

Supplementary Files.

Table S1. Diabetes and risk of hepatocellular carcinoma (HCC) in the pooled cohort of women and men (1986 – 2012; N=146,642), with further adjustment for oral hypoglycemic medication use, insulin use or both medication types

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Table S5. Diabetes and risk of Intrahepatic Cholangiocarcinoma (ICC) in women (1980-2012) and men (1986-2012)

Table S1.

Diabetes and risk of hepatocellular carcinoma (HCC) in the pooled cohort of women and men (1986 – 2012; N=146,642), with further adjustment for oral hypoglycemic medication use, insulin use or both medication types

Combined cohort	No Diabetes	Diabetes
<i>Cases / Person-Years</i>	70 / 3,460,215	37 / 275,370
Model 1; HR (95%CI)	1	5.03 (3.35-7.56)
Multivariable Model 2; HR (95%CI)	1	5.09 (3.28-7.91)
Multivariable Model 3; HR (95%CI)	1	4.80 (2.96-7.78)
Multivariable Model 4; HR (95%CI)	1	4.78 (3.05-7.49)
Multivariable Model 5; HR (95%CI)	1	4.54 (2.76-7.45)

Abbreviations: HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval

Model 1 = age (continuous, years), sex, race (white vs. non-white), and body mass index (<25kg/m² vs. 25-30kg/m² vs. ≥30kg/m²), updated over time.

Model 2 = Model 1 + family history of diabetes (no vs. yes), smoking status (past, current, never), alcohol intake (0 – 4.9 g/day, 5-14.9 g/day, ≥15 g/day), physical activity level (<3 METs/week, 3-8.9 METs/week, ≥9 METs/week), and regular aspirin use (non-use vs. use of ≥ 2 tablets/week), with all relevant variables updated over time.

Model 3 = Model 2 + oral hypoglycemic medication use (non-use vs. use).

Model 4 = Model 2 + insulin use (non-use vs. use).

Model 5 = Model 2 + use of either oral hypoglycemic medications or insulin (non-use vs. any use).

Table S2:

Insulin use, oral antidiabetic medications and risk of HCC, in men and women with type 2 diabetes from 1986-2012 (N=22,448)

	Diabetes without Insulin use	Diabetes with Insulin use
<i>Cases / Person-Years</i>	21 / 177,775	4 / 14,356
HR adjusted for age (95% CI)	1	2.10 [0.71-6.19]
Multivariable Model 2 †; HR (95% CI)	1	2.10 [0.71-6.21]
Multivariable Model 3 ‡; HR (95% CI)	1	2.04 [0.69-6.09]
	Diabetes without oral antidiabetic use	Diabetes with oral antidiabetic use
<i>Cases / Person-Years</i>	12 / 110,577	13 / 81,554
HR adjusted for age (95% CI)	1	1.39 [0.67-2.89]
Multivariable Model 2 †; (95% CI)	1	1.39 [0.66-2.90]
Multivariable Model 3 ‡; HR (95% CI)	1	1.45 [0.69-3.07]

Abbreviations: HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval

† Model 2 adjusted for age, sex, race, updated body mass index (<25kg/m², 25-30kg/m², ≥30kg/m²).

‡ Model 3 adjusted for Model 2 + smoking status (current, former, never), alcohol intake (0 g/day, 0.1-4.9 g/day, 5-14.9 g/day, ≥15 g/day), physical activity level, in METs / week (<3 METs/week, 3-8.9 METs/week, ≥9 METs/week), and family history of diabetes (no vs. yes).

Table S3.

Diabetes and risk of HCC among women (1980-2012) and men (1986-2012), after excluding any individual with incident HCC arising within 4 years of a diagnosis of type 2 diabetes*

	No diabetes	Diabetes
<i>Cases / Person-Years</i>	75 / 4,223,105	33 / 298,627
Age-adjusted Model; HR (95%CI)	1	4.16 [2.74-6.32]
Multivariable Model 2 [‡] ; HR (95% CI)	1	4.04 [2.62-6.22]
Multivariable Model 3 [§] ; HR (95% CI)	1	3.99 [2.55-6.26]

Abbreviations: HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval

[‡] Model 2 adjusted for age, sex, race (white vs. non-white), and updated body mass index (<25kg/m², 25-30kg/m², ≥30kg/m²).

[§] Model 3, adjusted for Model 2 + smoking status (current active smoker vs. former smoker vs. never-smoker), alcohol intake (0 – 4.9 g/day, 5-14.9 g/day, ≥15 g/day), physical activity level (<3 METs/week, 3-8.9 METs/week, ≥9 METs/week), regular aspirin use (≥ 2 aspirin tablets per week vs non-use), and family history of diabetes (no vs. yes). All relevant covariates are updated over time.

*N=4 individuals were diagnosed with HCC within 4 years of a confirmed diagnosis of type 2 diabetes, and were excluded from this analysis

Table S4.

Diabetes and Risk of HCC in women (1980-2012) and men (1986-2012), after excluding any case of HCC associated with HBV or HCV infection¹

Combined cohort	No Diabetes	Diabetes
<i>Cases / person-years (PY)</i>	60 / 4,192,248	31 / 295,750
Age-adjusted Model; HR (95%CI)	1	4.93 [3.16-7.70]
Multivariable Model 2 [‡] ; HR (95%CI)	1	4.70 [2.95-7.47]
Multivariable Model 3 [§] ; HR (95%CI)	1	4.82 [2.97-7.81]

Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; CI, confidence interval

¹Confirmation of HBV- or HCV-associated HCC was made through manual review of all patient charts with confirmed HCC, with subsequent exclusion of n=21 cases.

[‡]Model 2 adjusted for age, sex, race (white vs. non-white), and updated body mass index (<25kg/m², 25-30kg/m², ≥30kg/m²).

[§]Model 3, adjusted for Model 2 + smoking status (current, past, never), alcohol intake (0 – 4.9 g/day, 5-14.9 g/day, ≥15 g/day), physical activity level (<3 METs/week, 3-8.9 METs/week, ≥9 METs/week), regular aspirin use (≥ 2 aspirin tablets per week vs non-use), and family history of diabetes (no vs. yes). All relevant covariates are updated over time.

Table S5. Diabetes and risk of Intrahepatic Cholangiocarcinoma (ICC) in women (1980-2012) and men (1986-2012)

	No diabetes	Diabetes
<i>Cases / Person-years</i>	27 / 4,192,607	4 / 295,836
Age-adjusted Model; HR (95%CI)	1	1.32 (0.45-3.82)
Multivariable Model 2*; HR (95% CI)	1	1.12 (0.38-3.28)

Abbreviations: ICC, intrahepatic cholangiocarcinoma; HR, hazard ratio; CI, confidence interval

*Multivariable model 2, adjusted for age in years, sex, race and body mass index (<25kg/m², 25-30kg/m², ≥30kg/m²).