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Pancreatic cancer risk in diabetic patients using the Japanese Regional Insurance Claims

Tatsunori Satoh[1,2,3], Eiji Nakatani[3]✉, Hiroyuki Ariyasu[4], Shinya Kawaguchi[2], Kazuya Ohno[2], Hiroshi Itoh[5], Kaori Hayashi[1] & Takeshi Usui[3,6]

Pancreatic cancer presents a critical health issue characterized by low survival rates. Identifying risk factors in specific populations, such as those with diabetes, is crucial for early detection and improved outcomes. This study aimed to identify risk factors for pancreatic cancer in diabetic patients using a longitudinal cohort from the Shizuoka Kokuho database, spanning April 2012 to September 2021. Diabetic patients were identified and monitored for the onset of pancreatic cancer. Factors analyzed included age, sex, the Elixhauser comorbidity index, and specific comorbidities. Statistical analyses involved univariate and multivariate Cox proportional hazards regression. The study identified 212,775 as diabetic patients and 1755 developed pancreatic cancer during the period. The annual incidence rate of pancreatic cancer in this group was 166.7 cases per 100,000 person-years. The study identified older age, male sex, a history of liver disease, chronic pancreatitis, and pancreatic cystic lesions as significant risk factors for pancreatic cancer in diabetic patients. The study also highlighted the absence of a significant association between diabetes type or diabetic complications and the onset of pancreatic cancer. These findings may aid in the early diagnosis of pancreatic cancer in diabetic patients and may inform revisions in screening practices in diabetic patients.

Keywords Chronic pancreatitis, Cohort study, Diabetes, Pancreatic cancer, Pancreatic cystic lesions, Risk factors

Malignant pancreatic tumors, particularly pancreatic cancer (PC), are associated with notably poor prognoses, as evidenced by a 5-year overall survival rate of only 8.5% in Japan[1]. Conversely, patients with tumors measuring 10 mm or smaller have a significantly higher 5-year survival rate, exceeding 80%[2]. Nonetheless, cancer registry data reveal that only 1.7% and 4.1% of all PC patients are classified as UICC stage 0 and IA, respectively[2]. Therefore, early diagnosis is critical to improving the prognosis of PC. Identifying risk factors for PC is crucial for early-stage detection. The Japanese clinical practice guidelines for pancreatic cancer[3] list several risk factors: familial history[4], smoking[5–7], drinking[8,9], diabetes[10–13], obesity[14–18], chronic pancreatitis[19–21], pancreatic cystic lesions[22–25], gallstones/cholecystectomy[26], *H. pylori* infection[27], HBV infection[28] and HCV infection[29]. Diabetic patients, who regularly visit the hospital, present a practical opportunity for pancreatic surveillance. However, with approximately 10 million diabetic patients in Japan[30,31], it is impractical to conduct pancreatic surveillance on all of them. Effective surveillance for PC could be achieved by identifying diabetic patients at high-risk for PC who already require regular hospital visits. Nevertheless, there is a notable lack of research on pancreatic cancer risk factors within the diabetic population. This study, therefore, aimed to identify the risk factors that contribute to the development of pancreatic cancer in diabetic patients.

Materials and methods

Study design and data sources

Our study employed a cohort design utilizing the Shizuoka Kokuho database (SKDB)[32]. The SKDB is an administrative claims database for beneficiaries in Shizuoka Prefecture's municipal government insurance program, including the National Health Insurance and late-stage medical care system for the elderly. Shizuoka

[1]Division of Endocrinology, Metabolism and Nephrology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan. [2]Department of Gastroenterology, Shizuoka General Hospital, Shizuoka, Japan. [3]Graduate School of Public Health, Shizuoka Graduate University of Public Health, 4-27-2 Kitaando, Aoi-Ku, Shizuoka 420-0881, Japan. [4]Department of Diabetes and Endocrinology, Shizuoka General Hospital, Shizuoka, Japan. [5]Center for Preventive Medicine, Keio University, Tokyo, Japan. [6]Research Support Center, Shizuoka General Hospital, Shizuoka, Japan. ✉email: nakatani.eiji.int@gmail.com

Prefecture, with a population of approximately 3.6 million, features a climate and demographic profile representative of Japan. The SKDB covers a regional, population-based longitudinal cohort of 2,571,418 individuals from Shizuoka. All data from SKDB enrollees underwent preprocessing, which involved extensive cleaning and anonymization[32]. This dataset comprises basic subscriber information (e.g., sex, age, zip code, observation period, and reason for disenrollment, including death) and claims from public health insurance organizations (below 75 years for the National Health Insurance system and above 75 years for the Late-stage Elderly Medical Care System). The utility of the SKDB in real-world risk factor analysis is underscored by its comprehensive data on mortality and follow-up attrition, derived from the Basic Resident Registration System. The database has supported various studies, particularly in risk factor analysis[33–35].

Observation period and study population

In this database-nested cohort study, we utilized the SKDB from April 1, 2012, to September 30, 2021. Figure 1 illustrates the study schema. The investigation involved examining enrollees through the individually linked data in the databases, focusing on their annual health checkups and insurance claims. For each enrollee, the data availability spanned from the later of either their insurance registration date or April 2012, whichever was later, to the earlier of either their insurance withdrawal date or September 30, 2021. Diabetic patients were selected for cohort inclusion based on identification and extraction from the database. The exclusion criteria included those diagnosed with pancreatic cancer prior to or concurrent with their initial health checkup or insurance claim, a history of any cancer (apart from nonmelanoma skin cancer), and an observation period of less than one year. Additionally, diabetic patients who developed pancreatic cancer within 1 year following their diabetes diagnosis were excluded to avoid confounding with secondary diabetes caused by pancreatic cancer.

Definition of diabetic patients and outcome

Diabetic patients were identified by the prescription of one or more antidiabetic agents (Supplementary Table 1), including insulin (since antidiabetic agents are not commercially available in Japan), and insurance claims indicating diabetes mellitus (E10, E11, or E14) during the baseline period. In contrast, nondiabetic patients had no such prescriptions in the same timeframe. The primary outcome of the study was the incidence of pancreatic cancer, determined using International Classification of Disease 10 (ICD-10) codes from claims data (Supplementary Table 2). To improve specificity, provisional diagnoses of pancreatic cancer and diabetes were excluded.

Variables

Our analysis incorporated several candidate confounders, including age, sex, the Charlson-Elixhauser comorbidity index, and covariates previously identified in relevant reports[36–42]. We determined the presence of individual comorbidities using standard definitions from the Charlson-Elixhauser comorbidity index[43,44]. In assessing specific comorbidities, we utilized a one-year period prior to the medical examination date as the search timeframe. A comorbidity was considered present if it was confirmed in the insurance claims data. The type of diabetes agent was excluded from our variables. This exclusion stems from the study's design, which is not aligned with the Prevalent New-user Design, and therefore does not investigate the relationship between PC development and diabetes medications[45–47].

Statistical analysis

Frequencies and percentages were calculated for categorical variables, and the mean and standard deviation were calculated for continuous variables. For comparing continuous and categorical variables across groups, we employed the *t* test and chi-square test, respectively. Univariate and multivariate cause-specific Cox proportional hazards regression analyses were performed to explore factors associated with pancreatic cancer onset.

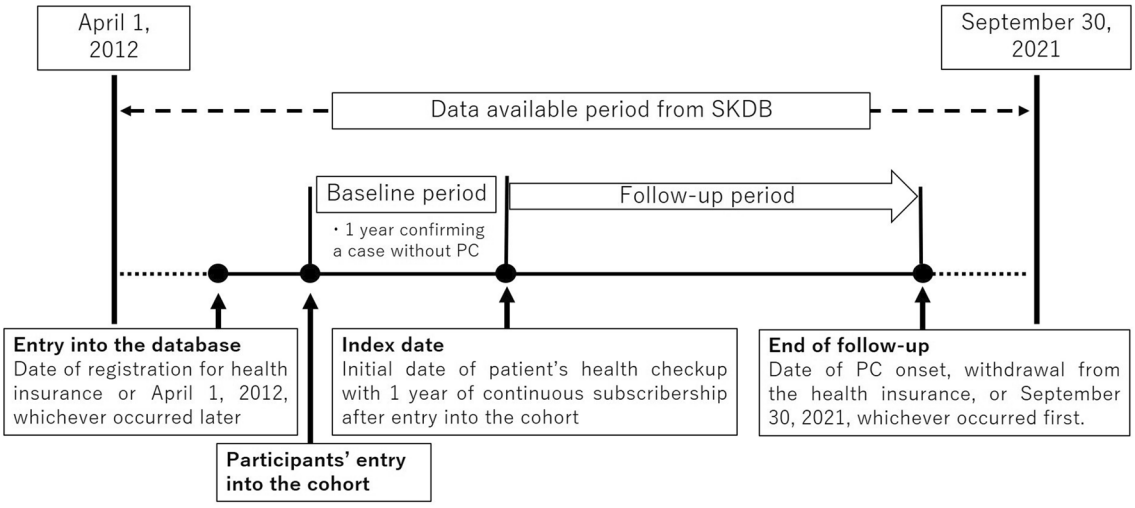

Figure 1. Study schema.

This method is suitable for our study as it deals with time-to-event data, allowing us to account for the varying follow-up times among participants. The hazard ratio (HR), 95% confidence interval (CI), and p-value of Wald test were calculated to estimate the relative risk of pancreatic cancer over time. In the regression analysis, we included both reported risk factors (e.g., pancreatic cysts) and potential risk factors (e.g., critical etiological and epidemiological factors). To ensure a conservative approach, no model selection was carried out, and all variables that reached statistical significance in the univariate regression analysis were entered into the multivariate regression analysis. We excluded one of two highly correlated variables (absolute Spearman's correlation coefficient >0.4) from the multivariable model to avoid multicollinearity. All p-values were two-sided, with a threshold of <0.05 set for statistical significance. The 95% CI for annual incidence rate of pancreatic cancer was calculated using the Normal approximation to the Poisson distribution, following the method outlined in Rosner's "Fundamentals of Biostatistics" (5th Ed). The Kaplan–Meier method estimated overall survival for the pancreatic cancer population, with cumulative incidence curves compared using the log-rank test. All analyses adhered to the intention-to-treat principle. For statistical analyses, we used SAS version 9.4 (SAS Institute, Cary, NC, USA), EZR version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), and R statistical software version 4.2.1 (The R Foundation for Statistical Computing).

Ethics

The data of all enrollees were anonymized to ensure participant confidentiality[32]. This study adhered to the principles of the Declaration of Helsinki. The study protocol received approval from the Medical Ethics Committee of the Shizuoka Graduate School of Public Health (SGUHPH_2021_001_067), and this committee waived the requirement for informed consent.

Results

Study population and baseline characteristics

The Shizuoka Kokuho database, which comprises 2,571,418 individuals, identified 212,775 as diabetic patients with a baseline period exceeding one year, as detailed in Fig. 2. Of these patients, 1755 developed pancreatic cancer during the observation period, which had a median duration of 5.1 years and a maximum of 8.5 years. The annual incidence rate of pancreatic cancer in this group was 166.7 cases per 100,000 person-years [95% CI 158.9–174.5], and incidence rates in patients newly diagnosed with diabetes and those with an existing diagnosis were 156.7 cases per 100,000 person-years [95% CI 141.9–172.8] and 169.9 cases per 100,000 person-years [95% CI 161.0–179.1], respectively. Table 1 presents the baseline characteristics of both the patients diagnosed with pancreatic cancer and those without the disease.

Identification of risk factors for pancreatic cancer in diabetic patients

Potential risk factors and significant variables were evaluated using univariate Cox regression analysis (Table 1). Identified candidate risk factors included older age, male sex, coexisting liver disease, cardiac arrhythmias, hypertension, chronic pancreatitis, and pancreatic cystic lesions, each with p-values below 0.05. These variables were subsequently incorporated into a multivariate model. The multivariable regression results, presented in Table 2, indicated that older age and male gender were associated with an increased risk of pancreatic cancer (HR: 1.267 [95% CI 1.150–1.395]). Liver disease emerged as a notable risk factor (HR: 1.13 [95% CI 1.01–1.26]). Significant correlations were found between the onset of PC and both chronic pancreatitis (HR: 1.98 [95% CI 1.48–2.64]) and pancreatic cystic disease (HR: 4.79 [95% CI 3.43–6.67]). Neither the type of diabetes nor the presence of diabetic comorbidities was associated with the onset of PC. Furthermore, the risk of pancreatic

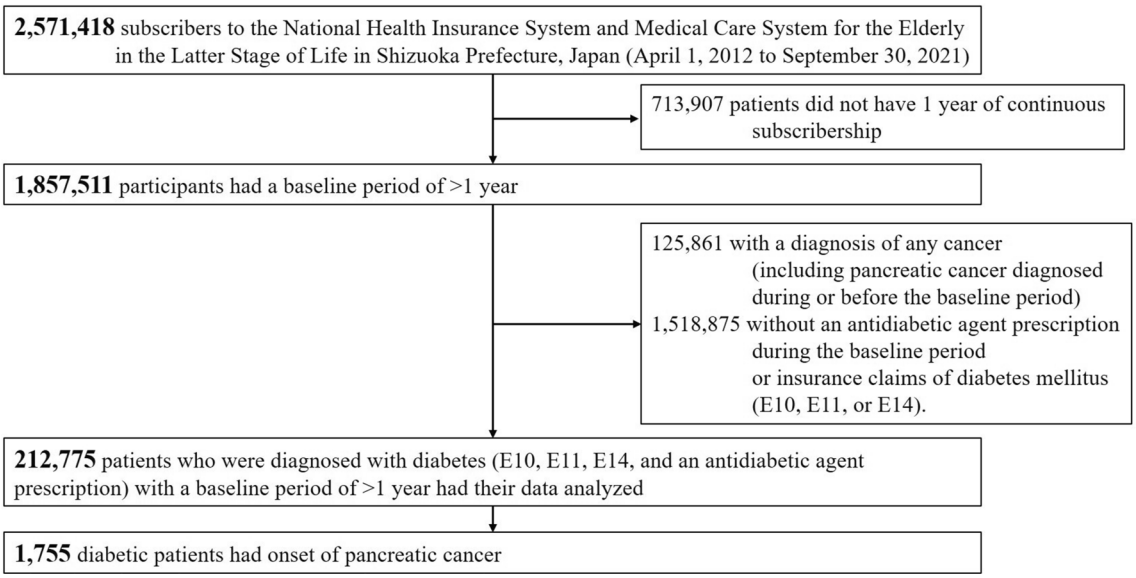

Figure 2. Flowchart for inclusion of participants in the study.

Variable	Category or unit	Patients with pancreatic cancer	Others	Univariable Cox model		
		n = 1755	n = 211,020	HR	95% CI	*p*-value
Age	1 year	73.60 ± 8.55	70.78 ± 8.55	1.032	1.027–1.037	< 0.001
Age	0–49 years	8 (0.5)	10,297 (4.9)	1		
	50–59 years	71 (4.0)	14,981 (7.1)	4.960	2.388–10.30	< 0.001
	60–69 years	532 (30.3)	68,656 (32.5)	7.218	3.591–14.51	< 0.001
	70–79 years	692 (39.4)	70,591 (33.5)	9.861	4.912–19.80	< 0.001
	80–89 years	415 (23.6)	40,269 (19.1)	10.99	5.459–22.12	< 0.001
	90 + years	37 (2.1)	6226 (3.0)	12.10	5.634–25.98	< 0.001
Sex	Male	877 (50.0)	107,726 (51.1)	0.898	0.817–0.986	0.024
	Female	878 (50.0)	103,294 (48.9)			
Cerebrovascular disease	Presence	400 (22.8)	48,707 (23.1)	1.033	0.924–1.155	0.563
Dementia	Presence	56 (3.2)	11,415 (5.4)	0.880	0.675–1.149	0.349
Myocardial infarction	Presence	78 (4.4)	9860 (4.7)	1.063	0.847–1.334	0.600
Renal disease	Presence	76 (4.3)	13,578 (6.4)	0.897	0.713–1.129	0.354
Rheumatic disease	Presence	71 (4.0)	7328 (3.5)	1.261	0.995–1.599	0.056
Liver disease	Presence	423 (24.1)	44,645 (21.2)	1.153	1.033–1.286	0.011
Hepatitis B	Presence	15 (0.9)	1896 (0.9)	1.063	0.639–1.766	0.815
Hepatitis C	Presence	37 (2.1)	3586 (1.7)	1.315	0.950–1.821	0.099
Congestive heart failure	Presence	295 (16.8)	38,958 (18.5)	1.088	0.960–1.233	0.186
Cardiac arrhythmias	Presence	293 (16.7)	32,667 (15.5)	1.204	1.062–1.365	0.004
Chronic pulmonary disease	Presence	341 (19.4)	42,889 (20.3)	0.989	0.879–1.113	0.852
Hypertension	Presence	1296 (73.8)	146,577 (69.5)	1.167	1.049–1.298	0.004
Pylori-infectious	Presence	50 (2.8)	4778 (2.3)	1.316	0.994–1.744	0.055
Peptic ulcer	Presence	367 (20.9)	40,303 (19.1)	1.095	0.976–1.229	0.120
DM type	Type 1	19 (1.1)	2444 (1.2)	1.056	0.672–1.659	0.814
Any diabetic complication	Presence	1612 (91.9)	191,455 (90.7)	0.900	0.758–1.068	0.226
Onset of diabetes	Already diagnosed	1359 (77.4)	140,114 (66.4)	1.000	0.999–1.001	0.875
HIV infection	Presence	1 (0.1)	40 (0.0)	3.736	0.526–26.54	0.188
History of cholecystectomy	Presence	56 (3.2)	7831 (3.7)	0.870	0.667–1.135	0.304
Chronic pancreatitis	Presence	49 (2.8)	2505 (1.2)	2.466	1.857–3.276	< 0.001
Pancreatic cystic disease	Presence	37 (2.1)	887 (0.4)	5.961	4.304–8.256	< 0.001

Table 1. Patients' baseline characteristics and variables for univariable Cox model analysis. HR; Hazard ratio, CI; confidence interval, DM; diabetes mellitus.

Variable (reference)	Category	HR	95% CI	*p*-value
Age (-49 years)	50–59 years	5.016	2.414–10.42	< 0.001
	60–69 years	7.322	3.640–14.73	< 0.001
	70–79 years	10.34	5.138–20.79	< 0.001
	80–89 years	11.45	5.672–23.10	< 0.001
	90 + years	13.20	6.123–28.45	< 0.001
Sex (female)	Male	1.267	1.150–1.395	< 0.001
Liver disease (absence)	Presence	1.128	1.010–1.193	0.039
Cardiac arrhythmias (absence)	Presence	1.050	0.924–1.193	0.455
Hypertension (absence)	Presence	1.007	0.903–1.123	0.898
Chronic pancreatitis (absence)	Presence	1.976	1.479–2.640	< 0.001
Pancreatic cystic disease (absence)	Presence	4.786	3.434–6.671	< 0.001

Table 2. Multivariable Cox regression analysis of pancreatic cancer onset. HR; Hazard ratio, CI; confidence interval.

cancer onset did not significantly differ between patients newly diagnosed with diabetes and those with an existing diagnosis.

Survival curve in pancreatic cancer onset subgroup

During the observation period, among 1755 diabetic patients diagnosed with PC, 1177 (67.1%) patients died, with a median survival period of 297 days. The 6-month, 1-year, 3-year, and 5-year survival rates were 60.5%, 45.8%, 28.2% and 21.6%, respectively. The overall survival rates of diabetic patients with PC are shown in Fig. 3a. A comparison of survival rates categorized by age revealed a decline in survival with increasing age ($p < 0.001$, Fig. 3b). The median survival periods for the age groups < 65 years, 65–< 75 years, 75–< 90 years, and ≥ 95 years were 658 days, 620 days, 234 days and 89 days, respectively.

Discussion

While numerous risk factors for PC have been identified in the general population, this large-scale cohort study specifically examines these factors among individuals with diabetes mellitus. Our findings indicate that among patients with a history of diabetes mellitus for more than one year, the annual incidence of PC was 166.7 cases per 100,000 person-years [95% CI 158.9–174.5]. In contrast, the incidence in the general population of Japan is 34.8 cases per 100,000 person-years[1]. Meta-analyses report the risk of PC in diabetic patients with a relative risk between 1.7[10] and 1.9[11]. Although it is known that the risk of pancreatic cancer is elevated in patients with diabetes, the present study, which reports on the incidence of pancreatic cancer among diabetic patients in a large cohort, is of considerable value and our results suggests a higher incidence of PC in our diabetic cohort. Given this increased incidence, monitoring diabetic patients could enhance medical outcomes. Furthermore, significant risk factors identified in diabetic individuals include advanced age, male sex, a history of liver disease, chronic pancreatitis, and pancreatic cystic lesions. These findings could be instrumental in promoting early diagnosis of PC in diabetic patients, suggesting the need for abdominal screening in diabetic patients with these risk factors.

The identified risk factors for the onset of pancreatic cancer in diabetic patients, except for a history of liver disease, were consistent with those in the general population. However, the existing risk factors and their associated risk values listed in the guidelines are often a compilation of each study, reported disparately across different population backgrounds. In this study, we have re-evaluated all previously reported risk factors simultaneously in a multivariate analysis within a single large-scale cohort study. The factors thus selected are considered to independently contribute to the incidence of pancreatic cancer in the diabetic cohort, which is a strength of this research.

Pancreatic cancer typically occurs more frequently in males than in females and is more prevalent in older individuals[48,49]. In our study, being male was identified as a risk factor. This gender disparity may be partially attributed to the higher rates of smoking and heavy drinking among males, factors known to escalate the risk of PC[5–9]. Furthermore, the role of potential yet unidentified factors (e.g., genetic predisposition) in influencing cancer incidence between genders warrants consideration. In diabetic patients, similar to the general population[48–51], age is a significant risk factor for pancreatic cancer. The disease is rare before the age of 50 years, with the median age at diagnosis for most pancreatic adenocarcinoma cases in the general population being approximately 70 years[48,52]. The results in diabetic patients were similar to those in the general population, suggesting that intensive PC surveillance may not be necessary for younger diabetic individuals.

Pancreatic cystic lesions including intraductal papillary mucinous neoplasm are known risk factors for PC[22–25] in the general population. Tada et al. reported that in Japanese patients with pancreatic cystic lesions, the observed incidence of pancreatic cancer was 22.5 times higher (95% confidence interval 11.0–45.3) than the expected mortality from this cancer in the general population[23]. However, these studies do not directly compare the risk for the incidence of pancreatic cancer with those of the general population. While multiple guidelines exist for the management of pancreatic cystic lesions[53–56], there is a notable variation among them, and finding the ideal balance between surveillance and intervention for specific types of lesions remains a subject of

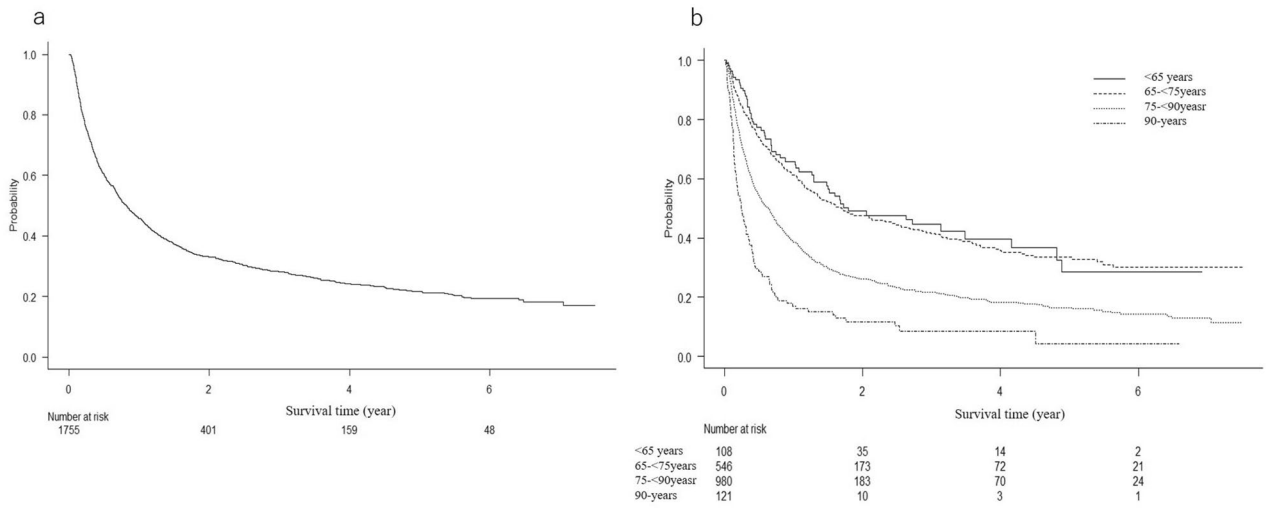

Figure 3. The overall survival rates of diabetic patients with pancreatic cancer.

considerable debate. Buerlein et al.[57] posited that prior to initiating a surveillance program for a pancreatic cystic neoplasm, it is crucial to consider various patient-specific factors and to discuss with the patient the potential risks and benefits of undergoing a surveillance program, as individuals' tolerance for risk can vary significantly. In this study, the prevalence of pancreatic cystic disease in diabetic patients was approximately 0.4%, which is lower than rates reported in recent studies[58]. Notably, this study is the first to identify pancreatic cystic lesions as a significant risk factor for developing pancreatic cancer in diabetic individuals, evidenced by a high hazard ratio (HR) of 4.79 [95% CI 3.43–6.67] (Table 2). The findings of the current study suggest that pancreatic cystic lesions in diabetic patients warrant regular monitoring.

Similarly, chronic pancreatitis is recognized as a risk factor for PC in the general population[19–21]. The international consensus guidelines for chronic pancreatitis[59] note that the risk of developing pancreatic cancer may differ among patients with chronic pancreatitis, depending on factors such as lifestyle and medical or surgical interventions. Ueda et al. have reported that the standardized incidence ratio (SIR) for pancreatic cancer in Japanese patients with chronic pancreatitis was 11.8 (95% CI 7.1–18.4)[21]; however, similar to pancreatic cystic lesions, this was not the result of an analysis of risk factors within a large-scale cohort population. Our study suggests that chronic pancreatitis may also act as a risk factor for the development of PC in diabetic patients. Consequently, patients with concurrent chronic pancreatitis and diabetes mellitus may benefit from pancreatic cancer surveillance.

Based on our findings, the coexistence of liver disease emerged as a risk factor in patients with diabetes. The underlying biological mechanisms linking liver disease and pancreatic cancer remain unclear; however, several liver diseases are known risk factors for pancreatic cancer[28,29]. Previous research indicates that serum levels of pancreatic enzymes rise with the progression of liver disease in diagnosed patients[60,61]. This suggests that liver disease may exert a biologic effect on the pancreas, particularly in those with diabetes.

Hypertension and arrythmia were identified as risk factors in univariate analysis but not as significant risk factors in multivariate analysis. Although hypertension has not been identified as a clear risk factor for pancreatic cancer, several solid tumors have been associated with hypertension[62]. Similarly, the evidence for a strong association between the development of pancreatic cancer and arrhythmia is limited. Nonetheless, chronic pancreatitis, a risk known factor for pancreatic cancer, can lead to arrhythmia[63]. Additionally, elevated levels of branched-chain amino acids, which are associated with early pancreatic cancer development, have been linked to arrhythmia[64]. The relationship between hypertension and arrhythmia with PC warrants further investigation.

In Japan, the five-year survival rate for pancreatic cancer in all patients is 8.5%; however, for surgical cases, it is 28.6%[1]. In our cohort of diabetic patients with pancreatic cancer, the five-year survival rate is 21.6% (Fig. 3a). Regular hospital visits for diabetes treatment may lead to earlier detection and surgical intervention in symptomatic pancreatic cancer. Despite this, the survival rate remains suboptimal, underscoring the necessity for innovative therapeutic strategies to enhance survival rates.

There have been reports in the literature on the relationship between diabetes medication and the risk of pancreatic cancer. Metformin, in particular, is well-known, with studies suggesting it may reduce the incidence of pancreatic cancer[10,65]. This study is an explorative investigation into potential predictors of pancreatic cancer incidence, rather than focusing on causal relationships[45–47]. Additionally, the New-user Design-based analysis is impractical with the current dataset, leading to a potential misinterpretation of results. Consequently, the analysis excludes consideration of various medications.

This study is not without its limitations. First, we could not gather data on family history, medication adherence, socioeconomic status, cancer stage, pathological findings, or genetic information. Notably, a family history of pancreatic cancer is a known risk factor for the disease[4], but this aspect was not included in our analysis. Second, the identification of pancreatic cancer was based on ICD-10 codes, which precluded the confirmation of additional details, including cancer stage. Similarly, pancreatic cystic lesions and chronic pancreatitis were cited as risk factors for pancreatic cancer; however, details about these diseases, such as the size of the pancreatic cysts and the treatment of chronic pancreatitis, were not obtained. Therefore, the impact of disease severity on pancreatic cancer risk has not been fully evaluated. Furthermore, Due to the characteristics of pancreatic tumors, some cases are not pathologically evaluated and may be registered as pancreatic cancer under the Japanese insurance system. This can result in lower malignancy tumors being classified as pancreatic cancer, potentially affecting the observed frequency and prognosis trends in this study. Third, as the age of disease onset could not be accurately ascertained, the age at diagnosis was used as a proxy. Fourth, we defined diabetic patients based on the prescription of one or more antidiabetic agents, leaving a gap in data for diabetic patients who do not use these medications. Furthermore, due to the nature of the administrative claims data used, the duration of diabetes mellitus could not be accurately determined. Therefore, it was not possible to provide the incidence of pancreatic cancer classified by the duration of diabetes. However, we did present the incidence rates based on whether diabetes was newly diagnosed or pre-existing, and found no significant differences in the impact on pancreatic cancer onset between these groups (Table 1, $p < 0.875$)". Fifth, an important limitation arises from the demographic composition of the database. Derived from Japan's National Health Insurance system, our dataset primarily comprises an older population. This demographic distribution may contribute to the high incidence of pancreatic cancer in this study and limits the representativeness of our data for younger pancreatic cancer patients. However, considering the higher prevalence of pancreatic cancer in the elderly, conducting a risk factor analysis with this dataset, which includes a significant elderly demographic, is still valuable. Finally, the study confirmed that enrollees with newly diagnosed pancreatic cancer did not have pancreatic cancer during the one-year covariate assessment window. However, if a patient who already had pancreatic cancer did not use insurance for pancreatic cancer treatment during the baseline period, he or she may have been treated as a new-onset patient. Despite these limitations, this study provides important insights into the association between pancreatic cancer and various risk factors in a large cohort of diabetic patients.

Conclusions

This cohort study has identified key risk factors for pancreatic cancer in diabetic patients. Findings indicate that advanced age, male sex, a history of liver disease, chronic pancreatitis, and pancreatic cystic lesions significantly increase the risk of pancreatic cancer in this population. These insights underscore the importance of targeted surveillance for early detection of pancreatic cancer in diabetic patients, particularly those with these risk factors. This study contributes to the understanding of pancreatic cancer in diabetics, offering a foundation for improved patient management and screening protocols.

Data availability

According to Shizuoka Prefecture's data use agreement with local insurers, readers cannot access the analyzed data. Researchers interested in accessing this dataset may submit an application to Shizuoka Prefecture to request access. Please contact the staff of Shizuoka Graduate University of Public Health (Email: info@s-sph.ac.jp).

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Author contributions

Study conception and design: T.S., E.N., and T.U. Acquisition of data: E.N. Analysis and interpretation of data: T.S. and E.N. Drafting of the work: T.S. Critical revision of the manuscript: T.S., E.N., H.A., S.K., K.O., H.I., K.H., and T.U.. Final approval of the manuscript: T.S., E.N., H.A., S.K., K.O., H.I., K.H., and T.U..

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to E.N.