

Low LDL Cholesterol, Albuminuria, and Statins for the Risk of Cancer in Type 2 Diabetes

The Hong Kong Diabetes Registry

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OBJECTIVE — LDL cholesterol <2.80 mmol/l was associated with increased cancer risk in type 2 diabetes. We explored the 1) interaction between low LDL cholesterol and albuminuria and 2) interaction between copresence of these two risk factors and statin use for cancer in type 2 diabetes.

RESEARCH DESIGN AND METHODS — We analyzed prospective data for 3,793 Chinese type 2 diabetic patients who remained naive for statin treatment and 1,483 patients in whom statin treatment was initiated during a median follow-up period of 5.24 years. All patients were free of cancer at baseline. Biological interactions were estimated using relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (S). RERI > 0, AP > 0, or S > 1 indicates biological interaction.

RESULTS — In 3,793 statin-naive type 2 diabetic patients, copresence of low LDL cholesterol and albuminuria increased cancer risk by 2.8-fold (hazard ratio 2.77 [95% CI 1.78–4.31]) with significant biological interactions (RERI 1.05 [0.04–2.06]; AP 0.38 [0.09–0.66]). In the whole cohort of 5,276 type 2 diabetic patients, there was interaction between nonuse of statins and copresence of low LDL cholesterol and albuminuria with increased cancer risk (RERI 2.87 [0.64–5.09] and AP 0.60 [0.29–0.90]). Statin nonusers with LDL cholesterol <2.80 mmol/l and albuminuria had a 4.9-fold risk of cancer compared with statin users with or without both risk factors.

CONCLUSIONS — In type 2 diabetes, there was interaction between low LDL cholesterol and albuminuria with increased cancer risks. The latter was attenuated in the presence of statin treatment.

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Type 2 diabetes predisposes patients to a variety of cancers (1–4). The prevalence of cancer in type 2 diabetic patients is one-third higher than that in the general population (5). Based on a prospective database, we reported that the association between LDL cholesterol

and cancer risk in type 2 diabetes was V-shaped with a nadir at 3.28 mmol/l and that LDL cholesterol levels <2.80 mmol/l and ≥ 3.80 mmol/l were both associated with elevated cancer risks (5).

Albuminuria is an early manifestation of generalized endothelial dysfunction

(6). This urinary marker is closely associated with hyperglycemia, obesity, and hypertension (7). Using a prospective registry, we found possible biological interactions between albuminuria and hyperglycemia with increased risk of ischemic stroke (7). Given the intimate relationships between albuminuria, dyslipidemia, and cancer risk, we asked whether there are biological interactions between low LDL cholesterol (<2.80 mmol/l) and albuminuria for the risk of cancer in type 2 diabetes. Given the inconsistent findings for use of lipid-lowering drugs and cancer risks (8–10) and a paucity of such data in type 2 diabetes, we also explore the potential interaction (a second-order interaction) between use of statins and copresence of low LDL cholesterol and albuminuria on cancer risks.

RESEARCH DESIGN AND METHODS

The Hong Kong Diabetes Registry (5,11) was established in 1995 at the Prince of Wales Hospital, the teaching hospital of The Chinese University of Hong Kong. The hospital serves a population of >1.2 million. The referral sources of the cohort included both community and hospital clinics in the catchment region. Less than 10% of the enrolled patients had hospital admissions within 6–8 weeks before assessment. The 1998 World Health Organization criteria (the 1985 criteria were used before July 1998) were used to diagnose diabetes (12). A 4-h assessment of complications and risk factors was performed on an outpatient basis, modified from the European DiabCare protocol (13). Once a patient had undergone this comprehensive assessment, he or she was considered to have entered this study cohort and would be followed until the time of death. Ethics approval was obtained from the Chinese University of Hong Kong Clinical Research Ethics Committee. The Declaration of Helsinki was adhered to and informed consent was obtained from all

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patients at the time of assessment for data analysis and research purposes.

The clinical end points included discharge diagnoses and mortality from enrollment to 30 July 2005, or otherwise censored on 30 July 2005. Details of all clinical end points were retrieved from the Hong Kong Hospital Authority Central Computer System, which recorded admissions to all public hospitals in Hong Kong. Mortality data were retrieved from the Hong Kong Death Registry and were cross-checked with hospital discharge status (11). We also extracted drug dispensing data from the Hospital Authority Computer System including the start dates and end dates for each of the drugs of interest. In Hong Kong public hospitals, all medications are dispensed on site in both inpatient and outpatient settings. These databases were matched by a unique identification number, the Hong Kong Identity Card number, which is compulsory for all residents in Hong Kong.

From 1996 to 2005, 7,387 diabetic patients were enrolled in the registry. We excluded the following patients from the first stage of analysis: 1) 328 patients with type 1 diabetes or missing details on types of diabetes (5), 2) 45 patients with non-Chinese or unknown nationality, 3) 175 patients with a known history of cancer or receiving treatment for cancer at enrollment, 4) 736 patients with missing values for any variables included in the analysis (see Table 3 for a list of variables), and 5) 2,310 patients who were exposed to statins from enrollment to dates of cancer, death, or censoring, whichever came first. Thus, in the first stage of analysis, we included 3,793 patients who remained naive for statin treatment throughout the observational period and had complete sets of variables for the analysis of the interaction between low LDL cholesterol and albuminuria. The reasons for these exclusions were as follows: 1) pretreatment LDL cholesterol levels of patients treated with statins at enrollment were unknown and 2) use of statins is a potential confounder for the risk association of cancer with LDL cholesterol (5). Of the 2,310 patients treated with statins, in 1,483 patients therapy was started during the follow-up period. We included these 1,483 patients in the above statin-naive cohort of 3,793 patients. In this second stage of analysis, we tested the interaction between use of statins and copresence of LDL cholesterol <2.80 mmol/l and albuminuria in these 5,276 patients.

Table 1—Clinical and biochemical characteristics of the study cohort stratified according to use of statins during follow-up period

	Non-statin users	Statin users	P
<i>n</i>	3,793	1,483	
Baseline variables and outcomes			
Age (years)	56 (22)	58 (18)	<0.0001*
Male sex	1,794 (47.3%)	676 (45.6%)	0.2619†
Smoking status			0.5662†
Ex-smoker	559 (14.7%)	231 (15.6%)	
Current smoker	594 (15.7%)	242 (16.3%)	
Alcohol drinking status			0.4829†
Ex-drinker	457 (12.1%)	187 (12.6%)	
Current drinker	298 (7.9%)	103 (7.0%)	
BMI, kg/m ²	24.6 (4.9)	25.0 (4.8)	<0.0001*
Duration of diabetes (years)	5 (9)	7 (10)	<0.0001*
Systolic blood pressure (mmHg)	132 (25)	138 (27)	<0.0001*
Diastolic blood pressure (mmHg)	75 (14)	76 (14)	<0.0001*
A1C (%)	7.0 (2.0)	7.7 (2.2)	<0.0001*
LDL cholesterol (mmol/l)	2.90 (1.06)	3.71 (1.15)	<0.0001*
HDL cholesterol (mmol/l)	1.27 (0.47)	1.22 (0.42)	<0.0001*
Triglycerides (mmol/l)	1.21 (0.88)	1.58 (1.11)	<0.0001*
Total cholesterol (mmol/l)	4.90 (1.17)	5.80 (1.30)	<0.0001*
ACR (mg/mmol)	1.63 (6.03)	3.78 (25.5)	<0.0001*
LDL cholesterol <2.80 mmol/l plus albuminuria	594 (15.7%)	101 (6.8%)	<0.0001†
eGFR (ml/min per 1.73 m ²)	107.2 (40.4)	99.4 (43.0)	<0.0001*
Prior myocardial infarction	21 (0.6%)	31 (2.1%)	<0.0001†
Prior stroke	112 (3.0%)	86 (5.8%)	<0.0001†
Cancer during follow-up	210 (5.5%)	34 (2.3%)	<0.0001†
Death (all-cause) during follow-up	337 (8.9%)	103 (7.0%)	0.0220†
Medications at enrollment			
Fibrates	83 (2.2%)	95 (6.4%)	<0.0001†
Oral antidiabetes drugs	2,402 (63.3%)	1,022 (68.9%)	0.0001†
Insulin	562 (14.8%)	350 (23.6%)	<0.0001†
ACEIs or ARBs	689 (18.2%)	427 (28.8%)	<0.0001†
Antihypertensive drugs other than ACEIs or ARBs	1,270 (33.5%)	591 (39.9%)	<0.0001†
Medications during follow-up period‡			
Fibrates	282 (7.4%)	251 (16.9%)	<0.0001†
Oral antidiabetes drugs	3,076 (81.1%)	1,343 (90.6%)	<0.0001†
Insulin	1,114 (29.4%)	794 (53.5%)	<0.0001†
ACEIs or ARBs	1,777 (46.9%)	1,109 (74.8%)	<0.0001†
Duration of use of statins (years)	—	2.07 (3.18)	

Data are median (25th–75th percentiles) or *n* (%). Albuminuria was defined as spot urinary ACR ≥2.5 mg/mmol in men and ≥3.5 mg/mmol in women. *Derived from a Wilcoxon two-sample test. †Derived from a χ^2 test. ‡From baseline to cancer, death, or censoring dates whichever came first.

Clinical and laboratory measurements

On the day of the visit, patients attended the center after 8 h of fasting and underwent clinical assessments and laboratory investigations as described previously (5). A sterile, random spot urinary sample was used to measure the albumin-to-creatinine ratio (ACR). Albuminuria was defined as ACR ≥2.5 mg/mmol in men and ≥3.5 mg/mmol in women. The abbreviated Modification of Diet in Renal Disease Study formula recalibrated for

Chinese (14) was used to estimate glomerular filtration rate (eGFR) expressed in milliliters per minute per 1.73 m²: $eGFR = 186 \times [SCR \times 0.011]^{-1.154} \times [age]^{-0.203} \times [0.742; \text{if female}] \times 1.233$, where SCR is serum creatinine expressed as micromoles per liter (original milligrams per deciliter converted to micromoles per liter) and 1.233 is the adjusting coefficient for Chinese. Lipids (total cholesterol, triglycerides, and HDL cholesterol) were measured by enzymatic methods on a Hitachi 911 automated an-

Table 2—HRs for the risk of cancer in relation to low LDL cholesterol, albuminuria, and statin use

	No. at risk	HR (95% CI)	P
Interaction models for albuminuria and low LDL cholesterol*			
Model 1†			
LDL cholesterol <2.8 mmol/l and normoalbuminuria vs. others	961	1.35 (0.89–2.07)	0.1603
LDL cholesterol ≥2.8 mmol/l and albuminuria vs. others	837	1.40 (0.97–2.02)	0.0718
LDL cholesterol <2.8 mmol/l and albuminuria vs. others	594	3.08 (2.08–4.56)	<0.0001
Model 2‡			
LDL cholesterol <2.8 mmol/l and normoalbuminuria vs. others	961	1.41 (0.92–2.16)	0.1129
LDL cholesterol ≥2.8 mmol/l and albuminuria vs. others	837	1.16 (0.78–1.74)	0.4576
LDL cholesterol <2.8 mmol/l and albuminuria vs. others	594	2.59 (1.69–3.96)	<0.0001
Model 3§			
LDL cholesterol <2.8 mmol/l and normoalbuminuria vs. others	961	1.45 (0.94–2.24)	0.0932
LDL cholesterol ≥2.8 mmol/l and albuminuria vs. others	837	1.27 (0.85–1.90)	0.2435
LDL cholesterol <2.8 mmol/l and albuminuria vs. others	594	2.77 (1.78–4.31)	<0.0001
Interaction models for copresence of LDL cholesterol <2.80 mmol/l plus albuminuria and nonuse of statins			
Model 1†			
Low LDL cholesterol and albuminuria = yes and use of statins vs. others	101	0.63 (0.09–4.64)	0.6476
Low LDL cholesterol and albuminuria = no and nonuse of statins vs. others	3,199	2.54 (1.72–3.76)	<0.0001
Low LDL cholesterol and albuminuria = yes and nonuse of statins vs. others	594	6.24 (3.86–10.07)	<0.0001
Model 2‡			
Low LDL cholesterol and albuminuria = yes and use of statins vs. others	101	0.67 (0.09–4.96)	0.6942
Low LDL cholesterol and albuminuria = no and nonuse of statins vs. others	3,199	2.21 (1.47–3.33)	<0.0001
Low LDL cholesterol and albuminuria = yes and nonuse of statins vs. others	594	4.43 (2.72–7.21)	<0.0001
Model 3§¶			
Low LDL cholesterol and albuminuria = yes and use of statins vs. others	101	0.64 (0.09–4.80)	0.6645
Low LDL cholesterol and albuminuria = no and nonuse of statins vs. others	3,199	2.31 (1.51–3.91)	<0.0001
Low LDL cholesterol and albuminuria = yes and nonuse of statins vs. others	594	4.81 (2.81–8.24)	<0.0001

*The analysis was performed in 3,793 patients without use of statins. †Adjusted for LDL cholesterol ≥3.80 mmol/l. ‡Further adjusted for age, sex, BMI, smoking status (current smoker plus ex-smoker), drinking status (current drinker plus ex-drinker), duration of diabetes, A1C, systolic blood pressure, HDL cholesterol, triglycerides, eGFR, and medications from enrollment to cancer, death, or censoring date, whichever came first. Medications include ACEIs or ARBs, oral antidiabetes drugs, insulin, fibrates and other antihypertensive drugs at enrollment. §Adjusted for covariates listed in ‡, but restricted cubic spline functions were used for all the continuous covariates. ||The analysis was performed in 3,793 patients without use of statins plus 1,483 patients who used statins during follow-up. ¶Stratified Cox models including deciles of propensity scores to adjust for likelihood using statins during follow-up. The propensity score was calculated using a logistic regression procedure with use of statins as the dependent variable and age, sex, BMI, LDL cholesterol, HDL cholesterol, triglycerides, smoking status, drinking status, A1C, systolic blood pressure, log (ACR + 1), eGFR, duration of diabetes, peripheral arterial disease, retinopathy, sensory neuropathy, prior history of myocardial infarction, and stroke as independent variables (The *c*-statistic was 0.80).

alyzer (Boehringer Mannheim, Mannheim, Germany) using reagent kits supplied by the manufacturer. LDL cholesterol was calculated using the Friedewald equation (15). The precision performance of these assays was within the manufacturer's specifications.

Definition of cancer

Hospital discharge principle diagnoses, coded according to the ICD-9, were used to identify cancer events. The end point of this study was defined as incident cancer (either fatal or nonfatal; codes 140–208) during the follow-up period.

Statistical analyses

SAS (release 9.10; SAS Institute, Cary, NC) was used for all analyses. Cox proportional hazards regression was used to obtain hazard ratios (HRs) of incident cancer with status of statin use, presence

of low LDL cholesterol, and albuminuria. Follow-up time was calculated as the period in years from the enrollment to the date of the first cancer event, death, or censoring, whichever came first.

To estimate the biological interaction between albuminuria and low LDL cholesterol (defined as <2.80 mmol/l), we created three new variables: 1) low LDL cholesterol = yes and albuminuria = no versus others; 2) low LDL cholesterol = no and albuminuria = yes versus others; and 3) low LDL cholesterol = yes and albuminuria = yes versus others (16,17). We also examined the second-order interaction between statin use and copresence of low LDL cholesterol and albuminuria. We created three variables using copresence of low LDL cholesterol and albuminuria as one risk factor and nonuse of statins as the other: 1) low LDL cholesterol plus albuminuria = yes and use of

statins = yes versus others; 2) low LDL cholesterol plus albuminuria = no and use of statins = no versus others; and 3) low LDL cholesterol plus albuminuria = yes and use of statins = no versus others (see Table 2).

We used three measures to estimate biological interactions: relative excess risk due to interaction (RERI); attributable proportion due to interaction (AP); and synergy index (S). The RERI is the excess risk due to interaction relative to the risk without exposure. AP refers to the attributable proportion of disease that is due to interaction among persons with both exposures. S is the excess risk from both exposures when there is a biological interaction, relative to the risk from both exposures without interaction (18). RERI > 0, AP > 0, or S > 1 indicates a biological interaction. In Cox models, the RERI is

the best choice among the three measures (19).

We used a structured analysis scheme to adjust for covariates. First, we obtained the three biological interaction measures after adjusting for high LDL cholesterol, i.e., ≥ 3.8 mmol/l. Second, we adjusted for age, sex, BMI, ever-smoking status, ever-alcohol drinking status, duration of diabetes, A1C, systolic blood pressure, HDL cholesterol, triglycerides, eGFR, and medications from enrollment to cancer, death, or censoring dates, whichever came first. These drugs included ACE inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), oral antidiabetes drugs, insulin, and fibrates and other antihypertensive drugs at enrollment. Third, because lipids are associated with cancer in a V-shaped or A-shaped relation (5,20), we used the restricted cubic splines with four knots at the 5th, 35th, 65th, and 95th percentiles of covariables to adjust for confounding effects due to nonlinear associations of lipids and other covariates in additional Cox models (5). To adjust for confounding effects due to the likelihood of drug use during follow-up period, we calculated a propensity score for use of statins, as described previously (21). We then used stratified Cox models on deciles of the likelihood to estimate the interaction of nonuse of statin and copresence of low LDL cholesterol and albuminuria on cancer risk. Proportionality and correlations between pairs of baseline covariates were checked as described (5). Two-sided $P < 0.05$ was considered significant.

RESULTS

Characteristics of the patients

Compared with statin-naïve patients, those in whom statin treatment was initiated during follow-up were older and had a longer duration of diabetes and poorer metabolic profile. During a median (25th–75th percentiles) follow-up period of 5.24 (2.99–7.10) and a mean \pm SD follow-up period of 5.01 \pm 2.36 years, the statin users were more likely to use other drugs and develop cardiovascular complications but less likely to have cancer and die (Table 1).

Among 3,793 patients never exposed to statins, 210 patients developed cancer during a median of 5.08 (interquartile range 2.84–7.07) years of follow-up with an incidence of 11.27 (95% CI 9.76–12.79) per 1,000 person-years. Patients who developed cancer were older, had higher systolic blood pressure and ACR

Table 3—Biological interactions of LDL cholesterol with albuminuria and copresence of these two risk factors with statin use for the risk of cancer in type 2 diabetes

Measures of biological interaction	Estimate (95% CI)
Interaction models for albuminuria and low LDL cholesterol*	
Model 1†	
RERI	1.32 (0.28–2.37)‡
AP	0.43 (0.18–0.68)‡
S	2.75 (1.01–7.49)‡
Model 2§	
RERI	1.01 (0.08–1.94)‡
AP	0.39 (0.11–0.68)‡
S	2.76 (0.78–9.71)
Model 3	
RERI	1.05 (0.04–2.06)‡
AP	0.38 (0.09–0.66)‡
S	2.46 (0.85–7.09)
Interaction models for LDL cholesterol < 2.80 mmol/l plus albuminuria and nonuse of statins¶	
Model 1†	
RERI	4.07 (1.56–6.76)‡
AP	0.65 (0.42–0.89)‡
S	4.48 (1.26–15.91)‡
Model 2§	
RERI	2.55 (0.57–4.52)‡
AP	0.58 (0.24–0.91)‡
S	3.90 (0.68–22.29)
Model 3 #	
RERI	2.87 (0.64–5.09)‡
AP	0.60 (0.29–0.90)‡
S	4.03 (0.82–19.78)

*The analysis was performed in 3,793 patients without use of statins. †Adjusted for LDL cholesterol ≥ 3.80 mmol/l. ‡Statistically significant with RERI > 0 , AP > 0 , or S > 1 indicating biological interaction. §Further adjusted for age, sex, BMI, smoking status (current smoker plus ex-smoker), drinking status (current drinker plus ex-drinker), duration of diabetes, A1C, systolic blood pressure, HDL cholesterol, triglycerides, eGFR, and medications from enrollment to cancer, death, or censoring date, whichever came first. Medications include ACEIs or ARBs, oral antidiabetes drugs, insulin, fibrates, and other antihypertensive drugs. ||Adjusted for covariates listed in †, but restricted cubic spline functions were used for all the continuous covariates. ¶The analysis was performed in 3,793 patients without use of statins plus 1,483 patients who used statins during follow-up. #Stratified Cox models on deciles of propensity scores were used to adjust for likelihood of using statins during follow-up. The propensity score was calculated using a logistic regression procedure with statin use as the dependent variable and the variables listed in Table 2, footnote ¶, as independent variables.

and lower eGFR, and were more likely to use tobacco, alcohol, and antihypertensive drugs (except for ACEIs or ARBs) than patients without cancer (supplementary Table, available in an online appendix at <http://care.diabetesjournals.org/cgi/content/full/dc09-0725/DC1>).

Biological interaction of low LDL cholesterol and albuminuria for cancer

Copresence of LDL cholesterol < 2.80 mmol/l and albuminuria was associated with a 3.1-fold risk of cancer compared with those without these risk factors after adjustment for LDL cholesterol < 2.80 mmol/l only, albuminuria only, and LDL cholesterol ≥ 3.80 mmol/l. These risk as-

sociations remained significant after adjustment for other covariates including their possible nonlinear associations with cancer. After exclusion of patients with follow-up < 2.5 years, the hazard ratio (HR) increased from 2.77 (95% CI 1.78–4.31) to 2.87 (1.54–5.34). The presence of either albuminuria only or LDL cholesterol < 2.80 mmol/l only was not associated with increased cancer risk (Table 2). RERI for interaction of LDL cholesterol < 2.80 mmol/l with albuminuria was 1.32 (0.28–2.37) and AP was 0.43 (0.18–0.68) after adjustment for LDL < 2.80 mmol/l only, albuminuria only, and LDL cholesterol ≥ 3.80 mmol/l. Statistical significance persisted after adjustment for other covariates including their possible

nonlinear associations with cancer (Table 3). The cumulative incidence of cancer in patients with both albuminuria and LDL cholesterol <2.8 mmol/l was higher than that for any other groups. Patients with either albuminuria or LDL cholesterol <2.80 mmol/l (but not both) had similar risks of cancer as those without exposures to both risk factors (Fig. 1A).

Biological interaction between copresence of low LDL cholesterol plus albuminuria and nonuse of statins for cancer risk

There was a significant interaction between nonuse of statins and copresence of LDL cholesterol <2.80 mmol/l and albuminuria for cancer risk. The RERI was 2.87 (95% CI 0.64–5.09) and AP was 0.60 (0.29–0.90) in a multivariable spline Cox model analysis (Table 3). Statin nonusers who had LDL cholesterol <2.80 mmol/l and albuminuria had a 4.8-fold risk of cancer compared with all others (HR 4.81, 95% CI 2.81–8.24). Patients with these two risk factors but treated with statins during follow-up did not have an increased cancer risk (0.64, 0.09–4.80) (Table 2).

Patients with LDL cholesterol <2.80 mmol/l and albuminuria but never treated with statins had the highest incidence of cancer, followed by statin nonusers without copresence of the two risk factors. Patients treated with statins with or without copresence of low LDL cholesterol and albuminuria had the lowest risk of cancer (Fig. 1B). After adjustment for the covariates listed in model 3 of Table 2, the HR of cancer of statins nonusers who had copresence of low LDL cholesterol and albuminuria versus statin users with or without copresence of both risk factors was as high as 4.94 (95% CI 2.92–8.37, $P < 0.0001$).

Sensitivity analysis

We included 827 patients who used statins at baseline in the cohort and applied the adjusting analysis scheme of model 3 (Table 2). The interaction between LDL cholesterol <2.80 mmol/l and albuminuria remained significant (RERI 0.78, 95% CI 0.03–1.53; AP 0.35, 0.08–0.63). The interaction between copresence of LDL cholesterol <2.80 mmol/l plus albuminuria and nonuse of statin were also significant (RERI 1.95, 0.49–3.41; AP 0.51, 0.24–0.79).

CONCLUSIONS— In this prospective analysis, we detected an interaction

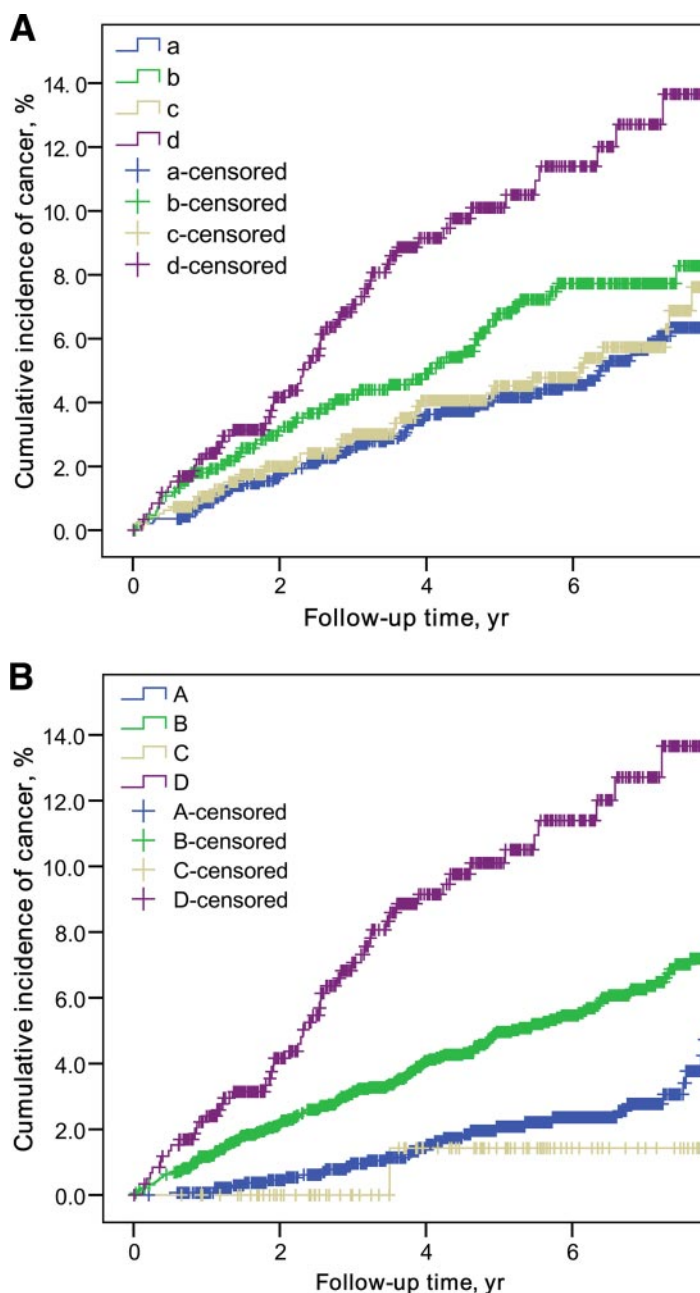


Figure 1—Cumulative incidence of cancer stratified by albuminuria, LDL cholesterol <2.80 mmol/l and status of statin use in type 2 diabetes. A was derived from 3,793 type 2 diabetic patients without use of statins (log-rank test, $P < 0.0001$): a, patients without either albuminuria or LDL cholesterol <2.80 mmol/l; b, patients with albuminuria only; c, patients with LDL cholesterol <2.80 mmol/l only; and d, patients with the copresence of LDL cholesterol <2.80 mmol/l and albuminuria. B was derived from 3,793 patients without use of statins plus 1,483 patients who used statins during follow-up (log-rank test, $P < 0.0001$): A, statin users who did not have the copresence of LDL cholesterol <2.80 mmol/l and albuminuria; B, statin nonusers who did not have the copresence of LDL cholesterol <2.80 mmol/l and albuminuria; C, statin users who had the copresence of LDL cholesterol <2.80 mmol/l and albuminuria; and D, statin nonusers who had the copresence of LDL cholesterol <2.80 mmol/l and albuminuria.

between LDL cholesterol <2.80 mmol/l and albuminuria for cancer in type 2 diabetes, suggesting that copresence of both risk factors confers an increased cancer risk, more than simple summation of

the risks attributable to low LDL cholesterol and albuminuria occurring in isolation. Because the increased cancer risk was not observed in patients with either one of the abnormalities, our findings

suggest that the increased risk of cancer in type 2 diabetic patients with low LDL cholesterol was conditional on the presence of albuminuria. Furthermore, we found a significant interaction between nonuse of statins and copresence of these two risk markers, suggesting that use of statins may confer the largest risk reduction for cancer in patients with copresence of low LDL cholesterol and albuminuria than in patients without.

In type 2 diabetes, albuminuria strongly predicts cardiorenal complications (22) and may serve as a composite marker of risk factors, including hypertension, inflammation, hyperglycemia, and obesity (7). Patients with type 2 diabetes, especially those of Asian origin, have a high prevalence of albuminuria. In a case series, 56% Asian type 2 diabetic patients had albuminuria compared with 40% of their Caucasian counterparts (23). In our analysis, patients with both exposures, i.e., LDL cholesterol <2.80 mmol/l and albuminuria, were more likely to have a longer diabetes duration, poor glycemic control, and renal dysfunction and use insulin (data not shown). Taken together, our findings suggest that dysregulation of lipid and glucose metabolism may interact with renal dysfunction to increase risk of cancer in type 2 diabetes.

In our previous analysis, we hypothesized that in type 2 diabetes, low LDL cholesterol may upregulate the activity or responsiveness of the mevalonate pathway, which leads to lipid synthesis, and the upregulated mevalonate pathway may be responsible for the increased risk of cancer (5). Based on results from this analysis, it is plausible that low LDL cholesterol in the presence of albuminuria may increase cancer risk by up-regulating the mevalonate pathway. Against this background, statins reduce LDL cholesterol by inhibiting hydroxymethylglutaryl-CoA reductase, the rate-limiting enzyme of lipid synthesis, and thus downregulate the mevalonate pathway. In keeping with this mechanism of action, we also found that statins attenuated the elevated risk of cancer in patients with copresence of low LDL cholesterol and albuminuria.

Apart from generating new hypotheses for basic scientists to investigate the molecular mechanisms underlying the risk association between cancer and type 2 diabetes, our findings have important clinical implications: 1) because the risk association of cancer with low LDL cho-

lesterol is dependent on albuminuria, it is plausible that measures that reduce albuminuria, such as control of hyperglycemia and hypertension, may reduce cancer risk in type 2 diabetes; 2) albuminuria can be used to stratify cancer risk in patients with low LDL cholesterol; and 3) use of statins in patients with low LDL cholesterol and albuminuria may reduce cancer risk.

On the other hand, our study has several limitations. First, we used results from a single urine and blood sample collected during a comprehensive assessment to stratify patients by albuminuria status and LDL cholesterol levels. These patients were managed in different clinics and repeat data for LDL cholesterol and albuminuria were not systematically collected. Second, principle discharge diagnoses were used to identify cancer cases and a small number of cancer events might have been missed. Third, the cohort was mainly clinic-based, albeit the overall clinical profile was comparable to many community-based cohorts (11). Fourth, our analysis is a hypothesis-generating exploration and the findings will need replication in independent cohorts.

In conclusion, in a prospective cohort of Chinese patients with type 2 diabetes, we detected a significant biological interaction between low LDL cholesterol and albuminuria for cancer. The association between cancer and copresence of both risk factors was attenuated in the presence of statin treatment. Independent replication and experimental studies are needed to confirm these findings and elucidate the underlying mechanism that will shed light on the prevention of cancer in type 2 diabetes.

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