

Diabetes as a Risk Factor of Pancreatic Cancer

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1. Introduction

Pancreatic cancer and diabetes have a complex bidirectional relationship. A large proportion (varied between 50%–80% by studies) of pancreatic cancer patients have concurrent diabetes or impaired glucose tolerance (15, 54). It has been debated for a long time whether diabetes is a predisposing risk factor for the development of pancreatic cancer or a consequence of disease onset (24, 37, 66). Because of the relatively low incidence of pancreatic cancer compared to other common cancers and the rapid fatality of this aggressive malignancy, epidemiological investigations faced many challenges. For example, early studies conducted by single institution often have limited study power. Population based case-control studies are easily subject to selection bias or information bias due to the rapid loss of patients with the most advanced disease. Misclassification bias seems unavoidable because there is no current clinical or laboratory methods to distinguish the type 2 diabetes from the pancreatic cancer caused type 3c diabetes (15). As a consequence of the obesity epidemic, the incidence of diabetes is increasing globally, which may have a significant impact on the pancreatic cancer burden. A better understanding of the association between diabetes and pancreatic cancer and the mechanism underlying this association would aid the development of novel strategies for the prevention and treatment of this cancer.

2. Epidemiological evidence

Up to date, more than 20 case-control studies (9, 11, 16, 20, 23, 28, 31, 37, 38, 44, 46, 48, 50, 56, 59, 65, 67, 93, 101) and the same number of cohort or nested case-control studies (1, 3, 5, 6, 13, 14, 27, 39, 43, 47, 55, 58, 63, 73, 76, 77, 78, 84, 94, 95) with information on the association between diabetes and pancreatic cancer have been reported. Findings from these individual studies were inconsistent. However, a consistent association of long-term diabetes and risk of pancreatic cancer was reported from three large scale meta-analyses (7, 22, 42) and three pooled data analyses (10, 21, 53) with each involved more than 1500 pancreatic cancer cases (**Table 1**). The first meta-analysis (22), conducted in 1995, included 20 of the 40 published case-control and cohort studies and reported an overall estimated relative risk (RR) of 2.1 and a 95% confidence interval (CI) 1.6-2.8. This value was relatively unchanged when analyses were restricted to diabetes with a duration of at least 5 years (RR, 2.0, 95% CI, 1.2-3.2) (22). The second, conducted in 2005, included 17 case-control and 19 cohort or nested case-control studies published from 1996 to 2005 and reported an overall RR of 1.8 and 95% CI (1.7-1.9) (42). Individuals diagnosed with diabetes within 4 years of their pancreatic cancer had a 50% greater risk than those with diabetes for ≥ 5 years (RR, 2.1, 95% CI, 1.9-2.3 vs. RR, 1.5, 95% CI, 1.3-1.8; $P = 0.005$). The third meta-analysis of 35 cohort studies reported a summary RR (95% CI) of 1.94 (1.66-2.27) (7). Subgroup analyses revealed that the

Table 1. Diabetes as a risk factor for pancreatic cancer

Reference	No. of studies	Case/control (No./No.)	Summary RR
Everhart & Wright, 1995 JAMA (22)	11 Case-Control 9 Cohort	2546 cases	2.10 (1.60-2.80)
Huxley et al, 2005 Br J Cancer (42)	17 Case-Control 19 Cohort	9220 cases	1.82 (1.66-1.89)
Ben et al, 2010 Eur J Cancer (7)	36 Cohort	1528 cases	2.11 (1.51-2.94)
Li et al, 2011 Can Cause Con (53)	3 Case-Control	2192/5113	1.80 (1.50-2.10)
Elena et al, 2013 Can Cause Con (21)	12 Cohort	1621/1719	1.40 (1.07-1.84)
Bosetti, 2014 Ann Oncol (10)	15 Case-Control	8305/13987	1.90 (1.72-2.09)

increased risk of pancreatic cancer was independent of geographic locations, sex, study design, alcohol consumption, body mass index (BMI) and smoking status. Similarly, a negative association was observed for diabetes duration and risk of pancreatic cancer.

In a pooled analysis of 2,192 pancreatic cancer patients and 5,113 cancer-free controls from three large case-control studies conducted in the United States, diabetes was associated with a 1.8-fold risk of pancreatic cancer (95% CI, 1.5-2.1) (53). Risk estimates decreased with increasing years with diabetes. Individuals with diabetes for ≤ 2 , 3-5, 6-10, 11-15 and >15 years had an RR (95% CI) of 2.9 (2.1-3.9), 1.9 (1.3-2.6), 1.6 (1.2-2.3), 1.3 (0.9-2.0), and 1.4 (1.0-2.0), respectively, ($P < 0.0001$ for trend) (53). A pooled data analysis conducted by the Pancreatic Cancer Cohort Consortium in 1621 pancreatic cases and 1719 matched controls from 12 prospective cohorts reported that self-reported diabetes was associated with a 40% increased risk of pancreatic cancer (95% CI, 1.07-1.84) (21). The highest risk was for those with diabetes duration

2-8 years (RR, 1.79, 95% CI, 1.25-2.55), but no association was found for those with >9 years of diabetes duration. The latest study reported by the Pancreatic Cancer Case Control Consortium involved 8305 cases and 13,987 controls pooled from 15 case-control studies (10). Overall, 1155 (15%) cases and 1087 (8%) controls reported a diagnosis of diabetes two or more years before cancer diagnosis (or interview, for controls), corresponding to a RR of 1.90 (95% CI, 1.72-2.09). Pancreatic cancer risk decreased with duration of diabetes, but a significant excess risk was still evident 20 or more years after diabetes diagnosis (RR, 1.30, 95% CI, 1.17-2.03).

One of the major concerns regarding the diabetes and pancreatic cancer associations is the reverse causality issue because pancreatic cancer could cause diabetes or diabetic state. The associations observed between risk of pancreatic cancer and long-term diabetes (> 5 years of duration) could not be explained by reverse causality because of the known rapid progression feature of pancreatic cancer. Another concern is whether diabetes is an independent

risk factor for pancreatic cancer since 80% of the type 2 diabetes patients are obese and smoking is an established risk factor for both diabetes and pancreatic cancer. In the three pooled analyses, all risk estimates were adjusted for other known risk factors for pancreatic cancer, e.g. smoking, obesity and family history, in addition to age, race and sex. Consistent risk estimates were also observed across strata of body mass index and tobacco smoking (10). Therefore, there is sufficient epidemiological evidence supporting the conclusion that long-term type 2 diabetes is an independent risk factor for pancreatic cancer.

Information on the association of type 1 diabetes and pancreatic cancer is quite limited. Most studies have either been restricted to people with type 2 diabetes or have made no distinction between types of diabetes. A systematic review and meta-analysis conducted in 2007 identified 3 cohort studies and 6 case-control studies with

information on type 1 diabetes (82). Based on 39 pancreatic cancer cases, the summary RR for pancreatic cancer in “young-onset” or type 1 diabetes versus no diabetes was 2.00 (95% CI, 1.37-3.01). Because the number of diabetes diagnosed in younger age (<45 years of age) is increasing (90), the impact of early diabetes onset on risk of pancreatic cancer deserve further investigations.

3. Evidence from biomarker studies

The hypothesis that long-standing diabetes is a risk factor for pancreatic cancer is also supported by results from biomarker studies. A number of studies have examined the serum or plasma levels of biomarkers for hyperglycemia, β -cell function and insulin resistance in relation to risk of pancreatic cancer using prediagnostic blood samples (Table 2).

Table 2. Plasma/serum biomarkers and risk of pancreatic cancer

Biomarker	No. of Studies	Observations
		RR (95%CI)
HbA1C (32, 97)	2	2.42 (1.33-4.39), 1.79 (1.17-2.70)
Glucose (29, 79)	2	1.65 (1.05-2.60), 2.13 (1.04-4.35)
C-peptide (62, 97)	4	Null x 2 (32, 100), 1.52 (0.87-2.46), 1.57 (1.08-2.30)
Insulin (83, 97)	2	2.01 (1.03-3.93), 2.22 (1.50-3.29)
Proinsulin/insulin (29)	1	Null
Adiponectin (4, 35, 86)	3	0.65 (0.39-1.07), 0.44 (0.23-0.82), 0.59 (0.40-0.87)
IGF1/2, IGFBP3 (57, 75, 85, 98)	4	Null
IGFBP1 (75)	1	2.07 (1.26-3.39)
IGF1/IGFBP3 (75, 100)	2	1.54 (0.89-2.66) 1.72 (1.05-2.83)
C-Reactive Protein (18, 33)	2	Null
sTNF-R2, sTNF-R1 (33)	1	1.52 (0.97-2.39) 1.97 (1.02-3.79)
AGE (34,45)	2	Null
RAGE (34,45)	2	0.46 (0.22-0.96), 0.46 (0.23-0.73)

IGF, Insulin-like growth factor; AGE, Advanced glycation end product; RAGE, receptor for advanced glycation end products; sTNF-R2 α , soluble tumor necrotic factor receptor 2.

In three prospective cohort studies with follow-up durations of more than 20 years, an increased risk of pancreatic cancer among subjects with high postload plasma glucose levels was observed (6, 29, 79). In the last of these studies, the risk of pancreatic cancer was 2.2-fold higher in individuals with a postload plasma glucose level greater than 200 mg/dL at baseline than in those with a level of no more than 119 mg/dL (29). Consistent with these findings, two additional studies have also shown a positive association of elevated HbA1C level and increased risk of pancreatic cancer (32, 97). Two studies directly examined the relationship between prediagnostic serum insulin levels and pancreatic cancer risk (83, 97). The first study demonstrated a 2-fold increase in risk after excluding cases diagnosed in the first 5 years of follow-up (RR, 2.01, 95% CI, 1.03–3.93) for the highest versus lowest quartile insulin level (83). The second one showed a RR (95% CI) of 1.57 (1.08-2.30) (97). Also, two studies showed an excessively high risk of pancreatic cancer associated with high levels of circulating proinsulin (C-peptide), a marker for β -cell function (62, 97). The RR (95% CI) was 1.52 (0.87-2.64) and 2.22 (1.50-3.29), respectively. However, this association was not observed in two other studies (32, 100). In the most recent study (97), it was found that the associations with insulin and proinsulin was stronger (highest vs lowest quintile, RR, 2.77, 95% CI, 1.28 to 5.99 for insulin and RR, 3.60, 95%CI, 1.68 to 7.72 for proinsulin) in cancers diagnosed 10 or more years after blood collection. In mutually adjusted models including HbA1c, insulin, and proinsulin, only proinsulin remained statistically significant (highest vs lowest quintile, RR, 2.55; 95% CI, 1.54 to 4.21; $P < .001$ for trend), which suggest that markers of peripheral insulin resistance, rather than hyperglycemia or pancreatic beta-cell dysfunction, were independently associated with pancreatic cancer risk. Furthermore, at least three studies (4, 35, 84) have found a significant association of increased risk of pancreatic cancer with lower plasma level of adiponectin, a key regulator of

glucose and fat metabolism and insulin sensitivity. These results indicate that both hyperglycemia markers and insulin resistance markers are associated with increased risk of pancreatic cancer. Although impaired glucose tolerance may precede the onset of pancreatic cancer rather than just be a consequence of this cancer, it is unlikely the altered glucose metabolism was caused by the cancer because all these studies used prediagnostic blood samples that were collected many years before the cancer onset. Findings from the biomarker studies not only provide supporting evidence for the association of diabetes and risk of pancreatic cancer, but also provide clues on the mechanisms underlying the association.

4. Mechanisms of diabetes-associated pancreatic cancer

The mechanism of the association between diabetes and pancreatic cancer is elusive but is known to include metabolic, hormonal, and immunological alterations that influence tumor growth (30). Insulin resistance and compensatory hyperinsulinemia as well as elevated levels of circulating insulin-like growth factors (IGFs) are perhaps the most hypothesized mechanisms underlying the association between type 2 diabetes and pancreatic cancer. Insulin per se is not a carcinogen, but insulin response via insulin receptor-mediated signaling transduction has a known mitogenic and cell proliferation stimulating effect. Insulin could also promote carcinogenesis through its effects on IGF-1. Insulin reduces the hepatic production of IGF binding proteins, which resulting in a higher level of circulating bioactive IGF1. IGF1 receptor-mediated initiation of signal transduction activates important intracellular signal pathways, including the Ras/Raf/mitogen-activated protein kinase and phosphoinositide-3 kinase/Akt/mammalian target of rapamycin (mTOR) pathways (71), both of which are frequently deregulated in pancreatic cancer. Several epidemiological studies failed to demonstrate a significant association of plasma

IGFI, IGF2, or IGFBP3 levels and the development of pancreatic cancer (57, 75, 85, 98). However, lower plasma IGFBP1 levels or combination of a higher level of IGF1 and lower level of IGFBP3 were associated with increased risk of pancreatic cancer(75, 100).

In addition to the direct growth-promoting effect of insulin and IGFs, type 2 diabetes may increase the risk of pancreatic cancer by the mechanism of inflammation. The adipose tissues regulate the release of inflammatory cytokines such as TNF- α , IL-6 and anti-inflammatory cytokine, such as IL10 and adiponectin. The pro-inflammatory cytokines not only contribute to insulin resistance, but also play an etiologic role in cell transformation and tumor progression. Furthermore, altered levels or functions of several molecules that are implicated in obesity and/or diabetes, such as NF- κ B, leptin (49), IGF1 (80), and peroxisome proliferator-activated receptor γ (PPARG) (96), may contribute to pancreatic cancer development by impairing immune function. Epidemiological studies did not find a significant association of risk of pancreatic cancer with plasma level of C-reactive protein (18, 33) but with an elevated level of TNF- α (33). Two studies have found that the circulating level of advanced glycation end products (AGE) was not but their soluble receptors (sRAGE) were significantly associated with reduced risk of pancreatic cancer (34, 45). AGEs are formed by nonenzymatic reactions of reduced sugars, such as glucose, with amino groups in proteins, lipids, and nucleic acids. Endogenous AGE formation is enhanced under hyperglycemia and AGE triggers rapid generation of intracellular reactive oxygen species and activates an array of key cell-signaling pathways that have been implicated in oncogenesis. AGEs exert their proinflammatory effects by binding to receptors RAGE. sRAGE has AGEs-binding properties but in the absence of intracellular domain that is essential for RAGE signaling, therefore, may neutralize circulating AGEs and protect against RAGE-mediated cascades. The inverse associations of sRAGE

and risk of pancreatic cancer support the hypothesis on inflammatory mechanisms.

A recent study has shown that that both obesity and type 2 diabetes are associated with increased pancreatic duct cell replication in humans (12). Using tissues obtained from surgical resection or autopsies the study found a 10-fold higher ductal cell replication in obese patients and 4-fold higher in lean diabetic patients compared with lean non-diabetic controls. Although it is not fully understood how the pancreatic ductal cell replication was regulated, gastrointestinal hormones, with incretin activity in response to food intake may play a role (61). Another hypothesis is that progenitor cells in the pancreas can be activated upon pancreatic injury to form new islet or acinar cells. So it is conceivable that type 2 diabetes may promote increased formation of cells from pancreatic progenitors due to the damage to pancreatic tissues.

5. Genetic factors

Genetic factors that modify the risk of diabetes-associated pancreatic cancer have been investigated in several studies using the candidate gene approach with a focus on genes involved in glucose metabolism (17), obesity or diabetes (26, 69, 72, 88), insulin resistance (87) and inflammatory pathways (19, 74). Some modest effects on risk of pancreatic cancer and possible interaction with diabetes were reported for a number of variants but no replication study has been conducted.

Recent genome wide association studies have identified several pancreas development genes (2), i.e. NR5A2, PDX1, and HNF1A as susceptibility factor for pancreatic cancer (52, 68, 70, 99). Among these genes, heterozygous mutations in PDX1 and HNF1A genes are responsible for type 4 and type 3 of the maturity onset diabetes of the young (MODY), respectively. NR5A2 is known to play a critical role in phosphatidylcholine signalling pathway regulating fatty acid and glucose homeostasis (51). Common variants of these genes have also been associated with risk of obesity (81) and type II

diabetes (40, 91) or fasting glucose level (60). On the other hand, emerging evidence suggest that these genes also act as an oncogene or tumor suppressor gene in pancreatic carcinogenesis (8, 25, 41, 92). It is conceivable that genes involved in organ development and differentiation may contribute to the ability of tumor cells to proliferate and evade cell death as well as reprogram progenitor cells to a state that give rise to a tumor

(64). Although initial data analysis in a limited sample did not find significant interaction of the pancreas development genes with diabetes in modifying the risk of pancreatic cancer (89), further examination of the GWAS data in adequately powered studies may reveal the genetic factors that predispose diabetics to pancreatic cancer.

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