Meta-analysis of studies using statins as a reducer for primary liver cancer risk

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Supplementary List 1 Search Strategy

PubMed

#1 (((cancer*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR malignanc*[Title/Abstract]

#2 ((liver[Title/Abstract]) OR hepatic[Title/Abstract]) OR hepatocellular[Title/Abstract]

#3 **#1** AND **#2**

#4 ((hepatocarcinoma[Title/Abstract]) OR "liver cell carcinoma*"[Title/Abstract]) OR hepatoma[Title/Abstract]

#5 **#3** OR **#4**

#6 ((((((((((statin*[Title/Abstract]) OR "HMG-CoA reductase inhibitor*"[Title/Abstract]) OR "Hydroxymethylglutaryl-CoA reductase inhibitor*"[Title/Abstract]) OR atorvastatin[Title/Abstract]) OR cerivastatin[Title/Abstract]) OR fluvastatin[Title/Abstract]) OR lovastatin[Title/Abstract]) OR pravastatin[Title/Abstract]) OR rosuvastatin[Title/Abstract]) OR simvastatin[Title/Abstract]) OR

pitavastatin[Title/Abstract]

#7 **#5** AND **#6**

EMBASE

#1 statin* AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#2 'hmg coa' AND reductase AND inhibitor* AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#3 'hydroxymethylglutaryl coa' AND reductase AND inhibitor* AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#4 atorvastatin AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#5 cerivastatin AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#6 fluvastatin AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#7 lovastatin AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#8 pravastatin AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#9 rosuvastatin AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#10 simvastatin AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#11 pitavastatin AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#12 **#1** OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7** OR **#8** OR **#9** OR **#10** OR **#11**

#13 cancer* AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#14 neoplasm* AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#15 carcinoma* AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#16 malignanc* AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#17 **#13** OR **#14** OR **#1**5 OR **#16**

#18 liver AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#19 hepatic AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#20 hepatocellular AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#21 **#18** OR **#19** OR **#20**

#22 **#17** AND **#21**

#23 hepatocarcinoma AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#24 liver AND cell AND carcinoma* AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#25 hepatoma AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim) AND ([chinese]/lim OR [english]/lim) AND [embase]/lim

#26 **#23** OR **#24** OR **#25**

#27 **#22** OR **#26**

#28 **#12** AND **#27**

Supplementary Table S1. Characteristics of included cohort studies, nested case-control studies, and post hoc analyses of RCTs on statin use and primary liver cancer risk

Study; location	Design	Age (y) [a]	Sample size	Data source	Study population	Definition of nonuser	Cancer cases	Follow -up [a](y)	Adjustment factors
Simon et al., 2016; USA [16]	Cohort	53.0	T: 9135 M:8745 W:390	Population -based	Subjects with HCV	Subjects using statins ≤28 cDDDs	239	7.4	Age, sex, alcohol, ACEIs, attainment of sustained virologic response, baseline FIB-4 score, BMI, caffeine intake, daily caffeine intake , diabetes, metformin use, NSAIDs, other lipid-lowering agent use, prior completed HCV treatment, race, smoking
Tsan et al., 2015; Taiwan [35]	Cohort	35.0 [b]	T:91265 M:66635 W:24630	Population -based	Subjects with HBV	Subjects using statins <28 cDDDs	2841	2.9	Interferon, income, urbanization
McGlynn et al., 2015; UK [12]	Nested case-control	67.0	T:5835 M:4178 W:1657	Population -based	General population	Subjects with one or no statin prescription	1195	≤23.0	Alcohol-related disorders, BMI, diabetes, HBV, HCV, smoking, metabolic disorders, use of antidiabetics, use of

									aspirin, use of paracetamol
Hsiang et al., 2015; China [26]	Cohort	38.1	T:53513 M:14145 W:39368	Hospital-based	Subjects with HBV	Subjects with no statin prescription	1298	4.6 [b]	Age, sex, albumin, ALT, comorbidities, creatinine, medications, platelet count, total bilirubin
Chen et al., 2015; Taiwan [21]	Nested case-control	62.6	T:1700 M:1325 W:375	Hospital-based	Subjects with diabetes	Unclear	340	≤11.0	Alcoholic liver damage, HCV, HBV, cirrhosis duration
Chen et al., 2015; Taiwan [13]	Cohort	NA	T:61898 M:35595 W:26303	Population-based	Subjects with HBV	Subjects using statins <28 cDDDs	1735	≤9.0	Age, sex, acetylcholinesterase inhibitors, anti-HBV drugs, area, aspirin, comorbidities, index year, nonstatin lipid-lowering drugs
Butt et al., 2015; USA [34]	Cohort	53.0 for statin users; 52.0 for statin non-users [b]	T:7248 M:6929 W:319	Population-based	Subjects with HCV	Subjects using statins ≤14 days or with no statin prescription	NA	≥2.0	FIB-4 score

McGlynn et al., 2014; USA [17]	Nested case-control	NA	T:562 M:418 W:144	Population-based	General population	Subjects with no statin prescription	94	8.1	Alcohol-related disorders, chronic obstructive pulmonary disease, diabetes, HCV, hypertension, race
Tsan et al., 2013; Taiwan [14]	Cohort	50.4 [b]	T:260864 M:128263 W:132601	Population-based	Subjects with HCV	Subjects using statins <28 cDDDs	27883	10.7	Age, sex, diabetes, income, liver cirrhosis, urbanization
Leung et al., 2013; Taiwan [36]	Cohort	58.3	T:34205 M:16150 W:18055	Population-based	General population	Subjects with one or no statin prescription	424	4.2	Age, sex, cardiovascular drugs, Charlson score, comorbidities, hormone-replacement therapy, non-statin lipid-lowering drugs, NSAIDs
King et al., 2013; USA [38]	Cohort	NA	T:136178 M:39634 W:96544	Population-based	General population	Unclear	125	≤20.0	Age, alcohol, aspirin, BMI, diabetes, smoking
Tsan et al., 2012; Taiwan [15]	Cohort	35.6 [b]	T:33413 M:19442 W:13971	Population-based	Subjects with HBV	Subjects using statins <28 cDDDs	1021	9.8	Age, sex, diabetes, income, liver cirrhosis, urbanization
Emberson et al., 2012; Europe, Australia, USA [39]	Post hoc analysis of RCTs	63.0	T:134537 M:95529 W:39008	Hospital-based	General population	Subjects with no statin prescription	68	4.8	None
Marelli et al., 2012; USA [33]	Cohort	64.2	T:91714 M:48059	Population-based	General population	Subjects with no statin	105	4.7	Age, sex, comorbidities, BMI, race, smoking

			W:43655			prescription			
Matsushita et al., 2010; Japan [22]	Post hoc analysis of RCTs	57.6	T:13724 M:7082 W:6642	Hospital-based	General population	Subjects with no statin prescription	12	5.1	Age, sex, smoking
El-Serag et al., 2009; USA [40]	Nested case-control	72.0	T:6515 M:6430 W:85	Hospital-based	Subjects with diabetes	Subjects with no statin prescription	1303	2.4	ACEIs, alcoholic liver disease, alcoholism, cirrhosis, HBV, HCV, anti-HCV drugs, NSAIDs, propensity to use statins, race
Friedman et al., 2008; USA [29]	Cohort	NA	T:361859 M:192598 W:169261	Population-based	General population	Subjects with no statin prescription	42	4.9 [b]	Calendar year
Sato et al.,2006; Japan [23]	Post hoc analysis of RCTs	NA	T:263 M:215 W:48	Hospital-based	Subjects with CHD	Subjects using statins for ≤25% of study period	1	4.8	Age, sex, pravastatin medicated, smoking, total serum cholesterol
Friis et al., 2005; Denmark [42]	Cohort	47.1	T:348262 M:175775 W:172487	Population-based	General population	Subjects with one or no statin prescription	171	3.5	Age, sex, calendar period, cardiovascular drugs, hormone-replace treatment, NSAIDs

Abbreviations: ACEIs, angiotensin converting enzyme inhibitor; ALT, alanine aminotransferase; BMI, body mass index; cDDDs, cumulative defined daily doses; CHD, coronary heart disease; HBV, hepatitis B virus; HCV, hepatitis C virus; M: men; NA, not available; NSAIDs, nonsteroidal anti-inflammatory drugs; RCT, randomized controlled trial; T, total; W: women.

[a] Mean value unless otherwise specified.

[b] Median value.

Supplementary Table S2. Characteristics of included case-control studies on statin use and primary liver cancer risk

Study; location	Study period	Age (y) [a]	Sample size	Data source	Study population	Definition of nonuser	Cases/ Controls	Adjustment factors
Peng et al., 2015; Taiwan [20]	2002-2011	68.0	T:6348 M:3241 W:3107	Population-based	General population	Subjects with no statin prescription	3174/ 3174	Age, sex, aspirin, alcohol-related illness, biliary tract disease, coronary artery disease, Charlson comorbidity index score, chronic pancreatitis, cirrhosis, chronic obstructive pulmonary disease, diabetes, gastric disease, haemochromatosis, HBV, HCV, inflammatory bowel disease, stroke, metformin
Björkhem-Bergman et al., 2014; Sweden [37]	2006-2010	NA	T:23964 M:12456 W:11508	Population-based	General population	Subjects using statins ≤9 months or with no statin prescription	3994/ 19970	Age, sex, acetylsalicylic acid, alcohol hepatitis, chemotherapy, diabetes, education, liver disease, NSAIDs, treatment with cortisone, viral hepatitis
Lai et al., 2013; Taiwan [18]	2000-2009	62.6	T:17400 M:12625 W:4775	Population-based	General population	Subjects with no statin prescription	3480/ 13920	Age, sex, alcoholic liver damage, cirrhosis, diabetes, duration of statin use, HBV, HCV, non-alcoholic fatty liver disease, non-statin lipid-lowering drug, drugs for HBV and HCV, use of metformin, use of thiazolidinedione

Chaiteerakij et al., 2013; USA [32]	2000-2010	61.4	T:421 M:208 W:213	Hospital-based	General population	Subjects with no statin prescription	165/ 256	None
Chiu et al., 2011; Taiwan [19]	2005-2008	66.0	T:2332 M1606 W:726	Population-based	General population	Subjects with no statin prescription	1166/ 1166	Sex, alcoholic liver disease, birth year, cirrhosis, diabetes, HBV, HCV, index date, number of hospitalizations, use of non-statin lipid-lowering drugs
Khurana et al., 2005;USA [41]	1998-2004	61.1	T:480306 M:440441 W:39865	Population-based	Subjects with HCV	NA	409/ 479897	Age, HCV

Abbreviations: cDDDs, cumulative defined daily doses; HBV, hepatitis B virus; HCV, hepatitis C virus; M: men; NA, not available; NSAIDs, nonsteroidal anti-inflammatory drugs; T, total; W: women.

[a] Mean value.

Supplementary Table S3. The Results of quality assessment for cohort studies and post hoc analyses of RCTs

Study	Selection				Comparability		Outcome			Total Score
	Representativeness of exposed cohort ☆	Selection of non-exposed cohort ☆	Exposure ascertainment ☆	No history of disease ☆	Comparable on confounders ☆☆		Outcome Assessment ☆	Adequate follow-up (≥10y) ☆	Loss to follow-up rate (≤20%) ☆	
Simon et al. 2016 [16]	☆	☆	☆	☆	☆	☆	☆		☆	8
Tsan et al. 2015 [35]	☆	☆		☆	☆				☆	5
Hsiang et al. 2015 [26]	☆	☆	☆	☆	☆	☆			☆	7
Chen et al. 2015 [13]	☆	☆	☆	☆	☆	☆			☆	7
Butt et al. 2015 [34]	☆	☆	☆	☆	☆		☆		☆	7
Tsan et al. 2013 [14]	☆	☆	☆	☆	☆		☆	☆	☆	8
Leung et al. 2013 [36]	☆	☆	☆	☆	☆				☆	6
King et al. 2013 [38]	☆	☆		☆	☆		☆	☆	☆	7
Tsan et al. 2012 [15]	☆	☆	☆	☆	☆		☆		☆	7
Emberson et al. 2012 [39]	☆	☆		☆	☆	☆	☆		☆	7
Marelli et al. 2011 [33]	☆	☆	☆	☆	☆		☆		☆	7
Matsushita et al. 2010 [22]	☆	☆		☆	☆	☆	☆		☆	7
Friedman et al. 2008 [29]	☆	☆	☆	☆	☆		☆		☆	7
Sato et al. 2006 [23]		☆	☆	☆	☆		☆		☆	6
Friis et al. 2005 [42]	☆	☆	☆	☆	☆		☆		☆	7

Abbreviations: RCTs, randomized controlled trials.

Supplementary Table S4. The Results of quality assessment for nested case-control studies and case-control study

Study	Selection				Comparability		Outcome			Total Score
	Adequate case definition ☆	Representativeness of cases ☆	Selection of controls ☆	Definition of controls ☆	Comparable on confounders ☆☆		Exposure ascertainment ☆	Ascertainment for cases and controls ☆	Non-response rate ☆	
Peng et al. 2015 [20]		☆	☆		☆	☆	☆	☆		6
McGlynn et al. 2015 [12]	☆	☆	☆	☆	☆	☆	☆	☆		8
Chen et al. 2015 [21]		☆	☆	☆	☆		☆	☆		6
McGlynn et al. 2014 [17]	☆	☆	☆	☆	☆		☆	☆		7
Björkhem-Bergman et al. 2014 [37]	☆	☆	☆	☆	☆	☆	☆	☆		8
Lai et al. 2013 [18]	☆	☆	☆	☆	☆	☆		☆		7
Chaiteerakij et al. 2013 [32]	☆	☆	☆	☆			☆	☆		6
Chiu et al. 2011 [19]	☆	☆	☆	☆	☆		☆	☆		7
El-Serag et al. 2009 [40]	☆	☆	☆	☆	☆	☆	☆	☆		8
Khurana et al. 2005 [41]		☆	☆	☆	☆			☆		5

Supplementary Table S5. Individual statin use and primary liver cancer risk

Type of statins	No. of studies	Cancer cases	Sample size	Random-effects model		Fixed-effects model		Tests for heterogeneity	
				RR	95% CI	RR	95% CI	*P*	I^2 (%)
Pravastatin	8	248	15172	0.71	0.58, 0.88	0.70	0.59, 0.83	0.29	17.5
Simvastatin	7	1945	10060	0.61	0.54, 0.69	0.62	0.57, 0.69	0.22	27.2
Atorvastatin	6	650	4855	0.53	0.42, 0.67	0.61	0.55, 0.68	<0.01	70.7
Fluvastatin	6	245	1506	0.65	0.52, 0.81	0.69	0.58, 0.81	0.25	24.3
Rosuvastatin	6	202	1195	0.49	0.34, 0.69	0.58	0.48, 0.70	0.10	45.8
Lovastatin	5	386	2111	0.65	0.56, 0.74	0.65	0.56, 0.74	0.67	0.0

Abbreviations: CI, confidence interval; RR, risk ratio.

Supplementary Table S6. Subgroup analyses of statin use and primary liver cancer risk based on the overall meta-analysis

Subgroup	Number of studies	RR	95% CI	I^2 (%)	$P_{heterogeneity}$	$P_{interaction}$ [a]
All studies	24	0.60	0.53, 0.69	85.0	<0.01	-
Study design						
Cohort study	11	0.53	0.46, 0.62	66.6	<0.01	0.10
Case-control study	6	0.71	0.60, 0.83	77.6	<0.01	
Nested case-control study	4	0.56	0.42, 0.75	71.0	0.02	
Post hoc analysis of RCTs	3	0.96	0.62, 1.49	0.0	0.62	
Source of subjects						
Population-based	17	0.58	0.50, 0.68	88.9	<0.01	0.29
Hospital-based	7	0.70	0.60, 0.82	11.0	0.35	
Sex						
Man	6	0.52	0.40, 0.69	77.5	<0.01	0.55
Women	6	0.47	0.36, 0.60	36.0	0.17	
Individual age						
≥50y	4	0.45	0.31, 0.65	76.0	<0.01	0.40
< 50y	4	0.53	0.42, 0.67	0.0	0.73	
Sample size						
≥10,000	15	0.61	0.50, 0.73	89.2	<0.01	0.97
<10,000	9	0.62	0.53, 0.73	61.4	<0.01	
Study location						
Asian	12	0.56	0.47, 0.67	83.2	<0.01	0.26
Western	12	0.65	0.54, 0.77	79.2	<0.01	
High-risk population [b]						

Yes	7	0.51	0.43, 0.59	67.4	<0.01	0.02
No	17	0.67	0.59, 0.76	69.3	<0.01	
Study quality						
High	17	0.61	0.52, 0.72	88.0	<0.01	0.78
Low	7	0.59	0.47, 0.73	66.8	<0.01	
Adjustment for diabetes						
Yes	12	0.63	0.53, 0.74	88.7	<0.01	0.43
No	12	0.57	0.46, 0.71	75.2	<0.01	
Adjustment for HCV						
Yes	9	0.66	0.57, 0.77	80.6	<0.01	0.24
No	15	0.56	0.48, 0.65	63.9	<0.01	
Adjustment for HBV						
Yes	8	0.63	0.51, 0.77	91.0	<0.01	0.49
No	16	0.57	0.51, 0.64	38.0	0.06	
Adjustment for confounders						
Unadjusted	2	0.79	0.45, 1.37	68.6	0.07	0.45
1-3 confounders	5	0.53	0.46, 0.62	0.0	0.78	
4-6 confounders	8	0.55	0.46, 0.67	44.1	0.08	
≥7 confounders	9	0.63	0.52, 0.77	89.9	<0.01	

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; RCTs, randomized controlled trials; RR, risk ratio.

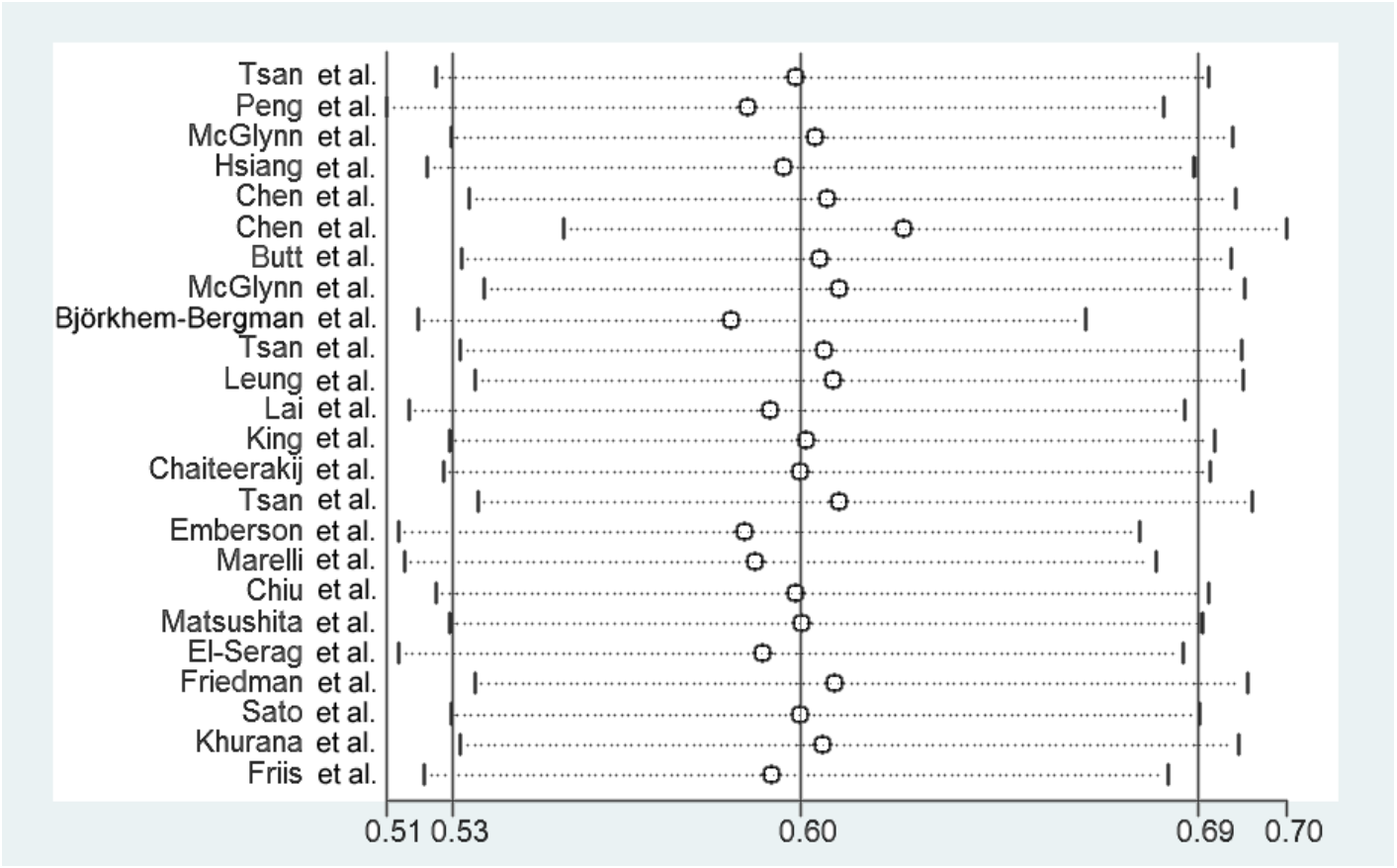
[a] $P_{interaction}$ between subgroups was calculated with meta-regression.

[b] "High-risk population" refers to subjects with HBV or HCV infection.

Supplementary Table S7. Sensitivity analyses of statin use and primary liver cancer risk

Category	n	RR	95% CI	I^2 (%)
Statistical model				
Random-effects model	24	0.60	0.53, 0.69	85.0
Fixed-effects model	24	0.65	0.63, 0.68	85.0
Analysis using unadjusted risk estimates	22	0.61	0.52, 0.72	90.3
Analysis within				
Observational studies	21	0.57	0.49, 0.67	86.5
Studies where non-users refer to persons with no statin prescription	13	0.68	0.60, 0.76	50.1
Analysis without				
Studies with sample size >100,000	18	0.60	0.52, 0.70	83.6
Studies with sample size <1,000	21	0.61	0.53, 0.70	86.6

Abbreviations: CI, confidence interval; RR, risk ratio.



Supplementary Fig. 1 Sensitivity analysis on parity and primary liver cancer risk: exclusion of a single study in turn. The study cited on the left is the one left out in each turn. The circle represents the summary risk estimates after exclusion of a single study, and the corresponding dot line represents 95% confidence interval. The middle vertical solid line represents summary risk estimates of all included studies, and left and right vertical solid line represent lower limit and upper limit, respectively.