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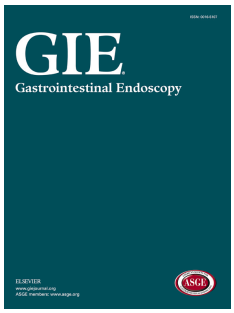

Pancreatic Cyst Features Predict for Future Development of Pancreatic Cancer: Results of a Nested Case-Control Study

Fady F. Youssef, MD, MS, Lin Liu, PhD, Wenyi Lin, BS, MS, Ranier Bustamante, BS, MS, Ashley Earles, BA, MPH, Thomas Savides, MD, Syed Fehmi, MD, Wilson Kwong, MD, Samir Gupta, MD, MSCS, Gobind Anand, MD

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Authors:

Fady F. Youssef, MD, MS[1,2]; fayoussef@health.ucsd.edu

Lin Liu, PhD[1,2]; l2liu@health.ucsd.edu

Wenyi Lin, BS, MS[3]; wel316@ucsd.edu

Ranier Bustamante, BS, MS[1]; ranier.bustamante@va.gov

Ashley Earles, BA, MPH[1]; aearles@health.ucsd.edu

Thomas Savides, MD[2]; tsavides@health.ucsd.edu

Syed Fehmi, MD[2]; sfehmi@health.ucsd.edu

Wilson Kwong, MD[2]; wtkwong@health.ucsd.edu

Samir Gupta, MD, MSCS[1,2]; s1gupta@health.ucsd.edu

Gobind Anand, MD[1,2]; gsanand@health.ucsd.edu

[1]Jennifer Moreno Veterans Affairs Healthcare System, San Diego, California

[2]Division of Gastroenterology, University of California San Diego, San Diego, California

[3]Division of Biostatistics, Herbert Wertheim School of Public Health and Longevity Science, University of California, San Diego, CA, USA

Correspondence:

Samir Gupta, MD, MSCS, AGAF

Gobind Anand, MD

Address: 3350 La Jolla Village Drive, MC 111D, San Diego, CA 92161

Journal Pre-proof

Journal Pre-proof

Email:

s1gupta@health.ucsd.edu

gsanand@health.ucsd.edu

Journal Pre-proof

Journal Pre-proof

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Authors:

Fady F. Youssef, MD, MS[1,2]; fayoussef@health.ucsd.edu

Lin Liu, PhD[1,2]; l2liu@health.ucsd.edu

Wenyi Lin, BS, MS[3]; wel316@ucsd.edu

Ranier Bustamante, BS, MS[1]; ranier.bustamante@va.gov

Ashley Earles, BA, MPH[1]; aearles@health.ucsd.edu

Thomas Savides, MD[2]; tsavides@health.ucsd.edu

Syed Fehmi, MD[2]; sfehmi@health.ucsd.edu

Wilson Kwong, MD[2]; wtkwong@health.ucsd.edu

Samir Gupta, MD, MSCS[1,2]; s1gupta@health.ucsd.edu

Gobind Anand, MD[1,2]; gsanand@health.ucsd.edu

[1]Jennifer Moreno Veterans Affairs Healthcare System, San Diego, California

[2]Division of Gastroenterology, University of California San Diego, San Diego, California

[3]Division of Biostatistics, Herbert Wertheim School of Public Health and Longevity Science, University of California, San Diego, CA, USA

Correspondence:

Samir Gupta, MD, MSCS, AGAF

Gobind Anand, MD

Address: 3350 La Jolla Village Drive, MC 111D, San Diego, CA 92161

Journal Pre-proof

Journal Pre-proof

Email:

s1gupta@health.ucsd.edu

gsanand@health.ucsd.edu

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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 is 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 suspected BD-IPMN diagnosis from 1999 to 2013.

Results

Age (HR 1.03 per year, 95%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/yr, 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) are significant predictors for pancreatic cancer on multivariable analysis.

Conclusions

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

Keywords: pancreatic IPMN; pancreatic cancer; pancreatic intraductal papillary mucinous neoplasm; Fukuoka guidelines; cyst growth rate

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BACKGROUND AND AIMS

Pancreatic cysts are common, and prevalence increases with age[1,2]. Previously, risk for malignant potential was deemed 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.

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 (Supplemental Table 1)[3-6]. These guidelines are based on low quality data and primarily represent expert opinion.

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

METHODS

Study Design and Population

The study base for this nested case-control study is a previously reported retrospective cohort of U.S. Veterans with pancreatic cysts, which was created using national Department of Veterans Affairs (VA) electronic health record data[7]. Cases had baseline pancreatic cysts and subsequently developed pancreatic cancer on follow-up. Controls were a 1:3 random sample of those with pancreatic cysts at baseline without pancreatic cancer on follow-up. Charts for cancer cases and controls were manually reviewed to confirm pancreatic cyst diagnoses, pancreatic cancer diagnoses, and to abstract cyst-specific

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characteristics. Exclusion criteria for cases and controls were absence of branch-duct intraductal papillary mucinous neoplasm (BD-IPMN), presence of main-duct IPMN, suspected benign cysts on imaging or pathology (e.g. 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 controls using Wilcoxon rank sum test and Fisher's exact test. Univariable and multivariable Cox proportional hazards regression were performed to determine predictors of development of future pancreatic cancer. Predictors included in multivariable analysis were age, sex, race, diabetes, smoking, BMI, 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 p-value < 0.10. All statistical analysis was performed using R 4.1.2 (The R Foundation).

Cyst Growth Rate Analysis

Overall cyst growth rate was calculated using the definition:

Definition: $\frac{(\max cyst\ size\ during\ surveillance - cyst\ size\ at\ diagnosis)}{(date\ of\ final\ surveillance\ imaging - date\ of\ cyst\ diagnosis)}$

As a secondary analysis, patients were stratified into two groups based on cyst growth: (a) clinical impression of cyst growth, defined by providers' documentation/progress notes abstracted from chart review versus (b) absence of clinical impression of cyst growth. The purpose of this secondary

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analysis is due to observed small measurement errors over a short follow-up time that may disproportionally represent large cyst growth, when in reality cyst size is clinically unchanged. Another reason for this secondary analysis is to mitigate interobserver variability in cyst measurement with the same imaging modality[8] and with different imaging modalities[9,10].

RESULTS

Among 7,211 Veterans with pancreatic cysts, 78 (1.08%) were confirmed to have suspected branch-duct IPMN and developed pancreatic cancer one year or later after pancreas cyst diagnosis based on individual chart review. Seventy-two pancreatic cancer cases met inclusion criteria for case-control study based on availability of cyst-specific characteristics, and 265 controls were identified (Supplemental Figure 1). Compared to controls, pancreatic cancer cases were older at cyst diagnosis (median 74.4 yrs vs. 67.4 yrs, $p = 0.002$) and had higher Charlson Comorbidity Index Score (median 3.0 vs. 2.0, $p = 0.001$); other demographic characteristics were similar between the two groups (Supplemental Table 2).

In regards to radiographic features (Table 1), cancer cases had larger cyst size at diagnosis and cysts ≥ 30 mm were more frequently identified in cancer cases as compared to controls. Pancreatic duct dilation, enhancing mural nodule, and higher proportion of Fukuoka high-risk stigmata and worrisome features were more frequently identified in cases as compared to controls. There was no difference in number of pancreatic cysts at diagnosis or cyst location between cases and controls. A greater proportion of cases underwent pancreas surgery. Cases had shorter follow-up time as compared to controls, but proportion with surveillance imaging and number of cross-sectional imaging studies did not differ between the two groups. Frequency of imaging techniques at cyst diagnosis, during cyst surveillance, and during cyst diagnosis and surveillance did not differ between the two groups with

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exception of cancer cases undergoing EUS more frequently than controls during the surveillance period (Supplemental Table 3).

In regards to cyst growth, patients with cancer had a greater increase in cyst size (median 5.0 mm vs. 0.0 mm; $p < 0.001$), had higher cyst growth rate (median 1.9 mm/yr vs. 0 mm/yr; $p < 0.001$), and more frequently had clinical impression of cyst growth (38.5% vs. 9.8%; $p < 0.001$) compared to controls (Supplemental Table 4, Supplemental Figure 2).

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

DISCUSSION

Incidentally discovered pancreatic cystic neoplasms are common, and risk factors for future pancreatic cancer are incompletely understood. Our study confirms multiple findings surrounding pancreatic cancer risk among people with pancreatic cysts reported in the literature and expands upon 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 utilizing a study base representing a usual care population, rather than a study group highly selected for pancreas resection, we have extended confidence in importance of these risk factors.

Furthermore, our study more confidently establishes cyst growth rate as predictor for future pancreatic malignancy. Specifically, median cyst growth was 5.0 mm vs. 0 mm ($p < 0.001$) and median

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cyst growth rate was 1.9 mm/yr compared to 0 mm/yr ($p < 0.001$) in cases versus controls. We found that 38.5% of cancer cases demonstrated clinical impression of cyst growth with a median cyst growth rate of 4.7 mm/yr, while 9.8% of controls demonstrated clinical impression of cyst growth, with a median cyst growth rate of 3.4 mm/yr. While Fukuoka and European guidelines recommended use of cyst growth rate as a predictor, current AGA guidelines did not based on a lack of evidence; our novel findings suggest 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 is a retrospective, case-control study. The study base is 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 use of a study base that is the largest reported cohort of pancreatic cystic neoplasms and has 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 utilizing 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 confidence in utilizing cyst size, pancreatic duct dilation, and presence of a mural nodule for risk stratification, and provide stronger support for utilizing 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, while a substantial proportion of controls (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.

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Figure 1: Forest Plots of Demographic and Radiographic Characteristics as Predictors of Pancreatic Cancer Among Patients with Suspected BD-IPMN. A) Demographic Characteristics. B) Radiographic Characteristics. C) Demographic and Radiographic Characteristics (Multivariable Analysis). Abbreviations: Ref, reference; PD, pancreatic duct; HRS, high-risk stigmata; WF, worrisome features.

Supplemental Figure 1: Study Flow of Case-Control Design. Abbreviations: ICD, International Classification of Diseases; NDI, National Death Index; BD-IPMN, branch-duct intraductal papillary mucinous neoplasm.

Supplemental Figure 2: A) Cyst Growth (mm) and B) Cyst Growth Rate (mm/yr) for Cases and Controls.

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Table 1: Radiographic Characteristics of Suspected BD-IPMN Patients with and without Pancreatic Cancer

		BD-IPMN Patients with Pancreatic Cancer (n = 72)	BD-IPMN Patients without Pancreatic Cancer (n = 265)	p-value
Number of Pancreatic Cysts at Diagnosis, n (%)	One Cyst	52 (72.2%)	194 (73.2%)	0.86
	Two Cysts	13 (18.1%)	41 (15.5%)	
	≥ Three Cysts	7 (9.7%)	30 (11.3%)	
Cyst Location, n (%)	Head/Uncinate	36 (50.0%)	105 (39.6%)	0.17
	Body	15 (20.8%)	82 (30.9%)	
	Tail	19 (26.4%)	77 (29.1%)	
	Unknown	2 (2.8%)	1 (0.4%)	
Median Cyst Size (mm) at Diagnosis (IQR)		25.0 (14.7 – 38)	15.0 (10.0 – 21.0)	< 0.001
Cyst Size ≥ 30 mm at Diagnosis or Surveillance, n (%)		40 (55.6%)	48 (18.1%)	< 0.001
Pancreatic Duct Dilation at Diagnosis or Surveillance, n (%)	No Dilation	49 (68.1%)	254 (95.8%)	< 0.001
	5 – 9.9 mm	17 (23.6%)	11 (4.2%)	
	≥ 10 mm	6 (8.3%)	0 (0%)	
Enhancing Mural Nodule at Diagnosis or Surveillance, n (%)	No Mural Nodule	61 (84.7%)	261 (98.5%)	< 0.001
	< 5 mm	7 (9.7%)	3 (1.1%)	
	≥ 5 mm	4 (5.6%)	1 (0.4%)	
Presence of any Fukuoka High-Risk Stigmata[a] at Cyst Diagnosis or Surveillance, n (%)		10 (13.9%)	1 (0.4%)	< 0.001
Presence of any Fukuoka Worrisome Feature[b] at Cyst Diagnosis or Surveillance, n (%)		55 (76.4%)	72 (27.2%)	< 0.001
Absence of any Fukuoka High-Risk Stigmata or Worrisome Feature at Cyst Diagnosis or Surveillance, n (%)		17 (23.6%)	192 (72.5%)	< 0.001
Pancreas Surgery During Follow-up, n (%)		5 (6.9%)	2 (0.8%)	0.006
Median Time to Cancer Diagnosis (months) (IQR)		36.1 (26.1 – 56.1)	--	--
Median Follow-up Time (months) (IQR)		36.1 (26.1 – 56.1)	47.7 (28.8 – 72.0)	0.02
Number with Surveillance Imaging, n (%)		59 (81.9%)	217 (81.9%)	1
Median Number of Cross-Sectional Imaging Studies (IQR)		4 (2 – 6)	3 (2 – 5)	0.77

[a]Fukuoka High-Risk Stigmata are defined as: 1) obstructive jaundice with cyst in head of pancreas, 2) main pancreatic duct (PD) ≥ 10 mm, or 3) enhancing mural nodule (≥ 5 mm).

[b]Fukuoka Worrisome Features are defined as: 1) cyst size ≥ 30 mm, 2) main PD 5-9 mm, 3) enhancing mural nodule (< 5 mm), 4) cyst growth rate ≥ 5 mm/2 years, 5) increased serum levels of CA19-9, 6)

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thickened or enhancing cyst walls, 7) abrupt change in PD with distal pancreas atrophy, or 8) lymphadenopathy.

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Supplemental Table 1: 2017 Fukuoka Consensus Guidelines, 2018 European Guidelines, and 2015 AGA Guidelines

2017 Fukuoka Consensus Guidelines	
High-Risk Stigmata	**Worrisome Features**
Obstructive jaundice with cyst in head of pancreas	Cyst diameter ≥ 30 mm
Main pancreatic duct dilatation ≥ 10 mm	Main pancreatic duct dilatation: 5 to 9.9 mm
Enhancing mural nodule (≥ 5 mm)	Enhancing mural nodule (< 5 mm)
	Growth rate ≥ 5 mm/2 yrs
	Increased serum levels of CA 19-9
	Thickened/enhancing cyst walls
	Abrupt change in caliber of pancreatic duct with distal pancreatic atrophy
	Lymphadenopathy
2018 European Guidelines	
Absolute Indications for Surgery	**Relative Indications for Surgery**
Obstructive jaundice (tumor related)	Cyst diameter ≥ 40 mm
Main pancreatic duct dilatation ≥ 10 mm	Main pancreatic duct dilatation: 5 to 9.9 mm
Enhancing mural nodule (≥ 5 mm)	Enhancing mural nodule (< 5 mm)
Solid mass	Growth rate ≥ 5 mm/yr
Positive cytology for malignancy/HGD	Increased serum levels of CA 19-9 (> 37 U/mL)
	New onset of diabetes mellitus
	Acute pancreatitis (caused by IPMN)
2015 AGA Guidelines	
Cyst diameter ≥ 30 mm	
Dilated main pancreatic duct	
Solid component	

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Supplemental Table 2: Demographic and Clinical Characteristics of Suspected BD-IPMN Patients at Time of Cyst Diagnosis

		BD-IPMN Patients with Pancreatic Cancer (n = 72)	BD-IPMN Patients without Pancreatic Cancer (n = 265)	p-value
Median Age (yrs) at Cyst Diagnosis (IQR)		74.4 (65.0 – 82.4)	67.4 (60.7 – 77.3)	0.002
Sex, n (%)	Male	71 (98.6%)	248 (93.6%)	0.14
	Female	1 (1.4%)	17 (6.4%)	
Race, n (%)	White	49 (68.1%)	205 (77.4%)	0.24
	Black	16 (22.2%)	40 (15.1%)	
	Other	7 (9.7%)	20 (7.5%)	
Diabetes Mellitus, n (%)		25 (34.7%)	86 (32.5%)	0.67
Tobacco, n (%)	Current Smoker	14 (19.4%)	68 (25.7%)	0.36
	Former Smoker	39 (52.4%)	120 (45.3%)	
	Never Smoker	18 (25.0%)	77 (29.1%)	
	Unknown	1 (1.4%)	0 (0%)	
Median Body Mass Index (IQR)		27.7 (25.0 – 31.3)	27.8 (24.4 – 31.4)	0.67
Median Charlson Comorbidity Index (IQR)		3 (2-5)	2 (1-4)	0.001

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Supplemental Table 3: Imaging Studies in Suspected BD-IPMN Patients with and without Pancreatic Cancer

	BD-IPMN Patients with Pancreas Cancer (n = 72)	BD-IPMN Patients without Pancreas Cancer (n = 265)	p-value
Cyst Diagnosis			
CT Abdomen, n (%)	61 (84.7%)	232 (87.5%)	0.56
CT Abdomen with Pancreas Protocol, n (%)	13 (18.1%)	45 (17.0%)	0.86
MR Abdomen, n (%)	24 (33.3%)	84 (31.7%)	0.78
MR/MRCP, n (%)	10 (13.9%)	32 (12.1%)	0.69
EUS, n (%)	11 (15.3%)	32 (12.1%)	0.55
EUS with FNA, n (%)	8 (11.1%)	21 (7.9%)	0.48
CT Abdomen with Pancreas Protocol, MR Abdomen, MR/MRCP, or EUS, n (%)	39 (54.2%)	139 (52.5%)	0.90
Cyst Surveillance (n = 59 and n = 217)			
CT Abdomen, n (%)	54 (92.5%)	185 (85.3%)	0.28
CT Abdomen with Pancreas Protocol, n (%)	21 (35.6%)	82 (37.8%)	0.88
MR Abdomen, n (%)	27 (45.8%)	90 (41.5%)	0.56
MR/MRCP, n (%)	12 (20.3%)	40 (18.4%)	0.71
EUS, n (%)	27 (45.8%)	38 (17.4%)	< 0.001
EUS with FNA, n (%)	24 (40.7%)	25 (11.5%)	< 0.001
CT Abdomen with Pancreas Protocol, MR Abdomen, MR/MRCP, or EUS, n (%)	47 (79.7%)	158 (72.8%)	0.37
Cyst Diagnosis and Surveillance			
CT Abdomen, n (%)	67 (93.1%)	247 (93.2%)	1
CT Abdomen with Pancreas Protocol, n (%)	28 (38.9%)	110 (41.5%)	0.79
MR Abdomen, n (%)	43 (59.7%)	124 (46.8%)	0.06
MR/MRCP, n (%)	21 (29.2%)	54 (20.4%)	0.11
EUS, n (%)	34 (47.2%)	64 (24.2%)	< 0.001
EUS with FNA, n (%)	28 (38.9%)	42 (15.8%)	< 0.001
CT Abdomen with Pancreas Protocol, MR Abdomen, MR/MRCP, or EUS, n (%)	61 (84.7%)	203 (76.6%)	0.15

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316 Supplemental Table 4: Cyst Growth Rate of Suspected BD-IPMN Patients with and without Pancreatic
317 Cancer

	BD-IPMN Patients with Pancreatic Cancer (n = 52)	BD-IPMN Patients without Pancreatic Cancer (n = 204)	p-value
Median Change in Cyst Size (mm) (IQR)	5.0 (1.5 – 14.5)	0 (-1.0 – 4.0)	< 0.001
Median Cyst Growth Rate (mm/yr) (IQR)	1.9 (0.3 – 4.1)	0 (-0.2 – 1.4)	< 0.001
Change in Cyst Size ≥ 5 mm, n (%)	28/51 (54.9%)	41/200 (20.5%)	< 0.001
Cyst Growth Rate ≥ 5 mm/2 yrs, n (%)	20/51 (39.2%)	20/200 (10.0%)	< 0.001
Clinical Impression of Cyst Growth, n (%)[a]	20/52 (38.5%)	20/204 (9.8%)	< 0.001
Clinical Impression of Cyst Shrinkage, n (%)	1/52 (1.9%)	8/204 (3.9%)	0.69
Median Change in Cyst Size (mm) in Individuals with Clinical Impression of Cyst Growth (IQR)[b]	18.0 (9.0-33.3)	9.5 (6.8-12.1)	0.034
Median Cyst Growth Rate (mm/yr) in Individuals with Clinical Impression of Cyst Growth (IQR)	4.7 (2.8-10.7)	3.4 (2.2-4.6)	0.13

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319 [a]Cyst growth based on clinical impression from providers as documented in progress notes abstracted
320 from chart review.
321 [b]n = 20 for cancer cases and n = 20 for controls.
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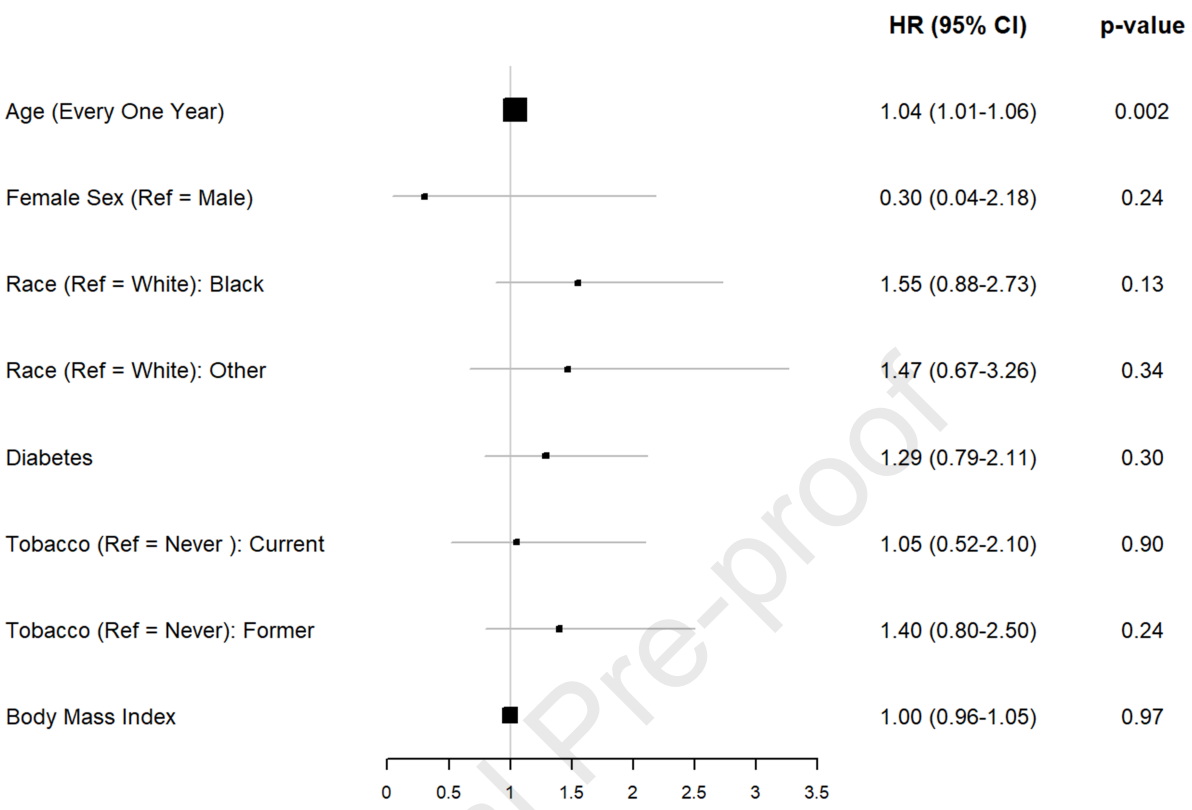

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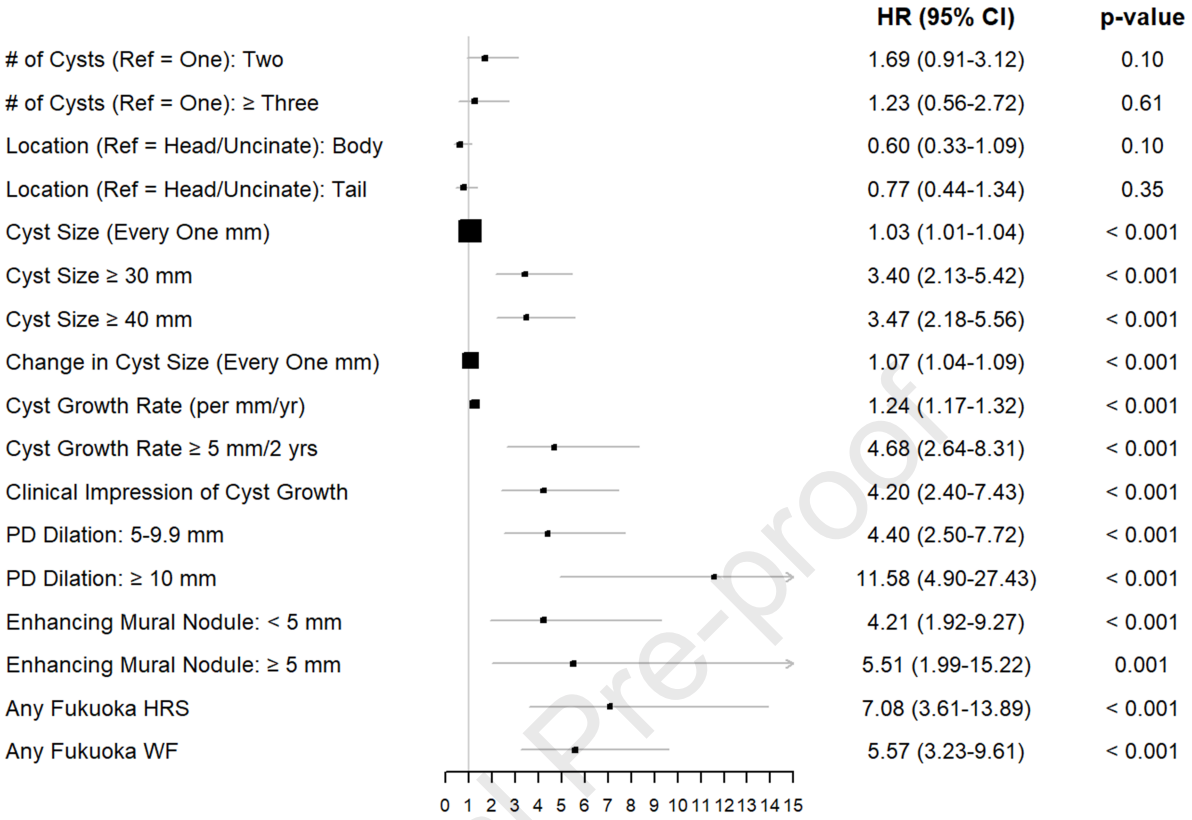

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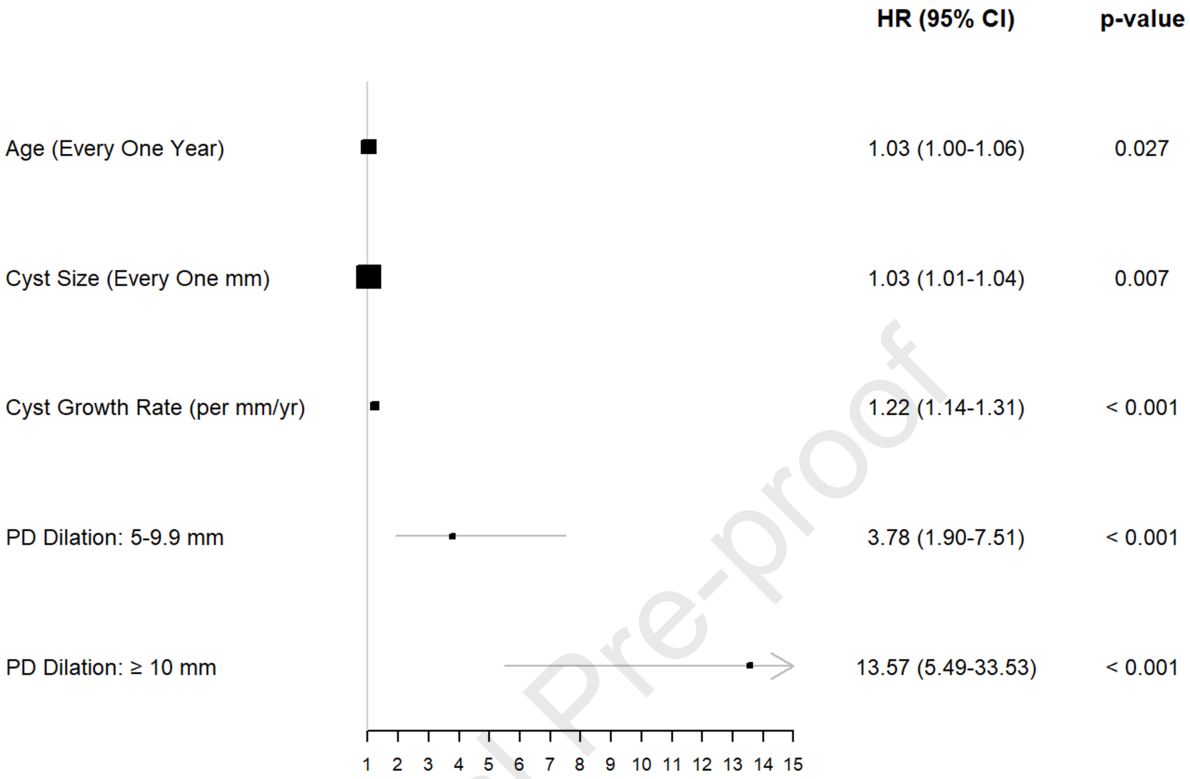

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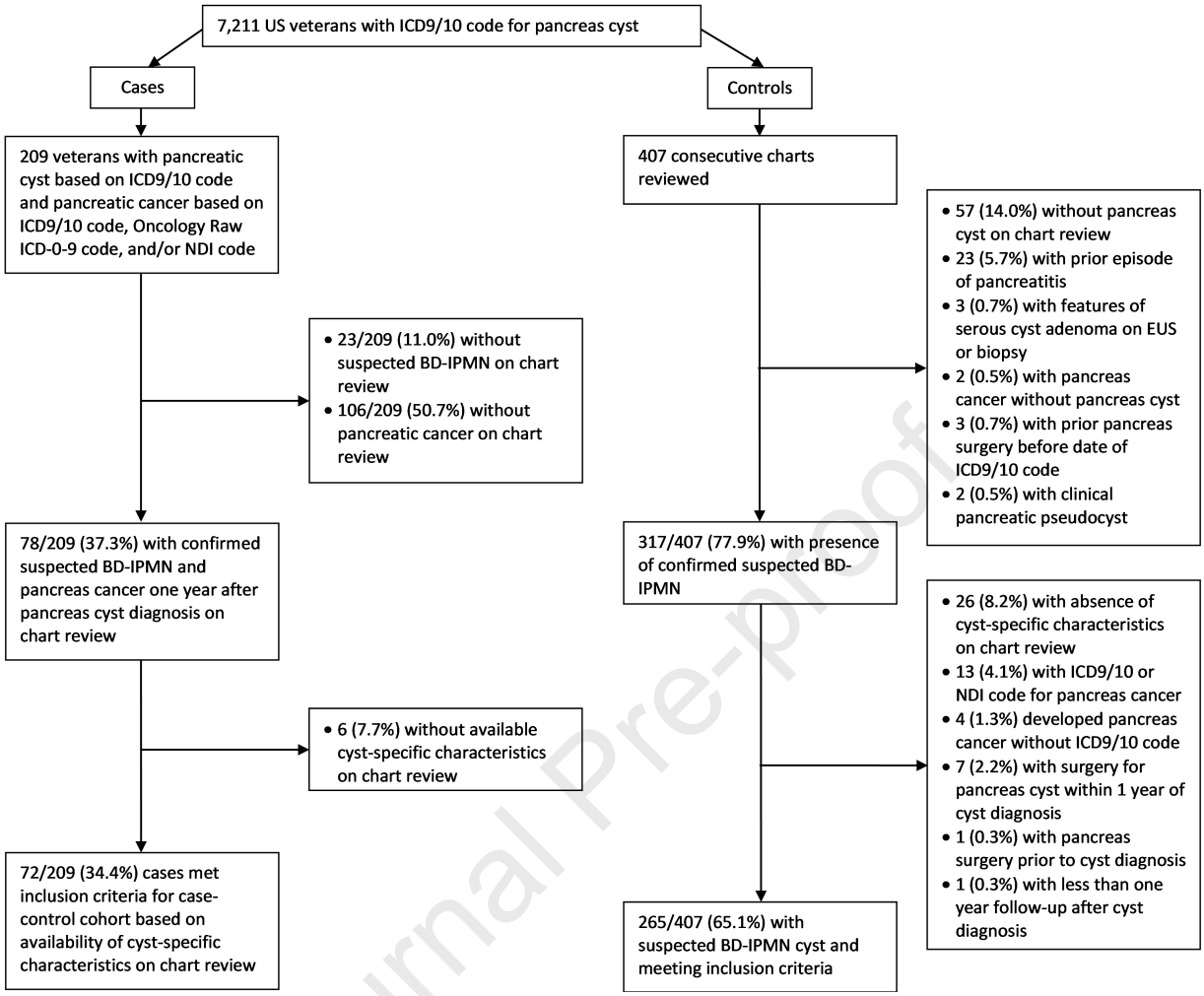

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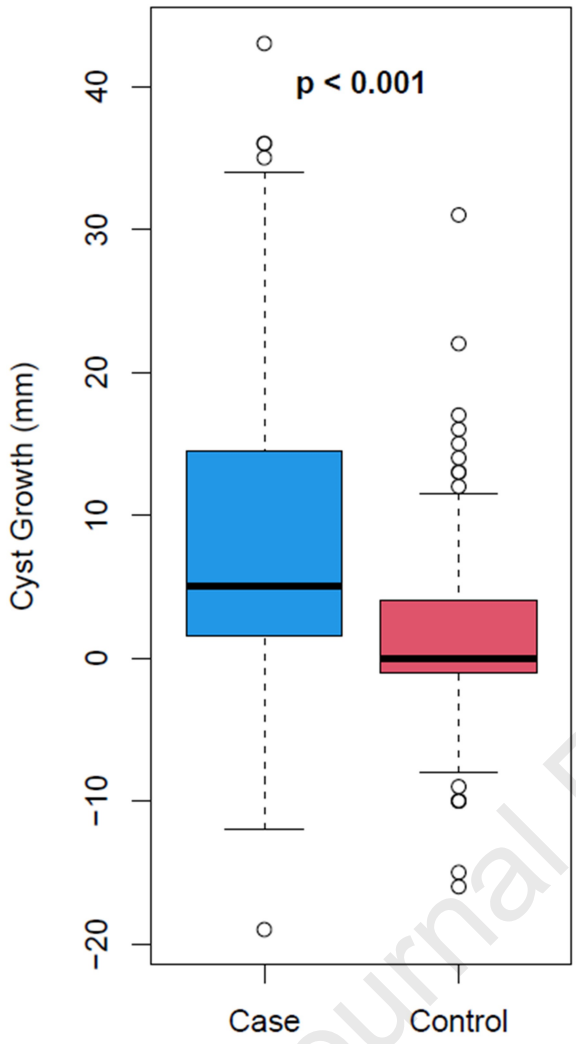

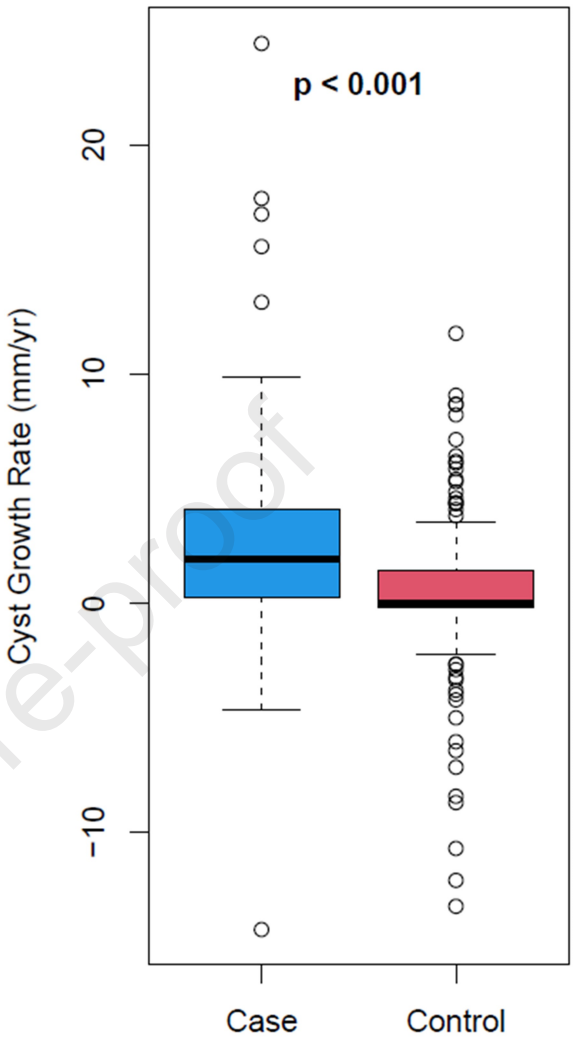

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Acronyms and Abbreviations

U.S. – United States

BD-IPMN – Branch-duct intraductal papillary mucinous neoplasm

ICD – International Classification of Diseases

VA – Veterans Affairs

HR – Hazard ratio

mm – millimeter

yr – year

CT – Computed Tomography

MR – Magnetic Resonance

MCN – mucinous cystic neoplasm

NDI – National Death Index

ICD-O-3 – International Classification of Disease for Oncology, Third Edition

VINCI – VA Informatics and Computing Infrastructure

IPMN – Intraductal papillary mucinous neoplasm

BMI – Body mass index

EUS – Endoscopic ultrasound

AGA – American Gastroenterological Association

OR – Odds ratio

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Author Contributions:

Fady Youssef – conception and design; analysis and interpretation of the data; drafting of the article; critical revision of the article for important intellectual content; final approval of the article

Lin Liu - conception and design; analysis and interpretation of the data; critical revision of the article for important intellectual content; final approval of the article

Wenyi Lin - conception and design; analysis and interpretation of the data; critical revision of the article for important intellectual content; final approval of the article

Ranier Bustamante - conception and design; analysis and interpretation of the data; critical revision of the article for important intellectual content; final approval of the article

Ashley Earles - analysis and interpretation of the data; critical revision of the article for important intellectual content; final approval of the article

Thomas Savides - analysis and interpretation of the data; critical revision of the article for important intellectual content; final approval of the article

Syed Fehmi - analysis and interpretation of the data; critical revision of the article for important intellectual content; final approval of the article

Wilson Kwong - analysis and interpretation of the data; critical revision of the article for important intellectual content; final approval of the article

Samir Gupta- conception and design; analysis and interpretation of the data; critical revision of the article for important intellectual content; final approval of the article

Gobind Anand – conception and design; analysis and interpretation of the data; critical revision of the article for important intellectual content; final approval of the article