Screening for Hepatocellular Carcinoma

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Section 4: Other Topics
Topic 1: Screening for Hepatocellular Carcinoma

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Epidemiology of HBV-Associated Hepatocellular Carcinoma

Liver cancer or hepatocellular carcinoma (HCC) is the sixth most common malignancy (Figure 1) and the fourth leading cause of cancer-related death worldwide (Figure 2).[1] In 2018, the age standardized incidence rates for liver cancer were highest in Eastern Asia and Sub-Saharan Africa, exceeding 14.1 per 100,000 persons, whereas the United States fell into the higher intermediate category with age standard incidence rates between 9.3 to 14.1 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]

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 has overall increased during the past 18 years corresponding with advancing age of the population, though the pace has slowed since 2014 (Figure 3).[4] In 2016, there was an estimated 33,482 liver and intrahepatic bile duct cancer cases reported in the United States, with expectations for this number to increase to 42,030 new cases in 2019, according to the Surveillance Epidemiology End Result (SEER) program of the NCI.[6]

In 2016, liver cancer was the seventh leading cause of cancer deaths in the United States (Figure 4). The number of liver cancer deaths in the United States has steadily increased from 1999 through 2016, with 26,569 liver cancer deaths in 2016 (Figure 5).[4] For age-adjusted death rates for HCC, there has been an overall 2.1% (95% CI 1.9% to 2.3%) increase in mortality among the United States population from 1999 through 2016 with 80% of the deaths occurring among those older than 55 years with HCC with underlying cirrhosis.[7] In 2016, whites had the highest number of cases, but the lowest incidence rate (per 100,000 persons) (Figure 6).[6] Only the Asian/Pacific Islander population saw a decrease in mortality during this period was among the Asian and Pacific Islanders. Men had much higher incidence than women of HCC in 2016, with an age-specific rate per 100,000 people of 12.6 among men versus 4.5 among women.[6] In the United States, liver cancer is more common in men than women, and among Asian/Pacific Islander and American Indian/Alaska Native populations.[6]
Risk Factors and Protective Factors for HBV-Associated 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.\[12\] In contrast to other causes of HCC, such as chronic hepatitis C virus (HCV) infection, where cirrhosis is nearly ubiquitous in HCC cases, HBV has oncogenic properties that can potentiate the development of HCC in the absence of cirrhosis.\[8,13\] The integration of HBV DNA into the host cellular genome can induce genetic damage and this process is thought to be a contributing factor in hepatocarcinogenesis. 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.\[11,14\] In addition to liver disease severity, a number of other factors have been associated with 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 relatively higher risk of developing HCC than younger persons with chronic HBV.\[14\] Further, a study in the United States that utilized national Veterans Administration data has shown 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.\[15\]
- **Male Gender**: The risk of HCC is elevated in men, approximately 2- to 4-fold higher risk compared with women.\[16\]
- **Heavy Alcohol Use**: Heavy alcohol use (definitions for this vary by study) has also been shown to correlate with HCC risk.\[17\] 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.\[18\]
- **Smoking**: There have also been many studies showing evidence to support association between tobacco smoking and risk of HCC.\[19\] 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.\[20\]
- **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 non-alcoholic fatty liver disease, an increasingly important driver of HCC in the United States and Asia.\[21,22\]
- **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.\[13,23,24\]
- **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 food (typically grains) in tropical and subtropical regions particularly in sub-Saharan African 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.\[25\]
- **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.\[26\]
- **Hepatitis B e Antigen (HBeAg)-Positive Status**: Several studies have shown a correlation of positive HBeAg status and increased risk for HCC.\[27,28,29\] 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.\[23\] 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.\[23,30\] 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.\[30\]

**Protective Factors**
There are a few factors that have been shown to lessen 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 historic vaccine shown to have a population-level impact on cancer prevention and shown convincingly to reduce the cumulative risk of HCC.[31]

- **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) or sustained HBV viral suppression with antiviral therapy has been shown to reduce but not eliminate the risk of HCC.[11] The HBV treatment-related risk reduction for HCC has been best shown with the oral antivirals entecavir and tenofovir DF.[32,33,34,35] 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 18%.\cite{6,10,36,37} Because HCC is typically detected only after the onset of symptoms, persons with diagnosed HCC usually have advanced disease, which portends an extremely poor prognosis, with an overall 5-year survival less than 10% and a median survival of only 12 months.\cite{9,10} In the United States, among persons with liver and intrahepatic bile duct cancer, this 5-year survival is second lowest among all cancers.\cite{6,10} Symptoms associated with HCC may include abdominal pain, anorexia, early satiety, weight loss, obstructive jaundice, fever, ascites, and bone pain (from metastases). In contrast, detection of very early-stage HCC can be cured with an excellent long-term prognosis.\cite{10}
Benefit of HCC Screening in Persons with HBV Infection

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.[9,10,36,38] Early detection with HCC is particularly important, given the very poor prognosis associated with advanced or metastatic HCC.[9,10,39,40]

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.[36] Surveillance is the process of serial application of the screening test to detect the presence of HCC before it becomes clinically suspected or evident.[36] 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.[41] This study enrolled 18,816 HBV 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 alpha-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.[41] The screening group had only a 58% compliance with screening, but notably had HCC diagnosed at an earlier stage (Figure 7) 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 8).[41] This study, however, had some methodologic limitations, conferring a high risk for bias.[42] 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.[43] There are also several observational trials and reviews involving patients with cirrhosis that have shown surveillance for HCC was associated with earlier-stage tumor detection and improved survival.[41,43,44] 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 exist 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.[45,46,47] 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 Screening Testing Methods**

**Biomarker Serologic Tests**

In general, existing serum biomarkers have a limited role in screening 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 as a 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%.[13,48] The AFP test on its own performs suboptimally compared to hepatic ultrasound for HCC screening.[49] The poor sensitivity is in part due to (1) the lack of uniform secretion of AFP by HCC tumors, particularly tumors less than 3 cm², and (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.[50] 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. Because of these reasons, AFP is no longer recommended as the only routine surveillance test.[43,49,51] 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.[52,53]

- **Des-Gamma-Carboxy Prothrombin (DCP):** Des-gamma-carboxy prothrombin (DCP) has been used widely in Japan for HCC diagnosis and surveillance.[54] 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).[55] Experience with DCP in other countries, specifically the United States, remains limited.[56]

- **GALAD Model:** The GALAD is a diagnostic model that incorporates five components (Gender, Age, AFP-L3%, AFP, and DCP) in combination with the patient’s gender and age to predict the probability of having HCC in patients with chronic liver disease; when used together with hepatic ultrasound, the GALAD may increase sensitivity and specificity of detecting early HCC, although the GALAD still requires further validation in population-based cohorts.[57,58]

- **Lens Culinaris Lectin-Binding Subfraction of AFP (AFP-L3%):** The AFP-L3% assay measures a subfraction of the AFP which has shown to be more specific though less sensitive than AFP.[13] 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 exomes that can aid in the early detection of HCC.[59]

**Radiographic Imaging**

At this time, ultrasound remains the cornerstone method for HCC screening. 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.[54,60,61] 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).[55,62,63] 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.[64] Guidelines
have been developed to standardize the interpretation and reporting in the context of HCC screening.[65] 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 screening test for HCC given the paucity of data to support its use for screening and the potential harms associated with recurrent radiation exposure and false-positive results.[66,67] 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.[43,48,67] 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 screening test. Apart from the high cost and necessity of contrast enhancement, false positive results can occur not infrequently with MRI that may trigger further diagnostic workup and associated harms (for example in increased time and anxiety on the part of 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 screening) test.[43] 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 in those patients in whom ultrasound performs poorly due to significant truncal obesity or marked parenchymal heterogeneity in the liver.[67]
Guidelines for HCC Screening

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 exceeds 0.2% per year.[13,42,67] The following summarizes recommendations major organizations regarding the indications for HCC screening in persons with chronic hepatitis B. All major organizations endorse HCC screening in persons with chronic HBV and cirrhosis, but some differences exist in recommendations for persons with chronic HBV without cirrhosis. All major organizations endorse ultrasonography with or without serum alpha-fetoprotein every 6 months as the screening method.[66,67,68,69]

2018 AASLD Guidance

For persons with chronic HBV infection, AAALD recommends that all adults with cirrhosis of any etiology, including chronic HBV infection, should have screening for HCC because screening improves overall survival and increases the detection of early-stage HCC.[69] The exception, however, is patients with severely decompensated disease, specifically Child-Turcotte-Pugh class C cirrhosis, unless they are awaiting liver transplantation. There are no empirical data to guide clinical decision-making for HCC screening and the exact threshold incidence of HCC to trigger screening remains unclear.[38,70,71,72] The following summarizes the 2018 AASLD Hepatitis B Guidance for specific indications and methods for HCC screening in HBsAg-positive adults.[69]

Indications for HCC Screening in HBsAg-Positive Adults

- All persons with cirrhosis
- Black men older than 40 years of age
- Asian men older than 40 years of age
- Asian females older than 50 years of age
- Persons with a first-degree family member with history of HCC
- Persons with hepatitis D virus

Recommended HCC Screening Method

The HCC screening method recommended in the 2018 AASLD Hepatitis B Guidance is ultrasonography every 6 months, with or without serum alpha-fetoprotein; the guidance notes that if ultrasonography is not readily available, then screening should consist of alpha-fetoprotein every 6 months.[69] The 2018 AASLD HCC Guidance recommends specific follow-up based on the results of the initial screening testing (Figure 9).[13] For adults with suspected HCC based on a screening test result, the 2018 AASLD HCC Guidance recommend further evaluation with either a multiphasic computed tomography (CT) or multiphasic magnetic resonance imaging.[13]

2018 EASL HCC Clinical Practice Guidelines

The European Association for the Study of the Liver (EASL) recommends HCC screening for patients with Child-Turcotte-Pugh class A or B cirrhosis, and those with Child-Turcotte-Pugh class C if they are awaiting transplantation.[66] In contrast to AASLD, the 2017 EASL Hepatitis B Guidelines recommend screening for HCC in selected patients with bridging fibrosis (Metavir stage F3). For these F3 patients, EASL advises risk group stratification (low, medium, and high) to aid in the decision to screen for HCC, based on individual assessment of known risk factors or locally produced HCC risk stratification scores, such as PAGE-B classification in Caucasians and REACH-B, GAG-HCC and CU-HCC in Asians.[11,66,73,74,75] If a patient has unknown cirrhosis status (or unknown stage of liver fibrosis), they should undergo evaluation of liver fibrosis stage, especially given the availability of improved noninvasive options for evaluating hepatic fibrosis, such as transient elastography or magnetic resonance elastography.[66,76]
Indications for HCC Surveillance in Persons with Chronic HBV

- All persons with cirrhosis
- Persons in a moderate or high-risk HCC group, using PAGE-B in Caucasians and REACH-B, GAG-HCC, and CU-HCC in Asians

Recommended HCC Surveillance Method

The recommended surveillance method is liver ultrasound with or without serum alpha-fetoprotein every 6 months. This guidance notes that other acceptable imaging modalities include abdominal CT or MRI, with or without contrast.

2015 Asian-Pacific Clinical Practice Guidelines

The Asian Pacific Association for the Study of the Liver (APASL) 2015 APASL Hepatitis B Guidelines hinges on two key factors when considering HCC screening in persons with chronic HBV: the incidence of HCC and the survival benefit to the patient if HCC is diagnosed and treated.\[68\] In addition, these recommendations may depend on economic values and resources within that society.\[24,68\] The 2015 APASL Hepatitis B Guidelines note that HCC risk calculators like REACH-B, can be used to assess HCC risk in patients with chronic HBV, but the authors also place some cautionary notes on the use of these predictive scoring tools.\[68\] The REACH-B study, for example, was performed in an untreated Taiwanese population and its applicability to patients on antiviral therapy for chronic HBV, or in those of different ethnic background or in geographic settings with different HBV genotypes remain largely unknown.\[58\] Such scoring tools have not been as predictive in Caucasian patients with chronic HBV infection.\[11\] In addition, an individual patient’s risk of HCC may rely on multiple risk factors so defining a HCC risk based on the incidence in a specific population may be challenging.

Indications for Screening for Persons with Chronic HBV Infection

- All adults with cirrhosis, except for those with Child’s C cirrhosis
- Persons without cirrhosis: Since the screening depends on the incidence and cost-effectiveness of screening in different Asian countries, the HCC surveillance recommendations should be determined individually for each country.

Recommended HCC Screening Method

For persons with chronic HBV, the APASL recommends surveillance using liver ultrasound with serum alpha-fetoprotein every 6 months.\[68\]

2020 Hepatitis B Primary Care Workgroup

The 2020 HBV Primary Care Workgroup Guidance indications and recommended methods for HCC surveillance are summarized below:\[77\]

Indications for HCC Surveillance in Persons with Chronic HBV

- All persons with cirrhosis
- The following populations, even in the absence of cirrhosis
  - Asian or black/African males older than 40 years of age
  - Asian females older than 50 years of age
  - Persons with a family history of HCC
  - Persons with hepatitis D virus coinfection
**Recommended HCC Surveillance Method in Persons with Chronic HBV**

The recommended surveillance method is liver ultrasound with or without serum alpha-fetoprotein every 6 months. This guidance notes that other acceptable imaging modalities include abdominal CT or MRI, with or without contrast.
Summary Points

- Cirrhosis is an important risk factor for developing HCC in persons with chronic HBV infection. Other risk factors include older age, male gender, 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 12%. Survival depends on the stage of HCC at the time diagnosis occurs, 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.
- Current guidelines from multiple organizations uniformly recommend HCC screening in all adults with chronic HBV infection and cirrhosis. For HBsAg-positive adults without cirrhosis, the indications for HCC screening differs among organizations.
- The recommended HCC screening method is hepatic ultrasound every 6 months, with or without serum alpha-fetoprotein.
Citations

   [WHO]

   [PubMed Abstract]

   [PubMed Abstract]

   [CDC and NCI]

   [PubMed Abstract]

   [NCI]

   [PubMed Abstract]

   [PubMed Abstract]

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    [PubMed Abstract]

    [PubMed Abstract]

    [PubMed Abstract]

    [PubMed Abstract]


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Figures

Figure 1 Global Number of New Cases of Cancer, 2018


World Estimated Number of New Cancers in 2018, Both Sexes, All Ages

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Number of People with Cancer</th>
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<tbody>
<tr>
<td>Lung</td>
<td>2,093,876</td>
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<tr>
<td>Breast</td>
<td>2,088,848</td>
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<tr>
<td>Colorectal</td>
<td>1,849,518</td>
</tr>
<tr>
<td>Prostate</td>
<td>1,276,106</td>
</tr>
<tr>
<td>Stomach</td>
<td>1,033,701</td>
</tr>
<tr>
<td>Liver</td>
<td>841,080</td>
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<td>Esophagus</td>
<td>572,034</td>
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<tr>
<td>Cervix</td>
<td>569,847</td>
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Number of People with Cancer
Figure 2 Global Cancer-Related Deaths, 2018


<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Number of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>1,761,007</td>
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<tr>
<td>Colorectal</td>
<td>880,792</td>
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<tr>
<td>Stomach</td>
<td>782,685</td>
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<td>Liver</td>
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<td>Breast</td>
<td>626,679</td>
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<td>Esophagus</td>
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<td>Pancreas</td>
<td>432,242</td>
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<tr>
<td>Prostate</td>
<td>358,989</td>
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Figure 3 Liver and Hepatic Duct Cancers in United States—Annual Number of New Cancers, 1999-2016

**Figure 4 Cancer-Related Deaths in United States 2016**


![Bar chart showing cancer-related deaths in the United States in 2016](chart)

- **Lung and Bronchus**: 38.5
- **Female Breast**: 20.0
- **Prostate**: 19.4
- **Colon and Rectum**: 13.7
- **Pancreas**: 11.0
- **Ovary**: 6.8
- **Liver and Intrahepatic Bile**: 6.7
- **Leukemias**: 6.3
- **Non-Hodgkin's Lymphoma**: 5.4
- **Corpus and Uterus, NOS**: 5.0

Age-Adjusted Death Rate (per 100,000 people)
Figure 5 Liver and Intrahepatic Bile Duct Cancer-Related Deaths, United States, 1999-2016

Figure 6 Liver and Intrahepatic Bile Duct Cancers and Rate by Race/Ethnicity, United States, 2016


<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Number of Cases</th>
<th>Incidence Rate (per 100,000 persons)</th>
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<tbody>
<tr>
<td>All Racial/Ethnic Groups</td>
<td>38,108</td>
<td>8.3</td>
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<tr>
<td>Black</td>
<td>4,925</td>
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<tr>
<td>Hispanic</td>
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<tr>
<td>Asian/Pacific Islander</td>
<td>2,287</td>
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<tr>
<td>White</td>
<td>25,377</td>
<td>7.6</td>
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<tr>
<td>American Indian/Alaska Native</td>
<td>443</td>
<td>11.4</td>
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</table>
**Figure 7 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.

Figure 8 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.

**Figure 9 AASLD Hepatocellular Carcinoma Surveillance**

The following graphic shows recommendations based on initial findings on hepatocellular carcinoma surveillance tests.