# Supplementary Material

**Supplementary Table 1. Principal studies evaluating metabolic risk factor for the development of HCC**

| Author,[Ref] | Series | Findings | Conclusion |
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| Nair, *et al.*[63] | Study conducted among 19,271 evaluable patients belonging to the UNOS database on all liver transplantations from 1991 to 2000 | Obesity was an independent predictor of HCC among individuals with alcoholic cirrhosis (OR, 32; 95%CI: 15-66; *P* = 002) and cryptogenic cirrhosis (OR, 111; 95%CI: 15-874; *P* = 02) However, it was not an independent predictor of HCC among subjects with hepatitis C, hepatitis B, PBC and AIH | Obesity was an independent risk factor for HCC in patients with advanced cirrhosis However, the risk seemed to be primarily associated with alcoholic liver disease and cryptogenic cirrhosis rather than other etiologies of CLD |
| Ohata, *et al.*[64] | Out of 218 HbsAg-negative individuals with chronic hepatitis or cirrhosis, 161 patients with chronic HCV infection who were followed for > 6 months were enrolled in this study<br>The average follow-up was 765 | At multivariate analyses hepatic steatosis was a significant independent risk factor for HCC (together with aging, cirrhosis, and no IFN treatment) | Hepatic steatosis is an independent risk factor for HCC in patients with chronic HCV infection |

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| | months (64 years) | | |
| Tanaka, *et al.*[65] | Clinical, viral and histological data of 266 patients who achieved SVR with IFN therapy and who were thereafter submitted to a regular follow-up for an average 99 ± 41-year period, were retrospectively reviewed | The cumulative incidence for HCC significantly differed according to liver fibrosis (F3-4) ($P$ = 00028), hepatic steatosis (Grade 2-3) ($P$ = 00002) and age (≥ 55) ($P$ = 0021) at the pre-interferon treatment | Although multivariate analysis was not performed in this study, data suggest that hepatic steatosis, together with fibrosis and age, was associated with HCC in individuals treated with IFN for cronic hepatitis owing to HCV infection |
| Ohki, *et al.*[66] | 62 patients with naıve NASH-HCC treated with PRA were divided into two groups based on VFA assessed with CT scan images: the high VFA group (> 130 $cm^2$ in males, > 90 $cm^2$ in females, $n$ = 27) and the others ($n$ = 35) | At multivariate analysis VFA (risk ratio 108, per 10 $cm^2$, $P$ = 0046) and older age (risk ratio 106 per 1 year, $P$ = 004) were independently associated with HCC recurrence | VFA is an independent risk factor of HCC recurrence after PRA in patients with naive NASH-HCC This study supports the notion that VFA links the previously reported nexus of BMI with HCC risk |
| El-Serag, *et al.*[67] | This prospective study enrolled 173,643 individuals with and 650,620 without diabetes | Diabetes was associated with an HRR of 198 (95%CI: 188 to 209, $P$ < 00001) of CNLD and an HRR of 216 (186 to 252, $P$ < 00001) of HCC | The presence of diabetes was associated with a two-fold increased risk of CNLD and HCC |

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| | Based on the duration of follow-up: either ≤ 5 years, 5 to 10 years, or > 10 years three subgroups of patients were identified | Diabetes was associated with the highest risk among those with a > 10-year follow-up | Diabetes preceded the diagnosis of both CNLD and HCC and there was a significant duration response<br>These findings strongly suggest cause and effect association |
| Tseng, *et al.*[68] | Out of 1,000,000 individuals who had been randomly selected from the Taiwanese National Health Insurance database, 494,080 men and 502,841 women without HCC were followed-up for two years | Diabetes was not a risk factor for HCC in either sex:[multivariable adjusted RR 0932 (CI 0788-1101) for men and 1158 (CI 0968-1386) for women] after considering the effects of confounding factors such alcohol-related diagnoses, CLD and potential detection bias | This study conflicts with other investigations in as much as it reported that diabetes was not an independent risk factor for HCC<br><br>The short duration of follow-up may account for these negative results |
| Regimbeau, *et al.*[69] | Out of 210 CLD patients submitted to hepatic resection owing to HCC, 18 (86%) had cryptogenic liver disease | Compared to matched controls in whom HCCs were associated with alcohol and CVH, in individuals with crypto-HCCs the prevalence of obesity (50% *vs.* 17% *vs.* 14%), diabetes (56% *vs.* 17% *vs.* 11%), AST /ALT < 1 (50% *vs.* 19% *vs.* 17%), and steatosis > 20% (61% *vs.* 17% *vs.* 19%) was | Evaluation of surgically treated patients supports the notion that obesity and diabetes mellitus are major risk factors for cryptogenic CLD in HCC patients |

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| | | significantly higher<br>Among these patiens with crypto-HCCs well-differentiated cancers (89%) were significantly more common ($P < 00001$ for all comparisons) than in patients with HCCs related to alcohol (64%) and in those with HCCs related to CVH (55%) | |
| Watanabe, *et al.*[70] | Prospective study of 85 consecutive HCC cases submitted to curative treatment options were followed-up to ascertain cancer recurrence | At multivariate analysis serum leptin concentration (HR 125, 95%CI:107-149, $P =$ 00035) as significant independent risk factor for HCC recurrence | Individuals with high serum leptin concentrations are at risk of recurrent HCC after surgical resection or RFA |
| Jain, *et al.*[71] | Clinicopathological study conducted on OLT recipients: 47 cases had NAFLD-cirrhosis (HCC was present in 8 of these); and 75 cases had alcohol-related cirrhosis (HCC was present in five of these) | The HCC steatohepatitic variant is a histologic hallmark of association with NAFLD-cirrhosis risk factors This type of HCC was much more common among those with alcohol-related cirrhosis | NAFLD risk factors are associated not only with cirrhosis but also with HCC |

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| Gupta, *et al.*[72] | 20 HCC cases were compared to 200 healthy controls | Compared to fasting insulin concentrations < 275 μU/ml, values > 610 μU/ml were associated with a 236-fold increased risk of HCC and insulin values in the 275-410 μU/ml range were associated with a 157-fold increased HCC risk | There seems to be a parallel gradient in the HCC risk, which mirrors increasing fasting insulin values |
| Ibrahim, *et al.*[73] | Three groups of individuals were evalated: 100 cases of HCV-related HCCs; 60 HCV- related CLD patients; and 40 healthy controls | HOMA-IR > 37, insulin > 9 μU/L and DM were found to be independent predictors of HCC | This study supports insulin resistance as a risk factor in HCV-related HCC |
| Kamachi, *et al.*[74] | Retrospective analysis of 92 consecutive HCC naive patients with HCV-related cirrhosis in Child-Pugh A class | At multivariate Cox analysis, sarcopenia (together with baseline α-fetoprotein > 40 ng/mL) were independently associated with HCC recurrence | Sarcopenia predicts HCC recurrence in patients submitted to curative procedures |
| Azuma, *et al.*[75] | 182 NAFLD patients were recruited; 22 out of 182 had HCC | At multivariate analysis, DR (OR 8654; *P* = 0017) was independently associated with the development of HCC after adjusting for the NFS<br><br>The AUC of DR was significantly higher than | DR and NFS are risk factors associated with the development of HCC in NAFLD patients<br><br>DR may guide HCC screening among |

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| | | that of diabetes (0731 *vs.* 0615; $P < 0001$) for predicting the development of HCC | NAFLD patients |
| Valdés-Peregrina, *et al.*[76] | 74 HCC cases (out of a series of 1863 liver biopsies) were identified, and 18 were cryptogenic | 23 patients (33%) had cirrhotic HCCs defined as ≤ 3 stage of fibrosis Of these 23, 8 had T2D and 6 HTN; SH-HCC variant was found in 4 and 5 had SH in the remnant liver<br><br>No molecular evidence of aflatoxin exposure was found in HCCs with/without "classical" risk factors | One out of three non-cirrhotic HCCs has either SH or conditions known to be associated with the MetS |
| Ohki, *et al.*[77] | 1431 CHC patients were divided into 4 groups based on their BMI values[underweight (< 185 kg/m$^2$, N = 112); normal (185 to less than 25 kg/m$^2$, N = 1023); overweight (25 to less than 30 kg/m$^2$, N = 265); and obese (> 30 kg/m$^2$, N = 31)] and followed-up for a mean 61-year period | The incidence rate of HCC significantly varied among the various BMI groups ($P$ = 007) After adjusting for confounding factors, compared to those underweight patients, both overweight and obesity were found to be independent risk factors of HCC [HR 186 (95%CI: 109-316; $P$ = 022) and 310 (95%CI: 141-681; $P$ = 005)] | Among CHC patients the risk of incident HCC increases in parallel with increasing BMI values |

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| Konishi, *et al.*[78] | This retrospective study recruited 197 HCV patients whose glucose tolerance was evaluated with the 75 g OGTT<br>The mean follow-up period was 7845 months | Compared to patients with either NGT or IGT, in patients with DM pattern* HCC occurred more frequently<br><br>At multiple LRA, advanced hepatic fibrosis, the DM pattern (at the 75 g OGTT), older age and GGT were all independent factors of HCC | Assessment of glucose tolerance with OGTT provides useful information regarding the risk of developing HCC among those with HCV infection |
| Takahashi, *et al.*[79] | 203 HCV-RNA-positive adults submitted to liver biopsy and a 75 g OGTT and treated with IFN were recruited<br><br>Aimed at identifying the development of HCC, the average follow-up was 520 ± 195 months | The independent predictors of HCC at multivariate analysis were: male sex, age > 65 years, excessive alcohol consumption, non-SVR, biopsy-proven steatosis, and 2-hour post-load hyperglycemia<br><br>Advanced fibrosis stages (HR 28), hepatic steatosis (HR 54), and 2-hour post-load hyperglycemia (HR 49) were significant risk | Post-load hyper-glycemia is a strong risk factor for the development of HCC among HCV-RNA positive individuals |

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| | | factors for the development of HCC after matching patients for sex, age, alcohol consumption, and response to IFN treatment<br><br>Among these, only hepatic steatosis (HR 57) and 2-hour post-load hyperglycemia (HR 69) remained significantly associated with HCC occurrence after matching for the stage of hepatic fibrosis | |
| Li, *et al.*[80] | Retrospective evaluation of 112 patients with HCC and chronic HBV infection and 210 (age- sex- and cirrhosis-) matched non-diabetic individuals with chronic HBV infection without HCC | At LRA, DM was associated with a 2-fold to 3-fold increased risk of HCC (AOR: 2402; 95%CI: 1150-5018) and HBV viral load was associated with a nearly 2-fold increased HCC risk (AOR: 1753; 95%CI: 1079-2849); cigarette smoking was associated with a 1-fold to 2-fold increased risk of HCC (AOR: 1665; 95%CI: 1031-2690) | Among Chinese individuals with chronic HBV infection, DM (together with cigarette smoking and high viral load) is an independent risk factor for the development of HCC |
| Kurosaki, *et al.*[81] | Retrospective single-center cohort study on 1279 CHC patients treated | At multivariate analysis, a higher steatosis extent was significantly associated with HCC | The finding that, in CHC, steatosis is a significant and independent risk factor |

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| | with IFN therapy in Japan<br><br>After IFN treatment, 393 were SVR and 886 non-SVR<br><br>All were followed-up (average period 45 years) with semi-annual surveillance for early diagnosis of HCC | irrespective of age, sex, BMI, stage of fibrosis, and non-SVR<br><br>The ARR of steatosis (304; CI 182-506, $P <$ 00001) was higher than that of age (109), sex (212), non-SVR (243) and BMI (169) | of HCC suggests that HCC may be prevented through treatment of steatosis |
| Ji, *et al.*[82] | This follow-up study (median post-SVR follow-up of 48 months) aimed at identifying those risk factors associated with HCC development post-SVR in a cohort of CHC patients<br><br>SVR was observed in 519 and 817 CHC patients after DAAs and PR therapy, respectively | By adjusted Cox analysis, the following baseline variables predicted incident HCC: age (≥ 55 years) [HR 24, 95%CI: 13-43)], NAFLD[HR 24, 95%CI (13-42), AFP (≥ 20 ng/ml) [HR 34, 95%CI: 20-58)], LSM (≥ 146 kPa) [HR 42, 95%CI (23-76)], and T2D [HR 42, 95%CI: 24-74)] | Post-SVR, in CHC baseline NAFLD was a risk factor for incident HCC, particularly in those treated with DAA |

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| Fan, *et al.*[83] | 5,754 CHB nucleos(t)ide analogue treated patients were followed for 5 years | WHR > 05 (i.e., central obesity) was associated with a significantly increased risk of incident HCC in the overall population (39% *vs.* 21%, HR: 206, *P* = 00001) and 745 propensity score matched pairs (47% *vs.* 23%, HR: 204, *P* = 0026), respectively<br><br>Central obesity was also independently associated with HCC risk (HR: 163, *P* = 0013) further to cirrhosis status and aMAP HCC risk score<br><br>Increased WHR within 1 year was associated with an aHR of 188 (95%CI: 112-313, *P* = 0017) | The WHR, a measure of central obesity, was associated with a two-fold increased risk of incident HCC at 5 years among CHB patients submitted to antiviral treatment with nucleos(t)ide analogues |
| Imai, *et al.*[84] | 333 individuals with chronic viral hepatitis owing to either HBV (69 patients) or HCV (264 patients), were classified as either cirrhotic or non-cirrhotic based on FIB-4 index values (> 325 and ≤ 325, | At LRA, age, sex, VAT, HbA1c, HTN, and HBV were independent risk factors for HCC in a non-cirrhotic liver | Visceral obesity is a risk factor for HCC in patients with non-cirrhotic chronic viral hepatitis |

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| | respectively) | | |

AIH: Autoimmune hepatitis; aMAP: age-male-albumin-bilirubin-platelets; aHR: adjusted Hazard Ratio; AOR: adjusted odds ratio; ARR: adjusted risk ratio; AST/ALT: aspartate aminotransferase/alanine aminotransferase ratio; AUC: area under the receiver operating characteristic curve; BMI: body mass index; CI: confidence interval; CHB: chronic hepatitis B; CHC: chronic hepatitis C; CLD: chronic liver disease; CNLD: chronic nonalcoholic liver disease; cryptoHCCs: cryptogenic HCCs; CT: computed tomography; CVH: chronic viral hepatitis; DAAS: direct-acting antiviral agents; DM: diabetes mellitus; DR: diabetic retinopathy; FIB-4: Fibrosis-4; GGT: gamma-glutamy transferase; HbA1c: glycosilated hemoglobin; HCC: hepatocellular carcinoma; HOMA-IR: homeostatic model assessment of insulin resistance; HR: hazard ratio; HRR: Hazard rate ratio; HTN: arterial hypertension; IFN: interferon; IGT: impaired glucose tolerance; LRA: logistic regression analysis; LSM: liver stiffness measurement; MetS: metabolic syndrome; NAFLD: Non-alcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; NFS: NAFLD fibrosis score; NGT: normal glucotolerance ; OGTT: oral glucose tolerance test; OLT: orthotopic liver transplant; OR: Odds Ratio; PR: pegylated-interferon plus ribavirin; PRA: percutaneous radiofrequency ablation; PBC: primary biliary cholangitis; RR: relative risk; RFA: radiofrquency ablation; SH: steatohepatitis; SVR: sustained virological response; T2D: type 2 diabetes; VAT: visceral adipose tissue; VATI: visceral adipose tissue index; VFA: visceral fat accumulation; WHR waist-to-height ratio.

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**Supplementary Table 2. Principal studies evaluatig metabolic risk factor for the development of CC**

| Author,[Ref] | Series | Findings | Conclusion |
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| Kuper, *et al.*[94] | This case-control study was conducted in Greece on 6 patients with CC; 333 with HCC; and 360 relatively healthy controls | A history of thyroid disease was found to be associated with CC; conversely, the following factors were not: HBV; HCV; tobacco; alcohol and DM<br><br>Compared to the other two cohorts of individuals, estradiol concentrations were higher in CC cases | Endocrine factors may be important risk factors in the development of CC |
| Shaib, *et al.*[95] | 625 cases of intrahepatic CC (≥ 65 years) diagnosed between 1993 and 1999 in the population-based SEER registries and 90,834 cancer-free controls randomly chosen in the SEER regions population | The following risk factors were significantly more prevalent among cases: nonspecific cirrhosis (aOR 272; $P < 0001$), alcoholic liver disease (aOR 74; $P < 0001$), HCV infection (aOR 61; $P < 0001$), HIV infection (adjusted odds ratio, 59; $P = 003$), DM (aOR 20; $P < 0001$) and IBD (aOR 23; $P = 002$) | Further to previously reported risk factors, this population-based study identifies novel factors associated with intrahepatic CC: HCV; HIV; cirrhosis and DM |
| Chang, *et al.*[96] | This study conducted in Taiwan assessed 5,157 cases of incident CC | The following factors were associated with an increased risk of CC: cholangitis, cholelithiasis, | This study confirms the association of CC with some |

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| | diagnosed from 2004 to 2008 compared to 20,628 matched controls from the NHIRD | cholecystitis, cirrhosis; ALD, CNALD; HBV; HCV, DM, chronic pancreatitis, IBD and PUD Additionally, sex and age differences were also observed | novel risk factors, including DM, IBD, HBV, HCV, and PUD (proxy for the presence of HP), pointing to the opportunity to focus on environmental and genetic causes of CC |
| Lee, *et al.*[97] | This hospital-based case-control study evaluated 81 patients with perihilar CC diagnosed from 2007 to 2013 compared to 162 matched controls | Multivariate analysis identified the following risk factors for perihilar CC: hepatolithiasis (aOR 1647), choledocholithiasis (aOR 939), DM (aOR 336) and heavy smoking (aOR 252) | The population attributable perihilar CC risk percentage for DM, heavy smoking, hepatolithiasis and choledocholithiasis was about 225%, 171%, 85% and 48%, respectively |
| Barner-Rasmussen, *et al.*[98] | 6,949 CC cases diagnosed from 1971 to 2014 were retrieved from the population based FCR<br><br>For each CC case, five controls were extracted from the PRDPDSA, | DM (OR 11), IBD (OR 2,6) and cirrhosis (OR 38) were associated with intra-hepatic CC, whereas cholelithiasis (OR 23) and HCV (OR 16) were associated with extra-hepatic CC<br><br>PSC was associated with a 30-fold increased risk of | Population-based data from Finland confirm the importance of acknowledged risk factors for CC with PSC having the highest OR |

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| | matched by age, gender, and municipality | intrahepatic CC and 25-fold increased risk of extrahepatic CC | |
| Welzel, *et al.*[99] | This nationwide Danish population-based case-control study included 764 ICC patients compared to 3,056 matched controls | ALD (OR = 1922, 95%CI: 555-6654); unspecified cirrhosis (OR = 759, 95%CI: 102-5657); cholangitis (OR = 63, 95%CI: 23-175); choledocholithiasis (OR = 2397, 95%CI: 29-1989); cholecystolithiasis (OR = 40, 95%CI: 20-799); and IBD (OR = 47, 95%CI: 165-139) were all significantly associated with ICC<br><br>Diabetes (but not obesity) was associated with ICC risk in the year prior to diagnosis of ICC (OR = 302, 95%CI: 105-869) | Further to prior bile duct diseases, ALD and DM also increase ICC risk |
| Palmer, *et al.*[100] | This meta-analytic review identified 11 published case-control studies on risk factors for ICC from both high and low prevalence regions | The following factors were associated with ICC: cirrhosis (OR 2292; 95%CI: 1824-2879); HBV (OR 510; CI 291-895); HCV (OR 484; CI 241-971); obesity (OR 156; CI 126-194); T2D,(OR 189; CI 174-207); smoking (OR 131; CI 095-182), | All studies except those evaluating cirrhosis, diabetes, and obesity exhibited significant heterogeneity |

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| | | and alcohol use (OR 281; CI 152-521) | Sensitivity analysis did not alter the OR for any risk factors except smoking<br><br>There was no evidence of publication bias |
| Chaiteerakij, *et al.*[101] | This study assessed the effects of metformin in 612 ICC patients observed at the Mayo Clinic (USA) from 2000 to 2010 compared to 594 matched controls identified among the Mayo Clinic Biobank participants | The following factors were associated with increased ICC risk: BTD (AOR 818; 95% CI 112-5988; $P < 0001$), cirrhosis (AOR, 80; 95%CI: 18-365; $P = 0007$), DM (AOR, 36; 95%CI: 23-55; $P < 0001$), and smoking (AOR, 16; 95%CI: 13-21; $P < 0001$)<br><br>While obesity and MetS were not associated with ICC, compared to diabetic patients not receiving metformin, the OR for ICC for those diabetic patients receiving metformin was decreased (OR, 04; 95%CI: 02-09; $P = 004$) | Further to confirming that DM and smoking are independent risk factors for ICC, this study also has the novel finding that, in DM patients, treatment with metformin was associated with a 60% reduced ICC risk |
| Ahrens, *et al.*[102] | This survey, conducted between | The following risk factors were significantly | While confirming that GD is a |

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| | 1995 and 1997 in 5 European countries, was based on 153 histologically proven cases of carcinoma of the ECC in adult men and 1,421 matched population controls | associated with ECC: GD (OR 249; 95%CI: 132-470); BMI > 30 at age 35 years (OR 258; 95%CI: 107-623)<br><br>Some increase in risk was found for alcohol consumption ≥ 40-80 g daily | risk factor of ECC, this study also highlights that overweight and obesity are strong risk factors for ECC in European adult men |
| Welzel, *et al.*[103] | By utilizing the SEER-Medicare database, this study evaluated 535 ICC and 549 ECC patients diagnosed from 1993 to 1999 compared to 102,782 cancer-free controls | In addition to traditional risk factors, the following conditions were associated with cholangiocarcinoma: PBC ($P$ = 00001 for both types), ALD (ECC, $P$ < 00001, ICC $P$ = 001), non-specific cirrhosis $P$ < 00001 for both types), DM ($P$ < 00001 for both types), thyroid disease (ECC $P$ = 0006, ICC $P$ = 004) and chronic pancreatitis ($P$ < 00001 for both types) Instead, metabolic risk factors such as obesity ($P$ < 001) and NAFLD ($P$ = 002) were solely related to ICC | ECC and ICC share several risk factors This study underlines that obesity and NAFLD seem to be relevant risk factors for ICC |
| Zhou, *et al.*[104] | This study from China enrolled 312 ICC cases and 438 matched controls | At multivariate analysis, the following risk factors were associated with ICC: HBsAg (aOR, 8876, 95%CI: 5973-13192), and hepatolithiasis (aOR, | In this study HCV, DM, HTN, smoking, and alcohol were not associated with ICC |

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| | | 5765, 95%CI: 1972-16851) | |
| Zhou, *et al.*[105] | This study from China enrolled 200 ECC cases and 200 matched controls | At multivariate analysis, the following risk factors were associated with ECC: current smoking (OR = 190, 95%CI: 108-334), heavy alcohol consumption (OR = 208, 95%CI: 139-313), and choledocholithiasis (OR = 668, 95%CI: 148-3027) | In this study HBV and DM were not associated with ECC |
| Choi, *et al.*[106] | This USA, Mayo Clinic- based case-control study evaluated 2,395 cases of CC cases (1,169 ICC, 995 perihilar, and 231 distal) observed from 2000 to 2014 compared to 4,769 matched controls selected from the Mayo Clinic Biobank | Aspirin, which was used by 247% of patients with CC and 446% of controls was significantly and inversely associated with all CC subtypes, with AOR 035 (95%CI: 029-042) for ICC; 034 (95%CI: 027-042) for perihilar CC and 029 (95%CI: 019-044) for distal CC, ($P < 0001$ for all)<br><br>PSC was more strongly associated with perihilar CC (AOR = 453, 95%CI: 104-999) than ICC (AOR = 934, 95%CI: 271-322) or distal CC (AOR = 340, 95%CI: 36-323)<br><br>DM was more associated with distal CC (AOR = | DM was associated with an increased risk of CC, whereas aspirin use was protective |

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| | | 42, 95%CI: 25-70) than perihilar CC (AOR = 29, 95%CI: 22-38) or ICC (AOR = 25, 95%CI: 20-32)<br><br>PSC-unrelated cirrhosis was associated with both ICC and perihilar CC, with AORs of 14 for both<br><br>IBD per se (i.e., other than with PSC) was not associated with CC | |
| Petrick, *et al.*[107] | 2,092 ICC and 2,981 ECC cases identified using the SEER-Medicare database from 2000 to 2011 were compared to 323,615 matched controls | NAFLD was associated with increased risks of ICC (OR = 352, 95%CI: 287-432) and ECC (OR = 293, 95%CI: 242-355)<br><br>Overweight/obesity were associated with ICC risk (OR = 127, 95%CI: 110-147)<br><br>Chronic viral hepatitis due to HBV, HCV and unspecified as well as disease of bile ducts were associated with both ICC and ECC | Risk factors for ICC and ECC were similar, and this study highlights the role of several risk factors including dysmetabolic conditions, viral hepatitis, PBC, Caroli disease, T1D, UC, chronic pancreatitis, gout and nonspecific cirrhosis |

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| | | Although sample size was limited, Caroli disease was associated with a strongly increased risk of ICC (OR = 3813, 95%CI: 1420-10238) and ECC (OR = 9681, 95%CI: 5102-18368)<br><br>While T1D, IBD, chronic pancreatitis, and gout were associated with increased risks of both ICC and ECC, lupus was associated with a decreased risk of ECC ($n$ < 11, OR = 040, 95%CI: 019-083) but had no association with ICC ($n$ = 13)<br><br>Alcohol-related disorders were associated with a 37-fold higher risk of ICC (OR = 372, 95%CI: 317-435) and a 26-fold higher risk of ECC (OR = 260, 95%CI: 223-304)<br><br>Smoking was associated with an increased risk of ICC (OR = 146, 95%CI: 128-166) and ECC (OR = 177, 95%CI: 159-196) | |

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| | | Nonspecific cirrhosis and duodenal/gastric ulcers were associated with a significantly increased risk of both ICC and ECC | |

ALD: Alcoholic liver disease; aOR: adjusted Odds Ratio; BMI: body mass index; BTD: biliary tract diseases; CC: cholangiocarcinoma; CI: confidence interval; CNALD: chronic nonalcoholic liver disease; DM: diabetes mellitus; ECC: extrahepatic cholangiocarcinoma; FCR: Finnish Cancer Registry; GD: gallstone disease; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HP -Helicobacter Pylori; HTN: arterial hypertension; IBD: inflammatory bowel disease; ICC: intrahepatic cholangiocarcinoma; MetS: Metabolic Syndrome; NAFLD: Non-alcoholic fatty liver disease; NHIRD: National Health Insurance Research Database; OR: Odds Ratio; PBC: primary biliary cirrhosis; PSC: primary sclerosing cholangitis; PRDPDSA: Population Registry of the Digital and Population Data Services Agency; PUD: peptic ulcer disease; SEER: Surveillance, Epidemiology, and End Results; T1D: type 1 diabetes; T2D: type 2 diabetes UC: ulcerative colitis.

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