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The Association of Recently-Diagnosed Diabetes and Long-Term Diabetes With Survival in Pancreatic Cancer Patients: A Pooled Analysis

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Abstract

Objectives—It is unclear whether long-standing diabetes or new-onset pancreatogenic diabetes contributes to poor prognosis in patients with pancreatic ductal adenocarcinoma (PDAC).

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Methods—We investigated the influence of diabetes diagnosed shortly before PDAC and long-term diabetes on overall survival in 2792 PDAC patients who had participated in three PDAC case-control studies in the Pancreatic Cancer Case-Control Consortium (PanC4). There were 300 patients with long-term diabetes of >3-years duration (11%) and 418 patients with recently-diagnosed diabetes of ≤3-years duration (15%). We performed Cox regression to determine the association of long-term diabetes and recently-diagnosed diabetes with overall survival, adjusting for study site, age, sex, race, stage of disease, surgery, chemotherapy, smoking history, and body mass index at diagnosis.

Results—In the overall population, neither long-term diabetes (Hazard ratio [HR], 1.10; 95% confidence interval [CI], 0.97–1.26), nor recently-diagnosed diabetes (HR, 1.06; 95% CI, 0.94–1.18) were associated with shorter survival. When stratified by stage of disease, long-term diabetes was associated with 42% increase in rate of death in persons with resectable PDAC (HR, 1.42; 95% CI, 1.13–1.78), while not associated with survival in PDAC patients with more advanced disease.

Conclusion—Long-term diabetes was associated with increased rate of death in patients with resectable PDAC.

Keywords

Pancreatic cancer; diabetes; survival; pooled analysis

INTRODUCTION

Diabetes is an established risk factor for pancreatic ductal adenocarcinoma (PDAC), which in turn also affects endocrine dysfunction, leading to hyperglycemia.¹ In a pooled-analysis of individual data from 15 case-control studies within the Pancreatic Cancer Case-Control Consortium (PanC4), we found that people with long-term diabetes (of more than 2-years duration) experienced an approximately 2-fold increased risk of PDAC.² Diabetes diagnosed within 2 years of the cancer diagnosis was much more strongly associated with PDAC (5 to 7-fold),² reflecting the reverse impact of PDAC on glucose metabolism. Such heterogeneity in the strength of the association between diabetes and PDAC by duration of diabetes has also been demonstrated by two meta-analyses of observational studies.^{3,4} A time-dependent analysis also showed that new-onset diabetes may be a harbinger of multiple cancer types, most notably of PDAC.⁵

PDAC-induced diabetes, which falls under the class of type 3c diabetes, shares some similarity in phenotype with type 1 and 2 diabetes, including β -cell dysfunction and insulin resistance,^{6,7} but is unique in that it is linked to pancreatic disease.⁸ Diabetes diagnosed shortly before PDAC often resolves after a pancreaticoduodenectomy, suggesting that the tumor itself is responsible for the endocrine dysfunction.⁹ Although the mechanism by which PDAC causes diabetes is unclear, studies point to the role of pancreatic polypeptide deficiency and defective hepatic insulin sensitivity,⁶ as well as adrenomedullin, which has been reported to mediate β -cell dysfunction.⁷

Outcome studies on PDAC patients show that diabetes may increase mortality in such patients independent of body weight and stage of cancer,^{10–15} though not all studies agree.¹⁶ Few studies have examined differences in PDAC survival according to whether diabetes was diagnosed shortly before PDAC ('new-onset diabetes') or diabetes was present for at least several years before PDAC ('long-term diabetes'), and disagree on whether the increased mortality is attributable more to new-onset diabetes,^{12,15} long-term diabetes^{14,17} or to both.¹³ Separating out the effects of new-onset, type 3c diabetes from long-term, type 2 diabetes is further complicated by the fact that the stage at diagnosis of PDAC may differ in patients with each type of diabetes. In spite of these difficulties, improving our knowledge on such relationships would help understand the mechanism by which diabetes may influence survival in patients with PDAC. In addition, identifying the effect modifiers of the relationship would help target the specific diabetes population that may require a more integrated management of PDAC and diabetes.

Therefore, the main aim of the study was to investigate the influence of new-onset diabetes and long-term diabetes on PDAC survival. To such end, we pooled data on over 2700 PDAC patients who are represented in PanC4.

MATERIALS AND METHODS

Study Populations

We collected data on PDAC patients from case-control studies in the PanC4 for whom diabetes status, duration of diabetes, cancer stage and vital status were available. Three case-control studies provided data: MD Anderson Cancer Center (MDACC), Ontario Pancreatic Cancer Study at Mount Sinai Hospital in Ontario, Canada (Ontario), and Memorial Sloan Kettering Cancer Center (MSKCC). Pathologically confirmed PDAC patients for the MDACC study were recruited through its cancer treatment center between 1998 and 2006.¹⁵ Pathologically confirmed PDAC cases for the Ontario study were identified through the Ontario Cancer Registry between 2003 and 2009.¹⁸ Pathologically or cytologically confirmed PDAC cases for the MSKCC study were recruited through its Pancreatic Tumor Registry between 2004 and 2010.¹⁹ The final pooled analysis included 2792 PDAC cases. This study was approved by the PanC4 Steering Committee and the Cedars-Sinai Medical Center's institutional review board. All participants provided informed consent for the original case-control studies.

Survival Outcome

The outcome of this study is overall survival due to any cause of death. Vital status and last date of follow-up for the MDACC study were obtained through patients' medical records, the MDACC tumor registry and the Social Security Death Index. Vital status and last date of follow-up for the Ontario study were obtained through clinical notes, clinical staff correspondences, death clearances in the Ontario Cancer Registry, public obituaries or through a follow-up call/mail. Vital status and last date of follow-up for the MSKCC study were determined through annual follow-up of the patient, update from the Social Security Death Index, electronic databases at MSKCC and from Death Notification Forms submitted

by the physicians' offices. Survival time was defined as time from PDAC diagnosis to date of death or date of last contact.

Diabetes Definition

Participants were considered to have diabetes if they reported having been diagnosed with diabetes in the past at the time of PDAC diagnosis. Diabetes diagnosed after PDAC diagnosis was not considered in the current study. The age at the onset of diabetes and the age at the time of the diagnosis of PDAC were recorded. The duration of diabetes was computed by subtracting the age at diagnosis of diabetes from the age at diagnosis of PDAC. Recently diagnosed diabetes was defined as diabetes with a duration of 3 years or shorter at the time of PDAC diagnosis, while long-term diabetes was defined as diabetes of greater than 3-years duration at the time of PDAC diagnosis. Other thresholds (1, 2, 4 and 5 years) for recently-diagnosed diabetes were considered for sensitivity analyses. Participants were considered to have insulin-dependent diabetes if they reported ever taking insulin or were recommended to take insulin. Details of the questions to solicit diabetes status, duration of diabetes and insulin use are available in Supplementary Table S1.

Covariates

Data on age at PDAC diagnosis, sex, race, ethnicity, and smoking status were obtained from interview-administered questionnaires. Clinical data on surgical and chemotherapeutic interventions of PDAC were obtained through medical chart reviews at each institution. Patients were staged by physicians following the American Joint Committee on Cancer staging based on the tumor-node-metastasis system.²⁰ Patients with Stage I or Stage II disease were considered to have local/resectable tumor, patients with stage III disease were categorized as having locally advanced tumors and patients with stage IV disease were categorized as having metastatic cancer. Body mass index (BMI) was computed from height and weight measured at the time of the interview in the MDACC and Ontario studies, or from height and weight reported by the patients at the time of diagnosis in the MSKCC study.

Statistical Methods

The distributions of categorical covariates in patients with recently diagnosed diabetes and long-term diabetes were compared to the distribution in patients without diabetes by chi-squared analysis in the pooled data and within each study. The distribution of age and BMI were compared by diabetes status using the *t*-test. Missing BMI data (9%) were imputed based on age, sex, race, pre-illness BMI (available in Ontario and MSKCC studies), within each study. Survival comparisons between diabetes groups were summarized by Kaplan Meier analysis, and differences in survival were tested by the log rank test. The associations of recently diagnosed diabetes and long-term diabetes with survival were assessed by Cox regression analysis, with adjustment for study site, age, sex, race (White, Black, other), stage of cancer (resectable, locally advanced, or metastatic), chemotherapy (yes, no), surgery for curative intent (yes, no), smoking status (never, former, current), and BMI. Age and BMI were treated as continuous variables. The proportional hazards assumption was tested for each covariate by including a log(time)*covariate interaction term in the multivariable model. If significant, the interaction terms with time were kept in the model. Hazard ratios

(HR) were used to estimate the magnitude of the association between diabetes status and survival. Sensitivity analyses by various thresholds of diabetes duration for recent-onset diabetes and long-term diabetes were conducted with multivariable models. Potential heterogeneity in the relationship between diabetes and survival by study site, sex, tumor stage, and BMI were explored using stratified analyses, and heterogeneity was tested by the significance of interaction terms between diabetes status and the effect modifiers of interest. Statistical significance was set at $P < 0.05$. Multivariable statistical analyses were conducted in SAS 9.3 (Cary, NC). Forest plots were graphed using R software version 3.2.3 (R Foundation, Vienna, Austria).

RESULTS

Distributions of demographic and clinical factors of the PDAC patients are summarized by study site and in the pooled data in Table 1. Overall, the mean age of the study population was 63. Males comprised 55% of the overall study population, and 91% of the patients were of White race. Forty-two percent of the total population was diagnosed at a resectable stage, varying from 29% in the MDACC study to 63% in the Ontario study. Long-term diabetes of more than 3 years was present in 11% of the PDAC participants, while recently diagnosed diabetes of ≤ 3 years in duration was present in 15% of the PDAC participants. Insulin was used by 8% of the patients in the three studies (Table 1).

PDAC patient characteristics are summarized by diabetes status in Table 2. In the pooled data, participants with long-term diabetes experienced shorter median survival than patients without diabetes (14.0 months vs. 15.6 months, log-rank $P = 0.004$), while survival in participants with recently diagnosed diabetes was not significantly different from that of participants without diabetes (15.0 months vs. 15.6 months, $P = 0.15$). Participants with long-term diabetes were older, more likely to be male, of Black race, less likely to receive surgery and had higher BMI than those without diabetes. Likewise, participants with recently diagnosed diabetes were older, more likely to be male, of Black race, and to have slightly greater BMI compared to participants without diabetes. These patterns of potential confounders were similar across the three studies, with the exception that in the Ontario and MSKCC studies, BMI of the recently diagnosed diabetes patients was not different from that of participants without diabetes (Supplementary Table S2).

Results from the Cox regression models to evaluate the association of long-term diabetes and recently diagnosed diabetes with PDAC survival are presented in Table 3. The coefficients for interaction terms with log(time) were significantly different from zero for age, sex, stage, chemotherapy, and study indicators, indicating non-proportionality of hazards by these factors. Therefore, these interaction terms were included in the multivariable models. Diabetes of more than 3-years duration was associated with 21% increased hazard of death in the pooled analysis, unadjusted for any other factors (HR, 1.21; 95% confidence interval [CI], 1.06–1.38). Adjusting for between-study variation, age, sex, race, smoking status and BMI did not attenuate this relationship. However, when the model was adjusted for cancer stage, long-term diabetes was no longer associated with death (HR, 1.09; 95% CI, 0.96–1.25). Further adjustment by surgery and chemotherapy did not influence the association. Recently diagnosed diabetes was not associated with death in any

of the models considered (HR, 1.06; 95% CI, 0.94–1.18 in fully-adjusted model, HR, 1.09; 95% CI, 0.97–1.21 in unadjusted model). When we examined the relationship between diabetes and survival using different durations of diabetes for recent diabetes, no HR for either long-term or recently diagnosed diabetes showed statistically significant departures from the null. We also examined the influence of insulin use *in patients with long-term diabetes* of more than 3 years and found that insulin-dependent diabetics did not experience a significantly shorter survival compared to non-insulin-dependent long-term diabetics (HR, 1.14; 95% CI, 0.85–1.50).

Study-specific HRs for the association of long-term diabetes with mortality from the multivariable models are presented in the forest plots in Figure 1. Notably, long-term diabetes was associated with higher hazard of death in the study conducted in Ontario (HR, 1.36; 95% CI, 1.07–1.73), but not in the other two studies. Recent diagnosis of diabetes was marginally associated with hazard of death in the study conducted in MDACC (HR, 1.16; 95% CI, 0.98–1.38), but not in the other two studies. Despite the different results, the interaction terms for diabetes and study sites were not significant for long-term diabetes ($P = 0.53$), nor for recent diabetes ($P = 0.48$).

Stratified multivariable-adjusted analyses of diabetes status and survival by sex, stage of disease, and BMI are presented in Table 4. Long-term diabetes was not associated with death in males, but female participants with long-term diabetes showed a 32% increased hazard of death compared to those without diabetes (HR, 1.32; 95% CI, 1.06–1.63). In both males and females, participants with long-term diabetes were older, heavier, and more likely to be Black, but the differences in proportion of Blacks and mean BMI were greater in females than in males (Supplementary Table S3). When stratified by stage of disease, among participants with resectable cancer those with long-term diabetes showed a 42% higher hazard of death compared to non-diabetics with resectable PDAC (HR, 1.42; 95% CI 1.13–1.78); this association was not observed in subjects with more advanced PDAC (Table 4). The interaction term between diabetes status and stage of disease was significant ($P = 0.047$). Here again, participants with long-term diabetes were older, heavier, and more likely to be Black across all stages to a similar extent (Supplementary Table S4). Long-term diabetics showed increased hazard of death in all three studies, but only one study reached statistical significance: (HR, 1.68; 95% CI, 1.06–2.66 in MDACC; HR, 1.35; 95% CI, 0.97–1.87 in Ontario; HR, 1.44; 95% CI, 0.92–2.24 in MSKCC). Finally, long-term diabetes was associated with a 19% increased hazard of death compared to no diabetes among participants who were overweight at the time of the diagnosis ($\text{BMI} \geq 25 \text{ kg/m}^2$), while the death rate did not vary by diabetes status in those who were not overweight (Table 4). Participants with long-term diabetes were older than non-diabetics in both BMI categories (Supplementary Table S5). In the overweight category, patients with long-term diabetes had even greater mean BMI compared to those without diabetes (30.6 kg/m^2 vs. 28.7 kg/m^2 , respectively). While the relationship between long-term DM and survival varied by sex, and BMI, the differences in the HR estimates by these covariates did not reach statistical significance (P for interaction > 0.05 ; Table 4) and therefore the results were not considered to be heterogeneous by sex and BMI.

DISCUSSION

In this pooled analysis of three large case series including 2792 patients with PDAC, we found that long-term and recently-diagnosed diabetes were not associated with overall survival. Of note, the apparent association between long-term diabetes and survival was attenuated by adjusting for stage at diagnosis. Long-term diabetes was associated with shortened survival in select populations, especially those with resectable PDAC.

Our overall study findings based on data from case-control studies differ somewhat from two large U.S.-based case series investigating the relationship between diabetes and survival in PDAC patients.^{10,14} One was a pooled analysis of 1006 PDAC patients that included patients identified through Harvard's Nurses' Health Study (NHS), Health Professionals Follow-up Study (HPFS), and Dana Farber Cancer Institute (DFCI),¹⁴ and another was an analysis of 504 exocrine PDAC patients identified in the Prostate, Lung, Colorectal, and Ovarian cancer (PLCO) screening trials.¹⁰ Both studies reported that patients with long-term diabetes of greater than 3 or 4 years duration experienced approximately 1.4 to 1.5-fold increased hazard of death compared to those without diabetes.^{10,14} Using a similar cut-off of 3 and 4 years duration of diabetes, we found that patients experienced 1.10 to 1.13-fold increased hazard of death, an association that did not reach statistical significance. The magnitude of this effect is similar to that observed in a large population-based study conducted in the UK on 3147 patients with PDAC, which showed a statistically significant increased hazard of death in patients with diabetes of longer than 5 years duration (HR, 1.16; 95% CI, 1.00–1.33).¹⁷ Overall, median survival in the Harvard Studies (3 months for long-term diabetes, 5 months for no diabetes) and in the PLCO trial (3.0 months for diabetes, and 4.6 months for no diabetes)^{10,14} were shorter than in our present study (14.0 months for diabetes, 15.6 months for no diabetes months). The Harvard study included patients with PDAC diagnosed in 1986 to 2013, and the PLCO trial included patients diagnosed in 1993–2001, while the earliest diagnosis date in the studies included in our pooled analysis was in 1998. Assessment of resectability and staging of PDAC has changed considerably in the past 3 decades to a more refined and broader inclusion of resectable PDAC,²⁰ which may have partially resulted in a higher proportion of resectable PDAC in the present analysis (29–63%) than in the cohort studies (13–18%).^{10,14} Moreover, these differences could reflect the fact that sicker patients with more advanced disease are less likely to enroll into case-control studies. Adjusting for stage did not appreciably influence the HRs for long-term diabetes in the Harvard studies (1.43 to 1.40 in NHS, HPVS and 1.56 to 1.53 in the DFCI), but attenuated the HRs in our study (1.20, to 1.09). The higher prevalence of resectable types in our study may have influenced the extent to which stage confounded the relationship between diabetes and survival.

The criteria for diabetes assessment have changed considerably over the past three decades, with broader definitions of diabetes leading to greater inclusion of patients with less severe diabetes.²¹ Also, glycemic control among diagnosed diabetics in the U.S. has improved over the years.²² Furthermore, and the proportion of patients with undiagnosed diabetes has decreased over time.²³ The prevalence of diagnosed diabetes in our pooled analyses was indeed higher (25%) than in cohorts established in more distant past: NHS/HPFS (18%), and the PLCO trial (12%).^{10,14} Therefore, it is possible that the self-reported diabetics in the

present analysis had on average better glucose control compared to the older cohorts. However, given that the impact of glucose control on PDAC survival is unknown,¹⁵ the influence of inclusion of patients with more moderate glucose control on PDAC survival is unpredictable.

The prevalence of recently diagnosed diabetes (15%) in this pooled analysis of case-control studies relying on self-reported diabetes status is higher as compared to that (5%) of the HPHS and NHS cohort studies,¹⁴ but lower compared to that (23–35%) reported in clinic-based studies that had required hemoglobin A1c or glucose levels to define diabetes status in patients who had not been diagnosed with diabetes by a physician.^{12,15,24–26} Because a considerable proportion of PDAC-associated diabetes cases are diagnosed within 1 year of the cancer diagnosis,^{24,27} cohort studies that have relied on bi-annual mail-in questionnaires prior to PDAC diagnosis may have underestimated the prevalence of new-onset diabetes,^{14,26} whereas assessment of diabetes in clinic-based case-control studies would have documented diabetes diagnosed close to PDAC diagnosis therefore would have had more updated ascertainment of diabetes. As in previous clinic-based studies,^{12,15,24,25} actively screening for hyperglycemia with laboratory tests in the pooled studies may have identified additional patients with new-onset diabetes, considering that underdiagnosis of diabetes is common.²³ Misclassification of new-onset diabetes may explain why the present analysis showed no significant relationship between recently-diagnosed diabetes and survival, whereas studies applying the glucose tests observed an elevated risk of death in new-onset diabetics.^{12,15,25} Although undiagnosed diabetics in the general population tends to be asymptomatic²⁸ and have moderate glucose control compared to diagnosed diabetics,²⁹ undiagnosed *pancreatogenic* diabetes may be correlated with more advanced PDAC and therefore worse prognosis. Moreover, undiagnosed diabetes has been correlated with poorer liver function,²⁹ which has been linked to worse outcomes in PDAC patients.³⁰ Further studies on PDAC-induced diabetes and outcomes in PDAC patients are warranted.

Long-term diabetes was associated with survival specifically in those with resectable PDAC, as also observed in the PLCO trial.¹⁰ Type 2 diabetes is marked with compensatory hyperinsulinemia that increases the bioavailability of insulin-like growth factor (IGF)-1, which in turn promotes PDAC cell proliferation and invasion and inhibits apoptosis.¹ A recent clinical trial of metformin, an insulin-sensitizing agent, in advanced PDAC patients showed no overall benefit on survival, while patients who experienced decreased insulin levels in response to metformin therapy survived longer.³¹ This suggests that diabetes may have a greater impact on tumor regrowth specifically via increased IGF.

Our study has several strengths, including a large sample size and diverse representation from multiple sites in North America (Ontario, New York, and Texas) and up-to-date outcome ascertainment for survival. There were a few limitations, however, including self-reported diabetes status, which may have led to under-diagnosis of diabetes as discussed above. Compared to the general PDAC population, there was an over-representation of surgically managed cases in the pooled analysis, especially in the Ontario study. Identification and recruitment of PDAC cases after diagnosis may have required additional time during which patients with advanced cancer became no longer available, or were less interested in the study due to declining health. We also lacked detailed information on

cancer intervention such as surgery type, and chemotherapeutic agent, which would have increased the precision of our model. It is unlikely, however, that self-reported diabetes would have been affected by cancer intervention status. Lastly, we lacked data on progression-free survival and time-varying prognostic factors relevant to diabetes, such as post-diagnosis weight change. Studying such factors will help elucidate the mechanisms by which diabetes may impact PDAC.

In conclusion, we found that long-term diabetes was associated with increased rate of death in patients with resectable PDAC types. Recently diagnosed diabetes was not related to survival in the populations considered, but further investigators are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1A.

Figure 1B.

FIGURE 1.

A, Association of long-term diabetes and survival in patients with pancreatic ductal adenocarcinoma. B, Association of recently diagnosed diabetes and survival in patients with pancreatic ductal adenocarcinoma.

TABLE 1

Summary of Demographic and Clinical Factors of Pancreatic Ductal Adenocarcinoma Patients From Three Participating Studies in PanC4

Variable	All Studies	MDACC	Ontario	MSKCC
Number of patients	2792	1243	790	759
Recruitment years		1998–2009	2003–2009	2004–2010
Age, mean (SD), y	63.3 (10.5)	61.9 (10.0)	64.7 (10.6)	64.0 (11.0)
Sex, male, n (%)	1533 (55)	735 (59)	403 (51)	395 (52)
Race, n (%)				
White	2538 (91)	1155 (93)	708 (90)	676 (89)
Black	123 (4)	71 (6)	13 (2)	39 (5)
Other	131 (5)	17 (1)	69 (8)	44 (6)
Stage of disease, n (%)				
Resectable	1159 (42)	355 (29)	498 (63)	306 (40)
Locally advanced	595 (21)	352 (28)	103 (13)	140 (18)
Metastatic	1038 (37)	536 (43)	189 (24)	313 (41)
Surgery for curative intent, n (%)	1085 (39)	354 (28)	449 (57)	282 (37)
Chemotherapy, n (%)	164 (59)	866 (70)	342 (43)	434 (57)
Smoking status, n (%)				
Never	1221 (44)	530 (43)	334 (42)	357 (47)
Former	1227 (44)	491 (40)	374 (47)	362 (48)
Current	344 (12)	222 (18)	82 (10)	40 (5)
Body mass index, mean (SD), kg/m ²	25.0 (4.9)	28.9 (6.0)	23.5 (4.2)	24.6 (4.5)
Diabetes status and duration, n (%)				
No diabetes	2074 (75)	932 (75)	592 (75)	549 (72)
Long-term diabetes (>3 years)	300 (11)	120 (10)	99 (13)	81 (11)
Recent diabetes (≤ 3 years)	418(15)	190(15)	99(13)	133 (18)
1 year	301 (11)	137 (11)	64 (8)	104 (14)
>1, ≤ 2 years	61 (2)	30 (2)	15 (2)	16 (2)
>2, ≤ 3 years	56 (2)	23 (2)	20 (3)	13 (2)
>3, ≤ 4 years	25 (1)	12 (<1)	5 (<1)	8 (1)
>4, ≤ 5 years	33 (1)	14 (1)	9 (1)	10 (1)
Insulin-dependent diabetes, n (%)				
Non-insulin dependent diabetes	494 (18)	203 (16)	162 (21)	129 (17)
Insulin-dependent diabetes	224 (8)	107 (9)	36 (5)	81 (11)

PanC4 indicates Pancreatic Cancer Case Control Consortium; MDACC, MD Anderson Cancer Center; Ontario, Ontario Pancreatic Cancer Study; MSKCC, Memorial Sloan Kettering Cancer Center; SD, Standard Deviation.

Demographic and Clinical Characteristics of Pancreatic Ductal Adenocarcinoma Patients by Diabetes Status From Three Participating Studies in PanC4

TABLE 2

Variable	No Diabetes	Long-term Diabetes (>3 y Duration)	P*	Recently Diagnosed Diabetes (< 3 years duration)	P†
N	2074	300		418	
Person-months	45,035	5352		8570	
Number of deaths	1799	266		373	
Median survival (months)	15.6	14.0	0.004	15.0	0.15
Age, mean (SD), y	62.8 (10.9)	64.6 (9.0)	0.002	64.6 (9.6)	0.0007
Sex, male, n (%)	1093 (53)	187 (62)	0.002	253 (61)	0.003
Race, n (%)					
White	1913 (92)	256 (85)	Ref	369 (88)	Ref
Black	73 (4)	23 (8)	0.0004	27 (6)	0.004
Other	88 (4)	21 (7)	0.02	22 (5)	0.29
Stage of disease, n (%)					
Resectable	881 (42)	114 (38)	Ref	164 (39)	Ref
Locally advanced	441 (21)	61 (20)	0.69	93 (22)	0.38
Metastatic	752 (36)	125 (42)	0.07	161 (39)	0.25
Surgery for curative intent, n (%)	831 (40)	100 (33)	0.03	154 (37)	0.22
Chemotherapy, n (%)	1233 (59)	175 (58)	0.7	234 (56)	0.19
Smoking status, n (%)					
Never	915 (44)	128 (43)		178 (43)	
Former	907 (44)	129 (43)	0.56	191 (46)	0.76
Current	252 (12)	43 (14)		49 (12)	
BMI, mean (SD), kg/m ²	24.7 (4.6)	27.0 (5.9)	<0.0001	25.4 (4.8)	0.004

P values correspond to Chi-square tests.

* Long-term vs. no diabetes

† Recently diagnosed vs. no diabetes

Ref indicates reference group for comparison of proportions in ordinal categories for race and stage

TABLE 3

Summary of Hazard Ratios From Cox Regression Analysis for the Association of Long-Term Diabetes (>3 Years Duration) and Recently Diagnosed Diabetes (≤ 3 Years Duration) With Survival in Pancreatic Ductal Adenocarcinoma Patients From Three Participating Studies in PanC4

Model	HR (95% CI)	
	Long-term Diabetes vs. No Diabetes	Recently Diagnosed Diabetes vs. No Diabetes
Using ≤ 3 years as definition of recently diagnosed diabetes		
Model 1, unadjusted	1.21 (1.06–1.38)	1.09 (0.97–1.21)
Model 2, adjusted for between-study variation	1.22 (1.07–1.39)	1.08 (0.97–1.21)
Model 3: Model 2+ age, sex, race	1.21 (1.06–1.38)	1.07 (0.96–1.20)
Model 4: Model 3+ smoking status, body mass index	1.20 (1.06–1.37)	1.07 (0.96–1.20)
Model 5: Model 4+ stage	1.09 (0.96–1.25)	1.05 (0.94–1.18)
Model 6: Model 5+ surgery and chemo	1.10 (0.97–1.26)	1.06 (0.94–1.18)
Model 6 with varying definitions of recently diagnosed diabetes		
Diagnosed ≤ 1 year before cancer diagnosis	1.09 (0.97–1.22)	1.06 (0.93–1.20)
Diagnosed ≤ 2 years before cancer diagnosis	1.08 (0.95–1.22)	1.07 (0.95–1.21)
Diagnosed ≤ 3 years before cancer diagnosis	1.10 (0.97–1.26)	1.06 (0.94–1.18)
Diagnosed ≤ 4 years before cancer diagnosis	1.13 (0.99–1.30)	1.04 (0.93–1.16)
Diagnosed ≤ 5 years before cancer diagnosis	1.11 (0.96–1.29)	1.06 (0.95–1.18)

TABLE 4

Stratified Analyses of Long-Term Diabetes (>3 Years Duration) and Recently Diagnosed (<3 Years Duration) Diabetes and Survival in Pancreatic Ductal Adenocarcinoma Patients From Three Participating Studies in PanC4

Variable	HR (95% CI)		P for interaction
	Long-term Diabetes vs. No Diabetes	Recently Diagnosed Diabetes vs. No Diabetes	
Sex			0.07
Male	0.99 (0.84–1.18)	0.99 (0.97–1.15)	
Female	1.32 (1.06–1.63)	1.16 (0.97–1.38)	
Stage of disease			0.047
Resectable	1.42 (1.13–1.78)	1.08 (0.89–1.31)	
Locally advanced	1.13 (0.85–1.52)	1.10 (0.87–1.40)	
Metastatic	0.94 (0.77–1.14)	1.01 (0.84–1.20)	
BMI			0.49
< 25 kg/m ²	1.03 (0.84–1.26)	1.01 (0.86–1.17)	
≥ 25 kg/m ²	1.19 (1.00–1.42)	1.09 (0.92–1.29)	

Models adjusted for age, sex, race, smoking status, BMI, stage of cancer, surgery, chemotherapy.