Risk Factors for Pancreatic Cancer and the Necessity of Long-Term Surveillance in Patients With Pancreatic Cystic Lesions

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Objectives: Pancreatic cystic lesions (PCLs) are a risk factor for pancreatic cancer (PC). Which PCLs should be surveilled and necessity of long-term observation are still controversial.

Methods: From January 2000 to March 2016, we enrolled 1137 patients with PCLs observed for 1 year. We defined PCLs with cyst size of greater than 30 mm, main pancreatic duct (MPD) of greater than 5 mm or mural nodule as high-risk group, and others as low-risk group (LRG). Kaplan-Meier method and Cox proportional hazard model were applied to assess incidence and risk factors of PC.

Results: In 107 high-risk group and 1030 LRG patients, mean observation period was 4.3 years and 5.0 years, respectively, and 5-year PC incidence was 12.0% and 2.8%, respectively. In LRG, MPD of greater than 3 mm, diabetes mellitus, and presumed branch-duct intraductal papillary mucinous neoplasia (BD-IPMN), defined as PCLs fulfilling any of multilocular formation, multiplicity, or MPD communication, were independent risk factors for PC. In 450 LRG observed for 5 years, 10-year PC incidence was higher in PCLs with our identified risk factors. There was no PC occurrence in PCLs not presumed BD-IPMN after 5-year observation.

Conclusions: Continuous surveillance is needed after 5-year observation, especially in LRG with our identified risk factors. For discontinuing surveillance, PCLs not presumed BD-IPMN at fifth year could be candidates.

Key Words: pancreatic cystic lesions, pancreatic cancer

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The 5-year survival rate of pancreatic cancer (PC) is less than 10% because of PC being diagnosed primarily in advanced stages.[1] This is because of the lack of initial symptoms and no appropriate tumor markers with sufficient clinical utility. To diagnose PC at early stages, we need to identify the patients with high risk for PC to perform detailed examination or strict surveillance of the cancers. Among various risk factors for PC, pancreatic cystic lesions (PCLs) are one of the good candidates for early detection of PC.[2,3] The hazard ratio (HR) of PC was reported to be 22.5 times higher in patients with PCLs than that in general population.[4] Moreover, in a systematic review, PC incidence was reported to be 0.7% per year in patients with PCLs.[5] Therefore, paying particular attention to PCLs is important for early detection of PC.

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Incidental and asymptomatic PCLs were frequently found in clinical sites, along with the progression of imaging modalities. The frequency of incidental detection of PCLs by magnetic resonance imaging (MRI) in the general population is reported to be 2.4% to 13.5%.[6,7] Abdominal ultrasonography (AUS) is useful as a noninvasive imaging modality to detect PCLs. However, it is often difficult to examine whole pancreas by AUS because of gastrointestinal gases and its location.[8] Therefore, computed tomography (CT), MRI, or endoscopic ultrasonography is needed for surveillance of whole pancreas. Considering these situations about PCLs, it is neither realistic nor economical to continue surveillance for all PCLs using these imaging modalities. Thus, assessment of the detailed risk factors for PC associated with PCLs is urgently needed to construct an appropriate surveillance strategy.

Pancreatic cystic lesions consist primarily of intraductal papillary mucinous neoplasia (IPMN).[9] In the IPMN international consensus guideline (ICG), worrisome features (WFs), and high-risk stigmata (HRS) were newly defined to stratify IPMN patients according to their risk for malignant progression.[10,11] Intraductal papillary mucinous neoplasia patients with WFs and/or HRS should receive detailed examinations or surgery because of their high-risk for PC. Compared with patients with WFs and/or HRS, IPMN patients without WFs and HRS are considered to be low risk for malignant progression. However, even in these low-risk PCLs of ICG, many previous reports demonstrated that PC incidence is approximately 0.4% to 1.9% per year.[3,4,12–17] Therefore, we need some kind of surveillance strategy for IPMN patients without WFs and HRS.

The American Gastroenterological Association (AGA) guideline published in 2015 recommended MRI at the first, third, and fifth year from initial diagnosis of low-risk PCLs and to discontinue surveillance at the fifth year if there is no change.[18] These recommendations may be reasonable in view of medical economic issues; however, there was no clear evidence for whether discontinuing surveillance of PCLs at the fifth year is safe. In PCLs with cyst size less than 1 cm, Mukewar et al[13] showed that 5-year PC incidence was 1.7%, and in patients with branch-duct (BD)-IPMN without WFs and HRS, Lawson et al[19] demonstrated that 7-year PC incidence was 1.2%. These researchers claimed that surveillance for low-risk PCLs without WFs and HRS should be tailored because of the low incidence of PC. On the other hand, Pergolini et al[12] demonstrated that PC occurrence was still observed after the lapse of 5 years from initial diagnosis in 20 of 363 patients with branch-duct intraductal papillary mucinous neoplasia (BD-IPMN) (5.5%). Other researchers also asserted that discontinuing surveillance at the fifth year is not always safe.[20,21] From these results, it remains controversial which PCLs should be surveilled and whether and when we should stop surveillance for PCLs.

In this study, we focused on 2 unresolved problems concerning surveillance of PCLs. First, we assessed risk factors for PC in low-risk PCLs to identify patients who truly need surveillance.

Considering both the low incidence of PC and the fact that PCLs are common, we need to identify more specific risk factors for PC associated with PCLs. Second, we examined the necessity of long-term surveillance for PCLs, particularly after 5 years, and we determined whether it is safe to stop surveillance at the fifth year from initial diagnosis.

MATERIALS AND METHODS

Study Design

This study was designed as a retrospective observational study in a single academic hospital. We reviewed medical database of thorough CT/MRI reports to select the patients with PCLs. As a general rule of our institution, we evaluate PCLs using contrast-enhanced CT or MRI as much as possible at the time of diagnosis. From January 2000 to March 2016, 2030 patients were determined having PCLs by CT and/or MRI at our hospital. After excluding 492 patients who were observed for less than 1 year, 167 patients diagnosed only by non–contrast-enhanced CT imaging, 106 patients coexisting PC at initial diagnosis or within 1 year, 27 patients whose observation interval was more than 3 years, and 101 patients with typical finding of other pancreatic cysts such as pseudocysts (n = 48), serous cystic neoplasm (n = 31), and mucinous cystic neoplasm (n = 22), we enrolled 1137 patients with PCLs observed for 1 year (Fig. 1). At initial diagnosis, 667, 269, and 201 patients were diagnosed using contrast-enhanced CT, MRI, or both, respectively. By imaging modalities, 89% of enrolled patients were observed at least once a year. Surgical indications for PCLs follow the ICG in 2006[22] and the revised version in 2012.[11]

This study was approved by the Institutional Review Board for Clinical Research at Osaka University Hospital (number 13550-3) and was performed in accordance with the Declaration of Helsinki. All authors had accessed and reviewed the study data and approved the final article.

Classification and Definition of Morphological Characteristics in PCLs

By contrast-enhanced CT and/or MRI at initial diagnosis, high-risk group (HRG) was defined as PCLs with any of following findings: cyst size of more than 30 mm, main pancreatic duct (MPD) diameter of more than 5 mm, and presence of mural nodule or enhancing cyst wall. Low-risk group (LRG) was defined as PCLs other than HRG, which is PCLs with cyst size of less than 30 mm, and MPD diameter less than 5 mm, and without mural nodule and enhancing cyst wall. When multiple PCLs were present, the region with the largest cyst was defined as cyst location. Cyst size and MPD diameter were expressed by the maximum size per diameter measured in the imaging studies. We defined disease progression as cyst size increase of more than 10 mm or MPD diameter increase of more than 2 mm according to a previous report.[23] Among LRG patients, PCLs fulfilling any of multilocular formation, multiplicity, and/or communication to MPD were defined as PCLs presumed BD-IPMN. In contrast, PCLs fulfilling all of unilocular formation, solitary, and no communication to MPD were defined as PCLs not presumed BD-IPMN.

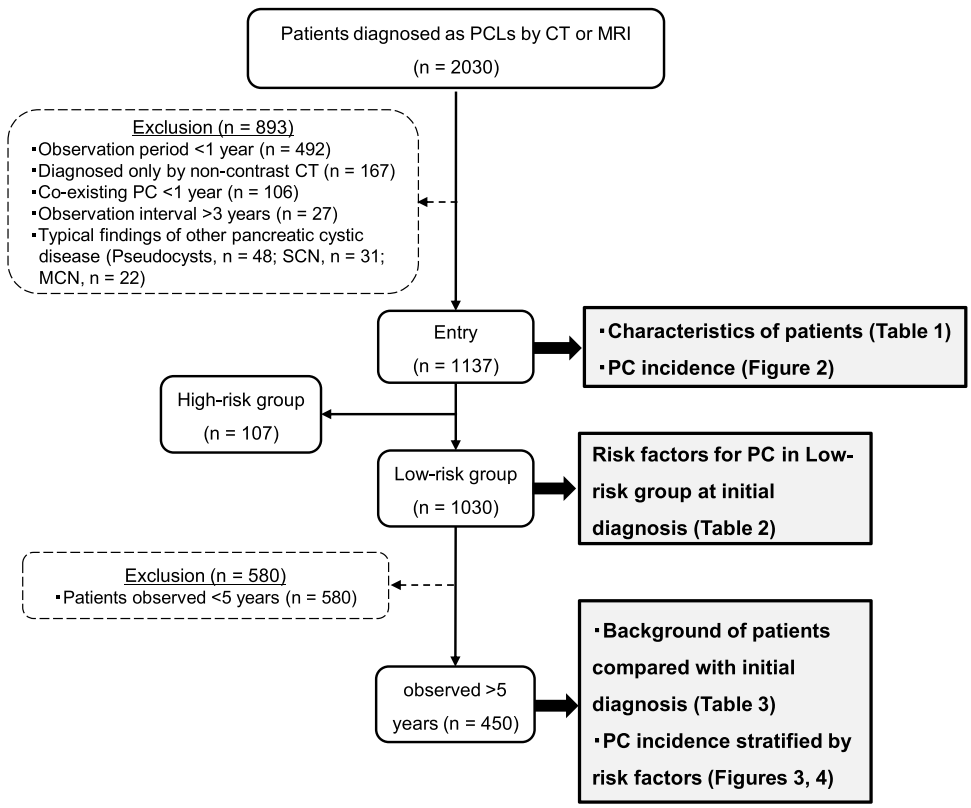


FIGURE 1. Flowchart of this study. Algorithm used for patients' inclusion and exclusion are shown. High-risk group was defined as PCLs with any of following findings: cyst size of more than 30 mm, MPD diameter of more than 5 mm, and presence of mural nodule or enhancing cyst wall. Low-risk group was defined as PCLs other than HRG, which is PCLs with cyst size of less than 30 mm, MPD diameter of less than 5 mm, and without mural nodule and enhancing cyst wall. SCN, serous cystic neoplasm; MCN, mucinous cystic neoplasm.

Definition of Clinical Data

Diabetes mellitus (DM) was diagnosed when levels of glycated hemoglobin (HbA1c) were in excess of 47 mmol/mol at initial diagnosis or the patients received medication for DM. Estimated glomerular filtration rate (eGFR) was calculated by age, sex, and serum creatinine levels at initial diagnosis.[24] Patients whose eGFR was less than 60 mL/min per 1.73 m^2 were diagnosed as having chronic kidney disease (CKD), according to a previous report.[25]

Definition of Malignancy in This Study

In this cohort, 42 patients were pathologically diagnosed as malignant, and 9 were clinically diagnosed as malignant. Pathological malignancy was proven by resected specimens (n = 32), endoscopic ultrasonography–guided fine needle aspiration (n = 6), endoscopic retrograde cholangiopancreatography (n = 2), biopsy of liver metastasis (n = 1), or cytology of ascites (n = 1). In 32 resected specimens, we defined both high-grade dysplasia (n = 6) and invasive carcinoma (n = 26) as malignant. Of 9 patients with clinical malignancy, positron emission tomography/CT was performed in 4 patients and fluorodeoxyglucose uptakes were detected in all cases. Of these 4 patients, 3 were treated in other hospitals and 1 chose to undergo best supportive care. In another 5 patients without positron emission tomography/CT imaging, pancreatic mass and liver metastasis were detected by cross-sectional imaging. Of these 5 patients, 3 selected best supportive care and 2 received chemotherapy.

We divided PC into 2 carcinogenesis forms according to a previous report.[26] One was PC derived from IPMN, which had the transition between IPMN and cancer by imaging or pathological findings. Another was PC concomitant with IPMN, which was apparently distant from the cysts by imaging studies.

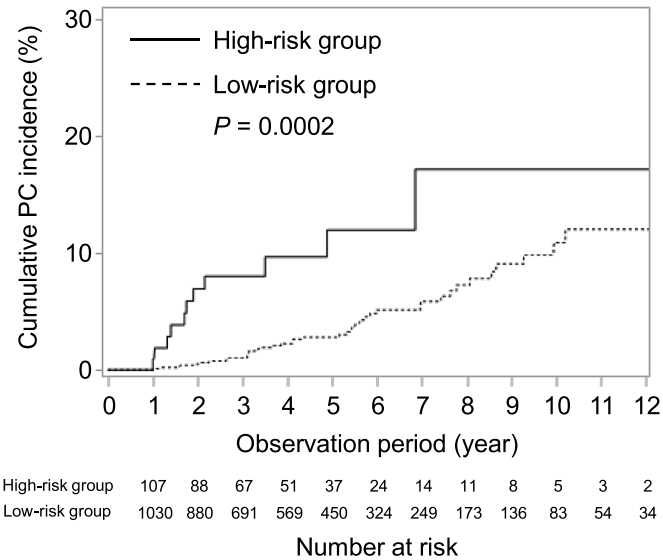
Statistical Analysis

For continuous variables, data were provided as the median and interquartile range unless otherwise indicated, and Kruskal-Wallis tests were applied. For categorical variables, Fisher exact tests were applied. Kaplan-Meier method and log-rank test were applied to assess PC incidence. The Cox proportional hazard model was applied to assess risk factors for PC. A 2-sided P value of <0.05 was considered statistically significant. Parameters with P values of <0.05 by univariate analysis were candidates for multivariate analysis. These analyses were calculated using JMP software (version 14.0.0; SAS Institute Inc, Cary, NC). Pancreatic cancer incidence adjusted by age and sex relative to Japanese nationwide cohort was calculated using the 2015 PC development database disclosed in Center for Cancer Control and Information Services.[27]

RESULTS

Characteristics at Initial Diagnosis and PC Incidence in Patients With PCLs

The numbers of HRG and LRG patients were 107 and 1030, respectively (Fig. 1). Mean (standard deviation [SD]) observation period was 4.32 (2.60) years in HRG and 5.03 (3.09) years in LRG (Fig. 2). High-risk group patients were older than LRG patients (Table 1). Morphologically, median cyst size was 11.4 mm and MPD diameter was 1.9 mm in LRG patients. Furthermore, in LRG patients, 68.3% presented with PCLs presumed BD-IPMN, which satisfy any of multilocular formation, multiplicity, and/or



	PC development, n	Observation period, year mean (SD) median [IQR]	PC incidence from initial diagnosis			
			3rd year	5th year	10th year	person-year
High-risk group (n = 107)	11	4.32 (2.60) 3.65 [3.48]	8.0%	12.0%	17.1%	2.38%
Low-risk group (n = 1030)	40	5.03 (3.09) 4.35 [4.42]	1.0%	2.8%	10.9%	0.77%

FIGURE 2. Pancreatic cancer incidence in patients with PCLs at initial diagnosis. In 107 HRG and 1030 LRG patients at initial diagnosis, cumulative PC incidence, number at risk, number of patients developed PC, observation periods, and PC incidence from initial diagnosis are shown. *P* value of PC incidence was calculated by log-rank test as 0.0002 (HRG vs LRG). IQR, interquartile range.

TABLE 1. Background of Patients at Initial Diagnosis of PCLs

	HRG	LRG	*P**
Number, n	107	1030	NA
Age, y			0.0138
Mean (SD)	69.5 (9.5)	67.2 (9.8)	
Median (IQR)	70.2 (11.9)	68.2 (13.0)	
Sex, M/F, n	64/43	493/537	0.0196
Cyst location, head/body/tail	44/19/23	475/355/200	0.0391
Cyst size, median (IQR), mm	31.8 (15.7)	11.4 (8.2)	<0.0001
MPD diameter, median (IQR), mm	5.1 (3.7)	1.9 (1.0)	<0.0001
Presumed BD-IPMN, n (%)	NA	703/1030 (68.3)	NA
HbA1c, median (IQR), mmol/mol	42.1 (14.8)	41.0 (10.9)	0.0436
DM, n (%)	24/106 (22.6)	190/1018 (18.7)	0.3622
eGFR, median (IQR), mL/min/1.73 m^2	69.6 (23.3)	70.0 (21.0)	0.5340
CKD, n (%)	34/104 (32.7)	258/986 (26.2)	0.1628
Hemodialysis, n (%)	3/104 (2.9)	11/986 (1.1)	0.1501
CEA, median (IQR), ng/mL	2.0 (2.4)	2.0 (3.0)	0.2694
CA 19-9, median (IQR), U/mL	13 (15)	14 (21)	0.5335

*Assessed by Kruskal Wallis test or Fisher exact test.

NA, not applicable; IQR, interquartile range; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; M, male; F, female.

communication to MPD. There was no significant difference in the frequencies of DM and CKD between HRG and LRG patients. During the entire observation period, development of PC was observed in 11 patients in HRG (10.3%, 11/107) and 40 patients in LRG (3.9%, 40/1030). The 5-year PC incidence in HRG was 12.0% and significantly higher than that in LRG, which was 2.8% (Fig. 2). On the other hand, PC incidence at the fifth year in LRG patients increased 26.1 times (95% confidence interval, 15.9–40.2) compared with Japanese nationwide cohort adjusted by age and sex. This result indicates that observation strategies are necessary, even in LRG patients.

Risk Factors for PC in LRG at Initial Diagnosis

We assessed risk factors for PC at initial diagnosis of LRG using the Cox proportional hazard model to identify LRG patients who really need surveillance. By univariate analysis, being male, cyst size of more than 20 mm, MPD diameter of more than 3 mm, presumed BD-IPMN, and DM were significant risk factors for PC in LRG (Table 2). In multivariate analysis among these factors, MPD diameter of more than 3 mm, presumed BD-IPMN, and DM were confirmed as independent risk factors for PC (Table 2). Hazard ratio for PC in LRG patients with MPD diameter of more than 3 mm, PCLs presumed BD-IPMN, and DM was 2.69, 3.73, and 2.98, respectively. The 5-year PC incidence in LRG patients with MPD diameter of more than 3 mm, PCLs presumed BD-IPMN, and DM was 9.3%, 3.8%, and 6.1%, respectively (Figs. 3A–C).

Among 40 patients initially diagnosed as LRG and developed PC, the numbers of PC derived from IPMN, PC concomitant with IPMN, and unclassified cases were 16, 15, and 9, respectively. By univariate analysis, cyst size of more than 20 mm, MPD diameter of more than 3 mm, and PCLs presumed BD-IPMN, DM, and CKD were significant risk factors for PC derived from IPMN (Supplemental Digital Content, Supplementary Table 1, http://links.lww.com/MPA/A781), whereas PCLs presumed BD-IPMN were a significant risk factor for PC concomitant with IPMN (Supplemental Digital Content, Supplementary Table 2, http://links.lww.com/MPA/A781).

Characteristics of Patients Initially Diagnosed as LRG and Followed for 5 Years: Comparing Data at Initial Diagnosis With Those at the Fifth Year

We assessed PC incidence in LRG patients observed for 5 years. After excluding 580 patients observed less than 5 years from 1030 LRG patients at initial diagnosis, 450 patients were observed for 5 years (Fig. 1). The mean (SD) observation period in these 450 patients was 7.87 (2.44) years. The median increase in cyst size and MPD diameter at the fifth year compared with those at initial diagnosis was 2.6 mm and 0.2 mm, respectively (Table 3). Thirty-nine patients (8.7%) progressed to HRG at the fifth year. Of these 450 patients, 156 were initially diagnosed with PCLs not presumed BD-IPMN, and morphological changes to presumed BD-IPMN were observed in 33 patients. The remaining 123 patients were diagnosed as PCLs not presumed BD-IPMN at both initial diagnosis and the fifth year. There was no significant difference in the frequency of DM between the data at initial diagnosis and the fifth year. Estimated GFR, which was affected by age, significantly decreased at the fifth year.

Incidence and Risk Factors for PC After 5-Year Observation From Initial Diagnosis

Among 450 LRG patients at initial diagnosis who were observed for 5 years, the 10-year PC incidence in HRG at the fifth year was 20.5% and significantly higher than that in LRG at the fifth year, which was 7.2% (Fig. 4A). In addition, we examined PC incidence after 5-year observation from initial diagnosis, stratified by identified risk factors (Figs. 4B–E). The 10-year PC incidence in patients with DM was 21.9% and significantly higher than in those without DM, which was 5.5% (Fig. 4B). The 10-year PC incidence in PCLs presumed BD-IPMN at the fifth year was 11.0% and significantly higher than that in PCLs not presumed BD-IPMN at the fifth year, which was 0% (Fig. 4C). Next, we stratified PC incidence according to cyst size, MPD diameter, and their progression, comparing data at initial diagnosis with that at the fifth year. There was no significant difference between the 10-year PC incidence in PCLs with cyst size of more than 20 mm at the fifth year and those

TABLE 2. Risk Factors for PC in LRG at Initial Diagnosis

	Univariate Analysis		Multivariate Analysis	
Factors	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, y				
<70	1			
≥70	1.19 (0.62–2.23)	0.5998		
Sex				
F	1		1	
M	2.38 (1.25–4.78)	0.0076	1.91 (0.99–3.88)	0.0536
Cyst location				
Head	1			
Body	0.72 (0.34–1.45)	0.3591		
Tail	1.03 (0.43–2.25)	0.9474		
Cyst size, mm				
<20	1		1	
≥20	2.21 (1.03–4.37)	0.0434	1.44 (0.66–2.91)	0.3392
MPD diameter, mm				
<3	1		1	
≥3	3.45 (1.65–6.72)	0.0017	2.69 (1.27–5.32)	0.0112
Presumed BD-IPMN				
No	1		1	
Yes	4.44 (1.78–14.8)	0.0006	3.73 (1.42–12.8)	0.0058
DM				
No	1		1	
Yes	2.99 (1.56–5.59)	0.0013	2.98 (1.53–5.66)	0.0017
eGFR, mL/min/1.73 m^2				
≥60	1			
<60	1.81 (0.87–3.56)	0.1071		
Hemodialysis				
No	1			
Yes	4.52 (0.25–21.2)	0.2309		
CEA, ng/mL				
<5	1			
≥5	0.53 (0.08–1.79)	0.3431		
CA 19-9, U/mL				
<40	1			
≥40	0.53 (0.09–1.82)	0.3556		

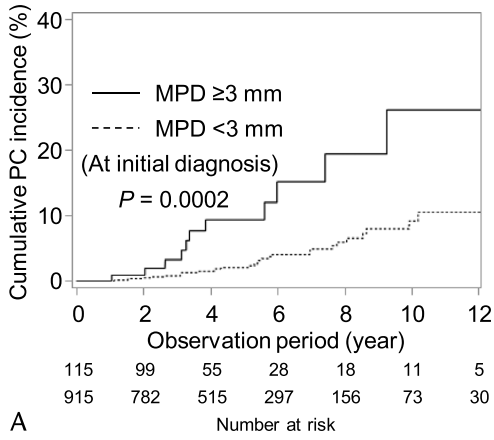
CI, confidence interval; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; M, male; F, female.

less than 20 mm. The 10-year PC incidence in PCLs with cyst size increase of more than 10 mm was significantly higher than in those less than 10 mm (Fig. 4D). The 10-year PC incidences were significantly higher not only in patients with MPD diameter of more than 3 mm at the fifth year but also in those with MPD diameter increases of greater than 2 mm (Fig. 4E). Elevation of carcinoembryonic antigen and carbohydrate antigen 19-9 levels, and decrease of eGFR were not significant risk factors for PC after 5-year observation (Supplementary Digital Content, Supplementary Fig. 1, http://links.lww.com/MPA/A781).

DISCUSSION

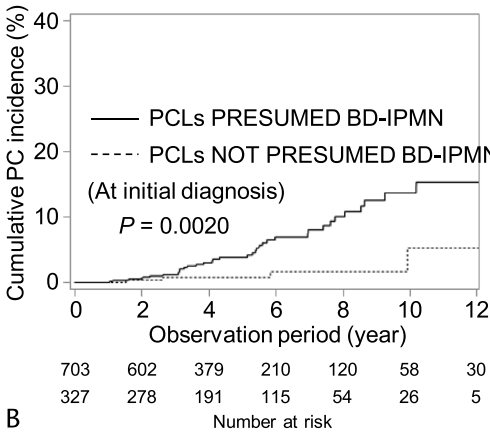
We recently performed follow-up imaging studies for PCLs every 6 months using contrast-enhanced CT or MRI if suitable in our hospital and continue surveillance for 5 years, because some previous reports demonstrated that PCLs have become widely known as a risk factor for PC, which occurred after 5-year observation from initial diagnosis. It is unresolved and urgent problems of which PCLs should be surveilled and whether and when stopping surveillance is safe still remain. In this study, we analyzed the incidence and risk factors for PC with special emphasis on PCLs with cyst size of less than 30 mm and MPD diameter of less than 5 mm, and without mural nodule and enhancing cyst wall. We showed that MPD diameter of more than 3 mm, DM, and morphologically presumed BD-IPMN at initial diagnosis were independent risk factors for PC in LRG. Even in patients observed for 5 years, there were significantly higher PC incidences in PCLs with those risk factors. In contrast, in patients with PCLs not presumed BD-IPMN and remaining morphologically unchanged throughout the 5-year observation, further PC occurrences were not observed after the lapse of 5-year observation.

Several reports have described characteristics of pancreatic cysts that are likely to develop into PC. In the analysis of a prospective cohort comprising 1058 patients examined by AUS, Tanaka et al[4] showed that HR for PC was statistically significant



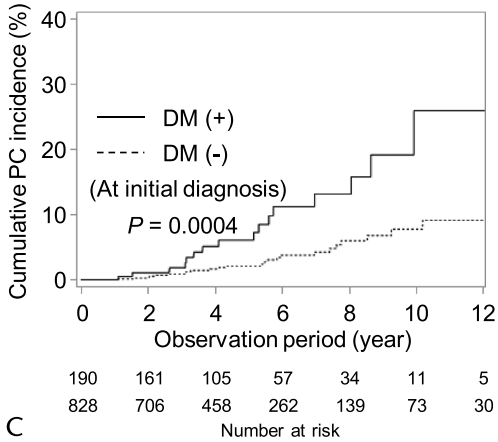
A

MPD diameter at initial diagnosis	PC development, n	PC incidence		
		3rd year	5th year	10th year
≥3 mm (n = 115)	11	3.2%	9.3%	26.1%
<3 mm (n = 915)	29	0.8%	2.1%	9.1%



B

PCLs presumed BD-IPMN at initial diagnosis	PC development, n	PC incidence		
		3rd year	5th year	10th year
Yes (n = 703)	36	1.2%	3.8%	13.6%
No (n = 327)	4	0.3%	0.8%	5.2%



C

DM at initial diagnosis	PC development, n	PC incidence		
		3rd year	5th year	10th year
Yes (n = 190)	16	1.8%	6.1%	25.9%
No (n = 828)	24	0.9%	2.1%	7.7%

FIGURE 3. Pancreatic cancer incidence according to identified risk factors in LRG at initial diagnosis. Cumulative PC incidence in 1030 LRG patients at initial diagnosis is shown during entire observation period. Pancreatic cancer incidence was assessed by Kaplan-Meier method in patients classified by (A) MPD diameter at initial diagnosis, (B) cyst morphology at initial diagnosis, or (C) DM at initial diagnosis. *P* value of PC incidence was calculated by log-rank test in each variable.

in patients with pancreatic cysts and its HR increased in PCLs with MPD diameter of more than 2.5 mm. In the analysis of a retrospective cohort comprising 168 patients with BD-IPMN, Tanno et al[28] showed that PC incidence was significantly higher in elderly patients. Because these results were derived by univariate analysis or simple comparisons, it was impossible to eliminate the influence of confounding among variables. Ohno et al[29] showed that development of symptom and disease progression, defined as cyst size increase of more than 10 mm, MPD diameter increase of more than 3 mm, or development of new mural nodule, were statistically significant risk factors for PC by multivariate analysis among 664 prospectively registered patients with PCLs. However, this analysis was also statistically limited in assessing risk factors for PC by multivariate analysis because the number of outcomes, which indicated PC occurrence, was 9 because of short follow-up period. Identification of risk factors for PC associated with PCLs based on statistically appropriate analysis has not been achieved to date. At the present time, prospectively registered and long-term observed

TABLE 3. Background of Patients Initially Diagnosed as LRG and Observed for 5 Years, Comparing Clinical Characteristics at Initial Diagnosis and the Fifth Year

	At Initial Diagnosis	At 5th Year	*P**
Number, n	450		NA
Age, y			<0.0001
Mean (SD)	65.4 (9.5)	70.4 (9.4)	
Median (IQR)	66.2 (12.5)	71.3 (12.2)	
Sex, M/F, n	218/232		NA
ICG classification, LRG/WFs/HRS, n	450/0/0	411/37/2	<0.0001
Cyst location, head/body/tail, n	203/166/81	206/160/84	0.9105
Presumed BD-IPMN, yes/no, n	294/156	327/123	0.0210
Cyst size, median (IQR), mm	10.7 (8.5)	14.1 (10.9)	<0.0001
Cyst size increase, median (IQR), mm	NA	2.6 (4.9)	NA
Cyst size increase, median (IQR), % to initial	NA	22.2 (43.2)	NA
MPD diameter, median (IQR), mm	1.8 (1.0)	2.1 (1.3)	<0.0001
MPD diameter increase, median (IQR), mm	NA	0.2 (0.7)	NA
MPD diameter increase, median (IQR), % to initial	NA	14.3 (41.7)	NA
DM, n (%)	82/444 (18.5)	94/444 (21.2)	0.3124
eGFR, median (IQR), mL/min/1.73 m^2	71.8 (21.5)	67.7 (20.8)	0.0053
CKD, n (%)	91/425 (21.4)	116/438 (26.5)	0.0939
CEA, median (IQR), ng/mL	2.0 (2.0)	2.0 (2.0)	0.7803
CEA increase (<5 to ≥5), n (%)	NA	19/350 (5.4)	NA
CA 19-9, median (IQR), U/mL	14 (22)	14 (20)	0.3422
CA 19-9 increase (<40 to ≥40), n (%)	NA	19/336 (5.7)	NA

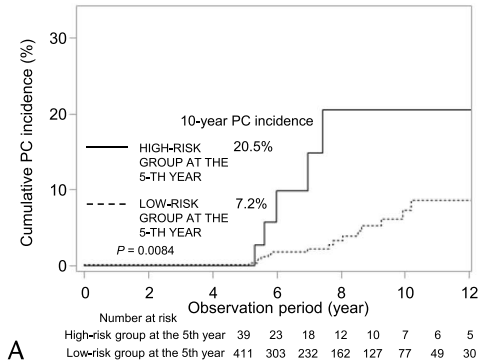
*Assessed by Kruskal Wallis test or Fisher exact test.

NA, not applicable; IQR, interquartile range; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; M, male; F, female.

large cohort of PCLs does not exist. In this study, we assessed a retrospective but large cohort with long-term observed patients with PCLs, revealing that 40 PCs developed from 1030 LRG patients. The number of outcomes was the largest compared with previous studies.[3–5,12–17,28–30] Because the number of analyzed variables and outcomes was statistically appropriate, the risk factors identified in this study are clinically worthwhile.

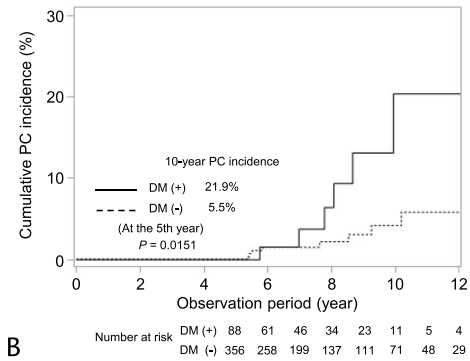
However, there are 2 major limitations in this study. First, statistically appropriate multivariate analyses using each form of carcinogenesis were impossible because the number of outcomes became small, when we divided the outcome into 2 carcinogenesis forms. Our results with univariate analysis were also limited, but it is compatible with previous reports that cyst size or MPD diameter was not a risk factor for PC concomitant with IPMN.[28,31] Stopping surveillance is not always safe just because pancreatic cysts are small, and it is still uncertain which PCLs should be surveilled at initial diagnosis. Future analysis using a large and prospective cohort is expected. Second, the 10-year PC incidence in LRG seemed high compared with the 5-year PC incidence, in the present study. We might empirically discontinue surveillance of LRG patients who do not exhibit disease progression or who seem to possess reduced potential for carcinogenesis. Selection bias was a conceivable disadvantage of this retrospective, long-term observed cohort. However, annual incidence of PC in LRG by person-year method in our results was 0.77%, which was extremely similar to that in a meta-analysis.[5] Therefore, it is feasible to analyze risk factors for PC using the present cohort. To evaluate the occurrence of PC during follow-up of PCLs, we excluded the cases with a follow-up period of less than 1 year and observation interval of 3 years or more and avoided selection bias as much as possible.

It is often difficult to accurately classify PCLs into BD-IPMN or other pancreatic cystic diseases using only imaging studies. Therefore, the definition of IPMN differs according to each report. Tada et al[17] defined PCLs fulfilling any of the following criteria as IPMN: secretion of mucus, filling defect during endoscopic retrograde cholangiopancreatography, and MPD diameter more than 3 mm. Ohno et al[29] defined PCLs with multilocular formation as BD-IPMN. In both studies, PC incidences were high in IPMN patients with their definitions. In the present study, we defined BD-IPMN as PCLs satisfying any of multilocular formation, multiplicity, and/or communication to MPD. Defined BD-IPMN was an independent risk factor for PC by multivariate analysis. In contrast, PCLs not presumed BD-IPMN were defined as lesions satisfying all of unilocular formation, solitary, and no communication to MPD. Interestingly, when all of these findings remained unchanged during 5-year observation, we found no further PC occurrence after 5-year observation. This result may be because PCLs not presumed BD-IPMN consist primarily of nonneoplastic pancreatic cysts, such as simple cysts. It is difficult to completely distinguish between simple cysts and early BD-IPMN lesions by imaging alone at initial diagnosis. However, by excluding PCLs that morphologically progressed to defined BD-IPMN after 5-year observation, nonneoplastic pancreatic cysts might be purified. We think that this contributes to identify the patients who were at extremely low risk for PC and do not have to follow up so much. These results can be the basis of decision for surveillance discontinuation after 5-year observation, as recommended by the AGA guideline.[18] However, this study is retrospective, and the results should be interpreted with caution in actual clinical practice. The number of cases with PCLs presumed simple cyst at both initial diagnosis and the fifth year was only 123. We cannot decide just from this study whether stopping surveillance of PCLs not presumed BD-IPMN at the fifth year is really safe or not. Another large scale prospective study is necessary.

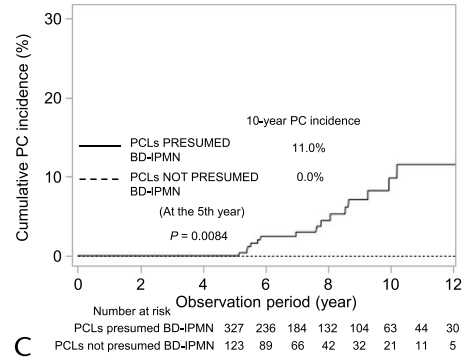


A

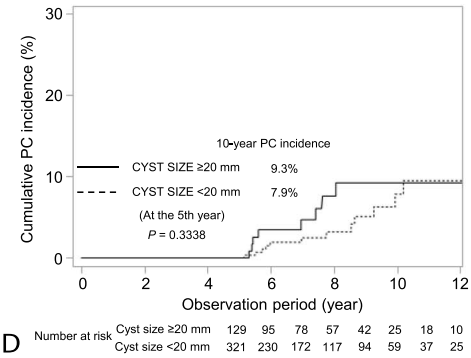
	PC Development, n	Observation Period, median [IQR], y
High-risk group at the 5th year (n = 39)	5	6.78 [3.06]
Low-risk group at the 5th year (n = 411)	15	7.35 [3.39]



B



C



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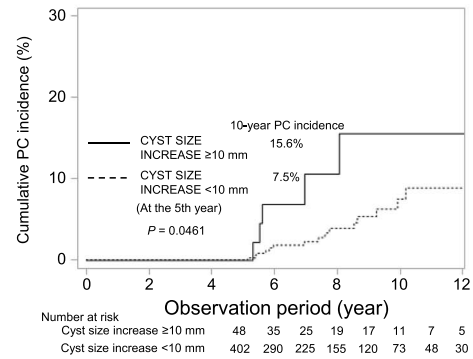

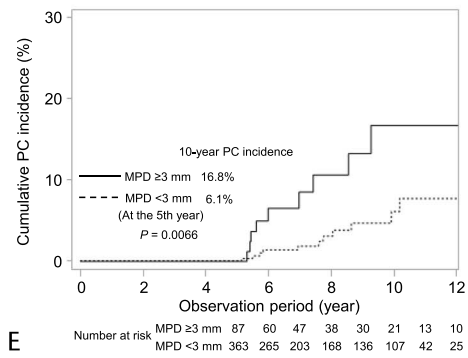

E

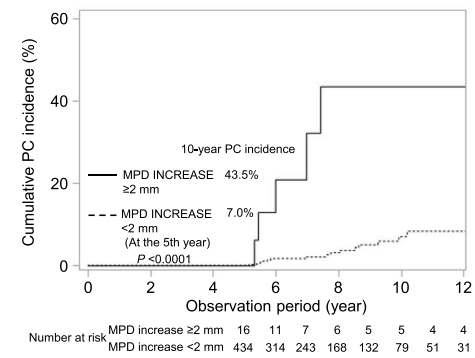

FIGURE 4. Pancreatic cancer incidence in LRG patients after 5-year observation, according to identified risk factors. The target cohort was 450 PCLs initially diagnosed as LRG and observed for 5 years. A, These 450 PCLs were classified into 39 HRG and 411 LRG according to CT and/or MRI performed at the fifth year. In both groups, cumulative PC incidence, number at risk, number of patients who developed PC, observation periods, and PC incidence from initial diagnosis are shown. In addition, PC incidence was assessed in patients classified by (B) DM, (C) cyst morphology, (D) cyst size and its change, and (E) MPD diameter and its change (all at the fifth year) by Kaplan-Meier method. *P* value of PC incidence was calculated by log-rank test. IQR, interquartile range.

In conclusion, continuous surveillance is needed after 5-year observation, especially in LRG with MPD diameter of more than 3 mm, presumed BD-IPMN, and DM. In contrast, PCLs not morphologically presumed BD-IPMN and remain unchanged during 5-year observation could be candidates for discontinuing surveillance at the fifth year as recommended by the AGA guideline.

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