

BRIEF COMMUNICATION

Statins and Reduced Risk of Liver Cancer: Evidence for Confounding

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Abstract

A negative association of statin use with liver cancer risk has been reported frequently. We added laboratory measurements, to our knowledge not included in previous investigations, to a case-control analysis of 2877 case patients and 142 850 matched control subjects enrolled in Kaiser Permanente Northern California. Addressing confounding by indication by restricting subjects to those with elevated cholesterol greatly attenuated the negative association; eg, the multivariable-adjusted odds ratio (OR) rose from 0.41 (95% confidence interval [CI] = 0.35 to 0.49) to 0.87 (95% CI = 0.55 to 1.39) for receipt of 18 or more prescriptions. Confounding by contraindication was addressed by controlling for degree of abnormality of liver function tests, alanine or aspartate transaminase, measured within one year of the elevated cholesterol and strongly related to risk. The negative association of statins disappeared for all numbers of prescriptions received, with an odds ratio of 1.21 (95% CI = 0.53 to 2.75) for 18 or more prescriptions. Findings cast doubt on the causality of the frequently observed preventive association.

Several observational studies have found markedly reduced risk of liver cancer associated with use of statins (1–3) and have cited statins' anticarcinogenic properties, including inhibited angiogenesis and metastasis and enhanced apoptosis (3). Avoidance of statins in patients with liver disease can lead to confounding by contraindication because statins may cause liver damage (1–3), and liver disease, particularly cirrhosis and chronic viral hepatitis, is a strong risk factor for liver cancer (4). Confounding by indication is also possible because chronic liver disease can lower cholesterol levels (5,6), reducing the apparent need for, and prescribing of, lipid-lowering drugs such as statins. After stratifying analyses by presence or absence of diagnosed liver disease, the inverse association has persisted within these subgroups (3). However, liver disease is heterogeneous and often undiagnosed; thus, residual confounding is likely. In this study, we assessed these possible sources of confounding with laboratory measurements of lipids and liver function used to guide prescribing of statins. To our knowledge, these have not been available in previous studies.

Kaiser Permanente Northern California (KPNC) is an integrated health care system serving over 3.7 million subscribers.

Electronic health records, including laboratory data collected since 1996, have been stored in a research database. It includes data on all prescriptions dispensed from KPNC pharmacies and a cancer registry that reports to the California Cancer Registry and the Surveillance, Epidemiology, and End Results (SEER) program (7), with complete coverage since 1988.

Our study cohort included subscribers to KPNC at any time between January 1, 1996, and June 30, 2014, with pharmacy benefits. We excluded HIV-positive individuals and those with prior registry-recorded cancer. We identified 2877 individuals with primary liver cancer (case patients). Histologic diagnoses were: hepatocellular (81.9%), cholangiocarcinoma (9.9%), and 13 other types (<2% each). For each case, we used risk set sampling to select up to 50 control subjects ($n = 142\ 850$), matched for birth year, sex, and year of joining KPNC. The index date was: for case patients, the date of diagnosis; for control subjects, the date that provided equal follow-back time to their matched case patients. Statin use was ascertained from cohort entry to one year before index date, as done previously (3). Institutional review board approval was obtained for the study. Written informed consent was waived.

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Of statin prescriptions filled by case patients and control subjects, 65.4% and 60.8% were lovastatin, 29.7% and 33.0% simvastatin, and 3.0% and 4.9% atorvastatin, respectively. Prescription durations were similar in case patients and control subjects (100-day supply = 67.0% of case patients and 66.8% of control subjects, 90-day supply = 13.9% of case patients and 11.7% of control subjects; 60-day supply = 6.9% of case patients and 6.9% of control subjects; 30-day supply = 5.4% of case patients and 5.8% of control subjects; 50-day supply = 3.3% of case patients and 4.7% of control subjects; 120-day supply = 1.8% of case patients and 1.9% of control subjects; all other supplies = 1.8% of case patients and 2.1% of control subjects).

We performed five analyses (Table 1), using conditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for number of prescriptions, representing approximate durations of use adjusted for race/ethnicity. Statin use categories were based on approximate durations in years if all prescriptions were for 100 days (1-2 prescriptions = less than 1 year; 3-7 prescriptions = 1-2 years; 8-17 prescriptions = 2-5 years; 18 or more prescriptions = 5 or more years; excluding prescriptions within the year prior to the index date). Possible

additional confounders ascertained during the same interval as statin use were entered into multivariable analyses in this sequence: hepatitis C, hepatitis B, chronic liver disease, alcohol-related disorders, diabetes, antidiabetic drugs, use of acetaminophen (synonymous with paracetamol previously studied [3], almost all prescriptions combined with opiate), body mass index, and cigarette smoking. Each variable changed an odds ratio by at least 10% in at least one analysis and was thus retained, except for acetaminophen use and alcohol-related disorders. Multivariable adjustment had little effect on our findings described below (Table 1).

We first included all case patients and control subjects (Table 1, Analysis A). We found a statistically significant approximate halving of risk associated with 18+ prescriptions (multivariable-adjusted OR = 0.41, 95% CI = 0.35 to 0.49), similar to what others have found (1-3). The risk ratio calculated in a meta-analysis of 11 observational studies including various levels of statin exposure was 0.57 (95% CI = 0.50 to 0.64) (2).

Next, we restricted analyses to subjects with elevated cholesterol (total ≥ 240 mg/dL and/or LDL ≥ 160 mg/dL) preceded by at least one year of membership and no evidence of prior statin

Table 1. ORs for risk of liver cancer associated with statin use

Analysis	Statin use (No. of dispensings)*	No. of case patients	No. of control subjects	Minimally adjusted† OR (95% CI)	Fully adjusted‡ OR (95% CI)
A: All case patients and control subjects with no prior cancer§	No use	2176	97 897	1.00 (Referent)	1.00 (Referent)
	1-2	110	6308	0.69 (0.56 to 0.83)	0.56 (0.45 to 0.69)
	3-7	152	9030	0.66 (0.56 to 0.78)	0.53 (0.44 to 0.65)
	8-17	203	12 403	0.64 (0.55 to 0.74)	0.48 (0.40 to 0.57)
	18+	236	17 212	0.52 (0.45 to 0.60)	0.41 (0.35 to 0.49)
B: Restricted to first elevated cholesterol, no previous statin use	No use	183	638	1.00 (Referent)	1.00 (Referent)
	1-2	22	106	0.74 (0.44 to 1.24)	0.62 (0.32 to 1.21)
	3-7	45	154	0.91 (0.60 to 1.37)	0.98 (0.58 to 1.67)
	8-17	53	249	0.77 (0.53 to 1.14)	0.71 (0.43 to 1.16)
	18+	91	376	1.05 (0.74 to 1.51)	0.87 (0.55 to 1.39)
C: Further adjusted for elevated cholesterol quintiles¶	No use	183	638	1.00 (Referent)	1.00 (Referent)
	1-2	22	106	0.71 (0.42 to 1.20)	0.59 (0.30 to 1.15)
	3-7	45	154	0.92 (0.61 to 1.38)	0.97 (0.57 to 1.64)
	8-17	53	249	0.76 (0.52 to 1.13)	0.68 (0.41 to 1.12)
	18+	91	376	1.04 (0.72 to 1.50)	0.81 (0.50 to 1.31)
D: Further restricted to those with ALT or AST test within one year after elevated cholesterol#	No use	67	143	1.00 (Referent)	1.00 (Referent)
	1-2	6	31	0.39 (0.15 to 1.01)	0.65 (0.18 to 2.30)
	3-7	26	45	1.14 (0.62 to 2.08)	1.66 (0.69 to 4.00)
	8-17	34	74	0.86 (0.50 to 1.48)	1.04 (0.48 to 2.24)
	18+	56	126	1.00 (0.59 to 1.70)	1.00 (0.46 to 2.18)
E: Further adjusted for ALT/AST categories	No use	67	143	1.00 (Referent)	1.00 (Referent)
	1-2	6	31	0.48 (0.16 to 1.44)	0.85 (0.21 to 3.44)
	3-7	26	45	1.44 (0.72 to 2.90)	1.92 (0.76 to 4.90)
	8-17	34	74	1.08 (0.59 to 1.98)	1.40 (0.62 to 3.14)
	18+	56	126	1.20 (0.65 to 2.21)	1.21 (0.53 to 2.75)
	ALT/AST Normal	98	355	1.00 (Referent)	1.00 (Referent)
	1-2x normal	58	50	5.21 (3.01 to 9.01)	3.46 (1.57 to 7.61)
2-3x normal	16	11	5.57 (2.16 to 14.36)	3.81 (0.87 to 16.77)	
>3x normal	17	3	30.61 (6.29 to 148.83)	22.74 (2.02 to 256.07)	

*Statin use categories were based on approximate durations in years if all prescriptions were for 100 days: 1-2: <1; 3-7: 1-2; 8-17: 2-5; 18+: 5+ years; excluding prescriptions within the year prior to the index date. ALT = alanine transaminase; AST = aspartate aminotransferase; CI = confidence interval; OR = odds ratio.

†Conditional on matching factors (sex, birth year, year of joining program, and follow-up time) and adjusted for race/ethnicity.

‡Additionally adjusted for: hepatitis C, hepatitis B, chronic liver disease, diabetes, antidiabetic drugs, body mass index closest in time to index date in four categories, below normal: <18.5; normal: 18.5-24.9; overweight: 25.0-29.9; obese: ≥ 30.0 ; and cigarette smoking, current, former, never, based on algorithm accounting for changes and inconsistencies, available from authors.

§2877 case patients and 142 850 control subjects.

||Same cholesterol test year for case patients and control subjects.

¶Quintiles based on the distribution of control subjects.

#Alanine aminotransferase or aspartate aminotransferase at least two years before index date.

use. Although criteria for elevation have changed, these were probably applicable during much of the period studied (8). We found 394 case patients and 1523 matched control subjects with elevated cholesterol in the same year, losing only two case-control sets for lack of such matched control subjects. Restricting to subjects with elevated cholesterol (Table 1, Analysis B) in the same year greatly attenuated the negative association; eg, multivariable-adjusted OR for 18 or more prescriptions rose from 0.41 (95% CI = 0.35 to 0.49) to 0.87 (95% CI = 0.55 to 1.39). Adjusting for quintile of elevated total cholesterol (based on the control subjects' distribution) had virtually no effect (Table 1, Analysis C) but was retained in further analyses.

Subjects were restricted further to those with an alanine transaminase (ALT) or aspartate transaminase (AST) test of liver function within one year after their elevated cholesterol and before receiving statins. Clinical guidelines suggest caution in prescribing statins if either of these is above three times the upper limit of normal (9). Here, this level is: ALT 109 U/L and AST 120 U/L. Among these 189 case patients and 419 control subjects, multivariable-adjusted odds ratios were higher for all numbers of prescriptions (Table 1, Analysis D), and the apparent risk reduction disappeared for all numbers of prescriptions, except the fewest. For 18 or more prescriptions, the odds ratio was 1.21 (95% CI = 0.53 to 2.75). If the wide confidence interval does not rule out its negativity, the finding for one to two prescriptions is more consistent with confounding than with a causal preventive association, where a dose-response relationship would be expected. Odds ratios were higher again after further adjusting for ALT/AST, categorized as normal (referent), 1 to 2 \times , 2 to 3 \times , and more than 3 \times the upper limit of normal, itself strongly associated with risk (Table 1, Analysis E).

We determined whether the association between statins and liver cancer varied by patient subgroup (3). The odds ratios in Analysis E for 18 or more prescriptions were 3.15 (95% CI = 0.31 to 32.22) for patients with diabetes and 0.65 (95% CI = 0.23 to 1.85) for patients without diabetes. To test whether this subgroup difference was statistically significant (two-sided $P < .05$), we added interaction terms to the logistic regression model, and the fitted model yielded a P value of .02 (Wald test) for the association of liver cancer with diabetes-by-18 or more prescriptions. Chronic liver disease was too rare in control subjects for subgroup analysis (Table 1).

For overall Analysis E above (Table 1), we required a minimum of two years between ALT/AST test and index date to address potential bias from liver cancer increasing liver enzyme levels (protopathic bias). We conducted three sensitivity analyses of Analysis E: inserting a two-year lag between statin dispensing and index date, increasing the ALT/AST-to-index date interval to four years, and restricting case patients to those with hepatocellular carcinoma. These had no material effect on our results or conclusions (data not shown).

The attenuation of risk reduction by restricting subjects to those with elevated cholesterol supports confounding by indication, ie, reduced cholesterol levels leading to less prescribing of statins in the presence of chronic liver disease, a major risk factor for liver cancer. Notably, among six metabolic risk factors, only serum cholesterol level was inversely related to risk of primary liver cancer in a large European prospective study (10).

Further attenuation and disappearance of apparent risk reduction by adjusting for liver function tests supports confounding by contraindication, ie, avoidance of prescribing statins for patients with liver disease. Restriction of subjects to those with elevated cholesterol and attention to liver function tests partially duplicates the criteria for entering patients into

randomized trials of statins, as advocated by Schneeweiss et al. for improving pharmacoepidemiologic studies (11).

Our design is consistent with clinical practice regarding statins. However, findings could have resulted from chance sampling variation because of relatively small numbers of subjects. Small numbers also limited the possibility of studying different etiological profiles individually. A stronger negative association for diabetics found elsewhere (3) differed from our stronger positive association, but our lower 95% confidence limit was well below 1.0. The role, if any, of diabetes in the statin/liver cancer relationship is unclear. Investigating it is complicated because diabetes can both predispose to and result from liver cirrhosis (12) and can be an indication for statin use (13).

Given our findings of confounding by indication and contraindication and that prevention of liver cancer has not been observed in randomized controlled trials of statins to date (1–3,14), causality of the preventive association found in observational studies remains uncertain.

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