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Diabetes and pancreatic cancer survival: a prospective cohort-based study

A T Toriola[*,1], R Stolzenberg-Solomon[2], L Dalidowitz[1], D Linehan[3] and G Colditz[1]

[1]Department of Surgery, Division of Public Health Sciences, Siteman Cancer Center, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8100, St Louis, MO 63144, USA; [2]Branch of Nutritional Epidemiology, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, 9609 Medical Center Drive, Room 6E420, Rockville, MD 20850, USA and [3]Department of Surgery, Section of Hepato-Pancreatico-Biliary and Gastrointestinal Surgery, Siteman Cancer Center, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8100, St Louis, MO 63144, USA

Background: Diabetes is a risk factor for pancreatic cancer but its association with survival from pancreatic cancer is poorly understood. Our objective was to investigate the association of diabetes with survival among pancreatic cancer patients in a prospective cohort-based study where diabetes history was ascertained before pancreatic cancer diagnosis.

Methods: We evaluated survival by baseline (1993–2001) self-reported diabetes history ($n = 62$) among 504 participants that developed exocrine pancreatic cancer within the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality were estimated using Cox proportional hazards model, adjusted for age, sex, body mass index, race, smoking, and tumour stage (local, locally advanced, and metastatic).

Results: The multivariable-adjusted HR for mortality comparing participants with diabetes to those without was 1.52 (95% CI = 1.14–2.04, P-value < 0.01). After excluding those diagnosed with pancreatic cancer within 3 years of study enrolment, HR for mortality among those with diabetes was 1.45 (95% CI = 1.06–2.00, P-value = 0.02).

Conclusions: Using prospectively collected data, our findings indicate that diabetes is associated with worse survival among patients with pancreatic cancer.

Pancreatic cancer is currently the fourth leading cause of cancer death but is projected to be the second leading cause before 2020 (Pancreatic Cancer Action Network, 2012). In 2013, 45 220 Americans will be diagnosed with pancreatic cancer and 85% (38 460) of them will die from the disease (Siegel *et al*, 2013). Thus, identifying factors that impact pancreatic cancer survival is of utmost priority.

The association of diabetes before pancreatic cancer diagnosis and survival among pancreatic cancer patients is poorly understood, probably, because few studies have investigated this association and most have been clinic-based studies that used retrospectively collected data or limited their analyses to pancreatic cancer patients who underwent surgical resection (McWilliams *et al*, 2010; Olson *et al*, 2010; Dandona *et al*, 2011; Hwang *et al*, 2013), although diabetes has been associated with an increased overall mortality (Seshasai *et al*, 2011). Another challenge is establishing the temporality of association between diabetes and pancreatic cancer in relation to survival because of the bidirectional relationship between diabetes and pancreatic cancer. To have a better understanding of whether diabetes impacts pancreatic cancer survival, the association of diabetes with pancreatic cancer survival should be evaluated in cohort studies where diabetes history is prospectively collected before pancreatic cancer diagnosis but these studies are lacking.

*Correspondence: Dr AT Toriola; E-mail: a.toriola@wustl.edu

We investigated the association of diabetes with survival among pancreatic cancer patients in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, where history of diabetes was ascertained before pancreatic cancer diagnosis. This knowledge could be useful in the clinical management and risk stratification among pancreatic cancer patients. In addition, it could provide an insight into possible mechanistic pathways that might impact survival among patients with pancreatic cancer.

MATERIALS AND METHODS

Design overview, study subjects, and endpoints. The PLCO Cancer Screening Trial is a randomized, two-armed, controlled trial designed to determine the effects of screening on disease-specific mortality for cancers of the prostate, lung, colorectal, and ovaries. The PLCO study design and characteristics of the participants have been described in detail elsewhere (Zhu *et al*, 2013). Briefly, the PLCO enroled 154 901 men and women aged 55–74 years from 10 centres in the United States between November 1993 and July 2001 (Zhu *et al*, 2013). Study participants filled a baseline questionnaire at study entry where they provided demographic, personal, and medical information, including history of diabetes.

Each eligible participant provided written informed consent. Pancreatic cancer diagnoses were determined from yearly questionnaires completed by participants or next of kin as well as state registries, death certificates, and physician reports and confirmed by PLCO staff (Oaks *et al*, 2010). At the time of last follow-up in December 2010, 627 primary newly diagnosed exocrine pancreas cancer cases had been identified. Pancreatic cancer stage was abstracted at the PLCO centres in categories of localised, locally advanced, and metastatic in 2010 from previously collected pathology reports and medical records used for cancer confirmation. As stage is an important prognostic factor, we decided *a priori* to include only those with information on tumour stage in our analyses. Tumour stage was classified as (i) local disease amenable to surgical resection; (ii) locally advanced disease with extra-pancreatic extension not amenable to surgical resection, but without distant metastases; and (iii) distant metastatic disease. The American Joint Committee on Cancer (AJCC)/International Union for Cancer Control (IUCC) tumour-lymph nodes-metastasis (TNM) staging was converted to the above categories. The AJCC/IUCC stages I and II corresponds to local disease, stage III corresponds to locally advanced disease, and stage IV corresponds to metastatic disease. We excluded participants with missing information on tumour stage ($N = 95$) and diabetes ($N = 28$). Therefore, our final analytic cohort for this study consisted of 504 exocrine pancreas cancer cases (437 were pancreatic ductal adenocarcinomas, PDAC). Baseline characteristics were similar for those who had information on tumour stage and those who did not. For instance, 14% of those with no information on stage had a positive history of diabetes compared with 12% of those with information on stage (*P*-value = 0.30).

Information on deaths and causes of death were obtained by linking the study population to the National Death Index (Miller *et al*, 2000). The institutional review boards of the National Cancer Institute and each of the centres that participated approved the study.

Statistical analysis. We compared baseline characteristics of participants who developed pancreatic cancer by diabetes history using χ^2-test for categorical variables and Wilcoxon Rank test for continuous variables. Survival was calculated from the day of pancreatic cancer diagnosis to the day of death or

December 2010, whichever came first. We used Cox proportional hazards model to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) of pancreatic cancer mortality by diabetes status. We first adjusted the model for age and tumour stage. In multivariable adjusted model, we adjusted for age, sex, body mass index (BMI), smoking status, race, and tumour stage. We conducted analyses stratified by sex and stage. Sex and stage were excluded from multivariable models stratified on these variables. Furthermore, because pancreatic cancer-induced diabetes could start 2 years before a diagnosis of pancreatic cancer is made, we conducted sensitivity analysis excluding participants who developed pancreatic cancer within 3 years of enrolment.

Survival curves were generated using Kaplan–Meier method. The proportional hazard assumption was tested and satisfied through the use of time-dependent covariate method. Statistical analyses were performed using SAS 9.3 statistical package (SAS Institute, Cary, NC, USA). Statistical significance was set at $P < 0.05$ and all *P*-values are two-sided.

RESULTS

Median age at baseline examination was 64 years. Baseline characteristics, by diabetes history, are listed in Table 1. Of the 504 participants with incident exocrine pancreatic cancer, 62 (12%) reported a history of diabetes before pancreatic cancer diagnosis. Participants with diabetes were comparable with those without diabetes for most characteristics except BMI. At the end of the follow-up period, 91% of the participants ($N = 460$) had died. Median survival was shorter for those with diabetes (92 days) than for those without diabetes (139 days, *P*-value 0.05). Death fractions for diabetic/non-diabetic patients were 92% *vs* 91%. Most of the deaths among people with diabetes occurred during the first 500 days of follow-up (Figure 1).

The majority (93%) of participants had pancreatic cancer listed as the cause of death on their death certificates (95% among those with diabetes and 93% among those without diabetes). Some other causes of death listed include ischaemic heart disease (four among those without diabetes and one among those with diabetes), cerebrovascular disease (four among those without diabetes and one among those with diabetes).

A history of diabetes was associated with reduced survival (Figure 1). In multivariable adjusted Cox regression model, the HR for mortality comparing those with diabetes to those without diabetes was 1.52 (95% CI = 1.14–2.04, *P*-value < 0.01) (Table 2). In analyses stratified by tumour stage, diabetes was associated with a 2.3-fold (95%CI = 1.16–4.58) and 1.5-fold (95% CI = 1.04–2.24) greater mortality among those with localised and metastatic diseases, respectively, but not among those with locally advanced disease (HR = 1.17, 95% CI = 0.62–2.20). In sensitivity analysis excluding participants who developed pancreatic cancer within 3 years of enrolment, diabetes was associated with increased hazard of mortality (HR = 1.45, 95% CI = 1.06–2.00, *P*-value = 0.02).

The results were identical in analysis limited to participants with PDAC ($n = 437$) (Supplementary Table 1).

DISCUSSION

In this prospective cohort-based study, we observed that participants who reported having diabetes before being diagnosed with pancreatic cancer had worse survival compared with those who did not have diabetes.

Table 1. Characteristics of participants with exocrine pancreatic cancer ($N=504$)[a] who had available information on tumour stage in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial by diabetes history			
Characteristics	**No history of diabetes, N (%)**	**Positive history of diabetes[b], N (%)**	**P-value**
Age at baseline			0.95
⩽59	100 (22.62)	12 (19.35)	
60–64	127 (28.73)	19 (30.65)	
65–69	122 (27.60)	18 (29.03)	
⩾70	93 (21.04)	13 (20.97)	
Gender			0.51
Male	237 (53.62)	36 (58.06)	
Female	205 (46.38)	26 (41.94)	
Race			0.69
White, non-hispanic	380 (85.97)	52 (83.87)	
Black, non-hispanic	23 (5.20)	4 (6.45)	
Hispanic	6 (1.36)	2 (3.23)	
Other	33 (7.47)	4 (6.45)	
Body mass index at baseline			<0.01
$<25\,kg\,m^{-2}$	163 (37.30)	9 (14.75)	
$25–29.99\,kg\,m^{-2}$	179 (40.96)	35 (57.38)	
$30–34.99\,kg\,m^{-2}$	78 (17.85)	12 (19.67)	
$⩾35\,kg\,m^{-2}$	17 (3.89)	5 (8.20)	
Smoking status at baseline			0.68
Never smoker	178 (40.27)	23 (37.10)	
Current smoker	83 (18.78)	10 (16.13)	
Former smoker	181 (40.95)	29 (46.77)	
Pack years of smoking			0.49
Never smoker	178 (40.27)	23 (37.10)	
<10	36 (8.14)	5 (8.06)	
10–20	43 (9.73)	3 (4.84)	
>20	185 (41.86)	31 (50.00)	
Mortality status			0.84
Dead	403 (91.18)	57 (91.94)	
Alive	39 (8.82)	5 (8.06)	
Cancer stage			0.35
Localised	78 (17.65)	15 (24.19)	
Locally Advanced	121 (27.38)	13 (20.97)	
Metastatic	243 (54.98)	34 (54.84)	
Median survival (days)	139	91.5	0.05

[a]A total of 504 participants who developed pancreatic cancer after enrolment had information on tumour stage.
[b]A total of 62 participants who developed pancreatic cancer reported a history of diabetes before cancer diagnosis.
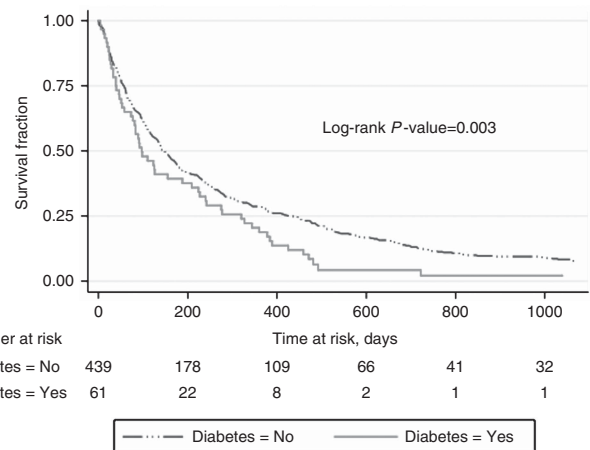

Figure 1. Kaplan–Meier survival curves: exocrine pancreas cancer.

Table 2. Associations of diabetes with mortality among participants with exocrine pancreatic cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial			
	No history of diabetes HR (95% CI)	**Positive History of diabetes HR (95% CI)**	**P-value**
All exocrine pancreas cancer ($N=504$)			
Model 1[a]	1.00 (ref)	1.44 (1.09–1.91)	0.01
Model 1[b]	1.00 (ref)	1.52 (1.14–2.04)	<0.01
Excluding pancreatic cancer cases diagnosed within 3 years of enrolment ($N=404$)			
Model 1[a]	1.0 (ref)	1.40 (1.03–1.91)	0.03
Model 1[b]	1.0 (ref)	1.45 (1.06–2.00)	0.02
Among males ($N=272$)			
Model 1[a]	1.0 (ref)	1.46 (1.01–2.18)	0.05
Model 1[b]	1.0 (ref)	1.69 (1.15–2.50)	0.01
Among females ($N=231$)			
Model 1[a]	1.0 (ref)	1.42 (0.92–2.20)	0.12
Model 1[b]	1.0 (ref)	1.33 (0.82–2.16)	0.25
Localised ($N=93$)			
Model 1[b]	1.0 (ref)	2.31 (1.16–4.58)	0.02
Locally advanced ($N=133$)			
Model 1[b]	1.0 (ref)	1.17 (0.62–2.20)	0.65
Metastatic ($N=277$)			
Model 1[b]	1.0 (ref)	1.52 (1.04–2.24)	0.03

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a]Adjusted for age and stage.
[b]Adjusted for age, sex, body mass index (BMI), race, smoking, and stage. Sex and stage not adjusted for in analyses stratified on these variables.

Previous studies have evaluated the associations of diabetes with survival among pancreatic cancer patients using retrospectively collected data and among patients who underwent surgical resection, with conflicting results (Chu et al, 2010; McWilliams et al, 2010; Olson et al, 2010; Dandona et al, 2011; Hwang et al, 2013). In a large study conducted within the United Kingdom, there was no survival difference between those with diabetes and those without (Hwang et al, 2013). However, the authors reported increased pancreatic cancer mortality among those who had long-term diabetes (>5 years). Diabetes was not associated with survival from pancreatic cancer in three clinical studies (McWilliams et al, 2010; Olson et al, 2010; Dandona et al, 2011).

Our study underscores the need for prospective studies to evaluate the associations of diabetes with survival among pancreatic cancer patients. In the Cancer Prevention Study II (CPS II), a history of diabetes was associated with higher death rates (Calle et al, 1998) but the analyses did not take into account tumour stage.

Experimental studies suggest that diabetes can impact pancreatic cancer survival through its effect on glucose metabolism and insulin resistance-related metabolic markers. There is emerging evidence that diabetes alters, and reprograms the intracellular metabolic environment to a metabolism more favourable to proliferation (Regel et al, 2012; Sah et al, 2013). Kras, p53, and c-Myc pathways impact pancreatic cancer proliferation and studies have shown that these pathways also affect energy metabolism by influencing glucose and glutamine utilisation (Regel et al, 2012). In addition, hyperinsulinaemia enhances pancreatic cell proliferation and invasiveness either directly or indirectly through its effects on insulin-like growth factor (IGF) pathway. Metformin, an anti-diabetic drug, has been shown to improve survival among pancreatic cancer patients (Sadeghi et al, 2012), possibly via its impact on insulin/IGF-I signalling (Rozengurt et al, 2010). Median overall survival was 15.2 months among pancreatic cancer patients treated with metformin compared with 11.1 months among the non-metformin group (Sadeghi et al, 2012). A better understanding of the biological mechanisms driving the association between diabetes and pancreatic cancer survival could provide insights into the development of targeted therapies for some pancreatic cancer patients.

Another possible explanation for the worse survival may be because diabetics have more comorbidities, especially cardiovascular comorbidities, than those without diabetes. These comorbidities might put those with diabetes at a survival disadvantage directly or indirectly as physicians may be less likely to use aggressive chemotherapy on patients with diabetes because of the comorbidities. Hence, diabetes status may be driving aggressiveness of treatment decisions. Nevertheless, in our study cohort, pancreatic cancer was reported as the cause of death in 95% of participants with diabetes and 93% of participants without diabetes and there appears to be no difference in death due to ischaemic heart disease and cerebrovascular accident between the two groups. Further, we had no information available on the history of chronic pancreatitis. The worse survival among those with diabetes could also be related to later stage at diagnosis, although information on tumour staging in our data does not support this.

The major strength of our study is its prospective nature. Information on diabetes was collected before pancreatic cancer diagnosis. In addition, we adjusted for stage, which is an important determinant of pancreatic cancer survival. Our study has the following limitations. A sizeable proportion of diabetes may be undiagnosed. Using haemoglobin A1C concentrations as a diagnostic test, up to 19% of people with diabetes in the United States are undiagnosed (Cowie et al, 2010). Because history of diabetes was based on self-report, prevalence of diabetes in our study population would have been underestimated; hence some participants with diabetes would have been misclassified as not having diabetes. Any misclassification, though, would have been non-differential. Finally, because PLCO is a multicenter study, patients diagnosed with pancreatic cancer were treated at different hospitals in different geographical locations; hence, treatment programs which were likely to vary among patients could have contributed to differences in survival but we had no information on the treatment programs, particularly surgery, received by the patients.

In conclusion, this survival analysis using incident cases ascertained from the PLCO prospective cohort, a history of diabetes before pancreatic cancer diagnosis was associated with higher mortality among pancreatic cancer patients. Studies characterising the molecular mechanisms driving this association are needed as these can provide insights into relevant pathways that could be targeted for possible therapeutic interventions.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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