Epidemiology of Primary and Secondary Liver Cancers

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ABSTRACT

Primary liver cancer is the sixth most common cancer worldwide with a wide geographic distribution. The incidence of primary liver cancer is increasing and there is still a higher prevalence in developing countries. Early recognition remains an obstacle and lack of it results in poor outcomes for hepatocellular carcinoma (HCC), the most prevalent primary liver cancer, and cholangiocarcinoma. The most common risk factors associated with HCC are hepatitis B and chronic hepatitis C infections, alcohol use, smoking, and aflatoxin exposure. Emerging risk factors such as obesity might play an important role in the future because of the increasing prevalence of this condition.

KEYWORDS: Primary liver cancer, hepatocellular carcinoma, cholangiocarcinoma, chronic hepatitis B, chronic hepatitis C

Objectives: Upon completion of this article, the reader should (1) become familiar with geographic distribution of primary liver cancers, (2) identify known risk factors for hepatocellular carcinoma, and (3) identify known risk factors for cholangiocarcinoma.

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PRIMARY LIVER CANCER

Incidence and Trends

WORLDWIDE

Liver cancer is the sixth most common cancer worldwide,[1,2] accounting for 5.7% of the overall incident cases of cancer. There is wide geographic variability in incidence with a majority of the cases occurring in developing countries (82%, 366,000 new cases estimated in males in 2002, 147,000 in women) compared with developed countries (74,000 new cases in men and 36,000 women).[3] In fact, liver cancer is the third most common cancer in developing countries among men after lung and stomach cancer. It is also between two and eight times more common in men than in women.[3–6] China alone accounts for 55% of the new cases of liver cancer, other high incidence areas being sub-Saharan Africa, Japan, and South-East Asia.[3–5] Between the years 1978 and 1992, while some centers in high-risk countries like China, India, and Spain recorded a decreasing incidence of liver cancer by as much as 30%, other centers in predominantly low-risk populations like Italy, Australia, and France recorded a nearly 100% increase in the number of cases of primary liver cancer.[4] Although some of this increase can be attributed to changes in the coding

Hepatic Malignancies; Editor in Chief, Brian Funaki, M.D.; Guest Editors, Charles E. Ray, Jr., M.D., William S. Rilling, M.D., F.S.I.R. *Seminars in Interventional Radiology*, volume 23, number 1, 2006. Address for correspondence and reprint requests: Kia Saeian, M.D., M.Sc., Division of Gastroenterology and Hepatology, Medical College of Wisconsin, 9200 W. Wisconsin Avenue, Milwaukee, WI 53226. [1]Division of Gastroenterology and Hepatology, Medical College of Wisconsin, Milwaukee, Wisconsin. 0739-9529,p;2006,23,01,047,063,ftx,en;sir00343x.

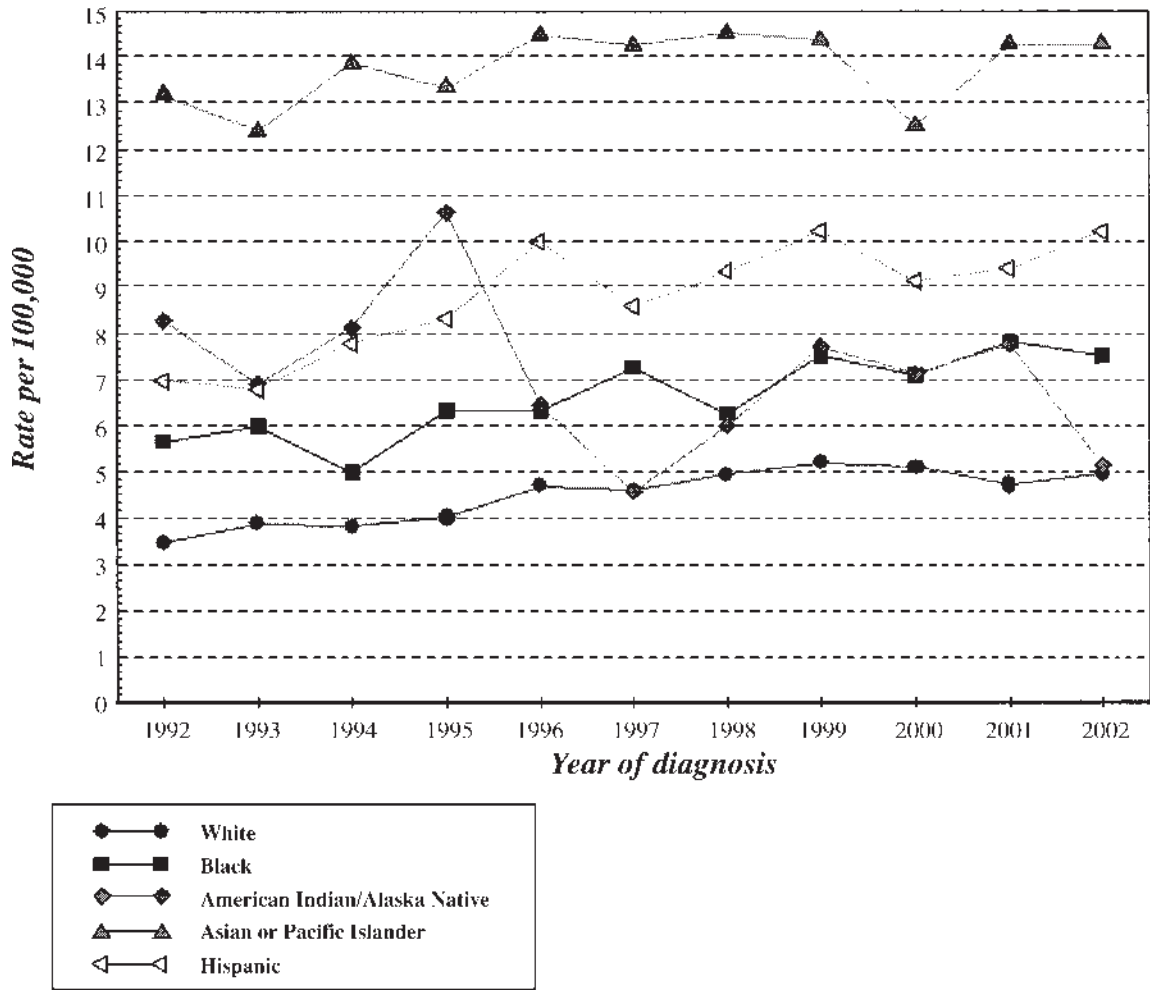

Figure 1 Incidence of primary liver cancer in the United States by race during 1992 to 2002. (Based on data from the Surveillance, Epidemiology, and End Results [SEER] Program.[10])

or diagnosis of hepatocellular carcinoma (HCC), the modes of treatment of cirrhosis and changing prevalence of the risk factors, particularly hepatitis C virus (HCV), may also play a role.[4]

There is also a global variation in the risk factors for HCC. Hepatitis B virus (HBV) and HCV infections account for 75% of the cases of primary liver cancer worldwide, with an even higher proportion in developing countries.[3] Among the two viruses, HBV is more common except in Japan where HCV infection in the most common cause of liver cancer.[7] In 1977 to 1978, HBV accounted for 42% of all cases of HCC in Japan. This number decreased to only 16% in 1998 to 1999, but number of cases related to HCV has increased to 70%.[7] Alcoholic liver disease accounts for a significant proportion of primary liver cancer cases in the United States and Europe, and both alcohol and tobacco use have significant effects in Asia and Africa.[8] Aflatoxin exposure also accounts for a significant number of cases in Asia,[8] especially China and Taiwan.

Liver cancer carries a very poor prognosis and is the third leading cause of cancer death worldwide.[3] Data from both the Surveillance, Epidemiology, and End results (SEER) and Eurocare show that primary liver cancer has the lowest overall survival rate worldwide among the 11 most common cancers, with a less than 10% 5-year survival.[3]

UNITED STATES

There are an estimated 17,550 new cases and 15,420 deaths due to primary liver cancer in 2005 in the United States[9] with an incidence rate of 5.4 per 100 000. Primary liver cancer has shown an average increase in incidence and mortality over the past 10 years, with annual percent changes (APC) of 3.3 and 1.9, respectively (Fig. 1[10]). This is in contrast to some of the other common cancers (breast, colorectal, lung, stomach), which have shown either significant decreases or no change in rates for these two parameters.[9] Liver cancer has the second highest APC in the time period 1992 to 2002 after thyroid cancer, and the highest APC (1.9) in mortality during the same time period. A majority of these cancers are diagnosed in older patients, with the highest incidence (26.4%) in the age group 65 to 74. The

median age of diagnosis is 64 years with a lifetime risk of being diagnosed with liver cancer of 0.89%.[9] The mean 5-year survival rates even in the United States is less than 10% with an average of 16.4 years of life lost per person dying of liver cancer.[9]

A majority of the cases of HCC are related to HCV (47%), HBV (15%), or both (5%).[11] Between 1995 and 1996 to 1998, the proportion of HCC patients with HCV nearly doubled from 18 to 31% in a study by Hassan et al, while those with HBV infection or other risk factors decreased slightly.[12]

HEPATOCELLULAR CARCINOMA

Several risk factors have been distinctly identified as being associated with HCC. Not surprisingly the prevalence and incidence patterns of HCC follow the patterns of the risk factors that will now be discussed individually.

Specific Risk Factors

HEPATITIS B AND HEPATITIS C

HBV and HCV infection are the main risk factors associated with HCC.[13–15] In most developed countries HBV and HCV infection are responsible for the majority of these tumors with rates dependent on the regional prevalence of infection. HCC develops from HBV and HCV infection after a latency period of one to three decades.[16–18] The population cohort most at risk for viral hepatitis (higher incidence of intravenous drug use, needle sharing, and unsafe sexual practice) during the 1960s and 1970s has now gone through this lag period.

Therefore, it follows that an increase in HCC was seen in the 1980s and 1990s. A predictive model suggests that in the United States the incidence of HCV-associated cirrhosis and subsequently HCC will peak in the next decade.[27] In the United States blacks and men are more prone to HBV and HCV infection than whites and women.[19–21] Although HCV infection rates remained steady through out 1980s[21] ($\sim$150,000 cases annually), they declined dramatically in early 1990s. Nevertheless, some 3.9 million persons in the United States have evidence of HCV infection with $\sim$2.7 million thought to have active viremia. In contrast $\sim$1 to 1.25 million persons are thought to harbor HBV infection with peak incidence of HBV infection reaching 11.5 per 100,000 in 1985 before declining to 6.3 per 100,000 in 1992 and a decline of 67% during 1990 to 2002 largely attributed to the effect of routine childhood vaccination.[22] About 55 to 85% of cases of acute HCV and 5% of cases of acute HBV infection become chronic.[21]

The pathogenesis of HCC in chronic HBV and HCV infection results from a series of steps from proliferation and apoptosis of host cells, inflammation, fibrosis, cirrhosis, and eventually dysplasia.[23] Nonfibrotic HBV livers may develop HCC,[24] whereas HCC in HCV almost universally develops in cirrhotic livers. In a study of 80 cases of HCC arising from nonfibrotic livers, no risk factor for HCC could be identified in 50/80 patients (62%) whereas 17 (21%) were found to have HBV and only 1/80 (2%) had HCV.[232] This study supports two notions. First, the majority of HCV patients are at risk for HCC only after cirrhosis develops, and second, HBV patients are at risk for HCC regardless of fibrosis, with the risk of HCC increasing with advanced fibrosis and cirrhosis. According to National Institute of Health Consensus Statement, the annual incidence of liver cancer is 0.5% in chronic HBV and 2.4% in cirrhotic patients.[25]

Based on the presumed mechanism of carcinogenesis, the interruption of the sequence of carcinogenesis either by antiviral or anti-inflammatory therapy will diminish the incidence of HCC. Early intervention in the form of HBV immunization has unequivocally reduced the incidence of HCC.[26] Treatment strategies directed at eradicating HBV and HCV may also diminish the incidence and/or progression of HCC but this remains to be proven.

Patients with HCV-related cirrhosis have a decreased risk of HCC with interferon (INF) therapy, even without complete biochemical and virological clearing. The current treatment options for HCV include combination therapy of INF plus the guanosine analogue, ribavirin, and most recently to the use of pegylated INF (Peg-INF) in combination with ribavirin.[28–31] The treatment options for chronic HBV in the United States include INF,[32–36] Peg-INF, or the nucleoside analogues lamivudine,[37–39] adefovir,[40] and entecavir.[41] Unfortunately, patients with decompensated liver disease are poor candidates for INF-based therapies and better-tolerated and more effective therapies are needed.

ALCOHOL

Many studies have shown the association between alcohol and HCC with most studies arriving at an odds ratio (OR) between 1.1 to 6.0.[42–49] Between 7 and 50% of the cases of HCC have been attributed to alcohol intake depending on the study population.[42,50–52] Men have a higher attributable risk of alcohol than women.[51]

Many studies have yielded a dose-response relationship between alcohol consumption and the risk of HCC.[42,46,49,53,54] In a study of 115 patients with HCC and 230 controls in the United States, those with any history of alcohol consumption had an adjusted OR of 2.4 (95% confidence interval [CI]: 1.3 to 4.4) to develop HCC compared with those with no alcohol intake. After stratifying by amount of consumption, those with $<$80 mL/d had a modest but not statistically significant increase in OR (1.7, 95% CI: 0.9 to 3.7) compared

with nondrinkers, but those with >80 mL/d ingestion of alcohol had a 4.5 (95% CI: 1.4 to 14.8) times greater odds of developing HCC compared with nondrinkers.[42] Other studies also found no or reduced risk of HCC with light to moderate alcohol consumption, suggesting a possible threshold effect.[44,45,55–57] Few studies have compared the risk of HCC with different alcoholic drinks. In a study by Yuan et al, the OR for each 10-g increment of ethanol was 1.12 (95% CI, 1.05 to 1.18) for beer, 1.10 (95% CI, 1.04 to 1.16) for spirits, and 1.07 (95% CI, 0.97 to 1.17) for wine.[49]

Yuan et al studied 295 cases with HCC and 435 controls in Los Angeles.[49] They found an elevated risk of HCC (1.1 to 3.2) with increased alcohol consumption expressed either in drink-years or number of drinks per day. There was no change in risk or a trend toward lower risk in those consuming smaller amounts of alcohol (zero to two drinks per day or <30 drink-years). In a large cohort study from Haimen city in China following 90,000 participants over 8 years, no association between current alcohol consumption and HCC was found in men or women. In fact, those with moderate consumption of alcohol had a slightly lower risk of development of HCC (OR 0.83).[56] However, this apparent protective effect of small amounts of alcohol may be fallacious due to the fact that the study participants might have decreased their amount of alcohol consumption after they were diagnosed with HCC.[51]

Quantifying the exact alcohol consumption that increases the risk of HCC has proven to be difficult because of the different measures of alcohol intake used by different studies. Although some studies measure alcohol consumption as number of grams per day, others use a dichotomous exposure variable, and yet others use both dose and time measures. Donato et al plotted regression curves measuring the relationship between daily alcohol consumption and risk of HCC.[54] This revealed a significant elevation above the null with doses greater than 60 g/d in their study.[54]

Alcohol is associated with HCC in most patients through the development of cirrhosis, which itself is a risk factor for HCC.[58,59] But up to 20 to 25% of the cases of HCC can arise in nonfibrotic livers.[60] In a series of 80 patients with HCC on the background of no or minimal portal fibrosis in the nontumoral liver tissue, 14% of the cases had only history of heavy alcohol consumption as their risk factor.[60] In another study of 174 patients with HCC and 610 controls from Italy, the OR of developing HCC due to alcohol use in the presence of cirrhosis of the liver was 5.5 (95% CI: 3.1 to 9.7) and without cirrhosis, 4.6 (95% CI: 1.5 to 13.8). Fifty-one of the HCC cases both with and without cirrhosis had a history of heavy alcohol consumption.[61] Grando-Lemaire et al found 63% of their HCC cases without cirrhosis had a history of intake of alcohol >30 g/d.[62] It is yet to be determined whether these cases represent a direct carcinogenic effect of alcohol on the liver cells,[60] similar to mechanisms that have been proposed for HBV infection.

Alcohol interacts with other factors in affecting the risk of HCC, most commonly HBV and HCV infections.[42,47,51,54] Alcohol has a more than additive effect on the risk of HCC in patients with HBV infection. In a study from Italy, people who were positive for hepatitis B surface antigen (HBsAg) had a relative risk (RR) of 9.1 (95% CI: 3.7 to 22.5) for developing HCC compared with those who were negative for antigen and had less than 80 g/d alcohol consumption. People who had >80 g/d alcohol consumption but no HBV infection had an RR of 4.2 (95% CI: 2.4 to 7.4). In the presence of both these risk factors, the OR of developing HCC was 64.7 (95% CI: 20 to 210).[51] Although other studies have supported this interaction,[63] a few did not find similar results.[56,64] There is a similar interaction with HCV infections and alcohol use.[47,52] In addition, alcohol has synergistic effect with other risk factors for HCC like smoking,[45,64,65] diabetes,[42,49] and other environmental exposures.[66]

HEMOCHROMATOSIS

The association between hemochromatosis and HCC is well known. Some of the early cohort studies report a 200-fold increase in the risk of HCC in patients with genetic hemochromatosis.[67] Hsing et al in a population-based study from Denmark found a standardized incidence ratio of 92.5 (95% CI: 25.0 to 237.9) in a cohort of patients with hemochromatosis compared with the expected rates in the population.[68] Although later studies have confirmed this association between hemochromatosis and HCC, they have arrived at lower ORs for development of HCC.[69–74] Whether this reflects earlier identification and treatment of patients remains to be seen.

In a large population study from Sweden, Elmberg et al followed 1847 patients with hemochromatosis for a total of 12,398 person-years.[72] A total of 62 cases of liver cancer were identified in this population, corresponding to a 20-fold increased risk. A majority (79%) of these cancers were HCC. There was a difference in the risk of liver cancer between genders. Men with hemochromatosis had a 30-fold increased risk of development of liver cancer, and women had only a sevenfold increased risk. The authors attribute the lower risk in women to blood loss during childbirth and menstruation and lower prevalence of alcohol consumption in women. However, they do not provide data on the prevalence of viral hepatitis or alcohol use in this population, both of which are also significant risk factors for the development of HCC. Fracanzani et al followed a cohort of 20 patients with hereditary hemochromatosis, and 230 matched controls with chronic liver disease. After adjusted for alcohol use, smoking, and family history, the

RR for development of HCC in patients with hereditary hemochromatosis was 1.8 (95% CI: 1.1 to 2.9).[74] Although most patients with hereditary hemochromatosis develop HCC in a background of liver cirrhosis, there have been case reports of HCC developing even in patients without cirrhosis.[62,75–79]

Cauza et al found a 20-fold increased risk of HCC in patients with hemochromatosis homozygous for the C282Y mutation of the HFE gene, but they did not find any increased risk in patients heterozygous for this mutation.[71] The risk of development of HCC in patients with heterozygous HFE gene mutations is controversial. Some studies did not find an increased risk of HCC in C282Y heterozygotes.[80,81] Boige et al found an equal prevalence of C282Y heterozygotes in a population of HCC patients when compared with a control group of patients with cirrhosis who did not have HCC.[80] Perl's Prussian blue stain of the liver iron load was similar between heterozygotes and those without the mutation. However, other studies have demonstrated an increased risk of HCC in patients with heterozygous mutations of the HFE gene.[82–84] Hellerbrand et al analyzed the presence of HFE gene mutations in three populations—137 patients with HCC but no history of hereditary hemochromatosis, 107 patients with cirrhosis without HCC, and 126 healthy controls. They found that heterozygosity for C282Y was more common in the patients with HCC (12.4%) than in patients with cirrhosis (3.7%) or healthy controls (4.8%). There was no difference in the frequency of H63D mutation between the three groups. C282Y heterozygotes had higher levels of ferritin and greater transferrin saturation and more deposition of iron within the HCC tissue as well as nontumor liver tissue, which suggests that C282Y heterozygosity may also have some role to play in the pathogenesis of HCC.[83] Fargion et al studied the interaction between HFE gene mutations and other external factors in the development of HCC.[82] Among the patients with HCC who were heterozygous for HFE mutations, there was an increased odds of alcohol use or having markers of chronic hepatitis, suggesting that HFE heterozygotes might be more predisposed to develop HCC than those without the gene mutations when exposed to alcohol or viral hepatitis.[82] Patients with wild-type HFE genes have a longer survival with HCC compared with those with HCC mutants.[85]

Different mechanisms have been proposed to explain the pathogenesis of HCC in patients with hemochromatosis. Direct toxicity of iron has been postulated to lead to the development of HCC, but mechanisms of how iron causes HCC are incompletely understood. Iron leads to the production of free radicals, which can lead to DNA damage and mutations, which in turn can lead to the development of cancer.[71,86–88] Higher levels of nitric oxide were found in the liver tissue of patients with hereditary hemochromatosis. Free radical oxygen and nitrogen species can cause an increased incidence of p53 mutations, which can contributed to carcinogenesis.[88] Transferrin iron may also have an immunological role to play in the development of HCC by facilitating tumor growth and impairing lymphocyte and macrophage function.[89]

AFLATOXIN

Aflatoxin is a well-recognized risk factor for the development of HCC. Some of the early studies showing an association between aflatoxin exposure and the development of HCC were from countries that had a high incidence of HCC.[57,90–92] Omer et al in a study from Sudan determined that 27 to 60% of HCC cases can be attributed to aflatoxin exposure in that country.[93]

Aflatoxin B1 (AFB1) is the most common aflatoxin linked to HCC. Although many of the early studies used dietary content of aflatoxin as a measure of exposure,[57] AFB-DNA adducts in tissues and fluids have been found to be a good measure of exposure status.[94,95] One of the first studies using AFB1-albumin as a measure of exposure was by Chen et al in a study of 6487 residents from an HCC endemic area with high mortality in Taiwan. People with detectable AFB1-albumin adducts in their serum had an OR of 3.2 (95% CI: 1.1 to 8.9) to develop HCC compared with those who did not.[96] Ross et al in a study of 18,244 people in China found a 3.8 (95% CI: 1.2 to 12.2) times higher risk of development of HCC for patients with evidence of aflatoxin metabolites after adjusting for alcohol, smoking, and HBV status.[97]

Studies have looked at the association between aflatoxin and other risk factors for HCC. One study in an aflatoxin endemic region in China found that nonsmokers were more likely to develop HCC than smokers, suggesting that cigarette smoke–induced cytochrome P450 activation may blunt the carcinogenic effect of aflatoxin on the liver.[98] Other studies have focused mainly on the interaction or synergism between aflatoxin B and chronic HBV infections as both these risk factors have a high incidence in regions of the world where the risk of HCC is the highest. Most of these studies have found an elevated risk with aflatoxin exposure and parallel chronic HBV infection.[97,99,100] Wang et al found that people who were positive for both HBsAg and aflatoxin have a greater risk of developing HCC that those with either risk factor or with neither, suggesting that aflatoxin might enhance the carcinogenic potential of HbSAg.[100] Different mechanisms have been proposed to explain the synergism between the two risk factors. Chronic HBV infection may induce the cytochrome P450s that metabolize the inactive AFB1 to the mutagenic AFB1–8,9-epoxide. Alternatively, hepatocyte necrosis and regeneration in the setting of chronic HBV infection might predispose the patient to p53 codon 249 mutation when exposed to

aflatoxin and subsequent clonal expansions can lead to HCC.[101]

The mutagenic effect of AFB1 results from hepatic activation to its metabolite AFB-1-exo-8,9-epoxide.[102] This induces a G → T transversion at the third position in codon 249 of the p53 gene.[103] High rates of these mutations (up to 50%) have been found in some countries in southeast Asia and south Africa, and few mutations were found in Europe, North America, or the Middle East.[104,105] Higher rates of these p53 codon 249 mutations in high aflatoxin exposure areas and fewer mutations in low exposure areas has led some authors to suggest that this codon 249 mutation may identify an endemic form of HCC that is associated with dietary aflatoxin intake. These mutations occur at a higher incidence in patients with HCC compared with those with cirrhosis or normal controls.[106]

DIABETES MELLITUS

Diabetes mellitus (DM) is common in patients with HCC,[69] and authors have proposed that up to 8% of the cases of HCC can be attributed to DM in certain populations.[44] A causal association between DM and HCC has been difficult to prove for several reasons. End-stage liver disease is associated with glucose intolerance and can lead to the development of diabetes.[69] This is a weakness in many of the cross-sectional studies that demonstrate an association between diabetes and HCC. Hemochromatosis can be a confounder in this association as it leads to both increased risk of HCC and DM.[69]

Although some of the early studies supported an association between DM and HCC,[48,107] the findings of some other studies did not concur.[108] Moreover, these studies were prior to the identification of the HCV. The first report of the association between HCC and DM came from a study in western Europe by Lawson et al who found a fourfold increased number of diabetics in patients with HCC.[109] Since then several studies have supported the association between the two conditions,[44,49,69,70,110–113] most authors finding an adjusted OR of 1.5 to 4.0. Case control studies for causal association of variables suffer from limitations. Information bias might lead to differential reporting of DM between cases (patients with HCC) and controls with higher reports among the cases. However, given that diabetes is a significant lifelong illness, this may not play a significant role.[44] Surveillance bias is unlikely given the rapid course of the tumor.[44]

These biases have been avoided by using the cohort design. One of the largest cohort studies to date was by El-Serag et al who followed over 700,000 patients with and without diabetes using the U.S. Veterans Affairs electronic patient records.[112] They found that diabetes was associated with a twofold increase in the risk of development of HCC. They also found a significant temporal association and duration response relationship between DM and HCC.[112] People with longer duration of follow-up were more likely to develop HCC. This study also excluded reverse causation (i.e., glucose intolerance caused by decreased liver function) by excluding all those with a history of liver disease prior to enrollment. Diabetes was also significantly associated with HCC even after excluding all patients with history of HBV or HCV infection, alcohol use, or underlying fatty liver disease. However, the generalizability of this study was limited by the fact that most of the patients were male veterans. The first population-based study in the United States was by Davila et al who used data from the SEER-Medicare database and found a threefold greater odds of HCC in patients with DM.[69]

Different causal mechanisms have been proposed to explain how diabetes can lead to the development of HCC. The hyperinsulinemia and insulin resistance in diabetes has been proposed to lead to mitogenesis and carcinogenesis in the hepatocytes.[113] The insulin resistance also leads to deposition of lipids within the liver, which leads to an oxidative stress. This can lead to microsatellite instability and cell damage, which increases the risk of HCC.[49,114] Another mechanism is the worsening of nonalcoholic steatohepatitis (NASH) due to DM-induced dyslipidemia,[44,69,113] which leads to cirrhosis and increased risk of HCC.

Various studies have found synergistic effects between DM and other risk factors for the development of HCC.[42,49,69,115] Davila et al showed that in patients with HCV and DM, the odds of developing HCC increased to almost 37.[69] Tazawa et al also found that DM increased the risk of HCC in patients with HCV,[115] and Hassan et al demonstrated an additive effect between DM and alcohol in the development of HCC.[42]

SMOKING

The IARC recently added smoking as a causal risk factor for HCC,[116] and as much as 25% of cases of HCC may be attributable to smoking.[43] But data about the association of smoking and HCC have been conflicting. Early studies showed a significant association between smoking and HCC in populations in Europe,[117,118] Asia,[43,53,119] and the United States, with most estimations of RR between 1.5 and 3.0. However, many other studies including some recent ones found no association between the two.[44,46,61,120–123]

In one of the largest case-control studies looking at the association between cigarette cancer and smoking, Kuper et al compared 333 cases of HCC with 360 hospital controls. They found that cigarette smoking exhibited a significant dose-response relationship with the development of HCC. People who smoke more than two packs a day (OR 1.6, 95% CI: 0.9 to 2.9) were more likely to develop HCC than people who smoked less

than two packs a day (OR 1.2, 95% CI: 0.8 to 1.9) or never smoked (OR: 1.0).[65] This dose-response relationship has been confirmed by some other studies,[56,118] although yet others did not find any such relationship.[53,55] Current smokers have a higher risk of HCC compared with former smokers.[49,124] Tsukuma et al studied a cohort of 917 outpatients in Japan and found an RR of 2.3 (95% CI: 0.9 to 5.86) and 1.68 (95% CI: 0.63 to 4.47) in current smokers and former smokers compared with nonsmokers, but this difference was not significant. The adjusted risk ratios were higher (7.96 and 3.44, respectively) in patients with liver cirrhosis but were not significantly different from the rate in nonsmokers in patients with chronic hepatitis.[124] In a large cohort study of 58,545 men and 25,340 women followed for 8 years in China, there was no association between smoking and HCC in men. In women, those smoking more than 10 cigarettes per day had an RR of 4.2 (95% CI: 1.3 to 13.8), and those smoking six to ten and one to five cigarettes per day had RRs of 2.0 (95% CI: 0.6 to 5.6) and 1.5 (95% CI: 0.4 to 6.3), respectively. However, the number of women who were smokers was small, and the number of HCC cases among women smokers was only eight.[56] Jee et al found a similar relationship among men but not among women.[43]

Smoking interacts with other environmental and viral factors in hepatic carcinogenesis. In a cohort study follow up of 1506 patients in Taipei, Yu et al[64] found a greater risk of development of HCC related to smoking in drinkers compared with nondrinkers (RRs of 9.3 and 1.85, respectively), thereby suggesting possible effect modification. Kuper et al also found a super-multiplicative association between cigarette smoking and alcohol consumption in the risk of developing HCC; heavy drinkers who smoke more than two packs a day had an OR of 9.6 (95% CI: 3.4 to 27.5) to develop HCC. This association was seen in the entire study population, as well as in the subclass who were negative for HBV and HCV infection.[65] Smoking also increases the risk of hepatitis B–[43,125] and hepatitis C–[47,126] associated carcinogenesis. Increased proliferation of hepatocytes in viral hepatitis may make the cells more prone to the carcinogenic effect of cigarette smoke and other environmental carcinogens.[47]

Genetic polymorphisms of many hepatic enzymes have been linked to the development of HCC in smokers, particularly those enzymes involved in the metabolism of environmental polycyclic aromatic hydrocarbons commonly found in cigarette smoke.[127,128]

NONALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in the United States and may lead to NASH.[129] Many case reports have suggested a relationship between NASH and HCC.[130–139] In one study of 105 consecutive patients with HCC, at least 13% of the cases were attributable to NASH.[134] Although patients in most case reports of HCC associated with NASH had underlying cirrhosis,[130,135,137,138] a few cases of HCC were seen in NASH patients without cirrhosis.[131,132,136,139] In a series of 641 patients with HCC from Italy, 44 patients had cryptogenic cirrhosis as their underlying risk factor. Most of these patients had other clinical features associated with NAFLD including diabetes and obesity. In a study from Japan comparing HCC related to alcohol liver disease with HCC related to NASH, the only difference was that there were significantly more women in NASH-HCC group.[140] Well-differentiated tumors are also more common in HCC associated with cryptogenic cirrhosis, which is a known stage in the natural history of NASH, than those arising from chronic viral hepatitis–related cirrhosis or alcoholic cirrhosis.[111]

Studies in animals have shown that *ob/ob* mice (obese mice) have a larger liver than lean mice. This is not accounted for by increased fat deposition but may represent increased hepatocyte proliferation and hyperplasia.[141] This obesity-related metabolic change in patients with NASH might increase the risk for HCC in these patients.[141,142]

OBESITY

Obesity is a recently recognized risk factor for HCC.[45,111,143–145] Marrero et al compared 70 patients with HCC with 70 patients with cirrhosis and 70 patients with no history of liver disease. Patients with a body mass index greater than 30 had a fourfold increased risk of HCC compared with those with cirrhosis and a 48-fold increased risk compared with those with no history of liver disease.[45] However, the carcinogenic effect of obesity may be restricted to patients with alcoholic or cryptogenic cirrhosis, not in patients with chronic viral hepatitis–related cirrhosis or other underlying diseases.[111,143] Ratziu et al compared the frequency of HCC in 27 patients with obesity-related cryptogenic cirrhosis and 391 patients with chronic HCV infection-related cirrhosis. They found an equal prevalence of cirrhosis in the two groups, suggesting a comparable carcinogenic potential.[144] Obesity has also been shown to interact with alcohol and tobacco in increasing the risk of HCC.[146]

Several mechanisms have been proposed to explain the mechanism by which obesity leads to the development of HCC.[147] The increased risk of HCC in obese individuals is likely mediated through the development of NAFLD. Hyperinsulinemia, insulin resistance, and elevated insulin-like growth factor levels may act as mitogenic factors and stimulate hepatocyte proliferation.[147] Alternately, free radical formation related to fatty liver, which is common in obese individuals, might predispose to the development of HCC.[147] With the rising incidence of obesity in the population in

the United States, the contribution of this risk factor to the development of HCC may also be increasing.

CHOLANGIOCARCINOMA

Cholangiocarcinoma is the second most common primary liver cancer, accounting for up to 15% of the cases.[148,149] Cholangiocarcinomas are of two types, intrahepatic (ICC) and extrahepatic. Some risk factors are well recognized like hepatolithiasis, liver fluke infection, primary sclerosing cholangitis (PSC), and thorotrast, whereas other risk factors like viral hepatitis, smoking, and alcohol are still being investigated. Up to half of the cases of ICC have no identifiable risk factors, suggesting other unknown causes.[148,150]

The role of alcohol as an etiologic factor for cholangiocarcinoma is still debated. In a study from Italy on 26 patients with ICC and 824 controls, no association was found between ICC and alcohol intake.[148] Other studies have also found no associations between the two.[150–152] However, Sorensen et al in a study of 11,605 patients with cirrhosis from the Danish national registry observed 17 cases of cholangiocarcinoma in patients with alcoholic cirrhosis, yielding a standardized incidence ratio of 15.3 (95% CI: 8.9 to 24.5). No cases of cholangiocarcinoma were observed in those with cirrhosis due to viral hepatitis in the same study.[153] Another case series from the United Kingdom identified heavy alcohol consumption in up to 45% of 112 patients with cholangiocarcinoma but there was no control group in this series.[154] Shin et al also found an association between heavy drinking and cholangiocarcinoma.[123]

Hepatitis C has more often been linked with cholangiocarcinoma than hepatitis B. Many studies have explored the link between chronic hepatitis B infection and found no association between the two.[148,151,155] A large case control study of 103 cases of cholangiocarcinoma found no association between HBV and cholangiocarcinoma in Thailand.[152] However, a few other studies have supported the association, reporting between 9 and 12% HBsAg seropositivity in patients with cholangiocarcinoma.[156,157]

On the other hand, people with chronic HCV infection have an OR between 5 and 10 of developing cholangiocarcinoma.[148,150,158] About 35% of patients with cholangiocarcinoma in Japan have circulating anti-HCV antibodies.[158] The largest population study of ICC in the United States was by Shaib et al, who used the SEER-Medicare database to identify risk factors in 625 cases with ICC and 90,834 controls. They found that HCV infection had an adjusted OR of 5.2 to 6.1 of developing cholangiocarcinoma.[150] Kobayashi et al followed 600 patients with HCV-related cirrhosis for a median of 7.2 years and found cumulative rates of cholangiocarcinoma were 1.6 and 3.5% at 5 and 10 years, respectively, which was ~1000 times higher than the rates in the general population in Japan.[159] Different mechanisms have been proposed to explain the pathogenesis of cholangiocarcinoma. HCV RNA sequences have been extracted from cholangiocarcinoma tumor tissue.[160] Bile duct epithelial cell injury directly due to HCV or due to associated cholangitis can lead to chronic inflammation and regenerative hyperplasia that can lead to malignant transformation.[161]

PSC is a well recognized risk factor for cholangiocarcinoma and up to one-third of patients with PSC in some series went on to develop cholangiocarcinoma.[162–166] The frequency reported has varied between population-based studies and liver transplantation–related studies with a higher prevalence of cholangiocarcinoma in the latter.[165] The annual incidence rates range from 0.6[165] to 1.5%.[162] The time to develop cholangiocarcinoma after the diagnosis of PSC also varied. In a series of 394 patients from five European countries, over half of the 48 patients who developed cholangiocarcinoma did so within the first year,[163] whereas Burak et al found the average interval between the diagnosis of PSC and cholangiocarcinoma was 4.1 years.[165] Small-duct PSC has a lower incidence of cholangiocarcinoma compared with large-duct PSC.[164,167] HLA DR4, DR5 genotypes, K-Ras, and p53 mutations have been associated with an increased risk of developing cholangiocarcinoma after PSC.[168,169] Between 2.5 and 7.5% of patients with inflammatory bowel disease (IBD) have PSC. Studies comparing patients with PSC and cholangiocarcinoma to those with cholangiocarcinoma alone have found no difference in the type or duration of IBD,[170–172] whereas one population-based study from the United States found an OR of 2.3 (95% CI: 1.4 to 3.8) between IBD and cholangiocarcinoma.[150]

The International Agency for Research on Cancer working group recognized infection with liver flukes (*Opisthorchis viverrini, Opisthorchis felineus, Clonorchis sinensis*) as a risk factor for cholangiocarcinoma.[173] It is estimated that ~35 million people are infected with *Clonorchis* globally, of whom 15 million are in China. In the United States up to 26% of Asian immigrants 20 years ago were found to have an active liver fluke infection,[174] though recent studies have identified far lower numbers (1.3%).[175] Many reviews have also identified the role of *Clonorchis* in cholangiocarcinoma.[149,176] Shin et al in a study from Korea of 41 patients with cholangiocarcinoma compared with 406 controls found that the presence of *Chlonorchis* in stool was associated with an OR of 2.7 (95% CI: 1.1 to 6.3).[123] A recent review by Choi et al examined the possible mechanisms of carcinogenesis of *Clonorchis*.[177] Liver fluke–induced biliary hyperplasia[177] or metabolic products[178,179] might act as carcinogens.

Between 2 and 70% of people in northern Thailand have active *O. viverrini* infection[180] due to the traditional habit of eating raw freshwater and

salt-fermented fish on a daily basis.[181] A case control study of 103 patients with HCC in Thailand found an OR of 5.0 between *Opisthorchis* infection and cholangiocarcinoma,[152] and other studies have confirmed this association.[149,182,183] Animal studies have identified inducible nitric oxide synthase (iNOS)-mediated nitrate and oxidative damage to the DNA in the bile duct epithelium might be responsible for chronic bile duct inflammation that leads to cholangiocarcinoma.[184] It may also induce an inflammatory response through a Toll-like receptor (TLR2)-mediated pathway leading to expression of iNOS and COX-2.[185]

Hepatolithiasis is a known risk factor for intrahepatic cholangiocarcinoma.[149,186] A case control study from Italy compared 26 patients with ICC with 824 controls with no known liver disease; 26.9% of ICC cases and 10.9% of the controls had hepatolithiasis, giving an OR for cholangiocarcinoma of 6.7 (95% CI: 1.3 to 33.4).[148] In various series 2.5 to 10% of patients with hepatolithiasis developed cholangiocarcinoma.[187–189] However, in one series, 43% of patients with ICC had coexisting hepatolithiasis.[190] The mechanism of carcinogenesis appears to be related to bile stasis, infection, or mechanical infection.[191] Some authors have shown overexpression of transforming growth factor-β (2) and β (3) receptors in hepatolithiasis; 80% of cholangiocarcinoma also have overexpression of the same receptors,[192] and other studies have shown a possible role of c-erbB-2 oncogene in both biliary proliferation in hepatolithiasis and cholangiocarcinoma.[193]

Thorotrast is a suspension of radioactive thorium dioxide and thorium 232 that was used as a contrast agent in the years around World War II.[194] It is a well-recognized risk factor for cholangiocarcinoma,[149] with cancer developing even decades after exposure.[194] ORs have varied from 1.5 to 316.[195] Cholangiocarcinoma accounts for 58% of the thorotrast-associated liver cancers.[196]

Some congenital anomalies of the hepatobiliary system predispose to cholangiocarcinoma, commonly choledochal cysts. Between 5 and 15% of patients with choledochal cysts develop cholangiocarcinoma,[176,197,198] with a lower risk in children who present before the age of 10 (overall risk of 0.7%).[176] Resection of the cyst appears to decrease the risk of cholangiocarcinoma, but internal drainage for management of cysts may not reduce the risk of cholangiocarcinoma.[199] There have been reports of cases of cholangiocarcinoma developing even after resection.[200]

OTHER PRIMARY LIVER CANCERS

Fibrolamellar Carcinoma

Fibrolamellar carcinoma (FLC) is an uncommon tumor usually occurring in younger patients with noncirrhotic livers.[5,201,202] It accounts for 0.5 to 1% of all cases of liver cancer.[203,204] Although there have been many case reports from different countries reporting FLC, there have been few population-based studies of the epidemiology of FLC. El-Serag et al used the SEER registry to identify epidemiological characteristics of FLC and to compare it with HCC.[203] Patients with FLC were younger (39 versus 65 years, $P < 0.0001$) and more likely to have localized disease and receive curative therapy. However, because the data was registry-based, the authors were not able to identify any risk factors.[203] Although some recent case reports have identified the hepatitis B core antigen within the tumor tissue in cases of FLC,[205] it is not commonly associated with any of the traditional risk factors for HCC including hepatitis B and hepatitis C infections.[5,201] There have also been reports of FLC arising from a previous focal nodular hyperplasia.[201]

Hepatoblastoma

Hepatoblastoma (HB) is the most common primary hepatic tumor of childhood arising from incompletely differentiated hepatocyte precursors.[5,201] It accounts for between 0.2 and 5.8% of all childhood malignant tumors[201] and occurs at an incidence of ~1 in 100,000.[206] It is also two to three times more common in boys.[5,206,207] It is almost exclusively seen in children younger than 3 years, though rare cases have been reported in adults.[208] An association with low birth weight has been proposed, with increasing proportion of low-birth-weight babies in infants with this tumor.[209–211] Other possible risk factors are less forthcoming, but HB is associated with several underlying genetic diseases including Beckwith-Weidman syndrome, Wilms' tumor, and familial polyposis coli.[201] Paraneoplastic syndromes, especially isosexual precocity, is also seen in association with this tumor.[201,212]

Mesenchymal Cancers of the Liver

ANGIOSARCOMA OF THE LIVER

Angiosarcoma of the liver (ASL) is the most common mesenchymal neoplasm of the liver, accounting for 2% of all cases of primary liver cancers.[213,214] About 10 to 20 cases are diagnosed in the United States each year.[213] Peak incidence of the cancer is in the sixth and seventh decades,[215] and it is four times as common in men as in women.[5] There is a strong association between ASL with occupational exposures.[214] However, 75% of the cases are not associated with any known etiologic factors.[215] A 45-fold increase in risk of ASL in seen in patients with exposure to the vinyl chloride monomer (VCM).[216,217] A review of 20 patients who died from

VCM-related ASL showed that the tumor occurred between 9 and 35 years after exposure to VCM.[218] The mechanism of VCM-associated ASL appears to be through mutations in *ras* and p53 genes mediated by the metabolites and adducts of VCM.[217] It has also been associated with exposure to arsenic,[219,220] thorotrast,[221,222] anabolic steroid,[215,223] and cyclophosphamide.[224] ASL has also been associated with hemochromatosis but not with viral hepatitis.[212]

EPITHELOID HEMANGIOENDOTHELIOMA

Epitheloid hemangioendothelioma is a neoplasm of the liver derived from the endothelial cells.[212] The infantile form (infantile hemangioendothelioma) is benign, but the adult variety, which is more common, is malignant.[206,212] The epidemiology of this tumor has been poorly characterized because of its rare occurrence, but it has been occasionally reported to be associated with vinyl chloride exposure.[6,206]

SECONDARY LIVER CANCER

Tumors metastatic to the liver are more common than primary tumors.[8] The most common sites of primary tumor are breast, lung, and colorectal cancer.[8,225–227] In a series of 912 breast cancer patients, 5.2% developed liver metastases.[228] Synchronous hepatic metastases may be identified in 10 to 20% of patients with colorectal cancer.[229,230] Liver metastases may be rarer in other primary tumors, with only 10% of distant metastases in head and neck cancers present in the liver.[231,232] Some authors have reported hepatic metastases in as many as 40 to 50% of adult patients with extrahepatic primary tumors.[227] In an autopsy series of 1500 patients with hepatic metastases from unknown primary tumors, Ayoub et al identified primary tumors in the lung, colon, or rectum in 27% of the patients.[226]

The high incidence of hepatic metastases have been attributed to two mechanisms.[227] First, the dual blood supply of the liver from the portal and systemic circulation increases the likelihood of metastatic deposits in the liver. Second, the hepatic sinusoidal epithelium has fenestrations that enable easier penetration of metastatic cells into the liver parenchyma.[227]

CONCLUSION

Primary liver cancer is the sixth most common cancer worldwide with an increasing incidence. The mortality from this cancer is also very high in part due to late recognition of the disease. Among the different liver cancers, HCC is the most common. Although the most common risk factors associated with HCC are HBV and HCV infections, other risk factors like alcohol use, smoking, and aflatoxin exposure also contribute significantly to the burden of this disease, particularly in developing countries. Emerging risk factors like NAFLD and obesity might play an important role in the future because of the increasing prevalence of these conditions. Metastatic liver tumors are more common than the primary tumors and are most commonly of breast, lung, or colorectal origin.

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