J Gastroenterol (2013) 48:238–246
DOI 10.1007/s00535-012-0622-z

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Risk factors and early signs of pancreatic cancer in diabetes: screening strategy based on diabetes onset age

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Received: 10 January 2012 / Accepted: 24 May 2012 / Published online: 28 June 2012

Abstract
Background Diabetes mellitus (DM) has long been recognized as a risk factor for pancreatic cancer (PaC) and recently has attracted attention as a manifestation of PaC. Diabetes is expected to be a clue for the early detection of PaC; however, no effective screening strategy has been established.
Methods Forty diabetic patients with PaC were identified and compared with 120 diabetic patients without any malignancies. We analyzed risk factors for and early signs of PaC, focusing on the DM-onset age.
Results As there were peaks at 40–45 years and 60–65 years in the distribution of DM-onset age, we analyzed the clinical characteristics of and risk factors for PaC according to DM-onset age: i.e., early-onset (<55 years) and late-onset (≥55 years). PaC was diagnosed within 2 years of DM onset (new-onset) in 0 % of the patients with early-onset DM, and in 33 % of those with late-onset DM. The mean duration of DM in patients with early-onset DM with PaC was longer than that in the late-onset patients (26 vs. 9 years; $P < 0.01$). A family history of DM (odds ratio [OR] 3.60) and use of insulin (OR 3.52) were significant risk factors in patients with early-onset DM, while the onset age of DM (OR 1.12) and multiple diabetic patients in the family (OR 6.13) were risk factors in those with late-onset DM. Body weight loss and exacerbation of DM were seen 12 months prior to PaC diagnosis in both groups.
Conclusions Our study revealed specific risk factors for and similar early signs of PaC in early-onset and late-onset DM. Thus, we could develop a screening strategy, combining these risk factors specific for DM-onset age with early signs of disease.

Keywords Pancreatic cancer · Diabetes · Risk factor

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Introduction

Pancreatic cancer (PaC) is the fifth leading cause of cancer death in Japan [1], and the fourth in the United States [2]. The pathogenesis of this neoplasm remains unclear, but some risk factors are candidates for screening, such as diabetes [3, 4], obesity [5, 6], cigarette smoking [3], a family history of PaC [3], chronic pancreatitis [3], and intraductal papillary mucinous neoplasm [7, 8].

Attempts at surveillance of high-risk individuals have been reported [9–11]. Of these risk factors, the association between PaC and diabetes mellitus (DM) has long been recognized, and new-onset DM has been a matter of great interest recently [12–14]. The prevalence of DM in PaC patients was reported to be 40 %, and half of the DM patients with PaC had new-onset DM with a duration of 2 years or less [12]. On the other hand, long-standing DM has also been reported to be a risk factor for PaC [15, 16]. Thus, two different relationships between DM and PaC are suggested: DM as a cause of, and as a consequence of, PaC.

However, these links have not been well studied and have not been used to improve screening strategies. In this

case–control study of diabetic patients treated at a specialized Japanese DM institute, we evaluated risk factors for PaC, according to DM-onset age, as well as temporal changes in diabetic status and body mass index (BMI) prior to PaC diagnosis.

Methods

Cases and controls

All cases and controls were treated for DM at the Institute for Adult Diseases, Asahi Life Foundation, Tokyo, Japan.

We identified 40 diabetic patients with a diagnosis of PaC from the medical records at the institute. As the study institute specializes in the treatment of lifestyle-related diseases, especially DM, all the PaC cases were referred to other hospitals. From the medical records of the study institute, histological diagnosis was confirmed in 26 cases, and the remaining 14 cases were confirmed to have PaC by the clinical course. The dates of diagnosis of PaC were between March, 1999 and May, 2011. As controls, 120 diabetic patients in whom no malignancies were detected between the onset of DM and their last visit to the above institute were randomly selected. The date of the last visit was between July, 2009 and May, 2011. The controls in this study were not matched for age or sex, in order to evaluate these variables as risk factors for PaC.

Data collection and definition

All patients filled in a questionnaire at their first visit. The questionnaire contained a history of smoking and alcohol intake, history of body weight, onset age of DM, history of other diseases, and history of family members' diseases limited to second-degree relatives. Patients visited the hospital every 1–3 months. Body weight, casual plasma glucose (CPG), and HbA1c (level according to the Japanese Diabetes Society; JDS) were measured at every visit.

The diagnosis of DM was based on the JDS criteria [17]. DM was diagnosed when hyperglycemia meeting the criteria for diabetes (fasting plasma glucose of 7.0 mmol/l [126 mg/dl] or higher; plasma glucose 2 h after 75-g glucose load of 11.1 mmol/l [200 mg/dl] or higher; or CPG load of 11.1 mmol/l [200 mg/dl] or higher) on two or more occasions on separate days. DM was also diagnosed by a single plasma glucose test meeting the criteria above if one of the following three conditions co-existed: typical symptoms of diabetes, HbA1c (JDS) of 6.5 % or higher by a standardized method, or unequivocal diabetic retinopathy.

Medical records, including the questionnaires filled in at the first visit, were retrospectively reviewed. The index date was defined as the date of diagnosis of PaC in diabetic patients with pancreatic cancer (DM with PaC), and as the date of the last visit in diabetic patients without pancreatic cancer (DM w/o PaC). Drugs used at any time between the onset of DM and the index date were reviewed. Hyperlipidemia and hypertension were also evaluated as lifestyle-related diseases, and associated medications were reviewed. A diagnosis of hyperlipidemia or hypertension was based on the need for medical treatment.

Clinical profile of diabetic patients with pancreatic cancer

We analyzed the relationship between DM-onset age and DM duration, comparing patients with DM with PaC and those with DM w/o PaC. The duration of DM was defined as the time from the date of diagnosis of DM to the index date. According to the analysis described above, we classified diabetic patients with PaC into two groups by their DM-onset age: early-onset DM (<55 years), and late-onset DM (≥55 years). The characteristics of patients with DM with PaC were compared between the early-onset and late-onset DM patients.

Risk factors for pancreatic cancer in diabetic patients

Comparing DM with PaC and DM w/o PaC, we investigated risk factors for PaC in patients with early-onset and late-onset DM. Odds ratios (ORs) and 95 % confidence intervals (95 % CIs) were calculated for each risk factor by logistic regression analysis.

Early signs of pancreatic cancer in diabetic patients

Body weight loss and DM exacerbation are frequently seen in patients with PaC. We extracted body weight, CPG, and HbA1c (JDS) data from the medical records, and compared the temporal changes in the 2 years prior to the index date in DM with PaC and DM w/o PaC.

Statistical analysis

Comparisons of nominal variables were conducted by the χ^2 test and Fisher's exact test, and continuous variables were compared by *t*-test. To investigate the relationship between onset age and duration of DM, regression lines and coefficients of determination were determined by the method of least squares. In the analysis of risk factors, ORs were calculated by logistic regression analysis. We conducted multiple logistic regression analyses, using the factors that were significant in univariate analysis. In terms of temporal changes in BMI, CPG, and HbA1c (JDS), we compared the two groups at the same time points by *t*-test,

as well as comparing different time points within each group by paired *t*-test. All statistical analyses were performed using JMP 9.0.0 statistical software (SAS Institute, Cary, NC, USA). Results are presented as means ± standard deviation and differences were considered significant when the *P* value was less than 0.05.

Results

Onset age and duration of diabetes

The characteristics of patients with DM with PaC and those with DM w/o PaC are shown in Table 1. All patients with DM with PaC had type 2 DM. Only two patients with DM w/o PaC had type 1 DM, and the others had type 2 DM. Patients with DM with PaC were older both at DM onset (53 ± 16 vs. 45 ± 12 years; $P < 0.01$) and at the index date (70 ± 9 vs. 65 ± 11 years; $P < 0.01$).

Diabetes-onset age distributions are shown in Fig. 1. Two peaks were seen in both DM with PaC (Fig. 1a) and in DM w/o PaC (Fig. 1b), although the older peak was more prominent in DM with PaC. In DM with PaC, the DM-onset age distribution had two peaks, at 40–45 years and 60–65 years. When we divided the subjects by the age of 55, which was between the 2 peaks, the proportion of late-onset DM was significantly higher in DM with PaC than in DM w/o PaC (53 vs. 27 %, $P < 0.01$).

The relationship between age of onset and duration of DM is shown in Fig. 2. There was a negative correlation in both DM with PaC (Fig. 2a) and in DM w/o PaC (Fig. 2b), although this correlation was stronger in DM with PaC. The r^2 values were 0.66 in DM with PaC and 0.28 in DM w/o PaC.

According to the distribution pattern of DM-onset age and the relationship between age of onset and duration of DM, we decided to classify diabetic patients with PaC into two groups by their DM-onset age: one with early-onset DM and the other with late-onset DM. The cut-off point was 55 years.

Comparison between early-onset diabetes and late-onset diabetes in patients with PaC

A comparison of early-onset DM (<55 years) and late-onset DM (≥55 years) in patients with PaC is shown in Table 2. Mean DM-onset age was 39 ± 7 years in early-onset DM, and 65 ± 9 years in late-onset DM ($P < 0.01$). DM duration was longer in early-onset DM (26 ± 11 years vs. 9 ± 9 years; $P < 0.01$), and there was no new-onset DM (within 2 years) in early-onset DM (0 vs. 33 %; $P < 0.01$). A family history of DM was more prevalent in early-onset DM (74 vs. 43 %; $P < 0.01$). More patients with early-onset DM were treated with insulin (78 vs. 40 %; $P = 0.02$) and sulfonylureas (94 vs. 65 %; $P = 0.03$).

Table 1 Characteristics of diabetic patients with and without pancreatic cancer (PaC)

	DM with PaC ($n = 40$)	DM w/o PaC ($n = 120$)	*P* value
Sex: male, *n* (%)	31 (76)	96 (80)	0.74
Age (years) at the index date[a]	70 ± 9	65 ± 11	<0.01
Onset age of DM (years)	53 ± 16	45 ± 12	<0.01
Duration of DM (years)	17 ± 13	19 ± 11	0.29
New-onset DM (<2 years), *n* (%)	7 (18)	7 (6)	0.02
BMI (kg/m^2) at onset of DM	26 ± 4	25 ± 4	0.67
BMI (kg/m^2) at the index date[a]	20 ± 3	22 ± 4	0.01
Heavy drinker, *n* (%)[b]	15 (39)	25 (23)	0.04
Heavy smoker, *n* (%)[c]	21 (55)	38 (33)	0.02
Family history of DM, *n* (%)[d]	23 (58)	55 (46)	0.20
Family history of PaC, *n* (%)[d]	4 (10)	6 (5)	0.24
Family history of cancer, *n* (%)[d]	21 (54)	46 (41)	0.16
Hyperlipidemia, *n* (%)	8 (20)	58 (48)	<0.01
Hypertension, *n* (%)	19 (48)	60 (50)	0.78
Use of insulin, *n* (%)	22 (58)	57 (48)	0.26
Use of sulfonylureas, *n* (%)	30 (79)	87 (73)	0.43
Use of biguanides, *n* (%)	12 (32)	56 (47)	0.10
Use of thiazolidines, *n* (%)	0 (0)	21 (18)	<0.01
Use of statins, *n* (%)	8 (20)	54 (45)	<0.01
Use of ARBs/ACE-Is, *n* (%)	11 (35)	50 (42)	0.53

DM diabetes mellitus, *BMI* body mass index, *ARB* angiotensin receptor blocker, *ACE-I* angiotensin converting enzyme inhibitor

[a] The date of diagnosis of pancreatic cancer in DM with PaC; the date of the last visit in DM without (w/o) PaC

[b] Daily alcohol intake 50 g or more

[c] Brinkman index 800 or more

[d] Family history in 2nd-degree relatives

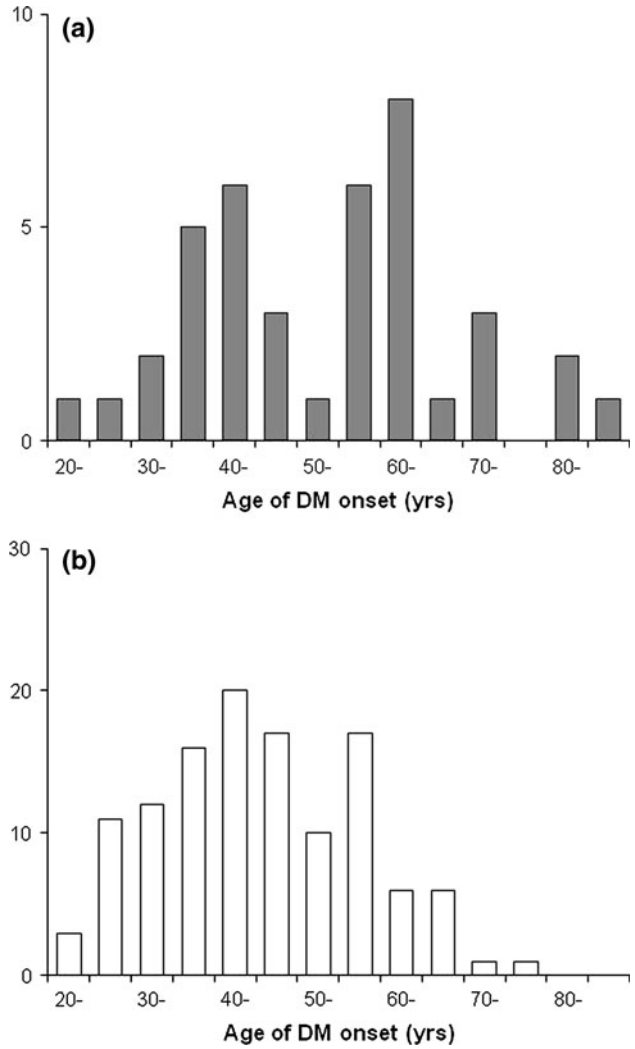


Fig. 1 Distribution of age of onset of diabetes mellitus (*DM*) **a** in diabetic patients with pancreatic cancer and **b** in diabetic patients without pancreatic cancer. *yrs* years

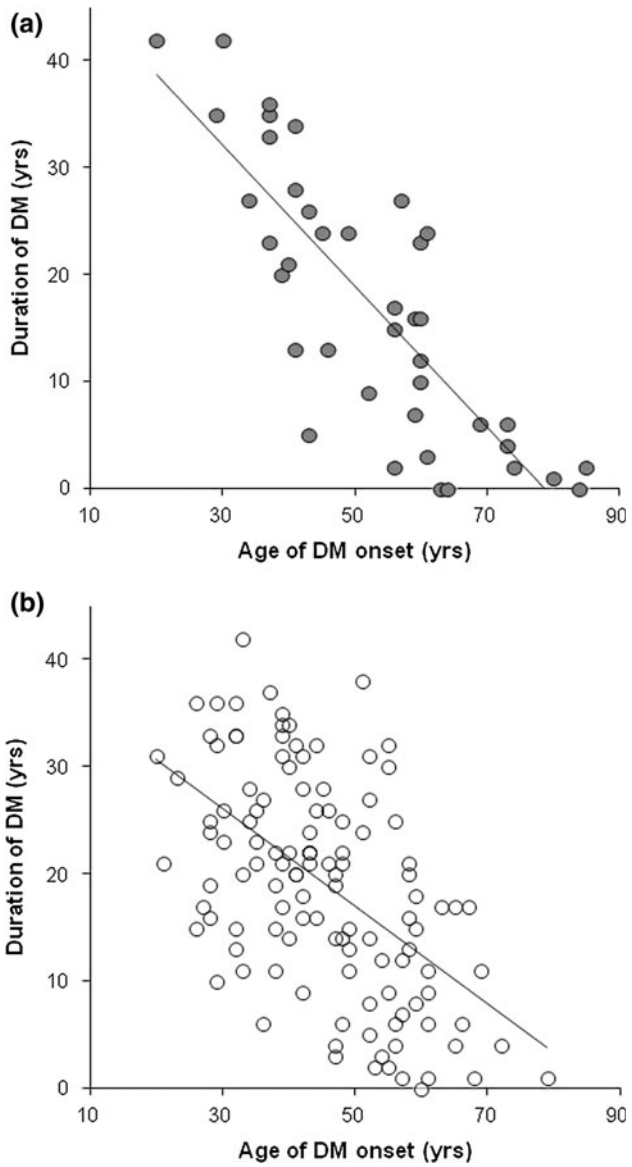


Fig. 2 Relationship between age of onset and duration of DM **a** in diabetic patients with pancreatic cancer and **b** in diabetic patients without pancreatic cancer. Regression lines are drawn in the figures: **a** $y = -0.66x + 51.9$ (r^2, 0.66), **b** $y = -0.46x + 39.8$ (r^2, 0.28)

Specific risk factors for pancreatic cancer in early-onset diabetes and late-onset diabetes

We examined risk factors for PaC in patients with early-onset and late-onset DM. The results of the univariate and multivariate analyses are shown in Table 3.

In patients with early-onset DM, a family history of DM (OR 3.60; 95 % CI 1.03–15.09; $P = 0.04$) and use of insulin (OR 3.52; 95 % CI 1.00–14.87; $P = 0.05$) were significant risk factors. Heavy smoking was associated with pancreatic cancer, but not significantly (OR 2.96; 95 % CI 0.91–10.35; $P = 0.07$). As to the insulin use, we further examined the relationship between the risk for PaC and the duration and the dose of insulin. The ORs were 4.77 (95 % CI 1.09–22.34; $P = 0.04$) in patients with a duration of insulin use of less than 5 years, and 2.47 (95 % CI 0.71–9.91; $P = 0.16$) in patients with a duration of 5 years or more. And the ORs were 3.50 (95 % CI 0.89–15.15; $P = 0.07$) in patients with a dose of less than 30 U/day, and 2.63 (95 % CI 0.72–10.81; $P = 0.14$) in patients with a dose of 30 U/day or more.

In patients with late-onset DM, DM-onset age (OR 1.12; 95 % CI 1.03–1.24; $P < 0.01$) and multiple diabetic patients in the family (OR 6.13; 95 % CI 1.20–37.91; $P = 0.03$) were significant risk factors. The presence of multiple cancer patients in the family was associated with pancreatic cancer, but not significantly (OR 8.10; 95 % CI 0.89–184.16; $P = 0.06$).

Table 2 Comparison of the characteristics of early-onset DM (<55 years) and late-onset DM (≥55 years) in patients with pancreatic cancer

	Early-onset DM ($n = 19$)	Late-onset DM ($n = 21$)	P value
Sex: male, n (%)	19 (100)	12 (57)	<0.01
Onset age of DM (years)	39 ± 7	65 ± 9	<0.01
Duration of DM (years)	26 ± 11	9 ± 9	<0.01
New-onset DM (<2 years), n (%)	0 (0)	7 (33)	<0.01
Age (years) at the index date[a]	65 ± 7	74 ± 8	<0.01
BMI (kg/m^2) at onset of DM	26 ± 4	25 ± 4	0.56
BMI (kg/m^2) at the index date[a]	22 ± 4	21 ± 4	0.13
Heavy drinker, n (%)[b]	9 (47)	6 (32)	0.32
Heavy smoker, n (%)[c]	12 (67)	9 (45)	0.18
DM(+) in family, n (%)[d]	14 (74)	9 (43)	<0.05
Multiple DM patients in family, n (%)[d]	5 (26)	7 (33)	0.63
PaC in family, n (%)[d]	1 (6)	3 (14)	0.37
Cancer(+) in family, n (%)[d]	10 (56)	11 (52)	0.84
Multiple cancer patients in family, n (%)[d]	3 (17)	5 (24)	0.58
Hyperlipidemia, n (%)	4 (21)	4 (19)	0.87
Hypertension, n (%)	7 (37)	12 (57)	0.20
Use of insulin, n (%)	14 (78)	8 (40)	0.02
Use of sulfonylureas, n (%)	17 (94)	13 (65)	0.03
Use of biguanides, n (%)	7 (39)	5 (25)	0.36
Use of thiazolidines, n (%)	0 (0)	0 (0)	–
Use of statins, n (%)	4 (21)	4 (19)	0.87
Use of ARBs/ACE-Is, n (%)	4 (31)	7 (39)	0.64

ARB, angiotensin receptor blocker; ACE-I, angiotensin converting enzyme inhibitor

[a] The date of diagnosis of pancreatic cancer in DM with PaC; the date of the last visit in DM w/o PaC

[b] Daily alcohol intake 50 g or more

[c] Brinkman index 800 or more

[d] Family history in 2nd-degree relatives

Table 3 Risk factors for pancreatic cancer in early-onset and late-onset diabetes

	Univariate		Multivariate	
	OR (95 % CI)	P value	OR (95 % CI)	P value
Early-onset DM ($n = 107$)				
Heavy smoker[a]	4.56 (1.58–14.40)	<0.01	2.96 (0.91–10.35)	0.07
DM(+) in family [b]	3.07 (1.07–10.16)	0.04	3.60 (1.03–15.09)	0.04
Use of insulin	3.20 (1.05–11.96)	0.04	3.52 (1.00–14.87)	0.05
Use of sulfonylureas	5.67 (1.06–104.98)	0.04	2.78 (0.44–54.29)	0.31
Use of statins	0.30 (0.08–0.90)	0.03	0.39 (0.10–1.34)	0.14
Late-onset DM ($n = 53$)				
Onset age of DM (per year)	1.09 (1.01–1.19)	0.03	1.12 (1.03–1.24)	<0.01
Multiple DM patients in family [b]	4.83 (1.16–25.16)	0.03	6.13 (1.20–37.91)	0.03
Multiple cancer patients in family [b]	9.69 (1.41–194.02)	0.02	8.10 (0.89–184.16)	0.06

OR odds ratio, *CI* confidence interval

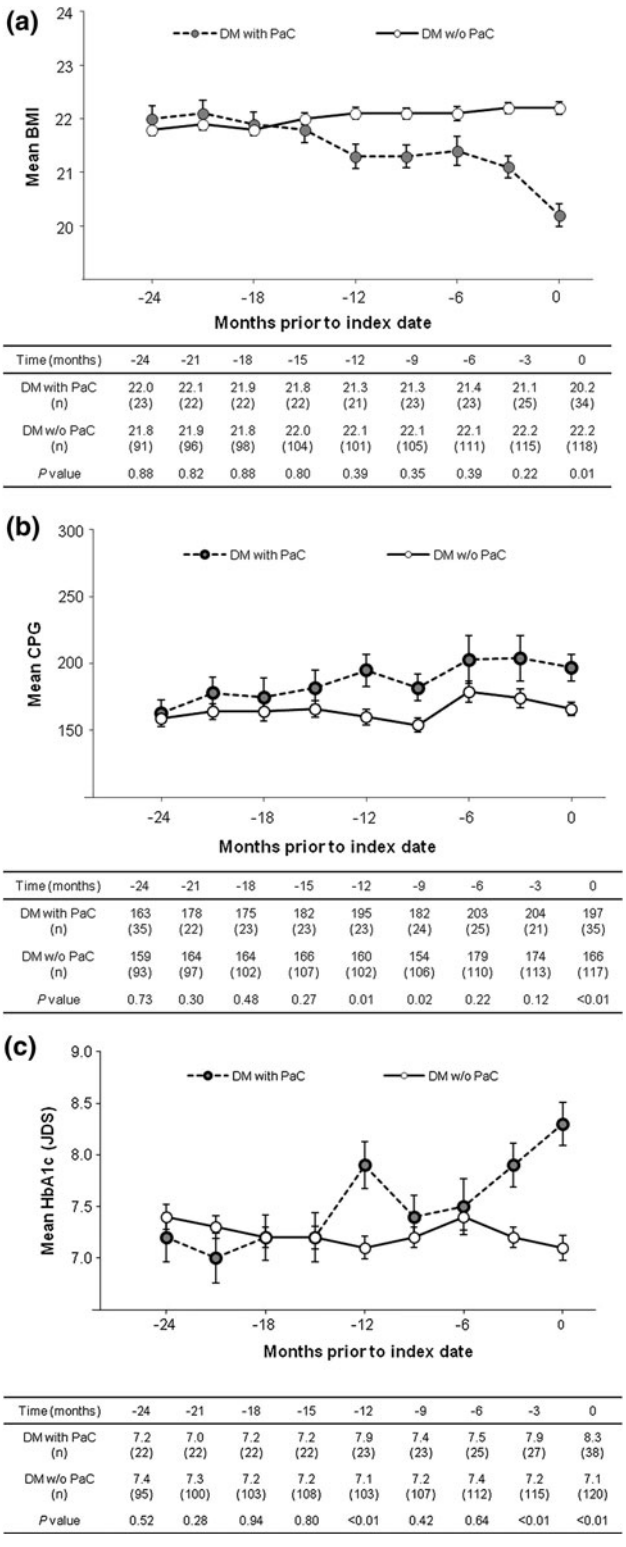
[a] Brinkman index 800 or more

[b] Family history in 2nd-degree relatives

Temporal changes in BMI, CPG, and HbA1c (JDS)

Temporal changes in BMI, CPG, and HbA1c (JDS) were compared between DM with PaC and DM w/o PaC (Fig. 3). There were no significant differences in BMI ($P = 0.88$), CPG ($P = 0.73$), or HbA1c (JDS) ($P = 0.52$) 24 months prior to the index date between DM with PaC and DM w/o PaC.

In DM w/o PaC, BMI and CPG showed no significant changes in the 2 years before the index date. HbA1c (JDS)



Time (months)	-24	-21	-18	-15	-12	-9	-6	-3	0
DM with PaC (n)	22.0 (23)	22.1 (22)	21.9 (22)	21.8 (22)	21.3 (21)	21.3 (23)	21.4 (23)	21.1 (25)	20.2 (34)
DM w/o PaC (n)	21.8 (91)	21.9 (96)	21.8 (98)	22.0 (104)	22.1 (101)	22.1 (105)	22.1 (111)	22.2 (115)	22.2 (118)
P value	0.88	0.82	0.88	0.80	0.39	0.35	0.39	0.22	0.01

Time (months)	-24	-21	-18	-15	-12	-9	-6	-3	0
DM with PaC (n)	163 (35)	178 (22)	175 (23)	182 (23)	195 (23)	182 (24)	203 (25)	204 (21)	197 (35)
DM w/o PaC (n)	159 (93)	164 (97)	164 (102)	166 (107)	160 (102)	154 (106)	179 (110)	174 (113)	166 (117)
P value	0.73	0.30	0.48	0.27	0.01	0.02	0.22	0.12	<0.01

Time (months)	-24	-21	-18	-15	-12	-9	-6	-3	0
DM with PaC (n)	7.2 (22)	7.0 (22)	7.2 (22)	7.2 (22)	7.9 (23)	7.4 (23)	7.5 (25)	7.9 (27)	8.3 (38)
DM w/o PaC (n)	7.4 (95)	7.3 (100)	7.2 (103)	7.2 (108)	7.1 (103)	7.2 (107)	7.4 (112)	7.2 (115)	7.1 (120)
P value	0.52	0.28	0.94	0.80	<0.01	0.42	0.64	<0.01	<0.01

Fig. 3 Temporal changes in mean **a** body mass index (*BMI*), **b** casual plasma glucose (*CPG*), and **c** HbA1c (Japanese Diabetic Society [*JDS*]) in diabetic patients with and without pancreatic cancer. *Bars* denote ±1 standard error of the mean. *DM with PaC* (*black circles*), diabetic patients with pancreatic cancer; *DM w/o PaC* (*white circles*), diabetic patients without pancreatic cancer. The *index date* was defined as the date of diagnosis of pancreatic cancer in DM with PaC, and the date of the last visit in DM w/o PaC

showed a small decrease, and compared with 24 months before the index date, the differences were significant at −21, −18, and −12 months.

In DM with PaC, BMI, compared with 24 months prior to the index date, showed a significant decrease from 12 months prior. CPG and HbA1c (JDS) showed significant increases from the same time, although the differences were not significant at −3 months for CPG, and at −9 months for HbA1c (JDS).

On comparing DM with PaC and DM w/o PaC, we found that CPG ($P = 0.01$) and HbA1c (JDS) ($P < 0.01$) were significantly higher in DM with PaC 12 months prior to the index date, but the difference in BMI was not significant ($P = 0.39$). At the index date, BMI was significantly lower ($P = 0.01$), and CPG ($P < 0.01$) and HbA1c (JDS) ($P < 0.01$) were significantly higher in DM with PaC than in DM w/o PaC. These trends were also seen in early-onset and late-onset DM.

Discussion

This case–control study of diabetic patients demonstrated two peaks in DM-onset age in DM patients with PaC, as well as showing specific risk factors for PaC in early-onset DM (<55 years) and late-onset DM (≥55 years). While treatment for DM was associated with PaC in early-onset DM, DM-onset age was a risk factor in late-onset DM. This suggests that diabetic patients with PaC comprise two subgroups. Bidirectional causality between PaC and DM has been recognized; thus, we speculate that early-onset DM with a long duration leads to PaC as a cause, and late-onset DM with a short duration arises as a consequence of PaC. Interestingly, both of these subgroups showed similar temporal changes in body weight and DM exacerbation as early signs of PaC. Thus, we could formulate different screening strategies, combining those risk factors specific to DM-onset age and common early signs.

Recent reports have emphasized new-onset DM as an early manifestation of PaC [12, 13]. However, the prevalence of PaC in new-onset DM is less than 1 % [18, 19], and it is neither cost-effective nor practical to screen all patients with new-onset DM. There have been many attempts to discover biomarkers for more effective screening [20–22], but such markers have not yet been established in the clinical setting. In the present study of patients with DM, the distribution of DM-onset age exhibited two peaks, and the age of onset and duration of DM were strongly negatively correlated in diabetic patients with PaC. We propose that the classification of diabetic

patients with PaC according to age of onset of DM would lead to a better understanding of the relationship between DM and PaC. We found that no PaC developed within 2 years of the diagnosis of DM in early-onset DM, but PaC was diagnosed in 33 % of the late-onset DM group within 2 years of the diagnosis of DM.

This analysis demonstrated specific risk factors according to DM-onset age. In patients with early-onset DM, there was a median 26-year interval between DM onset and the diagnosis of PaC. Long-term hyperinsulinemia and peripheral insulin resistance can be carcinogenic [23], and treatment for DM can influence carcinogenesis. There have been many studies of the relationship between PaC risk and DM medications. Biguanides [24–26] have been reported to reduce the risk of PaC, whereas sulfonylureas [24, 26, 27] and insulins [24, 26, 27] have been reported to increase the risk. Thiazolidines have been reported to have anticancer activity [28, 29], but a cohort study reported that the use of this class of drug was not associated with the incidence of PaC [27]. In our multivariate analysis, the use of insulin was a significant risk factor for PaC only in early-onset DM. In late-onset DM, the use of DM medication was not associated with PaC. However, in our analysis of the risk of insulin use, the duration of use and the dose of insulin tended to be inversely correlated with the risk for PaC. One of the reasons for this negative correlation may be that there were patients who started to use insulin because of the exacerbation of DM caused by PaC. The ORs for PaC of long or heavy insulin users were also high, but not significant. Further investigation in a larger study population is needed to clarify the carcinogenic effect of insulin.

We also found that a combination of body weight loss and DM exacerbation were early signs of PaC in diabetic patients, with these findings being seen 12 months prior to the diagnosis of PaC. With regard to DM as an early manifestation of PaC, Pannala et al. [14] reported increased fasting blood glucose and decreased BMI in PaC patients compared with age- and sex-matched controls, and the interval between these findings and the diagnosis of PaC was 12 months. Hart et al. [30] reported body weight loss in PaC patients with new-onset DM, with a mean period of 13 months from DM onset. Our retrospective analysis showed similar trends of body weight loss and elevated CPG and HbA1c (JDS) 12 months prior to the diagnosis of PaC. The advantage of our study was the availability of detailed data on body weight, CPG, and HbA1c (JDS) every 3 months. The transient decreases in HbA1c (JDS) 9 months prior to the index date in DM with PaC might reflect intensive treatment for exacerbated DM. This trend was more prominent in early-onset DM. A retrospective review of CT images [31, 32] has shown that resectable PaC could be detected on CT scans 6–18 months prior to diagnosis; thus, PaC could be detected earlier by screening patients with DM who have risk factors and show the early signs noted above. Several attempts at PaC screening using changes in carbohydrate antigen (CA) 19-9 levels as one of the early signs of PaC have been reported, but they have resulted in limited success [33–35]. In our study, CA19-9 levels were elevated in 18 of 26 PaC patients (69 %) in whom CA19-9 levels were measured (median, 744 U/ml; range 45–5740 U/ml). However, tumor markers were not routinely measured in our study, but were measured only after PaC was strongly suspected based on clinical symptoms as well as imaging studies. In addition, there were no serial data of CA19-9 in these patients. Thus, it is difficult to discuss the importance of tumor markers for the early detection of PaC in regard to this study.

Based on the results of this study, herein we suggest a diagnostic strategy for PaC, focusing on DM according to DM-onset age (Fig. 4). In the late-onset DM patients, PaC was often diagnosed soon after the diagnosis of DM. Screening examinations, such as endoscopic ultrasonography and magnetic resonance cholangiopancreatography, should be considered when late-onset DM is diagnosed. In the late-onset DM population older age is a risk factor for PaC, so a cut-off age should be determined from the aspects of cost-effectiveness. Having multiple diabetic patients in the family is another risk factor which could be useful for selecting subjects for screening. In the early-onset DM population, PaC was diagnosed during the follow up of DM. In this population, a family history of DM and use of insulin are risk factors. Screening examinations should be considered for patients with these risk factors, especially when early signs of PaC: i.e., body weight loss and DM exacerbation, are detected.

An important limitation of our study is that the control subjects were not age- or sex-matched with patients with PaC. However, because age and sex may be risk factors for PaC, age- and sex-matched controls do not necessarily

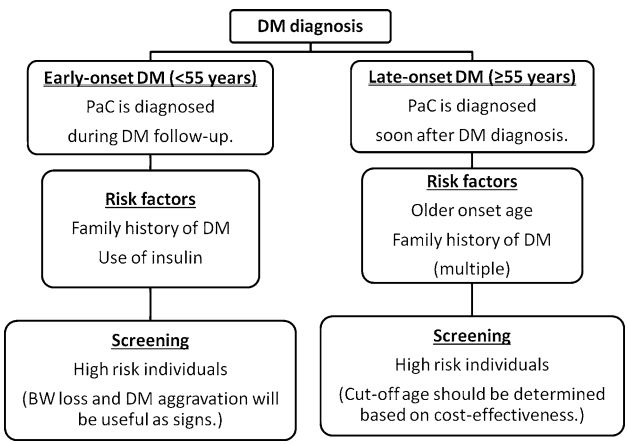


Fig. 4 A diagnostic strategy for PaC focusing on DM according to DM-onset age. *BW* body weight

represent properly matched controls. Our study population did not include patients diagnosed with DM concomitantly with PaC, because we studied patients who were diagnosed with DM prior to the diagnosis of PaC. Gullo et al. [36] reported that about 40 % of patients with PaC had a concurrent diagnosis of DM. Other limitations of the present study are its retrospective nature and small sample size. We also lacked fasting blood glucose data, which might be more sensitive than HbA1c (JDS). CPG did not show a clear trend, probably because of a large variance resulting from diet.

In conclusion, our study confirmed the existence of two types of relationship between DM and PaC, which could be differentiated by DM-onset age. There were specific risk factors for PaC in each group. In both groups, the combination of body weight loss and DM exacerbation were early signs of PaC, and were seen 12 months prior to the PaC diagnosis. The combination of risk factors specific to DM-onset age with early signs of PaC could lead to effective screening and should be confirmed in a subsequent prospective study.

Conflict of interest The authors declare that they have no conflict of interest

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