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Independent and joint effect of type 2 diabetes and gastric and hepatobiliary diseases on risk of pancreatic cancer risk: 10-year follow-up of population-based cohort

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Background: Type 2 diabetes mellitus, gastric and hepatobiliary comorbidities, and cancer share common risk factors: for example, tobacco, obesity, physical inactivity, high calorie intake, and metabolic disorders. Prior studies find type 2 diabetes and gastric and hepatobiliary comorbidities heightening risk of pancreatic cancer. Yet joint association of type 2 diabetes mellitus and gastric and hepatobiliary comorbidities on pancreatic cancer risk has not been assessed.

Methods: This study rates independent/joint effects of type 2 diabetes as well as gastric and hepatobiliary comorbidity on pancreatic cancer risk for a retrospective population-based cohort of 166 850 type 2 diabetics identified in 1997–1998 and followed for 10–11 years, comparing their cancer incidence with that of 166 850 non-diabetics matched for age, gender, and locale. Time-dependent Cox's proportional hazards model evaluted joint association of type 2 diabetes and chronic conditions on pancreatic cancer risk.

Results: A total of 1178 subjects were newly diagnosed with pancreatic cancer during follow-up, with incidence rates of 0.49 per 1000 person-years in type 2 diabetes and 0.26 per 1000 person-years in the non-diabetics. We observed greater magnitude of hazard ratios (HRs) of pancreatic cancer for patients with type 2 diabetes along with acute alcoholic hepatitis, acute pancreatitis, cholecystitis, and gastric ulcer compared with patients without type 2 diabetes or counterpart comorbidity (HR: 1.36, 95% confidence interval (CI): 1.19–1.56; 1.74, 1.23–2.45; 9.18, 7.44–11.33; and 2.31, 1.98–2.70, respectively). Main effects of type 2 diabetes were all statistically with narrow 95% CI and remained similar across risk stratification with various comorbidities: range 1.59–1.80.

Conclusions: Our study demonstrates that pre-existing type 2 diabetes, acute alcoholic hepatitis, acute pancreatitis, cholecystitis, and gastric ulcer independently or jointly predict subsequent pancreatic cancer risk. Clinicians must recognise burden of these gastric and hepatobiliary comorbidities and keep clinically vigilant for their diagnosis.

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Cancer has ranked number-one cause of death in Taiwan since 1982, and average age of those diagnosed with it shows trend a downward. Taiwan's Department of Health national statistics report cited pancreatic cancer in 2012 ranking ninth highest overall for cancer death among the Taiwanese population: 6.4 per 100 000 (Ministry of Health and Welfare, 2012).

Type 2 diabetes mellitus, gastric and hepatobiliary comorbidity, and cancers share common risk factors, including tobacco, alcohol, obesity, physical inactivity, a high calorie (particularly saturated fat) intake, and metabolic disorders (Giovannucci and Michaud, 2007; Xue and Michels, 2007; Cornier *et al*, 2008). The possible biological mechanism that type 2 diabetes and gastric and hepatobiliary comorbidity contributed to elevated risk of developing pancreatic cancer may be via inflammatory (Lee *et al*, 2008). Prior bench studies show that dysregulation of tuberous sclerosis 1 (TSC1)/TSC2/mTOR signalling pathway by IκB kinaseβ (IKKβ) is a common molecular switch for both cancer pathogenesis and diet- and obesity-induced insulin resistance (Lee *et al*, 2008). Obesity-derived chronic inflammation with insulin resistance is also associated with gastric and hepatobiliary comorbidity (Farrow and Evers, 2002).

Previous population studies using rate standardisation indicate pancreatic cancer strongly correlating with type 2 diabetes (Hemminki *et al*, 2010; Atchison *et al*, 2011; Ben *et al*, 2011a, b; Lin *et al*, 2014). Several studies further rated association of pancreatic cancer with type 2 diabetes (Coughlin *et al*, 2004; Jee *et al*, 2005; Ogunleye *et al*, 2009; Stevens *et al*, 2009; Chodick *et al*, 2010; Chen *et al*, 2011) to elucidate such association after adjusting for traditional risk factors in across ethnicities (Larsson *et al*, 2005; Ogunleye *et al*, 2009; Stevens *et al*, 2009; Chodick *et al*, 2010; Lam *et al*, 2011), but this line of study conducted in a Chinese population was limited (Chen *et al*, 2011). Since 2000, several case–control and cohort studies explored the association between type 2 diabetes and pancreatic cancer (Frye *et al*, 2000; Gapstur *et al*, 2000; Lund Nilsen *et al*, 2000; Silverman, 2001; Lin *et al*, 2002; Stolzenberg-Solomon *et al*, 2002; Bonelli *et al*, 2003; Inoue *et al*, 2003; Rulyak *et al*, 2003; Batty *et al*, 2004; Coughlin *et al*, 2004; Jee *et al*, 2005). One case–control study reported that type 2 diabetes was associated with 2.8-fold increased risk of pancreatic cancer (Bonelli *et al*, 2003) whereas two case–control studies did not observe a significant association (Frye *et al*, 2000; Silverman, 2001). Similarly, findings of most prior cohort studies supported this association with a relative risk ranging from 1.48 to 3.99 (Gapstur *et al*, 2000; Lin *et al*, 2002; Stolzenberg-Solomon *et al*, 2002; Inoue *et al*, 2003; Rulyak *et al*, 2003; Batty *et al*, 2004; Coughlin *et al*, 2004; Jee *et al*, 2005). Only two cohort studies did not support the hypothesis that patients with type 2 diabetes are more likely to develop pancreatic cancer (Lund Nilsen *et al*, 2000). However, none of these studies considered gastric and hepatobiliary comorbidity.

Some researchers exploring links between type 2 diabetes and pancreatic cancer took gastric and hepatobiliary comorbidity such as acute pancreatitis, chronic pancreatitis, alcoholic liver disease, pancreatic pseudocyst, cholelithiasis (Bansal and Sonnenberg, 1995), gallbladder disease (Bracci *et al*, 2009), hepatitis B, hepatitis C, cholecystitis, cholangitits, cholelithiasis, gastric ulcer, and duodenal ulcer (Chen *et al*, 2011) into account; none considered joint effect with type 2 diabetes on pancreatic cancer. This population-based study examined independent and joint association of type 2 diabetes and gastric or hepatobiliary comorbidity on pancreatic cancer risk in Taiwan.

MATERIALS AND METHODS

A single-payer National Health Insurance (NHI) program was implemented in March 1995. As of 2007, 22.60 million of Taiwan's 22.96 million populations enrolled. Nation-run Bureau of National Health Insurance (BNHI) contracted with 97% of hospitals as well as 92% of clinics nationwide (Ministry of Health and Welfare, 2012). Bureau of National Health Insurance performs quarterly expert reviews on random samples of every 50–100 ambulatory and in-patient claims in each hospital and clinic. False diagnosis reports entail a high penalty.

Our population-based cohort study used type 2 diabetes patients (aged $\geqslant$20 years) identified in 1997–1998 and followed up through 31 December 2010 or until the first manifestation of pancreatic cancer. Population with type 2 diabetes should have at least three ambulatory claims or at least one in-patient claim with diagnosis of ICD-9-CM code 250 or A-code A181 in 1997–1998. To exclude those individuals with type 1 diabetes, we have done two steps. First, we identify all individuals with type 1 diabetes from Registry for Catastrophic Illness database. Second, we excluded those individuals with type 1 diabetes identified in the first step from our study cohort with diabetes. We excluded subjects with type 1 diabetes ($N=3750$) and any cancer type at baseline ($N=135\,060$) from 633 680 patients with type 2 diabetes, aged $<$20 years ($N=17\,679$), and/or with incomplete information on gender as well as residential area ($N=4212$). This left 472 979 patients with type 2 diabetes. Subjects from the general population were selected from Longitudinal Health Insurance Database 2005 (LHID2005) created by National Health Research Institutes (NHRI) by randomly sampling 1 000 000 beneficiaries from Registry for Beneficiaries data files for year 2005. Our sample proved representative of the overall population (Tseng *et al*, 2012). Database contained all longitudinal reimbursement information of this random sample from 1996 to the end of 2010. There were a total of 874 053 subjects in 1997–1998 in the file of LHID2005; excluding those with type 1 diabetes ($N=363$) from Registry for Catastrophic Illness database, cancer ($N=28\,550$), diabetes ($N=121\,227$), and/or age under 20 years ($N=304\,293$) in 1997–1998, as well as those with incomplete information on sex and residential area ($N=11$), left 419 609 eligible non-diabetics. The same eligibility criteria applied to each group, yet distribution of age, gender, and residential areas was unbalanced between groups. To bolster comparability between cases of type 2 diabetes and persons without diabetes, we randomly selected equal numbers of type 2 diabetics and non-diabetics from each stratum of combination of age (5-year groups), sex and residential areas (25 counties or cities). This left 166 850 patients with type 2 diabetes and individuals without any diabetes in 1997–1998 (Figure 1). Baseline or index date for type 2 diabetes group was date of first outpatient visit or in-patient admission. For non-diabetics, index date was randomly assigned from 1 January 1997 to 31 December 1998 according to index date distribution of type 2 diabetes group.

All data sets can be interlinked via individual personal identification number (PIN), which was scrambled cryptographically by NHIRD to protect enrollee's privacy. Ambulatory care claims contain the individual's gender and birthday, date of visit, and codes for International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, or A-codes for three primary diagnoses. In-patient claims contain ICD-9-CM codes for principal diagnosis up to four secondary diagnoses. The primary outcome was a new diagnosis of pancreatic cancer (ICD-9-CM code 157; A-code A096), including all malignant pancreatic tumours such as adenocarcinoma and pancreatic endocrine tumours after index date during the follow-up. Gastric and hepatobiliary comorbidity comprised acute or chronic pancreatitis, acute hepatitis, alcoholic fatty liver or cirrhosis, acute alcoholic hepatitis, cholelithiasis, morbid obesity, alcohol dependence syndrome, pseudocyst of pancreas, jaundice, hepatitis B, hepatitis C, cholecystitis, cholangitis, gastric ulcer, and duodenal ulcer. Each individual patient's status of gastric and hepatobiliary comorbidities at each year was identified for time-dependent data analysis. Sociodemographic factors include age, gender, insurance premium,

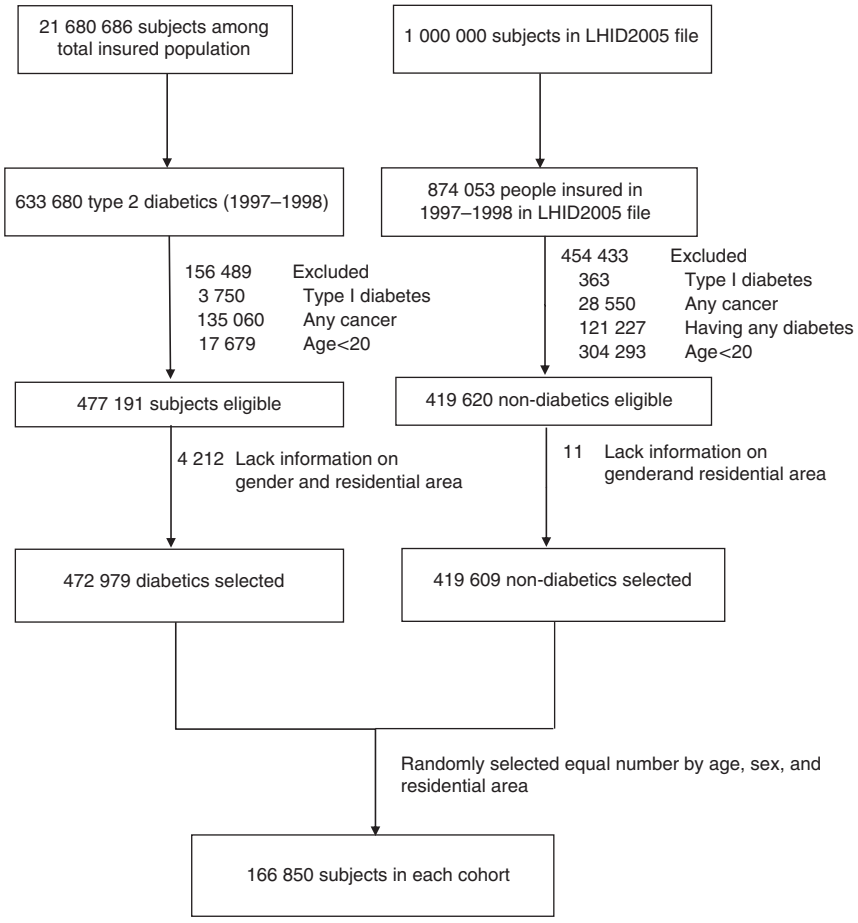

Figure 1. Flowchart of recruitment procedures.

and urbanisation degree of residential area. Age was divided into 17 groups with 5-year intervals from 20 to >90 years. Gender was categorised as male and female, insurance according to median of amounts of premiums, in which median value for these two groups was NT$19 200 from 1997 to 1998. We used an urbanisation indicator developed by Liu *et al* (2006), who categorised 365 Taiwan towns as per degrees of urbanisation: high- and medium-density urban areas, newly developed area, general area, ageing-society area, rural area, and non-developed area.

We compared baseline characteristic between subjects with and without type 2 diabetes using standardised mean differences. All standardised mean differences were less than 0.1 s.d., indicating a negligible difference in means or proportions between two groups. To explore the joint effect of type 2 diabetes and each gastric and hepatobiliary comorbidity, three dummy variables were created. Using individuals without type 2 diabetes and comorbidity as reference group, these three dummy variables measured the effects of type 2 diabetes only, comorbidity only, and combined type 2 diabetes and comorbidity. Time-dependent Cox's proportional hazards model evaluted hazards ratio (HR) of type 2 diabetes on pancreatic cancer. Time-dependent covariates included acute or chronic pancreatitis, acute hepatitis, alcoholic fatty liver or cirrhosis, acute alcoholic hepatitis, cholelithiasis, morbid obesity, alcohol dependence syndrome, pseudocyst of pancreas, jaundice, hepatitis B, hepatitis C, cholecystitis, cholangitis, gastric ulcer, and duodenal ulcer. Outcome variable was timed to occurrence of newly diagnosed pancreatic cancer during study period. A subject was censored if he or she died, developed non-pancreatic cancer, or else did not develop pancreatic cancer before end of the study. For selected independent variables that result in a 'best' model, we followed four steps (Hosmer and Lemeshow, 2000). First, selection process began with a careful univariable analysis of each variable. Second, on completion of univariate analysis, we selected variable whose univariable test has a P-value of <0.25 (Bendel and Afifi, 1977; Mickey and Greenland, 1989) as a candidate for our multivariable model. Third, enter candidate variables into the multivariable model. With some comorbidity variables highly collinear, we estimated their regression coefficients and compared these for significance. Only one such highly correlated variable remained in a multivariate Cox model. Finally, after refining a main effects model, we checked assumption of Cox's proportional hazard model for all variables in our multivariate model, further examining interactions between independent variables.

RESULTS

Table 1 shows baseline characteristics according to status of type 2 diabetes. Subjects with and without type 2 diabetes had similar distributions of gender, age, and residential area. Percentages of female and male were 44.44% and 55.56%. Compared with non-diabetics, type 2 diabetics had higher proportion of ageing society area, insurance premium less than NT$19,200, gastric and hepatobiliary comorbidities for acute alcoholic hepatitis, acute hepatitis, acute pancreatitis, alcoholic fatty liver and/or cirrhosis, nonalcoholic fatty liver, cholelithiasis, chronic pancreatitis, morbid obesity, alcohol dependence, pseudocyst of pancreas, jaundice, hepatitis B, hepatitis C, and cholangitis.

A total of 1178 subjects were newly diagnosed with pancreatic cancer during follow-up, with incidence rates of 0.49 per 1000 person-years in type 2 diabetics and 0.26 per 1000 person-years in

Table 1. Baseline characteristics of study cohorts by sociodemographic status and comorbidity in Taiwan

	Non-diabetes (%) ($N=166\ 850$)	Type 2 diabetes (%) ($N=166\ 850$)	Standardised mean difference
Sex			
Female	74 148 (44.44%)	74 148 (44.44%)	0.00
Male	92 702 (55.56%)	92 702 (55.56%)	0.00
Age, mean (s.d.)	50.47 (12.07)	50.71 (11.80)	−0.02
Urbanisation degree			
High density urban area	46 967 (28.48%)	47 128 (28.61%)	0.00
Medium density urban area	47 521 (28.81%)	48 861 (29.66%)	−0.02
Newly developed area	28 844 (17.49%)	28 045 (17.02%)	0.01
General area	24 458 (14.83%)	24 262 (14.73%)	0.00
Ageing society area	3440 (2.09%)	3655 (2.22%)	−0.01
Rural area	7264 (4.40%)	6773 (4.11%)	0.01
Non-developed area	6437 (3.90%)	6028 (3.66%)	0.01
Insurance premium			
INS-AMT < 19 200	41 195 (24.69%)	44 469 (26.65%)	−0.04
19 200≦INS-AMT	125 655 (75.31%)	122 381 (73.35%)	0.04
Comorbidity			
Acute alcoholic hepatitis	19 855 (11.90%)	37 973 (22.76%)	−0.29
Acute hepatitis	177 (0.11%)	91 (0.05%)	0.02
Acute pancreatitis	186 (0.11%)	252 (0.15%)	−0.01
Alcoholic fatty liver	19 864 (11.91%)	37 997 (22.77%)	−0.29
Non-alcoholic fatty liver disease	571 (0.34%)	391 (0.23%)	0.02
Alcoholic cirrhosis of liver	19 837 (11.89%)	37 990 (22.77%)	−0.29
Cholelithiasis	1126 (0.67%)	407 (0.24%)	0.06
Chronic pancreatitis	37 (0.02%)	245 (0.15%)	−0.04
Morbid obesity	113 (0.07%)	605 (0.36%)	−0.06
Alcohol dependence syndrome	317 (0.19%)	314 (0.19%)	0.00
Pseudocyst of pancreas	6 (0.00%)	13 (0.01%)	−0.01
Jaundice	62 (0.04%)	25 (0.01%)	0.02
Hepatitis B	1981 (1.19%)	2248 (1.35%)	−0.01
Hepatitis C	1774 (1.06%)	2141 (1.28%)	−0.02
Cholecystitis	3740 (2.24%)	1953 (1.17%)	0.08
Cholangitis	143 (0.09%)	43 (0.03%)	0.03
Gastric ulcer	41 906 (25.12%)	27 391 (16.42%)	0.21
Duodenal ulcer	41 976 (25.16%)	27 408 (16.43%)	0.22

the non-diabetics. Table 2 displays uni- and multivariate time-dependent Cox's proportional hazard models in a cohort of type 2 diabetics *vs* general population during 1999–2010. Our model building strategy determined a final multivariable model shown in Table 2. Significant adjusted HRs of pancreatic cancer in Cox proportional hazard models were type 2 diabetes (HR: 1.50, 95% CI: 1.32–1.71), age (per 5 years) (1.18, 1.75–1.21), men (1.31, 1.16–1.47), acute alcoholic hepatitis (1.36, 1.19–1.56), acute pancreatitis (1.74, 1.23–2.45), cholelithiasis (0.46, 0.33–0.62), chronic pancreatitis (2.55, 1.69–3.87), cholangitis (9.18, 7.44–11.33), gastric ulcer (2.31, 1.98–2.70), and duodenal ulcer (0.51, 0.43–0.60).

In sensitivity analysis by calculating follow-up starting 1 or 3 years after baseline to rule out the possibility of reverse causaility, type 2 diabetes also showed strong linkage with pancreatic cancer during follow-up starting 1 year after baseline (HR: 1.57, 95% CI: 1.38–1.78, $P<0.0001$), as well as follow-up beginning 3 years later (HR: 1.43, 95% CI: 1.25–1.63). Figure 2 shows adjusted HR of pancreatic cancer for joint effects of type 2 diabetes and acute alcoholic hepatitis, acute pancreatitis, nonalcoholic fatty liver disease, cholelithiasis, cholecystitis, cholangitis, gastric ulcer, and duodenal ulcer. We observed greater magnitude of HRs of pancreatic cancer for type 2 diabetics with acute alcoholic hepatitis, acute pancreatitis, cholecystitis, cholangitis and gastric ulcer *vs* patients with neither type 2 diabetes nor counterpart comorbidity (2.15, 1.81–2.56; 6.55, 2.52–17.04; 3.34, 2.16–5.16; 7.30, 1.01–52.78 and 4.41, 2.38–8.20, respectively). Independent effects of type 2 diabetes were all statistically significant, with narrow 95% CI, and remained similar across risk stratification with comorbidity (range 1.59–1.80). Factors exerting significant independent effect were acute alcoholic hepatitis (1.35, 1.18–1.55), cholecystitis (2.02, 1.47–2.77), and gastric ulcer (2.85, 1.56–5.18). Due to limited number of study subjects with chronic pancreatic or alcohol dependence syndrome, joint association of type 2 diabetes with these was not evaluated. In addition, we detected significant interaction of type 2 diabetes with cholelithiasis, gastric ulcer, and duodenal ulcer ($P=0.027$, 0.007, and 0.001, respectively).

DISCUSSION

This study evaluated association between type 2 diabetes and pancreatic cancer among a large prospective cohort to find positive association between type 2 diabetes and pancreatic cancer during 10–11 year follow-up. Our study's findings show that patients with type 2 diabetes are associated with increased risk of pancreatic cancer; sensitivity analyses remained similar after adjustment for sociodemography and time-dependent comorbidity, to rule out reverse causality. We observed significant joint associations between type 2 diabetes and acute alcoholic hepatitis, acute pancreatitis, cholecystitis, and gastric ulcer on pancreatic cancer risk.

Most previous studies correlating diabetes with pancreatic cancer indicate type 2 diabetes as a risk factor (Coughlin *et al*, 2004; Jee *et al*, 2005; Larsson *et al*, 2005; Inoue *et al*, 2006; Khan *et al*, 2006; Ogunleye *et al*, 2009; Stevens *et al*, 2009; Chodick *et al*, 2010; Chen *et al*, 2011; Lam *et al*, 2011), although one conducted in Japan observed no such association (Khan *et al*, 2006). Temporal association between diabetes and pancreatic cancer has been questioned; some studies had too short a follow-up (Chen *et al*, 2011; Lam *et al*, 2011). It is likely that pancreatic cancer could lead to diabetes by abnormal glucose metabolism (so-called 'reverse-causality' or effect-cause). The American Society of Clinical

Table 2. Risk factors of pancreatic cancer from uni- and multivariate time-dependent Cox's proportional hazard models in cohort of patients with and without type 2 diabetes during 1999–2010 ($n = 1156$ for pancreatic cancer)

Variable	Crude HR[a] (95% CI)	*P*-value	Adjusted HR[b] (95% CI)	*P*-value
Type 2 diabetes	1.61 (1.43–1.83)	<0.0001	1.50 (1.32–1.71)	<0.0001
Age (per 5 years)	1.19 (1.17–1.22)	<0.0001	1.18 (1.75–1.21)	<0.0001
Sex (men *vs* women)	1.29 (1.14–1.45)	<0.0001	1.31 (1.16–1.47)	<0.0001
Acute alcoholic hepatitis	1.49 (1.31–1.69)	<0.0001	1.36 (1.19–1.56)	<0.0001
Acute hepatitis	3.38 (2.37–4.83)	<0.0001		
Acute pancreatitis	3.10 (2.29–4.19)	<0.0001	1.74 (1.23–2.45)	0.0018
Alcoholic fatty liver	1.46 (1.28–1.66)	<0.0001		
Non-alcoholic fatty liver disease	1.31 (1.02–1.67)	0.0332	1.02 (0.79–1.32)	0.8674
Alcoholic cirrhosis of liver	1.38 (1.22–1.58)	<0.0001		
Cholelithiasis	1.07 (0.81–1.41)	0.6533	0.46 (0.33–0.62)	<0.0001
Chronic pancreatitis	4.64 (3.23–6.66)	<0.0001	2.55 (1.69–3.87)	<0.0001
Alcohol dependence syndrome	1.16 (0.64–2.09)	0.631	0.81 (0.44–1.50)	0.4988
Pseudocyst of pancreas	5.03 (1.89–13.40)	0.0012		
Hepatitis B	0.71 (0.52–0.98)	0.0392		
Hepatitis C	0.80 (0.56–1.15)	0.2218		
Cholecystitis	1.84 (1.40–2.40)	<0.0001	1.21 (0.90–1.62)	0.204
Cholangitis	11.81 (9.77–14.26)	<0.0001	9.18 (7.44–11.33)	<0.0001
Gastric ulcer	1.74 (1.55–1.95)	<0.0001	2.31 (1.98–2.70)	<0.0001
Duodenal ulcer	1.07 (0.94–1.21)	0.3187	0.51 (0.43–0.60)	<0.0001

Abbreviations: CI = confidence interval; HR = hazard ratio. Hazard ratios adjusted for residential area, insurance premium, and urbanisation indicator.
[a]Crude hazard ratios without multivariate adjustment.
[b]Variables with *P*-value less than 0.25 for crude hazard ratios entered into multivariate Cox's model.

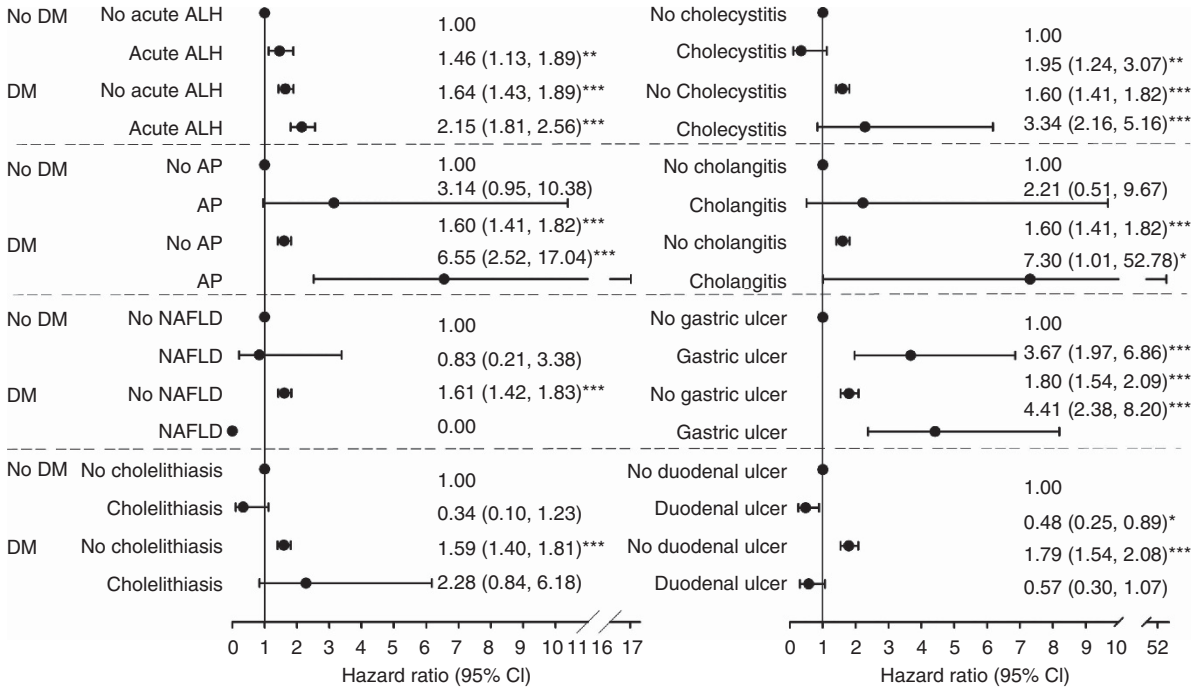

Figure 2. Joint relationship of gastric and hepatobiliary comorbidity and diabetes status on risk of pancreatic cancer. *$P<0.05$; **$P<0.01$; ***$P<0.001$. Abbreviations: DM = diabetes mellitus; ALH = alcoholic hepatitis; AP = acute hepatitis; NAFLD = non-alcoholic fatty liver disease.

Oncology (ASCO) Annual Meeting in 2010 reported temporal association between type 2 diabetes and pancreatic cancer as unclear (Matsubayashi *et al*, 2011). It may be that a small portion of pancreatic cancer belonging to neuroendocrine tumour secretes diverse hormones that cause florid stomach ulcers or uncontrolled high blood pressure and diabetes (Ghaneh *et al*, 2007). To rule out reverse causation or effect-cause association, we evaluated this association at the outset of follow-up; 1 and 3 years after baseline, HR remained significant. This finding enhances causative association.

Type 2 diabetes has been confirmed as a risk factor for development of pancreatic cancer (Larsson *et al*, 2005; Inoue *et al*, 2006; Ogunleye *et al*, 2009; Stevens *et al*, 2009; Chodick *et al*, 2010; Chen *et al*, 2011; Lam *et al*, 2011), but this association has so far

been described for its independent effect. Some previous studies accounted for acute pancreatitis, chronic pancreatitis, alcoholic liver disease, pancreatic pseudocyst and cholelithiasis (Bansal and Sonnenberg, 1995); one of them considered gallbladder disease (Bracci *et al*, 2009), whereas another adjusted for hepatitis B, hepatitis C, cholecystitis, cholangitits, cholelithiasis, gastric ulcer, and duodenal ulcer (Chen *et al*, 2011), however, none of them consider their joint effect with type 2 diabetes on pancreatic cancer. It is unclear whether type 2 diabetes and other gastric and hepatobiliary comorbidities have significant joint roles. Our research showed history of acute alcoholic hepatitis, acute pancreatitis, cholecystitis, and gastric jointly associated with type 2 diabetes for higher risk. Data further suggest acute alcoholic hepatitis, cholecystitis, and gastric ulcer as risk factors.

There is potential misclassification error due to some undiagnosed type 2 diabetes cases in subjects without type 2 diabetes. However, this proportion would be small because Department of Health in Taiwan provides integrated on-the-site screenings for hypertension, diabetes, and hyperlipidaemia in community and primary care settings for adults aged 40 years and over and its fee was covered by NHI program. This kind of misclassification error would result in underestimation of the effect if the association between type 2 diabetes and pancreatic cancer exists, indicating that the true effect would be stronger, a lesser threat to the validity of our finding. In addition, due to limited number of diagnoses can be coded in ambulatory or in-patient claim data, patients with number of diseases more than the number of diagnoses that can be coded in the administrative claim data would be less likely to be included in our study. Thus, our study sample may not be representative of the entire population with type 2 diabetes in term of number of comorbidity. If the incidence rates of pancreatic cancer were similar across subgroups of type 2 diabetic patients with number of comorbidity, then the estimate of HR would be valid. If not, then our study finding is only applicable to type 2 diabetic patients with comorbidity similar to our study sample.

Prior studies report antidiabetic medication altering association between diabetes and pancreatic cancer (Yang, 2009). Metformin and thiazolidinediones (TZDs) protect against tumorigenesis; sulphonylurea raised risk (Yang, 2009; Giovannucci *et al*, 2010; Lee *et al*, 2011). One study demonstrated great reduction in pancreatic cancer risk for metformin users (Lee *et al*, 2011), sulphonylureas elevating risk (Bodmer *et al*, 2012). We tallied about 10% each for sulphonylurea monotherapy and metformin monotherapy (data not shown). Impact of antidiabetic medication on linkage between type 2 diabetes and pancreatic cancer can thus be ignored. Among the merits of our study: it is based on a large and representative population-based sample, hence adequate to detect independent and joint effect of type 2 diabetes and such comorbidity. Also, high coverage rate of NHI program throughout our study could minimise the number of cohort subjects lost to follow-up. Availability of NHIRD data set during follow-up can facilitate time-dependent status of comorbidities. Still, there were limitations. First, we could not obtain data of behavioural factors: for example, tobacco, alcohol, obesity, BMI, and physical activity. We did not consider them, yet it is unlikely that the effect of type 2 diabetes and gastric or hepatobiliary comorbidities would arise solely to effect of behavioural factors, which was weakly or moderately associated with pancreatic cancer. Second, it lacks histological features or pathological stages of pancreatic cancer and thus could not evaluate histological patterns, molecular markers or clinical stages. Third, it is possible that the effect of type 2 diabetes is due to reverse causality. To rule out this possibility, we performed a sensitivity analysis by calculating follow-up starting 1 or 3 years after baseline and the HRs remained significant. However, it is difficult to rule out the possibility of reverse causality due to the weak to moderate association between type 2 diabetes and pancreatic cancer.

Our study highlights pre-existing type 2 diabetes, acute alcoholic hepatitis, acute pancreatitis, chronic pancreatitis, alcohol dependence, cholecystitis, and/or gastric ulcer portending pancreatic cancer. Significant joint effects of acute alcoholic hepatitis, acute pancreatitis, cholecystitis, and gastric ulcer along with type 2 diabetes on pancreatic cancer risk were likewise noted. Clinicians must recognise burden of these gastric and hepatobiliary comorbidities and keep clinically vigilant for diagnosis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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