

HIGHLIGHT ARTICLE

Diabetes and Pancreatic Cancer

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Summary

Pancreatic cancer is the fourth leading cause of cancer death in the United States. Risk factors for pancreatic cancer are smoking, family history, chronic pancreatitis, and diabetes. There is controversy with regards to the causal relationship between diabetes and pancreatic cancer because many patients with pancreatic cancer have new onset diabetes. Abstracts presented at the 2011 American Society of Clinical Oncology (ASCO) Annual Meeting highlighted and supported the positive association between pancreatic cancer and diabetes. Abstract #4102 reports a two-fold risk of pancreatic cancer in diabetic patients. Abstract #4063 also presented at the 2011 ASCO Meeting shows that metformin prolongs survival and decreases risk of death in patients with pancreatic malignancy and diabetes.

Introduction

Pancreatic cancer carries a poor prognosis. It is the fourth leading cause of cancer death in men and fifth leading cause of cancer death in women in the United States [1]. The overall five-year survival remains low. Surgical resection is the only chance at cure; however, majority of the patients present with unresectable disease. Additionally, the five-year survival rate of patients who even undergo pancreatectomy remains low. In one study based on a National Cancer database from 1985 to 1995, five-year survival of patients who underwent pancreatectomy alone was 32.8%, 24.8% for those with pancreatectomy followed by radiation and chemotherapy, and less than 9% for those treated without pancreatectomy [2].

Risk factors that have been associated with pancreatic cancer include family history, smoking, chronic pancreatitis and diabetes mellitus [1]. Previous studies have revealed a positive association between diabetes and pancreatic malignancy, but the causal relationship has not been clearly established. The pathogenesis from diabetes to development of pancreatic cancer is also unknown. The causal relationship is controversial

because previous studies revealed diabetes to be present in 60% to 81% of the pancreatic cancer patients and many patients have new onset diabetes [3, 4, 5]. This is supported by one study that showed new onset diabetes to be 52.3% of pancreatic cancer patients when comparing to controls of 23.6% ($P < 0.0001$) [6]. In another study, 40.2% of patients were diagnosed with diabetes at time of diagnosis of pancreatic cancer while 15.9% of patients were diagnosed within two years prior [7]. Additionally, pancreatectomy has been shown to resolve some patients' new onset diabetes and glucose intolerance. Thus, the diabetes appeared to be more of a clinical manifestation of the malignancy itself rather than a direct causal relationship.

What We Knew Before the 2011 American Society of Clinical Oncology (ASCO) Annual Meeting

Diabetes and Pancreatic Cancer: A Causal Relationship?

In 1994, the Italian Pancreatic Cancer Study Group had performed a case control study, where they studied 720 patients with pancreatic cancer and 720 patients as controls [8]. They had discovered a three-fold risk of pancreatic malignancy in diabetic patients (odds ratio: 3.04; 95% CI: 2.21-4.17) [8]. However, when they repeated the analysis to include only patients with diabetes for more than 3 years, there was no statistical significance (odds ratio: 1.43; 95% CI: 0.98-2.07). They then further pursued similar analysis in patients with diabetes for more than 10 and 15 years and discovered no statistically significant associations. Additionally, they also reported that 40.2% of patients with pancreatic cancer and diabetes were diagnosed concomitantly or 15.9% were diagnosed within two

Key words Diabetes Mellitus, Type 1; Diabetes Mellitus, Type 2; Metformin; Pancreatic Neoplasms

Abbreviations GPCR: G protein-coupled receptor; ASCO: American Society of Clinical Oncology

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years prior to diagnosis of cancer. Thus, they concluded that increased prevalence of diabetes in pancreatic cancer patients was likely related to the diabetes caused by the tumor.

However, repeated studies have confirmed an increased risk, and one study even confirmed an increased risk in patients with longstanding diabetes. In 1995, Everhart and Wright showed from a meta-analysis that in patients with more than five years of diabetes, the pooled relative risk remained at 2.0 (95% CI: 1.2-3.2) [9]. In that study, the relative risk of pancreatic malignancy, irrespective of the duration of diabetes, is 2.1 (95% CI: 1.6-2.8) [9]. Other meta-analysis studies have also reported a similar two-fold risk of pancreatic malignancy in diabetic patients (Table 1) [10, 11, 12]. One meta-analysis study revealed even a two-fold risk in type 1 diabetes patients (Table 1) [10]. In that study, type 1 diabetes was defined as young onset diabetes, diagnosed less than 30 years old or insulin dependent diabetes [10].

Many of the cohort and case control studies that showed a positive association between diabetes and pancreatic malignancy used self-reported diabetes as inclusion criteria rather than clinical data. A Korean ten-year prospective study investigated serum fasting glucose and its associations with malignancy [13]. In this study, the overall risk of malignancy was higher in the group with fasting serum glucose greater than 140 mg/dL than those with fasting serum glucose less than 90 mg/dL, and the association was strongest in pancreatic cancer [13]. The hazard ratio was 1.91 (95% CI: 1.52-2.41) in men and 2.05 (95% CI: 1.43-2.93) in women with fasting serum glucose greater than 140 mg/dL [13]. They also investigated duration of diabetes and associated pancreatic risk, and discovered consistent associations in only men. The hazard ratio was 2.0 (95% CI: 1.2-3.3), 2.4 (95% CI: 1.4-4.3), and 3.0 (95% CI: 1.8-5.0) for men with diabetes duration of less than 4.9 years, 5.0 to 9.9 years, and more than 10 years, respectively. Therefore, in men, the risk of pancreatic cancer increased with longer duration of diabetes.

Metformin Decreases Risk of Pancreatic Malignancy

Based on the positive association between hyperinsulinemia, diabetes and pancreatic cancer, researchers are currently investigating associations between metformin and pancreatic malignancy. Metformin decreases hyperglycemia by inhibiting hepatic gluconeogenesis and enhancing peripheral

insulin sensitivity. It allows for increased glucose uptake in skeletal and adipose tissues. It improves insulin binding to insulin receptors [14]. In one study, hyperinsulinemia created by feeding hamsters with high fat diet normalized when the hamsters were treated with two weeks of metformin [15]. In that study, hamsters fed high fat diet and metformin had lower numbers of pancreatic carcinoma, proliferative lesions, pre-neoplastic lesions than hamsters who were fed high fat diet alone [15]. The implications are further supported by a clinical study. In a Taiwanese cohort study, metformin users had decreased risk of pancreatic malignancy with hazard ratio of 0.15 (95% CI: 0.03-0.79) [16].

What We Learned at ASCO 2011 Annual Meeting

Evidence Supporting the Increased Risk of Pancreatic Malignancy in Diabetes Patients

Yacoub *et al.* (Abstract #4102) [17] conducted a retrospective cohort study based on the health-care database maintained by the Veterans Integrated Services Network 16 (VISN16), consisting of 10 Veterans Health Administration hospitals in South-Central USA. They studied patients from 1996 to 2006, comparing 110,919 diabetic patients to 211,695 non-diabetic patients. One-hundred and twenty-four (0.112%) patients in diabetic cohort and 140 (0.066%) in non-diabetic cohort developed pancreatic malignancy. Using stratified Cox regression, the hazard ratio for incidence of pancreatic cancer was 2.17 (95% CI: 1.70-2.77) when comparing the diabetic cohort to non-diabetic cohort (Table 1). This relative risk is similar to the risk described in other studies in Table 1.

Evidence Supporting Positive Benefit of Metformin in Pancreatic Cancer Patients with Diabetes

Sadeghi *et al.* (Abstract #4063) [18] performed a retrospective cohort study to investigate the survival benefit of metformin in patients with diabetes and pancreatic malignancy. The data was obtained from the MD Anderson Cancer Center (MDACC) from 2000 to 2009, with additional cases taken from tumor board registry at MDACC. A total of 302 patients were studied. Multivariate Cox proportional hazard regression model was used to determine the effects of metformin on survival in such patients. They report the median survival to be longer in metformin users when compared to non-users: 16.6 vs. 11.5 months (P=0.0044). They also report a 33% decrease risk of death in patients who used metformin compared to

Table 1. Recent meta-analysis that showed positive association between pancreatic cancer and diabetes.

Author	Country	Time frame	Study size	Diabetes type	Relative risk (95% CI)
Huxley <i>et al.</i> [12]	North America or Europe	1966-2005	17 case control 19 cohort	Type 2 diabetes	1.82 (1.66-1.89)
Ben <i>et al.</i> [11]	Japan, USA, Europe, Asia, or Korea	1974-2010	35 cohort	Type 2 diabetes Excluded type 1 (31 out of 35 cohort studies)	1.94 (1.66-2.27)
Stevens <i>et al.</i> [10]	-	1985-2006	3 cohort 6 case control	Type 1 diabetes	2.00 (1.37-3.01)
Yacoub <i>et al.</i> (Abstract #4102) [17] ^a	USA	1996-2006	1 cohort	Type 2 diabetes	2.17 (1.70-2.77)

^a Abstract from the ASCO 2011 Annual Meeting, Chicago, IL, USA; June 3-7, 2011.

those who did not, with hazard ratio of 0.67 (95% CI: 0.51-0.88; P=0.005). Overall, patients who had smaller and resected tumor, lower surgical stage, negative surgical margins, low serum CA 19-9, and metformin use had longer survival. With adjustment for insulin usage or other clinical predictors, the hazard ratio remained significant.

Discussion

The causal relationship between diabetes and pancreatic cancer is controversial. In 1994, the Italian Pancreatic Cancer Group showed that with longer duration of diabetes, the association between diabetes and pancreatic cancer was not statistically significant. However, in a subsequent study in 1995, the relative risk of pancreatic cancer in patients with diabetes for more than five years remained 2.0. In various meta-analysis studies, the pooled relative risk is also approximately two-fold risk. Abstract #4102 presented at the 2011 ASCO Annual Meeting [17] further supports this two-fold increased risk. Although many of the patients with pancreatic cancer have new onset diabetes, there have been studies that still show a positive association even in patients with longstanding diabetes. Thus, it seems likely that diabetes is a risk factor for pancreatic malignancy. The exact pathogenesis would need to be further delineated. Based on the positive association between hyperinsulinemia, diabetes and pancreatic cancer, therapeutic targets aimed to treat diabetes should decrease risk of pancreatic malignancy. In an aforementioned cohort study, metformin users do have a decreased risk of pancreatic malignancy [16]. In the Abstract #4063 presented at the 2011 ASCO Annual Meeting [18], patients with pancreatic cancer, diabetes, and metformin use had longer median survival and decreased risk of death. This implies that metformin may have some beneficial effects on slowing the progression of pancreatic malignancy. However, specific pathogenesis is unclear and would have to be further explored. There have been mice models revealing of metformin to significantly decrease the growth of pancreatic cancer cells xenografted into the flank of nude mice [19]. In that study, the authors propose that metformin interrupts the G protein-coupled receptor (GPCR), insulin receptor signaling by down-regulating the mTOR pathway [19]. The GPCR and insulin receptor pathways are associated with increased DNA synthesis and pancreatic cancer cell growth [19]. By negatively regulating GPCR and insulin receptor signally, and interrupting their cross talk, metformin is shown to decrease pancreatic cancer cell growth in mice (Figure 1). Translation from basic

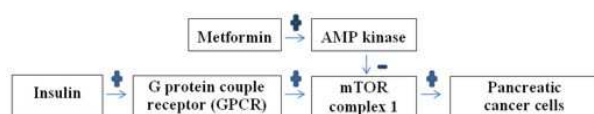


Figure 1. Metformin disrupts G protein-coupled receptor and insulin signaling and pancreatic cancer growth.

science research to clinical practice is yet to come. Additionally, in the abstract, the median survival is only prolonged by four months in patients who are metformin users compared to those who are non-users. This is still fairly poor prognosis, and further other treatments that work synergistically with metformin would have to be further explored.

Conflict of interest The authors have no potential conflicts of interest

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