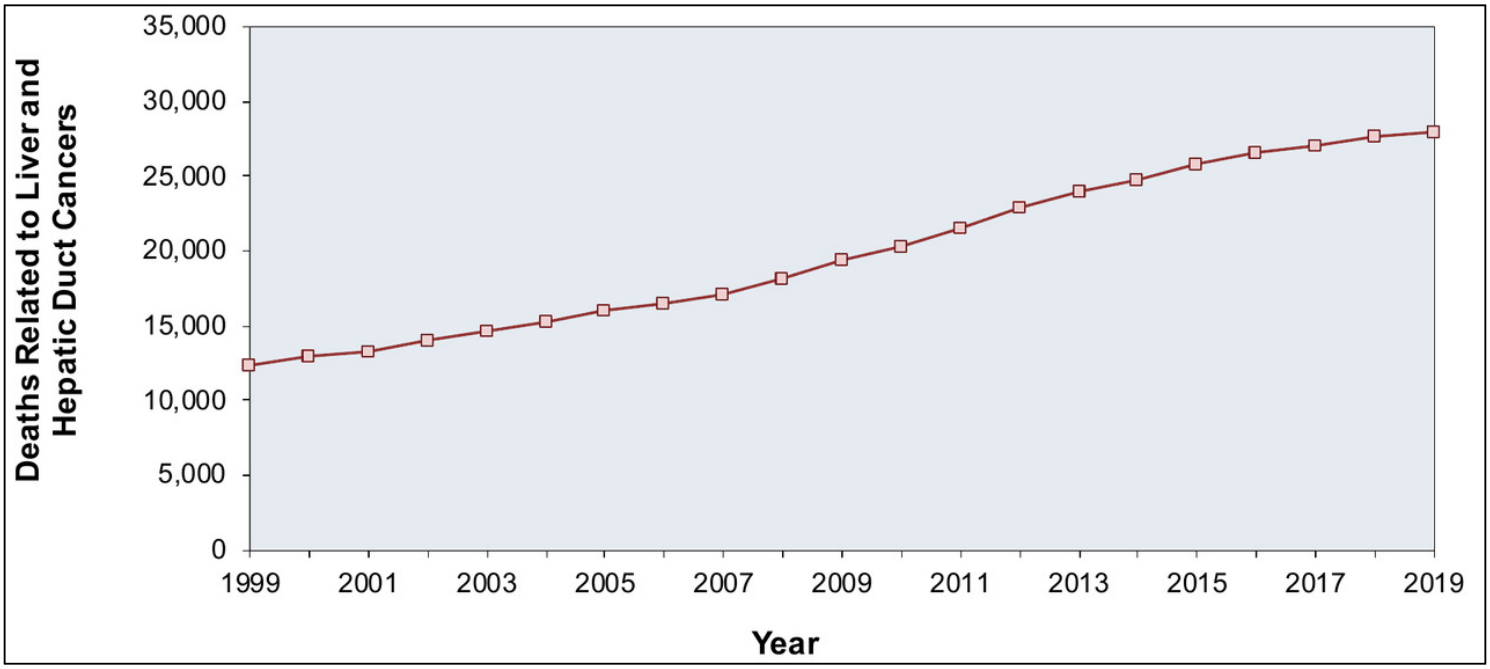

Figure 7 Liver and Intrahepatic Bile Duct Cancers and Death Rate by Race/Ethnicity, United States, 2019

Source: U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2021 submission data (1999-2019): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. Released in June 2022.

Age-Adjusted Liver and Intrahepatic Bile Duct Cancer Death Rates, United States, 2019

Race/Ethnicity	Death Rate (per 100,000 persons)
All Racial/Ethnic Groups	**6.6**
Black	7.9
Hispanic	9.0
Asian/Pacific Islander	8.2
White	6.3
American Indian/Alaska Native	7.0

Figure 8 5-Year Relative Survival by Stage at Diagnosis: Liver and Intrahepatic Bile Duct Cancer

Source: National Cancer Institute. Surveillance, Epidemiology, and End Result Program: Cancer Stat Facts: Liver and Intrahepatic Bile Duct Cancer.

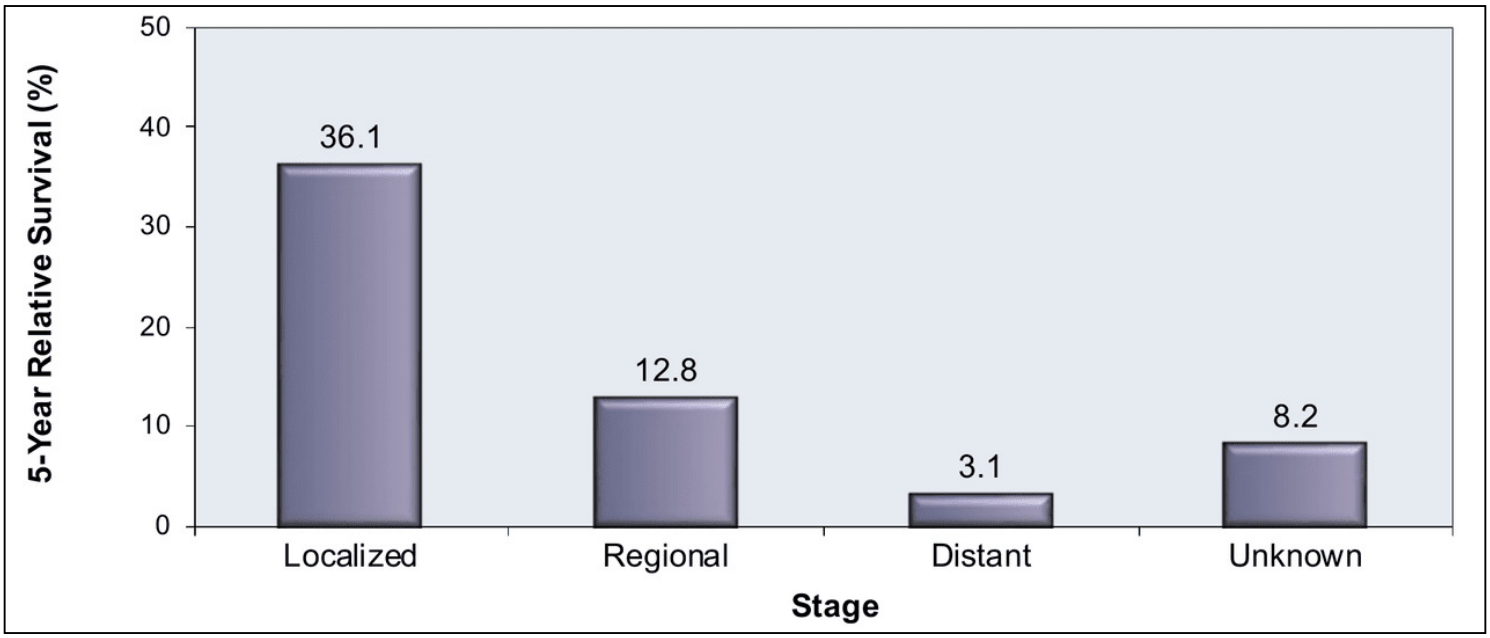

Figure 9 Impact of Screening on Stage of HCC at Time of Diagnosis

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 hepatocellular carcinoma (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.

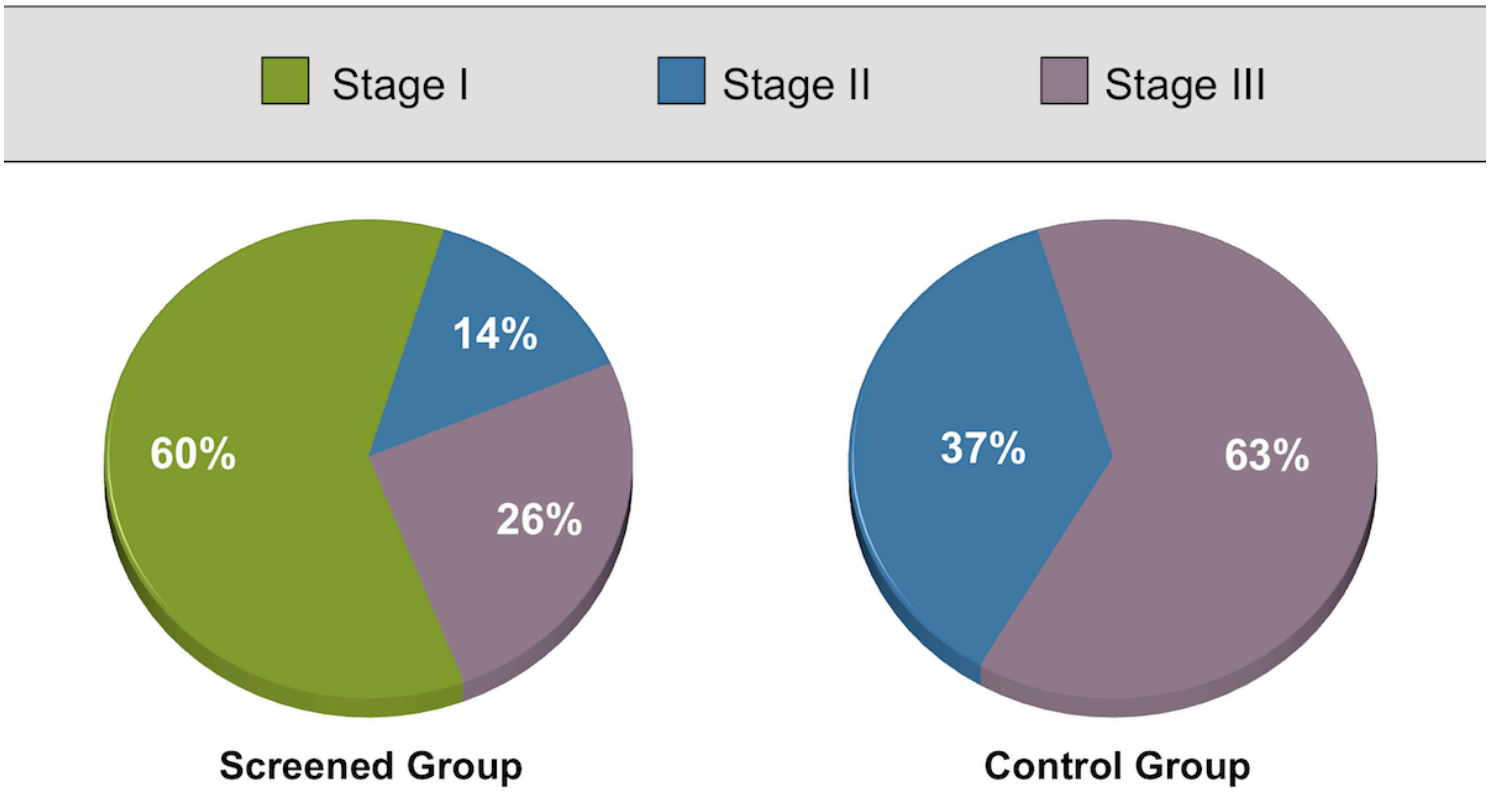

Figure 10 Impact of Screening on Survival after Diagnosis of HCC

In this trial, patients with chronic viral hepatitis who underwent screening for hepatocellular carcinoma (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.