Associations of Hyperglycemia and Insulin Usage With the Risk of Cancer in Type 2 Diabetes: The Hong Kong Diabetes Registry

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OBJECTIVE—Insulin has mitogenic effects, although hyperglycemia may be a risk factor for cancer in type 2 diabetes. It remains uncertain whether use of insulin increases cancer risk because of its effect on cell growth and proliferation or decreases cancer risk because of its glucose-lowering effect.

RESEARCH DESIGN AND METHODS—A 1:2-matched new insulin user cohort on age (±3 years), smoking status, and likelihood of initiating insulin therapy (±0.05) was selected from a cohort of 4,623 Chinese patients with type 2 diabetes, free of cancer, and naive to insulin at enrollment. Stratified Cox regression analysis on the matched pairs was used to obtain hazard ratios (HRs) of insulin therapy and A1C for cancer risk. A structured adjustment scheme was used to adjust for covariates.

RESULTS—Of 973 new insulin users, 971 had matched nonusers ($n = 1935$). The cancer incidence in insulin nonusers was much higher than that in insulin users (49.2 vs. 10.2, per 1,000 person-years, $P < 0.0001$). After further adjustment for all other covariates with a P value less than 0.3 and nonlinear associations with cancer, A1C was associated with an increased cancer risk (HR per percentage 1.26, 95% CI 1.03–1.55), whereas use of insulin was associated with a decreased cancer risk (HR of insulin users vs. nonusers: 0.17, 0.09–0.32). Consistent results were found in analyses including all 973 insulin users and 3,650 nonusers.

CONCLUSIONS—In Chinese patients with type 2 diabetes, hyperglycemia predicts cancer, whereas insulin usage was associated with a reduced cancer risk. ***Diabetes*** **59:1254–1260, 2010**

Insulin has mitogenic effects and is a stimulator and regulator of growth and proliferation of a variety of somatic cells (1). It is suggested that insulin resistance and hyperinsulinemia may be important risk factors for cancer (2–4). Recently, heated debates followed the publication of a series of observational studies that examined associations between use of insulin, in particular insulin glargine, and cancer (5–8), accompanied by an editorial (9). On the other hand, a randomized controlled trial of 1,017 patients followed for more than 4 years (1,524 days in the insulin glargine group and 1,522 days in the neutral protamine Hagedorn insulin group) reported that the insulin glargine group had numerically lower risks of all neoplasms (relative risk: 0.9, 95% CI 0.64–1.26) and all malignant neoplasms (relative risk 0.63, 95% CI 0.36–1.09) than the neutral protamine Hagedorn insulin group (10). Garg et al. (11) reviewed these studies and concluded that none of these observational studies found an overall increased cancer risk with insulin glargine.

Two studies have reported that hyperglycemia is associated with increased risks of colorectal cancer or non–specific site cancer (12,13). Our group reported that abnormal lipids that may stem from hyperglycemia (14) were predictive of cancer in type 2 diabetes (15,16). It has been established that there is cross talk between lipid biosynthesis and renin-angiotensin system (RAS) in atherosclerosis (17), which may be mediated by increased oxidative stress (18). Our group further reported that the cross talk may be associated with increased risk of cancer in type 2 diabetes via increased activity of hydroxymethylglutaryl-CoA reductase (HGMCR) and insulin-like growth factor-I (IGF-I) pathways (19). It is also proven that hyperglycemia has a potent but reversible effect on LDL oxidation (20). Thus, if tight control of hyperglycemia can improve lipid metabolism, attenuate RAS activity, and reduce oxidative stress, it is plausible that use of insulin may reduce risk of cancer in type 2 diabetes by lowering blood glucose.

Based on this premise, we argue that use of insulin in type 2 diabetes would have dual effects: increasing cancer risk because of its effect on cell growth and proliferation and decreasing cancer risk because of improved internal milieu. To test the overall effects of use of insulin on cancer in Chinese patients with type 2 diabetes, we explored associations among insulin use, hyperglycemia, and incident cancer using the Hong Kong Diabetes Registry.

RESEARCH DESIGN AND METHODS

Patients. The Hong Kong Diabetes Registry 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 more than 1.2 million. The referral sources of the cohort included general practitioners, community clinics, other specialty clinics, the Prince of Wales Hospital itself, and other hospitals. Enrolled patients with hospital admissions within 6–8 weeks prior to assessment accounted for less than 10% of all referrals. The methods for recruitment and clinical measurements have been described in the previous analysis (15). A 4-h assessment of complications and risk factors was performed on an outpatient basis, modified from the European DiabCare

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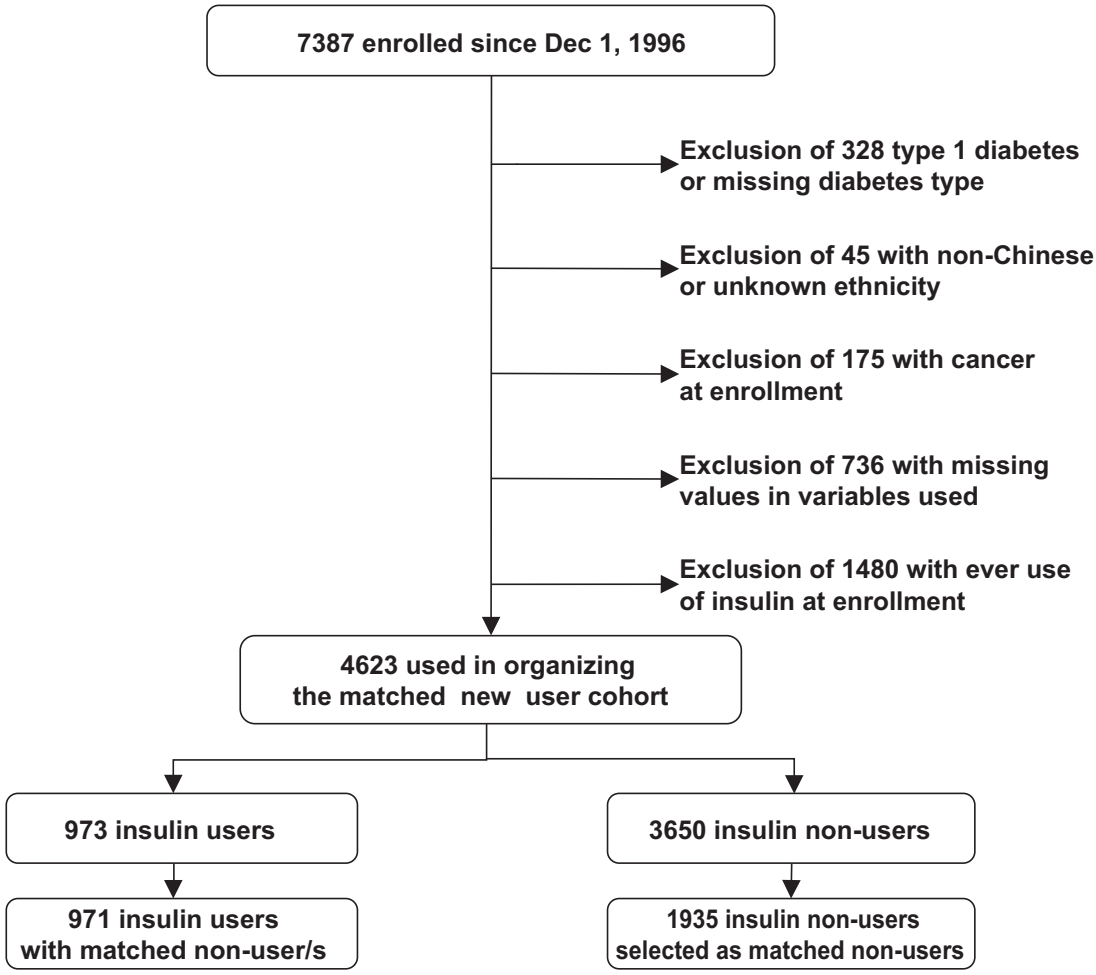

FIG. 1. Patient flow chart. Adjusted for use of insulin during follow-up period, and covariates as listed in the adjustment scheme of model 3 in Table 3 plus matching criteria (i.e., age, smoking status, and probability of using insulin during follow-up period).

protocol (21). 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. 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 the patients, at the time of assessment, for data analysis and research purposes.

Hong Kong has a highly subsidized health care system. The Hospital Authority is the governing body of all publicly funded hospitals and outpatient clinics. The public hospitals provide 95% of the total hospital bed–days and 80% of the outpatient visits, especially for patients with chronic and serious diseases, because of the noncompulsory nature of medical insurance in Hong Kong (22). In this analysis, the clinical end points, including discharge diagnoses and mortality from enrollment to 30 July 2005, were recorded or otherwise censored on 30 July 2005. Details of all medical admissions of the cohort by that date were retrieved from the Hong Kong Hospital Authority Central Computer System, which recorded admissions to all public hospitals (23). Mortality data from the Hong Kong Death Registry were also retrieved and cross-checked with hospital discharge status (22). In Hong Kong, all medications are dispensed on site in both inpatient and outpatient settings. Drug use data were extracted from the Hospital Authority computer system that recorded drug dispensary data in all public hospitals including the start dates and end dates for each of the major drugs. The databases were matched by a unique identification number, the Hong Kong Identity Card number, which is compulsory for all residents in Hong Kong.

Drug prescription data have been computerized since 1 December 1996. From that date to 8 January 2005, 7,387 diabetic patients were enrolled in the registry. We sequentially excluded 328 patients with type 1 diabetes or missing data on type of diabetes, 45 with non-Chinese or unknown nationality, 175 with a known history of cancer or who were receiving cancer treatment at enrollment, 736 with missing values on any variables used in the analysis (see Table 2 for the list of variables), and 1,480 who had used insulin before enrollment. In the remaining 4,623 patients, we created a new-user subcohort (n = 2,906) followed by sensitivity analysis in the original cohort (Fig. 1).

Study design. Prevalent users can contribute to two types of bias: *1*) insufficient ascertainment of clinically silent events that may occur early in therapy and *2*) the inability to control for disease risk factors that may have been altered by the study drugs under research (24). Thus, prevalent user bias is considered to be one of the major contributing factors that results in the discrepancies between observational studies and clinical trials (24). New-user designs are developed to eliminate both biases by restricting the analysis to people under observation at the start of the current course of treatment (24).

In this study, we used a new-user cohort study design with one insulin user matched to two nonuser subjects on *1*) age (±3 years); *2*) smoking status (current and former); and *3*) likelihood of initiating insulin therapy after enrollment (the likelihood of initiating insulin therapy in the nonusers was within the likelihood in the users ± 0.05). In the new-user cohort, follow-up in insulin users commenced at the time of initiation of insulin therapy, for example, 2 years after enrollment in the registry (24). To ensure comparability of these variables in the user and nonusers in each matched pair, the follow-up in the matched insulin nonusers also started at the same time after the enrollment as that of the case subject, that is, 2 years using the above example. To ensure that the matched nonusers had adequate follow-up period for comparison with the case subject, the time period of the nonusers from enrollment to the earliest date of cancer, death, or censoring times must be longer than the period of the matched user from enrollment to the date of initiating insulin therapy. For example, an insulin user started insulin 2 years after enrollment and then developed cancer 5 years after starting insulin therapy. A matched nonuser of the user developed cancer 6 years after enrollment. Thus, the user had 5 years of follow-up, whereas the nonuser had 4 years of follow-up in the new-user cohort. Any nonusers who died, developed cancer, or were censored within 2 years of enrollment were not eligible to be a matched nonuser of the user.

The likelihood of initiating insulin therapy was calculated using a logistic

regression procedure in the whole cohort with initiation of insulin therapy as the dependent variable. A forward stepwise algorithm ($P = 0.30$ for inclusion and removal) was used to select a group of predictors among age, sex, BMI, LDL cholesterol, HDL cholesterol, triglyceride, smoking status, alcohol intake, HbA_{1c} (A1C), systolic blood pressure, Ln (spot urinary albumin-to-creatinine ratio [ACR]+1), estimated glomerular filtration rate (eGFR), duration of diabetes, peripheral arterial disease, retinopathy, sensory neuropathy, prior myocardial infarction, and prior stroke at enrollment. Age, smoking status, duration of diabetes, A1C, HDL cholesterol, Ln (ACR+1), and retinopathy were selected for the predicting model (C statistic = 0.79 and P for Hosmer and Lemeshow test = 0.8288). The follow-up time in the new-user cohort was calculated as the period in years from the date of initiation of insulin therapy to the earliest date of cancer, death, or censoring. The follow-up time of the nonusers was calculated as the difference between the follow-up time of the nonuser in the original cohort design and the time period from enrollment to the date of starting insulin of the corresponding user.

The 1:2-matched insulin new-user cohort has the following features: *1*) without prevalent users; *2*) follow-up started at the time of initiation of insulin therapy; *3*) "baseline" characteristics in new users and matched nonusers in a matched pair were comparable (i.e., measured at the same time away from the starting time point of follow-up); and *4*) a new user and its matched nonusers in each matched pair had similar age, smoking status, and likelihood to initiate insulin therapy.

Clinical and laboratory measurements. Details of assessment methods and definitions of end points have been described elsewhere (15). In essence, on the visit day, patients attended the center after 8 h of fasting to undergo clinical assessments and laboratory investigations. Apart from documentation of demographic data and clinical assessment of complications, fasting blood samples were taken for measurement of plasma glucose, A1C, lipid profile (total cholesterol, HDL cholesterol and triglyceride, calculated LDL cholesterol), and renal function. A sterile, random spot urine sample was used to measure 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 (25) was used to estimate eGFR expressed in $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$: $eGFR = 186 \times (SCR \times 0.011)^{-1.154} \times (age)^{-0.203} \times (0.742$ if female$) \times 1.233$, where SCR is serum creatinine expressed as μmol/l (original mg/dl converted to μmol/l) and 1.233 is the adjusting coefficient for Chinese. Lipids (total cholesterol, triglyceride, and HDL cholesterol) were measured by enzymatic methods on a Hitachi 911 automated analyzer (Boehringer Mannheim, Mannheim, Germany) using reagent kits supplied by the manufacturer of the analyzer. LDL cholesterol was calculated using Friedewald equation (26). The precision performance of these assays was within the manufacturer's specifications.

Definition of cancer. A trained team of personnel of the Hospital Authority routinely coded all the hospital discharge principal diagnoses including cancer and noncancer hospital admissions according to the International Classification of Diseases, Ninth Revision (ICD-9). Hospital discharge principal diagnoses, coded by ICD-9, were used to identify cancer events. The end point of this study was defined as having first incident cancer during follow-up (regardless of whether it was fatal or nonfatal; codes 140–208).

Statistical analyses. The SAS (Release 9.10) was used to perform the statistical analysis (SAS Institute, Cary, NC). The propensity score was calculated in the original cohort and automatically exported to a new SAS dataset. Then, matching was performed using SAS programming. After the matched new-user cohort dataset was generated, we performed stratified Cox proportional hazard regression analysis on the matched pairs to obtain hazard ratios (HRs) of initiation of insulin therapy and A1C for incident cancer.

A structured adjustment scheme was used to adjust for covariates. First, we obtained HR of use of insulin and A1C without adjusting for other covariates. Because we have previously reported the nonlinear risk associations of cancer with LDL cholesterol at values <2.8 mmol/l and ≥3.8 mmol/l, which were further modified by other parameters (27), we secondly adjusted for covariates with $P < 0.30$ selected by the stepwise algorithm among these cancer-associated LDL cholesterol–related risk interaction terms (indicator terms for LDL cholesterol <2.8 mmol/l plus albuminuria and ≥3.8 mmol/l) (27): sex, duration of diabetes, alcohol intake (current and former), HDL cholesterol, triglyceride, systolic blood pressure, eGFR, Ln (ACR+1), use of antihypertensive drugs at enrollment, and use of ACE inhibitors or angiotensin II receptor blockers, statins, fibrates, and oral antidiabetic drugs (Table 1) from enrollment to cancer, death, or censoring dates, whichever came first. Third, restricted cubic spline was used in the stratified Cox model to adjust for nonlinear associations of covariates with cancer as previously reported (16). The curve of HR versus A1C was calculated using restricted cubic spline (28) as previously reported (15,29). In addition, a life table method (Statistical Package for the Social Sciences for Windows, Release 13.0; SPSS, Chicago, IL) was used to examine the differences in the cumulative incidences of cancer and death over time.

Correlations between pairs of baseline covariates were checked using the Pearson correlation test and none of the pairs was highly correlated (correlation coefficient <0.60). Proportional hazards were checked. A two-sided $P < 0.05$ was considered significant.

RESULTS

Characteristics of the original cohort. At enrollment, the median age of the cohort ($n = 4,623$) was 57 (25th-75th percentiles: 47–67) years with a median duration of diabetes of 5 (1–10) years. The median period from enrollment to the earliest date of cancer, death, or censoring was 5.11 (2.86–7.15) years. Cancer incidence was lower in insulin users than nonusers (5.8 per 1,000 person-years vs. 9.7 per 1,000, $P = 0.0082$) but death incidence was higher in insulin users than nonusers (24.0 vs. 9.6, $P < 0.0001$). The comparison of other variables, including drug use, is available in Table 1.

Characteristics of the new insulin user cohort. Of 973 patients who were started on insulin therapy, 971 had at least one matched nonuser (964 had two matched nonusers and seven had only one matched nonuser). Despite this careful matching, there were still significant differences in age, smoking status, and clinical and biochemical characteristics between insulin nonusers and users, albeit smaller than those in the original cohort. Compared with noninsulin users, insulin users had longer duration of diabetes, higher A1C, and worse lipid profile (higher LDL cholesterol, higher triglyceride, and lower HDL cholesterol), and were more likely to have albuminuria and renal dysfunction. Insulin users were also more likely to be treated with ACE inhibitors/angiotensin II receptor blockers, statins, and oral antidiabetic drugs (in particular, metformin) than insulin nonusers. The cancer incidence in insulin nonusers was much higher than in insulin users (49.2 per 1,000 person-years vs. 10.2, $P < 0.0001$). On the other hand, death incidence was comparable between insulin nonusers and users ($P = 0.8307$; Table 1).

Use of insulin and A1C for the risk of cancer. In the new-user cohort, A1C was marginally associated with an increased risk of cancer after adjusting for use of insulin, age, smoking status, and likelihood of use of insulin ($P = 0.0747$). After further adjusting for all other covariates with a $P < 0.3$ (HDL cholesterol, triglyceride, eGFR, and use of metformin), A1C per percentage was associated with a 1.24-fold increase in the risk of cancer (95% CI 1.03–1.49, $P = 0.0267$). The HR increased to 1.26 (95% CI 1.03–1.55, $P = 0.0230$) after adjusting for nonlinear associations of covariates.

Use of insulin was consistently associated with decreased risks of cancer after adjusting for A1C, age, smoking status, and likelihood of use of insulin. After further adjusting for HDL cholesterol, triglyceride, eGFR, and use of metformin as well as taking nonlinear associations of covariates with cancer into consideration, the multivariable HR was 0.17 (95% CI 0.09–0.32, $P < 0.0001$). On the other hand, use of insulin was not associated with death in the three adjusting models (Table 2). The cumulative incidence of cancer was markedly lower in insulin users than in nonusers, although the cumulative incidence of death was similar in insulin users and nonusers during 7 years of follow-up (Table 3).

For subsite-specific cancers, A1C was marginally associated with a higher risk whereas use of insulin was associated with lower risks of cancers of the digestive system (HR 0.19, 0.08–0.46) and cancers of the nondigestive systems (HR 0.20, 95% CI 0.10–0.41) (Table 4).

TABLE 1
Clinical and biochemical characteristics of the study patients in cohort design and new-user cohort design

Variables at enrollment	Cohort design			New-user cohort design*		
	Insulin nonusers	Insulin users	*P*	Insulin nonusers	Insulin users	*P*
n	3,650	973		1,935	971	
Age (years)	56 (20)	58 (20)	0.0022†	58 (21)	58 (20)	
Smoking status			0.0005‡			
Former	482 (13.2%)	176 (18.1%)		348 (18.0%)	175 (18.0%)	
Current	567 (15.5%)	150 (15.4%)		297 (15.4%)	149 (15.4%)	
Male sex	1,678 (46.0%)	453 (46.6%)	0.7452‡	964 (49.8%)	451 (46.5%)	0.0863‡
Alcohol use			0.0021‡			0.1164‡
Former	385 (10.6%)	140 (14.4%)		257 (13.3%)	139 (14.3%)	
Current	304 (8.3%)	68 (7.0%)		178 (9.2%)	68 (7.0%)	
BMI (kg/m^2)	24.8 (4.8)	24.5 (5.1)	0.0070†	24.9 (4.9)	24.5 (5.1)	0.0014†
Duration of diabetes (years)	4 (8)	8 (8)	<0.0001†	4 (9)	8 (8)	<0.0001†
Systolic blood pressure (mmHg)	133 (25)	136 (29)	0.0004†	135 (26)	136 (29)	0.1787†
Diastolic blood pressure (mmHg)	75 (13)	76 (15)	0.1025†	75 (14)	76 (15)	0.0413†
A1C (%)	6.9 (1.7)	8.1 (2.5)	<0.0001†	7.1 (2.0)	8.1 (2.5)	<0.0001†
LDL cholesterol (mmol/l)	3.10 (1.21)	3.20 (1.2)	0.0004†	3.00 (1.26)	3.20 (1.2)	<0.0001†
HDL cholesterol (mmol/l)	1.27 (0.43)	1.21 (0.46)	<0.0001†	1.26 (0.43)	1.21 (0.46)	0.0002†
Triglyceride (mmol/l)	1.32 (0.96)	1.45 (1.14)	0.0004†	1.40 (0.99)	1.45 (1.14)	0.3057†
Total cholesterol (mmol/l)	5.10 (1.30)	5.20 (1.30)	0.0011†	5.05 (1.40)	5.20 (1.30)	<0.0001†
ACR (mg/mmol)	1.39 (4.44)	5.00 (26.27)	<0.0001†	1.93 (8.76)	4.96 (26.79)	<0.0001†
Microalbuminuria	23.6% (863)	32.2% (313)	<0.0001‡	26.5% (513)	32.0% (311)	<0.0001‡
Macroalbuminuria	9.8% (356)	26.3% (256)		15.3% (296)	26.4% (256)	
eGFR (ml/min^{-1} per 1.73 m^2)	106.2 (36.6)	100.9 (50.3)	<0.0001†	101.2 (38.1)	100.9 (50.3)	0.1342†
<60	4.7% (173)	14.9% (145)	<0.0001‡	7.3% (142)	14.9% (145)	<0.0001‡
Retinopathy	612 (16.8%)	355 (36.5%)	<0.0001‡	454 (23.5%)	354 (36.5%)	<0.0001‡
Prior myocardial infarction	55 (1.5%)	13 (1.3%)	0.6942‡	42 (2.2%)	13 (1.3%)	0.1207‡
Prior stroke	144 (4.0%)	43 (4.4%)	0.5048‡	96 (5.0%)	43 (4.4%)	0.5255‡
Medications at enrollment						
Antihypertensive drugs other than ACEIs/ARBs	1,351 (37.0%)	377 (38.8%)	0.3210‡	828 (42.8%)	375 (38.6%)	0.0313‡
Events and medications after enrollment§						
Cancer during follow-up	169 (4.6%)	32 (3.3%)	0.0683‡	120 (6.3%)	32 (3.3%)	0.0009‡
Follow-up time to cancer, years	4.78 (4.43)	6.04 (3.55)	<0.0001‡	0.70 (1.23)	3.01 (3.51)	<0.0001‡
Incidence of cancer, per 1,000 person-years	9.7 (8.3–11.1)§	5.8 (3.8–7.8)§	0.0082‖	49.2 (40.6–57.8)§	10.2 (6.7–13.7)§	<0.0001‖
Death during follow-up	169 (4.6%)	133 (13.7%)	<0.0001‡	125 (6.5%)	132 (13.6%)	<0.0001‡
Follow-up time to death, years	4.78 (4.43)	6.04 (3.55)	<0.0001‡	0.77 (1.57)	3.09 (3.45)	<0.0001‡
Incidence of death, per 1,000 person-years	9.6 (8.1–11.0)§	24.0 (19.9–28.0)§	<0.0001‖	46.5 (38.5–54.4)§	41.2 (34.3–48.1)§	0.8307‖
ACEIs or ARBs	1,750 (48.0%)	705 (72.5%)	<0.0001‡	1,009 (52.1%)	703 (72.4%)	<0.0001‡
Statins	1,088 (29.8%)	506 (52.1%)	<0.0001‡	605 (31.2%)	506 (52.1%)	<0.0001‡
Fibrates	327 (9.0%)	121 (12.4%)	0.0011‡	163 (8.4%)	120 (12.4%)	0.0007‡
Acarbose	287 (7.9%)	269 (27.7%)	<0.0001‡	177 (9.2%)	269 (27.7%)	<0.0001‡
Glibenclimide	1,046 (28.7%)	396 (40.7%)	<0.0001‡	482 (24.9%)	395 (40.7%)	<0.0001‡
Gliclazide	1,692 (46.4%)	603 (62.0%)	<0.0001‡	956 (50.1%)	602 (62.0%)	<0.0001‡
Glimepiride	38 (1.0%)	33 (3.4%)	<0.0001‡	24 (1.2%)	33 (3.4%)	0.0001‡
Glipizide	399 (10.4%)	197 (20.3%)	<0.0001‡	221 (11.4%)	197 (20.3%)	<0.0001‡
Metformin	2,680 (73.4%)	837 (86.0%)	<0.0001‡	1,442 (74.5%)	835 (86.0%)	<0.0001‡
Pioglitazone	25 (0.7%)	17 (1.8%)	0.0019‡	18 (0.9%)	17 (1.8%)	0.0558‡
Rosiglitazone	106 (2.9%)	110 (11.3%)	<0.0001‡	64 (3.3%)	110 (11.3%)	<0.0001‡
Tolbutamide	10 (0.3%)	22 (2.3%)	<0.0001‡	8 (0.4%)	21 (2.2%)	<0.0001‡

Data are median (interquartile range; from 25th-75th percentiles), % (*n*), and *n* (%). *Matched on age, smoking status, likelihood of using insulin, and time before insulin use. †Derived from Wilcoxon two-sample test. ‡Derived from χ^2 test. §From enrollment to the earliest date of cancer, death, or censoring (95% CIs). ‖Derived from univariate Cox model analysis. ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.

Sensitivity analysis. We used the original cohort (*n* = 4,623) to perform the sensitivity analysis, in which age, smoking status, and likelihood of using insulin during follow-up were used as covariates. The HR of A1C for cancer was 1.11 (95% CI 0.98–1.26, *P* = 0.0974) and that of use of insulin for cancer was 0.47 (95% CI 0.31–0.71, *P* = 0.0003) in the model including only A1C and use of insulin without other covariates. After adjusting for the covariates of model 2 in Table 2, the HRs of A1C and use of insulin were 1.17 (1.04–1.33, *P* = 0.0125) and 0.49 (0.32–0.73, *P* = 0.0006), respectively. After further adjusting for nonlinear associations (model 3 in Table 2), the respective

TABLE 2
HRs of use of insulin for cancer in a cohort of 971 insulin new users and 1,935 insulin nonusers matched on age, smoking status, and the likelihood of using insulin

	HR*	95% CI	*P*
Models for cancer*			
Model 1†			
A1C (%)	1.16	0.99–1.36	0.0747
Use vs. nonuse of insulin	0.18	0.10–0.33	<0.0001
Model 2‡			
A1C (%)	1.24	1.03–1.49	0.0267
Use vs. nonuse of insulin	0.18	0.10–0.33	<0.0001
Model 3§			
A1C (%)	1.26	1.03–1.55	0.0230
Use vs. nonuse of insulin	0.17	0.09–0.32	<0.0001
Models for death*			
Model 1†			
Use vs. nonuse of insulin	1.27	0.92–1.75	0.1543
Model 2‖			
Use vs. nonuse of insulin	1.24	0.84–1.84	0.2739
Model 3¶			
Use vs. nonuse of insulin	1.28	0.85–1.94	0.2422

*Stratified Cox models on the matching pairs were used. †Not adjusted for other covariates. ‡Adjusted for HDL cholesterol, triglyceride, eGFR, and use of metformin. Other variables had a *P* value larger than 0.3 and not selected by the stepwise algorithm with $P = 0.30$. These variables included sex, alcohol drinking (previous and current), duration of diabetes, BMI, systolic blood pressure, LDL cholesterol–related risk (indicator terms for LDL cholesterol <2.8 mmol/l plus albuminuria and ≥3.8 mmol/l), Ln (ACR+1), use of antihypertensive drugs (other than ACEIs or ARBs) at enrollment, and use of drugs from enrollment to the earliest date of cancer, death, or censoring (ACEIs or ARBs, statins, fibrates, and oral antidiabetic drugs listed in Table 1). §Restricted cubic spline was further used to adjust for nonlinear associations between HDL cholesterol and triglyceride with cancer. ‖Adjusted for A1C, BMI, eGFR, Ln(ACR+1), use of antihypertensive drugs (other than ACEIs or ARBs) at enrollment, and use of ACEIs or ARBs, fibrates, gliclazide, and rosiglitazone from enrollment to the earliest date of cancer, death, or censoring (selected by the stepwise algorithm with $P = 0.30$). ¶Restricted cubic spline was further used to adjust for nonlinear associations among A1C, BMI, ACR, and eGFR with death.

HRs of A1C (1.18, 1.04–1.33, $P = 0.0102$) and use of insulin (0.48, 0.32–0.73, $P = 0.0006$) remained similar. The full range of association between A1C and cancer is shown in Fig. 2.

DISCUSSION

In a new insulin user cohort of Chinese patients with type 2 diabetes, hyperglycemia was associated with an increased cancer risk, whereas insulin use was associated with a reduced cancer risk. However, both insulin and noninsulin users had similar incidence of all-cause death.

A series of observational studies have examined whether insulin glargine users were at higher risk of cancer than users of other types of insulin or metformin (5–8). Whereas researchers from the U.K. observed that users of insulin or insulin secretagogues had a higher cancer risk than metformin users (8), in the Swedish study (6) and the Scottish study (7), there was no increased cancer risk in patients treated with insulin glargine compared with users of other types of insulin.

Because use of metformin may be associated with a lower cancer risk (30,31), the result from the U.K. study cannot address the association between use of insulin and cancer. Adding to this confusion, the German study (5) reported that insulin glargine users were at a lower overall risk of cancer than human insulin users after adjusting for age and sex (relative risk 0.86, 95% CI 0.79–0.94). However, after adjustment for dosage, the authors found a "dose-dependent" increase in cancer risk with glargine compared with human insulin (5). On the other hand, we and others (12,13) have reported that hyperglycemia was a risk factor for cancer in type 2 diabetes. Thus, the dose-effect relationship for cancer in the German study (5) may be confounded by severe hyperglycemia in the high-dose insulin glargine groups.

Traditional cohort design versus new-user design. It is usual to use cohort studies to address possible drug effects, but cohort study designs may have difficulties in controlling for some potential confounding factors. The so-called prevalent user bias is considered a major contributing factor that results in discrepancies between observational studies and clinical trials. Compared with traditional cohort study designs, a new-user design can eliminate insufficient ascertainment of events that occur early in therapy and allow better control for disease risk factors that may have been altered by the study drugs in question. One of the main rationales underlying new-user designs is to synchronize the beginning of study follow-up

TABLE 3
Life table analyses of development of cancer and total death in new insulin users and a matched cohort of insulin nonusers

	At risk at the beginning of the period	Cancer cases	Deaths in the period	Cumulative cancer rate (%)†	Cumulative death rate (%)‡
Insulin users					
Year 1*	971	12	50	1.3	5.4
Year 2*	807	6	20	2.2	8.0
Year 3*	628	4	20	2.9	11.2
Year 4*	487	7	18	4.5	14.9
Year 5*	334	1	14	4.8	18.9
Year 6*	226	1	6	5.4	21.5
Year 7*	126	0	1	5.4	22.3
Insulin nonusers					
Year 1*	1,935	90	73	6.5	5.2
Year 2*	751	21	25	9.9	8.9
Year 3*	389	3	15	10.8	12.7
Year 4*	220	4	6	12.8	15.1
Year 5*	133	1	5	13.6	18.3
Year 6*	73	1	0	15.2	18.3
Year 7*	36	0	0	15.2	18.3

*From the first day of follow-up through the end of the year. †*P* from Wilcoxon (Gehan) statistic <0.0001 for comparison between insulin users and nonusers. ‡*P* from Wilcoxon (Gehan) statistic = 0.7408 for comparison between insulin users and nonusers.

TABLE 4
HRs of use of insulin vs. nonuse for first incident cancers in a cohort of 971 insulin new users and 1,935 insulin nonusers matched on age, smoking status, and likelihood of using insulin

Cancer subtypes*	No. of cancers*	HR (95% CI) of A1C†	HR (95% CI) of insulin†
Lip, oral cavity, and pharynx	3		
Digestive organs and peritoneum	65	1.19 (0.95–1.51)	0.19 (0.08–0.46)
Upper digestive tract	10		
Lower digestive tract	25		
Liver and intrahepatic bile ducts	19		
Respiratory and intrathoracic organs	19		
Bone, connective tissue, skin, and breast	19		
Genitourinary organs	24		
Lymphatic and hematopoietic tissue	7		
Other and unspecified sites	15		
Cancers other than digestive organs and peritoneum cancer	87	1.13 (0.91–1.41)	0.20 (0.10–0.41)

*A total of 152 cancers of any type classified by the ICD-9 were analyzed. †Derived from stratified Cox models without adjusting for other covariates, but A1C and use of insulin were simultaneously entered in each of these models.

with initiation of the drug therapy (24). Failure to follow this principle may introduce major bias, such as confounding by risk factors that are associated with both therapy indication and clinical outcomes, with conclusions that are scientifically disastrous (32). This is clearly illustrated by the recent controversy on insulin use and cancer; in a non–new-user cohort design, patients with uncontrolled hyperglycemia may be at high risk of cancer but are also more likely to be given insulin. The latter was then erroneously identified as a risk factor for cancer.

On the other hand, by controlling for all confounders, including risk factors, complications, use of medications, and duration of follow-up with respect to start of insulin in a new-cohort design, we were able to show the independent cancer risk with A1C and that of reduction of cancer with insulin therapy. Our sensitivity analysis using the traditional cohort design without including prevalent users also shows similar results. However, in the latter analysis, because nonuse of insulin from enrollment to initiation of insulin treatment was treated as "on-insulin" period, this can attenuate the true association of insulin with cancer compared with the new-user cohort.

Adjustment for other confounders and competing risks. With improved survival from cardiorenal complications, cancer has become an important health hazard in diabetic patients. In this regard, competing risk (i.e., noncancer death) is unlikely to be a potential source of bias in our analysis because proportional hazard models such as Cox models can still give valid results when used to test HR (33). In addition, in this new-user cohort design, the cumulative death rates were similar in insulin users and nonusers during 7 years of follow-up, and the adjusted HRs of use of insulin for death were nonsignificant, suggesting that the impacts of competing risk on our results, if any, are very small.

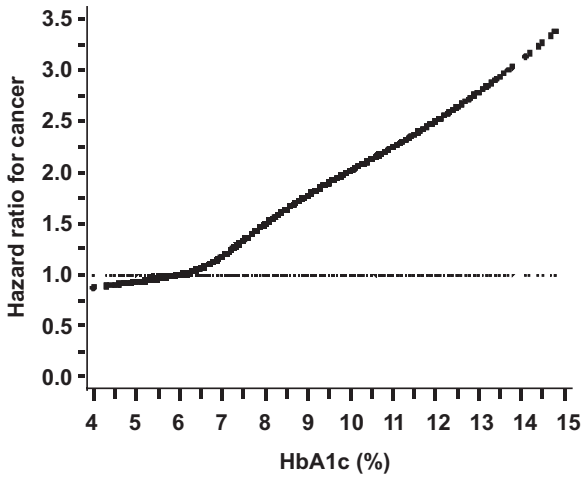

FIG. 2. Hazard ratio of A1C for incident cancer in the cohort of 4,623 Chinese patients with type 2 diabetes.

Hyperglycemia, dyslipidemia, inflammation, dysregulated cellular growth, insulin resistance, and hyperinsulinemia can all contribute to cardiorenal complications and cancer in diabetic patients. Recently, we reported potential cross talk between lipid metabolism and the RAS in development of cancer in type 2 diabetes, possibly via the IGF-I signaling and cholesterol biosynthesis pathways (19). Of note, hyperglycemia has a potent but reversible effect on LDL oxidation (20). Oxidized LDL (ox-LDL) enhances the expression and activation of RAS components; the latter can in turn stimulate the accumulation of LDL and its oxidation into ox-LDL, thus setting up a vicious cycle (18). Individually, ox-LDL and RAS activation induce oxidative stress and inflammatory cascade (18). Thus, it is plausible that insulin use may reduce oxidative stress and inflammation by lowering blood glucose and thus reduce cancer risk. Indeed, in patients in whom hyperglycemia is the predominant metabolic risk factor for cancer, the theoretic growth-promoting and mitogenic effects of insulin on cancer development may be less important.

Despite its biological plausibility, other methods are needed to confirm these arguments, such as mechanistic and intervention studies. Unlike a clinical trial, measurement of A1C during these follow-up visits in real practice was not standardized, and thus the availability and changes in A1C levels may be biased in this epidemiologic analysis. If insulin could increase cancer risk by modulating cell growth, circulating insulin levels would presumably be important. Patients who required insulin may have lower natural levels than those who did not; therefore, supplementary insulin in these patients may increase the circulating insulin level comparable only with a natural level, which is not likely to increase cancer risk. Nevertheless, hyperinsulinemia remains an important issue in cancer risk and further studies are required to determine this risk association.

Limitations and conclusions. These results need to be interpreted with caution because of study limitations. First, the follow-up time was relatively short, but the observed association of use of insulin on cancer was larger than expected. Second, because of the observational nature of the study, A1C was not systematically collected during follow-up visits. Third, principal discharge diagnoses were used to identify cancer cases. However, only a small number of cancer events would be missed, mainly due to patient emigration or treatment in the private sector. Fourth, the cohort was mainly clinic based, albeit the overall clinical profile was comparable with many community-based cohorts (22). Fifth, although we used a new-user study design (24), both measured and unmeasured confounders may still exist.

In conclusion, in a matched cohort of Chinese type 2 diabetic patients newly started on insulin, hyperglycemia was associated with an increased cancer risk, whereas insulin use was associated with a reduced cancer risk. Apart from reaffirming the importance of controlling hyperglycemia to prevent poor clinical outcomes, including cancer, at least in Chinese patients with type 2 diabetes, our use of a new-cohort design coupled with careful adjustment for confounding variables has provided a new strategy in pharmacoepidemiologic analysis.

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