Epidemiology and risk factors for hepatocellular carcinoma

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a primary liver malignant tumor that typically develops in the setting of chronic liver disease, particularly in patients with cirrhosis or chronic hepatitis B virus infection. Approximately 75 percent of primary liver tumors are HCC, with cholangiocarcinoma comprising most of the remaining cases [1].

This topic will review the epidemiology and risk factors for HCC. The approach to surveillance, clinical manifestations, diagnosis, and management of HCC are discussed separately:

- (See "Surveillance for hepatocellular carcinoma in adults".)
- (See "Clinical features and diagnosis of hepatocellular carcinoma".)
- (See "Staging and prognostic factors in hepatocellular carcinoma".)
- (See "Overview of treatment approaches for hepatocellular carcinoma".)

The natural history of hepatitis B virus infection and hepatitis C virus (HCV) infection is discussed separately. (See "Hepatitis B virus: Clinical manifestations and natural history" and "Clinical manifestations and natural history of chronic hepatitis C virus infection".)

The use of antiviral therapy for patients with chronic HCV and an established diagnosis of HCC, including data on reducing the risk of HCC recurrence, is presented separately. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection" and

"Management of potentially resectable hepatocellular carcinoma: Prognosis, role of neoadjuvant and adjuvant therapy, and posttreatment surveillance".)

The pathology of malignant liver tumors, including HCC, is discussed separately. (See "Pathology of malignant liver tumors".)

The epidemiology, risk factors, clinical manifestations, diagnosis, and treatment of fibrolamellar carcinoma, a rare variant of HCC, is discussed separately. (See "Epidemiology, clinical manifestations, diagnosis, and treatment of fibrolamellar carcinoma".)

EPIDEMIOLOGY

Incidence and mortality — Cancer of the liver and intrahepatic bile ducts is the sixth most frequently diagnosed malignancy worldwide, with approximately 900,000 new cases reported in 2020 [2]. In addition, primary liver cancer is the third most common cause of cancer-related mortality worldwide, with over 830,000 deaths in 2020 [2]. With a five-year survival of approximately 21 percent, liver cancer is among the most lethal gastrointestinal tumors [3].

Primary liver cancer incidence rates and death rates have been increasing in many parts of the world, including North America, Latin America, and central Europe [2,4-7]. In the United States, mortality from liver cancer has evolved over time [6,8,9], initially increasing for decades but subsequently stabilizing or declining [3]. These trends have been attributed to increasing detection of localized HCC. However, there is concern that the COVID-19 pandemic and its impact on subsequent delays in screening, diagnosis, and treatment of patients with HCC may reverse these positive epidemiologic trends [10-12]. (See "COVID-19: Considerations in patients with cancer".)

Geographic variation — The worldwide incidence of HCC varies according to geographic location. It was estimated that 72 percent of HCC cases occur in Asia, 10 percent in Europe, 8 percent in Africa, 5 percent in North America, and 5 percent in Latin America [2,13]. Mongolia has the highest incidence of liver cancer (93.7 per 100,000), but China has the greatest number of cases because of the high incidence (18.3 per 100,000) and its large population [1]. Differences in HCC prevalence are probably due to regional variations in exposure to hepatitis viruses and environmental pathogens [2]. As an example, the frequency of hepatitis B virus carriers is relatively high in regions with higher HCC incidence than regions with lower incidence. (See "Epidemiology, transmission, and prevention of hepatitis B virus infection".)

Sex and race — HCC has been reported more frequently in men than in women, with a male to female ratio of approximately 3:1 [2,14]. (See 'Geographic variation' above.)

Although not fully understood, the differences in sex distribution are thought to be due to variations in hepatitis carrier states, exposure to environmental toxins, and/or potentially protective effects of estrogen mediated through inhibition of interleukin 6 [15].

Population-based studies in the United States have identified racial and ethnic variations in the incidence of HCC, and they conclude that Asia-Pacific Islanders (APIs) have higher rates of HCC compared with other groups [16-18]. For example, in a database analysis from the United States, the incidence rates among APIs, Black Americans, Native Americans/Alaska Natives, and White Americans were 7.8, 4.2, 3.2, and 2.6 per 100,000 persons, respectively [17].

Year of birth — In the United States, a critical risk factor for HCC is HCV infection. (See 'Hepatitis C virus' below.)

Historically, the prevalence of HCV infection has been particularly high among individuals born between 1945 and 1965 (approximately 2.5 percent) [19]. (See "Epidemiology and transmission of hepatitis C virus infection", section on 'Epidemiology'.)

An analysis of multiple causes of death data from the National Center for Health Statistics provided evidence of an increased burden of HCV and HCC-associated mortality among this birth cohort [20]. Among persons dying between 1999 through 2013, for whom both HCV and liver cancer were listed as causes of death, those born from 1945 through 1965 had the largest increase in mortality rates from HCC and HCV, relative to individuals born before 1945 or after 1965.

Risk factors and screening for chronic HCV infection in adults is discussed separately. (See "Screening and diagnosis of chronic hepatitis C virus infection", section on 'Whom to test'.)

RISK FACTORS

Multiple risk factors for the development of HCC have been identified, and a common characteristic among many of them is injury to the liver parenchyma resulting in cirrhosis [21]. Chronic infection with hepatitis B virus (HBV) or HCV underlies many of these cases. In an analysis of 770,000 cases of HCC occurring worldwide, over 50 percent of cases were attributed to chronic HBV and 20 percent of cases were attributed to chronic HCV infection [22]. However, patients with chronic HBV infection are at risk for HCC even in the absence of cirrhosis. (See 'Hepatitis B virus' below.)

The approach to surveillance for patients at risk for HCC is discussed separately. (See "Surveillance for hepatocellular carcinoma in adults", section on 'High-risk groups'.)

Cirrhosis — Patients with cirrhosis from any etiology are at risk for developing HCC. It was estimated that up to one-third of patients with cirrhosis will develop HCC during their lifetime, with an annual incidence rate of 1 to 8 percent, based on long-term follow-up studies [23,24].

Viral hepatitis

Hepatitis B virus — Chronic HBV infection has been associated with increased risk for HCC [25-28]. While HCC can develop in patients with chronic HBV but without cirrhosis, the majority of patients with HBV who develop HCC will have cirrhosis [29]. Similarly, the annual incidence of HCC among those with HBV infection is higher in patients with cirrhosis compared with no cirrhosis (3.2 versus 0.1 cases per 100 person-years) [30].

In addition to cirrhosis, other HBV-related factors that were associated with HCC risk include (see "Hepatitis B virus: Clinical manifestations and natural history", section on 'Sequelae and prognosis of chronic HBV infection'):

- High viral load (ie, HBV DNA levels >10^6 copies /mL) [31].
- HBeAg positivity (an indicator of a prolonged replication phase) [32].
- HBsAg levels >1000 IU/mL in patients with HBeAg negative chronic HBV with low viral load (ie, inactive chronic HBV) [28,33,34].
- HBV genotype C [35]. (See "Clinical significance of hepatitis B virus genotypes", section on 'Hepatocellular carcinoma'.)
- Male sex (for patients who are HBsAg positive) [33,36].
- Viral coinfection (HCV or hepatitis D virus) [37,38]. (See "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection", section on 'Clinical manifestations'.)

  Coinfection with HBV and hepatitis E virus (HEV) was associated with increased HCC risk compared with HEV infection alone [39]. However, coinfection was associated with lower HCC risk compared with HBV infection alone, implying that HEV infection served to mitigate rather than promote the effect of HBV on HCC carcinogenesis.
- HBsAg clearance – Despite a generally favorable prognosis, clearance of HBsAg did not eliminate the risk of HCC [40,41]. In a study including 1271 patients, chronic HBV with average follow-up of 20 years, HCC incidence was lower in patients who were HBsAg negative compared with those who were HBsAg positive (37 versus 196 per 100,000 person-years), but still higher than the general population [41].

Other risk factors that can concurrently exist in persons with HBV infection and are associated with HCC risk include [40,42-46]:

- Age – Young age of HBV acquisition or older age among those with chronic infection.
- Lifestyle factors – Alcohol or tobacco use.
- Blood group B (in males only) [47].
- Family history of HCC [46].

Nomograms that identified patients with HBV who were at increased risk for HCC have been developed and validated [6]. (See "Surveillance for hepatocellular carcinoma in adults", section on 'Individualizing surveillance based on risk'.)

Hepatitis C virus — HCV infection has been associated with HCC risk, and cancer develops almost exclusively in HCV-infected patients with advanced stages of hepatic fibrosis or cirrhosis [36,48]. Estimates of the risk of developing HCC once cirrhosis has developed have ranged from 1 to 4 percent per year [49]. In the United States, HCV accounts for approximately one-third of HCC cases, while successful treatment lowers but does not eliminate HCC risk [50]. (See 'Treatment for viral hepatitis' below.)

In addition to cirrhosis, other risk factors that can concurrently exist in persons with HCV infection and have been associated with the development of HCC include [51]:

- Genotype – HCV genotype 1b, compared with genotypes 2a/c, although this observation may be confounded by other factors [52-55]. The effect of viral factors on disease progression (eg, cirrhosis) is discussed separately. (See "Clinical manifestations and natural history of chronic hepatitis C virus infection", section on 'Viral factors'.)
- Viral coinfection (HBV or human immunodeficiency virus infection) [56-58].
- Lifestyle factors – Alcohol or tobacco use. (See 'Lifestyle factors' below.)
- Metabolic factors – Diabetes mellitus, obesity. (See 'Metabolic factors' below.)

It is generally believed that HCC arises in the setting of rapid cellular turnover and the chronic inflammatory state induced by HCV. One theory is that there is an imbalance in the microenvironments and cytokines of HCV-infected livers, leading to increased inflammation and cell turnover, which ultimately causes cirrhosis. Poorly differentiated hepatocytes likely proliferate and develop into dysplastic nodules and HCC [59]. The pathology of HCC is discussed separately. (See "Pathology of malignant liver tumors", section on 'Hepatocellular carcinoma'.)

Hepatitis D virus — Hepatitis D virus (HDV) infection is caused by a defective virus that depends on HBV for its propagation and cannot establish infection on its own. The prevalence of HDV in patients with chronic HBV infection has varied across studies, while HDV coinfection rates ranging from approximately 10 to 30 percent have been reported. (See "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection", section on 'Epidemiology'.)

Chronic HDV infection has been associated with HCC risk beyond that attributable to chronic HBV infection [60,61]. In a meta-analysis of 93 studies including over 98,000 patients with HBV infection, concurrent chronic HDV infection was associated with higher risk of HCC compared with HBV infection alone (pooled OR 1.28, 95% CI 1.05-1.57) [60]. This association was strongest for patients with HBV-human immunodeficiency virus (HIV) coinfection (pooled OR 7.13, 95% CI 2.83-17.92).

Environmental toxins — Environmental toxins may contribute to the pathogenesis of HCC; however, toxins are probably not independent risk factors, but rather may act synergistically with other more common risk factors (eg, HBV infection).

- **Aflatoxin B1** – Dietary intake of aflatoxin B1, a mycotoxin that contaminates staple food products (eg, corn) has been associated with HCC, particularly in parts of Africa and Asia (where testing grain for aflatoxin is less commonly performed), and among HBV-infected individuals [62-64]. In a case-control study of HBV carriers from a large community-based cohort in Taiwan, the risk of developing cirrhotic HCC or noncirrhotic HCC was higher in patients with high levels of aflatoxin B1–albumin adducts compared with those with undetectable levels (OR 5.5, 95% CI [confidence interval] 2.2-13.6 and OR 5.4, 95% CI 1.1-26.2, respectively) [63]. Cases and controls were matched for age, sex, township of residence, and date of blood sample collection.

  Mutations of the p53 tumor suppressor gene have been demonstrated in patients with HCC who have chronically been exposed to aflatoxin B1 [65,66]. Similar findings have been demonstrated in animal models of hepatocarcinogenesis in which p53 mutations have been observed in laboratory animals exposed to HBV and aflatoxins [67].

- **Betel nut chewing** – Case control trials have suggested that betel nut chewing, which is widespread in certain regions of Asia, may be an independent risk factor for the development of cirrhosis and HCC [64,68,69]. It has also been implicated in the development of esophageal cancer and squamous cell head and neck cancer. (See "Epidemiology and pathobiology of esophageal cancer" and "Epidemiology and risk factors for head and neck cancer".)

- **Iron overload in patients without genetic susceptibility** – For patients without genetic susceptibility to iron overload, iron from non-dietary sources (eg, chronic transfusion of red blood cells for hereditary anemia) may be associated with cirrhosis and an increased risk of HCC. (See "Approach to the patient with suspected iron overload" and 'Genetic susceptibility' below.)

- **Contaminated drinking water** – Several studies conducted in rural China have noted a higher mortality rate from HCC among people who drink pond-ditch water compared with those who drink well water (100 versus fewer than 20 deaths per 100,000 population per year) [64,70]. The blue-green algal toxin Microcystin commonly contaminates these ponds and is thought to be a strong promoter of HCC [71].

Lifestyle factors

Alcohol — Alcohol intake and resulting cirrhosis have been linked to HCC in many reports [72-74], although the threshold dose and duration of use are uncertain. In a cohort study of 652 patients with biopsy-confirmed alcoholic cirrhosis with median follow-up of 29 months, 43 patients (7 percent) developed HCC, with an estimated incidence of 2.9 cases per 100 patient-years [75]. The relationship between alcohol and HCC could be a direct toxic effect, or an indirect one, since alcohol represents an important risk factor for cirrhosis, a predisposing factor for HCC [25].

Alcohol can act synergistically with other coexisting HCC risk factors (eg, viral hepatitis [76], diabetes mellitus [77], obesity [78-80]). (See 'Viral hepatitis' above and 'Metabolic factors' below.)

Furthermore, alcohol use has been associated with increased risk for other cancers (eg, esophageal cancer), and this is discussed in more detail separately [81]. (See "Overview of the risks and benefits of alcohol consumption" and "Epidemiology and pathobiology of esophageal cancer", section on 'Smoking and alcohol'.)

Tobacco — Tobacco use has been implicated as a risk factor for liver cancer in addition to other cancers (eg, lung, esophagus, stomach) [82,83]. (See "Overview of cancer prevention", section on 'Tobacco use'.)

Dietary factors — Data from epidemiologic studies suggest that dietary factors may play a role in the risk of developing liver cancer:

- **Sugar-sweetened beverages** — Higher intake of sugar-sweetened beverages has been associated with an increased risk of liver cancer [84-86]. In an observational cohort study from the Women's Health Initiative of 98,786 postmenopausal females, at median follow-

up of over 20 years and after adjusting for other risk factors, the consumption of one or more servings per day of sugar-sweetened beverages (regular non-diet soft drinks and fruit drinks) was associated with an increased incidence of liver cancer (HR 1.85, 95% CI 1.16-2.96) relative to the consumption of three or less of such beverages per month [86]. By contrast, increased consumption of artificially sweetened beverages was not associated with an increased incidence of liver cancer in this study.

Further details on healthy diet in adults and advice on dietary patterns for cancer prevention, including limiting or avoiding sugar-sweetened beverages, are discussed separately. (See "Overview of cancer prevention", section on 'Advice on dietary patterns' and "Healthy diet in adults", section on 'Added sugars and sugar-sweetened beverages'.)

Metabolic factors

Nonalcoholic fatty liver disease — Growing evidence suggests that nonalcoholic fatty liver disease (NAFLD) (and in particular, nonalcoholic steatohepatitis [NASH]-related cirrhosis), contributes to the development of HCC and represents an increasingly common risk factor for HCC in Western countries [87-91]. The estimated annual incidence rate of HCC in patients with NASH cirrhosis was approximately 1 to 2 percent [13]. In a large cohort study of patients with NASH cirrhosis, the incidence of HCC was 1 per 100 person-years of follow-up [92].

While several cohort studies demonstrated that HCC occurred in patients with NAFLD but without cirrhosis, the incidence of HCC in the absence of cirrhosis is low [89,92,93]. In a large cohort study of patients with NAFLD without cirrhosis, the incidence of HCC was 0.008 per 100 person-years of follow-up [89]. The epidemiology, diagnosis, management, and prognosis for patients with NAFLD are discussed separately. (See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults" and "Management of nonalcoholic fatty liver disease in adults".)

Diabetes mellitus — Epidemiologic studies suggest a possible link between diabetes mellitus and HCC [94-101], and multiple systematic reviews and meta-analyses have also found an association [102-104]. A systematic review that included 49 case-control and cohort studies estimated that HCC risk was increased in patients with diabetes mellitus by approximately 2.2-fold (risk ratio 2.2; 95% CI 1.7-3.0), although few studies adjusted for diet and obesity [102]. A meta-analysis of 14 prospective epidemiologic studies also found an increased risk of HCC among patients with diabetes (relative risk [RR] 1.9; 95% CI 1.2-2.3) [103].

A subsequent population-based cohort study confirmed the findings of the systematic review and meta-analysis. The study included 19,349 patients with newly diagnosed diabetes and 77,396 patients without diabetes [97]. The incidence of HCC was higher among patients with

diabetes compared with those without diabetes (21.0 versus 10.4 per 10,000 person-years), with an adjusted hazard ratio [aHR] of 1.7 (95% CI 1.5-2.0). (See 'Metformin' below.)

However, associations between diabetes and HCC should be interpreted with caution. In many cases, the onset of glucose intolerance results from the development of cirrhosis, so the diagnosis of diabetes mellitus in this context may be a surrogate for cirrhosis, which increases the risk of HCC. In addition, many patients with diabetes also have NAFLD, which has also been associated with an increased risk of HCC. (See 'Nonalcoholic fatty liver disease' above.)

Obesity — Obesity has been independently associated with liver cancer, while obesity and diabetes mellitus often coexist in patients with NAFLD [78,80,105-108]. In a meta-analysis of 11 cohort studies, the risk of liver cancer was greater in patients with obesity compared with those of normal weight (RR 1.89, 95% CI 1.51-2.36) [108]. (See "Overweight and obesity in adults: Health consequences".)

Genetic susceptibility — Several inherited disorders have been associated with development of HCC:

- Hereditary hemochromatosis – Data have demonstrated that genetic evidence of hereditary hemochromatosis (HH; ie, C282Y homozygotes) conferred an increased risk of HCC, and the risk was especially high in patients with cirrhosis [109,110]. The magnitude of risk for HCC and management of HH are discussed in more detail separately. (See "Clinical manifestations and diagnosis of hereditary hemochromatosis", section on 'Clinical manifestations' and "Management and prognosis of hereditary hemochromatosis".)

- Alpha-1 antitrypsin deficiency – Alpha-1 antitrypsin deficiency has been associated with an increased risk of cirrhosis and HCC. Liver disease associated with alpha-1 antitrypsin deficiency is discussed separately. (See "Extrapulmonary manifestations of alpha-1 antitrypsin deficiency", section on 'Hepatic disease'.)

- Acute intermittent porphyria – Acute intermittent porphyria (AIP), a disorder that resulting from an enzyme deficiency responsible for heme biosynthesis, has been associated with an increased risk of HCC [111-113]. In a population-based study, AIP was associated with markedly higher risk of HCC compared with the general population (standardized incidence ratio 70, 95% CI 23-164) [113]. Although the risk of HCC appears to be independent of the presence of cirrhosis [113], the role of iron overload is uncertain. (See "Acute intermittent porphyria: Management", section on 'Monitoring for disease complications'.)

Other factors — Porphyria cutanea tarda (PCT) is a disorder with cutaneous and hepatic manifestations that is caused by altered enzyme activity in the heme biosynthetic pathway. (See "Porphyria cutanea tarda and hepatoerythropoietic porphyria: Pathogenesis, clinical manifestations, and diagnosis".)

PCT has been associated with increased risk of HCC; however, underlying liver disease (eg, HCV infection, alcohol-associated liver disease) is also common in patients with PCT and likely is contributing to risk [114,115]. In a large population based study, HCC risk was increased in patients with PCT compared with the general population (aHR 19.7, 95% CI 8.8-44.0) [115]. (See "Porphyria cutanea tarda and hepatoerythropoietic porphyria: Management and prognosis".)

PROTECTIVE FACTORS

Vaccination for hepatitis B virus (HBV) prevention — Vaccination against HBV infection can prevent active infection, and thus protect against HBV-related HCC. (See "Hepatitis B virus immunization in adults".)

Treatment for viral hepatitis — Antiviral therapy has been associated with a protective effect:

- HBV treatment – Several studies have demonstrated that treatment for chronic HBV infection reduced HCC risk. Systematic reviews suggested that the relative risk is reduced by approximately 50 to 60 percent following treatment with interferon or nucleos(t)ide derivatives [116-119]. However, treatment did not eliminate HCC risk, and the benefit was not seen in patients who developed nucleos(t)ide resistance. (See "Hepatitis B virus: Overview of management".)

- HCV treatment – For patients with chronic HCV infection, data suggest that antiviral therapy decreased, but did not eliminate, HCC risk [120-127]. Antiviral therapies include (see "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Benefits of treatment'):

  - Direct-acting antiviral therapy – Accumulating evidence suggests that direct-acting antiviral (DAA) therapy resulting in sustained virologic response (SVR) reduced the risk of HCC [121,122,128]. In a study of over 22,000 patients with HCV who were treated with DAA therapy, patients who achieved SVR were less likely to develop HCC compared with patients without SVR (annual incidence rate 0.9 versus 3.5 percent; adjusted hazard ratio [aHR] 0.28, 95% CI [confidence interval] 0.22-0.36) [121]. The residual risk in patients with SVR was related to those with established cirrhosis, a known HCC risk factor [121,127]. (See 'Cirrhosis' above.)

The use and timing of antiviral therapy to reduce the risk of HCC recurrence for patients with chronic HCV infection and an established diagnosis of HCC are presented separately. (See "Management of potentially resectable hepatocellular carcinoma: Prognosis, role of neoadjuvant and adjuvant therapy, and posttreatment surveillance", section on 'HCV-related HCC' and "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Hepatocellular carcinoma'.)

- Interferon-based therapy – Long-term observational studies of patients treated with interferon-based therapy have demonstrated lower HCC risk in patients who achieved SVR compared with those who did not [120,123,124,129]. In a study of 530 patients with HCV infection who were treated with an interferon-based regimen with a median eight years follow-up, the risk of HCC was lower in patients with SVR compared with those without SVR (HR 0.19, 95% CI 0.08 to 0.44) [120].

Management for patients with chronic HCV infection, including antiviral therapy and monitoring disease progression, is discussed separately. (See "Overview of the management of chronic hepatitis C virus infection".)

Models for predicting risk of HCC may be used to determine an optimal follow-up regimen for each patient [130,131]. For example, a nomogram to predict the occurrence of HCC at one, three, and five years in patients with HCV-related cirrhosis was based upon the following factors: age, past alcohol intake, platelet count, gamma-glutamyl transpeptidase level, and SVR status [130]; independent validation is needed.

Medications

Statins — Observational studies have found that use of hydroxymethylglutaryl CoA reductase inhibitors (statins) was associated with a lower risk of HCC. Study populations have included United States veterans, Eastern Asian individuals with diabetes, Eastern Asian individuals with HBV or HCV infection, in addition to lower risk, general populations [132-138]. As an example, in a meta-analysis of ten studies with 1.6 million patients, compared with patients who did not use statins, statin users had a 37 percent decrease in the risk of developing HCC (odds ratio [OR] 0.63; 95% CI 0.52-0.76) [139]. This effect was most profound in Eastern Asian males with chronic HBV, who are at high risk for HCC. The effect was less dramatic in studies from the United States and Europe, where the proportion of patients with HCC due to chronic HBV infection is much lower [140].

These studies are difficult to interpret because of the complex relationship between cholesterol and liver disease. In patients with cirrhosis, low cholesterol levels are associated with more advanced disease, thrombocytopenia, lower albumin levels, and a higher risk of HCC;

paradoxically, these high-risk patients are less likely to be given statin therapy [140,141]. Thus, the purported benefit of statins may have been enhanced by selection bias (ie, patients at low risk for HCC were more likely to receive statin therapy). However, statins may reduce HCC indirectly by slowing progression of cirrhosis [142].

In addition, among patients with chronic viral hepatitis, statin type (ie, lipophilic [eg, atorvastatin, simvastatin] or hydrophilic [eg, pravastatin]) may influence the potential protective effect, although the data are not consistent:

- In a nationwide cohort study that included over 16,000 adults with chronic HBV or HCV infection, use of a lipophilic statin was associated with a lower 10-year cumulative risk of HCC compared with no statin (3 versus 8 percent; aHR 0.56, 95% CI 0.41-0.79). In contrast, the risk of HCC was not significantly lower in patients receiving a hydrophilic statin compared with no statin [143].

- Conversely, in a large cohort study including patients with cirrhosis of any etiology, no association was found between the type of statin and risk of HCC [141]. Thus, whether the type of statin impacts the magnitude of effect remains uncertain, and additional data from randomized trials are needed.

The clinical use and adverse effects of statins are discussed separately. (See "Statins: Actions, side effects, and administration", section on 'Chronic liver disease'.)

Aspirin and other nonsteroidal anti-inflammatory drugs — Long-term, regular use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with lower risk of HCC and lower liver-related mortality [144-149]:

- In a cohort study including over 130,000 participants who were followed for more than 26 years, there were 108 cases of HCC (ie, absolute incidence rate of <0.001 percent). Regular use of aspirin (≥2 standard dose [325 mg] tablets per week) was associated with a reduced risk of HCC compared with non-regular use (aHR 0.51, 95% CI 0.34-0.77) [144]. The association was dose-and duration-dependent; a decreased risk was apparent with use of 1.5 or more standard dose aspirin tablets for five or more years. In another cohort study including over 50,000 patients with chronic HBV or HCV infection who were followed for a median of nearly eight years, low-dose aspirin (≤160 mg daily) was associated with reduced risk of HCC (4 versus 8 percent; aHR 0.69, 95% CI 0.62-0.76) and lower liver-related mortality (11 versus 18 percent; aHR 0.73, 95% CI 0.67-0.81) compared with no aspirin use [147]. The risk of gastrointestinal bleeding was not significantly different in aspirin users compared with nonusers.

- Additional information is available from a systematic review and meta-analysis of 19 studies totaling over 147,000 at-risk individuals with chronic liver disease (including the large Swedish cohort described above), who were followed for at least six months, in whom **any** use of an NSAID or antiplatelet therapy for a defined period of time reduced the risk of HCC compared with no use (nine studies, 115,124 individuals, HR 0.51, 95% CI 0.36 -0.72) [148]. Use of NSAIDs or antiplatelet therapy also reduced liver-related mortality (three studies, 52,789 individuals, odds ratio [OR] 0.32, 95% CI 0.15-0.70). In this analysis, there was moderate evidence that use of aspirin was associated with an increase in gastrointestinal bleeding risk (four studies, 85,791 patients, OR 1.32, 95% CI 1.08-1.94), as did all antiplatelet therapies (two studies, 3884 patients, OR 2.65, 95% CI 1.20-5.85).

These data suggest that patients with chronic liver disease who take aspirin for cardiovascular prevention may have an additional benefit of reducing HCC risk. (See "Aspirin in the primary prevention of cardiovascular disease and cancer".)

Despite lack of randomized trials, some UpToDate contributors anticipate using low-dose aspirin as chemoprevention for patients with chronic viral hepatitis who are at risk for HCC, while other contributors await further studies to confirm these findings. (See "Surveillance for hepatocellular carcinoma in adults", section on 'High-risk groups'.)

Metformin — Several studies suggested that metformin was associated with decreased HCC risk [150-153]. For example, in a meta-analysis of eight observational studies including patients with diabetes mellitus, metformin therapy was associated with lower risk of HCC (OR 0.50, 95% CI 0.34-0.73) [154]. In addition, metformin has also been associated with lower overall cancer risk, and this is discussed separately. (See "Metformin in the treatment of adults with type 2 diabetes mellitus", section on 'Cancer incidence'.)

Lifestyle factors — Lifestyle factors associated with reduced risk of HCC and liver cancer include:

- **Coffee** – Several observational studies have suggested that coffee consumption was a protective factor against developing liver cancers, including HCC [155,156]. In a meta-analysis of 12 studies, regular coffee consumption was associated with reduced HCC risk compared with no or occasional coffee (RR 0.66, 95% CI 0.55-0.78) [155]. Coffee contains large amounts of antioxidants, suggesting biologic plausibility for the protective effect. (See "Vitamin intake and disease prevention", section on 'Antioxidants'.)

- **Diet** – Multiple dietary factors have been linked to reduced liver cancer risk [157,158]. For example, consumption of white meat, fish, omega-3 fatty acids, or vegetables was associated with a reduced HCC risk [157-162]. Dietary intake of vitamin E has also been

associated with a decreased risk of HCC among patients both with and without a self-reported history of liver disease or a family history of HCC [163]. (See "Overview of vitamin E".)

- **Physical activity** – Observational data have suggested that physical activity was associated with lower risk of liver cancer [164,165]. In a large, multinational cohort study with 15-year follow-up, physical activity was associated with lower HCC risk compared with sedentary lifestyle (HR 0.55, 95% CI 0.38 to 0.80) [164]. Possible mechanisms for risk reduction include the effect of exercise on glucose or lipid metabolism in the liver or on improving nonalcoholic fatty liver disease [165]. (See "Management of nonalcoholic fatty liver disease in adults", section on 'Weight loss'.)

Other factors — For patients with nonalcohol-associated steatohepatitis (NASH) and obesity, bariatric surgery has been associated with lower rates of liver-related complications including HCC [166]. Outcomes associated with bariatric surgery are discussed separately. (See "Outcomes of bariatric surgery", section on 'Nonalcoholic fatty liver disease'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hepatocellular carcinoma".)

SUMMARY

- **Incidence and mortality** – Cancer of the liver and intrahepatic bile ducts is among the most frequently diagnosed malignancies and causes of cancer-related mortality worldwide. (See 'Incidence and mortality' above.)
- **Risk factors**
  - **Sex** – Hepatocellular carcinoma (HCC) has been reported more frequently in men than in women, with a male to female ratio of approximately 3:1. (See 'Sex and race' above.)
  - **Chronic hepatitis B and C virus infection** – Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection is associated with increased risk for HCC. (See 'Viral hepatitis' above.)

- **Cirrhosis** – Patients with cirrhosis from any etiology are at risk for developing HCC. It was estimated that up to one-third of patients with cirrhosis will develop HCC during their lifetime, with an annual incidence rate of 1 to 8 percent, based on long-term follow-up studies. (See 'Cirrhosis' above.)

- **NAFLD** – Available evidence suggested that nonalcoholic fatty liver disease (and in particular nonalcoholic steatohepatitis [NASH]-related cirrhosis), has been an increasingly common risk factor for HCC in Western countries. For patients with NASH cirrhosis, the estimated annual incidence rate of HCC was approximately 1 to 2 percent. (See 'Nonalcoholic fatty liver disease' above.)

- **Protective factors**

  - **Hepatitis B vaccination** – Vaccination against hepatitis B virus (HBV) infection can prevent infection, and thus protects against HBV-related HCC. (See "Hepatitis B virus immunization in adults".)

  - **Treatment of chronic hepatitis B or C virus infection** – For patients with chronic HBV or HCV infection who are successfully treated with antiviral therapy, the risk of HCC has been reduced but not eliminated. (See 'Treatment for viral hepatitis' above.)

  - **Coffee** – Observational studies have suggested that coffee consumption is a protective factor against developing liver cancers, including HCC.

- **Surveillance** – Surveillance for HCC is indicated for patients with disorders that put them at increased risk for developing HCC (eg, cirrhosis, chronic hepatitis B infection). Further details are discussed separately. (See "Surveillance for hepatocellular carcinoma in adults".)

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