Epidemiology and Etiology of Hepatocellular Carcinoma and Bile Duct Cancer

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Epidemiology and Etiology of HCC and Bile Duct Cancer

Global Epidemiology of HCC

Most common type of primary liver cancer, accounting for 80-90% of all cases

Incidence:

- **6th most common cancer globally** ~900,000 new cases annually
- 3rd leading cause of cancer-related mortality, particularly in Asia

Geographic Distribution:

- Highest in East Asia and sub-Saharan Africa (>20 per 100,000)
- Intermediate in Southern Europe and Latin America
- Rising incidence in North America (~4-5 per 100,000)

Demographics:

- Male predominance (2-4:1 male-to-female ratio)
- Peak incidence at 50-60 years in high-risk regions
- Later onset (70+ years) in low-risk regions

Kim, D. Y. (2024). Changing etiology and epidemiology of hepatocellular carcinoma: Asia and worldwide. *Journal of Liver Cancer*, *24*(1), 62–70. https://doi.org/10.17998/jlc.2024.03.13

Incidence and mortality of HCC by country[7]

Country	Incidence		Mortality	
	Case	ASR (%)	Case	ASR (%)
China	410,038	18.2	391,152	17.2
Japan	45,663	10.4	28,155	4.8
Thailand	27,394	22.6	26,704	21.9
Vietnam	26,418	23.0	25,272	21.9
Indonesia	21,392	7.9	20,920	7.7
Republic of Korea	14,788	14.3	11,158	9.9
Philipphines	10,594	11.4	9,953	10.8
North Korea	5,607	15.5	5,228	14.4
Myanmar	5,466	10.0	5,281	9.7
Cambodia	3,142	24.3	2,946	22.9
Mongolia	2,236	85.6	2,060	80.6
Lao	1,272	24.4	1,192	22.9
United States	42,284	6.9	31,078	4.7

Incidence and mortality of HCC data adapted by GLOBOCAN 2020.

ASR, age-standardized rate per 100,000; HCC, hepatocellular carcinoma.

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Historical Etiologies of HCC

Hepatitis B Virus (HBV)

- Accounts for ~50% of HCC cases globally
- Direct oncogenic effect via HBV DNA integration
- Indirect effect through chronic inflammation
- 15-40% lifetime risk of HCC in endemic regions’

Hepatitis C Virus (HCV)

- Major cause in Europe, Japan, North America
- Primarily indirect carcinogenesis through cirrhosis
- 1-5% annual risk of HCC after cirrhosis develops

Cirrhosis (present in 80-90% of HCC cases)

Alcohol-related liver disease

- Synergistic effect with viral hepatitis
- Dose-dependent relationship

Metabolic dysfunction-associated steatotic liver disease (MASLD)

- Fastest growing cause of HCC in Western countries
- Associated with metabolic syndrome, obesity, diabetes

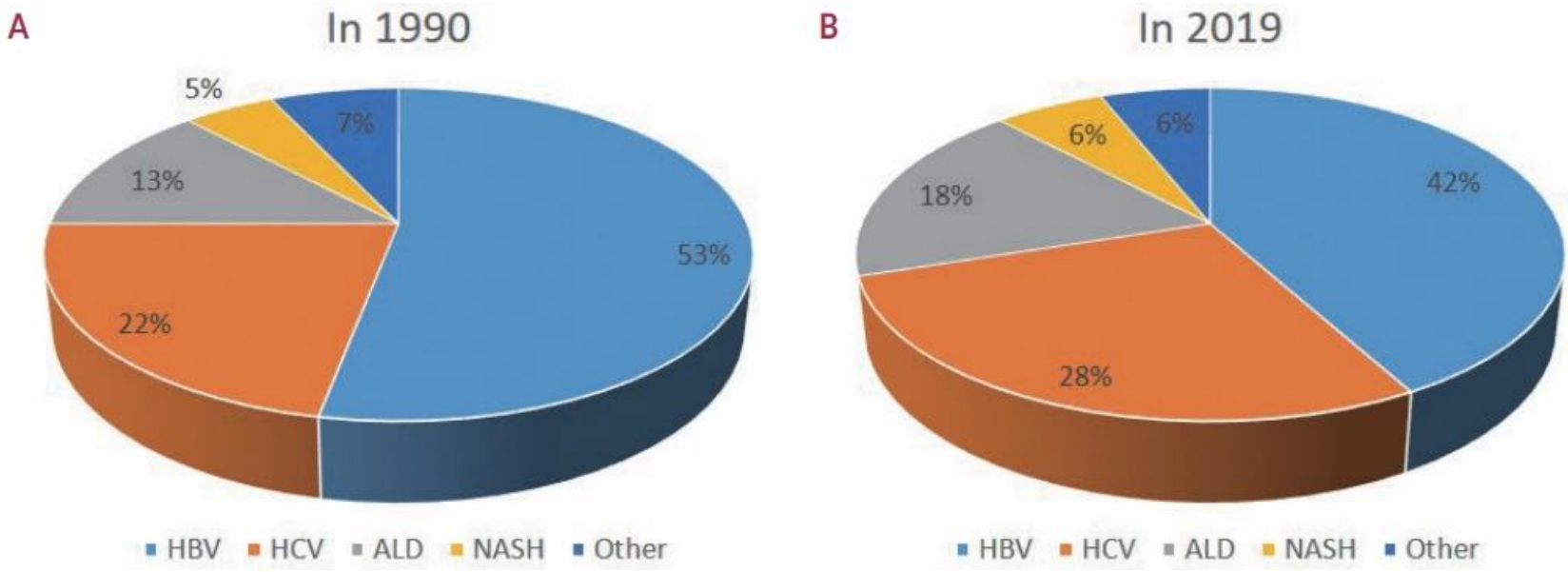
Aflatoxin B1 exposure

- Common in parts of Africa and Asia
- Synergistic effect with HBV
- Causes characteristic TP53 mutation (249ser)

Genetic and metabolic disorders

- Hereditary hemochromatosis (20% lifetime risk)
- Alpha-1-antitrypsin deficiency
- Wilson's disease
- Glycogen storage diseases

Changing Etiology of HCC In Asia and Worldwide



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Epidemiological Characteristics of MASLD-Associated HCC

- Metabolic dysfunction-associated steatotic liver disease is the most common liver disease in the world
- Its global prevalence in 2016 was approximately 25%, with a projected 15-56% rise by 2030
- The spectrum of MASLD ranges from steatosis to a more progressive form, metabolic dysfunction associated steatohepatitis (MASH)
- Variable risk for HCC which is largely driven by progression in fibrosis and cirrhosis
- HCC incidence of 0.21 per 1000 person-years among persons with MASLD of any severity, which was 7-fold higher than controls without MASLD

(2024). Doi.org. https://doi.org/10.1093/jcag/gwae025

- PNPLA3 rs738409 single-nucleotide polymorphism is associated with a 67% increased risk of HCC in individuals with MASH or alcoholic cirrhosis
- 2014 US Surgeon General's report revealed that current cigarette smoking was linked to a 70% increased risk of HCC, and former smoking was associated with a 40% increased risk
- Coffee consumption has consistently been linked to a decreased risk of HCC.

(2024). Doi.org. https://doi.org/10.1093/jcag/gwae025

Global Epidemiology of Cholangiocarcinoma

Incidence:

- ~2% of all cancer diagnoses globally
- Significant geographic variation
- Highest in Southeast Asia (>80 per 100,000)
- Western countries: 1-2 per 100,000

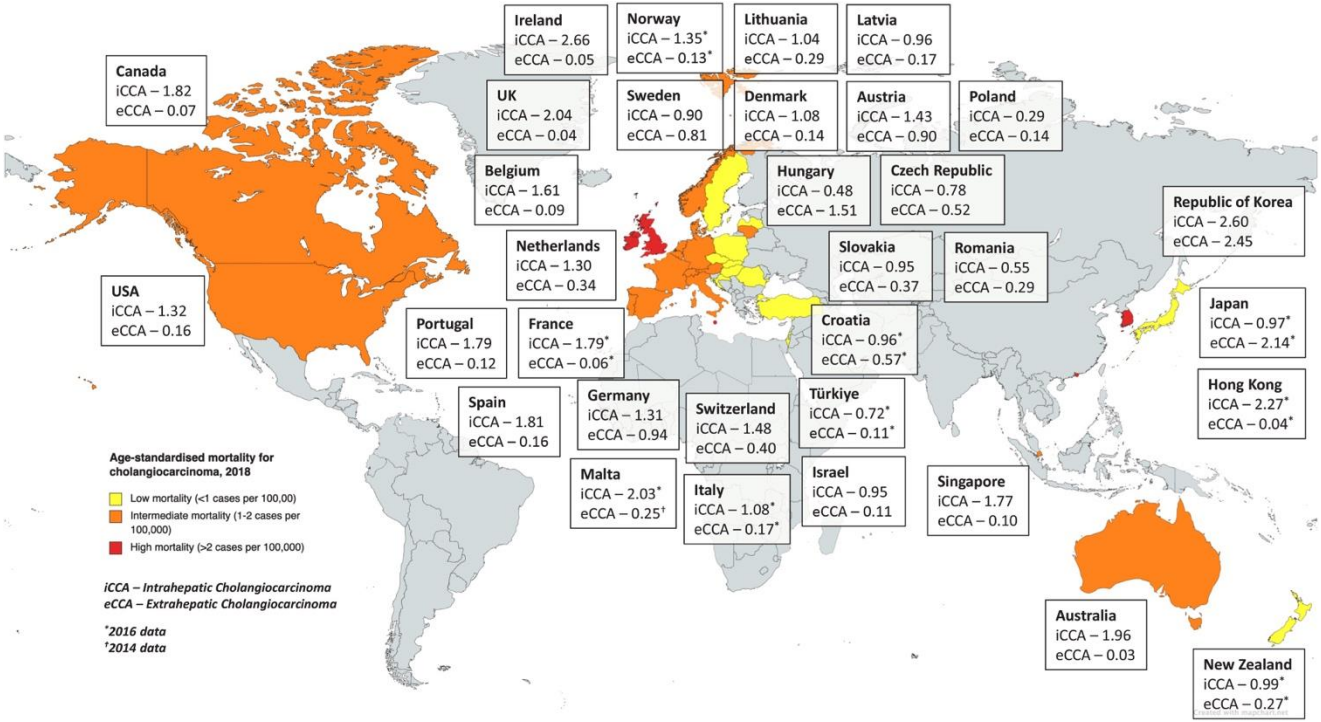
Classification:

- **Intrahepatic** (within liver parenchyma) - ~20%
- **Extrahepatic** (in bile ducts outside liver) - ~80%
- Perihilar
- Distal

Demographics:

- Slight **male predominance** (1.5:1)
- Peak incidence **50-70 years**
- **Increasing incidence** of intrahepatic form in Western countries
- **13th most common cancers in the US**
- **2.1% of all new cancer cases in the US**

Qurashi, M., Vithayathil, M., & Khan, S. A. (2023). Epidemiology of cholangiocarcinoma. *European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*, 107064. https://doi.org/10.1016/j.ejso.2023.107064



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National Data On Liver and Intrahepatic Bile Duct Cancer

NATIONAL CANCER INSTITUTE
Surveillance, Epidemiology, and End Results Program

National Cancer Institute. (2018). *Cancer of the Liver and Intrahepatic Bile Duct - Cancer Stat Facts*. SEER. https://seer.cancer.gov/statfacts/html/livibd.html

At a Glance

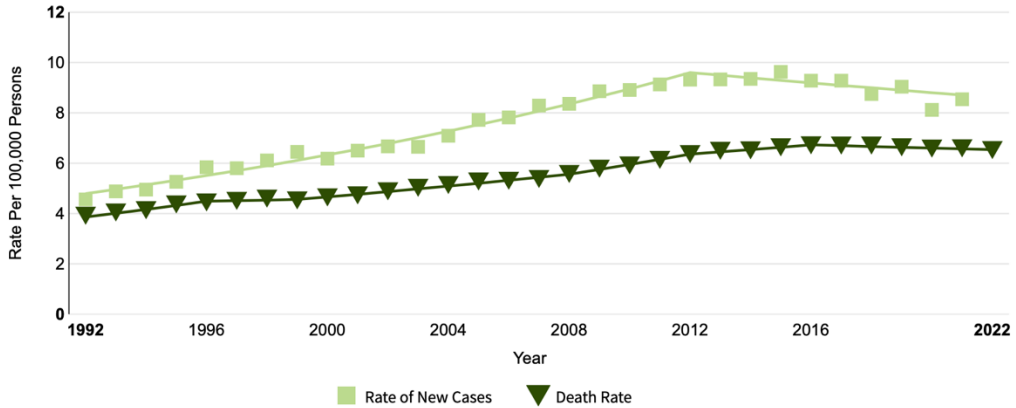
Estimated New Cases in 2024	41,630
% of All New Cancer Cases	2.1%

Estimated Deaths in 2024	29,840
% of All Cancer Deaths	4.9%

5-Year Relative Survival

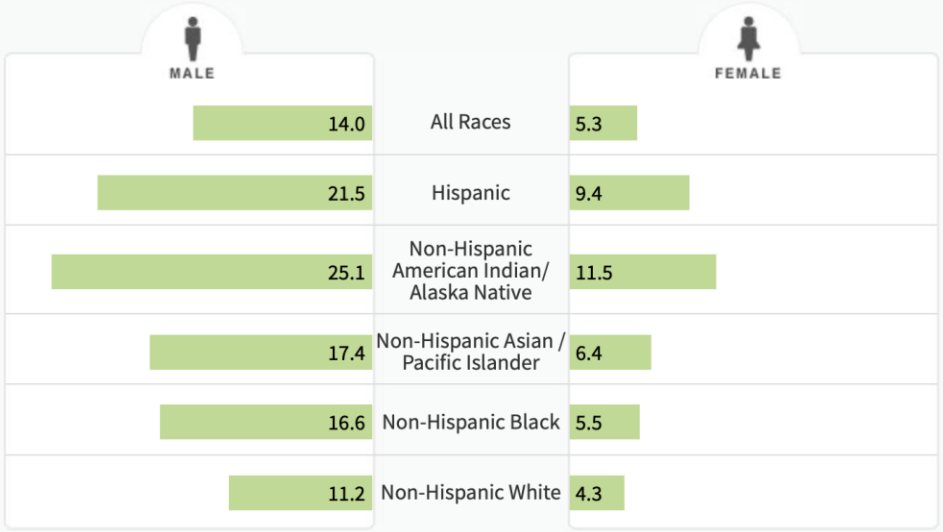
21.7%

2014–2020



National Cancer Institute. (2018). *Cancer of the Liver and Intrahepatic Bile Duct - Cancer Stat Facts*. SEER. https://seer.cancer.gov/statfacts/html/livibd.html

Rate of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Liver and Intrahepatic Bile Duct Cancer



SEER 22 2017–2021, Age-Adjusted

National Cancer Institute. (2018). *Cancer of the Liver and Intrahepatic Bile Duct - Cancer Stat Facts*. SEER. https://seer.cancer.gov/statfacts/html/livibd.html

Etiology of Cholangiocarcinoma

Parasitic Infections:

Liver flukes (Opisthorchis viverrini, Clonorchis sinensis)

- Major cause in endemic regions (Thailand, China, Korea)
- Chronic inflammation and cellular damage IARC classified as definite carcinogens

Hepatobiliary Conditions:

Primary sclerosing cholangitis (PSC5-15% lifetime risk of cholangiocarcinoma

Bile duct cysts/Choledochal cysts

- 10-15% lifetime risk
- Risk increases with age

Hepatolithiasis (intrahepatic stones) Common in East Asia 5-10% develop cholangiocarcinoma

Other Risk Factors:

Toxins

- Thorotrast (banned radiocontrast agent)
- 1,2-dichloropropane and dichloromethane (industrial solvents)

Chronic inflammatory conditions

- Inflammatory bowel disease (beyond PSC association)
- Chronic typhoid carriage

Genetic conditions

- Lynch syndrome
- Bile salt transport/metabolism disorders

Cirrhosis, viral hepatitis, and metabolic factors

- Emerging evidence for HBV, HCV association
- **Diabetes,** obesity, alcohol

Banales, J. M.. (2020). Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nature Reviews Gastroenterology & Hepatology*, *17*(9), 557–588. https://doi.org/10.1038/s41575-020-0310-z

- PSC is strongly associated with inflammatory bowel disease; 60-80% of patients with PSC have a history of ulcerative colitis and 7-21% have a history of Crohn's disease
- Patients with PSC have a 15% lifetime incidence of cholangiocarcinoma (equivalent to a 398-fold increased risk compared to the general population) and up to one third will develop cholangiocarcinoma within a year of being diagnosed with PSC
- Cholestasis leads to overexposure of cholangiocytes to bile acids that cause abnormal cell proliferation and cholangiocarcinogenesis
- Fibropolycystic Liver Diseases (FPLD) result of abnormal development of the embryonic sheet of biliary precursor cells (the ductal plate) that form the intrahepatic bile ducts and cholangiocytes
- Examples: congenital hepatic fibrosis, Caroli disease, choledochal cysts and biliary hamartomas
- 15% risk of developing cholangiocarcinoma

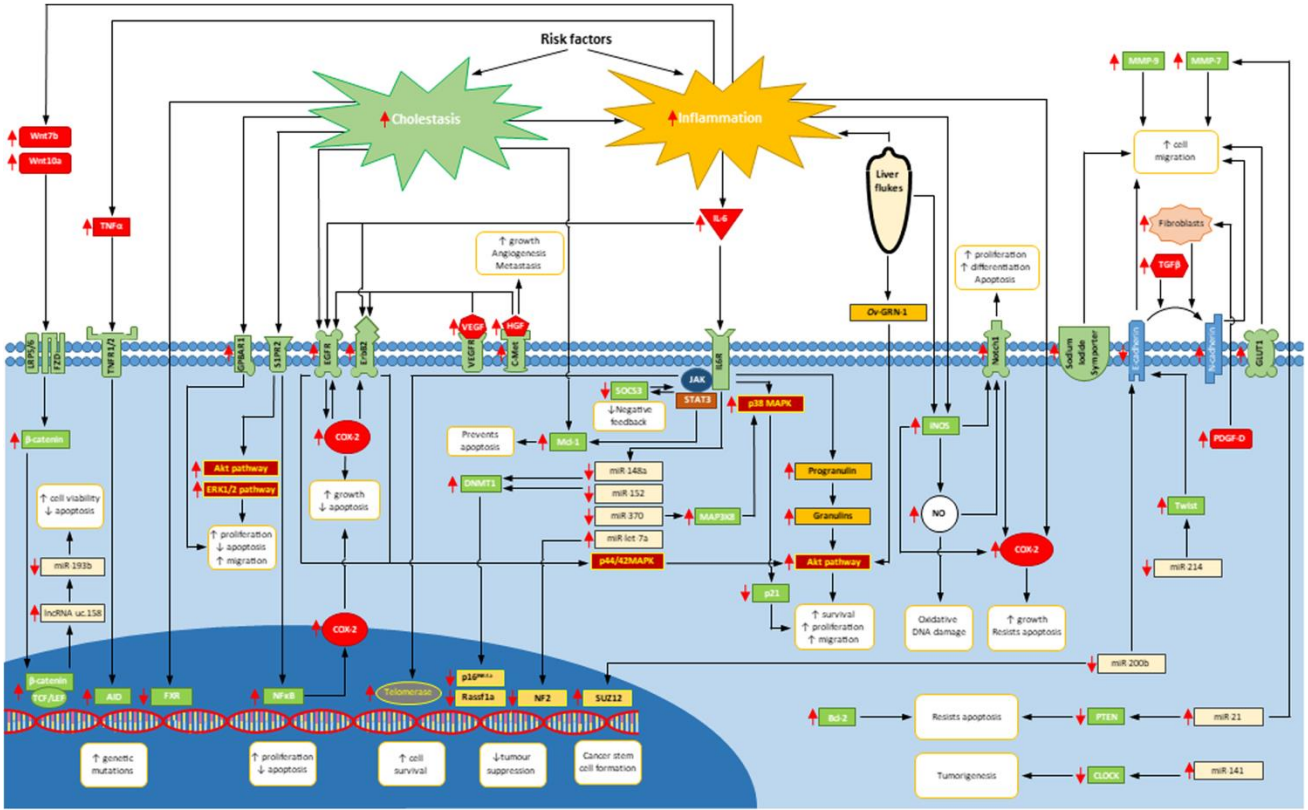
Labib, P. L., Goodchild, G., & Pereira, S. P. (2019). Molecular Pathogenesis of Cholangiocarcinoma. *BMC Cancer*, *19*(1). https://doi.org/10.1186/s12885-019-5391-0

- Patients with liver cirrhosis to have an Odds Ratio (OR) of 22.9 (95% Confidence Interval (CI) 18-2-28.8) for intrahepatic cholangiocarcinoma
- Gallstones are associated with an increased risk of both ICC and ECC
- choledocholithiasis was found to confer an OR of 6.94 (95% CI 5.64-8.54) for ICC and 14.22 (95% CI 12.48-16.20) for ECC
- Heavy alcohol consumption (≥5 drinks/day) conferred a hazard ratio of 1.68, although the 95%CI was 0.99-2.86
- In Lynch syndrome the lifetime risk of a pancreatic or biliary tract cancer is estimated at 2%
- Defects in genes coding for bile salt transporter proteins (BSEP/ABCB11, FIC1/ATP8B1 and MDR3/ABCB4) cause cholestasis leading to the release of inflammatory cytokines, chronic inflammation and subsequent cholangiocarcinogenesis
- Intraductal Papillary Neoplasms of the Bile Duct (IPNB) high risk of malignant transformation to cholangiocarcinoma, estimated to be as high as 40-80%.

Labib, P. L., Goodchild, G., & Pereira, S. P. (2019). Molecular Pathogenesis of Cholangiocarcinoma. *BMC Cancer*, *19*(1). https://doi.org/10.1186/s12885-019-5391-0

Molecular pathogenesis of cholangiocarcinoma

- IDH1/2 mutations (intrahepatic)
- FGFR2 fusions (intrahepatic)
- KRAS/TP53 mutations (extrahepatic)
- Epigenetic alterations



Thank you for your attention