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Association of dipeptidyl peptidase-4 inhibitor use and risk of pancreatic cancer in individuals with diabetes in Japan

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ABSTRACT

Aims/Introduction: This study was designed and carried out to investigate the association of dipeptidyl peptidase-4 inhibitor (DPP-4i) use with pancreatic cancer (PC) in individuals with diabetes in Japan.

Materials and Methods: The JMDC Claims Database, which contains the medical and prescription information of Japanese employment-based health insurance programs, was used. The primary outcome was duration to the first occurrence of PC (International Classification of Diseases 10th Revision code C25), both all and hospitalized, from prescription of DPP-4is or other oral glucose-lowering agents (GLAs).

Results: Individuals with diabetes who received DPP-4is (n = 61,430) or other oral GLAs (n = 83,304) were analyzed. Follow-up periods (median [interquartile range]) were 17 months (8–33) for DPP-4is and 14 months (7–28) for other oral GLAs. Kaplan–Meier curve analysis to determine the duration of first use of DPP4i or other oral GLA to diagnosis of PC disclosed no differences between the two groups in duration to all or hospitalized PC (log-rank test: all, P = 0.7140; hospitalized, P = 0.3446). Cox proportional hazards models showed that use of DPP-4is did not affect the PC risk adjusted for medications, age, sex and risk comorbidities (all, hazard ratio 1.1, 95% confidence interval 0.8–1.3, P = 0.6518; hospitalized, hazard ratio 1.1, 95% confidence interval 0.8–1.4, P = 0.6662). Similar results were obtained when individuals with ≥2 years oral GLA treatment and those with medical checkup data (e.g., smoking or drinking habit) available were analyzed.

Conclusion: This database study shows that there is not a significant PC risk due to DPP-4i treatment in individuals with diabetes in Japan, but larger studies with longer follow up are required to confirm these findings.

INTRODUCTION

Dipeptidyl peptidase-4 inhibitors (DPP-4is) are commonly used in the management of type 2 diabetes in East Asia; DPP-4is have a greater glycated hemoglobin-lowering effect in East Asians with type 2 diabetes, in whom diabetes is primarily due to β-cell dysfunction[1]. From the early stages of the development of DPP-4is, potential pancreatic cancer (PC) risk has been of concern because of the consequent expansion of the pancreas[2,3]. To evaluate whether use of DPP-4i is associated with PC, meta-analyses based on randomized clinical trials (RCTs)

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including cardiovascular outcome trials have been undertaken[4]. The development of pancreatic cancer involves multiple steps, including early activation of oncogenes and inactivation of tumor suppressor genes, which initiate the formation of pancreatic intraepithelial neoplasia (PanIN1and PanIN2) from normal epithelium[5]. It has been reported that ≥10 years are required from the occurrence of the aberrant cells to the birth of the parental cancer cells[6]. Thus, the observational periods of the several RCTs were too short to determine whether PC is associated with DPP-4i use.

We examined the JMDC Claims Database (JMDC Inc., Tokyo, Japan) covering the time period since DPP-4is entered the market in Japan to assess the association of longer-term use of DPP-4is with PC among individuals with diabetes in Japan.

MATERIALS AND METHODS

We used the JMDC Claims Database, which contains information on individuals aged <75 years in Japanese employment-based health insurance programs (e.g., age, sex, drug prescriptions and International Classification of Diseases 10th Revision [ICD-10] code diagnosis)[7]. Data can readily be tracked chronologically, even when an individual has visited more than one medical institution.

Individuals aged 30–74 years with medical claims and pharmacy data for a continuous period of ≥12 months from June 2009 to June 2019 (with 6 months of baseline observations and ≥6 months of observation after initiation of the index medication) were included. Individuals with E11 (n = 111,783) or E14 codes (n = 232,197) also having type 2 diabetes were subjected to further analysis; individuals with E10 (n = 3,413), E12 (n = 3) and E13 codes (n = 1,856) were excluded. The index date was the prescription date of the first claim for a new oral glucose-lowering agent (GLA) during the target period from December 2009 to December 2018. An oral GLA was considered a new medication if there were no claims for it in the preceding ≥6 months. Individuals receiving glucagon-like peptide-1 receptor agonist (GLP-1RA) in the preceding ≥6 months or on the index date were excluded from the study; those receiving insulin in the preceding ≥6 months or on the index date were included. Individuals with PC ≥6 months before or on the index date were excluded from the study; individuals with pancreatic diseases other than PC were included in the study. The observation period started on the index date and ended with one of the following events, whichever was first: (i) diagnosis of PC; (ii) initiation of another new GLA or GLP-1RA; (iii) end of the observation period; and (iv) end of eligibility. Individuals were included in different index drug groups if they met the criteria, thus allowing consideration of exposure to DPP-4is before initiation of the drug for which PC risk was being examined. PC was established by a claim for ICD-10 C25 code. PC risk comorbidities at baseline are summarized in Table 2. The primary outcome was first occurrence of PC diagnosis after the index date. Fisher's exact test was used to compare DPP-4is and other GLAs. Kaplan–Meier curve analysis was carried out to compare the duration to PC diagnosis. The log-rank test was carried out to analyze for significant differences in the time to PC between groups. Cox proportional hazards models (CPHMs) were built to compare the adjusted risk of PC with medications, age, sex and/or risk comorbidities as independent variables. To mitigate the limitation of our observation period, an additional analysis was carried out on individuals with ≥2-year use of DPP-4is or other oral GLAs. An additional analysis was carried out on individuals with health checkup data adjusted for body mass index,and alcohol and smoking habit, as well as age, sex and risk comorbidities in CPHMs.

Analyses were carried out using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.0.0 (The R Foundation for Statistical Computing, Vienna, Austria). A P-value <0.05 was considered statistically significant.

RESULTS

The incidence of all and hospitalized PCs in individuals receiving DPP-4is and other oral GLAs is shown in Table 1. We analyzed 61,430 individuals who received DPP-4is and 83,304 individuals who received other oral GLAs with and without pancreatic cancer risk factors (Table 2). The median follow-up periods were 17 months (interquartile range [IRQ months] 8–33) for DPP-4is and 14 months (IQR 7–28 months) for other oral GLAs. All and hospitalized PCs, respectively, were quantified in 142 and 92 individuals who received DPP-4is, and 161 and 102 individuals who received other oral GLAs. Kaplan–Meier curves for duration to all and hospitalized PCs, respectively, were similar in those who received DPP-4is and other oral GLAs (log-rank test: all, P = 0.7140; hospitalized, P = 0.3446; Figure 1). Kaplan–Meier curves for duration to all and hospitalized PCs, respectively, were also similar in individuals who had previous exposure to DPP-4is and those who did not (log-rank test: all, P = 0.1431; hospitalized, P = 0.1528; Figure 1). Use of DPP-4is did not affect PC risk adjusted for age, sex or risk comorbidities calculated using CPHMs (all, hazard ratio [HR] 1.1, 95% confidence interval [CI] 0.8–1.3, P = 0.6518; hospitalized, HR 1.1, 95% CI 0.8–1.4, P = 0.6662; Table 3). Post-hoc power was calculated for the HR of DPP-4is to the other oral GLAs (all, 0.9960; hospitalized, 0.9957). Previous exposure to DPP-4is also did not affect the adjusted PC risk using CPHMs (all, HR 1.0, 95% CI 0.7–1.4, P = 0.9078; hospitalized, HR 1.1, 95% CI 0.7–1.7, P = 0.5932; Table 4).

In the present study, as ≥20,000 individuals were found to be continued on DPP-4is without addition of other oral GLAs for ≥2 years (Figure S1), we analyzed this cohort for PC risk (DPP4is, n = 23,107; other oral GLAs, n = 27,589; Tables S1 and S2). The median follow-up periods were 59 months (IQR 40–77 months) for DPP-4is and 47 months (IQR 35–67 months) for other oral GLAs. No significant increase in adjusted PC risk calculated using CPHMs in individuals receiving DPP-4is or those having previous exposure to DPP-4is was found (Tables S3 and S4).

Table 1 | Incidence of all and hospitalized pancreatic cancers on different oral glucose-lowering agents

Oral glucose-lowering agents	Previous exposure to DPP-4i	*n*	%male	Age (years)		All pancreatic cancer						Hospitalized pancreatic cancer					
				mean	95%CI	Observation period, months			Total observation, patient years	Cases (%)	Incidence rate, cases/100,000 patient-years	Observation period, months			Total observation, patient years	Cases (%)	Incidence rate, cases/100,000 patient-years
						Median	First quartile	Third quartile				Median	First quartile	Third quartile			
ALL		1,44,634	72.7	53.5	53.5 - 53.5	16	8	30	2,60,013	303 (0.21)	117	16	8	30	2,60,166	194 (0.13)	75
DPP-4i		61,430	72.7	53.9	53.8 - 53.9	17	8	33	1,18,000	142 (0.23)	120	17	8	33	1,18,081	92 (0.15)	78
Others		83,204	72.7	53.1	52.8 - 53.1	14	7	28	1,42,013	161 (0.19)	113	14	7	28	1,42,086	102 (0.12)	72
	Yes	49,925	73.4	53.3	52.9 - 53.3	15	7	29	85,843	103 (0.21)	120	15	7	29	85,889	69 (0.14)	80
	No	33,279	71.6	52.8	52.4 - 52.9	12	5	26	56,170	58 (0.17)	103	12	5	26	56,197	33 (0.10)	59
Sulfonylureas		15,133	73.6	54.8	54.2 - 54.6	12	5	24	44,254	45 (0.30)	102	15	7	29	44,272	33 (0.22)	75
	Yes	10,359	73.3	55.1	54.5 - 55.0	13	6	24	30,235	32 (0.31)	106	16	8	30	30,250	22 (0.21)	73
	No	4,774	74.4	53.8	52.8 - 53.7	12	4	25	14,018	13 (0.27)	93	14	6	28	14,022	11 (0.23)	78
Glinides		8,213	71.7	52.6	52.5 - 52.7	15	7	29	17,170	25 (0.30)	146	16	7	31	17,188	16 (0.19)	93
	Yes	6,307	71.7	53.8	53.6 - 53.8	16	8	30	12,532	17 (0.27)	136	16	7	31	12,544	12 (0.19)	96
	No	1,906	71.9	51.0	50.8 - 51.1	14	6	28	4,639	8 (0.42)	172	15	7	33	4,644	4 (0.21)	86
Biguanides		43,587	72.6	53.3	52.8 - 53.2	16	7	31	1,35,300	70 (0.16)	52	14	6	29	1,35,370	42 (0.10)	31
	Yes	26,263	73.4	53.7	53.2 - 53.6	16	7	31	80,735	48 (0.18)	59	14	6	28	80,779	31 (0.12)	38
	No	17,324	71.5	52.4	51.8 - 52.4	15	6	33	54,565	22 (0.13)	40	15	6	32	54,590	11 (0.06)	20
Thiazolidines		10,289	73.8	54.0	53.6 - 53.9	14	6	29	30,637	17 (0.17)	55	13	5	24	30,657	7 (0.07)	23
	Yes	6,960	73.7	54.6	54.1 - 54.5	14	6	28	19,337	11 (0.16)	57	13	6	24	19,347	4 (0.06)	21
	No	3,329	73.9	53.2	52.8 - 53.2	15	6	32	11,299	6 (0.18)	53	12	4	25	11,310	3 (0.09)	27
α-GI		14,060	71.1	52.8	52.5 - 52.7	15	8	27	39,218	42 (0.30)	107	15	8	27	39,243	29 (0.21)	74
	Yes	8,424	71.0	53.5	53.1 - 53.3	16	8	28	20,972	25 (0.30)	119	16	8	28	20,985	18 (0.21)	86
	No	5,636	71.3	51.1	50.7 - 51.1	15	8	25	18,246	17 (0.30)	93	15	8	25	18,259	11 (0.20)	60
SGLT2i		34,916	74.5	53.2	53.2 - 53.3	15	7	29	85,721	43 (0.12)	50	15	7	29	85,748	28 (0.08)	33
	Yes	25,695	75.5	54.2	54.1 - 54.2	16	8	29	62,051	32 (0.12)	52	16	8	29	62,072	20 (0.08)	32
	No	9,221	71.6	51.8	51.7 - 51.9	14	7	28	23,670	11 (0.12)	46	14	7	28	23,676	8 (0.09)	34

Note: No statistically significant differences were observed in incidences of all pancreatic cancer (PC) and hospitalizations for PC between dipeptidyl peptidase-4 inhibitors (DPP-4is) and other oral glucose-lowering agents (GLAs) (Others) (Fisher's exact tests). Previous exposure to DPP-4is did not significantly affect incidences of all PC and hospitalizations for PC in individuals on other oral GLAs (Fisher's exact tests). Other oral GLAs include sulfonylureas, glinides, biguanides, thiazolidines, α-glycosidase inhibitors and sodium glucose cotransporter 2 inhibitors. α-GI, α-glycosidase inhibitors; CI, confidential interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

Table 2 | Pancreatic cancer risk factors (International Classification of Diseases-10) at baseline in patients on different oral glucose-lowering agents

Oral glucose-lowering agents	Previous exposure to DPP-4i	*n*	(%male)	Age (years)				Risk Factors (International Classification of Diseases -10)			
				Mean	95%CI			Chronic pancreatitis	Intraductal papillary mucinous neoplasia	Pancreatic cysts	Alcoholism
ALL		1,44,634	72.7	53.5	53.5	-	53.5	963 (0.7%)	97 (0.1%)	2,854 (2.0%)	1,819 (1.3%)
DPP-4i		61,430	72.7	53.9	53.8	-	53.9	377 (0.6%)	46 (0.1%)	1,093 (1.8%)	739 (1.2%)
Others		83,204	72.7	53.1	52.8	-	53.1	586 (0.7%)	51 (0.1%)	1,761 (2.1%)	1,080 (1.3%)
	Yes	49,925	73.4	53.3	52.9	-	53.3	412 (0.8%)	33 (0.1%)	1,183 (2.4%)	724 (1.5%)
	No	33,279	71.6	52.8	52.4	-	52.9	174 (0.5%)	18 (0.1%)	578 (1.7%)	356 (1.1%)
Sulfonylureas		15,133	73.6	54.8	54.2	-	54.6	118 (0.8%)	5 (0.0%)	250 (1.7%)	210 (1.4%)
	Yes	10,359	73.3	55.1	54.5	-	55.0	85 (0.8%)	2 (0.0%)	186 (1.8%)	150 (1.4%)
	No	4,774	74.4	53.8	52.8	-	53.7	33 (0.7%)	3 (0.1%)	64 (1.3%)	60 (1.3%)
Glinides		8,213	71.7	52.6	52.5	-	52.7	86 (1.0%)	9 (0.1%)	183 (2.2%)	148 (1.8%)
	Yes	6,307	71.7	53.8	53.6	-	53.8	69 (1.1%)	7 (0.1%)	146 (2.3%)	118 (1.9%)
	No	1,906	71.9	51.0	50.8	-	51.1	17 (0.9%)	2 (0.1%)	37 (1.9%)	30 (1.6%)
Biguanides		43,587	72.6	53.3	52.8	-	53.2	256 (0.6%)	24 (0.1%)	870 (2.0%)	529 (1.2%)
	Yes	26,263	73.4	53.7	53.2	-	53.6	188 (0.7%)	15 (0.1%)	600 (2.3%)	359 (1.4%)
	No	17,324	71.5	52.4	51.8	-	52.4	68 (0.4%)	9 (0.1%)	270 (1.6%)	170 (1.0%)
Thiazolidines		10,289	73.8	54.0	53.6	-	53.9	81 (0.8%)	8 (0.1%)	214 (2.1%)	153 (1.5%)
	Yes	6,960	73.7	54.6	54.1	-	54.5	54 (0.8%)	3 (0.0%)	162 (2.3%)	110 (1.6%)
	No	3,329	73.9	53.2	52.8	-	53.2	27 (0.8%)	5 (0.2%)	52 (1.6%)	43 (1.3%)
α-GI		14,060	71.1	52.8	52.5	-	52.7	136 (1.0%)	16 (0.1%)	292 (2.1%)	212 (1.5%)
	Yes	8,424	71.0	53.5	53.1	-	53.3	95 (1.1%)	13 (0.2%)	198 (2.4%)	139 (1.7%)
	No	5,636	71.3	51.1	50.7	-	51.1	41 (0.7%)	3 (0.1%)	94 (1.7%)	73 (1.3%)
SGLT2i		34,916	74.5	53.2	53.2	-	53.3	252 (0.7%)	15 (0.0%)	807 (2.3%)	400 (1.1%)
	Yes	25,695	75.5	54.2	54.1	-	54.2	205 (0.8%)	11 (0.0%)	606 (2.4%)	314 (1.2%)
	No	9,221	71.6	51.8	51.7	-	51.9	47 (0.5%)	4 (0.0%)	201 (2.2%)	86 (0.9%)

Note: Other oral glucose-lowering agents included sulfonylureas, glinides, biguanides, thiazolidines, α-glycosidase inhibitors and sodium glucose cotransporter 2 inhibitors. α-GI, α-glycosidase inhibitors; CI, confidential interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; SGLT-2i, sodium-glucose cotransporter 2 inhibitors.

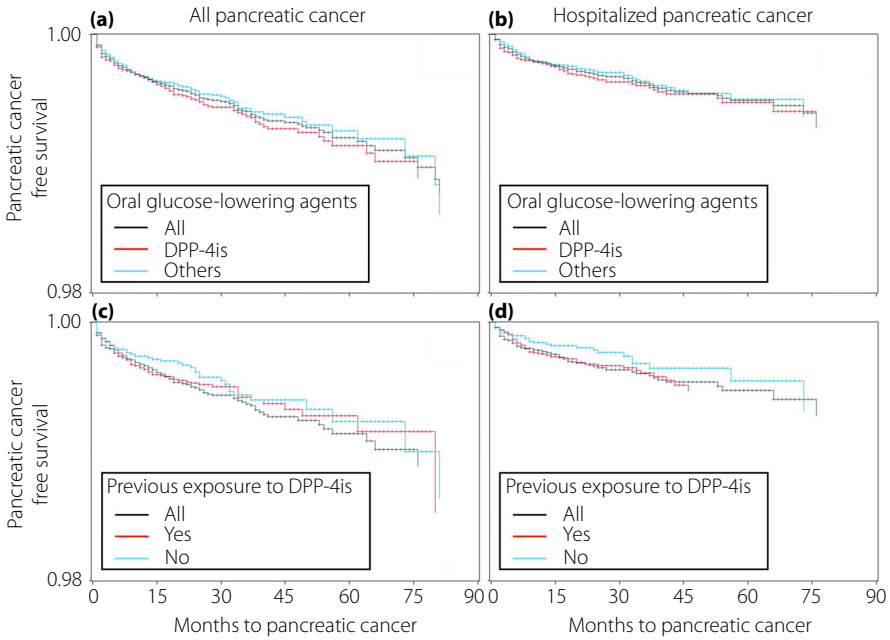

Figure 1 | Kaplan–Meier survival analysis on potential risk of pancreatic cancer in individuals with diabetes receiving dipeptidyl peptidase-4 inhibitors in Japan. Kaplan–Meier survival analysis of time to develop pancreatic cancer (PC) was carried out (a, c all; b, d hospitalized) in individuals taking dipeptidyl peptidase-4 inhibitors (DPP-4is), individuals on other oral glucose-lowering agents (GLAs; Others) and both groups all together (All; a, b), and in individuals taking other oral GLAs with previous exposure to DPP-4is, individuals taking other oral GLAs without previous exposure to DPP-4is and all together (All; c, d). Vertical lines show individuals excluded for reasons other than PC (e.g., initiation of another new oral GLA or GLP-1 receptor agonist, end of observation period or end of eligibility). The log-rank test showed no significant differences in the risk of PC between DPP-4i and other oral GLA use (all, $P = 0.7140$; hospitalized, $P = 0.3446$) or between individuals taking other GLAs with previous exposure to DPP-4is and those without (all, $P = 0.1431$; hospitalized, $P = 0.1528$). Other oral GLAs include sulfonylureas, glinides, biguanides, thiazolidines, α-glycosidase inhibitors and sodium–glucose cotransporter 2 inhibitors.

Health checkup data were available for some individuals in the JMDC Claims Database; we, therefore, investigated the association of DPP-4i use with PC risk calculated by CPHMs adjusted for alcohol and smoking habit, and body mass index, as well as age, sex and risk comorbidities (DPP4is, $n = 34{,}131$; other oral GLAs, $n = 46{,}285$; Tables S5–S7). This additional analysis also showed no increase in PC risk by current or previous exposure to DPP-4is (Table S8).

DISCUSSION

DPP-4is are used in ≥70% of Japanese individuals with type 2 diabetes due to their superior glycated hemoglobin-lowering effect in East Asians with type 2 diabetes, who are generally non-obese and present with β-cell dysfunction[1]. PC risk has been an important concern from the early stages of the development of DPP-4is.[2,3]

Recent meta-analyses of RCTs have been carried out to investigate the association of PC risk with use of DPP-4is.[4] The development of PC involves a multistep process of oncogene activation and tumor suppressor gene inactivation that initiates the formation of PanIN1 and PanIN2 cells from normal pancreatic epithelium[5]. Ten or more years from the occurrence of the aberrant cells to the birth of parental cancer cells are required in this process[6]. Hence, the median observational time of 2–3 years in conventional RCTs is too short to rule out associations of PC with long term DPP-4i use.

We initiated the current study to investigate association of long-term use of DPP-4is with PC risk. However, in this investigation, we found just 4,000 individuals with ≥5-year exposure to DPP-4is (Figure S1). We therefore analyzed those continuously receiving DPP-4is or other oral GLAs for ≥2 years (DPP4is, $n = 23{,}107$; other oral GLAs, $n = 27{,}589$). The median follow-up periods were 59 months (IQR 40–77 months) for DPP-4is and 47 months (IQR 35–67 months) for other oral GLAs. Considering that ≥10 years are required in the development of PC[6], the follow-up period in the current study might seem inadequate. In contrast, it has been reported that the use of incretin-related drugs for 1 year markedly increased the number of PanIN cells[3], and such precursor cells would be expected within the purview of the present study. Even so, larger studies with longer follow-up periods are required to establish these findings.

Furthermore, these results must be understood with the limitations of the study in mind. Its non-random design could introduce confounders, such as risk comorbidities. In addition, the claims database does not include potentially relevant information, such as glycemic and lipid control, and family history of PC. Furthermore, this investigation could not adjust for dosage or adherence to the drugs. Although the incidence of all

Table 3 | Adjusted pancreatic cancer risk in individuals with current exposure to dipeptidyl peptidase-4 inhibitors

	n	Events	All pancreatic cancer				Events	Hospitalized pancreatic cancer			
			Adjusted for age and gender		Adjusted for age, gender and risk comorbidities			Adjusted for age and gender		Adjusted for age, gender and risk comorbidities	
			HR (95%CI)	*P* value	HR (95%CI)	*P* value		HR (95%CI)	*P* value	HR (95%CI)	*P* value
Glucose-lowering agents (Others=0; DPP-4i=1)	Others 83,204; DPP-4i 61,430	Others 161; DPP-4i 142	1.1 (0.8-1.3)	0.6610	1.1 (0.8-1.3)	0.6518	Others 92;DPP-4i 102	1.1 (0.8-1.4)	0.6687	1.1 (0.8-1.4)	0.6662
Age			1.1 (1.1-1.1)	<.0001	1.1 (1.1-1.1)	<.0001		1.1 (1.1-1.1)	<.0001	1.1 (1.1-1.1)	<.0001
Gender (Male=0; Female=1)	Male 105,174; Female 39,460		0.7 (0.5-0.9)	0.0065	0.7 (0.5-0.9)	0.0108		0.6 (0.5-0.9)	0.0109	0.7 (0.5-0.9)	0.0140
Risk comorbidities											
Chronic pancreatitis	963	9			2.9 (1.5-5.8)	0.0022	4			2.0 (0.7-5.5)	0.1872
Intraductal papillary mucinous neoplasia	97	5			11.4 (4.5-28.4)	<.0001	3			10.5 (3.2-33.9)	<.0001
Pancreatic cysts	2,854	13			1.6 (0.9-2.7)	0.1230	8			1.5 (0.7-3.0)	0.3033
Alcoholism	1,819	8			1.5 (0.8-3.1)	0.2304	4			1.2 (0.5-3.3)	0.6941

Note: Cox proportional hazard models were built to compare the adjusted risk of all and hospitalized pancreatic cancer in 144,634 individuals, with age, gender, chronic pancreatitis, intraductal papillary mucinous neoplasia, pancreatic cysts, alcoholism, and oral glucose-lowering agents (GLAs) [dipeptidyl peptidase-4 inhibitors (DPP-4i) or other oral GLAs (Others)] as independent variables. Other oral GLAs included sulfonylureas, glinides, biguanides, thiazolidines, α-glycosidase inhibitors and sodium-glucose cotransporter 2 inhibitors. CI, confidential interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; HR, hazard ratio.

Table 4 | Adjusted pancreatic cancer risk in individuals receiving other oral glucose-lowering agents with previous exposure to dipeptidyl peptidase-4 inhibitors

	n	Event	All pancreatic cancer				Event	Hospitalized pancreatic cancer			
			Adjusted for age and gender		Adjusted for age, gender and risk comorbidities			Adjusted for age and gender		Adjusted for age, gender and risk comorbidities	
			HR (95%CI)	*P* value	HR (95%CI)	*P* value		HR (95%CI)	*P* value	HR (95%CI)	*P* value
Previous exposure to DPP-4i (No=0; Yes=1)	No 33,279; Yes 49,925	No 58; Yes 103	1.0 (0.7-1.4)	0.9504	1.0 (0.7-1.4)	0.9078	No 33; Yes 69	1.1 (0.7-1.7)	0.5803	1.1 (0.7-1.7)	0.5932
Age			1.1 (1.1-1.1)	<0.0001	1.1 (1.1-1.1)	<0.0001		1.1 (1.1-1.1)	<0.0001	1.1 (1.1-1.1)	<0.0001
Gender (Male=0; Female=1)	Male 60,489; Female 22,715		0.7 (0.4-0.9)	0.0258	0.7 (0.5-1.0)	0.0313		0.7 (0.4-1.1)	0.0813	0.7 (0.4-1.1)	0.0860
Risk comorbidities											
Chronic pancreatitis	586	4			2.5 (0.9-6.9)	0.0753	1			1.0 (0.1-7.1)	0.9810
Intraductal papillary mucinous neoplasia	51	2			9.5 (2.3-39.3)	0.0020	1			7.7 (1.0-56.7)	0.0447
Pancreatic cysts	1,761	8			1.7 (0.8-3.5)	0.1486	5			1.7 (0.7-4.1)	0.2712
Alcoholism	1,080	4			1.4 (0.5-3.9)	0.4904	2			1.2 (0.3-4.9)	0.7943

Note: Cox proportional hazard models were built to compare the adjusted risk of all and hospitalized pancreatic cancer in 83,204 individuals, with age, gender, chronic pancreatitis, intraductal papillary mucinous neoplasia, pancreatic cysts, alcoholism, and previous exposure to dipeptidyl peptidase-4 inhibitors (DPP-4i) (No or Yes) as independent variables. CI, confidential interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; HR, hazard ratio.

PCs in the present study (117 cases per 100,000 patient-years) is higher than that in previous epidemiological studies (27.6 cases per 100,000 patient-years)[8], the incidence rates in claims database studies are known to be two- to threefold higher than those in epidemiological studies[9]. Another limitation is that patients having pancreatic cancer were defined by ascription of ICD-10 code C25 in the database, which may well be imprecise. However, mitigating this limitation, when pancreatic cancer is diagnosed and treatment is required, the patient is generally hospitalized, thus ensuring the reliability of the diagnostic code. Finally, although ≥60% of individuals with diabetes in Japan are aged ≥75 years, those in the present analysis were aged <75 years. Despite these limitations, the current study provides important information for healthcare professionals and individuals with diabetes, especially those in East Asian countries where DPP-4is are commonly prescribed[1].

In conclusion, this database study found no significant association of increased risk of PC with DPP-4i use among individuals with diabetes in Japan, but larger studies with longer follow up are required to confirm these findings.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Incidence of all and hospitalized pancreatic cancers taking different oral glucose-lowering agents >2 years.

Table S2 | Pancreatic cancer risk factors (International Classification of Diseases 10th Revision) at baseline in individuals taking different oral glucose-lowering agents >2 years.

Table S3 | Adjusted pancreatic cancer risk in individuals taking dipeptidyl peptidase-4 inhibitors >2 years.

Table S4 | Adjusted pancreatic cancer risk in individuals taking oral glucose-lowering agents >2 years with or without previous exposure to dipeptidyl peptidase-4 inhibitors.

Table S5 | Incidence of all and hospitalized pancreatic cancers on different oral glucose-lowering agents in individuals with medical checkup data available.

Table S6 | Pancreatic cancer risk factors (International Classification of Diseases 10th Revision) at baseline in individuals taking different oral glucose-lowering agents with health checkup data available.

Table S7 | Adjusted pancreatic cancer risk in individuals with health checkup data available taking dipeptidyl peptidase-4 inhibitors.

Table S8 | Adjusted pancreatic cancer risk in individuals taking other oral glucose-lowering agents with previous exposure to dipeptidyl peptidase-4 inhibitors with health checkup data available.

Figure S1 | Histogram of the number of individuals for the duration using dipeptidyl peptidase-4 inhibitors (DPP-4is) and other oral glucose-lowering agents (Others).