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Results from A Longitudinal Cohort and Mendelian Randomization Study Show A Relationship Between the Age at Diabetes Beginning or the Length of Diabetes and the Risk of Developing Pancreatic Cancer Later

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Abstract

Background: The study aims to estimate the incidence of pancreatic cancer in people with new-onset type 2 diabetes (T2DM) and examine the connection between pancreatic cancer risk, age at diagnosis, and duration of diabetes.

Methods: Mendelian randomization (MR) in the east-Asian population and this longitudinal cohort study with 428,362 new-onset T2DM patients in Shanghai were used to investigate the association. All patients' and subgroups' incidence rates of pancreatic cancer were calculated and compared to the general population.

Result: During eight years of follow-up, a total of 1056 incident cases of pancreatic cancer were identified. T2DM patients had a standardized incidence ratio (SIR) of 154 (95% CI, 145–164), which was higher than the general population's annual pancreatic cancer incidence rate of 5528/100,000 person years. The older groups with T2DM had a significantly higher incidence of pancreatic cancer, which increased with age. However, the 20–54-year-old group had a higher SIR of 573 (95% CI, 449–722) and a relative risk of pancreatic cancer that was inversely related to age of T2DM onset. Any duration of diabetes was associated with an increased risk of pancreatic cancer. Pancreatic cancer was linked to fasting blood glucose levels below 10 mmol/L. T2DM had a positive correlation with the risk of pancreatic cancer, according to MR analysis.

Interpretation: Efforts toward early and close follow-up programs, particularly in people with young-onset T2DM, and the improvement of glucose control might be effective strategies for improving the detection of pancreatic cancer and the outcomes of its treatment.

Keywords: Type 2 diabetes mellitus; Pancreatic cancer; Onset age; Diabetes duration; Mendelian randomization

Introduction

The prognosis for pancreatic cancer is typically worse than that of most other tumors, and the 5-year survival rate is less than 5%. Pancreatic cancer is one of the leading causes of cancer death worldwide and in China. A cross-journal series of four reviews was published in 2020 by The Lancet Oncology, The Lancet Gastroenterology & Hepatology, and EBioMedicine [1]. It emphasized the need to collaborate in order to lessen the burden of pancreatic cancer and highlighted the progress being made in all areas of research. The overall prognosis of pancreatic cancer can be improved with early diagnosis and treatment, according to previous research. However, screening a large population is not considered feasible for the general population to detect the disease in its early stages. The way to analysis and therapy is to distinguish the populace at high-chance of pancreatic malignant growth as soon as possible [2].

Various modifiable gamble factors have been distinguished for pancreatic malignant growth, including smoking, heftiness, and liquor use, while age and familial disease disorders are viewed as nonmodifiable gamble factors for the illness. In populations of the Asia-Pacific region, diabetes may be a modifiable risk factor for pancreatic cancer.6 The global prevalence of type 2 diabetes (T2DM) is rising, and the increase in T2DM in Asia is anticipated to be greater and more rapid than that on other continents [3]. Impaired glucose metabolism is associated with adverse macro- and micro-vascular outcomes and with a higher incidence of cancers. The association between T2DM and the development of pancreatic cancer has indeed been recognized for more than a century. Convincing evidence has indicated that T2DM is associated with an increased risk for pancreatic cancer and that T2DM can worsen cancer stage and increase cancer-related mortality. However, few studies have investigated age of diabetes onset and diabetes duration in relation to the In addition, very little is known about how different levels of fasting blood glucose (FBG) affect the risk of pancreatic cancer in new-onset T2DM patients. In the present study, we used two-sample Mendelian randomization (MR) to look for additional evidence that type 2 diabetes and pancreatic cancer are linked in a separate east Asian population [4].

Methods

Concentrate on plan and populace

We played out a longitudinal partner study to evaluate the relationship of type 2 diabetes with the gamble of pancreatic disease. The Shanghai Municipal Center for Disease Control and Prevention (SCDC)'s Shanghai Standardized Diabetes Management System (SSDMS) data were the basis for the analysis. In accordance with the

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requirements of the National Basic Public Health Service Program (NBPHSP) in Shanghai, community health centers (CHCs) are required to provide management for T2DM patients and upload electronic records to SSDMS [5]. The system was established in 2004 and covers 241 community health service centers in 16 districts of Shanghai. The SCDC organized for the 16 district CDC to randomly select a proportion of patients with type 2 diabetes for quality control in the form of annual telephone and face-to-face investigations in order to ensure the accuracy and reliability of registration management information. These included newly diagnosed cases through community-based screenings or physical examinations as well as routine outpatient visits. The system did not include T1DM patients [6]. During the initial registration assessment, baseline information, such as height, weight, blood pressure, and glucose levels, were gathered for each SSDMS case of T2DM. In the current analysis, medication use, smoking history, alcohol consumption, and physical activity were not available from all patients in the current system.

Mendelian randomization

We used two-sample MR analyses with the TwoSampleMR and MRPRESSO packages to identify potential causal links between FBG level, T2DM, and pancreatic cancer. We used T2DM and FBG (in non-diabetic people) as exposures in our MR. The Asian Genetic Epidemiology Network conducted a large genome-wide association study (GWAS) of T2DM in the east Asian population. The Meta-Analyses of Glucose and Insulin-related traits Consortium provided Asia-ancestry GWAS summary statistics of FBG level in participants without T2DM. The GWAS of pancreatic cancer was extracted from the biobank in the east Asian population, the Biobank of Japan (BBJ). For MR analyses, we When there were no shared SNPs between exposures and outcomes, r2>0.8 proxies were added. At long last, the remained SNPs were considered as substantial instruments variations (IVs) utilized in MR [7].

Results

Baseline characteristics

This study looked at 428,362 patients with new-onset T2DM, with 205,694 males (48.02 percent) and 222,668 females (51.98 percent) participating. Females with T2DM were older (64,110,87 years vs. 62,114,27 years, P00001) and had lower FBG (7,18,61 vs. 7,34,81, P00001). Patients with pancreatic cancer were older (69,71,93 vs. 63,80,11, P0,0001), had a lower body mass index (BMI) (23,80,324 vs. 24,43,311 kg/m2), and had a higher FBG (7,69,246 vs. 7,26,171 mmol/L, P0,0001), respectively. According to Supplemental Table 3, patients with pancreatic cancer who were diagnosed within a year of T2DM had a lower baseline BMI (23.13.08 kg/m2) and higher glucose (8.24.13 mmol/L) than those who were diagnosed more than a year after diabetes [8].

The incidence rate of pancreatic cancer

During the study period, 1,056 incident cases of pancreatic cancer were found in patients who were followed from the time they were diagnosed with T2DM, with a mean follow-up of 45.2 years. In all T2DM patients, the crude incidence rates of pancreatic cancer were 5528 per 100.000 PYs (95 percent CI, 5199–5869) and 5961 (95 percent CI, 5468–6480) per 100,000 PYs for males and 5138 (95 percent CI, 4705–5596), respectively. In general, patients with T2DM had an ASR of 2075/100,000 PYs (95 percent CI, 1895–2254). The SIRs of pancreatic disease in T2DM versus overall public were 1·54 (95%CI, 1·45-1·64) in all T2DM patients, 1·54 (95%CI, 1·41-1·67) in guys and 1·57(95%CI, 1·44-1·71) in females (Table 2).

The outright and relative gamble of pancreatic malignant growth across various ages at beginning

The yearly occurrence of pancreatic disease expanded from 17·62 per 100,000 PYs in those with time of determination of T2DM 20-54 years to 40·76 in patients matured 55-64 years, 68·45 in those matured 65-74 years and 120·45 per 100,000 PYs in patients ≥75 years old. The older groups with T2DM had a significantly higher rate of pancreatic cancer. The SIR, which was inversely correlated with age at T2DM onset, was used to represent the relative risk of pancreatic cancer [9]. SIRs were 146 (95% CI, 130–162) in patients aged 65–74 years, 124 (95% CI, 112–137) in those new-onset T2DM group aged 75 years, with a significantly higher SIR of 573 (95% CI, 449–722) observed in those with age of diagnosis of T2DM between 20 and 54 years. When males and females were analyzed separately, similar patterns emerged (Table 2 and Figure 2). The incidence of pancreatic cancer in the cohort across sexes and age groups exhibited similar patterns after excluding patients whose pancreatic cancer was diagnosed before or within six months of T2DM confirmation [10].

The relationship between the duration of diabetes and the risk of pancreatic cancer We looked at the relationship between the duration of T2DM and the risk of pancreatic cancer every 12 months. In all eight years of follow-up, new-onset T2DM was significantly associated with an increased risk of pancreatic cancer, as shown in Figure 3 and Supplemental Table 4, with a higher crude rate and SIR among T2DM diagnosed within one year (64-31; 1·73), inside the 6-year (58·55;1·73), the 7-year (59·47; 1:79) and a total of seven years (57:42; 1·78). Comparable examples were found in guys and females dissected independently.

The relationship between various FBG levels and the risk of pancreatic cancer in patients with new-onset T2DM was the subject of our investigation. In categorical analysis, the risk of pancreatic cancer is significantly higher in the group with FBG 100 mmol/L than in the group with lower FBG [11]. Patients with FBG 10 mmol/L had a hazard ratio of 235 for pancreatic cancer (95% CI; 177–313), whereas those with FBG 6 mmol/L were not. Spline curves revealed a log-linear relationship between FBG and the risk of pancreatic cancer in all subjects after adjusting for sex, age, BMI, and SBP. After making adjustments for age, BMI, and SBP, the pattern of the association remained the same for both men and women. The pattern of the association between pancreatic cancer and FBG levels in patients with new-onset T2DM was similar after excluding patients whose pancreatic cancer was diagnosed before or within six months of T2DM confirmation [12].

Discussion

Over the course of eight consecutive years, we gathered data on new-onset T2DM and pancreatic cancer for the current study. The three most important findings are as follows: 1) MR analysis in an east-Asian population suggested that patients with new-onset T2DM have a higher risk of pancreatic cancer in both men and women among Chinese adults than the general population; 2) Our review researched both the outright and relative gamble of pancreatic disease across various age gatherings and carved out for the principal opportunity, as far as anyone is concerned, that albeit the outright gamble of pancreatic malignant growth expanded with age, the overall gamble of pancreatic disease was contrarily connected with age at beginning of T2DM, with an essentially higher SIR of 5·73 saw in those matured 20-54 years at beginning of T2DM; 3) In a large-scale T2DM study, we first reported the risk of pancreatic cancer and the duration of diabetes overall. The

association between T2DM and the development of pancreatic cancer has been investigated for more than a century.11,25,26 However, the observational results varied across different races and regions. Patients with diabetes diagnosed more than 5 years ago and those with higher FBG levels had an increased risk of pancreatic cancer, with the risk being 235 times higher among those with FBG 10 mmol/L compared to those with FBG 6 mmol/L [13]. A recent meta-analysis of 26 case-control studies in China involving 7,702 pancreatic cancer cases and 10,186 controls produced pooled results showing that patients with T2DM had an overall 369-fold (95% CI;) risk of pancreatic cancer.27 In a US cohort from female participants in the Nurses' Health Study and male participants in the Health Professionals Follow-Up Study, recent-onset diabetes was associated with a risk of pancreatic cancer that was 297-fold higher than When we compared the absolute and relative incidence of pancreatic cancer in T2DM with the general population, we found a positive association between T2DM and pancreatic cancer.28 The present study was consistent with the previous studies and identified a positive association between T2DM and pancreatic cancer. The positive association between T2DM and pancreatic risk, particularly in east-Asian patients, was further established by MR analysis.

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None

Conflict of Interest

None

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