

## Review Article

# Relationship between diabetes mellitus and the risk of pancreatic cancer

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**Abstract:** Patients with pancreatic cancer (PaC) are typically not diagnosed until the disease is at a surgically unresectable advanced stage, making it one of the most lethal malignancies worldwide. Patients with diabetes mellitus (DM), a disease that is increasing in prevalence worldwide, are two to three times more likely to develop PaC. Here, we review the clinical links between DM and PaC and the biological mechanisms that may contribute to these links. In particular, we examine molecular pathways that potentially account for development of PaC in patients who have had DM for various amounts of time. In addition, we also briefly discuss the potential effects of other factors such as different anti-diabetic medicines on PaC risk. Observational studies indicate that newly developed DM may be a manifestation of PaC and that the risk for this cancer is increased in long-term cases. Notably, development of PaC may be inhibited by using anti-diabetic medications, such as metformin. However, DM in long-term patients is more likely to be managed with insulin therapy, which is associated with an increased risk for developing PaC. How incretin-based drugs and thiazolidinediones impact the incidence of PaC remains unclear. Thus, further research is needed to elucidate these relationships and to determine the causality and impact of DM severity and disease duration as well as residual biases and misclassifications.

**Keywords:** Diabetes mellitus, pancreatic cancer, hypoglycemic drugs

### Introduction

Patients with pancreatic cancer (PaC) are typically not diagnosed until the disease is at a surgically unresectable advanced stage [1, 2], making it one of the most lethal malignancies worldwide. A 3-decade-long study in France estimated that the 5-year survival after diagnosis is <5% [1]. Moreover, PaC mortality rates have been increasing in patients of both sexes over the past several decades [3, 4]. Therefore, early identification in individuals with a high risk for developing PaC could markedly reduce the associated morbidity and mortality [5].

Although the epidemiology of PaC remains unclear, there are data indicating that in addition to a family history of PaC and certain genetic disorders, obesity, cigarette smoking, alcohol consumption, chronic pancreatitis, and hepatitis B virus infection are contributors [6-11]. Additionally, a link with diabetes mellitus (DM) has been examined, beginning as early as

1833 [12-15]. DM is a considerable public health issue in industrialized and developing countries and may increase the risk of breast, colorectal, bladder, and liver cancers [16-19]. The causal link between DM and PaC has been debated, as there is evidence that DM may develop early as a result of PaC [20, 21]. This clinical review presents the most recent epidemiological evidence linking DM and PaC and the potential molecular mechanisms by which these influence each other. The influence of anti-diabetic medications (ADMs) on PaC risk is also discussed.

### Epidemiology

#### *Association between DM and PaC*

As mentioned, the link between PaC and DM has been a matter of study for quite some time [14, 15, 22]. The risk for patients with DM to develop PaC is 2 to 3 times that in nondiabetics [5, 9, 23, 24], with higher risks in those of Asian

descent and Hispanic men than in whites or blacks [25]. In a study by Everhart and Wright [13], the pooled relative risk of PaC for patients with DM was 2.1 (95% confidence interval [CI]: 1.6-2.8) relative to nondiabetics. In the Netherlands, a prospective study found that DM was positively associated with PaC risk (multivariable-adjusted hazard ratio [HR], 1.79; 95% CI: 1.12-2.87) [26], which was in accordance with the findings from an earlier meta-analysis conducted by Ben et al. [5]. The higher risk for PaC in DM involves both type I and type II diabetes [25, 27-29]. In addition, various pathological types of PaC are associated with DM. Specifically, Batabyal et al. [28] found a 1.97-fold risk of pancreatic ductal adenocarcinoma in patients with DM in a meta-analysis of 88 studies, and Haugvik et al. [29] found that DM was linked with the development of sporadic pancreatic endocrine tumors.

### *Association between duration of DM and PaC*

Long-standing diabetes has been linked with PaC in at least 20 studies conducted over many years in various populations [13-15]. A population-based case-control study by Silverman et al. [30] found that the risk for PaC was increased by 50% in patients from three different areas in the United States who have been diabetic for at least 10 years, whereas the increase was not significant in those recently diagnosed with DM (within one year of the cancer diagnosis). Bosetti et al. [31] analyzed 15 studies within the PaC Case-Control Consortium and found that the increased risk (30%) was maintained for more than 20 years after a diagnosis of DM. Indeed, the meta-analysis by Everhart and Wright [13] revealed a relative risk of 2.0 (95% CI: 1.2-3.2) for PaC when DM was diagnosed at least 5 years earlier. The risk was higher in cohort studies using the pooled estimate (relative risk, 2.6) than in case-control studies (odds ratio, 1.8).

There are also data contradicting the influence of long-standing DM on the development of PaC [32-34]. Frye et al. [35] found that the prevalence of cases with prolonged DM was not higher among PaC patients than among patients with colorectal cancer or fractured femurs. Another population-based cohort study by Liao et al. [36] showed that PaC was associated with DM of a duration of <2 years, but not

long-standing disease, in patients in Taiwan, suggesting that DM may represent an early manifestation of PaC, in accordance with results from other studies [21]. Similarly, Grote et al. [37] reported that DM often manifests shortly before pancreatic tumors are diagnosed. In the study by Batabyal et al. [28], the risk for PaC was highest in patients with recent DM diagnoses but remained high for up to 10 years after, with a relative risk of 6.69 when DM was diagnosed within 1 year that decreased to 1.36 after 10 years. In patients with type II DM, those with a diagnosis <2 years before their cancer was detected had an incidence of PaC that was significantly higher than that in patients diagnosed 2-5 years earlier [38].

Thus, there are data indicating that patients with long-standing DM have a higher risk of PaC, suggesting that DM may lead to PaC while providing evidence against the reverse. For example, it is unlikely that the DM in a patient with long-standing disease was caused by advanced PaC, when the 1-year survival is <20% [13]. Nevertheless, DM is often diagnosed around the time that PaC is diagnosed [21, 39]. The inconsistencies among studies make it difficult to discern whether DM is in fact causing PaC or results from subclinical PaC [40].

### **Mechanisms linking DM and PaC**

#### *Mechanism of DM-associated pancreatic carcinogenesis*

The link between DM and the development of PaC involves (i) metabolic, (ii) hormonal, and (iii) immunologic alterations. First, obesity is a risk factor for both DM [41] and PaC [42]. Specifically, body mass index was found to contribute to the link between DM and PaC risk, most notably in patients with a low body mass index (170% increased risk for those in the lowest quartile) [30]. Second, DM involves insulin resistance, compensatory hyperinsulinemia, and upregulation of insulin-like growth factor-1 (IGF-1), and insulin promotes the growth of PaC cells via autocrine activation of the IGF-1 receptor [43]. Activation of the highly expressed IGF-1 receptor in PaC cells suppresses apoptosis and promotes their proliferation and invasion as well as angiogenesis [44]. Third, glucose levels (both fasting and postprandial) show a dose-dependent association with PaC

risk [45, 46]. Together, these findings indicate a causal role of DM for the development of PaC.

#### *Mechanism of pancreatic carcinogenesis-associated DM*

The association between PaC and the development of DM also involves hormonal alterations related to insulin resistance and cell alterations. For example, the islet amyloid polypeptide that is secreted by B-cells [47] induces insulin resistance *in vitro* and *in vivo* [48, 49], and PaC plasma samples from patients with diabetes have increased levels of this peptide, as shown by Permert and colleagues [50]. In patients with PaC, the development of DM may require peripheral insulin resistance [51]. This PaC-associated insulin resistance may involve the blockade of insulin receptors and subsequent impaired glucose transport, as suggested by results from *in vitro* studies [52, 53]. Moreover, PaC cells may secrete factors that contribute to this and can induce hyperglycemia in mice [8, 54]. One such factor may be a 2,030 MW peptide that was identified in sera from PaC patients as well as in the medium from cultured PaC cells [55]. Finally, there is evidence that the function of pancreatic beta cell islets can be comprised by developing tumors [47], resulting in reduced insulin secretion and the development of hyperglycemia.

#### **ADMs and PaC**

Increasing evidence from experimental and epidemiologic studies indicates that the development of PaC is modified with conventional oral ADM or insulin treatments [31]. The effects from various ADM treatments in DM patients on the development of PaC is reviewed in this section.

#### *Metformin*

For the treatment of type II DM, the biguanide oral hypoglycemic metformin is commonly prescribed. Metformin increases fatty acid oxidation and glucose utilization via the decreased production of glucose in the liver [23]. Its ability to suppress the development of PaC was suggested by several recent pooled case-control studies [23, 56, 57]. One such study by Li et al. [23] at a cancer center in Texas showed that the risk for PaC in DM patients treated with metformin was significantly lower, with an

adjusted odds ratio of 0.38 (95% CI: 0.22-0.69) that took into consideration demographic, clinical, and risk factors. Similarly, Lee et al. [57] found a benefit from metformin over other anti-hyperglycemics in Taiwanese patients by calculating the Charlson comorbidity index, with an HR for PaC of 0.15 (95% CI: 0.03-0.79).

There are a couple of possible explanations for the protection against PaC afforded by metformin. First, metformin systemically improves insulin sensitivity and promotes weight loss [58], and by reducing the level of circulating insulin, it was shown to block tumor development in a model of PaC induced by a high-fat diet and carcinogens [59]. Second, metformin stimulates adenosine monophosphate activated protein kinase, which inhibits the downstream mTOR pathway often activated in malignant cells [60, 61] and is involved in the polarity and division of cells [62]. Thus, metformin may exhibit antineoplastic effects systemically, via altering insulin sensitivity, and more directly, by acting on growth factor signaling pathways in cancerous cells.

Despite evidence for a lower PaC risk, other studies have failed to find a benefit from metformin. For example, Singh et al. [63] found only a slight trend towards a lower risk in metformin-treated patients. In addition, Ferrara et al. [64] found a slightly higher risk for PaC in patients who had a history of having taken metformin. These discrepancies may result from variability in the severity and/or duration of disease in the DM patients studied.

#### *Thiazolidinediones (TZDs)*

Patients with type II DM are also treated with thiazolidinediones (TZDs), which are agonists of peroxisome proliferator-activated receptors (PPARs) and act as insulin sensitizers. TZDs can inhibit pancreatic cell proliferation *in vitro* [65-67] and the invasiveness of PaC *in vivo* [68]. However, the link between TZDs and PaC risk is unclear, with conflicting results from clinical trials and epidemiologic data [69-74]. This may be due in part to the complexity of the actions of PPARs. For example, as a nuclear receptor, PPAR- $\gamma$  regulates gene transcription in cells of several tissue types. Although some animal toxicity studies indicate that PPAR- $\gamma$  and dual PPAR- $\alpha/\gamma$  agonists can increase cancer risk,

there are most studies suggesting that PPAR- $\gamma$  activation inhibits tumor growth [75].

As a type of malignancy, PaC cells proliferate uncontrollably and invade adjacent tissues [76]. These characteristics may be attenuated by PPAR- $\gamma$  activation [77, 78]. Activated PPAR- $\gamma$  binds preferentially to the retinoid X receptor  $\alpha$  to stimulate pathways that inhibit cell proliferation and differentiation. Interestingly, synthetic PPAR- $\gamma$  ligands can also influence cell growth independent of PPAR- $\gamma$  activation [79, 80].

A study by Ninomiya et al. [81] found enhanced cellular differentiation and reduced expression of angiogenesis-associated proteins in PaC cells treated with the pioglitazone, which has been shown to inhibit PaC growth in vivo [82]. However, Ferrara et al. [64] found no link between pioglitazone and a risk of cancer in the pancreas or in nine other common sites. Similarly, no significant risk for PaC with TZDs was found by Li et al. [23] nor in a study of Taiwanese diabetic patients by Kao et al. [83]. These discrepant results may reflect the complexity of PPARs signaling and suggest that unknown interactions may exist that impact the development of PaC and require further study.

### *Incretin-based drugs*

Glucagon-like peptide-1 receptor agonists such as exenatide and dipeptidyl peptidase-4 inhibitors such as sitagliptin are incretin-based drugs recently introduced to treat type II diabetes. However, there has been concern as to whether these drugs increase the risk for developing PaC [84]. Particularly, the adverse events database maintained by the U.S Food and Drug Administration indicates that treatments with exenatide and sitagliptin increase the rates of PaC by 2.9 and 2.7 times, respectively, compared with those from other ADM treatments [85]. Specifically, an observational study by Tseng et al. [86] found a higher risk of PaC (HR, 1.40; 95% CI: 1.13-1.75) in patients receiving a cumulative dose of <33,700 mg of sitagliptin.

However, there are also studies indicating that incretin-based drugs are not linked with PaC [87-98]. For example, Gokhale et al. [97] analyzed data from Medicare claims in the United States and showed that compared to sulfonyl-urea or TZDs, there was no increased risk for PaC with dipeptidyl peptidase-4 inhibitors, with

HRs of 0.62 (95% CI: 0.41-0.94) and 0.97 (95% CI: 0.65-1.43), respectively, after adjusting for the propensity scores. Similarly, Funch et al. [96] did not observe an increased risk in patients treated with the glucagon-like peptide-1 receptor agonist liraglutide. Thus, additional randomized controlled studies comprising large sample sizes are needed to resolve whether incretin-based drugs promote the development of PaC.

### *Insulin*

In addition to regulating glucose and lipid metabolism, insulin can promote proliferation of cells as well angiogenesis. Moreover, it appears that insulin may support the growth of tumors in the pancreas [99]. Diabetics taking insulin consistently show an increased rate of PaC, particularly those with long-term (>5 years) use (odds ratio, 2.78; 95% CI: 1.00-7.73) as reported by Li et al. [23] and by Ferrara et al. [64], who reported an HR of 3.1 (95% CI: 2.4-4.0) in patients that had previously received insulin treatment. Interestingly, an investigation by Currie et al. found that the risks for PaC (HR, 4.63; 95% CI: 2.64-8.10) as well as for colorectal cancer (HR, 1.69; 95% CI: 1.23-2.33) were higher in patients treated with insulin than in those treated with metformin [56]. However, a meta-analysis by Tan et al. [38] revealed that insulin therapy may actually decrease the incidence of PaC. The authors suggested that whereas locally produced insulin can promote the growth of pancreatic tumor cells, systemic insulin derived from therapeutic treatments acts primarily to regulate glucose in the blood, thereby limiting its availability to the tumor cells. Of note, the association between previous use of insulin and the risk of PaC was confounded by both the duration of diabetes in patients and their level of glycemic control. Thus, more studies need to be conducted that exclude such relevant factors.

### **Conclusion**

Observational studies indicate that newly developed DM may be a manifestation of PaC and that the risk for this cancer is increased in long-term cases. Notably, the development of PaC may be inhibited by the using of ADMs, such as metformin. However, DM in long-term patients is more likely to be managed with insulin therapy, which is associated with an



increased risk for developing PaC. How incretin-based drugs and TZDs impact the incidence of PaC remains unclear. Thus, further research is needed to elucidate these relationships and to determine the causality and the impact of DM severity and disease duration as well as residual biases and misclassifications. Future studies will also help to identify the possible effects of ADM type and dosage on the risk of PaC.

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### Disclosure of conflict of interest

None.

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