

Predictors for Pancreatic Cancer Diagnosis Following New-Onset Diabetes Mellitus

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OBJECTIVES: New-onset diabetes mellitus (NODM) in adults is often an early manifestation of pancreatic cancer (PaCa), but the incidence of PaCa in this cohort is rather low. We evaluated whether combining other patient factors such as age, smoking history, the absence of obesity, the presence of chronic pancreatitis (CP), and gallstone disease can result in a more enriched cohort.

METHODS: After a washout period of 2 years to exclude pre-existing PaCa or DM, 507,378 non-diabetic patients in the veterans' administration healthcare system were identified. Patients < 40 years ($n = 54,465$) and those with PaCa diagnosed before the diagnosis of diabetes ($n = 22$) were excluded. A total of 452,804 veterans were followed for development of DM or PaCa.

RESULTS: 73,811 patients (16.3%) developed NODM during the follow-up period. One hundred and eighty-three NODM patients (0.25%) were diagnosed with PaCa within 3 years. In comparison, 434 of 378,993 remaining patients (0.11%) developed PaCa in 3 years following inclusion into the study [relative risk (RR) = 2.27, 95% confidence intervals (CI) 1.96, 2.63; $P < 0.0001$]. The risk of PaCa diagnosis was higher among patients who were non-obese (RR = 1.51), were ≥ 65 years old (RR = 2.01), were heavy smokers (RR = 1.55), and had a history of CP (RR = 4.72) or gallstone disease (RR = 2.02). Using a combination of these risk factors in NODM patients resulted in up to 0.72% three-year risk of PaCa but captured only 17% of patients with PaCa.

CONCLUSIONS: Based on our findings, the likelihood of PaCa in adults with NODM even after adjusting for other potential risk factors for PaCa including age, body mass index, smoking, gallstones, and CP is probably not high enough to recommend routine evaluation for all these patients for underlying PaCa.

Clinical and Translational Gastroenterology (2015) 6, e118; doi:10.1038/ctg.2015.44; published online 22 October 2015

Subject Category: Pancreas and Biliary Tract

INTRODUCTION

Gullo *et al.*¹ noted that the increased prevalence of diabetes mellitus (DM) in patients with pancreatic cancer (PaCa) is largely due to DM of recent onset, presumably caused by the tumor. This has been subsequently confirmed by several studies^{2–6} and a recent meta-analysis.⁷ Recognition of new-onset DM (NODM) as an early manifestation of asymptomatic PaCa provides a unique window to detect early PaCa and might help improve the outcomes. Aggarwal *et al.*⁸ showed that 50% patients with PaCa have diabetes and it is frequently of new onset (within 36 months) in patients with PaCa compared with controls without PaCa. There is a wide variability in the reported PaCa incidence following NODM. Chari *et al.*⁵ have reported that 0.85% patients were diagnosed with PaCa within 3 years of diagnosis of NODM. However, Gupta *et al.*³ reported a much lower incidence of around 0.25% over 3 years in patients with NODM. The incidence of PaCa is not high enough to recommend further routine evaluation (1 PaCa per 332 NODM patients as per Gupta *et al.*³). A few studies looked for factors that might be associated with higher risk of PaCa in patients with NODM, but the data are inconclusive. Aggarwal *et al.*⁸ found no significant differences in the characteristics of DM related with PaCa, compared with DM without PaCa (age, body mass index, family history of DM, and smoking history). Pannala *et al.*⁹

noted that PaCa patients with DM were older, had a higher body mass index, and had a more frequent family history of DM compared with PaCa patients without DM.

In the present study, in a large veterans' administration (VA) cohort, we studied PaCa risk (especially within the 3 years) following new onset of DM and evaluated confounding factors including age, race, obesity, and a history of smoking, gallstone disease, and prior established chronic pancreatitis (CP) on the PaCa risk in these patients. We also evaluated the proposed strategy of combining two or more risk factors to further enrich the cohort with PaCa patients.

METHODS

Study design and patient selection. This was a retrospective cohort study. Data for this study were obtained from a national cohort of inpatient and outpatient records maintained by the Veterans Health Administration national medical care data sets from Fiscal Year 1998 using the International Classification of Diseases, Ninth Revision (ICD-9), Clinical Modification diagnoses.¹⁰ ICD-9 codes were recorded if a patient had any diagnosis or symptom during each visit/encounter.

All patients visiting the VA medical center for primary care were identified ($n = 534,956$). In an attempt to identify only new

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Received 27 December 2014; accepted 2 September 2015

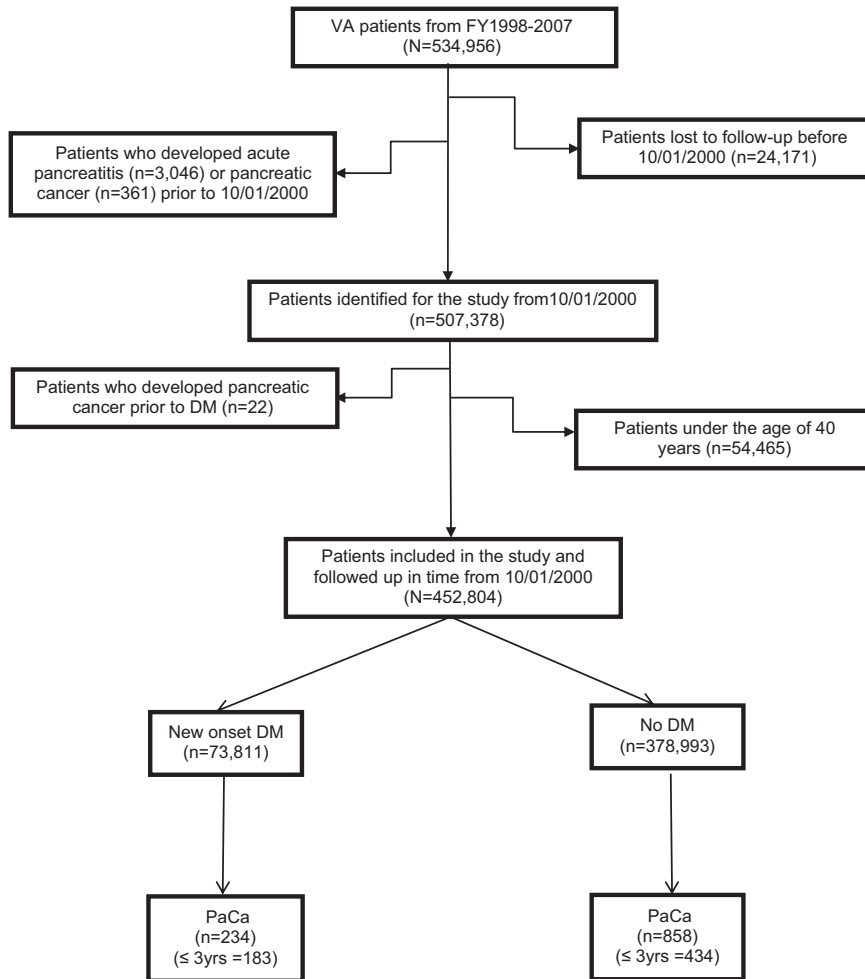


Figure 1 Veterans' administration patients by new-onset diabetes and pancreatic cancer status.

onset of DM, a 2-year washout period (October 1998–September 2000) was applied to rule out patients who had a pre-existing PaCa (pancreatic adenocarcinoma, $n=361$), pre-existing history of acute pancreatitis (single episode or recurrent episodes between 1998 and 2000, $n=3,046$) and patients in the database who were lost to follow-up before October 2000 ($n=24,171$). Only those patients who had at least 2 years of follow-up in the system were selected. After the 2-year washout period, 507,378 patients were selected from October 2000. Patients under 40 years of age ($n=54,465$) and patients with a diagnosis of PaCa before the diagnosis of diabetes ($n=22$) were excluded. Final cohort of patients included in the study was 452,804 (Figure 1). This study was approved by Institutional Review Board of Veterans Administration St Louis Health Care System.

Definitions

Pancreatic cancer. The primary outcome of interest was PaCa; defined as the presence of two or more ICD-9 codes 157.0, 157.1, 157.2, 157.3, and 157.9 less than 1 year apart. For patients with NODM, duration of the follow-up was calculated from the time of diagnosis of NODM to PaCa diagnosis. For the patients without NODM, duration of the

follow-up was calculated from the day after the 2-year washout period to the diagnosis of PaCa.

New-onset diabetes mellitus. The primary predictor of interest was the new onset of DM based on ICD-9 coding (ICD-9 code 250.0, either outpatient or inpatient) on at least 2 visits within a 12-month period. This included any patient who had a new diagnosis of diabetes from October 2000 without codes for diabetes in prior 2 years. Patients with diagnosis code for diabetes during the 2-year washout period (prevalent/established DM) were not included in the study.

Controls. All VA patients from October 2000 without the new-onset diabetes were considered as controls for this study.

Washout period. We had observed the VA patients and applied a 2-year washout period to exclude patients with pre-existing PaCa and patients with established DM. Any PaCa or DM diagnosed within the first 2 years of entry into the database were excluded, as the timeline of events leading to the diagnoses of either PaCa or DM before the start date of 1998 is not available in our data set.

Covariates. CP (ICD-9 code 577.1), history of obesity (ICD-9 code 278.0), history of smoking (nicotine dependence, ICD-9 codes 305.1 or V15.82), the presence of gallstones (ICD codes 574, 574.1, 574.3, 574.5, 574.7, 574.8, or 574.9)

defined on the basis of > 1 ICD codes before PaCa diagnosis or censorship, age at the time of entry into the study, race, and sex were extracted as well.

Reliability of ICD-9 codes. ICD-9 codes for PaCa had a positive predictive value of 70% within the VA system when compared with medical records.¹¹ DM codes had a sensitivity of 73.1% and specificity of 98.3%,³ and CP had a sensitivity of 87% and specificity of 86%¹² when compared with written patient charts.

Statistical analysis. Demographic characteristics (race and sex) and other characteristics (history of CP, obesity, smoking, gallstones, and age ≥ 65 years) for NODM patients and rest of the patients were assessed using frequencies and proportions. Age and time to PaCa diagnosis was calculated using mean ± s.d. Proportion of patients subsequently diagnosed to have PaCa was estimated. Incidence rates for PaCa (per 1,000 person-years) among patients with new diagnosis of DM (non-obese and obese) and remaining patients in the database each year were calculated. Relative risk (RR) of PaCa ≤ 3 years with 95% confidence intervals was computed for NODM vs. the remaining patients in the database. Among NODM patients, stratified analysis (Cochran–Mantel–Haenszel χ^2 -test) was performed to check for the role of CP, obesity, smoking, gallstone disease, race, and age ≥ 65 years for PaCa risk. Variables with a *P*-value < 0.2 in the univariate analysis were included in multiple logistic regression analysis, to identify the independent risk factors for PaCa. Follow-up time for the study participants ended on the date of diagnosis of PaCa, last visit to the VA, death, or 30 September 2007 (whichever occurred first). Statistical significance was set at *P*-value < 0.05 (two-tailed). All analyses were conducted using SAS version 9.2 (SAS, Cary, NC).

RESULTS

Patient characteristics. Table 1 summarizes the characteristics of 452,804 patients included in the final analysis. The mean age of the patients was 58.8 ± 11.9 years at the time of entry into the study. The majority of the patients were male (91%) and 28% of the study patients were obese. About 16% of the patients (*n* = 73,811) were diagnosed with DM during the study period (NODM). Among the patients with NODM, 34,576 patients (46.8%) were obese. About 4.5% had a gallstone disease and 1% of patients had a history of CP.

Increased incidence of PaCa after NODM. 234/73,811 (0.32%) Patients with new diagnosis of DM during the study period were diagnosed with PaCa compared to 858/378,993 (0.23%) controls; *P* < 0.0001; (patients without new diagnosis of DM after enrollment in the study). PaCa was diagnosed within 3 years following NODM in 183/73,811 (0.25%) patients. This was significantly higher than 434/378,993 (0.11%) of controls diagnosed with PaCa during the initial 3 years of follow-up during the study period (RR = 2.27, 95% confidence intervals = 1.96, 2.63; *P* < 0.0001). During the entire study period 1,092 patients were diagnosed with PaCa (0.24%). Two hundred and

Table 1 Patient characteristics

	NODM (<i>N</i> = 73,811)	Controls (<i>N</i> = 378,993)	All patients (<i>N</i> = 452,804)
Age in years (mean ± s.d.)	60.2 ± 11.1	58.5 ± 12.1	58.8 ± 11.9
Sex			
Male	69,322 (94%)	342,072 (88%)	411,394 (91%)
Female	4,489 (6%)	36,915 (12%)	41,404 (9%)
Unspecified	0	6	6
Race			
White	54,479 (74%)	285,147 (75%)	339,626 (75%)
Black	15,673 (21%)	63,061 (17%)	78,734 (17%)
Other	3,659 (5%)	30,785 (8%)	34,444 (8%)
Smoking	28,181 (57%)	129,231 (34%)	157,412 (34%)
CP	959 (1.3%)	3,996 (1.1%)	4,955 (1.1%)
Obesity	34,576 (46.8%)	90,079 (23.8%)	124,655 (27.5%)
Age > 65 years	22,425 (30.4%)	115,476 (30.5%)	137,901 (30.5%)
Gallstones	3,330 (4.5%)	10,856 (2.9%)	14,186 (3.1%)

Age, average age at the time of entry into study period; CP, chronic pancreatitis; N, number of patients; NODM, new-onset diabetes mellitus; %, column percentage.

Other race includes Asian, American Indian, Pacific Islander, or Unknown.

thirty-four patients (21.4%) were diagnosed with NODM preceding the cancer diagnosis. PaCa incidence decreased progressively each year following NODM and was not significantly higher than in controls after 3 years (Table 2A and Tables 2B and 2C).

Factors predictive of PaCa after diagnosis of NODM. Age > 65 years (RR = 1.70; *P* = 0.0003), non-obese patients (RR = 1.72; *P* = 0.0004), gallstone disease (RR = 2.31; *P* = 0.0019), and CP (RR = 4.42; *P* < 0.0001) were associated with significantly higher likelihood of PaCa diagnosis within 3 years after diagnosis of NODM on univariate analysis. There was a trend suggesting higher likelihood of cancer diagnosis following NODM in heavy smokers, but this did not reach statistical significance difference (*P* = 0.12). There was no significant difference in the risk of PaCa among different race groups.

Age > 65 years, smoking, history of gallstone disease, CP, heavy smoking, and non-obese patients were independent predictors of PaCa among NODM patients on multiple logistic regression analysis (Table 3). We then performed a risk stratification analysis for likelihood of PaCa diagnosis within 3 years after NODM in patients with one or more of these factors: age ≥ 65 years, non-obese patients (vs. obese patient), CP, gallstone disease, and smoking. The incidence of PaCa within 3 years following NODM progressively increased from 0.09% in patients without any of the above criteria to 0.72% in patients with ≥ 3 criteria (*P* < 0.001; Table 4). Of 183 patients with PaCa diagnosed within 3 years of NODM in our cohort, ≥ 1, ≥ 2, and ≥ 3 criteria were present in 170, 106, and 31 patients, respectively.

DISCUSSION

In the present retrospective analysis of a large VA data set, the incidence of PaCa in the first 3 years following NODM (0.25%) was significantly higher compared with non-diabetic controls

Table 2A Annual incidence of pancreatic cancer by NODM status

	NODM		Controls		Incidence/1,000 patient years	
	Patients at risk	PaCa	Patients at risk	PaCa	NODM	Controls
Year 1	73,811	89 (0.12%)	378,993	161 (0.04%)	1.31	0.45
Year 2	61,196	58 (0.09%)	349,781	131 (0.04%)	1.03	0.38
Year 3	50,558	36 (0.07%)	330,753	142 (0.04%)	0.79	0.44
Year 4	40,613	17 (0.04%)	312,665	107 (0.03%)	0.48	0.35

NODM, new-onset diabetes mellitus; PaCa, pancreatic cancer.

Table 2B Study characteristics by diabetes status

	Controls		Patients with NODM and non-obese		Patients with NODM and obesity	
	Patients at risk (N)	Patients diagnosed with PaCa (N, %)	Patients at risk (N)	Patients diagnosed with PaCa (N, %)	Patients at risk (N)	Patients diagnosed with PaCa (N, %)
Year 1	378,993	161 (0.04%)	39,235	63 (0.16%)	34,576	26 (0.08%)
Year 2	349,781	131 (0.04%)	31,664	35 (0.11%)	29,532	23 (0.08%)
Year 3	330,753	142 (0.04%)	25,802	23 (0.09%)	24,756	13 (0.05%)
Year 4	312,665	107 (0.03%)	20,453	8 (0.04%)	20,160	9 (0.04%)

DM, diabetes mellitus; NODM, new-onset diabetes mellitus; PaCa, pancreatic cancer.

Table 2C Incidence of pancreatic cancer by year and diabetes status

	Incidence rate per 1,000 patient years			NODM and non-obese			NODM and obese		
	NODM and non-obese	NODM and obese	Controls	Relative risk ^a	95% CI	P values	Relative risk ^a	95% CI	P values
Year 1	1.81	0.81	0.45	3.69	2.74–4.98	<0.0001	2.08	1.37–3.17	0.0006
Year 2	1.22	0.85	0.38	2.52	1.73–3.67	<0.0001	2.24	1.43–3.49	0.0004
Year 3	1.00	0.58	0.44	1.79	1.15–2.79	0.009	1.34	0.75–2.37	0.3119
Year 4	0.45	0.50	0.35	1.01	0.49–2.08	0.97	1.43	0.72–2.84	0.29

CI, Confidence interval; NODM, new-onset diabetes mellitus.

^aVersus controls (relative risk adjusted for age in years, sex, race, smoking status, alcohol status and history of gallstones).

(0.11%) in the first 3 years after entry into our database. We also noted that the likelihood of PaCa diagnosis was significantly higher in patients with age > 65 years, smokers, non-obese patients, patients with gallstone disease, and those with CP. Combining risk factors in addition to NODM resulted in a modest enrichment of the cohort with PaCa patients, but a large and clinically significant proportion of PaCa patients were excluded from the enriched cohort. In the subset of patients with pre-existing CP, the risk of PaCa cancer following NODM was about 1%.

Chari *et al.*⁵ had reported a much higher 3-year incidence of PaCa (0.85%) after diagnosis of NODM in a much smaller cohort of 2,200 patients with NODM of which 18 patients had PaCa diagnosis within 3 years. In our cohort, we observed a much lower likelihood of PaCa diagnosis following NODM that was similar to the likelihood observed by Gupta *et al.*³ in another VA-based data set. NODM, as an index event for PaCa, has potential clinical utility despite a rather low overall likelihood of PaCa in these patients. About 23% of PaCa diagnoses in our cohort were preceded by NODM within the preceding 3 years. Therefore, further evaluation of these patients for an underlying cancer seems to be a very tempting

next step. It has been suggested that the use of a “sieve” or a second filter could enrich the subset of patients with NODM for PaCa, to the extent that further imaging for PaCa would become cost-effective. This second filter should ideally be an easy-to-detect clinical parameter, or biochemical or molecular marker. Although no clinical characteristic(s) or biological marker(s) have been identified so far for potential use as “sieve” to enrich the population of NODM with those with an underlying cancer, it nevertheless is an interesting concept and is worthy of further study. In this study, we evaluated this concept using clinical characteristics associated with higher risk of PaCa, to determine its feasibility and potential limitations.

Age and smoking are known risk factors for PaCa but these have not been studied in detail in patients with NODM. We noted that age > 65 years and heavy smoking were independently associated with higher likelihood of PaCa diagnosis following NODM. A weak positive association with obesity and PaCa has previously been reported.^{13–15} However, patients with NODM, who have an underlying PaCa, tend to have lower body mass index than those without it.¹⁶ Patients with gallstone disease have previously been reported

Table 3 Independent predictors of pancreatic cancer in new-onset diabetes ≤ 3 years

	Odds ratio (95% CI)	P values
Age > 65 years	2.01 (1.51–2.68)	<0.0001
Non-obese	1.51 (1.14–1.99)	0.0035
Smoker	1.55 (1.12–2.14)	0.009
CP	4.72 (2.71–8.24)	<0.0001
Gallstones	2.02 (1.32–3.11)	0.0013

CI, confidence interval; CP, chronic pancreatitis.

Table 4 Risk of pancreatic cancer in new-onset diabetes using patient characteristics

	Total patients	PaCa	PaCa ≤ 3 years	P values
New DM without any criteria ^a	15,184	16 (0.11%)	13 (0.09%)	—
1 Criterion	29,297	81 (0.28%)	64 (0.22%)	0.0033
2 Criteria	25,384	95 (0.37%)	75 (0.30%)	<0.0001
3 Criteria	4,311	41 (0.95%)	31 (0.72%)	<0.0001
4 Criteria	273	1	0	—
5 Criteria	8	0	0	—
Overall	73,811	234 (0.32%)	183 (0.25%)	—

CP, chronic pancreatitis; DM, diabetes mellitus; PaCa, pancreatic cancer.

^aCriteria: age ≥ 65 years, non-obese, smoking, CP and gallstone disease.

to have higher risk of PaCa.^{17,18} Similarly, we noted a higher risk of PaCa in patients with gallstone disease.¹⁹ In this study, we also observed that the likelihood of PaCa following NODM was higher in patients with gallstone disease.

In our cohort, 93% of the patients with NODM and subsequent diagnosis of PaCa had at least one of the following risk factors: age > 65 years, the absence of obesity, smoking history, gallstone disease, and a history of CP. The risk of PaCa was 0.11% in patients without any of these risk factors and increased progressively as one, two, or three of these factors were present in patients with NODM reaching 0.72% in patients with three risk factors. Whether this 0.72% risk of cancer is sufficient to justify further routine evaluation for PaCa in patients with NODM needs further debate and cost-benefit assessment. However, the major limitation of this approach was the number of patients with PaCa, who were excluded from the enriched cohort. If we use the presence of two or three factors as a cutoff for further evaluation to look for an underlying PaCa, 59% and 83%, respectively, of NODM patients with underlying PaCa were excluded from the enriched cohort. Identification of a biological marker that is highly sensitive without necessarily being highly specific may potentially allow more patients with PaCa to be retained in the enriched cohort, but this assumption would need to be tested if and when such a marker were to be available.

In patients with a history of CP and NODM, about 1% of patients were diagnosed to have pancreatic cancer within 3 years following NODM. Even though CP predisposes to DM and development of DM in patients with CP is not unanticipated, the risk of an underlying PaCa is probably high enough to prompt further evaluation in these patients.

The present study has several strengths including a large sample size with adequate number of PaCa cases and 7 years of follow-up data. The study limitations include the use of administrative database, accuracy of the ICD-9 codes, and its retrospective design. The diagnosis of obesity, DM, and PaCa was made based on the ICD-9 Clinical Modification codes in the patient records and histological confirmation of coded PaCa diagnosis was not available from our study, raising a possibility of misclassification or under detection. Prevalence of smoking (34%) and obesity (27.5%) in our database was similar to prevalence in general VA population as reported by prior studies.^{10,20} We do not have the trends of the body mass index or weight change over the course of the follow-up period. Patients with prescription for insulin or antidiabetic agents were not available. Family history of PaCa was also not available. As our study population was a VA-based cohort, majority of the patients were male, with a trend toward having higher co-morbidities and smoking incidence compared with the general population. Thus, the study's applicability to general population and women cannot be reliably predicted.

Overall, based on our findings, NODM patients had increased risk of subsequent PaCa diagnosis. The likelihood of PaCa in adults with NODM is probably not high enough to recommend routine evaluation of all these patients for underlying cancer. PaCa risk is significantly higher in patients with age > 65 years, those with a history of CP, gallstone disease, smokers, and non-obese individuals. Enriching the cohort of patients with NODM for PaCa by using these risk factors in conjunction increased the likelihood to about 0.7%. However, its major limitation is the rather large proportion of patients with PaCa, with preceding NODM, who were excluded from the enriched cohort. Further studies are needed to confirm these findings and also investigate optimal strategies for further imaging in NODM with higher likelihood for PaCa based on associated risk factors.

CONFLICT OF INTEREST

Guarantor of this article: Banke Agarwal, MD.

Specific author contributions: Satish Munigala: study design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, and administrative support. Approved the final draft of this manuscript. Ajaypal Singh: drafting of the manuscript, critical revision of the manuscript for important intellectual content, and administrative support. Approved the final draft of this manuscript. Andres Gelrud: drafting of the manuscript and critical revision of the manuscript for important intellectual content. Approved the final draft of this manuscript. Banke Agarwal: study concept and design, interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, administrative support, and study supervision. Approved the final draft of this manuscript.

Financial Support: None.

Potential competing interests: None.

Acknowledgments. This material is the result of work supported with resources and the use of facilities at the VA Saint Louis Health Care System.

DISCLAIMER

The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ New-onset diabetes mellitus (NODM) can be an early manifestation of asymptomatic pancreatic cancer (PaCa).
- ✓ The incidence of PaCa in NODM is not high enough to recommend further routine evaluation.

WHAT IS NEW HERE

- ✓ PaCa risk in NODM patients is significantly higher in patients older than 65 years, those with a history of chronic pancreatitis (CP), gallstone disease, smokers, and non-obese individuals.
- ✓ Enriching the cohort of patients with NODM for PaCa by using these risk factors in conjunction increased the likelihood to about 0.7%, but excluded 83% patient with PaCa.
- ✓ In the subset of patients with pre-existing CP, the risk of PaCa cancer following NODM was about 1%.

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