Statins as Chemopreventive Agents in Gastrointestinal Cancers

Current Evidences and Future Directions

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OUTLINE

- CRC, HCC and gastric cancer epidemiology and burden
- Mechanisms of statin action on GI cancers
- Observational studies
- Clinical guidelines and conclusion

Mechanisms of statin action on GI cancers

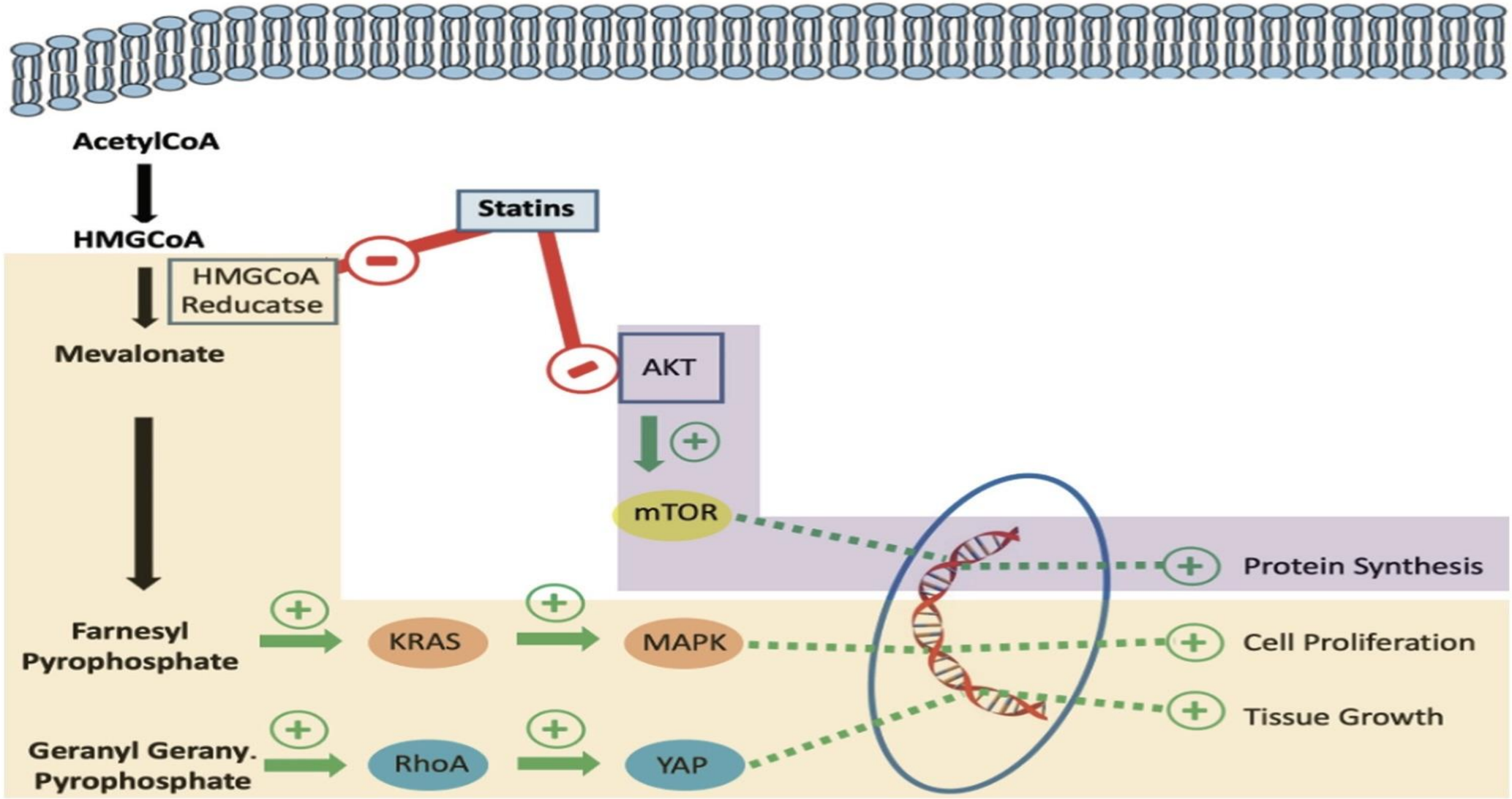
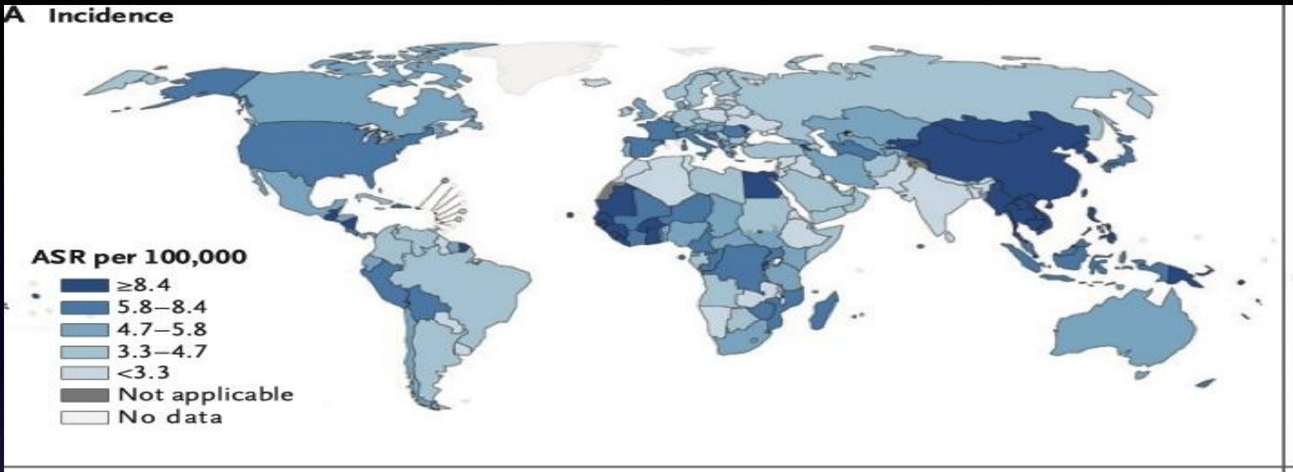
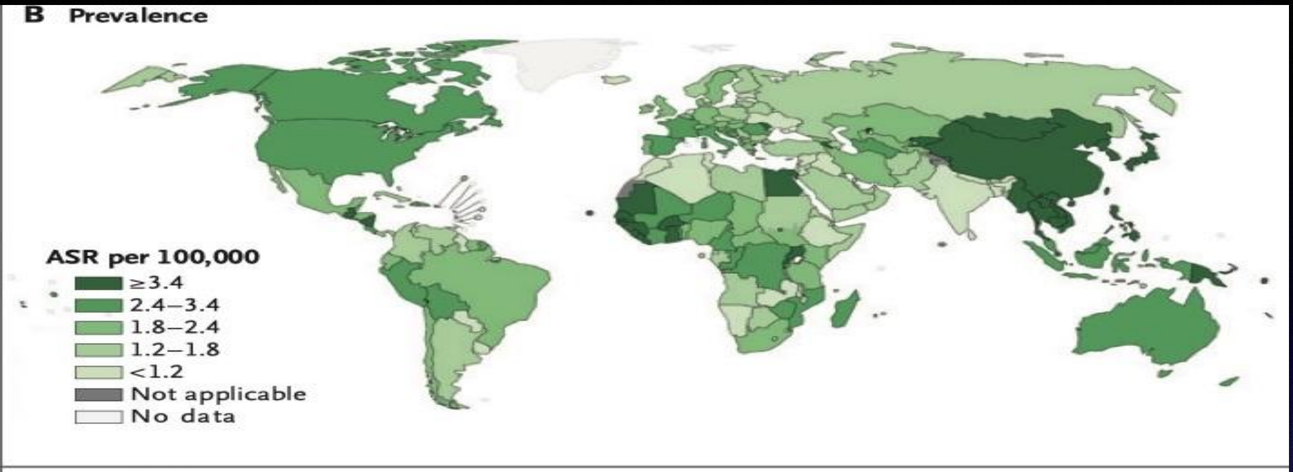
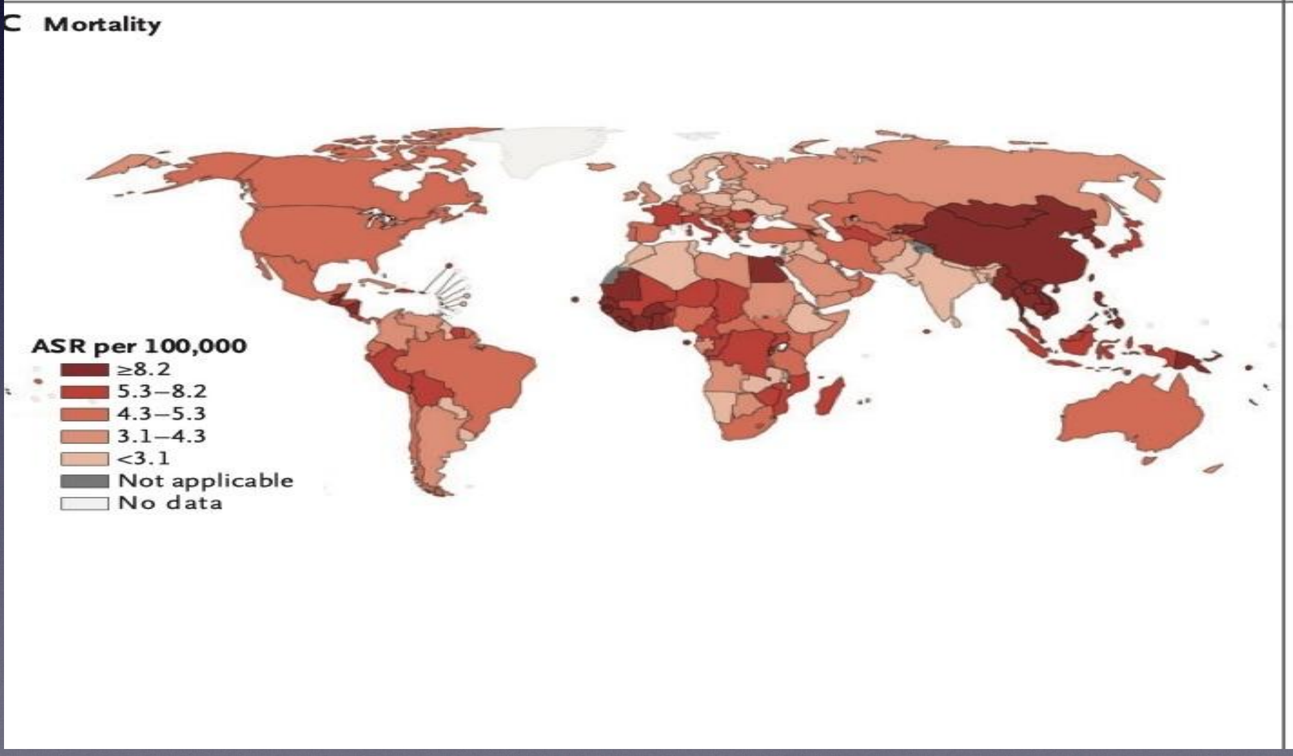


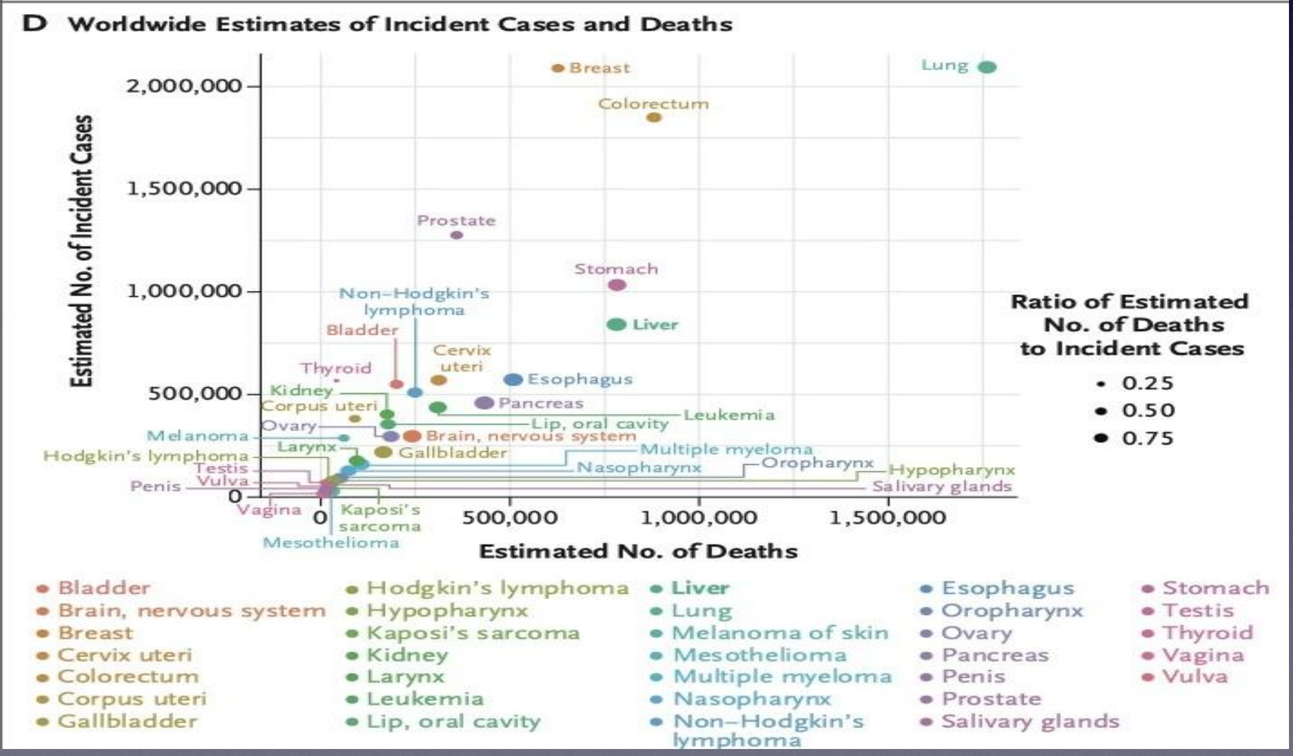
Figure 8. Suggested cellular mechanisms of action through which statins reduce the risk of cancer development.

Global Epidemiology of Hepatocellular Carcinoma









Rawla P, Sunkara T, Gaduputi V. *Epidemiology of Pancreatic Cancer: Global Trends, Etiology, and Risk Factors.* **N Engl J Med.** 2019;380(11):1030–1041.

Statin Use and Prognosis After Hepatic Resection for HCC: Evidence from a Nationwide Korean Cohort

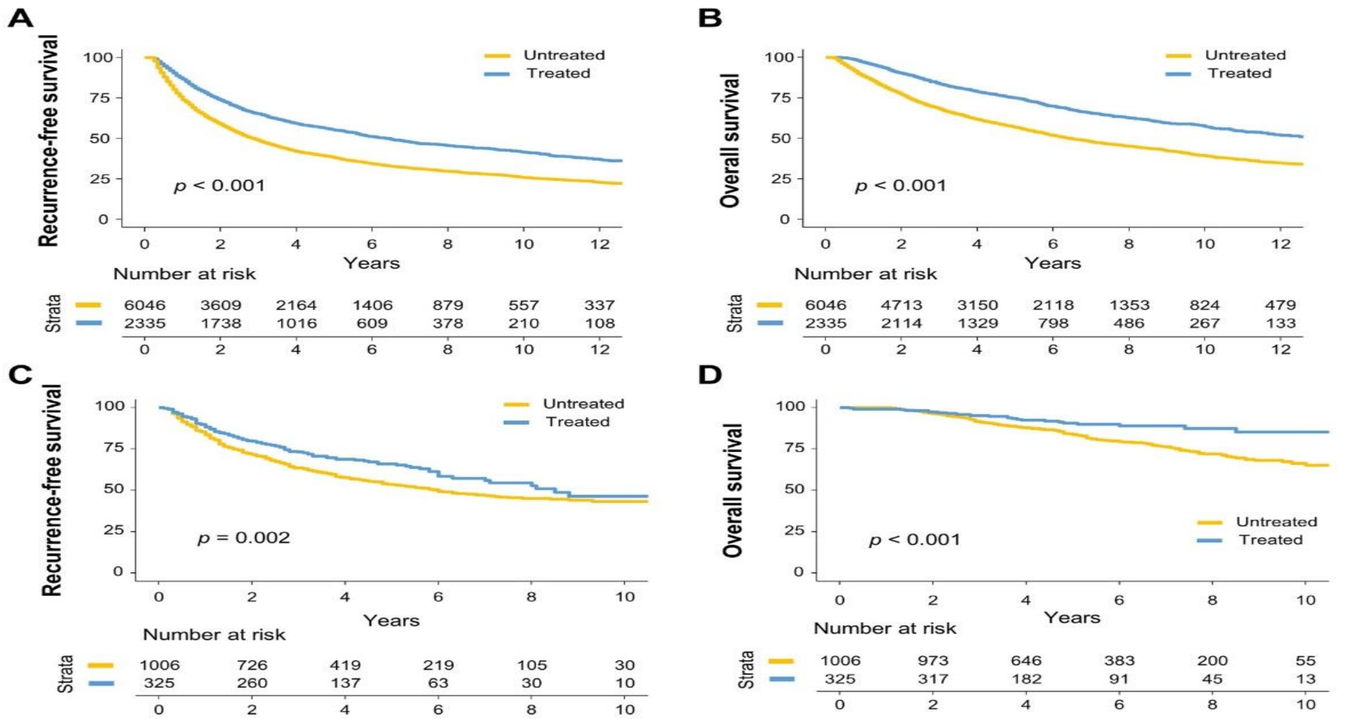
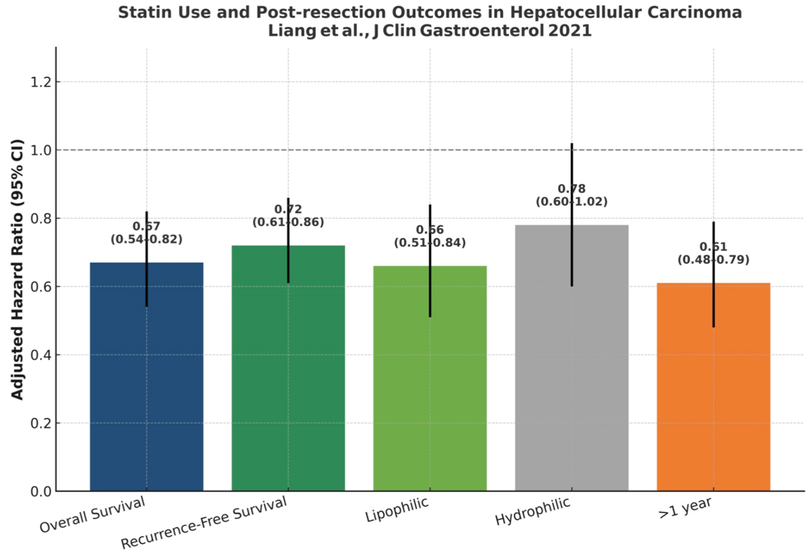


Fig. 2: Kaplan–Meier curves for recurrence-free survival and overall survival in patients who underwent resection for hepatocellular carcinoma. (A) Recurrence-free survival in the propensity score-matched nationwide cohort. (B) Overall survival in the propensity score-matched nationwide cohort. (C) Recurrence-free survival in the propensity score-matched validation hospital cohort. (D) Overall survival in the propensity score-matched validation hospital cohort.

Statin Use and Post-resection Outcomes in Hepatocellular Carcinoma

Liangetal.,JClinGastroenterol2021



Multicenter cohort of 5 321 patients after curative HCC resection. Statin use was associated with ~ 30–40 % lower risk of recurrence and death, especially with lipophilic and long-t

Jeon D, et al. *Association between statin use and the prognosis of hepatocellular carcinoma after resection: a nationwide cohort study, lancet, vol 65, 2023*

Statins Protect Against Liver Disease and Hepatocellular Carcinoma: Evidence from 1.8 Million Participants

Outcome	Cohort	HR (95% CI)	P-value
New liver disease	UKB	0.85 (0.78–0.92)	<0.001
Hepatocellular carcinoma	UKB	0.58 (0.35–0.96)	0.04
	TriNetX	0.26 (0.22–0.31)	0.003
Liver-related death	UKB	0.72 (0.59–0.88)	0.001
Duration effect (≥1 year)	PMBB	0.76 (0.59–0.98)	0.03

Greater protection in **men**, **diabetics**, and those with **high FIB-4**.

Carriers of **PNPLA3 rs738409** variant had **69% lower HCC risk** (HR 0.31).

No significant hepatotoxicity or myopathy signal.

Loomba R, et al. Association of Statin Use With Risk of Liver Disease, Hepatocellular Carcinoma, and Liver-Related Mortality. JAMA Network Open. 2023;6(6):e2320232.

Meta-Analysis: Statin, Metformin, Aspirin and Risk Reduction of Hepatocellular Carcinoma

Subgroup	HR (95% CI)	Significance
Overall	0.52 (0.37–0.72)	✅ Significant
HBV	0.53 (0.32–0.88)	✅
HCV	0.79 (0.64–0.99)	✅
NAFLD	0.68 (0.59–0.77)	✅
Cirrhosis	0.95 (0.91–0.99)	✅
Lipophilic statins	0.46 (0.37–0.57)	✅
Hydrophilic statins	0.48 (0.18–1.27)	❌ NS

Aspirin: HR 0.48 (0.27–0.87), but not significant after adjusting for statin/metformin use.
Metformin: No significant risk reduction (HR 0.57, p = 0.08).

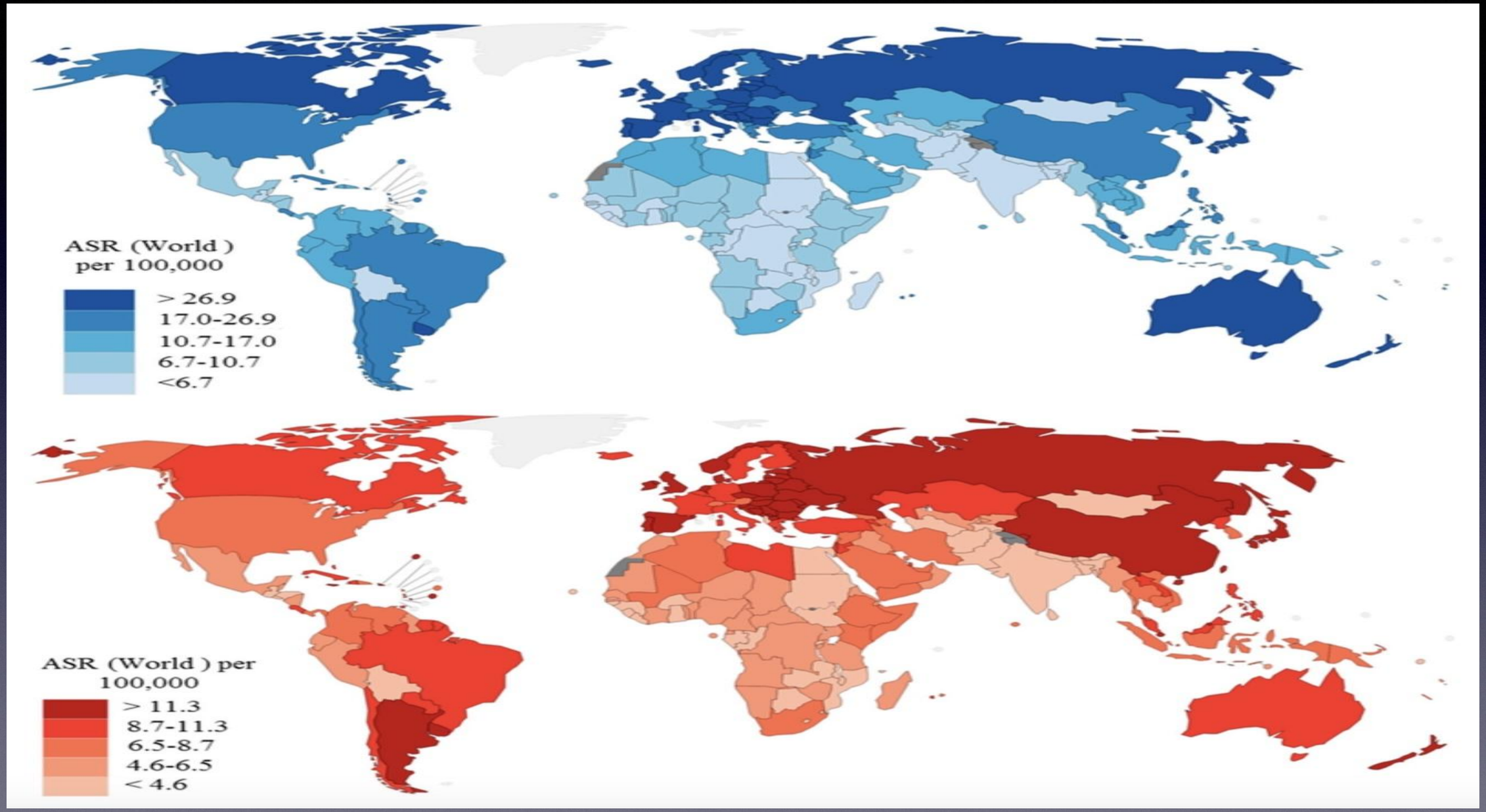
Zeng RW, et al.Meta-analysis: Chemoprevention of hepatocellular carcinoma with statins, aspirin, and metformin.Alimentary Pharmacology & Therapeutics. 2023;57(6):600–609

Statins and Risk Reduction of HCC in MASLD: Meta-Analysis of 291,684 Patients

Subgroup	Risk Ratio (95% CI)	Significance
Overall	0.40 (0.31–0.53)	✅ Significant
Lipophilic statins	0.42 (0.28–0.64)	✅ Stronger effect
Hydrophilic statins	0.57 (0.27–1.20)	❌ NS
Dose >600 cDDD	0.30 (0.21–0.43)	✅ 70% lower risk
300–599 cDDD	0.71 (0.55–0.91)	✅
30–299 cDDD	0.57 (0.40–0.82)	✅

Tarar ZI,et al, Statins decrease the risk of hepatocellular carcinoma in metabolic dysfunction-associated steatotic liver disease: A systematic review and meta-analysis,World Journal of Experimental Medicine. 2024; 14(4): 98543

Global Epidemiology of Colorectal Cancer



Shaukat, A.; Levin, T.R. *The Roadmap of Colorectal Cancer Screening.* **Cancers** 2021, **13**(5):1101.

Statins and Colorectal Cancer Risk — Population-Based Case-Control + Meta-Analysis (Spain)

Exposure	AOR (95% CI)	Comment
Current users	0.87 (0.83–0.91)	↓13% CRC risk
6–12 months use	0.85 (0.76–0.96)	Significant early effect
1–3 years use	0.79 (0.73–0.84)	Strongest effect
>3 years use	0.94 (0.87–1.02)	Diminished effect
Simvastatin	0.86 (0.80–0.93)	Significant
Rosuvastatin	0.58 (0.41–0.83)	Strongest effect
Moderate/High intensity	0.84–0.85	Consistent benefit
Meta-analysis (48 studies)	0.90 (0.86–0.93)	Confirmed protective effect

Rodríguez-Miguel A,et al,Statins and Colorectal Cancer Risk: A Population-Based Case-Control Study and Synthesis of the Epidemiological Evidence. Journal of Clinical Medicine. 2022; 11(6):1528.

Statins Reduce GI Cancer Incidence and Mortality: Korean National Cohort of 1 Million Individuals

Cancer type	Incidence HR (95% CI)	Mortality HR (95% CI)
Gastric	0.70 (0.65–0.74)	0.46 (0.39–0.53)
Colorectal	0.73 (0.69–0.78)	0.43 (0.36–0.51)
Esophageal	0.55 (0.43–0.71)	0.41 (0.27–0.50)
All-cancer mortality	—	0.55 (0.52–0.57)

Results **consistent after propensity-score matching**.

Dose–response trend: >1460 cDDD associated with >70% mortality reduction.

Kim D-S, et al,Statins and the risk of gastric, colorectal, and esophageal cancer incidence and mortality: a cohort study based on data from the Korean National Health Insurance Claims Database, J Cancer Res Clin Oncol. 2022;148(10):2855–2865

Statins Reduce Colorectal Cancer Risk in Inflammatory Bowel Disease — Systematic Review & Meta-Analysis (2025)

Outcome	Pooled Estimate (95% CI)	Significance	Comment
CRC (OR)	0.22 (0.01–7.81)	✖ P=0.21	Trend toward ↓ risk, not significant
CRC (HR)	0.77 (0.63–0.94)	✔ P<0.05	23% ↓ hazard, significant
UC subgroup (HR)	0.64 (0.51–0.80)	✔ P<0.05	36% ↓ risk
CD subgroup (OR)	0.36 (0.16–0.81)	✔ P<0.05	Fewer studies, consistent direction

No major publication bias detected in HR analysis.

Protective effect stronger in **ulcerative colitis** than Crohn's disease.

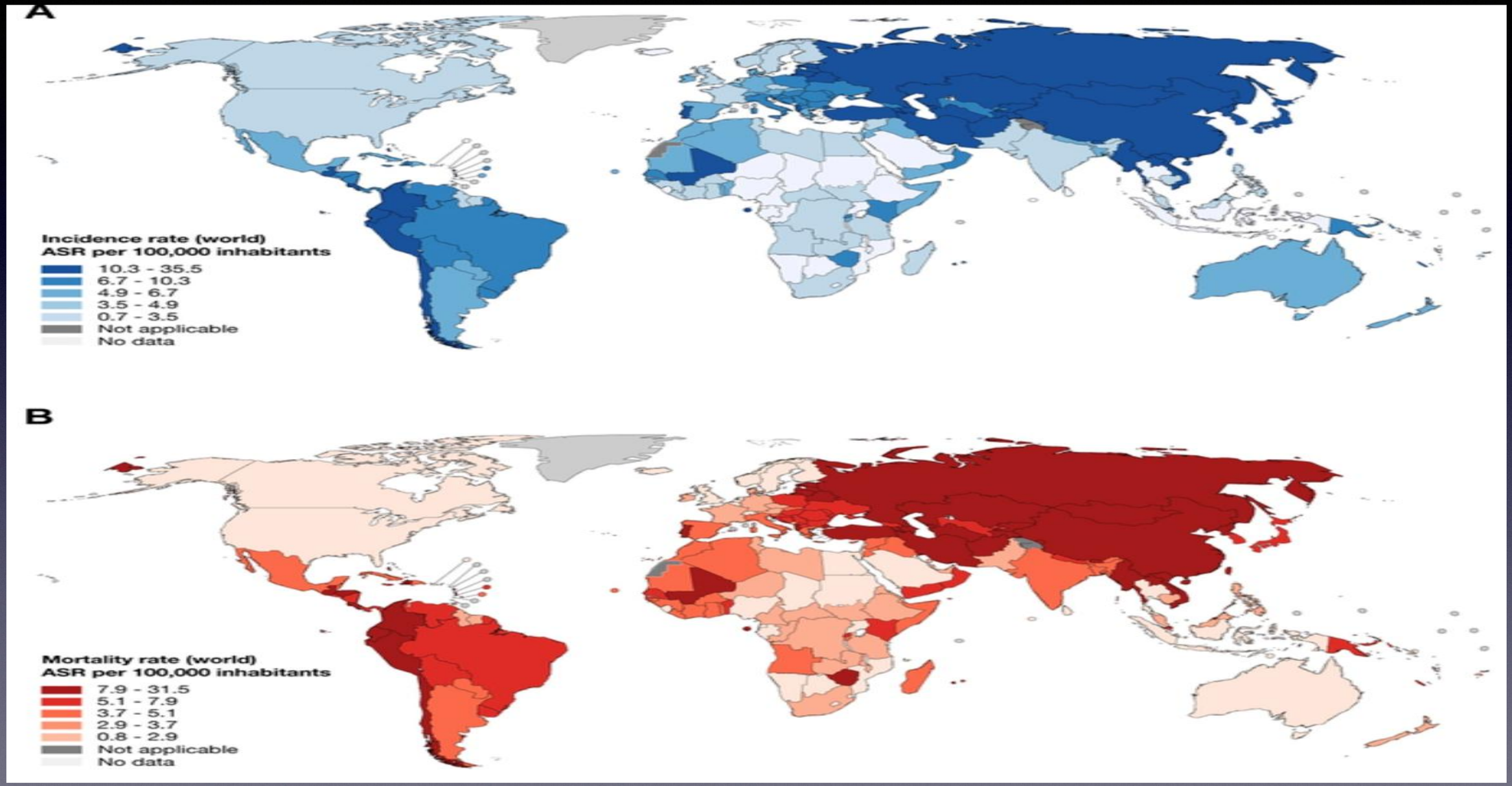
Sleiman J, et al, Statins and the Risk of Colorectal Cancer in Patients With Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis.Gastroenterology Research. 2025;18(3):108–118

Long-Term Statin Use and Colorectal Cancer Risk — NHS & HPFS Prospective Cohorts (USA)

Exposure	HR (95% CI)	Comment
Ever vs. never use	1.13 (1.01–1.27)	↑ Colon cancer risk
>15 years use	1.85 (1.30–2.61)	↑ Significant risk
Proximal colon	1.20 (1.04–1.39)	Risk elevation driven by proximal colon
Distal colon / Rectum	~1.0 / 0.83 (NS)	No effect or slight ↓ trend
Total cholesterol	0.93–1.02	No association

Zhang Y, et al, “Long-Term Statin Use, Total Cholesterol Level, and Risk of Colorectal Cancer: A Prospective Cohort Study.” American Journal of Gastroenterology. 2022;117(1):158–16

Global Epidemiology of Gastric Cancer



Echeverría-Garcés G, et al. Gastric cancer actionable genomic alterations worldwide. Front Pharmacol. 2024;15:1373007.

Statins and Gastric Cancer Risk — Meta-analysis of 11 Studies

Analysis	Pooled OR (95% CI)	Interpretation
All studies	0.68 (0.51–0.91)	32% ↓ GC risk
After excluding outlier	0.84 (0.78–0.90)	16% consistent ↓ risk
Asian populations	0.68 (0.53–0.87)	Stronger benefit
Western populations	0.86 (0.79–0.93)	Modest benefit
Long-term statin use	0.35 (0.16–0.76)	Clear duration–response
Post-hoc RCTs	0.83 (0.66–1.05)	Trend, not significant

No publication bias; heterogeneity resolved after excluding one outlier.

Estimated **NNT** (East Asia): 7,372 person-years to prevent one GC case.

Singh PP, Singh S. Statins are associated with reduced risk of gastric cancer: a systematic review and meta-analysis. Ann Oncol. 2013;24(7):1721–1730

Statins Lower Gastric Cancer Risk After *H. pylori* Eradication — Territory-Wide Propensity Score Matched Study

Group	Gastric Cancer Cases	SHR (95% CI)	P-value
Statin users	31 / 15,990 (2.4 per 10k PY)	**0.34 (0.19–0.61)**	<0.001
Non-users	138 / 47,615 (3.8 per 10k PY)	Reference	—

Non-cardia GC: SHR 0.48 (0.24–0.98)

Cardia GC: SHR 0.31 (0.09–1.03, borderline)
Dose–response:

- <5 years use → SHR 0.46 (0.25–0.86)
- ≥5 years use → SHR 0.43 (0.29–0.66)
- Every +100 cDDD → SHR 0.90 (0.81–0.99)

Absolute risk reduction: 2.6 fewer GC cases per 10,000 person-years.

Cheung KS, et al Statins were associated with a reduced gastric cancer risk in patients with eradicated Helicobacter pylori infection: a territory-wide propensity score–matched study. Cancer Epidemiol B

Statins Reduce Gastric Cancer Risk — Updated Meta-analysis of 20 Studies

Subgroup	RR (95% CI)	Interpretation
All studies	**0.72 (0.64–0.81)**	↓ 28% GC risk overall
Cohort	0.77 (0.66–0.90)	Significant protection
Case-control	0.61 (0.48–0.77)	Strongest association
RCTs	0.82 (0.65–1.04)	NS trend ↓ risk
Asian studies	**0.62 (0.53–0.73)**	Stronger effect
Western studies	0.88 (0.79–0.99)	Modest effect
High-quality studies	0.74 (0.66–0.82)	Consistent signal

Dose-response: ≥1460 cDDD → RR 0.22 (95% CI: 0.19–0.26)

Duration-response: ≥5 years use → RR 0.43 (95% CI: 0.29–0.66)

No publication bias detected (Egger's p = 0.09)

Su C-H, et al,Statins and the Risk of Gastric Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 2022;11:7180.

Aspirin, But Not Statins, and Gastric Cancer Risk — Stomach Cancer Pooling Project

Exposure	Pooled OR (95% CI)	Interpretation
Aspirin use (any)	**0.72 (0.54–0.95)**	↓ 28% GC risk
≥15 years aspirin use	**0.41 (0.18–0.95)**	Strong duration–risk trend
Statin use (any)	0.79 (0.52–1.18)	NS trend ↓ risk
Aspirin + Statin	0.84 (0.51–1.39)	No additive effect

Effect strongest among **individuals without family history of GC** (OR = 0.60).

Protective association **consistent across sex, histology, and *H. pylori* status**.

Statins showed no significant association, possibly due to low exposure frequency.

Pastorino R, et al. Aspirin but not statins is inversely related to gastric cancer with a duration–risk effect: Results from the Stomach Cancer Pooling Project Consortium. C

Hepatocellular carcinoma (HCC)

Aspect	Summary	References
Evidence	Multiple large observational studies and meta-analyses consistently report an association between statin exposure and lower HCC incidence (typical observational effect ~30–40% relative risk reduction). Evidence comes mainly from retrospective cohorts and population registries (HBV, HCV, NAFLD populations). No randomized trial data exist to establish causality.	Kim G et al., J Hepatol 2021 Pradelli D et al., J Gastroenterol Hepatol 2018
Mentions in guidelines	Major hepatology guidelines (AASLD 2023, EASL 2024, APASL 2023) acknowledge observational associations between statin use and reduced HCC risk but state the evidence is insufficient to recommend statins for primary HCC prevention.	Heimbach JK et al., Hepatology 2023 (AASLD guidance) European Association for the Study of the Liver, J Hepatol 2024
Recommendation	Statins are not recommended solely for HCC chemoprevention; they should be used when indicated for cardiovascular reasons.	Guideline statements (AASLD/EASL/APASL)
Take-home message	Consistent observational signal and biologic plausibility, but no guideline endorsement for chemoprevention — RCTs are needed.	—

Colorectal Cancer (CRC)

Aspect	Summary	References
Evidence	Multiple large **observational cohorts** and several **meta-analyses** report an association between statin use and reduced CRC incidence and mortality (typical relative risk reduction **20–30%**). Effects are most consistent in **long-term users** and **IBD-related CRC** cohorts. However, **prospective cohort studies** and **post-hoc RCT analyses** generally show **no significant effect**.	Bardou M et al., *Gastroenterology* 2010; Sehdev A et al., *Anticancer Res* 2014; Liu Y et al., *Front Oncol* 2022; Sleiman J et al., *Gastroenterol Res* 2025
Mentions in Guidelines	**AGA (2021)** and **ACG (2021)** CRC screening guidelines **do not recommend statins for CRC prevention**, and make **no statement** regarding chemoprevention. **ESMO (2022)** and **NCCN (2023)** likewise **omit statins** from preventive or adjuvant strategies.	Shaukat A et al., *Gastroenterology* 2021 (AGA); NCCN Colon Cancer v1.2023; ESMO GI Cancers 2022
Recommendation	**Statins are not recommended** for primary or secondary chemoprevention of colorectal cancer. Use should remain based on **cardiovascular indications**.	AGA, ACG, NCCN, ESMO Guidelines
Take-Home Message	Despite consistent observational associations and strong **biologic plausibility** (anti-inflammatory, pro-apoptotic, and mevalonate-pathway effects), **no guideline** currently endorses statin use for CRC prevention. **RCTs with defined exposure windows** are still needed to establish causality.	—

Gastric cancer

Aspect	Summary	References
Evidence	Several observational cohort studies and some meta-analyses (largely from East Asian populations) report modest inverse associations between statin use and gastric cancer risk (estimates variable; some studies show ~15–25% relative reduction). Heterogeneity is high and confounding (H. pylori status, socioeconomic factors) limits inference.	(Representative) Liu Y et al., Cancers (Basel) 2023 (meta-analysis of observational data)
Mentions in guidelines	Current gastric-cancer guidelines (NCCN, ESMO, ACG) do not mention statins as a preventive strategy.	NCCN Gastric Cancer guideline; ESMO Gastric Cancer guideline
Recommendation	No recommendation to use statins for gastric cancer prevention.	—
Take-home message	Observational signal exists in some regions, but insufficient evidence for practice change; no guideline mention.	—

