Epidemiology of Hepatocellular Carcinoma in the United States: Where Are We?
Where Do We Go?

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Hepatocellular Carcinoma (HCC) in the United States: Current Epidemiological Trends:

The incidence of HCC has almost tripled since the early 1980s in the United States where it is the fastest rising cause of cancer-related deaths[1]. According to population based Surveillance Epidemiology and End Results registry data, the overall HCC age adjusted incidence rates for liver and intrahepatic ducts cancer is as high as 8 per 100,000 underling population in 2010 **(Fig. 1)** of which at least 6 per 100,000 related to HCC. Men are at approximately three times higher risk than women. Asian men (i.e., Chinese, Korean, Filipino, and Japanese) have the highest age-adjusted incidence rates. However, the largest proportional increases have occurred among Hispanics followed by blacks and non-Hispanic whites, whereas the lowest proportional increases have occurred among Asians. In contrast to Asians/Pacific Islanders, HCC incidence rates are reported to be higher among Hispanics born in the United States than among foreign-born Hispanics[2]. HCC incidence rates have increased in each successive birth cohort born between 1900 and 1959 [3] **(Fig. 2)**. In addition, the age distribution of HCC patients has shifted to younger ages, with the greatest proportional increases among individuals 45–60 years old **(Fig. 2)**. There is a south to north gradient in the incidence and mortality of HCC; Southern states including Texas, Louisiana, and Mississippi have some of the highest HCC incidence rates in the nation **(Fig. 3)**. In one study, Texas Latino and especially South Texas Latinos had the highest age-adjusted HCC incidence rates (as high as 10.6/100,000)[4].

Risk factors for HCC

Most HCC risk factors (chronic infection with hepatitis B (HBV) and/or C virus (HCV) and alcoholic liver disease) operate by promoting the development of cirrhosis. Exceptions are rare in HCV-related HCC and mostly represent cases with at least bridging hepatic fibrosis[5]. While most cases of HBV-related HCC also occur in the background of cirrhosis (as high as 85% in some studies)[6], HBV can cause HCC in the absence of advanced fibrosis or cirrhosis. Although there are several mechanisms for non-alcoholic fatty liver disease-non-alcoholic steatohepatitis (NAFLD-NASH) related HCC conceivably in the presence of mild or no fibrosis[7], there are no systematic studies to confirm or quantify this contention[8]. Indirect measures of severity of hepatic fibrosis such as degree of liver stiffness using elastography is associated with risk of HCC[9].

The risk of developing HCC in cirrhosis patients varies with the underlying condition. The highest 5-year cumulative risks are seen in HCV cirrhosis (17% in the West and 30% in Japan), hemochromatosis (21%), HBV cirrhosis (10% in the West and 15% in Asia), alcoholic cirrhosis (8%-12%), and biliary cirrhosis (4%) [10],[11].

HBV: Most large studies and consistent data about the clinical course of HBV infection come from Asian countries, where HBV is endemic and vertical transmission is frequent. This pattern is different in areas that have low incidence of HCC (such as the U.S) where HBV infection is mostly acquired in adulthood either through sexual or parenteral routes. There have been only a few adequate studies in Europe and North America that determined the incidence of HCC in hepatitis B surface antigen (HBsAg)-positive individuals—most included only small numbers of HBsAg-positive patients.

Nevertheless, the summary HCC incidence rate in these regions is approximately 0.02 per 100 person-years in inactive carriers (HBsAg-positive but with normal levels of alanine aminotransferase, ALT), 0.3 in subjects with chronic HBV without cirrhosis, and 2.2 in subjects with HBV related compensated cirrhosis. On the other hand, cohort studies estimated the incidence rates of HCC among subjects with chronic HBV infection in East Asian countries to be 0.2 per 100 person-years in inactive carriers, 0.6 per 100 person-years for those with chronic HBV infection without cirrhosis, and 3.7 per 100 person-years for those with compensated cirrhosis.

Several demographic (male sex, older age, Asian or African ancestry, family history of HCC), viral (higher levels of HBV replication; HBV genotype; longer duration of infection; co-infection with HCV, HIV, or HDV), and environmental factors (exposure to aflatoxin, heavy intake of alcohol or tobacco) increase HCC risk among individuals with chronic HBV[2]. HBV viral load appears to be an important determinant of HCC risk. The incidence of cirrhosis and HCC increased in proportion to the serum level of HBV DNA[12] in Asian countries as well as Alaska[13]. HBV genotypes also seem to affect clinical outcomes. In North America and Western Europe, individuals with genotype D had a higher incidence of HCC than those with genotype A. Some data associate genotype B HBV with the development of HCC in young carriers without cirrhosis[14;15]. Mutations in the region of the HBV genome that encode the basal core promoter[16], have been associated with increased HCC risk, whereas those in the precore region have been associated with decreased HCC risk[17].

Aflatoxin causes a mutation at serine 249 in the tumor suppressor p53 that was detected in 30%–60% of HCC tumor samples collected from individuals in aflatoxin-endemic areas, most of whom also had HBV infections. Aflatoxin associated mutation is rarely detected in HCC cases diagnosed in the US.

HCV: HCV infection is associated with a 15- to 20-fold increase in risk for HCC compared with HCV-negative subjects. The rate of HCC in cohort studies of HCV-infected persons ranges from 1% to 3% over 30 years of chronic infection. Once HCV-related cirrhosis is established, HCC develops at an annual rate of 1%–8% (average 3.5%). Risk factors for HCC in HCV-infected individuals include male sex, co-infection with HBV or HIV, diabetes, obesity, and high level of alcohol consumption.

HCV viremia of any level is a strong risk factor for HCC compared to no viremia, however, while few studies reported a correlation between HCV viral load levels and risk of progression to cirrhosis [18] or HCC, most studies did not find such an association[18]. Reports of the association between HCV genotype and HCC risk are inconsistent but suggest a slightly greater risk of developing HCC in patients with HCV genotype 1b, and possibly genotype 3, than patients with other HCV genotypes[19].

Meta-analyses of observational studies from various countries[20] report additive effects of HBV and HCV on risk for HCC (35- to 165-fold increase), although a sub-additive effect has been suggested based on more recent studies, cohort studies, and studies conducted in areas in which HBV and HCV infection were not common[21]. Persons co-

infected with HCV (and to a lesser extent HBV) and HIV have faster progression to

cirrhosis and decompensated liver disease, especially during immunosuppression, than

patients with monoinfection.

For both HBV and HCV, men have 2-4 times greater risk of HCC across almost all liver

disease etiologies than women. Gender-based differences in behavior and

environmental exposures such as alcohol use might explain some of this difference.

However, male and female sex hormones may also play a role. Nested case-control

studies in China reported that baseline testosterone levels were higher in HBsAg

positive males compared to age-matched controls [22]. There is a functional

polymorphism, a trinucleotide polyglutamine (CAG) short tandem repeat, in exon 1 of the

AR gene, where increasing number of CAG repeats results in decreased androgen

receptor (AR) signaling. Carriage of the high risk AR allele (i.e., fewer CAGs) conveyed

greater risk of HBV-related HCC in Taiwanese males[22;23], whereas increased AR CAG

repeats were associated with greater HCC risk in females[24]. Molecular data indicate

that androgens contribute to the HCC development by acting as tumor promoters via

induction of DNA damage and oxidative stress while estrogens may act as general

suppressors of HCC through reduction in the proinflammatory effects of MyD88-

mediated secretion of IL6[25].

Metabolic Syndrome: Patients with metabolic syndrome or with various components of

metabolic syndrome (e.g., diabetes, obesity) also have higher incidence of HCC than

those without metabolic syndrome. There are also emerging reports of HCC in the

setting of metabolic syndrome arising in the absence of cirrhosis however the true

extent of this condition or its risk factors are unclear[27;28].

Diabetes: Meta-analyses of observational studies report pooled odds ratios of

approximately 2.5 for the association between diabetes and HCC independent of viral

hepatitis or alcohol use[29;30]. Cirrhosis causes glucose intolerance and type 2 diabetes,

and also leads to HCC, making it difficult to interpret the association between HCC and

diabetes especially in case-control and cross-sectional studies. However, this bias is

less likely to be present in longitudinal studies; several cohort studies also showed a

similar association between diabetes and HCC. This association is less consistent in

areas with a high incidence of HBV infection than in other regions. Factors that change

HCC risk among patients with diabetes are not clear, but it has been suggested that

long diabetes duration and high HbA1C increase the risk, while metformin treatment

decreases HCC risk[31].

Obesity: A meta-analysis of 26 prospective cohort studies, including 25,337

primary liver cancer cases demonstrated that a BMI ≥ 25 kg/m2 as well as a BMI ≥ 30

kg/m2 were associated with an increased risk of primary liver cancer. The summary

relative risk for a 5-unit increment in BMI was 1.39 kg/m2 (95% CI: 1.25-1.55) with the

most pronounced increase in risk among persons with a BMI >32 kg/m2. The

association between BMI and liver cancer was independent of geographic location,

alcohol consumption, or history of diabetes. However, obese males had a higher risk of

primary liver cancer than obese females. Furthermore, the association between

increasing BMI and HCC was much stronger in individuals with concomitant HCV

infection than in persons with HBV infection.

Nonalcoholic fatty-liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome, and it affects about a third of the US adult population. Epidemiologic studies support at least a modest association between NAFLD or NASH and HCC, but this association seems to be predominantly limited to those who develop cirrhosis.

The few population-based cohort studies of patients with NAFLD are limited by low number of HCC cases and inability to identify high risk sub-groups (such as cirrhosis, obesity, diabetes[8]). Several cross-sectional and case-control studies have evaluated this association indirectly by concomitantly examining the prevalence of diabetes and obesity in NAFLD/NASH -related HCC cases. Diabetes and obesity prevalence was greater in the NAFLD/NASH-related HCC cases compared to their respective controls with other chronic liver diseases. Prevalence of cirrhosis among HCC cases attributed to NAFLD/NASH ranged between 36% and 90%, with the majority of studies reporting cirrhosis rates ≥70%. These studies are limited due to the difficulty in ascertaining the exposure (histopathological features for confirmed NAFLD/NASH diagnosis) once cirrhosis is established. Furthermore, cirrhosis causes glucose intolerance and type 2 diabetes, and also leads to HCC, rendering it difficult to interpret the association between HCC and diabetes and to exclude reverse causality.

Recently, a genetic polymorphism of the patatin-like phospholipase domain-containing (PNPLA3) protein has been shown to be associated with an increase in hepatic fat deposition as well as an increase in the risk of HCC development[32]. This and other genetic markers may serve as a part of predictive algorithms to identify high risk groups for surveillance or chemoprevention.

Alcohol: Heavy alcohol intake, defined as ingestion of >50–70 g/day for prolonged periods, is a well-established HCC risk factor. However, even moderate alcohol consumption may increase the risk of HCC in women[33]. There is evidence for a synergistic effect between heavy ingestion of alcohol and HCV infection and, to a lesser extent, HBV infection on HCC risk; similar synergism may be present with diabetes. These factors presumably operate together to promote cirrhosis and further increase the risk in individuals with cirrhosis[34;35].

Cigarette Smoking: The association between cigarette smoking and HCC has been inconsistent with few studies finding a positive association and others finding no associations. Among studies reporting positive associations, several found that effects were limited to only those with HBV or HCV infection[36].

Burden of HCC related to the major risk factors in the US

Estimates of relative risk such as risk ratios or odds ratios for any of the individual HCC risk factors do not describe their contribution to HCC burden, which is also driven by the prevalence of the risk factor in the general population. Population attributable fraction (PAF) accounts for both an estimate of relative risk as well as prevalence of a given risk factor in the population, and it describes the proportional reduction in disease that would occur if exposure to a risk factor were to be eliminated. Metabolic syndrome is likely to have the greatest PAF **(Table 1)**. A population based study of SEER-Medicare diagnosed HCC cases reported the highest PAF was for

diabetes or obesity (36.6%), followed by alcohol-related disease (23.5%), HCV (22.4%),

and HBV (6.3%). Diabetes/obesity had the greatest PAF among whites and Hispanics

(38.9% and 38.1%), and HCV had the greatest PAF among Asians and blacks (35.4%

and 34.9%). The second greatest PAF were alcohol-related disorders in whites,

Hispanics, and blacks (25.6%, 30.1%, and 18.5%) and HBV in Asians (28.5%)[37].

Therefore despite having the lowest relative risk among the risk factors examined, the

high prevalence of diabetes/obesity translate into a high attributable fraction.

Among patients with HCC currently diagnosed in the US, 50%–60% are infected

with HCV, 10%–15% are infected with HBV, and 20-25% have alcoholic liver disease.

Approximately 20%-30% of HCC cases do not have any of the previously mentioned

factors but have some features of the metabolic syndrome. Several studies examined

time trends of risk factors among patients with HCC in the US; HCV-related HCC had

the largest proportional increases during the 1990s and early 2000, whereas the

proportion of HCC associated with HBV infection and alcoholic liver disease remained

relatively stable. However, based on the PAF arguments, these proportions may

change in the next 2-3 decades with declining HCV-related HCC and increasing

metabolic syndrome related cases.

Prevention of HCC

Prevention of HCC focuses on preventing these risk factors from ever developing

(primary prevention) or, once developed, treating them at an early enough stage

(secondary prevention) in order to reduce the risk of HCC. On the other hand

surveillance in patients at risk for HCC is intended to detect small, treatable cancer (tertiary prevention). The section below focuses on primary and secondary prevention.

HBV Vaccination Program

National HBV vaccination programs have been the most successful prevention strategy in reducing the incidence of HCC in HBV-endemic areas. These programs have dramatically reduced the prevalence of HBV (16% to 1.4% in China, 9.8% to 1.3% in Taiwan, and 9.3% to 0.9% in Spain) with a concomitant decrease in the incidence of HCC. Since the implementation of the universal vaccination program for newborns in Taiwan in 1986 to early 1990's, the average annual incidence of HCC in children between 6 and 14 years of age has fallen by 65 to 75%[38].

In these regions, HBV is the most important risk factor for HCC, and universal vaccination programs, with almost 100% penetration, have been successful in decreasing the rate of chronic HBV in the general population. In other regions (e.g., Spain) where HBV is mainly spread by different parenteral routes, a decline in HBV likely resulted from screening of blood products and use of disposable syringes and needles. However, there are still ~400 million individuals chronically infected with HBV in the world—a group that will not benefit from immunization and remains at increased risk for HCC. Of these, an estimated ~800,000 – 1.4 million live in the U.S.

Antiviral Treatment

There is moderately strong evidence that successful antiviral therapy for HBV or HCV substantially reduces but does not eliminate the risk of HCC in patients with viral

hepatitis who already developed cirrhosis; the residual annual HCC risk in those

patients may exceed the 1.5% threshold required by some cost-effectiveness models

for HCC surveillance.

HBV Treatment

One randomized controlled clinical trial evaluated efficacy of antiviral treatment on long-

term clinical outcomes in patients with HBV. In a large Taiwanese study, patients with

chronic HBV infection who also had cirrhosis or advanced fibrosis were randomly

assigned to receive 100 mg of lamivudine per day or placebo for up to 5 years; the

incidence of HCC was significantly reduced in the lamivudine group as compared with

the placebo group (3.9% vs. 7.4%; hazard ratio, 0.49; P=0.047)[39]; this trial was

terminated early (after a median duration of treatment of 32.4 months) because of a

significant difference between treatment groups in the number of end points reached.

Papatheodoridis et al. systematically reviewed data on HCC incidence from 21

studies including 2881 patients with HBV who were treated with medium-term

nucleos(t)ide analogues (lamivudine was the initial treatment in 19, emtricitabine in one,

and adefovir in one study)[40]. Only three of the 21 studies included untreated HBV

patients followed for at least 24 months (one from the only randomized controlled trial

on this topic as described above). A total of 168 (4.3%) patients receiving nucleos(t)ide

analogue therapy were diagnosed to have HCC during a mean/median follow-up of 40

(24–102) months. In the three studies with untreated controls, which were all of high

quality and large, the rate of HCC was significantly lower in the treated (22/779, 2.8%)

than in the untreated patients (34/534, 6.4%, *p* = 0.003). Of note, most of these data on

the effect of HBV treatment on the risk of HCC come from studies that used lamivudine.

Newer treatments with greater potency and better resistance profiles—such as entecavir and tenofovir—are expected to further reduce the incidence of HCC, though these data have just started to emerge[41].

A multinational European cohort study reported clinical outcomes in patients treated with entecavir for a median of 20 months[42]. Patients with a virologic response (defined as serum HBV DNA levels <80 IU/ml) had a significantly lower probability of developing hepatic decompensation, HCC, or death (HR 0.29, 95% CI 0.08 to 1.00, p=0.05). This effect was significant among patients with cirrhosis (HR 0.22, 95% CI 0.05 to 0.99, p=0.04) but not in those without cirrhosis (HR 0.24, 95% CI 0.02 to 3.76, p=0.27). Of the 372 patients in the trial, only three developed HCC. Although encouraging, this study is limited by a relatively small number of clinical events and a short follow up. A larger study following patients for a longer duration will be required to confirm a preventive effect of entecavir treatment in patients with HBV. In the interim, the existing data show that medium-term nucleos(t)ide analogue therapy significantly reduces but does not eliminate the risk of HCC, particularly in patients with cirrhosis. The use of all oral anti-viral agents in patients with cirrhosis is associated with improved virological, biochemical and clinical parameters at 1-year with tenofovir and entecavir being the most efficacious[43].

The effect of interferon on HCC incidence in patients with chronic HBV has also been evaluated in several studies and meta-analyses[44-46]. Most of the data suggest that interferon treatment decreases overall HCC incidence in sustained responders.

HCV Treatment

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A recent systematic review of observational studies examined the risk of HCC among HCV-infected adults who had been treated and either achieved a sustained virologic response (SVR) or did not respond to therapy[47]. SVR was associated with a reduction in the relative risk for HCC for patients at all stages of liver disease (hazard ratio, 0.24, 95% CI = 0.18 to 0.31, $P < 0.001$). Approximately 1.5% of patients responding to treatment develop HCC, compared with 6.2% of those who did not respond. SVR was associated with a similar reduction in the risk for HCC (hazard ratio, 0.23, 95% CI= 0.16 to 0.35, $P < 0.001$) in patients with advanced liver disease or cirrhosis; approximately 4.2% of patients with SVR developed HCC compared to 17.8% of those without SVR. Most studies included in this systematic review were from Asia. Given the fact that rates of HCC are higher in Asian populations than in European or U.S. populations, the absolute benefit of SVR on HCC risk may have been overestimated. Collectively however, these data show a moderate protective effect of treatment-related SVR on the development of HCC among HCV-infected persons. However, the absolute risk of HCC does not revert to baseline levels among those with cirrhosis, older age, high α-fetoprotein levels, low platelet counts, high fibrotic stage and diabetes[48;49]. Furthermore, HCC incidence in nonresponders to initial antiviral therapy is not reduced by maintenance IFN therapy. Newer and more effective therapies may further stem the risk of HCC in HCV infected persons.

Treatment of Non-alcoholic Fatty Liver Disease

There is currently no direct evidence to show that treatment for NAFLD/NASH by any modality (including bariatric surgery) can reduce this risk. Several agents may have

potential chemo-preventive effects in reducing the risk of HCC in patients at high risk for NAFLD (section below).

Chemoprevention of HCC

Diabetes Treatment: Several studies [29] indicate that the use of insulin-sensitizing agents (such as metformin) in diabetes may reduce the risk of HCC. In a meta-analysis[50] of these observational studies, metformin use was associated with a 70% reduction in the odds of HCC in patients with diabetes (odds ratio =0.30, 95% CI =0.17, 0.52; *P*<0.001). The proportion of patients with NAFLD/NASH was not reported. However, given that all patients had established diabetes, one expects NAFLD to be disproportionately high in these studies. Therefore, although the extent to which metformin (or similar insulin sensitizing agents) may reduce HCC risk in individuals with NAFLD/NASH remains unknown.

Statins: Epidemiological data also suggest a potential chemo-preventive effect of statins specific to HCC. In a large cohort of diabetics, we found that statin use was associated with a 54% reduction in the odds of HCC (odds ratio=0.46, 95% CI = 0.40–0.517). A recent study from Taiwan found a strong dose-response relationship between statin use and the risk of HCC in individuals with HBV [hazard ratio 0.66 (95% CI, 0.44 to 0.99), 0.41 (95% CI, 0.27 to 0.61), and 0.34 (95% CI, 0.18 to 0.67) for statin use of 28 to 90, 91 to 365, and > 365 days]. A meta-analysis of observational studies and randomized trials evaluated 4,298 cases of HCC in 1,459,417 patients, found a 41% overall reduction in HCC risk with the use of statins[51]. This finding was driven entirely by observational studies that are subjected to confounding by indication and healthy

patient bias. There was no benefit seen in the randomized trials, however, none of the

trials were powered to detect differences in HCC.

Coffee: Several studies suggested an inverse relation between coffee drinking

and risk of HCC. A meta-analysis combined the results from 16 studies, 8 of which were

case-cohort studies and the other 8 of which were case-control studies[52]. The summary

relative risk of developing HCC with coffee consumption was 0.60 (95% CI: 0.50-0.71).

The calculated summary RR was 0.72 (95% CI: 0.61-0.84) for low versus no coffee

consumption, 0.80 (95% CI: 0.77-0.84) for each extra cup of coffee consumed daily.

Consumption of caffeine from sources other than coffee or of decaffeinated coffee is

generally not associated with reduced levels of liver enzymes, fibrosis or HCC.

Biomarkers such as high alpha-fetoprotein, AST and/or ALT, and low platelet counts;

clinical features such as esophageal varices and type 2 diabetes have been used in

various algorithms to identify and enroll patients at high HCC risk in HCC surveillance

programs[26]. A similar approach (targeting patients at high risk for HCC) may improve

the effectiveness and cost-effectiveness of chemoprevention efforts in HCC.

Future Burden of HCC

In the US, the incidence of HBV-related HCC is likely to remain steady. Though

vaccination against HBV could prevent HCC, it does not prevent cancer in persons with

chronic infections. A larger proportion is chronically infected with HCV—most of them

are unaware of their infection status[53]. Testing persons at high risk for infection,

educating patients, and administering effective therapies for treating HBV and HCV is

therefore an important component of prevention against HCC.

A recent mathematical model based on the prevalence and natural history of

HCV in the U.S. general population of HCV-infected individuals estimated that the

number of HCC cases increased from 37,697 between 1990 and 1999 to 86,765

(+130%) between 2000 and 2009, with a projected increase to 130,366 (+50%) cases

between 2010 and 2019[54]. We found similar time trends in the prevalence of HCC in a

national cohort of Veterans with HCV[55]. Among HCV infected Veterans who visited the

VA in a given calendar year, the prevalence of HCC increased 19-fold from 0.07% (95%

CI, 0.04% to 1.0%) to 1.3% (95% CI, 1.23% to 1.35%) from 1996 to 2006 (p<0.0001).

Collectively, these data show that number of individuals with HCV related HCC has

continued to rise and is projected to peak in 2019.

Although the incidence of HCV-related HCC is expected decline after 2020, this

may not translate into a parallel decrease in the number of overall HCC cases. NASH-

related cirrhosis is rapidly becoming an important cause of HCC. Given the very high

prevalence of the metabolic syndrome in the U.S., even small increases in risk related

to NASH could translate into a large number of cases of HCC.

The recent breakthrough in the management of HCV may indeed change the

trajectory of HCC in the U.S. However, data show that the benefit of antiviral treatment

is primarily limited to patients with successful eradication of the virus. Recent data

show that approximately 45%-70% of individuals with HCV in the United States remain

unaware of their infection STATUS[53]. Based on the mathematical model by Davis et al.

[54], assuming an SVR rate of ~80%, antiviral treatment will decrease cases of cirrhosis

by a mere 5% in 2020. However, extending the treatment of half of infected persons would reduce HCC by 30.2%; treatment of all infected individuals would reduce the risk by 60.4% after just 10 years. Thus, a reduction in the incidence of HCC may not be achieved unless an increasing number of patients are diagnosed and treated.

The Centers for Disease Control and Prevention (CDC) recently recommended to test all persons in the United States born between 1945 and 1965 with the hope that this will identify 400,000 new persons with HCV[56]. However, issues related to patient consent, buy-in, and reimbursement may reduce its overall effectiveness. Furthermore, the degree to which increased identification will result in treatment with new, highly potent yet expensive treatment remains to be seen[57]. The success of the CDC's plan will likely be contingent upon the use of efficient and effective means of entering and retaining individuals in HCV care—steps that will need more focused efforts in the near-term.

Table 1. Burden of the main risk factors for HCC in United States.

	Prevalence in general US population	Risk estimate of HCC*	Current prevalence in HCC cases	Population attributable fraction
HBV	0.5-1%	20-25	10-15%	5-10%
HCV	1-2%	20-25	30-60%	20-25%
Alcoholic liver disease	10-15%	2-3	20-30%	20-30%
Metabolic syndrome	30-40%	1.5-2.5	20-50%	30-40%

*relative to controls without the risk factor

HBV: hepatitis B virus; HCV: hepatitis C virus

Figure Legends:

Figure 1: The time trends (1975-2010) of population-based age-adjusted incidence and mortality rates for liver and intrahepatic bile ducts cancer in the United States. Both sexes and all races are included.

Figure 2: State-specific population-based age-adjusted incidence rates for liver and intrahepatic bile ducts cancer. Both sexes and all races are included.

Figure 3: The time-trends of HCC by age groups and birth cohorts in the United States. Source: Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol* 2009;27:1485-1491.

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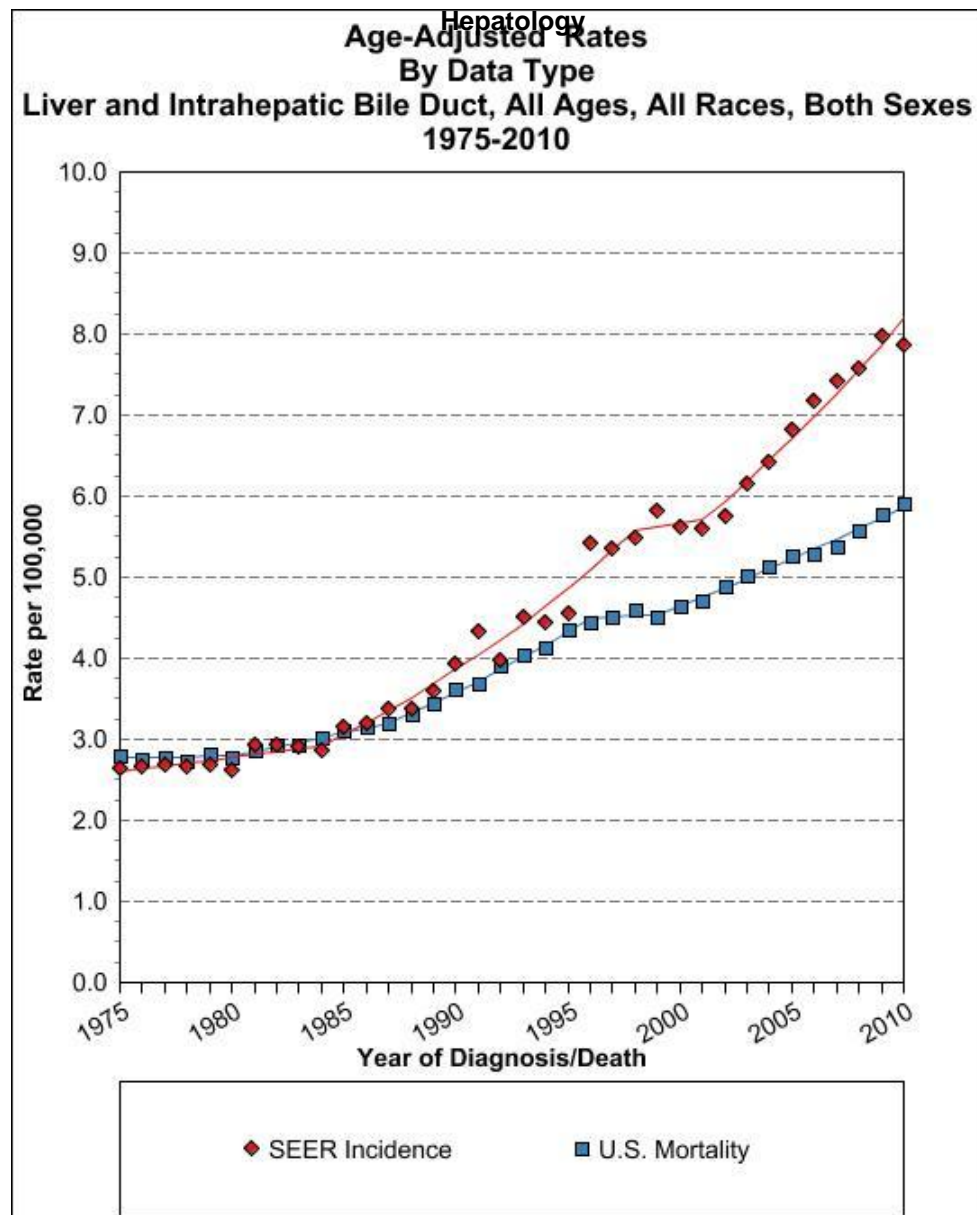
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Figure 1

Hepatology
Age-Adjusted Rates
By Data Type
Liver and Intrahepatic Bile Duct, All Ages, All Races, Both Sexes
1975-2010

◆ SEER Incidence   ■ U.S. Mortality

Cancer sites include invasive cases only unless otherwise noted.
Mortality source: US Mortality Files, National Center for Health Statistics, CDC.
Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 4.0.3, April 2013, National Cancer Institute.
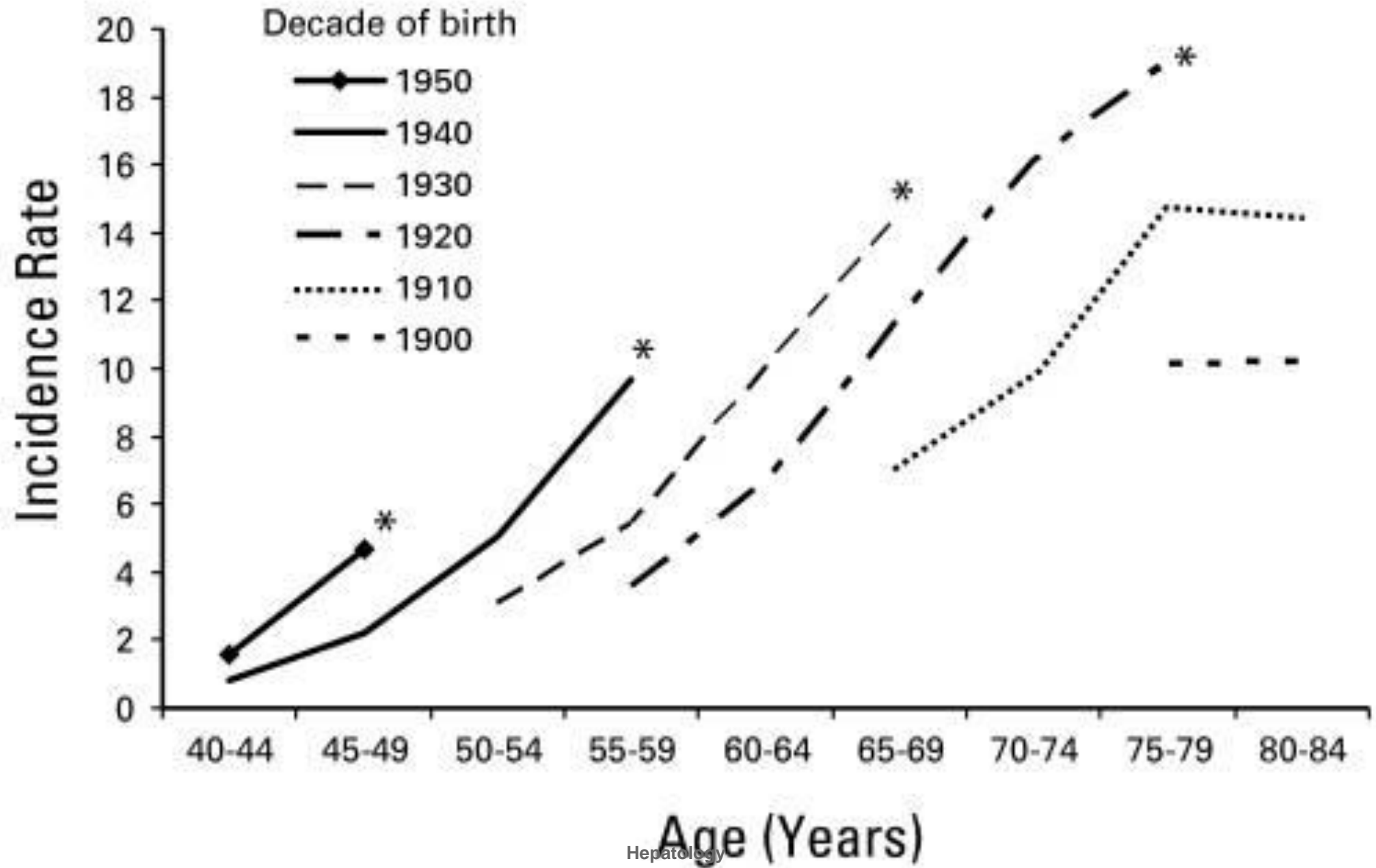
Figure 2

Figure 3

Incidence Rates† for United States, 2006 - 2010
Liver & Bile Duct
All Races (includes Hispanic), Both Sexes, All Ages

Age-Adjusted Annual Incidence Rate (Cases per 100,000)

Quantile Interval

- 7.4 to 10.4
- 6.7 to 7.3
- 6.1 to 6.6
- 5.7 to 6.0
- 4.9 to 5.6
- 3.4 to 4.8

Data Not Available◇

US (SEER + NPCR)
Rate (95% C.I.)
6.7   (6.7 - 6.8)

Created by statecancerprofiles.cancer.gov on 10/08/2013 9:48 am.
State Cancer Registries may provide more current or more local data.
Data presented on the State Cancer Profiles Web Site may differ from statistics reported by the
    State Cancer Registries (for more information).
† Incidence rates (cases per 100,000 population per year) are age-adjusted to the 2000 US standard population
    (19 age groups: <1, 1-4, 5-9, ... , 80-84, 85+). Rates are for invasive cancer only (except for bladder which is
    invasive and in situ) or unless otherwise specified. Rates calculated using SEER*Stat. Population counts for
    denominators are based on Census populations as modified by NCI. The 1969-2011 US Population Data File is used
    for SEER and NPCR incidence rates.
◇ Data not available for this combination of geography, cancer site, age and race/ethnicity.