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**Epidemiology of Hepatocellular Carcinoma**

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**International incidence, mortality, temporal trends**

Primary liver cancer is the seventh most frequently occurring cancer in the world and the second most common cause of cancer mortality (1). The highest incidence rates in the world are found in Asia and Africa (**Figure 1**) (2). Mongolia has the highest incidence at 93.7 per 100,000, but China has the greatest number of cases, due to both an elevated rate (18.3 per 100,000) and the world's largest population (1.4 billion persons) (1).

Globally, hepatocellular carcinoma (HCC) is the dominant type of liver cancer, accounting for approximately 75% of the total (2). Incidence rates of HCC have been decreasing in some high-rate areas but increasing in many low-rate areas (**Figure 2**) (3). In the interval between 1978 and 2012, HCC incidence declined in many Asian countries and Italy, but increased in India, the Americas, Oceania, and most European countries (3). In more recent years, however, the increase in some countries, such as the US, has abated, as rates in various subgroups have plateaued or declined (4, 5).

Prognosis of HCC is poor in all regions of the world(6). As a result, incidence and mortality rates are roughly equivalent. In 2018, the estimated global incidence rate of liver cancer per 100,000 person-years was 9.3 while the corresponding mortality rate was 8.5 (1).

**Demographic characteristics**

***Age***. In most populations, incidence rates of HCC and age are directly correlated until approximately 75 years of age (2). The median age at diagnosis, however, is generally somewhat younger. In the US, for example, the median age at diagnosis among men is between ages 60 and 64 years, while the median age among women is 65-69 years (7). By contrast, in Africa, there is a significant difference in median age at diagnosis between Egypt (58 years) and other African countries (46 years) (8).

***Sex.*** In most countries, incidence rates among men are two to four-fold higher than rates among women (2). For example, in the U.S., the 2016 age-adjusted incidence rate among men was 10.4 per 100,000, while the rate among women was 2.9 per 100,000. The greatest sex differences are seen in Europe, where rates among men can be greater than four-fold higher than rates among

women (e.g., France M:F ratio = 5.0 and Malta M:F ratio = 4.8) (2). In some countries, however, the rates among men and women are much more similar. For example, Uganda (M:F ratio = 1.1), Costa Rica (M:F ratio = 1.6), Ecuador (M:F ratio = 1.0) and Colombia (M:F ratio = 1.6) report nearly equal rates (2).

***Race/ethnicity.*** In multi-ethnic societies such as the US, racial/ethnic disparities can be striking. In 2001, Asians/Pacific Islanders had the highest HCC rates in the US (11.3 per 100,000), but rates among Asians/Pacific Islanders began declining thereafter. As a result, in 2016, American Indians/Alaskan Natives had the highest incidence (11.4), followed by Hispanics (9.8), Asians/Pacific Islanders (9.1), non-Hispanic blacks (8.1), and non-Hispanic whites (4.6) (7).

The wide variability in incidence of HCC by geographic region, age, sex and race/ethnicity is largely, but not entirely, related to the prevalence, and age at acquisition, of major risk factors.

**Risk factors**

***Hepatitis B Virus (HBV).*** HBV is a DNA virus that induces chronic necroinflammatory disease that promotes mutations in liver cells and leads to HCC (9). When evaluating tumor tissue from HBV carriers, HBV DNA is commonly integrated into the genome (10).

The lifetime risk of developing HCC among HBV carriers ranges from 10-25% (10). In a US study, the annual HCC incidence was estimated to be 0.42% overall (11), but incidence can vary depending on whether the person has an active HBV infection and/or cirrhosis (12). Cofactors that also increase risk among HBV carriers include demographic characteristics (e.g., male sex, older age, Asian or African ancestry, family history of HCC), viral factors (e.g., high HBV replication levels, HBV genotype, infection duration, coinfection with HCV or HIV), and environmental exposures (e.g., aflatoxin, alcohol, tobacco, obesity, diabetes) (12). Some risk factors have been incorporated into scoring systems or surveillance recommendations, such as the one devised by the American Association for the Study of Liver Diseases based on cirrhosis, family history of HCC, age, and Asian or African American race/ethnicity. However, these recommendations may not be accurate for predicting HCC risk among HBV carriers who undergo antiviral therapy (13). Further, US data show

that HCC risk is extremely low among individuals, including African Americans, who are less than 40 years of age.

Randomized controlled trials have shown that antiviral treatment of HBV infection can achieve sustained reductions in HBV-DNA levels and improve liver function and histology (14). The primary drugs used are nucleos(t)ide analogs (NAs) (15). Increasing evidence suggests that NA treatment can reduce, but not eliminate, the short and medium-term risk of HCC (16, 17). A meta-analysis found that HCC incidence was significantly lower among persons treated with the first NAs introduced, primarily lamivudine (17). Fewer studies have evaluated risk reduction with the newer NAs. Studies from Taiwan and Japan, however, have reported significantly lower risks of HCC in conjunction with entecavir therapy (18, 19). A US study investigating the effect of entecavir or tenofovir reported that the 5-year HCC risk was lower among persons with cirrhosis, but the overall risk was still higher than among persons without cirrhosis (20). Among patients on long-term NA therapy, older age, male sex, cirrhosis, low platelet count, and diabetes are likely HCC co-factors and have been incorporated in validated risk scores for HCC prediction (21).

HBV vaccination programs are a key HCC prevention strategy. The 30-year report on the neonatal HBV vaccination effort in Taiwan noted that HCC incidence declined 80% and mortality declined 92% in cohorts born after the vaccination program began (22). Many other countries that implemented programs in the 1980s, such as China, Singapore, and Spain are seeing reductions similar to those of Taiwan in the prevalence of HBV in vaccinated cohorts (10).

***Hepatitis C Virus (HCV).*** Chronic HCV infection is a firmly established risk factor for HCC, increasing risk by 10-20 fold (9). HCV is a RNA virus that does not integrate into the host's genome and is, thus, unlikely to be the primary initiator of tumorigenesis. Rather, as approximately 90% of HCV-associated HCC cases are preceded by cirrhosis, HCV likely promotes tumorigenesis through repetitive damage, regeneration and fibrosis (23). The annual incidence of HCC in persons with HCV-related cirrhosis ranges from 0.5-10% (24).

A US model based on a population of HCV carriers estimated that the number of HCV-associated HCC cases increased by 130% between 1990-1999 and 2000-2009 (25). As the 1945-1965

birth cohort has a higher HCV prevalence than other birth cohorts, it has been estimated that the numbers of HCV-associated HCCs in the US will peak around 2020 (24, 26).

Among persons with active HCV infections, co-factors for HCC include male sex, Hispanic ethnicity, HCV genotype 3, longer duration of infection, coinfections with HBV or HIV, insulin resistance, obesity, diabetes, tobacco and alcohol (24, 27). The main factor that decreases HCC incidence is sustained virologic response (SVR) achieved via antiviral therapy (28). Several large studies of direct-acting antiviral (DAA) therapy, and meta-analyses of these studies (29), have demonstrated that HCC risk, while not eliminated, is reduced by 50-80% among persons who achieve SVR (30, 31). While HCC risk is reduced with SVR, the rates do not revert to baseline, especially among persons with cirrhosis. For example, it has been reported that the risk of HCC was reduced 76% in a cohort of patients who achieved SVR and the annual incidence of HCC was 0.9%, with the highest rate (1.0-2.2%) seen in conjunction with cirrhosis (32). Longer follow up of this cohort showed that cumulative 1, 2, and 3-year risks of HCC were 1.1%, 1.9% and 2.8%, respectively. These incidence rates are at, or below, the threshold for cost-effective HCC surveillance (32). Among patients who achieve SVR, HCC risk if higher in association with alcohol use, older age, infection with HCV genotype 3, and elevated markers of hepatic fibrosis (33).

***Alcohol***. While excessive alcohol consumption is a well-established risk factor for liver cancer (34), the effect of lower levels of consumption has not been as thoroughly investigated. In a meta-analysis of prospective studies, heavy alcohol consumption (≥3 drinks/day) was associated with a 16% increased risk of HCC, but there was no association with lower levels of consumption (<3 drinks/day) (35). A US pooling project found, however, that lower levels of consumption (<3 drinks/day) were associated with a significantly decreased risk of HCC, even after excluding non-drinkers (36). The relationship varied by diabetes status however; there was no association with lower level consumption among persons with diabetes, while there was a 35% decreased risk among persons without diabetes (36). In addition, alcohol may have a stronger association with HCC risk among women than men. This could be due to differences in alcohol dehydrogenase activity (37), or due to a stronger association between alcohol and cirrhosis among women (38). In a meta-analysis examining heavy drinking (>4 drinks/day), alcohol was associated with an almost four-fold increased

risk among women, but only a 59% increased risk among men (34). The trends of alcohol use and alcoholic liver disease vary among countries. In the US, several recent reports have reported a notable increase (39).

***Metabolic Syndrome, Diabetes, and Obesity.*** Increasing evidence suggests that metabolic syndrome, a collection of conditions including insulin resistance, abdominal obesity, atherogenic dyslipidemia and hypertension, increases risk of HCC. A 2014 meta-analysis estimated that metabolic syndrome was associated with an 81% increased risk (40). Treating one of the metabolic syndrome conditions, dyslipidemia, with statins, however, may ameliorate risk by 37-42% (41, 42).

Studies in diverse populations have reported that diabetes is associated with a 2 to 3-fold increased risk of HCC, with a significantly greater relative risk among men than women (43). Longer duration of diabetes may be also associated with an incremental increase in risk of HCC, but the relationship between diabetes severity or blood sugar control and HCC risk is unclear (44). The treatment of type 2 diabetes with metformin has been reported to decrease the risk of HCC, whereas treatment with insulin or sulfonylureas has been reported to increase risk (45-47). Metformin is a first-line therapy, however, while insulin and sulfonylureas are not, thus the correlation of medication with disease severity might lead to an overestimation of risk reduction by metformin (10).

It is well-established that excess adult adiposity increases the risk of liver cancer (48), but several studies also suggest that there is an effect of adiposity at earlier ages. A Danish study reported that a one-unit increase in body mass index (BMI) z-score at ages 7 or 13 years was associated with a 20-30% increased risk of liver cancer (49), while studies from the US and Sweden found that obesity in early adulthood was associated with 2 to 3-fold increased risk (50-52). BMI may not accurately capture important elements of obesity, thus recent studies have examined waist and hip circumference as measures of excess abdominal and gluteofemoral adiposity, respectively. Cohort studies in Europe and the US have reported that persons with the high waist circumference have a 2-fold increased HCC risk, which remains unchanged after adjustment for BMI or hip circumference (53-55). Further, excess abdominal size in one of the studies was associated with an

increased HCC risk, even among individuals who had a BMI of 18.5–≤25 kg/m$^2$, but excess gluteofemoral size alone conferred no increased risk (54).

***Nonalcoholic Fatty Liver Disease (NAFLD).*** The overall prevalence of NAFLD among US adults is 32.8%, but the prevalence varies by sex (men 34.7%; women 31.0%), and race/ethnicity (Mexican-Americans 41.2%; whites 32.5%; blacks 29.1%) (56). Among persons with NAFLD, 20-30% are estimated to progress to non-alcoholic steatohepatitis (NASH), which then progresses to cirrhosis in 10-20% of cases (57, 58). NAFLD is now a leading cause of cirrhosis and NASH is the second-leading cause of liver transplantation related to HCC in the US (59). The increasing number of HCCs due to NASH could offset the reductions in HCV-related HCC expected after 2020 (24). Factors related to HCC risk associated with NAFLD include clinical factors (cirrhosis, diabetes, obesity, hypertension), demographic characteristics (age, race/ethnicity), and genetic susceptibility (e.g., genetic variability in *PNPLA3*).

Between 70 and 80% of NAFLD-related HCCs develop in cirrhotic livers, but the HCC risk is lower than that associated with HCV-related cirrhosis. While 20-30% of NAFLD-related HCCs develop in the absence of cirrhosis (60), the determinants of this proportion are unclear.
An analysis of studies investigating the link between NAFLD and HCC risk found that HCC risk varied from 0 to 38% after follow-up of 5-10 years. In comparison, persons with NAFLD-related cirrhosis had an HCC incidence ranging from 2.4 to 12.8%. A recent large cohort study reported an HCC incidence of 0.21 per 1000 person-years among persons with NAFLD, which was significantly higher than the risk among persons without NAFLD (60). There was also an increase in risk with each additional metabolic trait; for example, HCC risk was 2.6-fold higher in NAFLD patients with diabetes, obesity, dyslipidemia and hypertension compared to NAFLD patients without any of these traits (61). While weight loss can reduce NAFLD severity, no studies have shown weight loss to affect HCC risk.

There is no high-level evidence to support or refute the value, method, or frequency of HCC surveillance among the NAFLD population. However, based on cost-effectiveness modelling, clinical practice guidelines recommend considering HCC surveillance among persons with cirrhosis when the expected annual HCC incidence is 1.5% or higher (62).

***Aflatoxin $B_1$.*** Aflatoxins, mycotoxins produced by fungi of the *Aspergillus* species, contaminate a variety of foodstuffs, most notably, maize, ground nuts, and tree nuts. Of the four principal aflatoxins, $B_1$, $B_2$, $G_1$, and $G_2$, the most potent is aflatoxin $B_1$ ($AFB_1$) (63). $AFB_1$ occurs in many locations around the world, especially in countries with warm, humid environments. The development of $AFB_1$ biomarkers enabled the link between HCC and $AFB_1$ to be definitely established and prompted IARC to classify $AFB_1$ as a group 1 human carcinogen (63). $AFB_1$ is particularly carcinogenic when it co-occurs with chronic HBV infection as the combination of factors has a synergistic effect on HCC risk. A 2012 meta-analysis estimated that $AFB_1$ alone increased HCC risk by 6-fold, HBV alone by 11-fold, and the two factors together by 54-fold (64).

$AFB_1$ contamination of crops is difficult to combat because contamination can occur both pre- and post-harvest (65). A very successful effort, however, was the replacement of maize with rice as the dietary staple in parts of China; an effort has been largely credited for the current decline in HCC rates (66, 67). However, the single most effective way to reduce HCC risk in regions where $AFB_1$ and HBV co-occur is to vaccinate against HBV in order to eliminate the synergistic effect on risk.

***Tobacco.*** In a review of 113 studies, the 2014 US Surgeon General's report found that current cigarette smoking was associated with a 70% increased risk of liver cancer, while former smoking was associated with a 40% increased risk (68). A recent study, however, reported that years since smoking cessation was inversely associated with HCC risk, with individuals who stopped smoking >30 years ago having an HCC risk similar to that of never-smokers (36).

***Dietary factors.*** Coffee has been consistently associated with decreased risk of liver cancer (69). A 2017 meta-analysis of both cohort and case-control studies reported that an extra two cups of coffee per day was associated with a 35% reduced risk (70). Coffee has also been associated with lower liver enzyme levels, slower progression of fibrosis, and lower risk of diabetes. The mechanisms underlying a possible protective effect of coffee, however, are not clear. Experimental evidence suggests there may be beneficial effects of caffeine as well as many other coffee components (e.g., diterpenes) in reducing inflammation, fibrosis, insulin resistance and oncogenesis (71).

High iron intake has been long associated with increased risk (72, 73). The consumption of traditional iron-rich beer is associated with HCC in southern and central Africa (74). Further, a recent meta-analysis of prospective studies in Asia, Europe, and the US found that higher serum ferritin levels were associated with a 49% increased HCC risk, while higher serum iron levels were associated with a 2.5-fold greater risk (72).

**Genetic susceptibility**

Mutations in the genes for hemochromatosis (*HFE*), alpha 1-antitrypsin deficiency (*SERPINA1)*, glycogen storage diseases (*G6PC, SLC37A4)*, porphyrias (*HMBS, UROD*), tyrosinemia (*FAH)* and Wilson's Disease (*ATP7B)* increase susceptibility to HCC. Polymorphisms, originally examined in candidate-locus studies, have also been related to risk. A 2011 meta-analysis found that polymorphisms in *UGT1A7*, *MnSOD* and *IL-1B* were all significantly associated with risk (75). More recently, genome-wide association studies (GWAS) conducted in Asian populations where HBV or HCV were factors reported increased risks in association with a number of loci, most commonly ones located in the *HLA* region (*HLA-DP, HLA-DQ, HLA-DR, MICA)* (76-85). Another reported association maps to chromosome 1p36.22, a region that may harbor a tumor suppressor gene for HCC (85). The *KIF1B* gene in this region has been reported to be associated with apoptosis, and its association with HCC was replicated in subsequent studies from other Asian populations. Associations with *STAT4, GRIK1, EFCAB11,* and *EFCAB11* have also been found (77, 78, 80). In non-Asian populations, a polymorphism in the *PNPLA3* gene has been demonstrated to be associated with HCC. The rs738409 SNP was first reported to be related to NAFLD (86), conferring a 4-fold increased risk among persons homozygous for the risk allele and an almost 2-fold increased risk among heterozygotes (87). Subsequent examinations of the polymorphism and risk of HCC also found associations. As reported by a recent meta-analysis, there is evidence of a significant association among white populations (OR=1.75), but no evidence of an association among Asian populations (88).

**Population Attributable Risks**

The extent to which individual risk factors contribute to the HCC burden can be estimated by calculation of population attributable fractions (PAFs), which are important measures for developing cancer control policies. PAFs are dependent on the strength of the risk factor-HCC association and the prevalence of the risk factor in the population, thus, PAFs vary widely by geographic location. For example, although it has been estimated that the global HBV PAF is 56%, the PAF for North America is estimated at just 7%, while the PAF for Eastern Asia is estimated at 69% (89). Similarly, the global HCV PAF is estimated at 20%, but the PAF for Eastern Asia is estimated at 11% while the PAF for Northern Africa is estimated at 79% (89). The global $AFB_1$ PAF is estimated to be 17%, but the PAF ranges from 8% to 21% in populations where HBV is absent versus present, respectively (64). For alcohol, the global PAF is estimated at 26%, although the PAF in Eastern Europe is notably higher (39%) than the PAF in South Asia (13%). For obesity, the global PAF is estimated at 9%, with notably higher PAFs in North America (24%) than in Southeast Asia (4%) and sub-Saharan Africa (4%). For diabetes, the global PAF is estimated to be 7%, with higher PAFs in Oceania (12%) and the Middle East (12%) and lower PAFs in sub-Saharan Africa (4-5%).

**Conclusions**

HBV and HCV remain the most important global risk factors for HCC. However, the prevalence of both factors should decline in the coming years due to HBV vaccination of newborns, and more effective treatment of both HBV and HCV carriers. The prevalence of NAFLD/NASH is increasing and may soon overtake viral factors as the major cause of HCC globally. Excessive alcoholic consumption also remains an important risk factor. Due to climate change, so $AFB_1$ could become a more dominant risk factor in the coming decades. These changing trends suggest that more effort needs to be focused on combating obesity and diabetes to decrease the incidence of NAFLD, and more effective strategies to control alcohol use and mycotoxin growth need to be implemented.

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**Figure 1.** Global age-adjusted incidence rates of liver cancer, estimated for 2018. Data source: GLOBOCAN 2018. Graph production: IARC (http://gco.iarc.fr/today), World Health Organization.

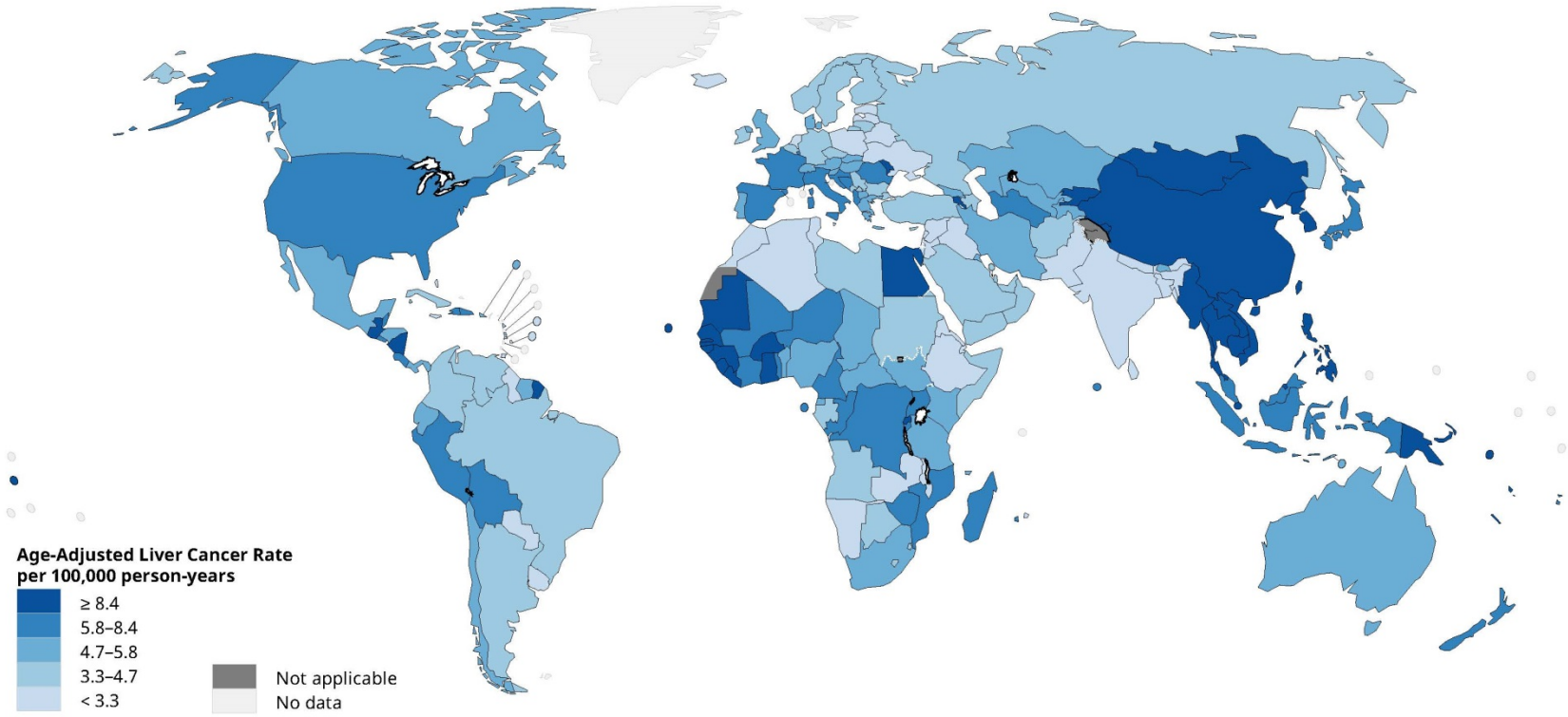

**Figure 2.** Trends in hepatocellular carcinoma incidence rates by country, 1978-1982 through 2008-2012. Rates are per 100,000 person-years and age-adjusted to the world standard population.