Low HDL Cholesterol, Metformin Use, and Cancer Risk in Type 2 Diabetes

The Hong Kong Diabetes Registry

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OBJECTIVE—The AMP-activated protein kinase (AMPK) pathway is a master regulator in energy metabolism and may be related to cancer. In type 2 diabetes, low HDL cholesterol predicts cancer, whereas metformin usage is associated with reduced cancer risk. Both metformin and apolipoprotein A1 activate the AMPK signaling pathway. We hypothesize that the anticancer effects of metformin may be particularly evident in type 2 diabetic patients with low HDL cholesterol.

RESEARCH DESIGN AND METHODS—In a consecutive cohort of 2,658 Chinese type 2 diabetic patients enrolled in the study between 1996 and 2005, who were free of cancer and not using metformin at enrollment or during 2.5 years before enrollment and who were followed until 2005, we measured biological interactions for cancer risk using relative excess risk as a result of interaction (RERI) and attributable proportion (AP) as a result of interaction. A statistically significant RERI >0 or AP >0 indicates biological interaction.

RESULTS—During 13,808 person-years of follow-up (median 5.51 years), 129 patients developed cancer. HDL cholesterol <1.0 mmol/L was associated with increased cancer risk among those who did not use metformin, but the association was not significant among those who did. Use of metformin was associated with reduced cancer risk in patients with HDL cholesterol <1.0 mmol/L and, to a lesser extent, in patients with HDL cholesterol ≥1.0 mmol/L. HDL cholesterol <1.0 mmol/L plus nonuse of metformin was associated with an adjusted hazard ratio of 5.75 (95% CI 3.03–10.90) compared with HDL cholesterol ≥1.0 mmol/L plus use of metformin, with a significant interaction (AP 0.44 [95% CI 0.11–0.78]).

CONCLUSIONS—The anticancer effect of metformin was most evident in type 2 diabetic patients with low HDL cholesterol.

Patients with type 2 diabetes have increased cancer risk, although the risk association of cancer with antidiabetes drugs remains controversial (1). This is in part attributed to heterogeneity in causalities, phenotypes, and treatment responses. In addition to age and smoking status, abnormal lipids are strong predictors of cancer in type 2 diabetes (2). Our group has reported a V-shaped risk association of HDL cholesterol with cancer, with an optimal level of 1.22 mmol/L and a rapid increase above and below the optimal point (2). Low HDL cholesterol is a common feature of type 2 diabetes (3) and obesity, the latter often considered a linking factor for cancer risk because of insulin resistance (4). However, apolipoprotein (Apo) A-1, the main lipoprotein of HDL cholesterol, also can stimulate the phosphorylation of AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC) to increase glucose uptake in muscle (5) and insulin sensitivity. In this light, the AMPK pathway is considered to be a master switch in sensing and regulating energy metabolism by balancing catabolism (lipolysis) and anabolism (protein and glycogen storage) (6). A large number of factors can activate or inhibit the AMPK signaling pathway, and one of these is the upstream signal, LKB1, a tumor suppressor. In experimental studies, inhibition of the LKB1-AMPK pathway results in tumor formation (7), whereas metformin activates the LKB1-AMPK pathway and inhibits cancer cell growth (8). In support of these findings, epidemiological studies have reported reduced cancer risk (9) and associated mortality (10) in type 2 diabetic patients treated with metformin compared with other antidiabetes drugs. This study argued that the anticancer effects of metformin, if any, would be most evident in patients with low HDL cholesterol.

RESEARCH DESIGN AND METHODS—We selected a prospective cohort from the Hong Kong Diabetes Registry enrolled between 1 December 1996 and 8 January 2005 because drug dispensary data became fully computerized and available for analysis purposes in 1996. A detailed description of the Hong Kong Diabetes Registry is available elsewhere (11–13). Briefly, the registry was established at the Prince of Wales Hospital, the teaching hospital of the Chinese University of Hong Kong, which serves a population of >1.2 million. The referral sources of the cohort included general practitioners, community clinics, other specialty clinics, the Prince of Wales Hospital, and other hospitals. Enrolled patients with hospital admissions within 6–8 weeks prior to assessment accounted for <10% of all referrals. A 4-h assessment of complications and risk factors...
was performed on an outpatient basis, modified from the European DiabCare protocol (14). Once a patient had undergone this comprehensive assessment, he/she was considered to have entered this study cohort and would be followed until the time of death. Ethical approval was obtained from the Chinese University of Hong Kong Clinical Research Ethics Committee. This study adhered to the Declaration of Helsinki, and written informed consent was obtained from all patients at the time of assessment, for research purposes.

By 2005, 7,387 diabetic patients were enrolled in the registry since December 1996. We sequentially included 1) 328 patients with type 1 diabetes or missing data on types of diabetes; 2) 45 patients with non-Chinese or unknown nationality; 3) 175 patients with a known history of cancer or receiving cancer treatment at enrollment; 4) 736 patients with missing values on any variables used in the analysis (see Table 1 for a list of variables); and 5) 3,445 patients who used metformin during 2.5 years before enrollment. The remaining 2,658 patients were included in the analysis. The cutoff point of 2.5 years was chosen because any duration longer than that did not lead to any noticeable changes in the hazard ratios (HRs) and 95% CIs of metformin use for cancer (Supplementary Table 1).

### Clinical measurements and data retrieval

Patients attended the center after an 8-h fast and underwent a 4-h structured clinical assessment that included laboratory investigations. A sterile, random-spot urinary sample was collected to measure albumin-to-creatinine ratio (ACR). In this study, albuminuria was de-identified from the Chinese University of Hong Kong Clinical Research Ethics Committee. This study adhered to the Declaration of Helsinki, and written informed consent was obtained from all patients at the time of assessment, for research purposes.

Data on types of diabetes; patients with type 1 diabetes or missing data on types of diabetes; 2) 45 patients with non-Chinese or unknown nationality; 3) 175 patients with a known history of cancer or receiving cancer treatment at enrollment; 4) 736 patients with missing values on any variables used in the analysis (see Table 1 for a list of variables); and 5) 3,445 patients who used metformin during 2.5 years before enrollment. The remaining 2,658 patients were included in the analysis. The cutoff point of 2.5 years was chosen because any duration longer than that did not lead to any noticeable changes in the hazard ratios (HRs) and 95% CIs of metformin use for cancer (Supplementary Table 1).

### Table 1—Clinical and biochemical characteristics of the study cohort stratified according to occurrence of cancer during follow-up period

| Event | Noncancer (n = 2,529) | Cancer (n = 129) | P |
|-------|----------------------|-----------------|---|
| Age (years) | 55 (44–66) | 64 (55–72) | <0.0001* |
| Male sex | 1,236 (48.9) | 71 (55.0) | 0.1718† |
| Employment status | | | |
| Full-time | 926 (36.6) | 29 (22.5) | <0.0001† |
| Housewife | 699 (27.6) | 36 (27.9) | |
| Retired | 654 (25.9) | 58 (50.0) | |
| Other | 250 (9.9) | 6 (4.7) | |
| Smoking status | | | |
| Ex-smoker | 365 (14.4) | 26 (20.2) | |
| Current smoker | 390 (15.4) | 30 (23.3) | |
| Alcohol intake | | | |
| Ex-drinker | 298 (11.8) | 28 (21.7) | |
| Current drinker | 198 (7.8) | 7 (5.4) | |
| BMI (kg/m²) | 24.3 (22.0–26.5) | 23.9 (22.2–26.4) | 0.6937* |
| Duration of diabetes (years) | 4 (1–9) | 5 (2–12) | 0.0180* |
| SBP (mmHg) | 132 (120–146) | 134 (125–148) | 0.0827* |
| Diastolic blood pressure (mmHg) | 75 (68–82) | 75 (67–82) | 0.9706* |
| A1C (%) | 6.9 (6.1–8.2) | 7.2 (6.1–8.6) | 0.2575* |
| LDL cholesterol (mmol/L) | 3.20 (2.60–3.80) | 3.20 (2.90–3.74) | 0.0154* |
| HDL cholesterol (mmol/L) | 1.26 (1.07–1.52) | 1.25 (0.99–1.53) | 0.3760* |
| HDL cholesterol <1.0 mmol/L | 398 (15.7) | 35 (27.1) | 0.0006 |
| Triglycerides (mmol/L) | 1.26 (0.9–1.86) | 1.16 (0.84–1.66) | 0.0700* |
| ACR (mg/mmol) | 1.54 (0.67–8.54) | 3.07 (0.93–11.04) | 0.0063* |
| Albuminuria | 968 (38.3) | 64 (49.6) | 0.0100+ |
| Estimate GFR (ml/min per 1.73 m²) | 105.5 (84.0–127.7) | 99.8 (81.6–118.8) | 0.1047+ |
| Duration of metformin use (years) | 3.09 (1.21–5.65) | 1.21 (0.57–3.57) | 0.0008* |
| Mean daily metformin dosage (g) | 1.01 (0.82–1.56) | 1.05 (0.64–1.42) | 0.1981* |
| Pioglitazone | 19 (0.8) | 0 (0) | 1.0+ |
| Rosiglitazone | 72 (2.8) | 1 (0.9) | 0.2618+ |
| Metformin | 1,226 (48.5) | 40 (31.0) | <0.0001† |
| Follow-up time (years) | 5.70 (3.23–7.44) | 2.52 (1.09–4.51) | <0.0001† |

Data are median (25th to 75th percentile) or n (%). *Derived from Wilcoxon two-sample test. †Derived from χ² test. ‡Derived from Fisher exact test. $From enrollment to the earliest date of cancer, death, or censoring. \*Among metformin users only.

## Friedewald equation

(T16). The precision performance of these assays was within the manufacturer’s specifications.

Drug usage data were extracted from the Hong Kong Hospital Authority Central Computer System, which recorded all drug dispensary data in public hospitals, including the start dates and end dates for each of the drugs of interest. In Hong Kong, 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.

A trained team at the Hong Kong Hospital Authority coded all hospital admissions. All medical admissions of the cohort from enrollment to 30 July 2005 were retrieved from the Hong Kong Hospital Authority Central Computer System, which recorded admissions to all public hospitals in Hong Kong. Collectively, these hospitals provide 95% of the total hospital bed-days in Hong Kong (17). Additionally, mortality data from the Hong Kong Death Registry during the period were retrieved and cross-checked with hospital discharge status.

Hospital discharge principle diagnoses, coded by the International Statistical Classification of Diseases and Related Health Problems 9th Revision (ICD-9), were used to identify cancer events. The outcome measure of this study was incident cancer (fatal or nonfatal; codes 140–208) during the follow-up period.

Statistical analyses
We used biological interactions to test whether metformin use was associated with a greater cancer risk reduction in patients with low HDL cholesterol than in those with normal or high HDL cholesterol. The Statistical Analysis System (release 9.10) was used to perform the statistical analysis (SAS Institute, Cary, NC), unless otherwise specified. Follow-up time was calculated as the period in years from the first enrollment since 1 December 1996 to the date of the first cancer event, death, or censoring, whichever came first. Cox proportional hazard regression was used to obtain the HRs and 95% CIs of the variables of interest.

We first plotted the full-range association of HDL cholesterol and cancer and further refined cutoff points of HDL cholesterol for cancer risk in the cohort without prevalent metformin users, using restricted cubic spline Cox models (11). Then, we examined the biological interaction for cancer risk between low HDL cholesterol and nonuse of metformin using three measures: 1) relative excess risk caused by interaction (RERI); 2) attributable proportion (AP) caused by interaction; and 3) the synergy index (S) (18). A detailed calculation method of additive interaction, including the definition of three indicator variables, an SAS program, and a calculator in Microsoft Excel (www.epinet.se), was described by the authors. The RERI is the excess risk attributed to interaction relative to the risk without exposure. AP refers to the attributable proportion of disease, which is caused by the interaction in subjects with both exposures. S is the excess risk from both exposures when there is biological interaction relative to the risk from both exposures without interaction. A simulation study showed that REPI performed best and AP performed fairly well, but S was problematic in the measure of additivity in the proportional hazard model (19). The current study refined the criteria as either a statistically significant REPI >0 or AP >0 to indicate biological interactions.

The following two-step adjustment scheme was used in these analyses: 1) only adjusting for LDL cholesterol-related cancer risk indicators (LDL cholesterol ≥3.80 mmol/L and LDL cholesterol <2.80 mmol/L plus albuminuria) (11,12), triglycerides (2), and high HDL cholesterol, where appropriate (2), and 2) further adjusting for age, sex, employment status, smoking status, alcohol intake, duration of diabetes, BMI (≥27.6 and <24.0 kg/m²) (2), systolic blood pressure (SBP), and A1C (20) at enrollment and use of statins (13), fibrates, other lipid-lowering drugs, ACE inhibitors/angiotensin II receptor blockers (ARBs) (13), and insulin (20) during follow-up. Use of drugs during follow-up was defined as use of the drugs from enrollment to cancer, death, or censoring date, whichever came first. By definition, the use of any drugs after the first cancer event was coded as nonuse of these drugs, and any drug users had been given at least one prescription of the drug during follow-up. The total metformin dosage divided by the total number of days during which metformin was prescribed was used as daily metformin dosage. We also used propensity score to adjust for the likelihood of metformin use.

Sensitivity analyses were performed to address 1) the impacts of undiagnosed cancer by limiting the analysis to patients who were followed for ≥2.5 years (n = 2170); 2) the impact of incomplete exclusion of patients who used metformin during 2.5 years before enrollment by limiting the analysis to patients who were enrolled on or after 1 July 1998 (n = 1707); 3) the impact of prevalent bias by reinclusion of 3,445 patients who used metformin during 2.5 years before enrollment; and 4) inclusion of subjects with missing values in univariable analysis and without adjusting for the propensity score to maximize the valid sample size (n of the valid sample size = 2,996 and n of the sample size with missing values in HDL cholesterol = 53 [i.e., 1.74% missing-value rate]).

RESULTS
Characteristics of the patients
The median age of the cohort was 56 years (25th to 75th percentiles [interquartile range [IQR] 45–67]) at enrollment. During 13,808 person-years of follow-up (5.51 years [3.08–7.39]), 129 patients developed cancer. In the cohort, 16.3% (n = 433) of patients had low HDL cholesterol <1.0 mmol/L and 46.7% (n = 1,243) had HDL cholesterol ≥1.30 mmol/L. Patients with low HDL cholesterol were more likely to use insulin, develop cancer, and die prematurely. Patients who developed cancer were older, more likely to use tobacco and alcohol, and had longer disease duration. They had high LDL cholesterol, low HDL cholesterol, and albuminuria and were more likely to have premature death than those free of cancer. Patients who developed cancer were less likely to use statins and metformin during the follow-up period than patients without cancer (Table 1).

HDL cholesterol and cancer
Compared with patients with HDL cholesterol ≥1.0 but <1.3 mmol/L, patients with HDL cholesterol <1.0 mmol/L (HR 2.22 [95% CI 1.38–3.58]) and those with HDL cholesterol ≥1.3 mmol/L (1.61 [1.05–2.46]) had increased cancer risk in univariable analysis. After adjusting for other covariates (Supplementary Fig. 1), HDL cholesterol <1.0 mmol/L for cancer remained significant (2.41 [1.46–3.96]) but not HDL cholesterol ≥1.3 mmol/L (P = 0.1197). Additional subgroup univariable and multivariable analyses indicate that low HDL cholesterol
was associated with increased cancer risk only among those who did not use metformin but not among those who did (power = 0.37) (Table 2).

**Use of metformin and cancer**

Use of metformin was associated with a decreased risk of cancer in a dose-response manner. After adjusting for covariates, patients with HDL cholesterol <1.0 mmol/L and who were not treated with metformin had a 5.8-fold risk of cancer compared with the referent group, who had HDL cholesterol ≥1.0 and used metformin. Patients with HDL cholesterol ≥1.0 mmol/L but who were not treated with metformin also had higher cancer risk than the referent group. However, the cancer risk associated with HDL cholesterol <1.0 mmol/L was rendered non-significant among those who used metformin (Table 2 and Supplementary Table 2). There was a significant interaction between low HDL cholesterol and nonuse of metformin for cancer risk, after adjusting for covariates (AP 0.44 [95% CI 0.11–0.78]) (Table 3).

**Sensitivity analyses**

The series of sensitivity analyses showed a consistent trend toward an interactive effect of nonuse of metformin and HDL cholesterol <1.0 mmol/L on the risk of cancer, although not all interactions in these sensitivity analyses reached statistical significance (Supplementary Tables 2 and 3).

**CONCLUSIONS**—In this study, we observed that HDL cholesterol <1.0 mmol/L and nonuse of metformin was associated with a 5.8-fold cancer risk compared with metformin users with HDL cholesterol ≥1.0 mmol/L. The significant additive interaction indicates that the increased cancer risk as a result of a combination of nonuse of metformin and HDL cholesterol <1.0 mmol/L was more than the addition of the risks attributed to the presence of either nonuse of metformin or low HDL cholesterol alone. In other words, the significant interaction suggests that the use of metformin may confer an extra cancer benefit in type 2 diabetic patients with low HDL cholesterol.

Although there are ongoing debates about the associations between insulin usage and cancer in diabetes, epidemiological studies have consistently found that the use of metformin is associated with reduced cancer risk. Among these studies, Libby et al. (9) reported that metformin use was associated with a 54% (95% CI 47–60) lower crude incidence and a 37% (25–47) lower adjusted incidence of cancer than metformin nonusers over a period of 10 years. In support of these findings, we also found a 50% lower adjusted cancer risk among metformin users with HDL cholesterol ≥1.0 mmol/L and a 72% lower adjusted risk among metformin users with HDL cholesterol <1.0 mmol/L.

Several lines of evidence support the pivotal role of AMPK, which can be...
ApoA-I gene transcription, which is the major lipoprotein component of HDL lipid particles (23). In this regard, ApoA-I has been shown to stimulate phosphorylation of AMPK and ACC (5). More recently, Kimura et al. (24) reported that HDL can activate AMPK through binding to both sphingosine 1-phosphate receptors/Gi proteins and scavenger receptor class B type I (SR-BI)/protein PDZK1, with LKB1 being involved in the SR-BI signaling. Given the close relationship between HDL cholesterol and the AMPK pathway, the interactive effects of metformin use and HDL cholesterol on cancer risk is thus plausible.

Several limitations in the study have been noticed. 1) A single measurement of triglyceride with cancer.

| Table 3—Measures for estimation of biological interaction between low HDL cholesterol and nonuse of metformin for the risk of cancer in type 2 diabetes |
|-------------------------------------------------|-----------------|-----------------|
| Measures of biological interaction | Estimate (95% CI) | P |
| Between HDL cholesterol <1.0 mmol/L and nonuse of metformin | | |
| Model 1**‡ | | |
| RERI | 3.00 (–0.14 to 6.14) | 0.0611 |
| AP | 0.49 (0.18–0.79)‡ | 0.0017 |
| S | 2.38 (1.07–5.28) | 0.1091 |
| Model 2**‡‡ | | |
| RERI | 2.55 (–0.49 to 5.60) | 0.0999 |
| AP | 0.44 (0.11–0.78)‡ | 0.0105 |
| S | 2.17 (0.94–4.99) | 0.1331 |

*Adjusted for LDL cholesterol-related risk indicators (LDL cholesterol ≥3.8 mmol/L and LDL cholesterol <2.8 mmol/L plus albuminuria), HDL cholesterol ≥1.30 mmol/L, and the nonlinear association of triglyceride with cancer. ‡Further adjusted for age, sex, employment status, smoking status, alcohol intake, duration of diabetes, BMI (≥27.6 or <24 0 kg/m²), AIC, and systolic blood pressure at enrollment and use of statins, fibrates, other lipid-lowering drugs, ACE inhibitors/ARBs, and insulin during follow-up. ‡‡Stratified Cox model analyses on deciles of the propensity score of use of metformin were used to control for likelihood of starting metformin therapy during follow-up.

| Table 4—HRs of the copresence of HDL cholesterol <1.0 mmol/L and nonuse of metformin during follow-up versus all other groups for site-specific cancers and fatal and nonfatal cancers |
|-------------------------------------------------|-----------------|-----------------|
| Cancer subtypes | Number of cancers | HR (95% CI)* | P |
| 1) Lip, oral cavity, and pharynx | 6 | 4.06 (2.39–6.89) | <0.0001 |
| 2) Respiratory and intrathoracic organs | 16 | 2.31 (1.17–4.54) | 0.0153 |
| 3) Genitourinary organs | 16 | 3.42 (1.80–6.49) | 0.0002 |
| 4) Lymphatic and hematopoietic tissue | 19 | 2.70 (1.67–4.37) | <0.0001 |
| 5) Bone, connective tissue, skin, and breast | 7 | | |
| 6) Other and unspecified sites | 19 | | |
| Cancer at sites other than digestive organs and peritoneum (1–6 combined) | 77 | 4.06 (2.39–6.89) | <0.0001 |
| 7) Digestive organs and peritoneum | 65 | 2.31 (1.17–4.54) | 0.0153 |
| Fatal and nonfatal cancers | | | |
| Fatal cancer | 56 | 3.42 (1.80–6.49) | 0.0002 |
| Nonfatal cancer | 119 | 2.70 (1.67–4.37) | <0.0001 |

*Univariable Cox models with stratification on deciles of the propensity score of use of metformin during follow-up were used to obtain the HRs. †Classification was based on the ICD-9 (there are overlaps among site-specific cancers). ‡‡Nonfatal cancer events developed before fatal cancer.

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