Review

Epidemiology of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma

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Nader N. Massarweh, MD, MPH[1,2], and Hashem B. El-Serag, MD, MPH[1,3]

Abstract

Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) are the most frequently occurring types of primary liver cancer and together are among the most common incident cancers worldwide. There are a number of modifiable and nonmodifiable HCC and ICC risk factors that have been reported. A review of the existing literature the epidemiology and risk factors for HCC and ICC was performed. There are a number of major infectious, lifestyle, metabolic, and heritable risk factors for both HCC and ICC. Some of these risk factors are either potentially preventable (eg, alcohol and tobacco use) or are currently treatable (eg hepatitis infection). In most cases, the molecular pathway or mechanism by which these etiologic factors cause primary liver cancer has not been well delineated. However, in nearly all cases, it is believed that a given risk factor causes liver injury and inflammation which results in chronic liver disease. Given the rising prevalence of several common HCC and ICC risk factors in the western world, the best opportunities for improving the care of these patients are either through the prevention of modifiable risk factors that are associated with the development of chronic liver disease or the identification of at risk patients, ensuring they are appropriately screened for the development of primary liver cancer, and initiating treatment early.

Keywords

epidemiology, cirrhosis, hepatitis, hepatocellular carcinoma, intrahepatic cholangiocarcinoma

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Introduction

Among the various types of primary liver cancers, hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) are the most common accounting for roughly 70% and 15% of cases, respectively.[1] Over the last several decades in the United States, the incidence of HCC and possibly ICC has steadily risen, and in the coming decades, there are anticipated to be continued increases.[2-6] This, in combination with the high rate of cancer-related mortality, underscores the fact that optimal management of primary liver cancer remains a challenge.[6,7] Despite established screening guidelines for detecting incident cancer among at risk patients, the often asymptomatic nature of these cancers frequently results in patients presenting with late stage disease not amenable to curative treatment. For those who are detected through screening and who present with early stage disease, cirrhosis is not only a common etiologic factor but a condition that can complicate or limit the available treatment options. As such, the best opportunities for improving the care of these patients are either through the prevention of underlying liver disease or the identification of at risk patients, ensuring they are appropriately screened for the development of primary liver cancer and initiating treatment early.

[1] U.S. Department of Veterans Affairs Health Services Research and Development Center of Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, USA
[2] Michael E. DeBakey Department of Surgery, Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX, USA
[3] Department of Medicine, Baylor College of Medicine, Houston, TX, USA

Corresponding Author:
Nader N. Massarweh, Michael E. DeBakey Department of Surgery, Michael E. DeBakey VA Medical Center, Baylor College of Medicine, 2002 Holcombe Boulevard, OCL 112, Houston, TX 77030, USA.
Email: massarwe@bcm.edu

Hepatocellular Carcinoma

Hepatocellular carcinoma is the most common primary liver malignancy. In the United States, the burden of HCC has been increasing for a number of years and it is currently among the most commonly diagnosed new cancers and the fastest rising causes of cancer-related deaths.[7] Current estimates from the Surveillance, Epidemiology, and End Results population-based cancer registry suggest there has been a nearly 4-fold increase in HCC incidence over the last 4 decades (1.6 per 100 000 in 1975-1977 to 4.8 per 100 000 in 2005-2007) and that this increasing incidence may continue further into the future.[4,8] Furthermore, long-term survival for patients diagnosed with HCC is poor, making it a major cause of cancer-related mortality.[7]

There are a number of established HCC risk factors (Figure 1). A common characteristic among them is injury to the liver parenchyma resulting in the eventual development of cirrhosis. However, as the epidemiology of chronic liver disease in the United States has changed, so too have the number of cases arising in livers without a background of cirrhosis. For example, nonalcoholic fatty liver disease (NAFLD) is now the most common etiology of chronic liver disease in the United States and has brought an appreciation for the role of metabolic factors in the cancer development pathway.[9] Although many patients with NAFLD will develop varying degrees of fibrosis, the minority will go on to develop cirrhosis.[10,11]

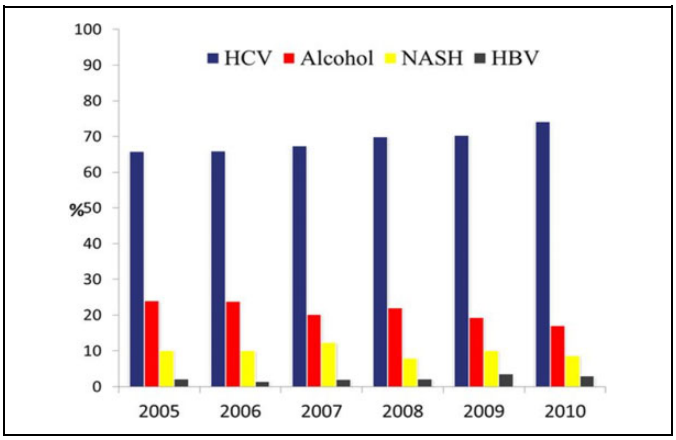

Figure 1. HCC prevalence by specific risk factor. HBV indicates hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C; NASH, nonalcoholic steatohepatitis. Reprinted from Mittal S, Sada YH, El-Serag HB, et al. Temporal trends of nonalcoholic fatty liver disease-related hepatocellular carcinoma in the veterans affairs population. *Clin Gastroenterol Hepatol*. 2015;13(3):594-601, with permission from Elsevier.

Intrahepatic Cholangiocarcinoma

Classification of cholangiocarcinoma into intrahepatic, perihilar, and distal subgroups has helped standardize the diagnosis, treatment, and study of this malignancy (Figure 2). After HCC, ICC is the second most common primary hepatic malignancy accounting for 10% to 20% of newly diagnosed liver cancers.[12] The incidence of ICC in the United States may have risen over the last several decades, with an average annual incidence of 1.6 per 100 000/year since 2000, although recent data suggest the incidence of ICC has remained stable between 1992 and 2007 with only slight fluctuations.[3,5,13] Misclassification of Klatskin tumors does not appear to play a significant role in these trends. But, it is unclear whether the observed increased incidence is a function of the prevalence of cirrhosis and related risk factors or an increase in the rate of diagnosis because of improved screening programs and more frequent use of cross-sectional imaging for other reasons. Long-term survival for patients with ICC is even worse than for HCC which may be a related to a high propensity for regional and distant metastases as well as the lack of effective systemic therapy options.

Relative to HCC, substantially less is known about the epidemiology of ICC, especially in western countries. Many ICCs are actually detected during HCC screening in at risk patients or those who are undergoing treatment (eg, hepatic resection or transplantation) for a presumed diagnosis of HCC. As such, many of the commonly cited HCC risk factors are shared by ICC. For this reason, it is believed that inflammation and subsequent injury to the bile ducts also plays a role in ICC carcinogenesis. Although several ICC-specific risk factors have been identified, the mechanisms by which they lead to the development of ICC is less clear. But, again bile stasis and inflammation are believed to be inciting factors.

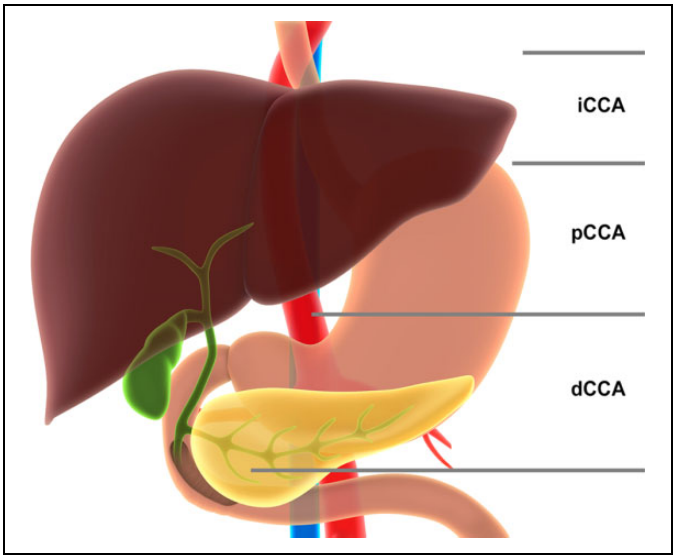

Figure 2. Anatomic cholangiocarcinoma classification. dCCA indicates distal cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma.

Risk Factors

Cirrhosis

The association between cirrhosis and primary liver malignancies has long been established. Relative to patients without cirrhosis, cirrhosis can be associated with an over 30-fold

increase in HCC risk and a 10-fold to 20-fold increase in ICC risk.[14-16] One of the likely reasons for this consistently identified and strong association is that cirrhosis is in the common pathway through which many of the other risk factors discussed herein lead to the development of HCC and ICC. Furthermore, understanding its role in the development of HCC and ICC is complicated by the fact that many patients with underlying liver disease have well-compensated cirrhosis, and thus their disease may go clinically undetected until they develop decompensated liver function or they present with advanced cancer. For example, over 20% of patients presenting with HCC are simultaneously identified as having previously undiagnosed cirrhosis.[17]

Viral Hepatitis

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most common etiologic factors worldwide and account for the majority of incident cases of HCC (40%-50%). At present in the United States, 45% to 55% of new HCC cases are attributed to HCV, 10% to 15% to HBV, 5% are coinfected with HBV and HCV, and 30% to 35% are not infected with either.[18] Together, they are estimated to account for nearly 60% of all cases of cirrhosis worldwide.[19] In turn, a recent study estimated HBV and HCV account for approximately 25% of HCC cases in the United States.[20] HBV and HCV are known risk factors for the development of cirrhosis, which is present in 80% to 90% of patients with HCC.[21] With regard to ICC, HBV and HCV infections have both been associated with approximately 2-fold increases in risk.[22,23] As such, efforts aimed at treatment of those who are currently infected and prevention of viral transmission are likely to have a dramatic impact on the future incidence of HCC and potentially ICC as well.

Hepatitis B Virus

While less frequently an etiologic factor in the United States, HBV is the most common HCC risk factor worldwide and is believed to account for nearly half of all diagnosed HCCs.[24] Compared to an average risk, uninfected individual, the risk of developing HCC is increased 15-fold to 20-fold with HBV infection.[25,26] There are 6 HBV genotypes, but only C and D (and possibly B) appear to be associated with the highest incidence of HCC. In the United States, the estimated incidence rates of inactive carriers, chronic carriers without cirrhosis, and chronic carriers with compensated cirrhosis are 0.02, 0.3, and 2.2 per 100 person-years.[21] The vast majority (70%-90%) of HBV-associated cases of HCC occur after the development of cirrhosis; however, cancer can also develop in patients with a noncirrhotic liver.[21,27] Conversely, the minority of individuals with acute HBV infection in the United States will become chronic carriers.[28] But, those who do will have an increased risk of developing cirrhosis and potentially HCC.

The annual incidence of HCC among those with HBV infection is significantly higher among those with cirrhosis (3.16/100 person-years) relative to those without (0.10/100 person-years).[14] The risk of HCC associated with HBV infection is estimated between 15-fold and 20-fold relative to those who are not HBV-infected, and this risk is nearly doubled in patients who are coinfected with HCV.[18,26] There are a number of other possible etiologic factors that can concurrently exist in HBV-infected individuals which may also be associated with, or even further increase, risk of developing HCC. For example, age (young age of HBV acquisition or older age among those with chronic infection), male sex, race (eg, Asians and Pacific Islanders), lifestyle factors (eg, heavy alcohol and possible tobacco use), viral (HBV DNA levels) and serologic (HBeAg positivity) data, HBV genotypes, and the duration of infection have all been shown to increase the risk.[21]

There are antiviral medications that are effective in the treatment of HBV by chronically suppressing, but not eradicating, the infection. Successful treatment is associated with a considerable reduction in HCC risk, but not complete elimination. For example, patients with chronic HBV infection treated with lamivudine have lower rates of progression of cirrhosis, lower Child-Pugh scores, and an approximately 50% lower rate of developing HCC.[29]

The association between HBV infection and the development of ICC is not as strong as for HCV, especially in western regions where HBV is uncommon, but has been reported in observational studies and a meta-analysis (4-fold to 6-fold increase in risk).[16,23,30] In addition, it is unclear whether ICC developing in HBV-infected individuals is a consequence of the virus itself or is more related to the eventual development of cirrhosis from chronic infection. However, there are some potentially important histologic and pathologic differences between ICCs that arise in HBV-infected and uninfected individuals that potentially support differences in the mechanism and biology of the disease. For example, HBV-associated ICC are more frequently mass forming, have a lower rate of lymphatic involvement, and a higher rate of capsule formation.[31] In addition, survival after resection is significantly better in HBV-positive patients. Future work is needed to better understand whether the observed difference in survival is related to actual differences in disease biology or is simply a function of lead-time bias in HBV-positive patients who undergo screening.

Hepatitis C Virus

HCV is the leading cause of HCC and probably ICC in the United States. Relative to the uninfected population, HCV-infected patients have an approximately 17-fold increased risk of developing HCC.[32] The "HCV epidemic" in North America appears to have begun in the 1960s to 1970s (potentially related to the high rate of injection drug use at that time) with a subsequent plateau or decrease in infection rates in the 1980s to 1990s, likely related to the development of an effective screening test for the virus.[33] Data derived from recent model simulations suggest the peak incidence of HCV infection-related complications, including decompensated cirrhosis and HCC, will occur sometime in the next decade with eventual decreases after the year 2020.[34]

HCV clearly increases a patients' risk for cirrhosis with 15% to 35% of HCV-infected individuals developing liver disease at 25 to 30 years.[35,36] HCC that develops in a background of HCV appears to result from chronic inflammation causing injury to the liver parenchyma and subsequent fibrosis.[37] Once cirrhosis is established, HCV-infected patients with active infection are expected to develop HCC at an annual rate of 1% to 4%.[21] However, HCC can also occur, although infrequently, in HCV-infected patients with fibrosis but in the absence of cirrhosis.[38] The risk of developing HCC varies by geography but is associated with an approximately 10-fold to 20-fold increase in risk.[18,26] For ICC, HCV infection is more consistently associated with a higher risk relative to HBV (2-fold to 4-fold increase).[23,39] In addition, the consistency of this association across a variety of geographies and populations would all seem to support HCV as an important ICC risk factor.[40]

As with HBV, there are additional concurrent risk factors that can modify the individual's risk for HCC such as sex, race, ongoing alcohol use, diabetes, a secondary viral infection (ie, HBV or HIV), and viral genotype.[41,42] With respect to the latter, there are several HCV genotypes, with variable risk based on the viral subtype. For example, in a recent meta-analysis, genotype 1b was found to be associated with a 78% increased risk of HCC relative to all other genotypes and a 60% increased risk among patients with cirrhosis.[43] However, genotype 3 is currently considered the most difficulty to eradicate and is associated with highest risk of cirrhosis (incidence rate of 30 per 1000 person-years) and HCC (incidence rate of 7.9 per 1000 person-years).[42,44] There are highly effective, but expensive, new HCV treatments (directly acting antivirals). While a sustained viral response with the use of older antiviral medications (like interferon and ribavirin) in chronically infected patients with HCV is associated with a decreased risk of liver-associated morbidity and HCC, the risk remains relatively high in certain subgroups including those who already developed cirrhosis, diabetes, or are cured at an old age.[45,46] The long-term impact of viral clearance on future HCC risk with these newer medications among patients cured of HCV is not yet known.

Alcohol Use

The association between heavy alcohol use and HCC risk has been consistently demonstrated in multiple studies. Although the risk estimates for HCC (1.5-3) are modest compared to viral hepatitis (15-25), alcohol abuse remains a pervasive problem in the United States.[47] As such, it is not a surprise that roughly 13% to 23% of HCC cases are attributable to alcohol-related disorders; however, this effect is modified by the patient's race (alcohol accounts for the second highest population-attributable fraction of HCC in whites, blacks, and Hispanics, but the associated risk varies) and sex (higher risk in males).[20,48] The effect of alcohol is also potentiated by other concurrent risk factors for chronic liver disease, especially viral hepatitis and probably obesity. While the association between ICC and alcohol use has not been studied to the same extent as HCC, the available data do suggest a weak association related to the development of chronic liver disease and cirrhosis.[16]

There are, however, several areas of uncertainty regarding the relationship between primary liver cancer and alcohol. First, the cutoff that clearly constitutes "heavy" use and the duration that puts patients at risk for chronic liver disease has not been clearly defined and is quite variable across studies (use—from >240 to ≥560 g/wk; duration—from at least 1 year to at least 5 years to an undefined time period).[49] Second, there are unanswered questions of whether alcohol itself is carcinogenic or its effect in the carcinogenic pathway is through the development of cirrhosis. Nonetheless, alcohol remains an important contributing etiologic factor to chronic liver disease and, as such, to primary liver cancer as well.

Tobacco Use

It is estimated that approximately 1 in 5 Americans regularly smoke cigarettes.[50] As is the case for a number of other cancers, tobacco use has consistently been associated with an increased risk of developing HCC and has been labeled as a risk factor for liver cancer by the World Health Organization International Agency for Research on Cancer.[51] In a recent, large meta-analysis, relative to individuals who never smoked, there was a 51% increased risk for current smokers and a nonsignificant 12% increased risk for former smokers.[52] In a US hospital-based case-control study, regular, but not irregular, cigarette smoking and the duration of smoking history were found to be a significant risk factor only among men.[53] With regard to noncigarette tobacco products, there was no clear association. For ICC, the data are less consistent. In a meta-analysis of case-control studies, smoking was associated with a nonsignificant 31% increase in the odds of ICC (95% confidence interval [CI]: 0.95-1.82). However, ascertainment of smoking in the studies included in this analysis was variably based on administrative data and patient history.[16] By comparison, in a population-based study, smoking was associated with a statistically significant 80% increase in the odds of ICC (95% CI: 1.0-3.2).

Metabolic Factors

The prevalence of obesity in the United States has increased dramatically.[54,55] With it, there has been a recognition of metabolic syndromes, or a cluster of conditions related to obesity, blood pressure, and glucose and lipid metabolism with an underlying pathophysiology of insulin resistance, as an important etiologic factor for a number of different cancers.[56] These metabolic derangements are increasingly appreciated as etiologic factors for patients without cirrhosis who develop HCC.[57] For example, NAFLD is now the leading cause of cirrhosis in the United States.[9] It is currently estimated that roughly 30% to 40% of new HCC cases are attributable to metabolic disorders.[20,48] Although the intrahepatic molecular changes and the exact mechanism by which metabolic syndrome leads to

chronic liver disease and/or HCC are yet to be defined, development of steatosis and nonalcoholic steatohepatitis (NASH) likely play a role.

Nonalcoholic Fatty Liver Disease/NASH

Nonalcoholic fatty liver disease is a disorder in which excess triglycerides accumulate in liver cells causing steatosis—a phenomenon that occurs in the absence of excessive alcohol intake. Because some element of insulin resistance is identified in nearly all cases of NAFLD, it is believed to occur as a consequence (the hepatic manifestation) of metabolic syndrome. While the mechanism of liver additional injury is not clear, NASH occurs in up to one-third of patients and is believed to cause liver cell injury, inflammation, and eventual fibrosis with 10% to 20% of patients going on to develop cirrhosis.[11] The prevalence of NAFLD in the general population has doubled over the last 2 decades and is now a common cause of chronic liver disease and cirrhosis affecting approximately 1 in 5 adults in the United States.[9,58,59] While there has been an increase in the proportion of cirrhosis and HCC cases associated with NAFLD over the last decade, in a systematic review evaluating the association between HCC and NAFLD/NASH, both the etiology and degree of concurrent chronic liver disease had an important impact on HCC risk.[60] Furthermore, relative to patients with active HCV-related cirrhosis, in patients with cirrhosis related to NASH the risk of HCC was far less.[61]

Although the presence of cirrhosis in patients with NAFLD can generally be readily identified in those presenting symptomatically either with jaundice, ascites, or other stigmata of portal hypertension, the recognition of underlying liver disease is more difficult among those with well-compensated cirrhosis. Many patients can remain well compensated for years, during which time they remain at risk of developing HCC. At present, there is unfortunately not a clear means of identifying patients with NAFLD who are at risk for progressing to cirrhosis until they either present with signs or symptoms or are incidentally discovered. Several studies suggest underrecognition of cirrhosis is one of the main reasons for HCC surveillance underuse in the United States, with over one-fifth of patients who present with HCC having unrecognized cirrhosis.[17] Additional data also indicate a small but important proportion of NAFLD/NASH-related HCC develops in the absence of prior significant liver damage or cirrhosis.[62]

Diabetes

Diabetes is an important component of metabolic syndrome. As mentioned, obesity and/or insulin resistance are present in the majority of patients identified as having NAFLD. Therefore, the question of whether diabetes results in liver damage which is a cause of NAFLD, or whether diabetes itself increases risk above and beyond that associated with chronic liver disease is an important but as yet unanswered one. Furthermore, reverse causality, where diabetes is a consequence of chronic liver disease that precedes development of HCC, is a concern when interpreting the data regarding diabetes-HCC association. However, there are several lines of evidence suggesting diabetes, in particular type II, is associated with an increased HCC risk.

In a systematic review that included a variety of study designs and populations, diabetes was associated with 2-fold to 3-fold increase in the risk of HCC.[63] Given the diversity of the studies included in this analysis, the consistency of the positive association, the geographic variability of study populations, and the temporal association between diabetes and HCC speak to the fact that diabetes is a true risk factor. However, the data did not address the issue about the coexistence of NAFLD or other forms of chronic liver disease. When the association was evaluated in a more recent meta-analysis of cohort studies (that inherently reduce the likelihood of reverse association) which only included patients with chronic liver disease of varying etiology, there was again a consistent 1.5-fold to 2-fold increased risk of HCC.[64]

Further strengthening the argument that diabetes plays a role in carcinogenesis is the fact that medical management can actually modify a patient's risk of developing HCC. There are several studies, both experimental and epidemiologic, suggesting the use of metformin is associated with decreased HCC risk.[65-68] In a meta-analysis of observational studies, the type of medication used also appeared to influence HCC risk—while use of metformin is associated with a decreased risk, the use of thiazolidinedione does not affect the risk, but use of either insulin and sulfonylureas both may increase the risk.[69] These data also support the premise that more severe (as evidenced by the use of stronger antiglycemic medications) and prolonged (as evidence by duration) forms of diabetes may be associated with an incremental increase in risk.

For ICC, there are far fewer sources of data describing the association with diabetes. In the only US population-based study using the Surveillance, Epidemiology, and End Results cancer registry linked to Medicare claims data, there was a 50% increase in the likelihood of ICC among patients with diabetes.[15] This finding was corroborated in more recent meta-analyses of observational studies.[16,70] As with HCC, medical management of diabetes with metformin may decrease cancer risk.[71] Taken together, the data for ICC and HCC suggest diabetes creates a common carcinogenic mechanism through a liver injury pathway. However, additional data to further evaluate this hypothesis are needed.

Obesity

As another common and increasingly observed condition in patients with metabolic syndrome, multiple sources of data associate obesity with increased HCC risk. But, as is the case with diabetes and NAFLD, it is unclear whether this increased risk is a function of physiologic and/or molecular changes induced by obesity or is more related to chronic liver disease caused by metabolic changes common to these entities.

However, there are in vitro data suggesting there are unique molecular changes that occur in patients with obesity, such as hepatocyte epigenetic aging and formation of hepatotoxins through changes in gut microbes, and thus plausible ways for HCC to develop in the absence of significant chronic liver damage.[72,73]

Obesity is most commonly evaluated based on a patient's body mass index (BMI), but this measure may not adequately capture all domains of obesity that are relevant to HCC risk. For example, there are alternative anthropomorphic measures (eg, waist-to-height ratio, weight gain, and weight loss) which have also been used. However, regardless the measure, the data consistently demonstrate an association with adiposity, especially abdominal visceral fat. In a meta-analysis of observational studies, relative to those who have a BMI consistent with normal weight (18.5-24.9 kg/m^2), there were 17% and 89% increased risks of developing liver cancer associated with being overweight (25-30 kg/m^2) and obese ($\geq$30kg/m^2), respectively, with a dose-response relationship.[74] When waist-to-height ratio and weight gain are evaluated instead, the association remains significant.[75] With regard to weight loss, there have been histologic changes noted in the livers of patients who have undergone bariatric surgery as well as decreases in the risk of mortality and complications related to chronic liver disease.[76,77]

For ICC, obesity has similarly been identified as a risk factor. In the aforementioned meta-analysis and US population-based cohort studies, overweight and obesity was associated with 56% and 70% increase in risk, respectively.[15,16] However, this association has not been reported as consistently as for HCC. For example, in a Danish population–based case-control study (considered a low-risk population for liver disease and ICC), obesity was not associated with risk.[78] As such, it remains unclear whether ICC is truly associated with obesity or if other coexisting factors in other populations (eg, chronic liver disease related to NAFLD, alcohol use, hepatitis, etc), and/or the higher rate of biliary stone disease in patients with obesity confounds this association.

Genetic Susceptibility

There are several heritable disorders that have been associated with an increased risk of HCC. Hemochromatosis is a disorder in which iron is absorbed and deposited within the liver parenchyma, and over time, continued iron overload can lead to cirrhosis.[28] This metabolic disorder is a risk factor for HCC.[79] Hemochromatosis is heritable disorder with an autosomal recessive inheritance pattern. Affected individuals are believed to be at an approximately 20-fold increased risk of developing HCC.[80] α 1-antitrypsin deficiency is associated with an increased risk of both cirrhosis and HCC.[28] This disease demonstrates an autosomal recessive pattern with codominant expression.[81] Both acute intermittent porphyria and porphyria cutanea tarda, disorders that result in an enzyme deficiency responsible for heme biosynthesis, are also associated with an increased risk for HCC. In a population-based study, both forms were associated with a significantly increased risk of primary liver cancer (21-fold for porphyria cutanea tarda and 70-fold for acute intermittent porphyria), and porphyria cutanea tarda was associated with an 8-fold increased risk of mortality from cirrhosis.[82] Unlike for HCC, discrete heritable conditions have not been as well defined for ICC. This may in part be due to the fact that the pathogenic mechanisms underlying the development of ICC have yet to be clearly delineated. As with HCC, inflammation is believed to play a key role by causing cholestasis and promoting proliferation of cholangiocytes in an environment conducive to the development of genetic alterations and upregulated proliferation.[83]

The importance of the interplay between genetic predisposition and environmental factors is increasingly apparent. A recently funded, multicenter, genome-wide association study of HCC is ongoing and intended to provide data on individual susceptibility and HCC risk, to explore the effect of genetic variation on survival in patients with HCC, and to explore the impact of patient race.[84] Similarly, a multicenter, genome-wide association study of ICC is also underway and recruiting study participants.[85]

Intrahepatic Cholangiocarcinoma–Specific Risk Factors

Congenital/Anatomic Disorders

Choledochal cysts. Choledochal cysts (CCs) are a spectrum of congenital dilations of the bile duct and have been reported to be a premalignant condition. Cysts are currently described using the 5-tier Todani classification system: (I) fusiform dilation of the common bile duct, (II) common bile duct diverticulum, (III) choledochocele, (IVA) multiple cysts of the intra and extrahepatic bile ducts, (IVB) multiple cysts of the extrahepatic bile duct, and (V) intrahepatic bile duct cysts (Caroli disease).[86] Although the manner in which CCs lead to the development of cholangiocarcinoma is unclear, bile stasis and reflux of pancreatic secretions are believed to play a role.[87-89] The duration of the condition appears to influence the patient's risk of developing ICC. Among CCs, types IV and V are associated with ICC, whereas types I-III are associated with extrahepatic cholangiocarcinoma. It has also been reported that CCs increase the risk of other forms of biliary cancer such gallbladder.[90,91]

Primary sclerosing cholangitis. Primary sclerosing cholangitis (PSC) is an entity in which multiple fibrotic strictures develop along the intrahepatic and extrahepatic bile ducts causing cholestasis. ICC, as well as other types of cholangiocarcinoma, is reported to occur in 7% to 15% of patients with PSC with an approximately 0.5% to 1% incidence per year.[92] The etiology of PSC is unclear as is the manner in which it may lead to ICC. There are no definitive data to suggest smoking and/or alcohol consumption confer an increased risk of cholangiocarcinoma in patients with PSC. However, bile stasis with infection and/or inflammation is suspected.

Hepatolithiasis. Stones in the intrahepatic bile ducts have traditionally been more commonly identified in those of Asian descent. The presumed pathway by which intrahepatic stones cause ICC is bile stasis leading to bacterial infection and chronic inflammation—this is supported by the high reported rate of infected bile (94%) in these patients.[93] Hepatolithiasis is an uncommon entity in the United States.

Infectious/Toxic Exposure

Parasitic infection. Although not common in the United States, there is a substantial historical body of epidemiologic data to support the role of liver flukes (in particular *Clonorchis sinensis* [Korea] and *Opisthorcis viverrini* [Thailand]) in the development of ICC—a 2-fold to 5-fold increased risk has been associated with infection.[94] As with CCs, the manner in which carcinogenesis results from infestation of the host's biliary tract by these flat worms is unknown, but chronic inflammation is suspected.[95]

Thorotrast. Of historical significance, Thorotrast was a radiologic contrast now banned for over a half century. Exposure was associated with an over 300-fold increased risk of developing ICC.[94]

Factors Associated With Risk Reduction

Although there are a number of factors associated with the development of HCC and ICC, there are also a number of factors that have been identified as conferring a potentially protective effect. In national case-control study of patients with type 2 diabetes in Asia, the use of statins was associated with a significant decrease in the risk of HCC (odds ratio: 0.36; 95% CI: 0.22-0.60) with a notable dose–response relationship between risk and increasing doses.[96] For ICC, the data are sparse and at this time not consistent. With regard to antidiabetic medications, a recent meta-analysis including over 480 000 patients from 13 studies compared risk and risk reduction among the various forms of these drugs.[97] The results demonstrated that that Metformin use was associated with a decreased risk relative to no medication (relative risk [RR]: 0.49; 95% CI: 0.25-0.97), insulin (RR: 0.30; 95% CI: 0.18-0.50), and sulfonylurea (RR: 0.44; 95% CI: 0.27-0.72), but not thiazolidinediones. Similarly, thiazolidinediones were associated with a decreased risk relative to insulin (RR: 0.33; 95% CI: 0.14-0.78). For patients with ICC, the available data suggest the use of Metformin may lower cancer risk (odds ratio: 0.40; 95% CI: 0.20-0.90).[71] Because inflammation is believed to play a key role in the development of liver cancer, the effect of nonsteroidal anti-inflammatory medications and more specifically Aspirin have been examined. The recently published results of the Liver Cancer Pooling Project suggest aspirin use is associated with a 32% decrease in the risk of HCC and a 36% lower risk of ICC in men but not in women.[98] Coffee consumption has also been linked to a reduced severity and progression of liver disease as well as a lower risk of HCC. Using data pooled from 12 prospective studies, the overall estimated risk reduction was 34% with a differential effect for low consumption (RR: 0.78; 95% CI: 0.66-0.91) and high consumption (RR: 0.50; 95% CI: 0.43-0.58).[99] The findings from the previously mentioned Liver Cancer Pooling Project also suggested a decreased HCC risk associated with caffeinated coffee consumption but no effect on ICC risk.[100]

Differences by Sex and Race

Both sex and race have an impact on HCC incidence.[101] Although the incidence of HCC in the United States has increased in both men (age-adjusted incidence from 6.9 per 100 000 in 2000 to 10.8 in 2012) and women (2.3 per 100 000 in 2000 to 3.2 in 2012), the majority (73%) of cases occur in men. The average annual percentage change rate is also higher in men relative to women (3.7% vs 2.7%). With regard to race, over time, age-adjusted incidence rates have significantly increased overall across all groups. However, with the exception of whites, recently the annual percentage change among most groups has either plateaued or decreased.

For ICC, the distribution of incident cases is more equally distributed among the sexes (53% of cases occur in men).[3] However, while the incidence rate of ICC is similar among those under the age of 60 years (men: 0.1 per 100 000 [20-39 years] and 1.2 [40-59 years], women: 0.1 [20-39 years] and 0.7 [40-59 years]), among those over the age of 60, the incidence rate is more heavily weighted toward men (men: 5.6 [60-79 years] and 9.8 [$\geq$80 years], women: 3.9 [60-79 years] and 6.9 [$\geq$ 80years]). With regard to race, the highest incidence rates have been among Asian and Hispanic patients.[3] However, there are currently no data to suggest there has been much change in incidence among any racial group.[13]

Conclusion

The prevalence of a number of common HCC and ICC risk factors has increased in the western world. Accordingly, primary liver cancer should continue to be an important focus for public health initiatives because of the high case mortality rate and because many of the risk factors are detectable, preventable, and/or modifiable. Although the underlying mechanisms behind carcinogenesis for many of these risk factors has not been clearly delineated, efforts focused on early detection of those at risk, implementation of interventions to mitigate the risk associated with specific factors, and initiation of treatment soon after diagnosis are likely to have the greatest impact on patients with primary liver cancer.

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