

## New-Onset Diabetes and Pancreatic Cancer

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See CME exam on page 1301.

**Background & Aims:** Although many individuals with pancreatic cancer have diabetes, the association between new-onset diabetes mellitus and the subsequent incidence of pancreatic cancer is unclear. **Methods:** We conducted a retrospective cohort study to estimate the incidence of pancreatic cancer subsequent to a new diabetes diagnosis and to evaluate factors associated with a subsequent pancreatic cancer diagnosis. We used the Veterans Health Administration National Patient Care Database to assemble a cohort of 1,421,794 US veterans without prior diabetes or pancreatic cancer diagnoses. We recorded coding for new diabetes diagnoses ( $\geq 2$  International Classification of Diseases-9 codes for diabetes within a 12-month period), pancreatic cancer, age, sex, race, and common gastrointestinal symptoms. **Results:** A total of 36,631 (2.6%) of the 1,421,794 veterans were diagnosed with new-onset diabetes in 1999; 149 subsequently received a diagnosis of pancreatic cancer. Pancreatic cancer incidence in patients with new-onset diabetes (83.8/100,000 person-years) was 2.2-fold higher (95% confidence interval, 1.84–2.56) than in nondiabetics, and was highest during the first 2 years after diabetes diagnosis. One additional pancreatic cancer was diagnosed for every 332 new diabetics over 6 years. A subsequent pancreatic cancer diagnosis (among new-onset diabetics) was associated independently with younger age groups, changes in bowel habits, constipation, epigastric pain, and malnutrition. **Conclusions:** New-onset diabetes was associated with a significantly increased rate of pancreatic cancer diagnosis, particularly in the first 2 years after diabetes diagnosis. Factors associated with pancreatic cancer diagnosis included younger age groups and the presence of gastrointestinal symptoms. The absolute incidence of pancreatic cancer was low.

Pancreatic cancer is diagnosed in more than 31,000 individuals per year in the United States and has an expected 5-year survival rate of less than 4%.<sup>1</sup> Although improved survival has been shown in patients who are candidates for primary resection,<sup>2</sup> pancreatic cancer is difficult to diagnose at an early resectable stage.

Diabetes has been postulated to be both a risk factor for and a consequence of pancreatic cancer.<sup>3–19</sup> Eight percent to 64% of individuals with pancreatic cancer are diabetic.<sup>3,20–22</sup> Meta-analyses of cohort and case-control studies with up to 10 years follow-up evaluation have shown that patients with prevalent

diabetes have approximately twice the risk of developing pancreatic cancer compared with those without diabetes after censoring of pancreatic cancer diagnosed in the first year of follow-up evaluation.<sup>14,23</sup>

Pancreatic cancer may be a cause of new-onset diabetes.<sup>24</sup> Existing case-control and cohort studies suggest that patients with pancreatic cancer have an increased risk for a recent diagnosis of diabetes before their cancer diagnosis.<sup>4,6–8,11,16,25</sup> Firm conclusions about this association, however, and the evaluation of the time intervals between the diabetes diagnosis and the cancer diagnosis, are limited by the small number of incident cases in most of these studies.

A possibility for decreasing the mortality of pancreatic cancer is the application of screening and treatment for early pancreatic cancers to patients with new-onset diabetes using invasive and noninvasive imaging tests. One study reported that 5 of 36 (13.9%) patients referred with new-onset diabetes had pancreatic cancer,<sup>26</sup> whereas another found that 6 of 115 (5.2%) newly diagnosed, hospitalized diabetics had pancreatic cancer.<sup>27</sup> Although these findings are alarming, surveillance for pancreatic cancer in individuals with new-onset diabetes cannot be recommended currently, given both the uncertainty of pancreatic cancer incidence with respect to the incidence of new adult-onset diabetes in large populations,<sup>3</sup> and a lack of data showing improvement in survival or quality of life from this surveillance strategy. However, if new-onset diabetics at highest risk for pancreatic cancer could be identified using knowledge of additional markers or risk factors, screening of this population might potentially identify early pancreatic cancers that would be more amenable to treatment.

The primary aims of the present study were to determine the incidence of pancreatic cancer in a large cohort of US veterans with new-onset diabetes and to determine additional factors that may highlight individuals at highest risk for underlying pancreatic cancer.

## Materials and Methods

### Data Source

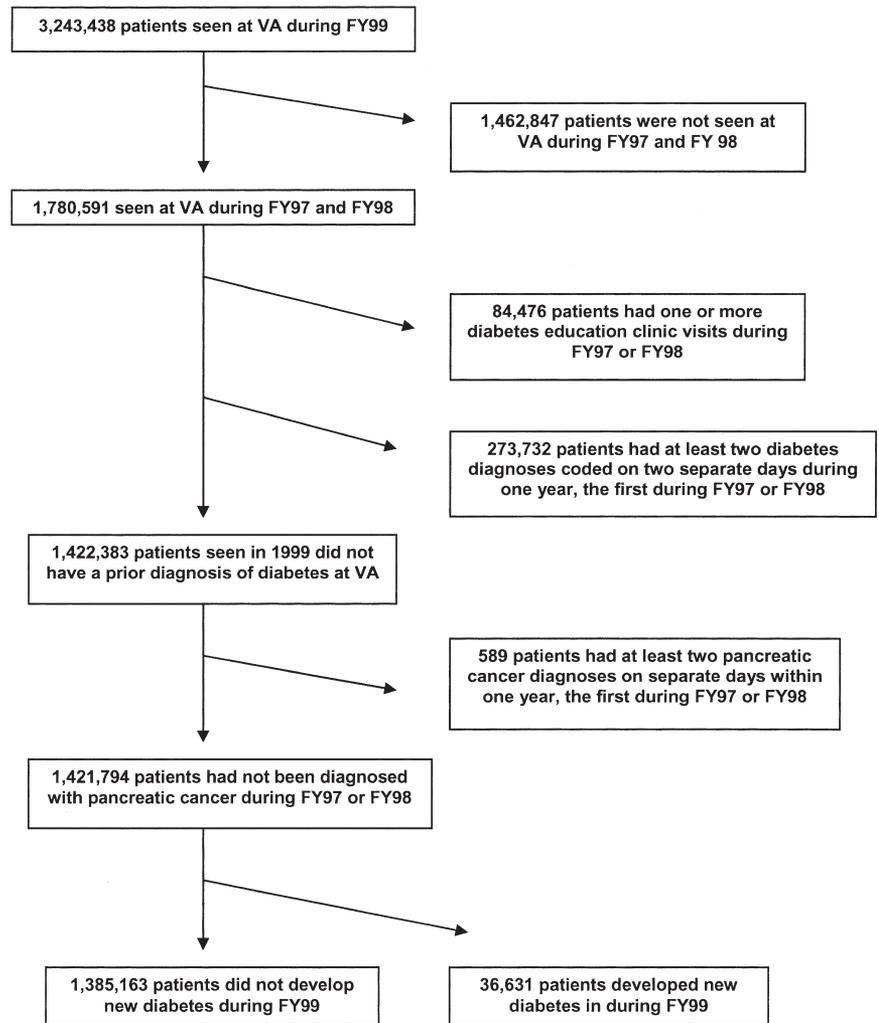
Veterans Health Administration (VA) facilities electronically transfer diverse data from all outpatient and inpatient

**Abbreviations used in this paper:** CI, confidence interval; GI, gastrointestinal; ICD, International Classification of Diseases; RR, rate ratio; VA, veterans affairs.

This is a US government work. There are no restrictions on its use.

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**Figure 1.** Cohort assembly. VA, veterans affairs facility; FY, fiscal year.

encounters to a centralized VA National Patient Care Database.<sup>28,29</sup> Data collected include International Classification of Diseases (ICD)-9 coding for diagnoses and symptoms, as recorded at the time of the encounter with a veteran.

**Design and Participants**

A retrospective cohort study was conducted of all US veterans aged 40 years and older seen at least once at a VA facility during fiscal year 1999 (October 1, 1998 to September 30, 1999), who also had been seen at the VA during fiscal years 1997 and 1998 as documented in the VA National Patient Care Database.

The following subjects were excluded from the cohort: (1) subjects with a prior history of diabetes or pancreatic cancer (defined as  $\geq 2$  visits coded for diabetes or pancreatic cancer during fiscal years 1997 or 1998) and (2) subjects who attended a diabetes education clinic during fiscal years 1997 or 1998. This left a final analytic cohort of 1,421,794 veterans (Figure 1). Primary outcome and exposure data then were extracted for eligible subjects for the years 1999–2004.

**Measurements**

The primary outcome of interest was pancreatic cancer; this was defined as the presence of ICD-9 codes 157.0–157.9 on 2 separate occasions within 1 year in fiscal years 1999–2004.

The primary predictor of interest was new-onset diabetes beginning in fiscal year 1999, as defined by ICD-9 coding for diabetes (ICD-9 codes 250.0–250.9) on 2 outpatient or inpatient visits within a 12-month period. The presence of 2 or more ICD-9 codes for diabetes within a 24-month period in the VA database is 73.1% sensitive and 98.3% specific for the diagnosis of diabetes, using a direct patient survey for a history of increased blood sugar level or diabetes as a gold standard.<sup>30</sup> The addition of data regarding prescription of diabetes-specific medications or presence of increased hemoglobin A1c does not substantially improve sensitivity or specificity.<sup>30</sup>

Secondary predictors of interest included ICD-9 coding for gastrointestinal (GI) symptoms, including abdominal pain (789.0), epigastric pain (789.06), dyspepsia (536.8), change in bowel habits (787.99), constipation (564.00), diarrhea not otherwise specified (787.91), heartburn (787.1), gas (787.3), moderate malnutrition (263.0), mild malnutrition (263.1), age at diabetes diagnosis, race, and sex. A full list of the measured ICD-9 symptom variables is provided in Appendix A; see supplemental material online at [www.cghjournal.org](http://www.cghjournal.org).

**Statistical Analysis**

We estimated incidence rates for pancreatic cancer (per 100,000 person-years) for new-onset diabetics and nondiabetics

**Table 1.** Demographic Characteristics of Cohort

Characteristic	Nondiabetics		New-onset diabetics	
	Pancreatic cancer (N = 2481)	No pancreatic cancer (N = 1,382,682)	Pancreatic cancer (N = 149)	No pancreatic cancer (N = 36,482)
Age, y	66.4 ± 10.8	61.8 ± 12.7	66.3 ± 10.5	63.6 ± 11.4
Race				
White	1439 (58.0%)	734,883 (53.2%)	88 (59.1%)	19,971 (54.8%)
Black	424 (17.1%)	165,204 (12.0%)	29 (19.5%)	4995 (13.7%)
Hispanic, white	84 (3.4%)	48,603 (3.5%)	9 (6.0%)	1925 (5.3%)
Hispanic, black	9 (0.4%)	4015 (0.3%)	1 (0.7%)	112 (0.3%)
Asian	8 (0.3%)	5706 (0.4%)	0 (0.0%)	169 (0.5%)
Native American	12 (0.5%)	3624 (0.3%)	0 (0.0%)	128 (0.4%)
Unknown	505 (20.4%)	420,525 (30.4%)	22 (14.8%)	9182 (25.2%)
Male	2417 (97.4%)	1,277,620 (92.4%)	145 (97.3%)	35,411 (97.1%)

using direct standardization to adjust for age, sex, and race/ethnicity; rate ratios then were evaluated using Poisson regression.<sup>31</sup> We also evaluated the time interval between the onset of diabetes or study entry and a subsequent cancer diagnosis. Because the focus of the analysis was on the prospective rate of pancreatic cancer diagnosis among new-onset diabetics, cancer diagnoses reported within 1 day of the diabetes diagnosis were omitted. We performed additional analyses that omitted pancreatic cancers in case and reference groups diagnosed within 1, 3, or 12 months after the diabetes diagnosis to determine the influence of cancer diagnoses made around the time of the initial diabetes diagnosis. These additional analyses help determine if a window of opportunity may exist for earlier cancer diagnosis and interventions that might improve overall cancer-associated mortality.

Follow-up time for cohort participants who developed pancreatic cancer ended at the date of diagnosis, whereas the follow-up period for those who did not develop pancreatic cancer was censored when they were lost to follow-up evaluation, died, or were accounted for at the end of the study period. Among the diabetics, we calculated the cumulative incidence of pancreatic cancer as a first event.<sup>32</sup> The cumulative incidence calculation provides a conservative incidence estimate by calculating the proportion diagnosed with pancreatic cancer among all cohort participants, including subjects who were censored from competing causes of death or who were only diagnosed with cancer outside the VA system. Cox proportional hazards models were used to estimate the independent associations between GI symptoms and the risk of pancreatic cancer, adjusting for age, sex, and race/ethnicity.<sup>33</sup> In this analysis, GI symptoms were treated as time-dependent covariates, with the symptom indicator being reset from 0 to 1 at the time of the first report of the symptom before the pancreatic cancer diagnosis. All analyses were conducted using SAS version 8.2 (SAS Inc., Cary, NC).

The study was approved by our institutional research ethics review board before initiation.

## Results

In our cohort of 1,421,794 veterans, 36,631 patients (2.6%) developed new-onset diabetes in fiscal year 1999. Demographic characteristics are presented in Table 1. As expected for an older US veteran population, subjects were almost exclu-

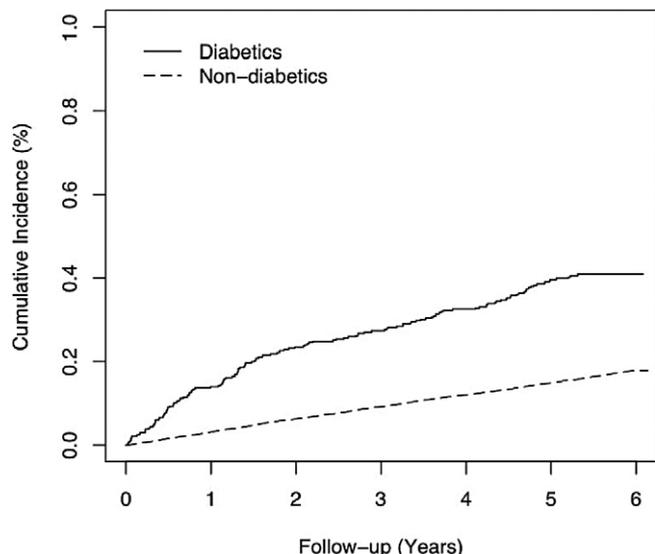
sively male. The majority of study subjects were white; the race/ethnicity was unknown for 30%.

Among patients with new-onset diabetes, 149 pancreatic cancers were recorded from 1 day to 5.3 years after the diagnosis of diabetes. The cumulative incidence of pancreatic cancer over 6 years was 0.5% (Figure 2), and the average incidence was 83.8/100,000 person-years. Among nondiabetics, 2481 pancreatic cancer cases were recorded over 6.8 million person-years of follow-up evaluation, and the average incidence was 37.8/100,000 person-years. Thus, the rate ratio (RR) for pancreatic cancer for new-onset diabetics compared with nondiabetics was 2.17 (95% confidence interval [CI], 1.84–2.56). Based on the difference in cumulative risk between new-onset diabetics and nondiabetics, 1 additional pancreatic cancer was observed among every 332 new diabetics.

Table 2 shows the incidence of pancreatic cancer in new-onset diabetics and nondiabetics stratified by year of follow-up evaluation, adjusted for age, sex, and race/ethnicity. New-onset diabetes was associated most strongly with a pancreatic cancer diagnosis in the first 2 years after diabetes diagnosis: RR of 3.91 (95% CI, 2.93–5.23) during year 1 and RR of 2.75 (95% CI, 1.94–3.88) during year 2. The incidence of pancreatic cancer decreased significantly during subsequent years of follow-up evaluation (*P* for trend <.0008).

There were unusual association patterns across the different age strata. During the first year after diagnosis, new-onset diabetes was associated significantly with pancreatic cancer within most but not all 5-year age strata (Table 3). There was an overall trend between increasing age and the rate of pancreatic cancer (*P* for trend = .07); however, the strongest associations existed for the younger age groups (age, 45–59 y). The 1-year RR of pancreatic cancer in new-onset diabetics aged 45–49 years (RR, 16.9; 95% CI, 6.10–46.8), for example, was markedly higher than that in persons aged 65–69 years (RR, 3.15; 95% CI, 1.44–6.86) (Table 3).

The exclusion of cancers diagnosed within 30 days (RR, 2.11 overall; 95% CI, 1.78–2.50; and RR = 3.35 for year 1 follow-up evaluation; 95% CI, 2.45–4.59) or within 90 days (RR, 2.10 overall; 95% CI, 1.76–2.49; and RR = 3.55 for year 1 follow-up evaluation; 95% CI, 2.61–4.83) from the diabetic cohort continued to show an association between a diabetes diagnosis and pancreatic cancer. If pancreatic cancers diagnosed in the first year of follow-up evaluation were omitted from the analysis, the



**Figure 2.** Cumulative incidence of pancreatic cancer among new-onset diabetic vs nondiabetic veterans over 6 years of follow-up evaluation. —, diabetics; ---, nondiabetics.

RR for pancreatic cancer for years 2–6 remained significantly increased (RR, 1.73; 95% CI, 1.42–2.12) for new-onset diabetics vs nondiabetics.

GI symptoms, including changes in bowel habits, constipation, diarrhea, dyspepsia, dysphagia, epigastric pain, gas, and mild or moderate malnutrition, were associated with a subsequent diagnosis of pancreatic cancer in unadjusted Cox models; the strongest associations were with epigastric pain (relative hazard, 4.95; 95% CI, 2.31–10.6) and moderate malnutrition (relative hazard, 9.63; 95% CI, 5.55–16.7). After adjusting for age, sex, and race/ethnicity, a multivariate Cox model showed that changes in bowel habits, constipation, epigastric pain, and moderate malnutrition were associated independently ( $P < .05$ ) with a subsequent pancreatic cancer diagnosis, and there were trends ( $.05 < P < .1$ ) for independent associations with diarrhea, dyspepsia, and dysphagia (Table 4). Moderate malnutrition was associated most strongly with pancreatic cancer (relative hazard, 8.48; 95% CI, 4.54–15.86). The median intervals

**Table 2.** Incidence of Pancreatic Cancer by Year and Diabetes Status

Follow-up period	Incidence per 100,000 person-years <sup>a</sup>		RR	95% CI	P value
	New diabetics	Nondiabetics			
Overall	83.8	37.8	2.17	1.84–2.56	<.0001
Years 2–6	54.5	31.3	1.73	1.42–2.12	<.0001
Year 1	133.3	32.8	3.91	2.93–5.23	<.0001
Year 2	98.3	34.3	2.75	1.94–3.88	<.0001
Year 3	38.9	35.3	1.17	0.69–1.99	.5677
Year 4	57.7	37.2	1.60	1.01–2.54	.0450
Year 5	89.2	41.3	2.25	1.51–3.35	<.0001
Year 6	37.3	52.4	0.68	0.25–1.81	.4382

<sup>a</sup>Adjusted for age, sex, and race/ethnicity.

**Table 3.** First-Year Incidence of Pancreatic Cancer by Age and Diabetes Status

Age, y	Incidence per 100,000 person-years <sup>a</sup>		RR	95% CI	P value
	New diabetics	Nondiabetics			
40–44	0.0	7.7	0.00	—	—
45–49	133.2	8.3	16.91	6.10–46.83	<.0001
50–54	112.7	23.5	4.73	2.02–11.06	.0003
55–59	199.7	37.0	5.52	2.48–12.28	<.0001
60–64	67.3	39.7	1.77	0.55–5.69	.3362
65–69	108.5	38.4	3.15	1.44–6.86	.0039
70–74	109.9	48.8	2.42	1.12–5.22	.0247
75–79	151.5	46.9	3.45	1.67–7.14	.0008
80–84	362.8	58.1	6.74	2.85–15.93	<.0001
≥85	476.7	43.3	10.54	2.30–48.24	.0024
Overall	133.3	32.8	3.91	2.93–5.23	<.0001

<sup>a</sup>Adjusted for sex and race/ethnicity.

between the first record of GI symptoms and a diagnosis of pancreatic cancer were 2–29 months.

### Discussion

This study shows, in a large cohort of US veterans, that patients with a new diabetes diagnosis had a higher subsequent incidence of a pancreatic cancer diagnosis than patients without a diabetes diagnosis. The association was particularly strong within 2 years of a new diabetes diagnosis, accounting for 86 of 149 (58%) identified cancers, but a 2-fold increase in rate persisted for more than 1 year subsequent to the diabetes diagnosis. Cumulatively, these data suggest that new-onset diabetes confers a sustained increase in risk for subsequent pancreatic cancer diagnosis, and likely represents a marker for pancreatic cancer in a subset of newly diabetic individuals.

In contrast to prior epidemiologic studies that evaluated long-standing diabetes as a possible causative or inductive factor for subsequent pancreatic cancer, we centered on identifying the association of new-onset diabetes as a marker for a subsequent diagnosis of pancreatic cancer. Our secondary analysis, which showed that omission of cancers diagnosed within 1, 3, or 12 months of new-onset diabetes diagnosis did not substantially affect the association of new diabetes to pancreatic cancer, suggests that a potential window for early detection and intervention may exist to identify persons with less advanced cancers for curative intervention.

Our work extends the existing research on the association between diabetes and pancreatic cancer. Two studies from Olmsted county evaluated the relationship of new-onset diabetes to pancreatic cancer. Ragozzino et al<sup>6</sup> identified 1135 subjects with new-onset diabetes with 9800 person-years of follow-up evaluation but identified only 9 cases of pancreatic cancer, 4 of which occurred within the first year of diabetes diagnosis, yielding an overall RR of 3.8 (95% CI, 1.2–9.0). The second study, by Chari et al<sup>25</sup> identified 2122 subjects older than 50 years of age with incident diabetes using medical record review. In more than 5799 person-years of follow-up evaluation, 18 subjects with pancreatic cancer were detected

**Table 4.** Gastrointestinal Symptoms Associated With Pancreatic Cancer

Gastrointestinal symptom	Number of patients affected	Median (range) from symptom onset to pancreatic cancer, mo	Hazard ratio	95% CI	P value
Change in bowel habits	4	20 (4–32)	3.50	1.27–9.69	.0157
Constipation	36	14 (0–83)	1.78	1.20–2.65	.0045
Diarrhea	18	6 (0–65)	1.61	.96–2.70	.0710
Dyspepsia	17	10 (0–82)	1.58	.94–2.67	.0855
Dysphagia	17	29 (1–87)	1.58	.93–2.66	.0882
Epigastric pain	7	4 (1–30)	3.45	1.57–7.58	.0020
Malnutrition	11	2 (0–18)	8.48	4.54–15.9	<.0001

NOTE. Results adjusted for age, sex, and race.

within 3 years of new-onset diabetes, yielding a cancer incidence of 310/100,000 person-years. Compared with Surveillance, Epidemiology, and End Results program data, the observed-to-expected ratio of pancreatic cancer was 7.94 (95% CI, 4.70–12.55), and the estimated 3-year incidence of pancreatic carcinoma was 0.85%. Both studies were limited by a small number of outcomes, precluding analysis of pancreatic cancer incidence per year after a diabetes diagnosis.

Observations from clinical and experimental studies support that diabetes may be a marker for pancreatic cancer in select individuals. Diabetes associated with pancreatic cancer may result from insulin resistance induced by a paraneoplastic syndrome,<sup>22,24,34–36</sup> or pancreatic cancer-associated  $\beta$ -cell dysfunction in insulin production.<sup>37</sup> Experimental animal studies suggest that glucose intolerance may be an early feature of pancreatic cancer.<sup>24,38,39</sup> Hyperglycemia induced by pancreatic cancer in human beings may be cured or ameliorated by surgical resection of the pancreatic tumor.<sup>35,37,40</sup>

Although we have identified an increased rate of pancreatic cancer diagnosis shortly after new-onset diabetes, the relatively low absolute cumulative incidence (0.5% over 6 years) raises questions about the potential role of surveillance for pancreatic cancer in patients with new-onset diabetes, especially given the limitations and potential complications of current imaging modalities. Surveillance with endoscopic retrograde pancreatography, computerized tomography, or endoscopic ultrasound does not have a proven treatment benefit for detected cancers, could result in work-up of incidental findings and procedure-related morbidity, and is of uncertain cost effectiveness. The finding that only 1 excess pancreatic cancer was observed for every 332 new diabetics, combined with the lack of clearly effective treatments for even early stage pancreatic cancers, suggests that surveillance strategies would not substantially benefit the newly diabetic population at this time.

Focusing detection efforts for cancer on an enriched high-risk population of individuals with new-onset diabetes may prove to be more effective, although the absolute rate of cancer in these groups is still low. Our analysis suggests that a young age at diabetes onset or the presence of several GI symptoms, including a change in bowel habits and malnutrition, are associated with an even higher rate of subsequent pancreatic cancer diagnosis. A time interval between the coding for GI symptoms and the pancreatic cancer diagnosis was observed for all symptom variables that reached statistical significance. These findings complement a large population-based, case-control study

of subjects with pancreatic cancer (both with and without diabetes) who showed a heightened risk of many GI symptoms, including unusual belching, appetite loss, weight loss, constipation, diarrhea, abdominal pain, and jaundice before cancer diagnosis.<sup>41</sup> The use of new tumor markers, such as cancer antibodies, may enhance the ability to detect early tumors in high-risk populations.<sup>42,43</sup>

Strengths of this study include its large size, comprehensive database, and the availability of a comparable reference group. The cohort contained 36,631 new-onset diabetics with more than 168,000 person-years of follow-up evaluation and 149 pancreatic cancer diagnoses. This large size increased the precision of the estimates and permitted subgroup analyses by year after diabetes diagnosis and by age strata.

Our study had several potential limitations. The use of administrative data may result in ascertainment bias with an underdetection or misclassification of diabetes, cancer, or GI symptoms diagnoses.<sup>44</sup> However, a correlation study of administrative data with individual medical records from the VA reported excellent agreement ( $\kappa = 0.795$ – $0.823$ ) between the administrative diabetes diagnoses and the medical record diagnoses. A careful study of the optimal manner in which to identify diabetic patients in the VA system reported that 2 or more diagnostic codes for diabetes over 24 months in the outpatient and/or inpatient data set is 73% sensitive and 98% specific for the diagnosis of diabetes.<sup>30</sup> Histologic confirmation of coded pancreatic cancer diagnoses was not available, raising the possibility that some pancreatic cancers may have been classified incorrectly; whether such misclassification could be differential or nondifferential cannot be determined. Our study also was limited by a lack of information regarding tobacco use, body mass index, and diet history, all of which potentially modify pancreatic cancer risk. Race coding was unknown for 30% of patients; pooling this potentially mixed group as an unknown race category could have resulted in some residual confounding, affecting the accuracy of the estimated association of diabetes and pancreatic cancer. Finally, our cohort was 92% men, limiting the applicability of our results to women, and requiring further study of the association of new-onset diabetes with pancreatic cancer in women.

Overall, our findings indicate that new-onset diabetes is a marker of an increased rate of subsequent pancreatic cancer diagnosis, that this increased rate persists for several years after the diabetes diagnosis, that the rate is particularly marked for the youngest patients with new-onset diabetes,

and that several GI symptoms are associated with a further increase in cancer rate among patients with new-onset diabetes. The overall cancer incidence among diabetics (0.5%), however, is relatively low. Future work should focus on identifying individuals with new-onset diabetes at highest risk for pancreatic cancer, and whether identification of these individuals can lead to treatment that reduces pancreatic cancer-associated mortality.

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