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New-onset Diabetes, Longitudinal Trends in Metabolic Markers, and Risk of Pancreatic Cancer in a Heterogeneous Population

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Abstract

Background & Aims—Observational studies of predominantly white populations have found new-onset diabetes to be associated with increased risk of pancreatic cancer. We sought to determine whether this relationship applies to other races or ethnicities and to identify metabolic profiles associated with increased risk of pancreatic cancer.

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Zuo-Feng Zhang, Veronica Wendy Setiawan - study concept and design; interpretation of results; critical revision of the manuscript for important intellectual content; study supervision; obtained funding; approval of final draft

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Methods—We conducted a population-based cohort study of Asian, black, Hispanic and white patients from Kaiser Permanente Southern California from 2006 through 2016 (n=1,499,627). Patients with diabetes were identified based on glucose and hemoglobin A1c (HbA1c) measurements. We used Cox regression to assess the relationship between diabetes status and duration and pancreatic cancer. For patients with recent diagnoses of diabetes (1 year or less) we compared longitudinal changes in glucose, HbA1c, and weight, from time of diabetes diagnosis through 3 years prior to the diagnosis, in patients with vs without pancreatic cancer.

Results—We identified 2,002 incident cases of pancreatic cancer from nearly 7.5 million person-years of follow-up. Compared to patients without diabetes, individuals who received a recent diagnosis of diabetes had an almost 7-fold increase in risk of pancreatic cancer (relative risk, 6.91; 95% CI, 5.76–8.30). Among patients with a recent diagnosis of diabetes, those who developed pancreatic cancer had more rapid increases in levels of glucose (slope: cases, 37.47 mg/dL vs non-cases, 27.68 mg/dL) and HbA1c (slope: cases, 1.39% vs non-cases, 0.86%) in the month preceding the diagnosis of diabetes, and subtle weight loss in the prior years (slope: cases –0.18 kg/interval vs non-cases 0.33 kg/interval). These longitudinal changes in markers of metabolism were stronger for specific race and ethnic groups.

Conclusions—In a study of a large ethnically diverse population, we found risk of pancreatic cancer to be increased among patients with a diagnosis of diabetes in the past year among different races and ethnicities. Weight loss and rapid development of poor glycemic control were associated with increased risk of pancreatic cancer in multiple races.

Keywords

racial variation; type 2 diabetes; obesity; pancreas

INTRODUCTION

Pancreatic cancer is an aggressive malignancy that is often late diagnosed because it is generally asymptomatic at earlier stages.¹ Understanding its etiology may improve our ability to identify high-risk patients and enhance earlier detection. While type 2 diabetes has been recognized as a risk factor for pancreatic cancer in epidemiologic studies,² there is also evidence that diabetes may be a manifestation of the pancreatic tumor. Past studies have shown that there is a higher prevalence of new-onset diabetes among pancreatic cancer cases, and that glucose metabolism improves following tumor resection.^{3,4} Although still unclear, current literature suggests that adults with recent-onset diabetes have a higher pancreatic cancer risk compared to individuals with long-standing diabetes.^{2,5,6}

The relationship between recent-onset diabetes and pancreatic malignancy has been explored in mainly case-control studies⁷ or within cohorts of primarily white individuals.^{8–11} Furthermore, many of the cohort studies consisted solely of diabetes patients and could only report a standardized incidence ratio because they lacked data on a non-diabetes comparison group.^{9–11} We recently demonstrated that African Americans and Latinos with recent-onset diabetes experienced elevated pancreatic cancer risk compared to those with long-standing diabetes in the Multiethnic Cohort.¹² Other than these latest findings, however, research in

ethnically diverse populations is quite limited, especially with granular details on metabolic parameters associated with diabetes (*e.g.* glucose, hemoglobin A1c [HbA1c], and weight).

To further investigate the relationship between diabetes duration and pancreatic cancer in a more representative sample, we conducted a retrospective cohort study of patients from Kaiser Permanente Southern California (KPSC). Our objective was to validate and assess the generalizability of previous findings by evaluating pancreatic cancer risk in a diverse population with comprehensive and longitudinal medical information from electronic health records. In addition, we aimed to establish a metabolic profile of diabetes patients to help characterize those who are at high risk of developing pancreatic cancer.

METHODS

Study Population

We conducted a retrospective cohort study of patients from KPSC, a large integrated health system throughout Southern California. KPSC's diverse member population of over 4 million individuals is representative of the Southern California region.¹³ All patient data, including information on hospital visits, diagnosis codes, and laboratory tests, are stored in the electronic health record.

Patients were eligible for the study if they met the following inclusion criteria during 2006–2016: aged 45–90 years, 2 years of continuous membership, and available information for body mass index (BMI), smoking, and alcohol use. The two-year membership requirement was used to ensure that individuals were in the KPSC system long enough to establish an accurate medical history. Otherwise eligible patients were further excluded if they did not have a glucose (fasting, random or oral glucose tolerance) or HbA1c measurement (N=67,486), were not in the four major race/ethnicity groups (Asian, non-Hispanic black, Hispanic, non-Hispanic white) (N=80,801), or had a prior diagnosis of pancreatic cancer (N=523) (Figure 1). The date of cohort entry was the January 1st of the first year after the patient met all inclusion criteria (*e.g.* if a patient met the final inclusion criterion in December 2006, the cohort entry date would be January 1, 2007).

This study was approved by the KPSC Institutional Review Board (IRB).

Exposure Assessment

Individuals were identified as having diabetes if they had any of the following laboratory-based glycemic measurements according to American Diabetes Association (ADA) guidelines: HbA1c $\geq 6.5\%$, fasting glucose ≥ 126 mg/dL, random glucose ≥ 200 mg/dL or two-hour oral glucose tolerance test ≥ 200 mg/dL. The date of the earliest test within the diabetes range was considered the diabetes diagnosis date. Individuals were classified as prevalent diabetes if their diabetes diagnosis was on or before cohort entry and were categorized as incident diabetes if the diagnosis was after cohort entry. For incident diabetes patients, we evaluated diabetes duration as ≤ 1 year and >1 year using the time elapsed since diabetes diagnosis.

Assessment of other covariates

Covariate data were obtained from the most recent record prior to cohort entry. BMI was grouped into <25, 25–30, ≥ 30 kg/m², smoking was categorized as never, former, and current, and alcohol was treated as a dichotomous variable. Pancreatitis (yes vs. no) was identified using International Classification of Diseases (ICD) codes (ICD-9: 577.0, 577.1; ICD-10: K85.x, K86.0, K86.1) and family history of pancreatic cancer (yes vs. no) was attained from the patient history files. Education information was obtained from the geocoding database¹³ and was categorized as high school or less, some college, and college graduate.

Outcome

Our primary outcome of interest was time from cohort entry to pancreatic cancer diagnosis. Patients in the final study cohort were censored at the first of the following: death, end of membership or end of study on December 31, 2016. Pancreatic cancer cases were identified from the internal KPSC cancer registry, which reports to the Surveillance, Epidemiology and End Result (SEER) program and meets its high reporting standards.¹⁴ Mortality information was obtained from inpatient records, the internal cancer registry and the California state death index.

Statistical Analyses

Baseline characteristics were compared across diabetes status using ANOVA for age and chi-square tests for all other variables. Pancreatic cancer incidence rates, age-standardized to the United States 2000 standard population and truncated to age 45+, were calculated for each group.

The relationship between diabetes and pancreatic cancer incidence was analyzed using Cox proportional hazards regression. Both diabetes status (prevalent, incident vs. none) and duration (incident ≤ 1 year, incident >1 year, vs. none) were treated as time-varying exposures. All models included age at cohort entry, gender, race/ethnicity, smoking status, BMI, alcohol intake, family history of pancreatic cancer, pancreatitis, and education as covariates.

Additional analyses were conducted within subgroups defined by gender, race/ethnicity, BMI, smoking status, alcohol intake and pancreatitis. Heterogeneity was evaluated using models with an interaction term for the exposure (diabetes status/duration) and the subgroup variable of interest.

Schoenfeld residuals were used to confirm no violation of the proportional hazards assumption, while Martingale and deviance residuals were used to evaluate model fit. All analyses were conducted using SAS 9.3 (Cary, NC).

Metabolic Profiling of Incident Diabetes Patients

To investigate which patients are at highest risk for pancreatic cancer, we evaluated metabolic profiles of incident diabetes patients at different timepoints of diabetes progression. Specifically, we examined fasting glucose, HbA1c and weight measurements from diabetes diagnosis up to three years prior in six-month intervals. For the time period

containing the diabetes diagnosis, we included all measurements up to 30 days before and after diagnosis. If a patient had multiple measurements within a given interval, the average of those measurements was used.

Longitudinal changes in these metabolic markers were assessed using generalized estimating equations with the metabolic marker as a continuous outcome, time period as the exposure (to model the trend), age, gender and race as covariates, and patient as the clustering variable. Due to large increases in glucose and HbA1c during the period immediately prior to diabetes, the models for these markers included a spline term at this time interval (6 months to 1 month prior to diabetes) to model the change in trend. All models were run separately for patients with and without pancreatic cancer. Heterogeneity between cases and non-cases was evaluated using models with an interaction term for time period and case status. The models for glucose and HbA1c also included an interaction for the spline term and case status.

Furthermore, we ran all of the aforementioned models within race/ethnicity subgroups to evaluate whether the trends or changes in slope between cases and non-cases varied by race/ethnicity. Overall heterogeneity for the trend was evaluated using a model with two-way interactions for time period by case status, case status by race, and time period by race, and a three-way interaction for time period, case status and race. For glucose and HbA1c, we examined overall heterogeneity for the change in slope using two-way interactions for the spline term by case status, case status by race, and spline term by race, and a three-way interaction for the spline term, case status and race. The p-values for the three-way interactions were used to determine whether there was significant heterogeneity in the trend or change in slope by both case status and race/ethnicity.

Sensitivity Analyses

To assess the accuracy of the identification of incident diabetes, we re-ran all analyses dropping incident diabetes patients who did not have a prior metabolic test in the normal range (3.5%) or had a prescription for metformin within the past year (7.7%). In order to address the potential effects of diabetes treatment, we also re-ran the metabolic profile analyses dropping metabolic measurements taken within the 30 days after diabetes diagnosis. We also repeated the analyses using patient-day-weighted averages to account for multiple measurements in a given day. Given the ADA's recommendation changes in 2010 to use HbA1c for diabetes screening¹⁵, we re-ran the metabolic analyses stratified by patients who were diagnosed with diabetes before (16.1%) and after (84.9%) 2010 to address potential differences in glycemic test ordering. Results were unchanged in all situations and thus we only present findings from the original models.

RESULTS

The final study cohort consisted of 1,499,627 patients at-risk for pancreatic cancer. The study population was on average 57.9 years old (standard deviation 10.9) and consisted of 55.2% females. Whites comprised nearly half of the cohort (45.7%), followed by Hispanics (32.5%), Asians (11.1%) and blacks (10.7%). From nearly 7.5 million person-years of

follow-up, 2,002 persons developed pancreatic cancer, translating to an age-adjusted incidence rate of 30.7 cases per 100,000 person-years.

Among the entire cohort, 110,699 developed incident diabetes (7.4%), 332,932 had prevalent diabetes (22.2%) and 1,055,996 never had diabetes (70.4%). Age-adjusted incidence rates for pancreatic cancer were highest in incident diabetes patients (43.7 cases per 100,000 person-years), followed by prevalent diabetes patients (41.2 cases per 100,000 person-years) and lowest in non-diabetes patients (23.8 cases per 100,000 person-years). Prevalent and incident diabetes patients were more likely to be older, male, non-white, former smokers, and non-alcohol users. These individuals also tended to have higher BMI, lower education, and pancreatitis (Table 1). Within the race/ethnicity subgroups, blacks (26.5%), Hispanics (25.2%) and Asians (24.6%) had the highest proportion of prevalent diabetes while blacks (9.2%) and Asians (8.9%) had the greatest proportion of incident diabetes (Supplemental table 1).

Pancreatic cancer risk was elevated three times for incident diabetes (relative risk [RR] 3.17, 95% CI 2.75–3.65) and roughly two times for prevalent diabetes (RR 1.85, 95% CI 1.67–2.05) compared to individuals without diabetes. When evaluating diabetes duration, patients with incident diabetes for 1 year and >1 year had almost seven times (RR 6.91, 95% CI 5.76–8.30) and two times (RR 1.96, 95% CI 1.62–2.38) the risk of pancreatic cancer, respectively, compared to individuals without diabetes. Similar patterns of associations for diabetes status/duration were present across all race/ethnicity subpopulations (Table 2), as well as within subgroups of gender, BMI, smoking status, and alcohol intake (Supplemental tables 2 & 3).

Metabolic Profiling of Incident Diabetes Patients

Among the 110,699 incident diabetes patients, 306 individuals were diagnosed with pancreatic cancer, with an average time of 1.5 years (standard deviation 1.8 years) from diabetes to pancreatic cancer diagnosis. Approximately 75% of patients had glucose measurements at diabetes diagnosis and 25–38% had measurements in the preceding time intervals. For HbA1c, 68% had measurements around diabetes diagnosis and 10–14% had measurements in the periods before. For weight, around 90% had measurements at diabetes diagnosis and 65–80% had measurements in the prior intervals.

When evaluating changes in metabolic markers over time (Table 3), cases and non-cases had similar values and minor increases in fasting glucose in the three years to one month prior to diabetes diagnosis (cases: 1.19 mg/dL/interval; non-cases: 0.81 mg/dL/interval; p-heterogeneity=0.06). However, the change in slope immediately before diabetes diagnosis was much higher for cases compared to non-cases (cases: 37.47 mg/dL; non-cases: 27.68 mg/dL; p-heterogeneity<0.01; Figure 2a). This pattern was similar for HbA1c, where cases and non-cases had similar values and trends up to one month prior (cases: 0.03%/interval; non-cases: 0.04%/interval; p-heterogeneity=0.38), but cases had a much larger change in slope compared to non-cases during the interval right before diabetes (cases: 1.39%; non-cases: 0.86%; p-heterogeneity<0.001; Figure 2b). For weight, cases had a non-significant negative trend, while non-cases had a significant increasing trend over time (cases: -0.18 kg/interval; non-cases: 0.33 kg/interval; p-heterogeneity<0.001; Figure 2c). In contrast to

glucose and HbA1c, differences in weight between cases and non-cases were observed starting from three years prior to diabetes (Figure 2).

Though there was no overall significant heterogeneity by race/ethnicity, patterns in the trends appeared to be stronger for specific subgroups (Table 3). For glucose, the difference between cases and non-cases for the change in slope was greatest among blacks and Asians, while there was hardly any difference among Hispanics (Supplemental figure 1). For HbA1c, whites and blacks had the largest differences between cases and non-cases for the change in slope (Supplemental figure 2). For weight, the negative trend for cases was strongest among Hispanics (Supplemental figure 3).

DISCUSSION

In this study, we evaluated the influence of diabetes status, diabetes duration, and metabolic profiles on pancreatic cancer risk within a large and diverse population-based cohort. We observed that patients with incident and prevalent diabetes had three and two times the risk, respectively, of pancreatic cancer compared with patients without diabetes. In addition, this risk was elevated nearly seven times for incident diabetes patients with 1 year of disease duration. Among incident diabetes patients, those who developed pancreatic cancer had greater increases in fasting glucose, HbA1c and weight loss in the time leading up to diabetes. The longitudinal changes in metabolic characteristics between cases and non-cases also appeared to be more pronounced for specific race/ethnicity groups.

Prior epidemiologic studies have found that diabetes is associated with a two times higher risk of pancreatic cancer, with higher risks observed for those with shorter disease durations.^{2,6} Our main findings are generally consistent with past research, as both incident and prevalent diabetes patients had around a two to three times greater risk compared to non-diabetes patients. The elevated risk among incident diabetes patients was driven primarily by the seven-fold increased risk for those who had diabetes for 1 year, while those with longer disease durations had risks resembling that of prevalent diabetes patients. These results add support for the hypothesis that pancreatic cancer patients with diabetes for shorter periods may actually have a distinct form of diabetes that is induced by the pancreatic tumor.^{3,5}

Importantly, we observed that these patterns of association were similar across race/ethnicity. Most of the prior literature on diabetes duration has been focused on white populations and only a sparse number of studies have examined this relationship among minorities.^{12,16,17} Despite this, our results are congruent with previous research showing that shorter durations of diabetes are also associated with higher pancreatic cancer risk among non-whites. To our knowledge, this is the first population-based cohort study to evaluate multiple race/ethnicity groups with sufficient power to detect a range of associations.

In our metabolic profiling of incident diabetes patients, we found that pancreatic cancer cases and non-cases had similar levels of fasting glucose and HbA1c in the time before diabetes, but cases had much higher increases in these glycemic markers in the final month preceding diabetes. Conversely, cases consistently had lower weight compared to non-cases, and both groups had subtle, yet opposite, trends in weight measurements leading up to

diabetes. Interestingly, differences in weight between cases and non-cases predated the time when the glycemic markers started to differ across case status. Though the degree of weight loss across the two groups was minor, our results indicate that weight changes may occur earlier in the pathogenesis of pancreatic cancer.

These metabolic changes have been associated with pancreatic cancer in past studies of new-onset diabetes^{18–20} and have been identified as significant parameters in recent risk prediction models.^{21,22} In particular, the Enriching New-onset Diabetes for Pancreatic Cancer model from the Mayo Clinic reported that increases in blood glucose and weight loss by diabetes diagnosis were predictive markers of pancreatic cancer risk.²² Additionally, the model developed in The Health Improvement Network in the United Kingdom found that higher levels of HbA1c and larger decreases in BMI at diabetes diagnosis were also significant predictors of pancreatic malignancy.²¹ As these previous studies were all conducted in mainly white populations, our study is the first to show that these metabolic changes can also be used to determine risk in heterogeneous populations with different lifestyles and genetic susceptibilities. The general consistency in findings across multiple racial/ethnic groups suggests that prediction models developed in predominantly white individuals^{21,22} would apply broadly to minority populations in the United States.

Our results may have important clinical implications for the early detection of pancreatic cancer among new-onset diabetes patients. Understanding these metabolic trends across cases and non-cases can help guide the development of prediction algorithms that utilize prior routine measurements of weight and glycemic markers. These models can also incorporate race/ethnicity-specific trends in their risk calculations, as some patterns seemed to be stronger in certain race/ethnicity subgroups. For instance, based on our findings, the formula for blacks and whites could have greater weight on HbA1c, while the model for Hispanics could have a larger effect from changes in adiposity. Finally, there appears to be a potential critical window for improved screening and intervention, given that the average time between diabetes and pancreatic cancer in our cohort was 1.5 years. When evaluating the 306 incident diabetes patients with pancreatic cancer, we observed that trends in metabolic markers began to shift around 1.5–2 years prior to pancreatic cancer diagnosis, roughly corresponding with the onset of diabetes (Supplemental table 4/Supplemental figure 4).

The major strengths of this study include the diverse patient population and the largest number of pancreatic cancer cases among all past cohort studies, which make our findings more robust and generalizable. Establishing a cohort from members of an integrated health system further assured that individuals had similar healthcare access and were less likely to be lost to follow-up. We also had more reliable and complete data by using the prospectively collected electronic health records. In particular, using glucose and HbA1c tests for both exclusion criteria and case ascertainment controlled for healthcare utilization and improved the accuracy of identifying diabetes patients, respectively. Though this excluded a large subset of patients, this was done to maximize the specificity of diabetes classification and to ensure that we could properly evaluate their glycemic profiles. Of note, we had considerable concordance with diabetes identified by ICD code (73%), and only <0.5% of eligible patients with diabetes ICD codes were missing glycemic measurements. Finally, this is the

first study to evaluate longitudinal trends in metabolic markers across multiple race/ethnicity groups.

However, only a proportion of patients had available metabolic measurements in each time interval, so our findings for metabolic changes are based on a subset of patients that have more clinic visits. This could include a spectrum of patients from healthy individuals compliant with annual physicals to individuals with greater disease burden that necessitates more frequent encounters. The smaller subset appeared to limit the power in the race/ethnicity subgroup analyses, as the differences between cases and non-cases in the change in slope for glucose and HbA1c were not significant among non-white subgroups. However, these results became significant after combining the data for all non-white patients together. Furthermore, many patients were excluded due to missing data on BMI, smoking and alcohol. These were primarily patients whose memberships ended during the early years of the study period when the electronic health record system was being implemented in KPSC, so information on these risk factors was not available and could not be imputed. Lastly, we did not have much information on systemic insulin levels, another potential important metabolic biomarker,²³ as this lab test is not frequently ordered by KPSC providers.

In this population-based cohort study, we illustrate that the elevated pancreatic cancer risk associated with new-onset diabetes is also present among multiple racial/ethnic minorities. Additionally, the metabolic profiles of these incident diabetes patients appear to have distinct patterns for certain race/ethnicity groups, suggesting that some biomarkers could have more clinical relevance or utility for specific populations. These findings offer more insight into the complex diabetes-pancreatic cancer relationship and may help guide decisions towards tailoring prevention techniques and methods for identifying patients most appropriate for screening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ADA	American Diabetes Association
HbA1c	Hemoglobin A1c
ICD	International Classification of Diseases
KPSC	Kaiser Permanente Southern California
SEER	Surveillance, Epidemiology and End Result

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Need to Know

Background

Observational studies of predominantly white populations have found new-onset diabetes to be associated with increased risk of pancreatic cancer.

Findings

In a study of a large ethnically diverse population, we found risk of pancreatic cancer to be increased among patients with a diagnosis of diabetes in the past year among different races and ethnicities. Weight loss and poor glyceemic control were associated with increased risk of pancreatic cancer in multiple races.

Implications for patient care

Patients with a recent diagnosis of diabetes should be evaluated for pancreatic cancer.

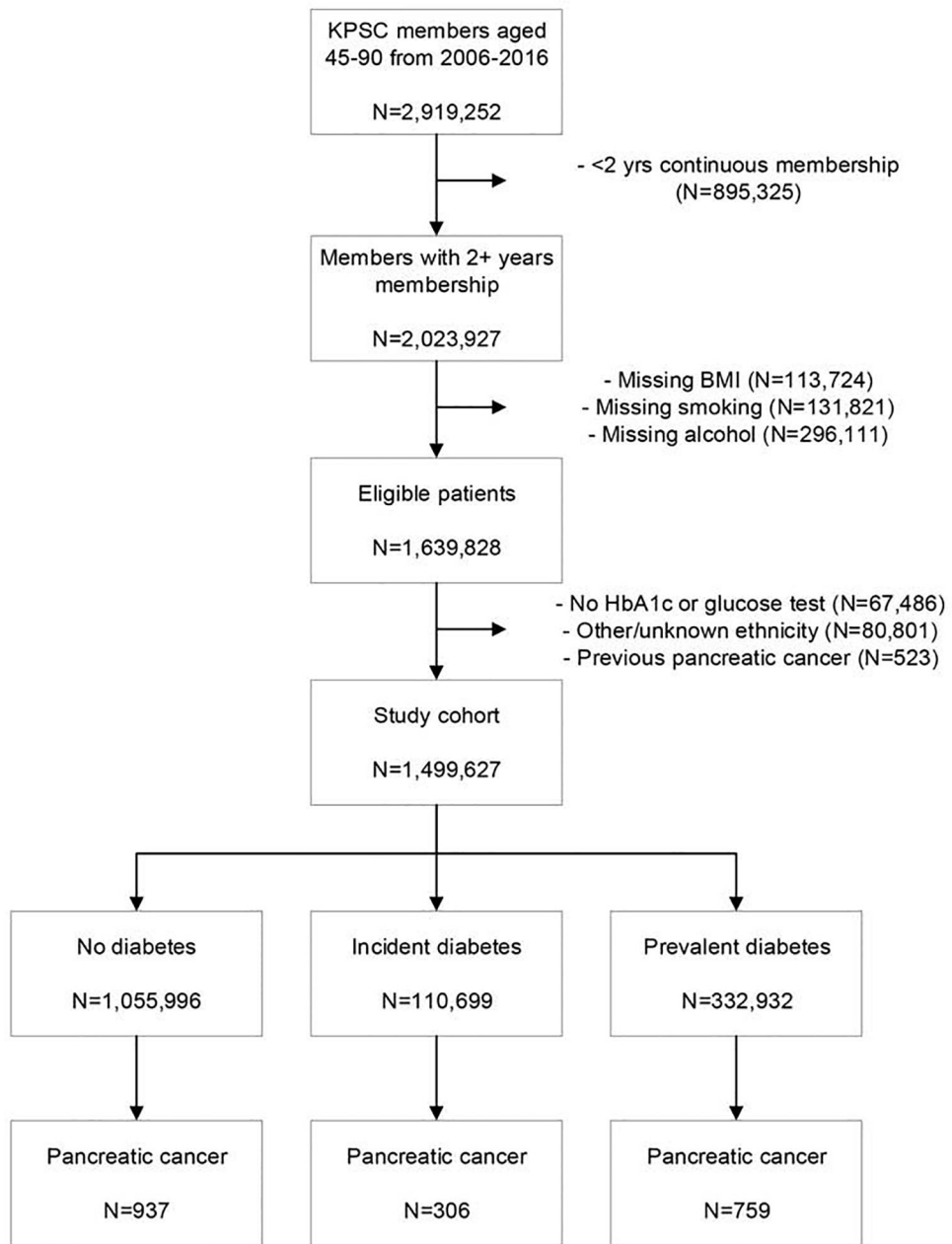


Figure 1:
Flowchart of study cohort

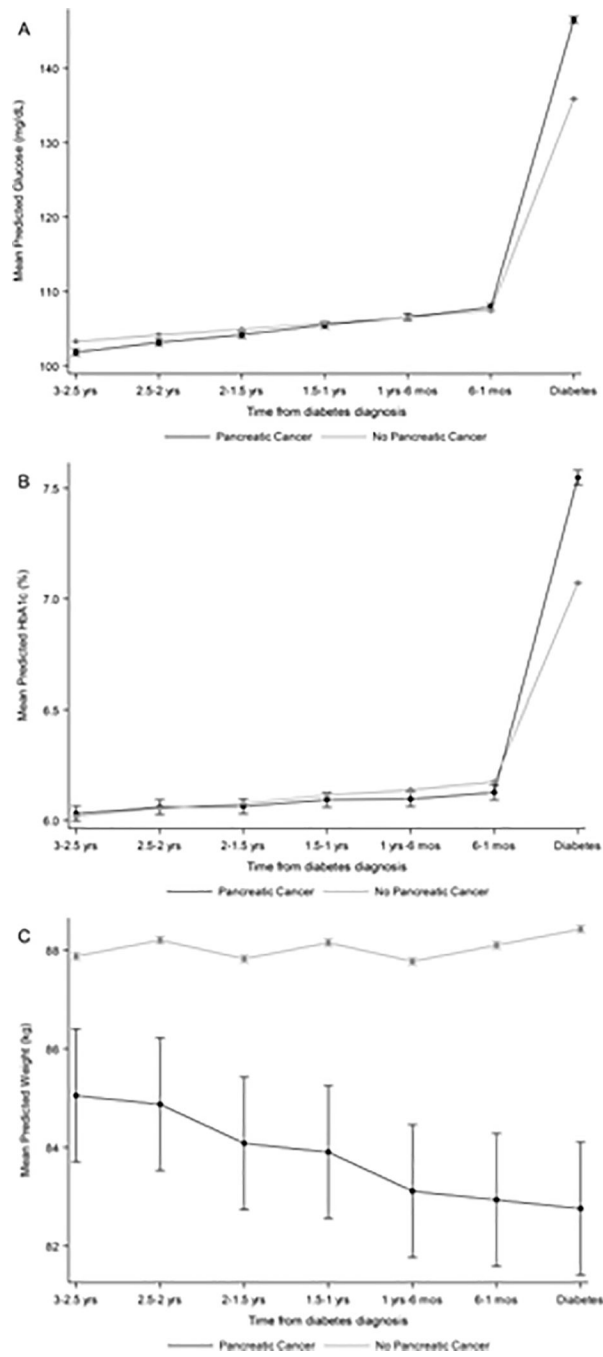


Figure 2: Predicted mean values of (a) fasting glucose, (b) HbA1c and (c) weight during the three years prior to diabetes, across pancreatic cancer status

Table 1:

Baseline characteristics of study cohort, by diabetes status

Characteristic	Total (N=1,499,627)			No diabetes (N=1,055,996)			Incident diabetes (N=110,699)			Prevalent diabetes (N=332,932)		
	N	%		N	%		N	%		N	%	
Pancreatic cancer cases	2,002	0.1		937	0.1		306	0.3		759	0.2	
Person-years, total	7,462,072.5			5,060,344.5			726,055.0			1,675,673.1		
Follow-up time (years), mean (SD)	5.0 (3.0)			4.8 (2.9)			6.6 (2.5)			5.0 (3.0)		
Time to pancreatic cancer (years), mean (SD)	3.8 (2.5)			3.6 (2.5)			4.3 (2.4)			3.7 (2.5)		
Incidence rate, age-adjusted [†]	30.7			23.8			43.7			41.2		
Age, mean (SD)	57.9 (10.9)			56.5 (10.5)			59.5 (10.8)			61.8 (11.2)		
Age group												
45–50	433,225	28.9		353,854	33.5		23,417	21.2		55,954	16.8	
50–54	249,754	16.7		187,661	17.8		19,124	17.3		42,969	12.9	
55–59	227,267	15.2		158,721	15.0		18,244	16.5		50,302	15.1	
60–64	191,088	12.7		125,114	11.9		15,673	14.2		50,301	15.1	
65–69	153,534	10.2		93,519	8.9		12,945	11.7		47,070	14.1	
70	244,759	16.3		137,127	13.0		21,296	19.2		86,336	25.9	
Gender												
Female	827,460	55.2		608,694	57.6		59,145	53.4		159,621	47.9	
Male	672,167	44.8		447,302	42.4		51,554	46.6		173,311	52.1	
Race/ethnicity												
Asian	166,395	11.1		110,579	10.5		14,836	13.4		40,980	12.3	
Black	160,228	10.7		103,112	9.8		14,730	13.3		42,386	12.7	
Hispanic	487,185	32.5		327,726	31.0		36,892	33.3		122,567	36.8	
White	685,819	45.7		514,579	48.7		44,241	40.0		126,999	38.2	
BMI kg/m ² , mean (SD)	29.2 (6.2)			28.3 (5.7)			31.2 (6.5)			31.2 (6.8)		
BMI kg/m ² category												
<25	379,339	25.3		308,552	29.2		16,887	15.3		53,900	16.2	
25–30	555,925	37.1		410,837	38.9		36,280	32.8		108,808	32.7	
30	564,363	37.6		336,607	31.9		57,532	52.0		170,224	51.1	
Smoking status												

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Characteristic	Total (N=1,499,627)		No diabetes (N=1,055,996)		Incident diabetes (N=110,699)		Prevalent diabetes (N=332,932)	
	N	%	N	%	N	%	N	%
Never	967,251	64.5	703,859	66.7	67,582	61.1	195,810	58.8
Past	392,214	26.2	253,045	24.0	30,909	27.9	108,260	32.5
Current	140,162	9.4	99,092	9.4	12,208	11.0	28,862	8.7
Alcohol user								
No	864,634	57.7	570,286	54.0	67,683	61.1	226,665	68.1
Yes	634,993	42.3	485,710	46.0	43,016	38.9	106,267	31.9
Education ²								
High school or less	586,579	39.1	388,368	36.8	47,785	43.2	150,426	45.2
Some college	523,205	34.9	370,140	35.1	40,980	37.0	112,085	33.7
College graduate	318,594	21.2	243,112	23.0	19,828	17.9	55,654	16.7
Missing	71,249	4.8	54,376	5.2	2,106	1.9	14,767	4.4
Family history of pancreatic cancer	16,066	1.1	12,068	1.1	1,063	1.0	2,935	0.9
Pancreatitis	18,418	1.2	8,510	0.8	1,403	1.3	8,505	2.6

¹Incidence rate per 100,000 person-years, age-standardized to US Census 2000 standard population, truncated to ages 45+.

²Based on population geocoding files and not specific to individual patient.

All tests comparing distribution of risk factors across diabetes status had p-values <0.0001.

Table 2: Association between diabetes status and duration and pancreatic cancer, among the entire cohort and within race/ethnicity subgroups

Exposure	Total (N=1,499,627)			Asian (N=166,395)			Black (N=160,228)			Hispanic (N=487,185)			White (N=685,819)			p ³
	N Cases	Person-years	RR (95% CI) ²	N Cases	Person-years	RR (95% CI) ²	N Cases	Person-years	RR (95% CI) ²	N Cases	Person-years	RR (95% CI) ²	N Cases	Person-years	RR (95% CI) ²	
Diabetes status ¹																0.25
None	937	5,060,344.5	1 (ref)	67	519,170.1	1 (ref)	117	528,713.0	1 (ref)	166	1,439,741.3	1 (ref)	587	2,572,720.0	1 (ref)	
Incident	306	726,055.0	3.17 (2.75–3.65)	34	98,859.0	3.21 (2.04–5.03)	37	100,617.6	2.82 (1.91–4.14)	82	235,261.2	4.12 (3.10–5.47)	153	291,317.3	2.90 (2.37–3.55)	
Prevalent	759	1,675,673.1	1.85 (1.67–2.05)	73	211,612.1	1.72 (1.22–2.43)	116	230,597.3	1.74 (1.33–2.28)	213	579,355.2	2.19 (1.77–2.71)	357	654,108.5	1.77 (1.54–2.03)	
Diabetes duration ¹																0.09
None	937	5,060,344.5	1 (ref)	67	519,170.1	1 (ref)	117	528,713.0	1 (ref)	166	1,439,741.3	1 (ref)	587	2,572,720.0	1 (ref)	
Incident 1 yr	175	102,711.5	6.91 (5.76–8.30)	19	13,729.9	7.48 (4.17–13.41)	20	13,540.9	6.01 (3.68–9.82)	38	34,371.0	7.50 (5.09–11.06)	98	41,069.8	6.89 (5.37–8.83)	
Incident >1 yr	131	623,343.4	1.96 (1.62–2.38)	15	85,129.1	2.25 (1.24–4.10)	17	87,076.7	1.65 (0.97–2.80)	44	200,890.2	2.73 (1.91–3.89)	55	250,247.5	1.65 (1.24–2.19)	

¹ Incident diabetes status and duration treated as time-varying exposures.

² From a Cox proportional hazards regression with age at cohort entry, gender, race, smoking, BMI, alcohol, pancreatitis, family history of pancreatic cancer and education as covariates.

³ P-values for heterogeneity across race/ethnicity.

Table 3:

Predicted trends for longitudinal measurements of fasting glucose, HbA1c and weight among patients with incident diabetes, by case status and race/ethnicity

Parameter ¹	Total (N=110,699)				Asian (N=14,836)				Black (N=14,730)				Hispanic (N=36,892)				White (N=44,241)					
	Pancreatic Cancer		No Pancreatic Cancer		Pancreatic Cancer		No Pancreatic Cancer		Pancreatic Cancer		No Pancreatic Cancer		Pancreatic Cancer		No Pancreatic Cancer		Pancreatic Cancer		No Pancreatic Cancer			
	Estimate (CI) ²	Estimate (CI) ²	p ³	Estimate (CI) ²	Estimate (CI) ²	p ³	Estimate (CI) ²	Estimate (CI) ²	p ³	Estimate (CI) ²	Estimate (CI) ²	p ³	Estimate (CI) ²	Estimate (CI) ²	p ³	Estimate (CI) ²	Estimate (CI) ²	p ³	Estimate (CI) ²	Estimate (CI) ²	p ⁴	
Glucose (mg/dL)																						
Slope 3 yrs-1 mo	1.19 (0.71-1.67)	0.81 (0.78-0.84)	0.06	1.70 (0.50-2.90)	0.91 (0.84-0.97)	0.27	-0.20 (-1.55-1.16)	0.88 (0.79-0.97)	0.14	1.38 (0.34-2.43)	1.01 (0.95-1.06)	0.45	1.62 (0.90-2.33)	0.80 (0.75-0.84)	0.03	1.62 (0.90-2.33)	0.80 (0.75-0.84)	0.03	1.62 (0.90-2.33)	0.80 (0.75-0.84)	0.16	
Change in slope at 1 mo	37.47 (31.51-43.43)	27.68 (27.38-27.97)	<0.01	34.49 (18.57-50.42)	18.98 (18.32-19.63)	0.07	44.65 (24.36-64.95)	27.46 (26.57-28.36)	0.11	30.94 (20.87-41.01)	29.99 (29.42-30.57)	0.85	38.98 (30.53-47.43)	28.72 (28.29-29.14)	0.02	38.98 (30.53-47.43)	28.72 (28.29-29.14)	0.02	38.98 (30.53-47.43)	28.72 (28.29-29.14)	0.28	
HbA1c (%)																						
Slope 3 yrs-1 mo	0.03 (0.00-0.06)	0.04 (0.04-0.04)	0.38	0.03 (-0.12-0.19)	0.03 (0.03-0.04)	0.05	0.01 (-0.05-0.08)	0.04 (0.03-0.04)	0.41	0.01 (-0.05-0.07)	0.04 (0.04-0.04)	0.24	0.04 (0.01-0.08)	0.04 (0.03-0.04)	0.84	0.04 (0.01-0.08)	0.04 (0.03-0.04)	0.84	0.04 (0.01-0.08)	0.04 (0.03-0.04)	0.31	
Change in slope at 1 mo	1.39 (1.12-1.67)	0.86 (0.85-0.87)	<0.001	0.92 (0.43-1.41)	0.62 (0.59-0.64)	0.09	1.37 (0.74-2.00)	0.93 (0.90-0.97)	0.20	1.27 (0.81-1.74)	1.01 (0.99-1.04)	0.15	1.48 (1.05-1.91)	0.79 (0.78-0.81)	<0.01	1.48 (1.05-1.91)	0.79 (0.78-0.81)	<0.01	1.48 (1.05-1.91)	0.79 (0.78-0.81)	0.72	
Weight (kg)																						
Slope 3 yrs-diagnosis	-0.18 (-0.44-0.08)	0.33 (0.31-0.34)	<0.001	-0.19 (-0.49-0.11)	0.23 (0.20-0.26)	<0.01	0.24 (-0.39-0.87)	0.40 (0.36-0.44)	0.67	-0.30 (-0.70-0.09)	0.31 (0.28-0.33)	<0.01	-0.16 (-0.61-0.28)	0.35 (0.32-0.37)	0.03	-0.16 (-0.61-0.28)	0.35 (0.32-0.37)	0.03	-0.16 (-0.61-0.28)	0.35 (0.32-0.37)	0.65	

¹ Metabolic markers were evaluated from diabetes diagnosis up to three years prior in six-month intervals.

² From a GEE model with the metabolic characteristic as a continuous outcome variable (identity link), time period as the main exposure, age, gender and race as covariates, and patient as the clustering variable. Glucose and HbA1c models included a spline term at the 6-1 month time interval to model the change in slope. Models were run separately for cases and non-cases.

³ P-value for heterogeneity across cases and non-cases. Obtained from a GEE model with a time period*case status interaction term. Glucose and HbA1c models included an additional interaction term for change in slope*case status.

⁴ P-value for heterogeneity across cases status and race. Glucose and HbA1c models included an additional three-way interaction for change in slope*case status*race. Glucose and HbA1c models also included three-way interaction for change in slope.