Annual fasting plasma glucose variation increases risk of cancer incidence and mortality in patients with type 2 diabetes: the Taichung Diabetes Study

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Abstract

The study aims to examine whether the annual variations in fasting plasma glucose (FPG) measurements, represented by the coefficient of variation (CV), predict cancer incidence and mortality in the subsequent years independent of traditional risk factors of type 2 diabetic patients. A computerized database of patients with type 2 diabetes of 30 years old and older ($n=4805$) enrolled in the Diabetes Care Management Program of a medical center before 2006 was analyzed using a time-dependent Cox's proportional hazards regression model. The mortality rates for the first, second, and third tertiles of the first annual FPG-CV were 8.64, 12.71, and 30.82 per 1000 person-years respectively. After adjusting for mean FPG, HbA1c, and other risk factors, the annual FPG-CV was independently associated with cancer incidence, cancer mortality, and cancer incidence or mortality, and the corresponding hazard ratios for the third vs first tertile of the annual FPG-CV were 3.03 (1.98, 4.65), 5.04 (2.32, 10.94), and 2.86 (1.91, 4.29) respectively. The annual variation in FPG was a strong predictor of cancer incidence and mortality in type 2 diabetic patients; therefore, glucose variation may be important in the clinical practice of care management and cancer prevention.

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Introduction

Recently, cohort and case–control studies proposed a link between type 2 diabetes and cancer, especially in the colon (Larsson *et al.* 2005, Limburg *et al.* 2006, Flood *et al.* 2010, He *et al.* 2010, Hemminki *et al.* 2010), liver (Fujino *et al.* 2001, El-Serag *et al.* 2004), pancreatic (Gullo *et al.* 1994, Wang *et al.* 2003), breast (Mink *et al.* 2002, Michels *et al.* 2003), and prostate (Rodriguez *et al.* 2005, Waters *et al.* 2009, Li *et al.* 2010). Type 2 diabetes mellitus (DM) and many types of cancer share common risk factors, such as smoking, alcohol consumption, obesity, physical inactivity, and

high caloric intake, particularly saturated fat intake (World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) 1997). In addition, some possible biological mechanisms show the independent contribution of diabetes as a risk factor for cancer. These findings indicate that increased levels of insulin-like growth factor 1 (IGF1) in the serum and plasma act as a promoter of tumor cell growth. Epidemiological and experimental evidence shows the association between IGF1 and colorectal, prostate, and breast cancers (Bohlke *et al.* 1998, Chan *et al.* 1998, Cohen *et al.* 2000, Grimberg & Cohen 2000).

Moreover, recent bench studies show that the dysregulation of tuberous sclerosis 1 (TSC1)/TSC2/mTOR signaling pathway by IKB kinase (IKKB) is a common molecular switch for both cancer pathogenesis and diet- and obesity-induced insulin resistance and links obesity-derived chronic inflammation with insulin resistance and cancer pathogenesis (Greten *et al.* 2004, Hu *et al.* 2004, Lee *et al.* 2004, 2008).

Glucose stability is one of the classical risk factors that has been explored to explain the increasing mortality and morbidity of diabetes. Two studies by the same investigators examined the relationship of a 3-year variation in fasting plasma glucose (FPG), measured by coefficient of variation (CV), to cancer mortality in diabetic patients ≥ 65 years old (Muggeo *et al.* 1995) and 56–74 years (Muggeo *et al.* 2000). Although they failed to detect its ability to predict cancer mortality rates during a 5-year follow-up period, they observed the relationship of cancer mortality with FPG variation during a 10-year follow-up period. However, they did not adjust for several important comorbidities and complications or consider cancer incidence. In addition, they did not determine whether glycemic variation is also an important predictor of cancer incidence and mortality in younger patients with type 2 diabetes.

The Taichung Diabetes Study is a population-based cohort study of more than 5000 middle-aged and older Chinese patients with type 2 diabetes enrolled into the Diabetes Care Management Program (DCMP). DCMP, established by the Taiwan Bureau of National Health Insurance (BNHI) in 2002, provides financial incentives for physicians to increase follow-up visits, including annual eye examinations, annual self-care education and assessment, and annual laboratory tests, such as fasting lipid profiles, HbA1c, and FPG. DCMP provides a unique opportunity to quantify the overall effect of annual FPG variations on cancer-specific incidence and mortality. Thus, this study examines the association between annual glucose variation, as measured by the CV of all FPG measurements within each year and the cancer-specific incidence and mortality of a large number of type 2 diabetes patients of 30 years old and above who were followed for an average of 4.56 years.

Materials and methods

A retrospective cohort study was conducted on enrollees into the DCMP of China Medical University Hospital (CMUH), Taichung, Taiwan. The BNHI set up the DCMP as a nursing case management program in 2002. The enrollees were patients diagnosed with DM

based on the American Diabetes Association criteria (International Classification Disease, Ninth Revision, Clinical Modification, abbreviated as ICD-9-CM; Code of 250). Upon entering the DCMP, the enrollees received a series of medical tests for blood, urine, body measurements, and their lifestyle and medical history were obtained (using a standardized computerized questionnaire administered by a case management nurse). The patients had to follow the guidelines for the managed care of diabetes proposed by the BNHI.

We identified patients with type 2 diabetes enrolled into the DCMP program in CMUH via an automated registry at the end of August 2006. The inclusion criteria were patients enrolled into the registry during the study period (August 2002 to August 2006) that were available for at least 1 year of follow-up for estimating FPG variability and 1 year of follow-up for determining the outcomes. The baseline was set as 1 year after the entry date, and the endpoint was set as August 2008, or until the patient's death. The exclusion criteria were patients with cancer at the beginning of the study and those with type 1 diabetes (ICD-9-CM; Code of 250.x1/x3). A total of 4805 continuously enrolled patients with type 2 diabetes fulfilled these criteria. The current study was approved by the Ethical Review Board of CMUH.

After a 12 h overnight fast, blood was drawn from the antecubital vein, with minimal trauma, and was sent for analysis within 4 h after collection. Biochemical markers, such as FPG, high-density lipoprotein cholesterol (HDL-C), and triglyceride were analyzed by a biochemical autoanalyzer (Beckman Coulter Synchron system, Lx-20, Fullerton, CA, USA) at the Clinical Laboratory Department of CMUH. For both interassay and intra-assay CV, FPG were both 4%. Plasma cholesterol and triglyceride levels were determined via an enzymatic colorimetric method. The HDL-C level was measured using a direct HDL-C method and the low-density lipoprotein cholesterol (LDL-C) level was measured by a direct LDL-C method. The interassay and intra-assay CV for triglyceride were 6.8 and 5% respectively; the inter-assay and intra-assay CV for HDL-C were 4.5 and 4.5% respectively; and the interassay and intra-assay CV for LDL-C were 4.5 and 3% respectively.

The primary outcomes were measured in terms of cancer incidence and mortality. Taiwan's National Death Index, a file tallying the deaths of all citizens based on death certificates, was used to identify possible decedents with cancers during the follow-up period. After the deaths were identified, they were confirmed through the cancer registry of CMUH. By cross-referencing the unique identification number

Table 1 The comparisons of sociodemographic factors, lifestyle behaviors, diabetes-related variables, drug-related variables, diabetes-related diseases, and blood biochemical indexes according to cancer-specific incidence or mortality with type 2 diabetes enrolled in the Diabetes Care Management Program at the CMUH, Taichung, Taiwan ($n=4805$)

Variables	Cancer incidence or mortality cases n (%)		<i>P</i> value
	No ($n=4618$)	Yes ($n=187$)	
Sociodemographic factors			
Gender			0.07
Female	2278 (49.33)	79 (42.25)	
Male	2340 (50.67)	108 (57.75)	
Age (years) ^a	58.47 (11.47)	65.10 (10.34)	<0.001
Lifestyle behaviors			
Smoking			0.99
No	3764 (81.51)	153 (81.82)	
Yes	854 (18.49)	34 (18.18)	
Alcohol drinking			0.19
No	4119 (89.19)	173 (92.51)	
Yes	499 (10.81)	14 (7.49)	
Diabetes-related variables			
Duration of diabetes medication (years) ^a	6.97 (7.04)	8.38 (7.66)	0.01
Type of DM treatment			0.64
Oral hypoglycemic drug	3787 (82.01)	157 (83.96)	
Inject insulin	79 (1.71)	1 (0.53)	
Both	454 (9.83)	18 (9.63)	
Both not	298 (6.45)	11 (5.88)	
Drug-related variables			
Hypertension drug treatment			1.00
No	2573 (55.72)	104 (55.61)	
Yes	2045 (44.28)	83 (44.39)	
Diabetes-related diseases			
Obesity			0.92
No	3141 (68.02)	126 (67.38)	
Yes	1477 (31.98)	61 (32.62)	
Hypertension			1.00
No	2597 (56.24)	105 (56.15)	
Yes	2021 (42.98)	82 (43.85)	
Hyperlipidemia			0.90
No	3145 (68.10)	126 (67.38)	
Yes	1473 (31.90)	61 (32.62)	
DKA			0.73
No	4559 (98.72)	186 (99.47)	
Yes	59 (1.28)	1 (0.53)	
HHNK			1.00
No	4515 (97.77)	183 (97.86)	
Yes	103 (2.23)	4 (2.14)	
Severe hypoglycemia			0.80
No	4508 (97.62)	184 (98.40)	
Yes	110 (2.38)	3 (1.60)	
Stroke			0.04
No	4275 (92.57)	165 (88.24)	
Yes	343 (7.43)	22 (11.76)	
Coronary artery disease			1.00
No	4265 (92.36)	173 (92.51)	
Yes	353 (7.64)	14 (7.49)	
Myocardial infarction			0.19
No	4259 (92.23)	167 (89.30)	
Yes	359 (7.77)	20 (10.70)	
Peripheral neuropathy			1.00
No	3914 (84.76)	158 (84.49)	
Yes	704 (15.24)	29 (15.51)	

Table 1 continued

Variables	Cancer incidence or mortality cases <i>n</i> (%)		<i>P</i> value
	No (<i>n</i> =4618)	Yes (<i>n</i> =187)	
Intermittent claudication			0.52
No	4552 (98.57)	186 (99.46)	
Yes	66 (1.43)	1 (0.53)	
Neuropathy			0.36
No	4248 (91.99)	168 (89.84)	
Yes	370 (8.01)	19 (10.16)	
Nephropathy			0.46
No	4132 (89.48)	171 (91.44)	
Yes	486 (10.52)	16 (8.56)	
Blood biochemical indexes			
Triglyceride (mg/dl) ^a	166.90 (217.20)	148.70 (114.30)	0.04
High-density lipoprotein (mg/dl) ^a	41.06 (11.31)	39.71 (9.64)	0.07
HbA1c (%) ^a	8.26 (1.90)	8.20 (1.76)	0.64
Fasting plasma glucose (mg/dl) ^a	163.90 (59.02)	159.20 (53.83)	0.28

DKA, diabetic ketoacidosis; HHNK, hyperglycemic hyperosmolar non-ketoacidosis. Differences in continuous variables were tested by Student's *t*-test. Differences in categorical variables were tested by the χ^2 test.

^aMean $\pm$ s.d.

with this computerized file, 70 cancer deaths were identified from this cohort by 2008. The deaths were classified according to the International Classification of Diseases, 9th Revised Edition. Mortality from malignant neoplasms was defined as codes 140–208. Cancer incidence cases were identified via cross-referencing with cancer registry and via follow-up visits. A total of 172 new DM type 2 cases were identified, 55 of which died of cancer during the follow-up period. Thus, 187 new cases or deaths were included in the analysis.

Statistical analysis

The annual CV of all FPG measurements within each year was computed for each patient using the dataset from electronic laboratory records. The FPG-CV was calculated only when the three or more FPG measurements were recorded within each year. The patients were grouped into tertiles based on the first year of FPG-CV.

Kaplan–Meier cumulative incidence plots were generated to show the time-to-event for all endpoints. We used the time-dependent Cox proportional hazard models to evaluate the association of FPG-CV categories with the primary outcome measures by considering time variations in FPG-CV. We calculated the hazard ratios (HR) and their 95% confidence intervals after adjusting for age and multiple variables. Three multivariate models were conducted. The first multivariate model was adjusted for age (continuous), obesity, hypertension, antihypertensive treatment (yes, no),

smoking (never, past, current), exercise (yes, no), alcohol consumption (yes, no), hyperlipidemia, and type of treatment (oral hypoglycemic drug, insulin injection, both, or diet or exercise). The second model included a mean FPG, estimated glomerular filtration rate (eGFR), and HbA1c. The third model included complications at the baseline (diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar non-ketoacidosis (HHNK), severe hypoglycemia, stroke, myocardial infarction (MI), peripheral neuropathy, intermittent claudication, neuropathy, and nephropathy).

To assess whether the FPG-CV estimates on cancer incidence or mortality were sensitive to diabetic complication, we excluded patients with stroke, cardiovascular disease (CVD), diabetic ketoacidosis (DKA), and hyperglycemic, hyperosmolar, non-ketoacidosis (HHNK) and performed a multivariate analysis. We tested the proportionality assumption by including an interaction term for the FPG-CV categories with person-time in the Cox models and found no statistically significant violation. We calculated *P* for the trend of the FPG-CV categories across tertiles. All analyses were performed using SAS version 9.2 (SAS, Cary, NC, USA). All *P* values were two tailed, and a *P* value <0.05 was considered statistically significant.

Results

Over an average of 4.68 years of follow-up, 187 patients with diabetes died of cancer or developed cancers, with a crude rate of 8.32/1000 person-years

Table 2 The comparisons of baseline sociodemographic factors, lifestyle behaviors, diabetes-related variables, drug-related variables, diabetes-related diseases, and blood biochemical indexes according to tertiles of coefficient of variation (CV) of baseline fasting plasma glucose with type 2 diabetes enrolled in the Diabetes Care Management Program at the CMUH, Taichung, Taiwan ($n=4805$)

	Baseline FPG-CV, <i>n</i> (%)			
Variables	≤ 14.41 (<i>n</i> = 1580)	14.41–25.10 (<i>n</i> = 1594)	> 25.10 (<i>n</i> = 1631)	<i>P</i> value
Sociodemographic factors				
Gender				0.001
Female	733 (46.39)	839 (52.63)	785 (48.13)	
Male	847 (53.61)	755 (47.37)	846 (51.87)	
Age (years) ^a	58.31 (11.11)	58.45 (11.11)	59.42 (12.18)	0.01
Lifestyle behaviors				
Smoking				<0.001
No	1332 (84.30)	1311 (82.25)	1274 (78.11)	
Yes	248 (15.70)	283 (17.75)	357 (21.89)	
Alcohol drinking				0.18
No	1425 (90.19)	1406 (88.21)	1461 (89.58)	
Yes	155 (9.81)	188 (11.79)	170 (10.42)	
Diabetes-related variables				
Diabetes medical history (years) ^a	5.05 (5.94)	7.03 (6.66)	8.94 (7.89)	<0.001
Type of DM treatment				<0.001
Oral hypoglycemic drug	1361 (86.14)	1403 (88.02)	1180 (72.35)	
Inject insulin	6 (0.38)	14 (0.88)	60 (3.68)	
Both	42 (2.66)	106 (6.65)	324 (19.87)	
Diet or exercise	171 (10.82)	71 (4.45)	67 (4.11)	
Drug-related variables				
Hypertension drug treatment				0.02
No	891 (56.39)	920 (57.72)	866 (53.10)	
Yes	689 (43.61)	674 (42.28)	765 (46.90)	
Diabetes-related diseases				
Obesity				0.001
No	1019 (64.49)	1103 (69.20)	1145 (70.20)	
Yes	561 (35.51)	491 (30.80)	486 (29.80)	
Hypertension				0.01
No	917 (58.04)	916 (57.47)	869 (53.28)	
Yes	663 (41.96)	678 (42.53)	762 (46.72)	
Hyperlipidemia				0.74
No	1078 (68.23)	1094 (68.63)	1099 (67.38)	
Yes	502 (31.77)	500 (31.37)	532 (32.62)	
DKA				<0.001
No	1568 (99.24)	1582 (99.25)	1595 (97.79)	
Yes	12 (0.76)	12 (0.75)	36 (2.21)	
HHNK				<0.001
No	1554 (98.35)	1569 (98.43)	1575 (96.57)	
Yes	26 (1.65)	25 (1.57)	56 (3.43)	
Severe hypoglycemia				<0.001
No	1560 (98.73)	1558 (97.74)	1574 (96.51)	
Yes	20 (1.27)	36 (2.26)	57 (3.49)	
Stroke				0.005
No	1481 (93.73)	1497 (92.79)	1480 (90.74)	
Yes	99 (6.27)	115 (7.21)	151 (9.26)	
Coronary artery disease				0.17
No	1473 (93.23)	1473 (92.41)	1492 (91.48)	
Yes	107 (6.77)	121 (7.59)	139 (8.52)	
Myocardial infarction				0.009
No	1480 (93.67)	1466 (91.97)	1480 (90.74)	
Yes	100 (6.33)	128 (8.03)	151 (9.26)	
Peripheral neuropathy				<0.001
No	1434 (90.76)	1363 (85.51)	1275 (78.17)	
Yes	146 (9.24)	231 (14.49)	356 (21.83)	

Table 2 continued

Variables	Baseline FPG-CV, n (%)			P value
	≤ 14.41 (n=1580)	14.41–25.10 (n=1594)	> 25.10 (n=1631)	
Intermittent claudication				<0.001
No	1568 (99.24)	1577 (98.93)	1593 (97.67)	
Yes	12 (0.76)	17 (1.07)	38 (2.33)	
Neuropathy				<0.001
No	1503 (95.13)	1479 (92.79)	1434 (87.92)	
Yes	77 (4.87)	115 (7.21)	197 (12.08)	
Nephropathy				<0.001
No	1492 (94.43)	1445 (90.65)	1366 (83.75)	
Yes	88 (5.57)	149 (9.35)	265 (16.25)	
Blood biochemical indexes				
Triglyceride (mg/dl) ^a	148.76 (128.86)	168.50 (238.93)	180.85 (250.46)	<0.001
High-density lipoprotein (mg/dl) ^a	40.98 (10.34)	41.04 (11.04)	41.01 (12.28)	0.99
Mean HbA1c of the first year (%) ^a	7.19 (1.10)	7.87 (1.31)	8.60 (1.52)	<0.001
Mean fasting plasma glucose of the first year (mg/dl) ^a	145.43 (32.87)	158.24 (36.92)	176.76 (54.85)	<0.001

Differences in continuous variables were tested by Student's *t*-test. Differences in categorical variables were tested by χ^2 test.
^aMean (s.d.).

(9.50 men and 7.10 women). Liver cancer had the highest incidence and mortality ($n=18$ for mortality and $n=34$ for incidence) followed by lung cancer ($n=16$ for mortality and $n=21$ for incidence) and colon cancer ($n=10$ for mortality and $n=18$ for incidence). Altogether, these cases accounted for 42.25% of all cancer incidence and deaths. Table 1 summarizes the comparisons of baseline sociodemographic factors, lifestyle behaviors, diabetes-related variables, drug-related variables, comorbidities, complications, and blood biochemical indices in terms of cancer incidence and mortality of patients with diabetes who were enrolled in the DCMP of a medical center. Compared with patients who died of cancer or developed cancer during the follow-up period, the patients who did not have cancer had a younger mean age, shorter duration of diabetes medication, lower prevalence of strokes, and a higher mean triglyceride levels. Lower FPG-CV was associated with lower mean age, duration of diabetes medication, triglyceride levels, mean HbA1c, and FPG on the first year and lower prevalence of female gender, smoking, treatment with both oral hypoglycemic drugs and insulin injection, antihypertensive drug treatment, hypertension, DKA, HHNK, severe hypoglycemia, stroke, MI, peripheral neuropathy, intermittent claudication, neuropathy, and nephropathy (Table 2).

Figure 1 presents the Kaplan–Meier cumulative incidence of the time-to-event for cancer incidence, cancer mortality, and cancer incidence or mortality within the subgroups defined by the baseline FPG-CV.

The median follow-up time ranged from 5.22 years, for patients with FPG-CV <14.41%, to 5.13 years, for patients with FPG-CV ≥25.10%. Baseline FPG-CV was a powerful predictor of cancer incidence, cancer mortality, and cancer incidence or mortality (Fig. 1). We found that patients with FPG-CV ≥25.10% have increased cancer incidence (log-rank $P<0.001$, Fig. 1a), cancer mortality (log-rank $P<0.001$, Fig. 1b), and cancer incidence or mortality (log-rank $P<0.001$, Fig. 1c). Figure 2 shows the means and standard errors of FPG-CV from years 1 to 6 based on cancer incidence and mortality. The individuals who died of cancer or developed cancer had higher FPG-CV than those without cancer incidence or mortality from years 0 to 3 and 5 (all $P<0.01$).

Table 3 shows the HRs for cancer incidence, cancer mortality, and cancer incidence or mortality according to the tertiles of the time-dependent annual FPG-CV. Compared with patients with annual FPG-CV ≤14.41%, the age-adjusted HRs for cancer incidence among patients with annual FPG-CV >25.10% were 2.79 (95% confidence interval 1.86–4.17). For cancer mortality, the HRs were 5.32 (2.52–11.21), whereas the HRs for cancer incidence or mortality were 2.61 (1.78–3.82).

We found significant linear trends across annual FPG-CV categories for cancer incidence, cancer mortality, and cancer incidence or mortality. When the mean FPG, eGFR, and HbA1c were considered, the effect of FPG-CV remained the same and statistically significant. After adjusting further for complications, the multivariate-adjusted HR was 3.03 (1.98, 4.65) for

Figure 1 Risk from cancer incidence (a), cancer mortality (b), and cancer incidence or mortality (c) for baseline FPG-CV.

cancer incidence, 5.04 (2.32, 10.94) for cancer mortality, and 2.86 (1.91, 4.29) for cancer incidence or mortality among patients in the third tertile compared with those in the first tertile.

Sensitivity analyses were conducted to investigate the potential for bias because of comorbidities by excluding patients who developed stroke, CVD, DKA, HHNK, and nephropathy ($n=3612$). Similar significant associations were found for the HRs for cancer incidence (2.91, 1.82–4.65), cancer mortality (5.52, 2.24–13.56), and cancer incidence or mortality (2.76, 1.76–4.32) among patients in the third tertile compared with those in the first tertile.

Discussion

This study shows that the annual variation in FPG measurements predicts cancer incidence and cancer mortality among type 2 diabetes patients of 30–93 years old. Compared to patients with FPG-CV $\leq 14.41\%$, those with FPG-CV from 14.41 to 25.10% and $>25.10\%$ have a 1.63- and 3-fold higher cancer incidence and mortality respectively. These findings are relevant to the clinical management of patients with type 2 diabetes. Managed care facilitates the routine FPG measurements; hence, these routine glycemic assessments of patients with diabetes should be used for improving treatment strategies.

Consistent with the study by *Muggeo et al. (2000)*, risk of cancer-specific mortality increased with FPG variation in our study. Instead of the time-dependent annual FPG variation, they measured the 3-year FPG variation among older patients with type 2 diabetes and observed the relationship of cancer mortality with FPG variation during 10 years of follow-up. In our study, predicting cancer mortality rates remained significantly stable when the means of FPG, eGFR, and HbA1c were considered. To rule out the possibility that comorbidities and complications account for the relationships observed in the current study, we further adjusted for comorbidities and complications. The associations remained significant.

We observed a significant association between the annual FPG variation during follow-up and cancer mortality, which was consistent with the previous studies (*Muggeo et al. 2000*). These observed associations have three possible explanations. First, malignancies result in glucose variability through impaired feeding. To rule out this possibility, we compared the mean FPG-CV of the last annual measurement with that of the remaining ones among patients who developed cancer or died of cancer during the follow-up, which were 23.82 and 22.69%

Figure 2 Mean variation of fasting plasma glucose according to cancer incidence (a), cancer mortality (b), and cancer incidence or mortality (c).

respectively. Considering the FPG-CV in the last and the remaining annual measurements of new cancer cases or those who died of cancer during the follow-up were consistently high, we could rule out that glucose variation is a predictor of cancer incidence and mortality. Secondly, although cancer treatment may have a detrimental effect on glucose control, it does not account for the relationship between diabetes and cancer because we excluded patients with cancer at the start of the study period. Thirdly, insulin resistance and the progression of cancer may share the same mechanism; therefore, glucose variability could account for this relationship better. A recent bench study showed that the dysregulation of the TSC1/TSC2/mTOR signaling pathway by IKKB is a common molecular switch for both cancer pathogenesis and diet- and obesity-induced insulin resistance and links obesity-derived chronic inflammation with insulin resistance and cancer pathogenesis (Greten *et al.* 2004, Hu *et al.* 2004, Lee *et al.* 2004, 2008). Under this mechanism, the relationship between FPG variation and cancer mortality becomes more plausible over time.

Metabolic syndrome is a cluster of endocrine-metabolic disturbances characterized by insulin resistance, impaired glucose regulation, hypertension, raised triglycerides, and low HDL-C (Alberti *et al.* 2006, Cust *et al.* 2007). Insulin resistance caused by obesity or an inherited genetic defect has been hypothesized as the mechanism underlying metabolic syndrome. Insulin resistance is a pathological condition with reduced glycogen synthesis and storage and high levels of circulating glucose. For its role in cancer risk, insulin may act directly as a mitogenic and anti-apoptotic growth factor in tissues (Nagamani & Stuart 1998, Cust *et al.* 2007). Insulin also increases IGF1 bioactivity (Kaaks & Lukanova 2001, Kaaks *et al.* 2002, Cust *et al.* 2007). The shared metabolic factors that underlie both DM2 and cancer, including visceral adiposity, inflammation, hyperglycemia, and hyperinsulinemia, lead to increased insulin receptor substrate (IRS). IRS stimulates Ras phosphorylation, which signals proteins and potentially increases tumor cell growth and proliferation. Another possible mechanism is that IRS-associated PI3K signaling is compromised by insulin-resistant states, such as in type 2 diabetes. This phenomenon results in the disruption of downstream GLUT4 translocation, which drives PI3K signaling towards AKT/mTOR. AKT and mTOR affect both the metabolic and the mitogenic pathways.

In addition, the components of metabolic syndrome have each been linked to the development of cancer. Hypertension may increase cancer risk by blocking and

Table 3 The hazard ratios (HRs) of cancer incidence or mortality according to tertiles of time-dependent annual FPG-CV in patients with type 2 diabetes enrolled in Diabetes Care Management Program of a medical center ($n=4805$)

Variables	Cancer incidence ($n=172$) HR (95% CI)	<i>P</i> for trend	Cancer mortality ($n=70$) HR (95% CI)	<i>P</i> for trend	Cancer incidence or mortality ($n=187$) HR (95% CI)	<i>P</i> for trend
Age adjusted						
FPG-CV (%)		<0.001		<0.001		<0.001
≤14.41	1.00		1.00		1.00	
14.41–25.10	1.60 (0.99, 2.59)		1.45 (0.57, 3.68)		1.58 (1.00, 2.48)*	
>25.10	2.79 (1.86, 4.17) [†]		5.32 (2.52, 11.21) [†]		2.61 (1.78, 3.82) [†]	
Multivariate adjusted ^a						
FPG-CV (%)		<0.001		<0.001		<0.001
≤14.41	1.00		1.00		1.00	
14.41–25.10	1.66 (1.03, 2.69)*		1.50 (0.59, 3.82)		1.64 (1.04, 2.59)*	
>25.10	2.95 (1.96, 4.45) [†]		5.44 (2.54, 11.62) [†]		2.78 (1.88, 4.10) [†]	
Multivariate adjusted ^b						
FPG-CV (%)		<0.001		<0.001		<0.001
≤14.41	1.00		1.00		1.00	
14.41–25.10	1.67 (1.02, 2.74)*		1.46 (0.57, 3.72)		1.64 (1.03, 2.62)*	
>25.10	3.00 (1.96, 4.60) [†]		5.09 (2.35, 11.03) [†]		2.83 (1.89, 4.24) [†]	
Multivariate adjusted ^c						
FPG-CV (%)		<0.001		<0.001		<0.001
≤14.41	1.00		1.00		1.00	
14.41–25.10	1.66 (1.01, 2.71)*		1.45 (0.57, 3.69)		1.63 (1.03, 2.60)*	
>25.10	3.03 (1.98, 4.65) [†]		5.04 (2.32, 10.94) [†]		2.86 (1.91, 4.29) [†]	

FPG-CV, coefficient of variation of fasting plasma glucose. * $P<0.05$; [†] $P<0.001$.

^aMultivariate-adjusted age, smoking, alcohol drinking, hypertension, hypertension drug treatment, obesity, hyperlipidemia, and type of diabetes treatment.

^bMultivariate-adjusted age, smoking, alcohol drinking, hypertension, hypertension drug treatment, obesity, hyperlipidemia, type of diabetes treatment, mean annual fasting plasma glucose, estimated glomerular filtration rate, and HbA1c.

^cMultivariate-adjusted age, smoking, alcohol drinking, hypertension, hypertension drug treatment, obesity, hyperlipidemia, type of diabetes treatment, mean annual fasting plasma glucose, estimated glomerular filtration rate, HbA1c, DKA, HHNK, severe hypoglycemia, stroke, myocardial infarction, peripheral neuropathy, intermittent claudication, neuropathy, and nephropathy.

subsequently modifying apoptosis, thereby affecting cell turnover (Mason 1999, Soler *et al.* 1999, Russo *et al.* 2008). Hyperglycemia may not only promote tumorigenesis indirectly by stimulating insulin production but may also have a direct effect because cancer cells depend on glycolysis for energy (Levine *et al.* 1990, Yun *et al.* 2009). The possible mechanism for the relationship between obesity and carcinogenesis, and the progression of multiple cancer sites, is through the signaling pathways that regulate key functions, including cancer cell proliferation, apoptosis, metastasis, and angiogenesis (Overvad 2002). Our study demonstrates that glucose variation, characteristics of diabetes, predicts cancer incidence and mortality. Future study on whether this relationship results from insulin resistance, the mechanisms underlying metabolic syndrome, or glucose variation may be a marker for metabolic syndrome is warranted.

In addition to its strengths, such as the relatively large number of patients with diabetes, a sufficiently long follow-up period, standardized procedure for data

collection, and available information on a large number of potential confounding factors, this study is the first to use time-dependent annual glucose variations for exploring the relationship between glucose variation and cancer incidence and mortality. In addition, it is the first study that examines the relationship between cancer incidence and mortality and glucose variations among Chinese patients.

Our study is limited by potential residual and unrecognized confounding variables because our study is observational. In addition, measurement errors could be possible because of the large amount of data collected during clinical practice.

In summary, the annual FPG-CV may be included in the evaluation of glucose control in type 2 diabetic patients as a predictive factor for cancer incidence and mortality. Factors that may reduce FPG variations should be explored over time. Clinical trials with large sample sizes that involve interventions for maintaining a stable glycemia should provide conclusive evidence that glucose stability actually reduces cancer incidence and mortality.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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