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Pancreatic cyst features predict future development of pancreatic cancer: results of a nested case-control study

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Abstract

Background and Aims: Risk factors for pancreatic cancer among patients with pancreatic cysts are incompletely characterized. The primary aim of this study was to evaluate risk factors for development of pancreatic cancer among patients with pancreatic cysts.

Methods: We conducted a retrospective case-control study of U.S. veterans with a suspected diagnosis of branch-duct intraductal papillary mucinous neoplasm from 1999 to 2013.

Results: Age (hazard ratio [HR], 1.03 per year; 95% confidence interval [CI], 1.00–1.06), larger cyst size at cyst diagnosis (HR, 1.03 per mm; 95% CI, 1.01–1.04), cyst growth rate (HR, 1.22 per mm/y; 95% CI, 1.14–1.31), and pancreatic duct dilation (5–9.9 mm: HR, 3.78; 95% CI, 1.90–7.51; ≥10 mm: HR, 13.57; 95% CI, 5.49–33.53) were found to be significant predictors for pancreatic cancer on multivariable analysis.

Conclusions: Age, cyst size, cyst growth rate, and high-risk or worrisome features were associated with a higher risk of developing pancreatic cancer. Applying current and developing novel strategies is required to optimize early detection of pancreatic cancer after cyst diagnosis.

Pancreatic cysts are common, and prevalence increases with age.[1,2] Previously, risk for malignant potential was deemed to be high, and surgical resection was often performed as initial management for pancreatic cysts across many centers. As additional studies examining natural history of pancreatic cysts have emerged, a more conservative approach with periodic surveillance has been adopted.

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Risk factors for future development of pancreatic cancer among patients with pancreatic cysts remain incompletely characterized. Multiple guidelines recommend surveillance of pancreatic cystic neoplasms based on cyst-specific characteristics (Supplementary Table 1, available online at www.giejournal.org).[3–6] These guidelines are based on low-quality data and primarily represent expert opinion.

Prior studies examining the risk of future pancreatic cancer in individuals with pancreatic cysts have been limited by small study size, selection bias because of reliance on surgical and endosonographic series, and/or short follow-up. To address these research and clinical care gaps, we evaluated patient and cyst-specific risk factors for development of pancreatic cancer among patients with pancreatic cysts using a large national cohort with a long follow-up.

METHODS

Study design and population

The study base for this nested case-control study was a previously reported retrospective cohort of U.S. veterans with pancreatic cysts, which was created using national Department of Veterans Affairs electronic health record data.[7] Cases had baseline pancreatic cysts and subsequently developed pancreatic cancer on follow-up. Control subjects were a 1:3 random sample of those with pancreatic cysts at baseline without pancreatic cancer on follow-up. Charts for cancer cases and control subjects were manually reviewed to confirm pancreatic cyst diagnoses and pancreatic cancer diagnoses and to abstract cyst-specific characteristics. Exclusion criteria for cases and control subjects were absence of branch-duct intraductal papillary mucinous neoplasm (BD-IPMN), presence of main-duct IPMN, suspected benign cysts on imaging or pathology (eg, serous cystadenoma), or absence of cyst-specific characteristics based on manual chart review. Main-duct IPMNs were excluded because they harbor a high risk of malignancy and the accepted approach is surgical resection.[3,5] Hereafter, the term “pancreatic cyst” refers to suspected BD-IPMN.

Statistical analysis

Demographic and clinical characteristics were compared between cases and control subjects using the Wilcoxon rank sum test and Fisher exact test. Univariable and multivariable Cox proportional hazards regression were performed to determine predictors of development of future pancreatic cancer. Predictors included in the multivariable analysis were age, sex, race, diabetes, smoking, body mass index, number of cysts, cyst location, cyst size at diagnosis, cyst growth rate, pancreatic duct dilation, and presence of mural nodule. For multivariable regression, backward variable elimination of insignificant covariates was performed until remaining covariates had a $P < .10$. All statistical analysis was performed using R 4.1.2 (The R Foundation, Vienna, Austria).

Cyst growth rate analysis

Overall cyst growth rate was calculated using the following definition:

$$\frac{(\text{maximum cyst size during surveillance} - \text{cyst size at diagnosis})}{(\text{date of final surveillance imaging} - \text{date of cyst diagnosis})}$$

As a secondary analysis, patients were stratified into 2 groups based on cyst growth: clinical impression of cyst growth, defined by providers' documentation and progress notes abstracted from chart review, versus absence of clinical impression of cyst growth. The purpose of this secondary analysis was because observed small measurement errors over a short follow-up time may disproportionally represent large cyst growth, when in reality cyst size is clinically unchanged. Another reason for this secondary analysis was to mitigate interobserver variability in cyst measurement with the same imaging modality[8] and with different imaging modalities.[9,10]

RESULTS

Among 7211 veterans with pancreatic cysts, 78 (1.08%) were confirmed to have suspected BD-IPMN and developed pancreatic cancer ≥1 year after pancreas cyst diagnosis based on individual chart review. Seventy-two pancreatic cancer cases met the inclusion criteria for the case-control study based on availability of cyst-specific characteristics, and 265 control subjects were identified (Supplementary Fig. 1, available online at www.giejournal.org). Compared with control subjects, pancreatic cancer cases were older at cyst diagnosis (median, 74.4 years vs 67.4 years; $P = .002$) and had higher Charlson Comorbidity Index scores (median, 3.0 vs 2.0; $P = .001$); other demographic characteristics were similar between the 2 groups (Supplementary Table 2, available online at www.giejournal.org).

In regard to radiographic features (Table 1), cancer cases had a larger cyst size at diagnosis, and cysts ≥30 mm were more frequently identified in cancer cases as compared with control subjects. Pancreatic duct dilation, enhancing mural nodule, and a higher proportion of Fukuoka high-risk stigmata and worrisome features were more frequently identified in cases as compared with control subjects. No difference was found in the number of pancreatic cysts at diagnosis or cyst location between cases and control subjects. A greater proportion of cases underwent pancreatic surgery. Cases had a shorter follow-up time as compared with control subjects, but the proportion with surveillance imaging and number of cross-sectional imaging studies did not differ between the 2 groups. Frequency of imaging techniques at cyst diagnosis, during cyst surveillance, and during cyst diagnosis and surveillance did not differ between the 2 groups with the exception of cancer cases undergoing EUS more frequently than control subjects during the surveillance period (Supplementary Table 3, available online at www.giejournal.org). In regard to cyst growth, patients with cancer had a greater increase in cyst size (median, 5.0 mm vs 0 mm; $P < .001$), had a higher cyst growth rate (median, 1.9 mm/y vs 0 mm/y; $P < .001$), and more frequently had a clinical impression of cyst growth (38.5% vs 9.8%, $P < .001$) compared with control subjects (Supplementary Table 4 and Supplementary Fig. 2, available online at www.giejournal.org).

On univariable analysis, age, cyst size at diagnosis, cyst size ≥30 mm, change in cyst size, cyst growth rate, clinical impression of cyst growth, pancreatic duct dilation, enhancing mural nodule, and presence of any Fukuoka high-risk stigmata or worrisome feature were

significantly associated with an increased risk of pancreatic cancer (Fig. 1A and B). On multivariable analysis, age, index cyst size at diagnosis, cyst growth rate, and pancreatic duct dilation of 5 to 9.9 mm and ≥10 mm were all significant predictors for pancreatic cancer (Fig. 1C).

DISCUSSION

Incidentally discovered pancreatic cystic neoplasms are common, and risk factors for future pancreatic cancer are incompletely understood. Our study confirmed multiple findings surrounding pancreatic cancer risk among people with pancreatic cysts reported in the literature and expands on the existing evidence gaps. Consistent with prior work, we identified age, cyst size, cyst growth rate, pancreatic duct dilation, and presence of a mural nodule as risk factors for development of future pancreatic cancer. By using a study base representing a usual care population rather than a study group highly selected for pancreatic resection, we have extended the confidence in the importance of these risk factors.

Furthermore, our study more confidently established cyst growth rate as predictor for future pancreatic malignancy. Specifically, the median cyst growth was 5.0 mm versus 0 mm ($P < .001$) and the median cyst growth rate was 1.9 mm/y compared with 0 mm/y ($P < .001$) in cases versus control subjects, respectively. We found that 38.5% of cancer cases demonstrated a clinical impression of cyst growth with a median cyst growth rate of 4.7 mm/y, whereas 9.8% of control subjects demonstrated a clinical impression of cyst growth, with a median cyst growth rate of 3.4 mm/y. Although Fukuoka and European guidelines recommended the use of cyst growth rate as a predictor, current American Gastroenterological Association guidelines did not, based on a lack of evidence; our novel findings suggest the cyst growth rate should be considered as a marker of pancreatic cancer in future clinical practice guidelines.

Several limitations may be considered in interpreting our study. This was a retrospective, case-control study. The study base was limited to a population of U.S. veterans and may not be generalizable to all populations. We were limited to usual care imaging reports, and thus some cyst features may be inconsistently reported or under-reported. Strengths of this study include the use of a study base that is the largest reported cohort of pancreatic cystic neoplasms with a long median follow-up time. In addition, the study base is a national cohort, and thus this study is not subject to surgical or endosonographic referral bias.

In summary, by using a study base consisting of a large national cohort, we have quantified the risks of future pancreatic cancer based on radiographic features of pancreatic cysts. Our findings increase the confidence in using cyst size, pancreatic duct dilation, and presence of a mural nodule for risk stratification and provide stronger support for using cyst growth rate as a risk factor for future pancreatic cancer. Notably, a substantial portion of pancreatic cancer cases (23.6%) never developed concerning imaging features, whereas a substantial proportion of control subjects (27.5%) had high-risk or worrisome imaging features and never developed pancreatic cancer. Thus, further research is needed to help improve identification of patients with pancreatic cysts who are at high risk for pancreatic cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

DISCLOSURE

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Abbreviations:

BD-IPMN	branch-duct intraductal papillary mucinous neoplasm
CI	confidence interval
HR	hazard ratio
IPMN	intraductal papillary mucinous neoplasm

REFERENCES

1. Chang YR, Park JK, Jang JY, et al. Incidental pancreatic cystic neoplasms in an asymptomatic healthy population of 21,745 individuals: large-scale, single-center cohort study. Medicine 2016;95:e5535. [PubMed: 28002329]
2. Kromrey ML, Bülow R, Hübner J, et al. Prospective study on the incidence, prevalence and 5-year pancreatic-related mortality of pancreatic cysts in a population-based study. Gut 2018;67:138–45. [PubMed: 28877981]
3. Tanaka M, Fernández-Del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology 2017;17:738–53. [PubMed: 28735806]
4. European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. Gut 2018;67: 789–804. [PubMed: 29574408]
5. Vege SS, Ziring B, Jain R, et al. American Gastroenterological Association Institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology 2015;148:819–22; quiz e12–3. [PubMed: 25805375]
6. Scheiman JM, Hwang JH, Moayyedi P. American Gastroenterological Association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology 2015;148:824–48. [PubMed: 25805376]
7. Anand GS, Youssef F, Liu L, et al. Pancreas cancer incidence and pancreas cancer-associated mortality are low in national cohort of 7211 pancreas cyst patients. Dig Dis Sci 2021;67:1065–72. [PubMed: 33783688]
8. Dunn DP, Brook OR, Brook A, et al. Measurement of pancreatic cystic lesions on magnetic resonance imaging: efficacy of standards in reducing inter-observer variability. Abdom Radiol 2016;41:500–7.
9. Maimone S, Agrawal D, Pollack MJ, et al. Variability in measurements of pancreatic cyst size among EUS, CT, and magnetic resonance imaging modalities. Gastrointest Endosc 2010;71:945–50. [PubMed: 20231021]
10. Boos J, Brook A, Chingkoe CM, et al. MDCT vs. MRI for incidental pancreatic cysts: measurement variability and impact on clinical management. Abdom Radiol 2017;42:521–30.

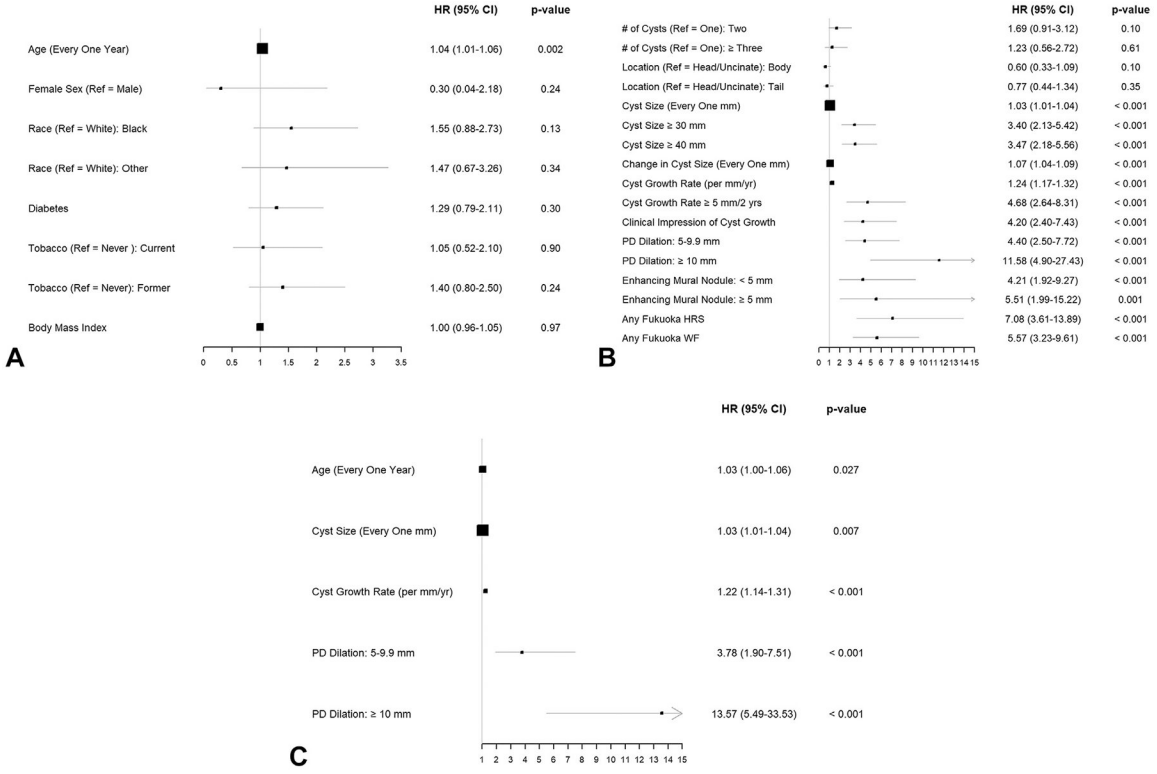

Figure 1.

Forest plots of demographic and radiographic characteristics as predictors of pancreatic cancer among patients with suspected branch-duct intraductal papillary mucinous neoplasm. **A**, Demographic characteristics. **B**, Radiographic characteristics. **C**, Demographic and radiographic characteristics (multivariable analysis). *HR*, Hazard ratio; *CI*, confidence interval; *Ref*, reference; *PD*, pancreatic duct; *HRS*, high-risk stigmata; *WF*, worrisome features.

TABLE 1.

Radiographic characteristics of suspected BD-IPMN patients with and without pancreatic cancer

Characteristics	BD-IPMN patients with pancreatic cancer (n = 72)	BD-IPMN patients without pancreatic cancer (n = 265)	*P* value
No. of pancreatic cysts at diagnosis			.86
1	52 (72.2)	194 (73.2)	
2	13 (18.1)	41 (15.5)	
≥3	7 (9.7)	30 (11.3)	
Cyst location			.17
Head/uncinate	36 (50.0)	105 (39.6)	
Body	15 (20.8)	82 (30.9)	
Tail	19 (26.4)	77 (29.1)	
Unknown	2 (2.8)	1 (.4)	
Cyst size at diagnosis, mm	25.0 (14.7–38)	15.0 (10.0–21.0)	<.001
Cyst size ≥30 mm at diagnosis or surveillance	40 (55.6)	48 (18.1)	<.001
Pancreatic duct dilation at diagnosis or surveillance			<.001
No dilation	49 (68.1)	254 (95.8)	
5–9.9 mm	17 (23.6)	11 (4.2)	
≥10 mm	6 (8.3)	0 (0)	
Enhancing mural nodule at diagnosis or surveillance			<.001
No mural nodule	61 (84.7)	261 (98.5)	
<5 mm	7 (9.7)	3 (1.1)	
≥5 mm	4 (5.6)	1 (.4)	
Presence of any Fukuoka high-risk stigmata* at cyst diagnosis or surveillance	10 (13.9)	1 (.4)	<.001
Presence of any Fukuoka worrisome feature† at cyst diagnosis or surveillance	55 (76.4)	72 (27.2)	<.001
Absence of any Fukuoka high-risk stigmata or worrisome feature at cyst diagnosis or surveillance	17 (23.6)	192 (72.5)	<.001
Pancreatic surgery during follow-up	5 (6.9)	2 (.8)	.006
Time to cancer diagnosis, mo	36.1 (26.1–56.1)	N/A	N/A
Follow-up time, mo	36.1 (26.1–56.1)	47.7 (28.8–72.0)	.02
No. with surveillance imaging	59 (81.9)	217 (81.9)	1
No. of cross-sectional imaging studies	4 (2–6)	3 (2–5)	.77

Values are n (%) or median (interquartile range).

BD-IPMN, Branch-duct intraductal papillary mucinous neoplasm; *N/A*, not applicable.

*Fukuoka high-risk stigmata are defined as obstructive jaundice with cyst in the head of the pancreas, main pancreatic duct ≥10 mm, or enhancing mural nodule (≥5 mm).

†Fukuoka worrisome features are defined as cyst size ≥30 mm, main pancreatic duct 5–9 mm, enhancing mural nodule (<5 mm), cyst growth rate ≥5 mm/2 y, increased serum levels of CA19–9, thickened or enhancing cyst walls, abrupt change in the pancreatic duct with distal pancreas atrophy, or lymphadenopathy.