RESEARCH

Insulin therapy and biliary tract cancer: insights from real-world data

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Abstract

Objective: The association between insulin therapy and the risk of biliary tract cancer (BTC) is uncertain. We aimed to assess this risk in type 2 diabetic patients.
Methods: Using electronic medical data from the Shanghai Hospital Link database, 202,557 patients with type 2 diabetes (164,997 insulin never-users and 37,560 insulin ever-users) were identified in this study between January 1, 2013, and December 31, 2016, with follow-up until December 31, 2019. By propensity score matching, an ever-user was matched with a never-user. Cox proportional hazards regression analysis was used to estimate risk ratios (HRs) and 95% CIs for three subtypes of BTC (intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangiocarcinoma (ECC), and gallbladder cancer (GBC)).
Results: At a mean follow-up of 5.33 years, 143 cases of BTC were observed. The crude incidence rates (per 100,000 person-years) of ECC, ICC, and GBC in ever-users:never-users were 10.22:3.63, 2.04:2.04, and 8.17:6.01, respectively. Insulin therapy was associated with an increased risk of ECC (HR, 4.10; 95% CI, 1.54–10.92; $P = 0.005$) compared to patients who never used insulin. No statistically significant results were observed for insulin and ICC/GBC. Consistent results were also found in the original cohort.
Conclusions: The relationship between insulin therapy and BTC is type-specific. Further studies are warranted to provide evidence on the identification of ECC risk groups among type 2 diabetic patients.

Key Words
- diabetes
- insulin
- biliary tract cancer
- cholangiocarcinoma

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Introduction

Biliary tract cancer (BTC) originates from the epithelium of the biliary tree and can be divided into intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangiocarcinoma (ECC), and gallbladder cancer (GBC) (1, 2). BTC is rare cancer with incidence rates ranging from 0.3 to 6 per 100,000 inhabitants per year in most parts of the world, and its prevalence is relatively high in specific regions, such as China, South Korea, and Thailand, where the incidence rate is higher than 6 per 100,000 inhabitants per year (3, 4). In addition, some studies have shown

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that the prevalence of BTC among patients with type 2 diabetes (T2D) is greatly increased (5, 6, 7, 8), but the exact mechanism is not clear.

Studies have shown that insulin and insulin-like growth factor (IGF) are involved in the development and progression of malignancies (9, 10). Insulin has been reported to be associated with an increased risk of several cancer sites, such as the liver, pancreas, colorectum, and breast (11, 12, 13). However, in a large number of studies on insulin and cancer, only one study has examined the relationship between insulin and BTC. But because only two cases of BTC occurred in 2156 insulin users, the study by Schlesinger *et al*. did not observe an association between insulin therapy and an increased risk of BTC (14).

It is difficult to study the relationship between insulin and BTC because of the low prevalence. This study aimed to investigate the association of insulin therapy with the risk of three subtypes of BTC using real-world data.

Materials and methods

Database

The data used in this study were obtained from the Shanghai Hospital Link Database (SHLD). SHLD is a part of the Shanghai Shenkang Hospital Development Center, an administrative arm of the Shanghai government that monitors 60 tertiary general and specialty hospitals in the city, covering >99% of Shanghai residents. Hospitals in China are organized according to a three-tier system, which recognizes hospitals for their ability to provide medical services and medical education, and conduct medical research. According to this system, hospitals are designated as primary, secondary, or tertiary institutions (15). All tertiary hospitals under the jurisdiction of the SHLD are required to upload all medical data (i.e. outpatient, emergency, and inpatient data) to the SHLD. After encryption, SHLD began releasing this data for academic research in 2013. In 2019, a report of the risk of 23 types of cancer among patients with type 2 diabetes was published using SHLD. This study included 410,191 patients with T2D and standardized incidence ratios were calculated to evaluate the cancer risk (16).

This study was approved by the ethics committee of SHLD and Ruijin Hospital (No. 2020-226Y). To protect privacy, patient identification information was encrypted. All diseases were identified according to the International Classification of Diseases 10th Revision, Clinical Modification (ICD-10-CM), and related diagnostic records.

Inclusion and exclusion criteria

The patient inclusion flow chart is shown in Fig. 1. Patients aged 18–99 years with T2D (E11) diagnosed between January 1, 2013, and December 31, 2016, were identified. We excluded patients with missing information on gender, cholecystectomy, diagnosis of cancer prior to enrollment, ≤365 days of follow-up, and only one recorded diabetes visit.

Patients who had ever used insulin were defined as those who with at least one visit for type 2 diabetes before the first insulin prescription and had ever been prescribed insulin ≥2 times after enrollment to ensure that they were new insulin users and continued to use insulin during follow-up. Patients who had never used insulin were defined as never-users. The index date was defined as the date of the first insulin prescription for ever-users and the date of diagnosis of T2D for never-users and then followed until the diagnosis of incident BTC (ICC (C22.1), GBC (C23), and ECC (C24.0)) death or December 31, 2019, whichever came first.

Variables

Demographic data, such as age, sex, and factors correlated with insulin use, diabetes severity, or cancer risk, were all extracted from SHLD. The ICD-10-CM codes for related confounders are hypertension (I10–I15), stroke (I60–I69), ischemic heart disease (I20–I25), nephropathy (E11.2, N00–N08, N17–N19, and N25–N27), oculopathy (E11.3, H33, H35, and H54), peripheral arterial disease (E11.5, I70–I75, I77–I79, I96, and M30–M31), chronic obstructive pulmonary disease (J40–J47, a surrogate for smoking), biliary stone (K80), and liver diseases (B18.0–B18.2, K70.0, K70.3, K71.7, K74, K75.8, and K76.0). Drugs include biguanides, dipeptidyl peptidase 4 inhibitors, sulfonylureas, thiazolidinediones, calcium channel blockers, statin, and aspirin.

Propensity score matched method

In consideration that the baseline characteristics might be imbalanced between insulin ever-users and never-users in the original cohort, the propensity score matching (PSM) was used to create a PS-matched cohort (the matched cohort) of ever-users and never-users. The PS was created by

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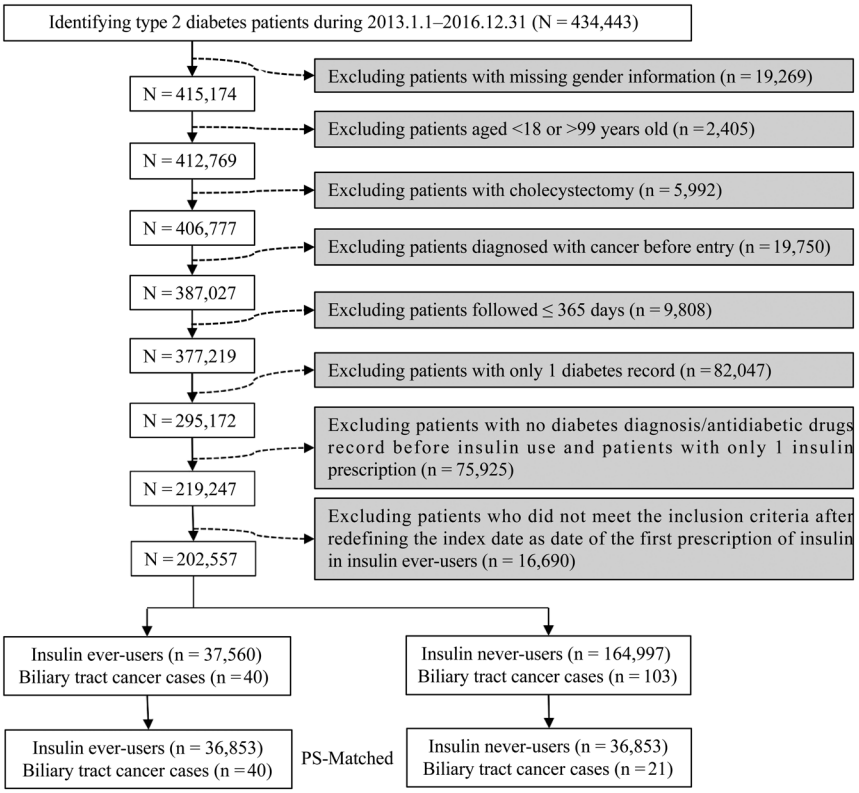

Figure 1
Flow chart of study population selection. This study identified 434,443 patients with type 2 diabetes (T2D) between January 1, 2013, and December 31, 2016. The gray boxes show the subjects excluded from the study (see inclusion and exclusion criteria). Finally, 202,557 T2Ds were included and divided into insulin ever-users and never-users. In addition, a propensity score matched method was adopted to further reduce the effect of confounding factors to validate the results of the original cohort. PS matched: propensity score matched.

multivariable logistic regression with all the characteristics listed in Table 1. Standardized mean differences were calculated for all the covariates, and a value less than 10% may indicate relatively balanced (17).

Statistical analysis

Baseline characteristics between ever-users and never-users of insulin were compared by Student's *t*-test for age and by

Table 1 Baseline characteristics of insulin never-users and ever-users.

Variables	Original cohort				Matched cohort			
	Never-users (*n* = 164,997)	Ever-users (*n* = 37,560)	*P*-value	SMD	Never-users (*n* = 36,853)	Ever-users (*n* = 36,853)	*P*-value	SMD
Age	61.37 (13.18)	63.66 (13.06)	<0.01	0.17	63.50 (12.65)	63.63 (13.10)	0.19	0.01
Sex (male)	85,332 (51.72)	19,478 (51.86)	0.63	0.00	19,258 (52.26)	19,095 (51.81)	0.23	0.01
DPP4-inhibitor	17,085 (10.35)	6268 (16.69)	<0.01	0.19	5964 (16.18)	5884 (15.97)	0.43	0.01
Biguanides	85,199 (51.64)	22,223 (59.17)	<0.01	0.15	21,420 (58.12)	21,626 (58.68)	0.13	0.01
Sulfonylureas	69,114 (41.89)	17,682 (47.08)	<0.01	0.11	16,973 (46.06)	17,241 (46.78)	0.05	0.02
TZDs	24,279 (14.71)	8418 (22.41)	<0.01	0.20	7992 (21.69)	8016 (21.75)	0.84	<0.01
COPD	36,743 (22.27)	9454 (25.17)	<0.01	0.07	9320 (25.29)	9229 (25.04)	0.45	0.01
Hypertension	85,661 (51.92)	23,545 (62.69)	<0.01	0.22	22,856 (62.02)	22,951 (62.28)	0.48	0.01
IHD	47,686 (28.90)	15,192 (40.45)	<0.01	0.24	14,734 (39.98)	14,732 (39.98)	0.99	<0.01
Nephropathy	28,132 (17.05)	11,903 (31.69)	<0.01	0.35	11,535 (31.30)	11,295 (30.65)	0.06	0.01
Oculopathy	13,403 (8.12)	6225 (16.57)	<0.01	0.26	5734 (15.56)	5649 (15.33)	0.39	0.01
PAD	25,060 (15.19)	9445 (25.15)	<0.01	0.25	8972 (24.35)	8949 (24.28)	0.85	<0.01
Stroke	35,981 (21.81)	11,601 (30.89)	<0.01	0.21	11,210 (30.42)	11,195 (30.38)	0.91	<0.01
Aspirin	61,694 (37.39)	19,723 (52.51)	<0.01	0.31	19,024 (51.62)	19,094 (51.81)	0.61	<0.01
CCB	75,493 (45.75)	24,416 (65.01)	<0.01	0.40	23,491 (63.74)	23,722 (64.37)	0.08	0.01
Statins	78,091 (47.33)	24,087 (64.13)	<0.01	0.34	23,160 (62.84)	23,402 (63.50)	0.07	0.01
Liver diseases	4048 (2.45)	1957 (5.21)	<0.01	0.14	1868 (5.07)	1790 (4.86)	0.19	0.01
Biliary stone	7240 (4.39)	2315 (6.16)	<0.01	0.08	2200 (5.97)	2216 (6.01)	0.82	<0.01

Age was presented as mean (s.d.), other variables are presented as number (%) of participants with a condition.
CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; DPP4-inhibitor, dipeptidyl peptidase 4 inhibitor; IHD, ischemic heart disease; PAD, peripheral arterial disease; SMD, standardized mean differences; TZDs, thiazolidinediones.

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chi-square test for other variables. The results were presented as means with S.D. for continuous variables or frequencies with percentages for categorical variables. Crude incidence rates (CIRs) of BTC and its subtypes were calculated for never-users and ever-users. The numerator was the case number of BTC/each subtype and the denominator was the person-years of follow-up. Cox proportional hazards regression was performed to estimate hazard ratios (HRs) with 95% CIs for ECC, ICC, and GBC, adjusting for all covariates shown in Table 1. *P*-value < 0.01 was considered statistically significant. All statistical analyses were performed using R language software, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

This study included 202,557 patients with T2D in the final analysis (164,997 insulin never-users and 37,560 insulin ever-users). Among them, a total of 143 cases of BTC occurred with 40 cases in ever-users and 103 cases in never-users. The CIRs of BTC in ever-users and never-users were 20.43 and 11.67 per 100,000 person-years, respectively. For three subtypes, the CIRs of ECC, ICC, and GBC in ever-users and never-users were 10.22 and 3.63 per 100,000 person-years, 2.04 and 2.04 per 100,000 person-years, and 8.17 and 6.01 per 100,000 person-years, respectively (Supplementary Table 1, see section on supplementary materials given at the end of this article).

Figure 2 and Table 2 show the HRs by insulin exposure in the matched cohort and the original cohort. Compared with never-users, those with insulin treatment were associated with a significantly increased risk of ECC (HR: 4.10; 95% CI, 1.54–10.92; $P = 0.005$), and a similarly positive result was found in the original cohort (HR, 2.38; 95% CI, 1.33–4.27; $P = 0.004$). However, no significant

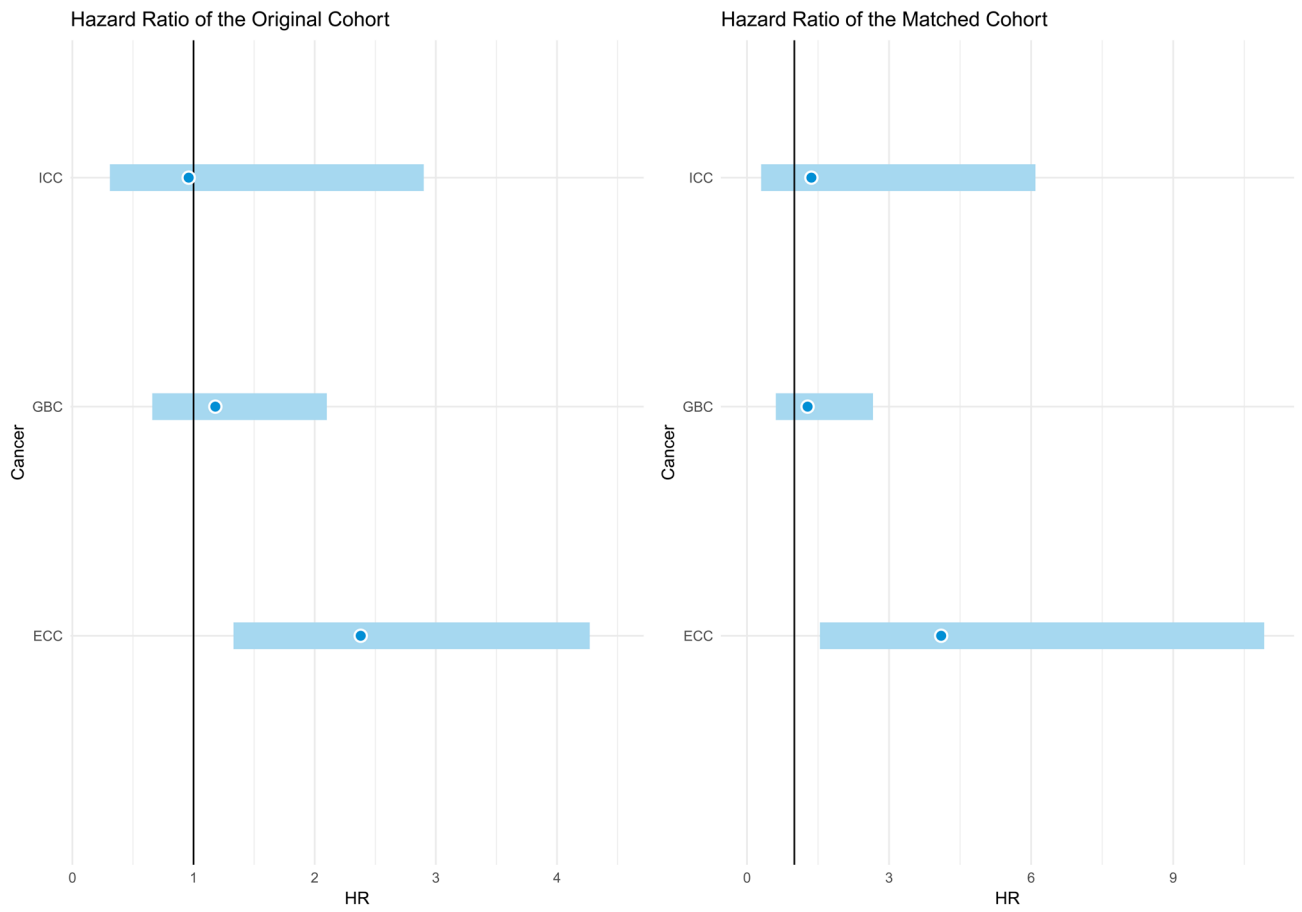

Figure 2
Forest plot of the hazard ratio. In the original cohort, insulin therapy was associated with a significantly increased risk of ECC, but no significant results were obtained in the analysis of the correlation between insulin therapy and the risk of ICC/GBC. Consistent results were also found in the matched cohort. BTC, biliary tract cancer; ICC, intrahepatic cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; HR, hazard ratio.

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Table 2 Insulin therapy and the risk of three subtypes of BTC.

Cancer type	Original cohort			Matched cohort		
	No. cases never:ever	HR (95% CI)	*P*-value	No. cases never:ever	HR (95% CI)	*P*-value
ICC	18:4	0.96 (0.31–2.90)	0.935	3:4	1.36 (0.30–6.09)	0.686
GBC	53:16	1.18 (0.66–2.10)	0.581	13:16	1.28 (0.61–2.66)	0.512
ECC	32:20	2.38 (1.33–4.27)	0.004	5:20	4.10 (1.54–10.92)	0.005

BTC, biliary tract cancer; ECC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; HR, hazard ratio; ICC, intrahepatic cholangiocarcinoma.

associations were observed in ICC and GBC in both matched and original cohorts.

Discussion

The findings suggest that insulin therapy is associated with a significantly increased risk of ECC in insulin users, while no significant results were obtained in the analysis of the correlation between insulin therapy and the risk of ICC/GBC.

Lifting the fog between insulin therapy and the risk of ECC is a pressing question. First, in exploring the exact mechanism, close attention should be paid to the altered action of exogenous insulin. When exogenous insulin acts on the human body, it can cause liver hypoinsulinemia and peripheral hyperinsulinemia, which are important factors in promoting tumorigenesis (18). In addition, the most widely used type of exogenous insulin in clinical practice is the long-acting insulin analog (19), which differs from natural insulin in terms of post-receptor signaling and biological effects because it is structurally modified (20, 21). In addition to activating the insulin receptor cascade response, long-acting insulin analogs can also affect the IGF-1 receptor cascade response (22). And there is evidence from Alvaro's study that IGF-1 or IGF-1R is strongly expressed in cholangiocarcinoma and not in normal cholangiocytes (23). It is indicated that long-acting insulin analogs may play a role in biliary carcinogenesis by the activation of IGF-1R.

In terms of risk heterogeneity among the three subtypes of BTC, the main reason may lie in differences in cellular origin. According to available findings, ICC originates from hepatic progenitor cells, hepatocytes, or cholangiocytes, whereas ECC and GBC mostly originate from cholangiocytes (1, 24). Particularly, ECC cells are mainly derived from cells located in the peribiliary glands (PBGs), which contain stem/progenitor cells for biliary tree regeneration and can differentiate toward islet cells in T2D (25). Long-term sustained hyperinsulin and hyperglycemic stimulation promote the proliferation of PBG cells, and small genetic mutations that accumulate in this process can sometimes lead to tumors (26). Thus, differences in cellular origin may be the main reason for the risk heterogeneity of three subtypes of BTC.

Strengths and limitations

Our study has several strengths. First, we analyzed the correlation between insulin therapy and the risk of three subtypes of BTC in T2D patients in Shanghai and found risk heterogeneity. Secondly, this is the first study using electronic medical records to investigate the effect of insulin therapy on the risk of BTC and reach meaningful conclusions, which bridges the knowledge gap in this field. However, our study also has limitations. First, we were unable to calculate the insulin dosage and duration of use to determine the dose-response relationship. Because of these limitations, we corrected for all available confounders in order to reach a reliable conclusion. Although we failed to evaluate the dose–response relationship, our study revealed a type-specific relationship between insulin therapy and the risk of BTC, which can be informative for the identification of specific BTC risk groups among diabetic patients. Secondly, we still suffered from residual confounding effects due to the lack of data for some potential confounders, such as data on blood glucose level and glycosylated hemoglobin, which are implications for the severity of diabetes. In order to reduce this confounding effect, we adjusted for several diabetes-related complications, including diabetic nephropathy, diabetic eye diseases, and peripheral arterial diseases, which indicate advanced diabetes. Although this strategy can return a more reliable result, it does not completely eliminate these residual confounding effects. Finally, we failed to identify the types of insulin to clarify the heterogeneity between insulin types and the risk of BTC. Further study is necessary to provide more information.

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Conclusion

The results of this study suggest that the relationship between insulin therapy and the risk of biliary tract cancer is type-specific, which shows a significantly increased risk of subtype ECC in insulin users among T2D patients. Given that the prevalence of ECC among insulin users is much higher compared to non-users, the findings of our study can provide useful information for the prevention of ECC in diabetic patients. In patients with T2D who are exposed to risk factors for ECC, such as bile duct cysts and primary sclerosing cholangitis, we suggest that ultrasound examinations of the liver and biliary system as well as carcinoembryonic antigen detections should be performed regularly after insulin administration. Because of the low incidence of BTC in diabetic patients, the development of specific ECC prevention strategies would not have an impact on the use of insulin for glycemic control in all diabetic patients. As the present study is only a revelation from real-world data, further prospective studies and basic experiments are still needed to validate our results.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-21-0546.

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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Data availability

The data sets analyzed during the current study are available from the corresponding author on reasonable request.

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