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EDITORIAL

Diabetes Type 2 and Pancreatic Cancer: A History Unfolding

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ABSTRACT

Pancreatic Cancer is the fourth cause of cancer-related deaths in the United States. Up to 80% of pancreatic cancer patients present with either new-onset type 2 diabetes or impaired glucose tolerance at the time of diagnosis. Recent literature suggests that diabetes mellitus type 2 is a risk factor, a manifestation and a prognostic factor for pancreatic cancer. This article is intended to clarify the evidence about diabetes as a risk factor for pancreatic cancer.

INTRODUCTION

Ductal adenocarcinoma of the pancreas is the fifth leading cause of death related to cancer in developed countries after lung, stomach, colorectal and breast cancer, with 23% of the patients alive 1 year after diagnosis and a 5 year survival rate of 6% mostly due to advanced stage at the time of the diagnosis [1]. It is the thirteenth most common type of cancer worldwide and the eight most common cause of cancer-related deaths [2]. It is the fourth cause of cancer-related deaths in the United States, with a lifetime risk of 1.32% and annual incidence of 11.4 per 100,000[1, 3]. Up to 80% of pancreatic cancer patients present with either new-onset type 2 diabetes or impaired glucose tolerance at the time of diagnosis [4]. This article is intended to clarify the evidence about diabetes as a risk factor for pancreatic cancer.

Ductal Adenocarcinoma Risk Factors

Carcinogen exposure is a major modifiable risk factor for pancreatic cancer. Tobacco smoke is responsible for 20% to 30% of pancreatic cancers [5]. Smoking cessation can decrease the risk to close to a never-smoker after 5 years [6]. Environmental tobacco smoke increases the risk of ductal adenocarcinoma, especially if exposure starts in childhood [6]. Data from the Nurses' Health Study suggests that in utero exposure to smoking is a risk factor for pancreatic cancer [7]. Occupational exposures, especially chlorinated hydrocarbon and organochloride compounds have been linked to pancreatic cancer [8, 9].

Infections and inflammation of the pancreas have been associated with pancreatic cancer. There is a possible association of Helicobacter pylori and pancreatic cancer [10]. Hepatitis B but not hepatitis C is a risk factor for pancreatic cancer [11]. Chronic pancreatitis, hereditary pancreatitis and tropical pancreatitis have been defined as risk factors for pancreatic cancer [12, 13].

Older age, African-American race and Ashkenazi Jewish heritage are consolidated non-modifiable risk factors for pancreatic cancer [14]. Familial history plays a role in 10-20% of ductal adenocarcinoma of the pancreas. Although sporadic pancreatic cancer (none or one first-degree relative with pancreatic cancer) does not increase the risk for pancreatic cancer, familial pancreatic cancer (two or more first-degree relatives affected) imparts a18.3 observed to expected ratio (CI 4.74-44.5) to ductal adenocarcinoma of the pancreas [15]. The wide confidence interval above can be a result of different genes or epigenetic influences in the risk of familial pancreatic cancer, although none of the established genes (BRCA2, DPC4, pp16) were present in the cohort followed by that study[15]. That is especially insightful considering 90% of all cases of pancreatic cancer have p16 mutations and 50% have DPC4 mutations [16]. However, in less than 20% of the cases familial pancreatic cancer is associated with a germline mutation rendering a genetic syndrome **(Table 1).** Patients with BRCA2 mutations, the most common genetic alteration in familial pancreatic cancer, may have increased susceptibility to platinum analogues and mitomycin C [17]. Patients with genetic syndromes predisposing to pancreatic cancer and

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Table 1. Genetic syndromes associated with familial pancreatic cancer.

Syndrome	Gene mutation	Relative risk to DPAC
Familial breast cancer	BRCA2	3.5 to 10 fold [19]
	PALB2	
Familial atypical multiple mole	p16	12 to 20-fold [20]
Melanoma		
Peutz-Jeghers	STK11/LKB1	100-fold [21]
Hereditary nonpolyposis	hMSH2,hMLH1	Up to 8.6-fold [22]
colorectal syndrome		
Hereditary pancreatitis	PRSS1	50-fold [23]
	SPINK1	
Ataxia-telangiectasia	ATM	2.4-4.8-fold [24]

more than two relatives with pancreatic cancer should be screened for pancreatic cancer with endoscopic ultrasound [18]. Obesity and the metabolic syndrome increase the risk for pancreatic cancer [25, 26]. Fatty infiltration of the pancreas and steatopancreatitis have been linked to pancreatic cancer [27].

Is Diabetes Mellitus a Risk Factor or an Earlier Marker for Pancreatic Cancer?

When diagnosed 1 year previous to pancreatic cancer, diabetes imparts a 2-fold relative risk for developing ductal adenocarcinoma of the pancreas [28]. When diabetes had been diagnosed for less than 4 years, patients had a 50% greater risk of pancreatic cancer compared with individuals who had diabetes for more than 4 years (OR 2.1 *vs*. 1.5; P=0.005) [29]. Diabetes and impaired glucose tolerance (IGT) are present in 80% of the patients with ductal adenocarcinoma of the pancreas [30].

The low prevalence of pancreatic cancer in the general population means that even a highly sensitive and specific test for DPAC would result in a high false positive rate, rendering new-onset diabetes an attractive screening tool for sporadic pancreatic cancer [31]. Pannala *et al*. suggest that the association of new-onset diabetes with a biomarker could be used to screen patients older than 50 years-old to endoscopic ultrasound confirmation of ductal adenocarcinoma of the pancreas. However, the most promising biomarker of pancreatic cancer associated with diabetes, connexin26, has no development since 2004, although its expression in ductal adenocarcinoma and prognostic value has been confirmed [32]. However, prospective studies involving a large population is essentially needed.

It has been hypothesized that the increased risk of diabetes in the first 10 years after diagnosis actually is a consequence of asymptomatic pancreatic cancer. However, cohorts such as Calle *et al*. have been trying to disprove this, proving that diabetes mellitus type 2 is really a cause, not a consequence of pancreatic cancer. Nevertheless, ductal adenocarcinoma of pancreas can induce peripheral insulin resistance [33]. Furthermore, pancreatic cancer resection can resolve diabetes, fueling even further the debates over the origin of pancreatic cancer-associated Diabetes [34].

The **Table 2** offers a chronologic landscape of the understanding of the association of diabetes mellitus and pancreatic cancer. As in any subject, case-control studies offer less statistical power than well-designed cohort studies and meta- analyses offer the strongest evidence of all. Caution is advised while interpreting the following meta-analysis as they grouped cohorts and case-controls or were designed from retrospective studies.

The Prognostic Significance of Diabetes in Ductal Pancreatic Adenocarcinoma

In 2011, in a case control performed by Dehayem *et al*., Diabetes did not seem to contribute to earlier diagnosis, clinical features, tumor size or prognosis of pancreatic cancer [48]. However, previous studies have established pancreatic cancer as a prognostic factor [49]. Following a surgical database covering 11 years of resected pancreatic adenocarcinoma at MD Anderson, Busaidy *et al*. compared diabetic and non-diabetic patients and found a worse overall mortality and median survival in diabetic patients [50]. A retrospective study utilizing the Veterans Affairs Central Cancer Registry collected data from 1995 and 2008 and compared survival data between patients with and without diabetes mellitus. In that study, patients with diabetes had a better overall survival [51]. On the other hand, Shama *et al*. showed that diabetes mellitus confers a poor survival to pancreatic cancer patients [52]. The baseline characteristics of those populations should be taken in account when interpreting these results. The gender and mean age of the two studies influences the number of comorbidities,duration of diabetes and thus time for development of diabetes complications, factors that influence peri-operative and cardiovascular mortality, as well as performance status [53]. Moreover, the distinct metrics used to assess (median survival and overall survival) outcomes preclude immediate conclusions. As an example, having diabetes in the Veterans Affairs system, where an emphasis in preventive medicine is practiced, could translate into more frequent clinical follow-up and earlier diagnosis of ductal pancreatic adenocarcinoma than in the overall population, generating a lead-time bias that cofound the median survival. Besides, overall survival includes cancer-related and other causes of death and the abovementioned comorbidities, as well as the absolute perioperatory and cardiovascular mortality should be discriminated in the presentation of the study.

Future Perspectives

The elucidation of the hormonal [54], paracrine [55] and autocrine [56, 57] mediators of pancreatic cancer and its relationship to new-onset diabetes will clarify the pathogenesis and/or natural history of ductal adenocarcinoma of pancreas, defining new targets for therapy. A better definition of the epidemiology of pancreatic cancer, defining if poorly controlled diabetes (and its metabolic derangements) or if an intrinsically genetic [58], epigenetic [59, 60, 61], immunologic [62, 63], gastrointestinal microbiota [64, 65] or tissue microenvironment characteristic of Diabetes Mellitus

Table 2. Studies favoring Diabetes as a consequence of pancreatic cancer.

Study	Year	Type	Population	Relevant result	Control
Blot *et al.* [35]	1978	Cross-sectional	The whole 3,056 counties of US	In females, Diabetes Mellitus (DM) was correlated with DPAC	N/A
Cuzick *et al.* [36]	1989	Case-control	216 (DPAC)	DM diagnosed in year previous to DPAC diagnosis imparts RR= 4.1	279
Permet *et al.*	1993	Cohort	36 (DPAC)	75% of DPAC patients had diabetes or IGT	8
Balkau *et al.* [37]	1993	Cohort (17 years f/u)	6,988	After excluding first 5 years of follow-up, Diabetes RR for DPAC was 4.1 (684 IGT 5,992 normoglycemic as controls)	6,676
Vecchia *et al.* [38]	1994	Case-control	9,991	RR: 2.3 for DPAC in patients with Diabetes (declines after 5 years)	7,834*
Gullo *et al.* [39]	1994	Case-control	720 (DPAC)	In DPAC, Diabetes was diagnosed concomitantly in 40% of the cases	720
Evehart *et al.*	1995	Case-control		Diabetes> 5 years results in RR of 2 for pancreatic cancer	
Lee *et al.* [40]	1996	Case-control	282 (DPAC)	Diabetes RR 2.8 for pancreatic cancer in Asians	282
Calle *et al.*[41]	1998	Cohort (12 years f/u)	1,08,89,586	Diabetes confers RR for DPAC that decreases but it is still 40% higher from 9 to 12 years of f/u	NA
Silverman *et al.* [42]	1999	Case-control	484 (DPAC)	No trend in risk for DPAC in Diabetes on insulin compared not on insulin	2099
Huxley *et al.*	2005	Meta-analysis (17 case-controls and 19 cohorts)	9220 (1,299 in the cohort)	Diabetes durations <5 years imparts 50% higher risk for DPAC than Diabetes duration >5 years	7,896
Gupta *et al.* [43]	2006	Cohort	1421794 Veterans	New-onset Diabetes (2 years or less) confers RR of 2.2 for DPAC.Controls were new-onset diabetes.	36,631
Pannala *et al.* [44]	2008	Case-control	512	75% of the Diabetes casesIn DPAC patients were new onset (<2 years from diagnosis)	933
Chari *et al.* [45]	2008	Case-control	1172	Diabetes is more commonly diagnosed in the 3 years prior to DPAC diagnosis	Healthy (2344)
Li *et al.* [46]	2011	Meta-analysis (3)	2,192	Diabetes diagnosed for >10 years is still a risk factor for DPAC	5,113
Ben *et al.* [47]	2011	Meta-analysis (35)		Diabetes duration < 1 year carries the strongest risk for DPAC	

N/A non applicable F/u: follow-up

type 2 [66, 67, 68, 69] patients crossroads with pancreatic cancer molecular pathways will redefine therapeutic targets. Gene sequencing, mRNA profiling, lymphocyte flow cytometry, microbe identification microarray and PCR studies comparing Diabetes type 2 patients in different stages of natural history (measured as time for diagnosis and diabetic concurrent complications) will outline molecular overlaps between pancreatic cancer and diabetes.

Molecular biomarkers will be crucial to determine which patients with new-onset diabetes should be screened with endoscopic ultrasound for pancreatic cancer [70]. Also, hyperinsulinemia can have negative predictive value if other hormonal, paracrine or autocrine molecules are found to play a role alternative to insulin resistance in the development of new-onset diabetes associated with pancreatic cancer [71].

Metformin is a classic example of where the field is heading, where defining a disease and prognostic risk factor leads to a question if its therapy improve outcomes. Metformin improves survival in pancreatic cancer and is a prognostic factor [72]. In a reverse case of tumor biology charting, the acquired knowledge of the mechanism of action of metformin is expanding the understanding of the ductal adenocarcinoma of the pancreas cancer pathways. This is serendipitous as the FDA has been emphasizing the role of genomic technologies in repurposing and repositioning drugs in an era of increased costs in drug development [73].

Executive Summary

Diabetes Mellitus type 2 is a risk factor, a manifestation and a prognostic factor for pancreatic cancer. The development of molecular biomarkers that distinguish new-onset diabetes from incidental long-term diabetes in patients older than 50 years will change current paradigms on pancreatic cancer screening, especially if associated with endoscopic ultrasound confirmation. The current advances in genomics, epigenomics, human microbiota and immunology will use the guidance of epidemiologic studies in order to detail pancreatic adenocarcinoma molecular pathways and prospective treatment targets, designing better drugs and refining the population selection for therapies.

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Conflict of Interests

Authors declare no conflict of interests for this article.

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