

**ASSOCIATION OF DIABETES AND PANCREATIC CANCER: A COMPREHENSIVE
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ABSTRACT

It has been found that glucose intolerance including frank diabetes is associated with pancreatic cancer in >75% of the cases. Because of the very poor survival associated with this malignancy, prevention of the disease assumes prime importance. There is lack of consensus whether diabetes is a predisposing factor for pancreatic cancer or diabetes is caused due to it. The purpose of this review article is to evaluate the available literature on this debatable topic.

KEYWORDS: Diabetes; Pancreatic Cancer; Glucose intolerance.**INTRODUCTION**

The pancreatic cancer is a disease of poor prognosis which, even if treated with surgery and adjuvant treatment, has median survival of only 6-8 months. It has been found that glucose intolerance including frank diabetes is associated with pancreatic cancer in >75% of the cases. According to the "Warburg hypothesis", the growth of cancer tissue is dependent on glycolysis, thereby, creating high demand of glucose. This occurs because ATP generation by glycolysis requires much more glucose molecules than the process of oxidative phosphorylation. The basic principle of positron emission tomography, which is being increasingly used these days, is the preferential uptake of fluoro-deoxy-glucose by the tumor tissue. Most tumors have been found to harbor up regulated insulin-dependent glucose uptake into the cell. This is vital for the growth of the tumor due to their high turnover rate. However, there is lack of consensus whether diabetes is a predisposing factor for pancreatic cancer or diabetes is caused due to it. The purpose of this review article is to evaluate the available literature on this debatable topic.

METHODS AND MATERIALS

An electronic search of the Pubmed database was performed to obtain key literature in the field of pancreatic cancer and its association with diabetes using the following search terms: <pancreatic cancer>, <pancreatic adenocarcinoma>, <diabetes> and <glucose intolerance>. The Pubmed database was chosen as it

remains the most widely used resource of medical journals and indexes only peer-reviewed literature.

The search results were narrowed by applying following filters: English, Full articles, human studies, last 5 years, systematic reviews and core clinical journals. The data from the relevant articles were studied and evaluated to write this review article.

RESULTS AND DISCUSSION

The five year survival rate of pancreatic cancer is less than 5%.^[1] Only 10-15% cases are resectable at the time of diagnosis.^[2] Because of the very poor survival associated with this malignancy, prevention of the disease assumes prime importance. Since diabetes is associated with pancreatic cancer, it has attracted the attention of researchers worldwide. However, it is still not clear whether diabetes is a cause of pancreatic cancer or the consequence of this dreaded disease. In a meta-analysis by Bosetti et al,^[3] 15% cases and 8% controls reported a diagnosis of diabetes 2 or more years before cancer diagnosis corresponding to an Odds Ratio (OR) of 1.90 (95% confidence interval, CI, 1.72–2.09). Similar risk was observed across patients of different body mass index and history of tobacco smoking. It was observed that pancreatic cancer risk decreased with duration of diabetes, but a significant excess risk was still evident 20 or more years after diabetes diagnosis (OR 1.30, 95% CI 1.03–1.63).^[3] Among diabetics, long duration of oral hypoglycemic use was associated with a decreased pancreatic cancer risk (OR 0.31, 95% CI 0.14–0.69, for

≥15 years). Conversely, insulin use was associated with a pancreatic cancer risk in the short term (OR 5.60, 95% CI 3.75–8.35, for <5 years), but not for long term use (OR 0.95, 95% CI 0.53–1.70, for ≥15 years).^[3] This study showed that 30% excess risk persists for more than two decades after diabetes diagnosis, thus supporting a causal role of diabetes in pancreatic cancer.

In a meta-analysis by Huxley *et al.*,^[4] the combined summary odds ratio was 1.82 (95% confidence interval (95% CI) 1.66–1.89), with evidence of heterogeneity across the studies ($P=0.002$ for case-control and $P=0.05$ for cohort studies) that was explained, in part, by higher risks being reported by smaller studies and studies that were reported before 2000. Individuals in whom diabetes had only recently been diagnosed (< 4 years) had a 50% greater risk of the malignancy compared to individuals who had diabetes for ≥5 years (OR 2.1 vs 1.5; $P=0.005$).^[4] In a review by Anderson *et al.*,⁵ obesity and diabetes both were found to independently increase the risk of several common malignancies by about two-fold. This risk is reduced by successful treatment. Type 3c diabetes (pancreatogenic diabetes; diabetes induced by other pancreatic diseases) is more common than previously realized.^[5]

Liao *et al* reported that there is a linear dose response relation between fasting blood glucose concentration and the rate of pancreatic cancer among prediabetics and diabetics, with every 0.56 mmol/L increase in fasting blood glucose associated with a 14% increase in the rate of pancreatic cancer.^[6] They concluded that efforts towards early detection of prediabetes and lifestyle changes to improve glucose metabolism could represent a viable strategy to curb the increasing incidence of pancreatic cancer.^[6] The explanation that can be offered to the above findings is that pancreatic cancer cells depend heavily on glucose for growth. While the normal pancreas metabolises glucose through oxidative phosphorylation, pancreatic cancer cells preferentially metabolise glucose through aerobic glycolysis, which generates less energy but more metabolites are required for biosynthetic functions to sustain cell proliferation and thus confers a survival advantage.

Bosetti *et al* observed a non-significant reduced risk of pancreatic cancer in diabetics using oral hypoglycemics, the risk decreasing with longer duration of use.^[3] Conversely, the risk was elevated among insulin users and particularly in those with a shorter duration of use. Although the duration of oral hypoglycemic use is likely to mirror the time between diabetes diagnosis and cancer diagnosis/interview, the addition of a term for the duration of diabetes in the models did not meaningfully affect our risk estimates. Soranna *et al* reported a lower pancreatic cancer risk in diabetics using oral hypoglycemics than in those using insulin.^[7] Metformin has been shown to be associated with a reduced risk of pancreatic cancer, the favorable effect being mediated by both, its ability to lower glycemic and insulin levels, and

to its tumor growth inhibitory activity. An explanation for increased risk, insulin, in fact, tends to be prescribed in patients with more advanced diseases and its short term excess risk may be due to a progressive worsening of diabetes after pancreatic cancer.^[8] An important limitation of these studies is that history of diabetes was self-reported. However, diabetes is a serious chronic condition and it has been reliably recalled in other epidemiological studies.^[9] Furthermore, it is possible that self-reported information on medical conditions is reported more accurately in cases than in population-controls, but not necessarily in hospital-controls.

The discovery that risk of pancreatic cancer progressively increases with worsening hyperglycemia has important implications. The increasing incidence of pancreatic cancer might be attributed to the rapid increase in prediabetics/diabetics, a global epidemic affecting 14.2% (629 million) of the world's adult population.^[10] Furthermore, prediabetes could provide an important opportunity for prevention of pancreatic cancer, the most effective strategy to reduce related mortality, given that, pancreatic cancer evades early detection and responds poorly to treatment. Prediabetes precedes overt type 2 diabetes and can be improved or even reversed through changes in lifestyle.^[3]

Genetic mutations, such as activation of the KRAS2 oncogene, inactivation of the tumor-suppressor gene CDKN2A, inactivation of the tumor-suppressor gene TP53 and deletion in pancreatic cancer 4 (DPC4) gene defects are seen in those with pancreatic cancer.^[3] Approximately 80% of those patients diagnosed with pancreatic cancer, are identified as having concomitant diabetes with a poor prognostic factor.^[11] Damaged pancreatic tissue, secondary to pancreatic cancer, leads to diabetes as islet cells and beta cells are taken over by malignancy. Additionally, those on certain anti-diabetic regimens are shown to be at a higher risk of developing pancreatic cancer due to the effect of stimulation on the pancreatic beta and islet cells.^[4]

In a recent study by Li *et al.*,^[11] new-onset diabetes was a significant independent predictor for risk of death in metastatic patients (HR=1.35, 95% CI=1.11–1.63, $P=0.002$) and in all patients (HR=1.23, 95% CI=1.09–1.40, $P=0.001$). Both recent onset and long term diabetes were significantly associated with old age, obesity, hypertension and coronary artery disease as well as weight loss. Recent onset diabetes was also significantly related to larger tumors and elevated level of CA19-9 but not to tumor site and presence of biliary obstruction. They concluded that diabetes in general and recent onset diabetes in particular, is associated with poor outcome of pancreatic cancer.^[11] Mao *et al* compared patients with pancreatic cancer and diabetes with their non-diabetic counterparts, the former showing significantly higher all-cause mortality (pooled HR: 1.13; 95% CI: 1.04–1.22).^[12] Subgroup analyses showed that diabetes was associated with poorer survival

in patients with resectable disease (HR: 1.37; 95% CI: 1.15-1.63) than those with unresectable disease (HR: 1.07; 95% CI: 0.89-1.29). The HR (95% CI) was 1.52 (1.20-1.93) for patients with recent onset diabetes (≤ 2 years of diabetes duration) and 1.22 (0.83-1.80) for those with longstanding diabetes (> 2 years). They concluded that diabetes is associated with higher mortality in patients with pancreatic cancer. The effect of diabetes on overall survival was associated with the stages of tumor and the duration of diabetes.^[12]

Giovannucci et al concluded that Diabetes (primarily type 2) is associated with increased risk for some cancers (liver, pancreas, endometrium, colon and rectum, breast, bladder).^[13] Diabetes is associated with reduced risk of prostate cancer.^[14] For some other cancer sites there appears to be no association or the evidence is inconclusive. The association between diabetes and some cancers may partly be due to shared risk factors between the two diseases, such as aging, obesity, diet, and physical inactivity. Possible mechanisms for a direct link between diabetes and cancer include hyperinsulinemia, hyperglycemia, and inflammation. Healthful diets, physical activity, and weight management reduce risk and improve outcomes of type 2 diabetes and some forms of cancer and should be promoted for all.

CONCLUSIONS

The incidence of diabetes is continuously increasing and pancreatic cancer is one of the most lethal forms of malignancy known. Diabetes when associated with pancreatic cancer makes the prognosis worse and can represent malfunctioning of the entire pancreatic-gut axis. Diabetes has been shown to be both, a potential cause as well as the effect of pancreatic cancer. Patients with diabetes should be strongly encouraged by their health care professionals to undergo appropriate cancer screenings as recommended for all people in their age and sex. More research is needed to identify the diabetic patients at high risk of pancreatic cancer, and also to improve the treatment for patients with pancreatic cancer with diabetes.

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