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**| RESEARCH ARTICLE**

## **Association between Diabetes Mellitus and Pancreatic Cancer: A Comprehensive Narrative Review**

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**| ABSTRACT**

Pancreatic cancer (PC) is extremely aggressive, with symptoms occurring only in the advanced stage. The relationship between Type 2 Diabetes Mellitus (T2DM) and PC is complex. However, it is unclear whether long-standing diabetes causes cancer or whether cancer proceeds the development of impaired glucose metabolism. PubMed, Google Scholar, Scopus and Cochrane library were consulted to look for relevant literature. We narrowed down 20 articles after implementing inclusion and exclusion criteria. The database was searched using the keywords "Pancreatic Cancer" AND "Diabetes Mellitus." This narrative literature review aims to analyze the literature on the analysis of the metabolic association of T2DM, the risk of carcinogenesis of the pancreas and their association, and the current understanding of metabolic pathways involved in cellular growth and metabolism. About 80% of patients with pancreatic disease have a previous diagnosis of diabetes within five years. We explored the literature to find metabolic associations between PC and T2DM due to insulin resistance, hyperinsulinemia, hyperglycemia, low-grade chronic inflammation, and insulin-like growth factor axis alteration.

**| KEYWORDS**

Mellitus, Pancreatic Cancer, Oncology, Insulin, Hyperglycemia

**| ARTICLE INFORMATION**

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### **1. Introduction**

Pancreatic cancer is one of the most aggressive cancers in the world. It is the 4th most leading cause of death amongst other malignancies, with around 45000 confirmed patients and around 38000 deaths in a single year in the United States [Khadka et al. 2018, Becker et al 2014]. It is predominantly found in males between 40-85 years of age, with a five-year survival rate ranging from 2% to 9% [Goral 2014, Ilic et al. 2023]. Risk factors for pancreatic cancer are both genetic and acquired risk factors. Genetic conditions include Lynch syndrome (HNPCC), Peutz-Jegher-syndrome (PJS), hereditary pancreatitis (HP), ataxia telangiectasia (AT), hereditary breast and ovarian cancer syndrome (HBOC), familial adenomatous polyposis (FAP), cystic fibrosis (CF), and familial atypical multiple mole melanoma syndromes (FAMMM). These conditions could lead to the development of pancreatic cancer

anywhere from 2 to 132 folds over the average population. Tobacco exposure, alcohol use, chronic pancreatitis, diabetes mellitus, obesity, and diet, along with some abdominal surgeries and infections, are identified to be some of the modifiable risk factors for the development of pancreatic cancer [Becker et al. 2014]. Pancreatic cancer is highly aggressive as it remains silent clinically in its early stages and becomes evident only when it metastasizes to different organs and invades the surrounding tissue [Vincent et al. 2011]. Identifying and Screening high-risk individuals can reduce false positives and increase the detection rate, thus reducing mortality [Pereira et al. 2020].

The prevalence of Diabetes Mellitus (DM) in 2013 by IDA (International et al.) was 9.6% in adults aged 20-79 years [Song et al. 2015]. Diabetes Mellitus is a metabolic disease primarily caused by a defect in insulin secretion and or action, with marked hyperglycemia symptoms that include polydipsia, polyuria, polyphagia, weight loss, and blurred vision [Khadka et al. 2018]. Convincing evidence suggests that Type 2 Diabetes Mellitus (T2DM) causes an increased risk for several cancers, such as colorectal, endometrium, breast, pancreas, liver, and bladder, and diabetes is known to advance the cancer stage and increase mortality [Giovannucci et al. 2010]. Specifically, various epidemiological studies have found an association between T2DM and an increase risk of Pancreatic Cancer (PC) [Bosetti et al 2014].

DM and PC share common risk factors such as obesity, age, insulin resistance, and genetic factors [[Khadka et al. 2018]. One possible mechanism for establishing a direct link between DM and PC is hyperinsulinemia, hyperglycemia, and inflammation [Giovannucci et al. 2010]. However, whether DM is a cause or a consequence of PC remains controversial. New-onset DM could be a symptom caused by PC development, and patients with long-term DM might be at increased risk for PC [[Khadka et al, 2018; Song et al., 2015]. Reports from previous studies conducted primarily on Western populations show that individuals with pre-diabetes or diabetes (fasting blood glucose 5.6-6.9 mmol/L or post-load blood glucose 7.8-11.0 mmol/L) have an increased risk of Pancreatic Cancer [Pang et al. 2017]. However, the duration of diabetes Mellitus has a significant relationship with the development of Pancreatic Cancer, with the increasing duration being significantly associated with decreasing risk for PC [Khadka et al., 2018]. The risk of developing PC in a patient with DM also depends on antidiabetic treatment administration. Patients taking insulin alone or combined with oral antidiabetic medication for less than five years had an increased risk of developing PC compared to a decreased risk among those who took it for more than or equal to 5 years [Khadka et al. 2018]. Results from a study conducted by [Yu-Qi Shi et al. 2020] suggest that the antidiabetic drug Metformin is associated with survival benefits in patients with concurrent DM and PC [Yu-Qi Shi et al. 2020].

On the contrary, DM has also been found to be a consequence of PC, as various studies have reported that PC-related DM improves following the resection of pancreatic tumors despite surgically removing a variable amount of pancreatic tissue [Khadka et al. 2018]. While approximately 85% of pancreatic cancer patients have frank diabetes or impaired glucose tolerance, as per studies, new-onset diabetes (less than 30 days) and glucose intolerance in elderly patients are alarming signs of pancreatic cancer [Khadka et al. 2018]. A Meta-analysis conducted by [Song et al. 2015] shows an increased risk of PC was demonstrated in patients with diabetes lasting more than two years. Therefore, regular medical examinations of patients with long-term diabetes could be meaningful and helpful in predicting, early diagnosing, and treating PC [Song et al. 2015].

In this literature review, we will discuss the duration of diabetes to the development of Pancreatic Cancer and use it as an indicator to prevent the development of Pancreatic Cancer.

## **2. Review**

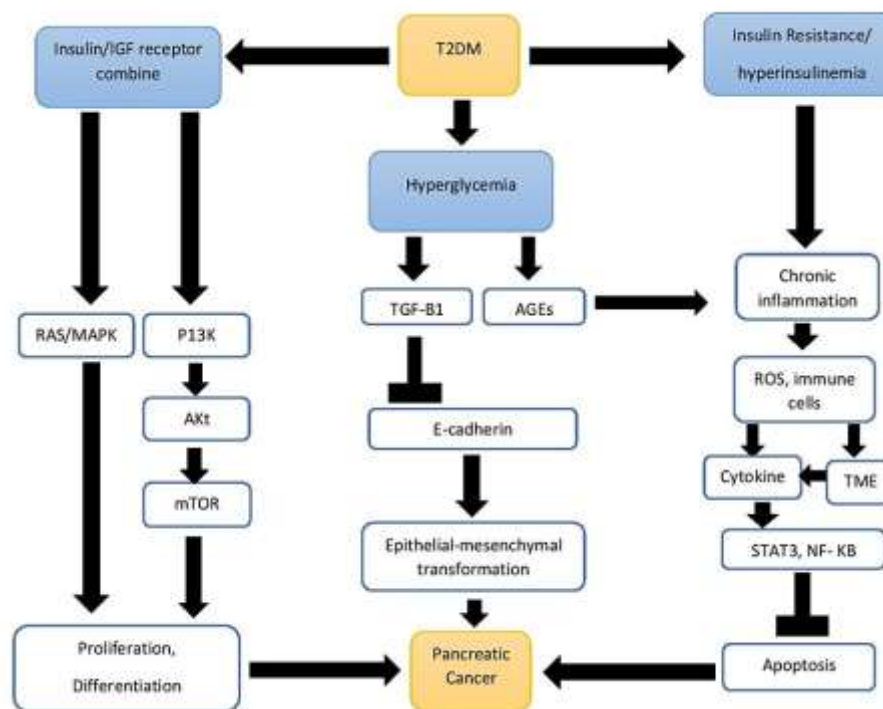
### **2.1 Mechanism of Development of Pancreatic Cancer in Long-standing Type 2 Diabetes Mellitus**

Epidemiological studies have shown that type 2 DM is a risk factor for PC [Li et al. 2019]. Patients with T2DM had an 80% higher risk of developing pancreatic cancer than those without diabetes [Brodovicz et al. 2012]. Studies have shown poor outcomes in all diabetic patients; however, more clarification is required to understand the role of the duration of diabetes on the outcome of pancreatic cancer. Almost 50-80% of the patients with pancreatic cancer have impaired glucose tolerance/ Diabetes [Wang et al 2003]. In patients with pancreatic cancer, about 85% of these patients have diabetes and are diagnosed less than two years prior to the diagnosis of cancer diagnosis or during the cancer treatment [Li et al. 2012]. Patients with new-onset diabetes, diagnosed with diabetes no more than two years before cancer diagnosis, are usually considered as having “secondary diabetes” caused by pancreatic cancer itself [Wakasugi et al. 2001]. Considering that the mortality rate in pancreatic cancer is high, a person diagnosed with diabetes secondary to PC would not survive many years without a cancer diagnosis [Li et al. 2012]. Long-standing diabetes raises the risk of PC by 40%-100%, whereas NOD increases the risk of PC by four to seven-fold. It implies that about 1-2% of patients recently diagnosed with diabetes might develop PC within three years [Biadgo et al. 2016]. Additionally, NOD has aggressive tumor biology and is a comparatively higher risk for recurrence after pancreatic resection and could contribute towards the factors responsible for poorer outcomes [Chu et al. 2010, Lee et al 2018].

Long-standing Type 2 diabetes is a significant risk factor for pancreatic cancer and frequently occurs with malignancy [Batabyal et al. 2014, Hausmann et al 2014]. A meta-analysis of 36 studies studying the association between Type 2 diabetes and pancreatic cancer suggested that in addition to cigarette smoking and obesity, evidence from the review indicated that type 2 diabetes is most likely the modifiable risk factor for pancreatic cancer. Individuals diagnosed with diabetes for less than four years had a 50% more risk of malignancy than individuals with diabetes for more than five years [Hausmann et al. 2014, Huxley et al 2005]. In patients with long-standing T2DM, although the risk of developing PC decreases with time, it remains a risk factor for PC, independently of obesity and smoking [Li et al. 2011]. However, some studies did not find any significant impact of long-standing diabetes on prognosis in PC after adjusting confounders like BMI, disease staging, smoking status, and age [Roy et al. 2021].

Mechanisms forming an association between T2DM and PC are complex and multifaceted [Duan et al 2021]. Many hormonal, metabolic, and immunological alterations affect tumor growth and, therefore, establish an association between the mechanism of diabetes and pancreatic cancer. According to the most hypothesized mechanisms, chronic inflammation, insulin resistance, compensatory hyperinsulinemia, and increased circulating Insulin-like growth factors (IGFs) play a significant role in establishing an association between type 2 diabetes and pancreatic cancer [Roy et al. 2021]. Beta cell destruction, Insulin resistance activation of the signal pathways, and inflammatory cascade ultimately lead to cell proliferation, invasion, metastasis, and angiogenesis.

Increased  $\beta$ -cell mass and pancreatic  $\beta$ -cell hyperactivity contribute to insulin secretion in response to insulin resistance. Insulin not only promotes cell proliferation but also increases glucose use. Both of these are vital to tumor development and progression. Insulin, by reducing hepatic production of IGF-binding proteins, also upregulates the bioavailability of IGFs. The antiapoptotic and mitogenic activities of IGF-1 play a vital role by acting as growth stimuli in cells expressing insulin and the IGF-1 receptor (IGF1R). Both IGF-1 and IGF1R are highly expressed in pancreatic cancer cells. IGF-1-mediated signaling transduction not only accelerates the proliferation, invasion, and expression of angiogenesis mediators but also decreases apoptosis in pancreatic cancer cells [Li et al. 2019, Li 2012, Deng et al 2022]. High glucose concentrations also increase intracellular oxidative stress by reactive oxygen species (ROS) levels and stimulate overexpression of MMP-3 in pancreatic cancer cells [Muniraj et al. 2012, Rozengurt 2014]. In addition, it causes gemcitabine resistance and cancer invasion by ROS/MMP-3 signaling pathway shown in Figure 1 [Rozengurt 2014].



**Figure 1: The mechanism between type 2 diabetes and pancreatic cancer**

Source [Rozengurt 2014]

This flow chart is made from the beginning by using the literature in [Rozengurt 2014].

T2DM; type 2 diabetes mellitus, IGF-1; insulin-like growth factor-1, MAPK; mitogen-activated protein kinase, P13K; phosphatidylinositol-3 kinase, mTOR; mammalian target of rapamycin, TGF-B1; transforming growth factor-B1, AGEs; advanced glycation end product, ROS; Reactive oxygen species, YME; tumor microenvironment, STAT3; signal transducer and activator of transcription 3, NF-KB; nuclear factor kappa B.

## **2.2 Clinical Significance of Differentiating Diabetes Secondary to Pancreatic Disease from T2DM**

Diabetes mellitus, secondary to exocrine pancreatic disease, is called type 3 DM. The causes of exocrine pancreatic disease are acute or chronic pancreatitis, pancreatic cancer, cystic fibrosis, and hemochromatosis. The most common cause is chronic pancreatitis, while pancreatic cancer is the second most common cause [Ewald et al. 2013].

It is essential to differentiate diabetes from secondary causes of pancreatic disease compared to T2DM. We must go into detail to discuss various aspects of the differentiation. The causal relationship between pancreatic cancer and diabetes was established in some patients as the cancer resection resolved diabetes. According to [Gullo et al. 200], pancreatic cancer-associated diabetes (known as new-onset diabetes) was either present at the time of cancer or two years before the cancer diagnosis. Due to the close association, diabetes can be considered for screening purposes in early pancreatic cancer [Pannala et al. 2009].

Secondly, differentiation is essential for identifying people with an increased risk of diabetic complications. It is observed that diabetes secondary to pancreatic disease has worse glycemic control than T2DM. For instance, diabetes in 31,789 adults, including 559 with diabetes secondary to pancreatic diseases from a population-based study revealed that Hb1AC levels were significantly high in patients with diabetes secondary to pancreatic disease compared to T2DM at the time of diagnosis (8.3% vs. 7.9%,  $p=0.002$ ). The risks of poor glycemic control related to DM secondary to pancreatic diseases were 30 % and 70% at 1-year and 5-year follow-ups, respectively. The glycemic variability occurs in chronic pancreatitis vs. T2DM, comparable with high variability in CP-associated diabetes. One small case-control study suggested that CP with diabetes has an increased risk of microvascular complications compared to T2DM; further study is required for comparison [Hart et al. 2021].

More importantly, differentiation of DM secondary to pancreatic disease from T2DM can help to guide treatment decisions. The initial treatment for diabetes secondary to pancreatic diseases is Metformin, especially in patients with chronic pancreatitis. Patients with diabetes secondary to pancreatic diseases require insulin within 12 months period. It is suggested that the use of insulin at one year and five years was 1.4% and 4% for people with T2DM compared to 16 % and 30% for people with diabetes secondary to pancreatic diseases. The need for insulin was higher in people with chronic pancreatitis, at 46% at 5-year whereas 21% at five years for people with acute pancreatitis [Hart et al. 2021]. As chronic pancreatitis is associated with exocrine insufficiency, fat malabsorption, and vitamin deficiencies, pancreatic enzyme replacement might be beneficial. It can also improve incretin release in patients with chronic pancreatitis [Ewald et al. 2013].

There are various biomarkers associated with diabetes secondary to pancreatic diseases. A critical biomarker named oxyntomodulin, a GLP-1 agonist, regulates exocrine pancreatic secretion. It was demonstrated by the studies that its level is decreased in individuals with diabetes secondary to acute pancreatitis when compared with healthy subjects and acute pancreatitis without diabetes [Hart et al. 2021]. According to [Sharma et al. 2009], rising blood glucose levels indicate the future development of pancreatic cancer [Roy et al. 2021]. The ratio of glucagon/insulin can be used as a potential biomarker in pancreatic cancer patients with DM. The serum glucagon/insulin ratio with a cut-off of 7.4 ng/mlU can help differentiate new-onset diabetes in pancreatic cancer from T2DM with 77% sensitivity and 69% specificity. The gut polypeptides, such as GIP and PP levels, are lower in patients with pancreatic cancer than in T2DM and healthy individuals. After the mixed meals, a decreased response of PP was also observed in one study, but a difference in fasting PP levels among patients with pancreatic cancer with or without diabetes and T2DM was not found [Roy et al. 2021].

A high CA19-9 marker from the standard range has been associated with more than a 5 percent increased risk of pancreatic cancer within two years. It is essential to understand that CA 19-9 levels are affected by glycemic control, so cut-off levels should be optimized to detect pancreatic cancer in diabetes mellitus patients. The biomarker thrombospondin 1, a multimeric protein, is lower in pancreatic cancer patients with diabetes and non-diabetes. The levels are even lower twenty-four months before the onset of pancreatic cancer, with an AUC of 0.86 when combined with the CA 19-9 level [Roy et al. 2021]. The thrombospondin-1 levels were not lower in T2DM than in pancreatic cancer-associated diabetes. Another biomarker, Vanin-1, a protein involved in paraneoplastic islet cell dysfunction, is increased in pancreatic cancer. According to Huang et al. [Roy et al. 2021], the increased level of vanin-1 and matrix metalloproteinase using PCR real-time quantitative analysis is helping to distinguish pancreatic cancer-related diabetes from T2DM. Using the AUC for vanin-1 and matrix metalloproteinase, which is 0.950, the sensitivity is 95 %, and the specificity is 76% [Roy et al. 2021]. Another important biomarker is galectin-3, a galactoside-binding lectin involved in

pancreatic cells' proliferation, migration process, and invasion. The protein S100A9, toll-like receptor -4, has a role in the inflammatory process. Galectin-3 and S100 A9 levels are higher in pancreatic cancer-associated diabetes than in T2DM. The AUC of galectin-3 and S100A9 is 0.83 and 0.77, respectively, which can differentiate pancreatic cancer-related DM and T2DM [c]. Also, serum microRNAs have recently become essential to be used as biomarkers. The six microRNAs, known as miRNAs, are miR-483-5p, miR-19a, miR-29a, miR-20a, miR-24, miR-2, can help to differentiate pancreatic cancer-related DM to Diabetes mellitus, with the AUC of 0.885 (95%CI: 0.784-0.98600). The metabolites have been studied using liquid or gas chromatography, mass spectrometry, and nuclear MRI techniques. Recently, the immune-related proteins, which include cytokines, adhesion molecules, and chemokines known as GM-CSF, IL-31, FASL, ICAM1, RANTES, AND RESISTIN, were also found to help differentiate pancreatic cancer-associated diabetes and T2DM, with AUC of 0.96. Overall, we have found various biomarkers to detect pancreatic cancer earlier in diabetes, but using these biomarkers is not routine and requires further guidelines for clinical use [Roy et al. 2021].

Pancreatic cancer has various risk factors, including age, sex, family history, and diabetes. Alcohol, smoking, and obesity are nonmodifiable [Zhao et al 2020]. To understand the impact of risk factors in detail, a case-control study was conducted in Rome at a teaching hospital named Agostino Gemelli. This case-control study comprised 80 patients and 392 controls based on age, sex, type 2 DM status, hypercholesterolemia, smoking habits (if current tobacco user or previous users, and non-users), history of alcohol use (drink beer, wine, or hard liquor once a day at least) [Torre et al. 2014]. The study showed that the statistical difference for smoking status was  $P=0.007$ , while for alcohol consumption and hypercholesterolemia was  $P<0.001$  and  $P<0.001$ , respectively; these risk factors had increased the risk of causing pancreatic cancer [Torre et al. 2014].

For each statistically significant factor, a population-attributable risk percentage known as PAR% was calculated after adjusting the Odds ratio for the factor and the prevalence in the control group. The PAR % was 8.6%, 10.9%, 13.9 %, and 29%, respectively, for smoking status, DM, consumption of alcohol, and hypercholesterolemia [Torre et al 2014].

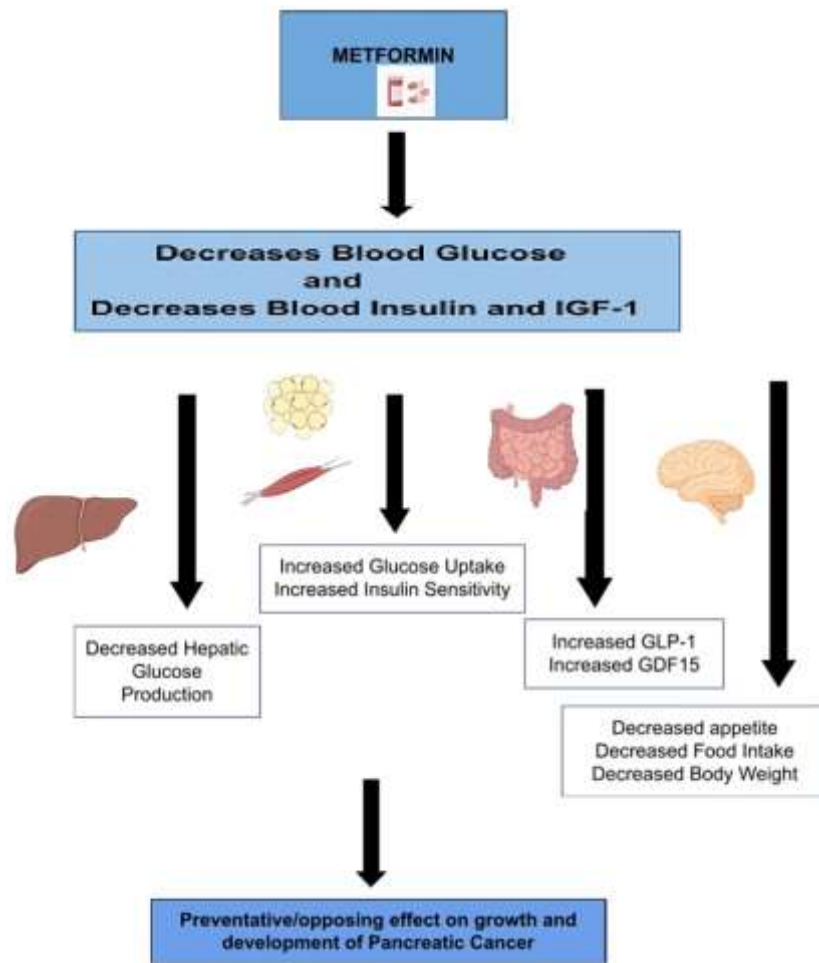
The synergistic interaction between alcohol consumption and diabetes, smoking status and diabetes, and alcohol consumption and smoking status was calculated. The synergistic effect was apparent with SI (synergism index) =17.61 and SI=17.77, respectively, between alcohol consumption and smoking status, alcohol consumption, and diabetes [Torre et al. 2014].

The study had some limitations, such as recall bias and underreporting. This means the prevalence of smoking and alcohol consumption could not be ascertained. In addition, the study did not consider the history of pancreatic cancer in the family. Physical activity, aspirin use, and the drugs used for DM (type of medication and starting date) were not considered [Torre et al. 2014].

### **2.3 Effects of Antidiabetic Medications on Pancreatic Cancer**

Antidiabetic medications directly affect the factors mediating an association with T2DM and PC (especially Pancreatic Ductal Adenocarcinoma), and some may even impact this cancer's development, progression, and outcome [Andersen et al. 2017]. Mainly, insulin has been reported to possibly further increase the risk of pancreatic cancer, while Metformin might reduce it. Thiazolidinediones and Sulfonylureas have shown no consistent role in pancreatic cancer [Bosetti et al. 2014, Li et al 2011, Andersen et al 2017, Soranna et al 2012]. According to an analysis conducted by (C. Bosetti et al. 2014), the use of antidiabetic medications in people with diabetes showed a nonsignificant risk reduction of pancreatic cancer (odds ratio OR 0.92) compared to patients not using antidiabetics. Increasing the duration of oral antidiabetic use for  $\geq 15$  years decreased the OR to 0.31. The risk of developing PC was significantly higher in patients using insulin OR 2.66 compared to patients not using insulin, with a decline seen with increasing the duration of use  $\geq 15$  years (OR 0.95) [Bosetti et al. 2014].

In other studies, the use of sulfonylureas was associated with an increased risk of PC, but to a lesser extent than that for insulin [Khadka et al. 2018]. Additionally, a large amount of evidence from epidemiologic and preclinical studies suggests that Metformin reduces the risk of developing pancreatic cancer and improves outcomes in patients with early-stage pancreatic cancer by the mechanism shown in Figure 2 [Eibl et al. 2021].



**Figure 2: Mechanism of action of metformin in reducing pancreatic cancer**

Source: [Eibl et al. 2021].

IGF; Insulin like growth factor 1, GLP; Glucagon like peptide, GDF; Growth Differentiation factor 15

This figure has been made from scratch by consulting the literature in [Eibl et al. 2021].

Figure created with biorender.com

However, two randomized clinical trials that compared metformin therapy in T2DM patients with placebo/usual care or active glucose-lowering therapy yielded no significant impact of the use of Metformin on cancer events [Andersen et al. 2017, Walker et al 2015]. In contrast to this, in a retrospective study of patients with pancreatic neuroendocrine tumors, a significant association was found between the use of metformin and longer progression-free survival [Pusceddu et al. 2018]. Another study showed that Metformin promotes a survival benefit in patients with Post Pancreatitis Diabetes Mellitus(PPRD) but not Pancreatic Cancer Related Diabetes(PCRD) [Cho et al. 2019]. A study conducted in Korea concluded that patients taking metformin in combination with thiazolidinedione or metformin plus dipeptidyl peptidase-4 inhibitor had a lower risk of PC compared to metformin-only patients [Lee et al. 2018]. Glucagon-like peptide-1-based therapy has shown the potential to promote pancreatic cancer [Elashoff et al. 2011]. The use of incretin-based therapies in T2DM remains controversial, with studies showing a doubling of the risk of PC after the prescription of incretin-based therapies [Boniol et al. 2017]. There was no association reported between the use of Liraglutide with an increased risk of PC [Funch et al. 2019].

A rare cause of hypoglycemia in a patient with T2DM is insulinoma, which presents with recurrent and progressive hypoglycemia and improved glycemic control in an otherwise diabetic patient without an intervention. It should not be missed in patients on glucose-lowering therapy or those with persistent hypoglycemia despite insulin cessation. The only cure for suitable patients is surgical management, whereas medical management is challenging in patients with unresectable insulinoma [Kumar et al. 2022, Singbo et al 2021]. While the association of diabetes and insulinoma delays the diagnosis, it does not change the prognosis or

favor carcinoma frequency [Schmitt et al. 2008]. A patient with previously stable diabetes presenting with unexplained hypoglycemic episodes can be suspected of insulinoma [Siraj et al. 2006].

#### 2.4 Screening Modalities

Diabetes mellitus patients are screened for PC based on associated clinical factors, level of biomarkers, or a combination of both [Roy et al 2021]. NOD diagnosed within three years has a 6-8 times increased risk of PDAC (Pancreatic ductal adenocarcinoma) compared to the general population, but the prevalence of PDAC in such circumstances is low (0.8%- 1%). Therefore, NOD recognition can indicate the early manifestation of pancreatic cancer and help diagnose early-stage asymptomatic pancreatic cancer [Roy et al. 2021, Pannala et al 2009]. International guidelines on the early detection of pancreatic ductal adenocarcinoma recommend targeted screening of individuals whose lifetime risk of developing pancreatic ductal adenocarcinoma is higher than 5%. This target includes high-risk groups such as individuals with NOD [Pereira et al. 2020]. [c] introduced the Enriching New-Onset Diabetes for Pancreatic Cancer (END-PAC) model, which aims to estimate the risk of pancreatic cancer based on three key factors: weight fluctuation, blood glucose changes, and age at the onset of diabetes mellitus (DM). A score of  $\geq 3$  successfully identified 78% of patients with pancreatic cancer, demonstrating an 85% specificity. Furthermore, a score of 3 or higher indicated a significantly increased prevalence of pancreatic ductal adenocarcinoma (PDAC) by 4.4-fold. Conversely, an END-PAC score below 0 was observed in 49% of patients, indicating a shallow risk of developing pancreatic cancer [Sharma et al. 2018]. A model was also suggested by [Boursi et al. 2017], utilizing The Health Improvement Network, an extensive primary care electronic research database in the United Kingdom. This analysis involved examining data from 109,385 individuals who developed new-onset diabetes. Three hundred ninety patients (0.4%) were subsequently diagnosed with pancreatic ductal adenocarcinoma (PDA) within three years. The final model, which achieved an area under the curve (AUC) of 0.82 (95% CI, 0.75-0.89), encompassed various factors such as age, body mass index (BMI), changes in BMI, smoking habits, the use of PPI (Proton pump inhibitors) and anti-diabetic medications, as well as levels of HbA1C, cholesterol, hemoglobin, creatinine, and alkaline phosphatase [Boursi et al. 2017]. At a screening threshold of 1% for pancreatic ductal adenocarcinoma (PDAC), approximately 6% of patients with (NOD) would need systemic screening. The sensitivity was 44.7%, specificity 94.0%, and positive predictive value (PPV) 2.6%, respectively. While these model systems show promise in narrowing the screening population, their limitations lie in suboptimal sensitivity and lower PPV [Roy et al 2021]. A recent publication introduced the protocol for a multicenter, prospective observational study called the NODES Trial. This study monitors individuals over 60 who have developed new-onset diabetes within the last six months. It aims to gather clinical data and reliable biomarkers to track their progress. The study aims to identify biomarkers that can effectively differentiate patients with pancreatic ductal adenocarcinoma (PDAC). These studies are crucial for enhancing our understanding and establishing a screening protocol in individuals with new-onset diabetes, enabling the early detection of PDAC whenever feasible [Roy et al. 2021].

In clinical practice, it presents a challenge to distinguish new-onset diabetes (NOD) caused by pancreatic cancer (PC) from the more frequently observed type 2 diabetes mellitus (T2DM) using clinical and biochemical factors [Roy et al. 2021, Munigala et al. 2015], study identified Age > 65 years, smoking, history of gallstone disease, CP (chronic pancreatitis), heavy smoking, and non-obese patients were independent predictors of PaCa (Pancreatic Cancer) among NODM patients on multiple logistic regression analysis [Munigala et al. 2015].

Chen et al. (2010) observed the association between recent-onset diabetes accompanied by weight loss and a significantly heightened risk of developing pancreatic cancer. Moreover, advanced age, prior maintenance of a healthy weight, and the absence of intentional weight loss further amplify this risk [Yuan et al. 2020]. Additionally, enhancing the identification of metabolic abnormalities that manifest before detecting pancreatic ductal adenocarcinomas (PDACs) can improve the likelihood of early detection. Metabolic parameters include (glucose, serum lipids, triglycerides, total, low-density, and high-density cholesterol, and total body weight) [Sah et al. 2019].

Considering the shortage of early diagnostic tools for pancreatic cancer, an association was formed by collaboration between the National Institutes of Health, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Cancer Institute (NCI) named Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC) [c]. CPDPC is a platform that works to understand the complex mechanisms and interrelations between pancreatitis, diabetes, and pancreatic cancer by conducting various trials and studies [Pandol et al. 2021]. Magnetic resonance Imaging as a Non-invasive Meth for the Assessment of Pancreatic fibrosis (MINIMAP) is an ongoing prospective study conducted by CPDPC on well-phenotyped patients to understand the potential of MRI in defining Pancreatic cancer's severity [Tirkes et al. 2021]. UK Early Detection Initiative (UK-EDI), which Cancer Research UK funds, is conducting trials to find the link between new-onset diabetes mellitus and pancreatic cancer with the primary goal of developing methods to diagnose pancreatic cancer early [UK-EDI 2023]. CPDPC is also supporting an ongoing study named DETECT (Evaluation of a Mixed Meal Test for Diagnosis and Characterization of Pancreatogenic Diabetes Secondary to Pancreatic Cancer and Chronic Pancreatitis), which aims to distinguish pancreatic cancer-associated diabetes with

type 2 diabetes by studying the response of pancreatic polypeptide to a mixed meal [Pereira et al. 2021]. Besides clinical trials, Electronic health records can be vital in predicting the relationship between pancreatic cancer and new-onset diabetes. In a study conducted in Rochester, USA, A model named (END-PAC) was developed for risk stratification of patients for developing pancreatic cancer in patients with new onset diabetes using their age, changes in weight, and blood glucose [Sharma et al. 2018]. Another study was conducted in the UK, which developed a pancreatic ductal adenocarcinoma prediction model with about 5% 3-year predicted risk using the impaired fasting glucose values along with basic clinical parameters (age, BMI, PPIs, total cholesterol, LDL, ALT, ALP) stored in the electronic data [Boursi et al. 2017]. Thus, electronic health models can be of great importance in detecting tumors at an early stage and reducing mortality.

Studies surveying the effect of diabetes in patients with pancreatic cancer who have received chemotherapy have demonstrated that a history of diabetes is linked with a higher death rate. A Study done by [Kleef et al. 2016] significantly showed an increased mortality rate in patients with diabetes mellitus who received adjuvant chemotherapy [Kleef et al. 2016]. Similar outcomes were demonstrated by (Hank et al. 2020), which revealed that overall survival was higher in nondiabetic patients, whereas it was lower in diabetic patients who were treated with chemotherapy [Hank et al. 2020].

There are various pathways hypothesized to lead to the worse outcome of Pancreatic cancer with diabetes, which include an alteration in the microenvironment of the tumor as a result of hyperglycemia and increased progression of tumor size due to sterol binding protein pathway [Zhou et al. 2019]. The CPDPC has also conducted three studies to identify the knowledge gaps in this area [Serrano et al. 2018, Josea et al 2021]. Although these studies show improved survival without diabetes, certain complications of chemotherapy or resection might need consideration on the impact of overall survival. Long-term diabetes also leads to complications of the heart and kidney that might influence drug interaction and patient survival. The clinical significance of separating primary T2DM and secondary T2DM due to pancreatic disease is well recognized. However, more research is required to develop biomarkers that distinguish primary and secondary diabetes. These studies will contribute to improving the method of diagnosis and categorization and identifying opportunities for early detection, prevention, and better treatment alternatives.

### **3. Methodology**

PubMed, Google Scholar, Scopus and Cochrane library were consulted to look for relevant literature. We narrowed down 20 articles after implementing inclusion and exclusion criteria. The database was searched using the keywords "Pancreatic Cancer" AND "Diabetes Mellitus." This narrative literature review aims to analyze the literature on the analysis of the metabolic association of T2DM, the risk of carcinogenesis of the pancreas and their association, and the current understanding of metabolic pathways involved in cellular growth and metabolism. About 80% of patients with pancreatic disease have a previous diagnosis of diabetes within five years. We explored the literature to find metabolic associations between PC and T2DM due to insulin resistance hyperinsulinemia.

### **4. Conclusions**

In this review, we have found the existence of a bidirectional association between PC and DM, with diabetes being both a risk factor and a consequence of Pancreatic Cancer. Insulin has been shown to increase the risk. New onset diabetes recognition can indicate the early manifestation of pancreatic cancer and could lead to early-stage asymptomatic pancreatic cancer diagnosis.

Similarly, regular medical examinations of patients with long-term diabetes could be meaningful and helpful in predicting, diagnosing, and treating PC. Additionally, various biomarkers can detect pancreatic cancer earlier in diabetes but are not routinely used, and further guidelines are required for their clinical use. Clinically cost-effective and valuable screening tools to detect PC could be crucial in improving outcomes in PC.

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**Conflicts of Interest:** The authors declare no conflict of interest.

The figures and flowchart has been made from scratch using the text source reference number mentioned below the figure.

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### **References**

- [1] Andersen DK, Korc M, Petersen GM. (2017). Pancreatogenic diabetes, and pancreatic cancer.. 2017, 66:1103-1110. 10.2337/db16-1477
- [2] Becker AE, Hernandez YG, Frucht H, Lucas AL (2014). Pancreatic ductal adenocarcinoma: risk factors, screening, and early detection. *World J Gastroenterol* . 2014, 20:11182-98. 10.3748/wjg.v20.i32.11182
- [3] Bosetti C, Rosato V, Li D. (2014) Diabetes, antidiabetic medications, and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case-Control Consortium. *Ann Oncol*. 2014, 25:2065-2072. 10.1093/annonc/mdu276



- [4] Brodovicz KG, Kou TD, Alexander CM, O'Neill EA, Engel SS, Girman CJ, Goldstein BJ. (2012). Impact of diabetes duration and chronic pancreatitis on the association between type 2 diabetes and pancreatic cancer risk. *Diabetes, Obesity and Metabolism*. 2012, 14:1123-8. 10.1111/j.1463-1326.2012.01667.x
- [5] Biadgo B, Abebe M (2016). Type 2 diabetes mellitus and Its association with the risk of pancreatic carcinogenesis. *Korean J Gastroenterol*. 2016, 67:168-77. 10.4166/kjg.2016.67.4.168
- [6] Batabyal P, Hoorn VS, Christophi C, Nikfarjam M. (2014). Association of diabetes mellitus and pancreatic adenocarcinoma: a meta-analysis of 88 Studies. *Ann Surg Oncol*. 2014, 21:2453-2462. 10.1245/s10434-014-3625-6
- [7] Boniol M, Franchi M, Bota M. (2017). Incretin-based therapies and the short-term risk of pancreatic cancer: results from two retrospective cohort studies. *Diabetes Care*. 2017, 41:286-292. 10.2337/dc17-0280
- [8] Boursi B, Finkelman B, Giantonio BJ, et al. (2017) A clinical prediction model to assess risk for pancreatic cancer among patients With new-onset diabetes. *Gastroenterology*, . 2017, 152:840-850. 10.1053/j.gastro.2016.11.046
- [9] Cho J, Scragg R, Pandol SJ, Goodarzi MO, Petrov MS (2019) Antidiabetic Medications and Mortality Risk in Individuals With Pancreatic cancer-related diabetes and postpancreatitis diabetes: A Nationwide Cohort Study. *Diabetes Care*. 2019, 42:1675-1683. 10.2337/dc19-0145
- [10] Chu CK, Mazo AE, Goodman M, et al. (2010) Preoperative diabetes mellitus and long-term survival after resection of pancreatic adenocarcinoma. *Ann Surg Oncol*. 2010, 17:502-13. 10.1245/s10434-009-0789-6
- [11] Duan X, Wang W, Pan Q, Guo L (2021) Type 2 diabetes mellitus intersects with pancreatic cancer diagnosis and development. *Frontiers in Oncology*. 2021, 11:730038. 10.3389/fonc.2021.730038
- [12] Deng J, Guo Y, Hu X, et al. (2022) High glucose promotes pancreatic ductal adenocarcinoma gemcitabine resistance and invasion through modulating ROS/MMP-3 signaling pathway. *Oxid Med Cell Longev*. 2022, 3243647. 10.1155/2022/3243647
- [13] Ewald N, Bretzel RG. (2013) Diabetes mellitus secondary to pancreatic diseases (Type 3c) — Are we neglecting an important disease? *European Journal of Internal Medicine*, 24:203-206. 10.1016/j.ejim.2012.12.017
- [14] Ewald N, Hardt PD (2013) Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. *World J Gastroenterol*. 2013, 19:7276-81. 10.3748/wjg.v19.i42.7276
- [15] Eibl G, Rozengurt E (2021) Metformin: review of epidemiology and mechanisms of action in pancreatic cancer. *Cancer Metastasis Rev*. 2021, 40:865-878. 10.1007/s10555-021-09977-z
- [16] Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. (2011) Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology*. 2011, 141:150-6. 10.1053/j.gastro.2011.02.018
- [17] Funch D, Mortimer K, Ziyadeh NJ, et al. (2019) Liraglutide use and evaluation of pancreatic outcomes in a US commercially insured population. *Diabetes Obes Metab*. 2019, 21:1837-1848. 10.1111/dom.13739
- [18] Goral V (2015) Pancreatic cancer: Pathogenesis and diagnosis. *Asian Pac J Cancer Prev*. 2015, 16:5619-24. 10.7314/apjcp.2015.16.14.5619
- [19] Giovannucci E, Harlan DM, Archer MC, et al. (2010) Diabetes and cancer: a consensus report. *Diabetes Care*. 2010, 33:1674-85. 10.3322/caac.20078
- [20] Hank T, Sandini M, Qadan M, et al. (2020) Diabetes mellitus is associated with unfavourable pathologic features, increased postoperative mortality, and worse long-term survival in resected pancreatic cancer. *Pancreatol*. 2020, 20:125-131. 10.1016/j.pan.2019.10.007
- [21] Hausmann S, Kong Bo, Michalski C, Michalski C, Erkan M, Friess H.: The role of inflammation in pancreatic cancer. *Adv Exp Med Biol*. 2014, 816:129-151. 10.1007/978-3-0348-0837-8\_6
- [22] Huxley R, Moghaddam AA, González AB, Barzi F, Woodward M. (2005) Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer*. 2005, 92:2076-2083. 10.1038/sj.bjc.6602619
- [23] Hart PA, Andersen DK, Petrov MS, Goodarzi MO (2021) Distinguishing diabetes secondary to pancreatic diseases from type 2 diabetes mellitus. *Curr Opin Gastroenterol*. 2021, 35:520-525. 10.1097/MOG.0000000000000754
- [24] Ilic M, Ilic I (2023) Epidemiology of pancreatic cancer. *World J Gastroenterol [Internet]*. 2023, 19:9694-705. 10.3748/wjg.v22.i44.9694
- [25] Josea S, Ann RJ, Sudhirb S, Sharmisthab G, Aynura UA, Andersen, Dana KA. (2021) The national institutes of health's approach to address research gaps in pancreatitis, diabetes and early detection of pancreatic cancer. *Gastroenterology*. 2021, 37:480-485. 10.1097/MOG.0000000000000758
- [26] Khadka R, Tian W, Hao X, Koirala R (2018) Risk factor, early diagnosis and overall survival on outcome of association between pancreatic cancer and diabetes mellitus: Changes and advances, a review. *Int J Surg* . 2018, 52:342-6. 10.1016/j.ijssu.2018.02.058
- [27] Kumar S, Melek M, Rohl P (2022) Hypoglycemia due to metastatic insulinoma in insulin-dependent type 2 diabetes. *Front Endocrinol (Lausanne)*. 2022, 13:906012. 10.3389/fendo.2022.906012
- [28] Kleeff J, Costello E, Jackson R, et al. (2016) The impact of diabetes mellitus on survival following resection and adjuvant chemotherapy for pancreatic cancer. *Br J Cancer*. 2016, 115:887-894. 10.1038/bjc.2016.277
- [29] Li Y, Bian X, Wei S, He M, Yang Y (2019) The relationship between pancreatic cancer and type 2 diabetes: cause and consequence. *Cancer Manag Res*. 2019, 11:8257-8268. 10.2147/CMAR.S211972
- [30] Li D (2012) Diabetes and pancreatic cancer. *Mol Carcinog*. 2012, 51:64-74. 10.1002/mc.20771
- [31] Lee S, Hwang HK, Kang CM, Lee WJ. (2018) Adverse oncologic impact of new-onset diabetes mellitus on recurrence in resected pancreatic ductal adenocarcinoma: a comparison with long-standing and non-diabetes mellitus patients. *Pancreas*. 2018, 47:816-822. 10.1097/MPA.0000000000001099
- [32] Li D, Tang H, Hassan MM, Holly EA, Bracci PM, Silverman DT. (2011) Diabetes and risk of pancreatic cancer: a pooled analysis of three large case-control studies. *Cancer Causes Control*. 2011, 22:189-97. 10.1007/s10552-010-9686-3
- [33] Lee DY, Yu JH, Park S, et al. (2018) The influence of diabetes and antidiabetic medications on the risk of pancreatic cancer: a nationwide population-based study in Korea. *Sci Rep*. 2018, 8:9719. 10.1038/s41598-018-27965-2
- [34] Muniraj T, Chari ST (2012) Diabetes and pancreatic cancer. *Minerva Gastroenterol Dietol*. 2012, 19:9-26. 10.1530/ERC-12-0105
- [35] Munigala S, Singh A, Gelrud A, Agarwal B (2015) Predictors for pancreatic cancer diagnosis following new-onset diabetes mellitus. . 2015, 6:118. 10.1038/ctg.2015.44

- [36] Pang Y, Kartsonaki C, Guo Y, et al. (2017) Diabetes, plasma glucose and incidence of pancreatic cancer: A prospective study of 0.5 million Chinese adults and a meta-analysis of 22 cohort studies. *Int J Cancer*. 2017, 140:1781-1788. 10.1002/ijc.30599
- [37] Pereira SP, Oldfield L, Ney A, et al. (2020) Early detection of pancreatic cancer. *Lancet Gastroenterol Hepatol* [Internet. 2020, 5:698-710.
- [38] Pannala R, Basu A, Petersen GM, Chari ST (2009) New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. *Lancet Oncol*. 2009, 10:88-95. 10.1016/S1470-2045(08)70337-1
- [39] Pandol SJ, Forsmark CE, (2021) Consortium for the study of chronic pancreatitis, diabetes, and pancreatic cancer: achievements and future directions: Achievements and future directions. *Curr Opin Gastroenterol* . 2021, 37:486-90. 10.1097/MOG.0000000000000765
- [40] Pusceddu S, Vernieri C, Di MM, et al. (2018) Metformin use is associated with longer progression-free survival of patients with diabetes and pancreatic neuroendocrine tumors receiving Everolimus and/or Somatostatin Analogues. *Gastroenterology*. 2018, 155:479-489. 10.1053/j.gastro.2018.04.010
- [41] Roy A, Sahoo J, Kamalanathan S, Naik D, Mohan P, Kalayarasan R. (2021) Diabetes and pancreatic cancer: exploring the two-way traffic. *World J Gastroenterol*. 2021, 27:4939-4962. 10.3748/wjg.v27.i30.4939
- [42] Rozengurt E (2014) Mechanistic target of rapamycin (mTOR): a point of convergence in the action of insulin/IGF-1 and G protein-coupled receptor agonists in pancreatic cancer cells. *Front Physiol*. 2014, 5:357. 10.3389/fphys.2014.00357
- [43] Song S, Wang B, Zhang X, Hao L, Hu X, Li Z, Sun S (2015) Long-term diabetes mellitus is associated with an increased risk of pancreatic cancer: a meta-analysis. *PLoS One*. 2015, 10:0134321. 10.1371/journal.pone.0134321
- [44] Shi YQ, Zhou XC, Du P, Yin MY, Xu L, Chen WJ, Xu CF. (2020) Relationships are between metformin use and survival in pancreatic cancer patients concurrent with diabetes: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2020, 99:21687. 10.1097/MD.00000000000021687
- [45] Soranna D, Scotti L, Zambon A, et al. (2012) Cancer risk associated with use of metformin and sulfonylurea in type 2 diabetes: a meta-analysis. *Oncologist*.. 2012, 17:813-22. 10.1634/theoncologist.2011-0462
- [46] Schmitt J, Sanchis SB, Moreau F, et al.(2008) Association of malignant insulinoma and type 2 diabetes mellitus: a case report. *Ann Endocrinol (Paris)*. 2008, 69:69-72. 10.1016/j.ando.2007.11.002
- [47] Siraj ES, Samuel G, Saber S, Samuel S, Hamrahian AH, Reddy SS. (2006) Metastatic malignant insulinoma in a patient with type 2 diabetes mellitus: case presentation and literature review. *Endocr Pract*. 2006, 12:411-6. 10.4158/EP.12.4.411
- [48] Sharma A, Kandlakunta H, Nagpal SJ, et al. (2018) Model to determine risk of pancreatic cancer in patients with new-onset diabetes. *Gastroenterology*. 2018, 155:730-739. 10.1053/j.gastro.2018.05.023
- [49] Singbo J, Locketz M, Ross IL (2021) Challenge of coexisting type 2 diabetes mellitus and insulinoma: a case report. *J Med Case Rep*. 2021, 15:479. 10.1186/s13256-021-03047-2
- [50] Sah RP, Sharma A, Nagpal S, et al. (2019) Phases of metabolic and soft tissue changes in months preceding a diagnosis of pancreatic ductal adenocarcinoma. *Gastroenterology*. 2019, 156:1742-1752. 10.1053/j.gastro.2019.01.039
- [51] Serrano J, Andersen DK, Forsmark CE, et al. (2018) Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer: From Concept to Reality. . 2018, 47:1208-1212. 10.1097/MPA.0000000000001167
- [52] Torre G, Sferrazza A, Gualano MR, et al. (2014) Investigating the synergistic interaction of diabetes, tobacco smoking, alcohol consumption, and hypercholesterolemia on the risk of pancreatic cancer: a case-control study in Italy. *Biomed Res Int* . 2014, 29:3-5. 10.1155/2014/481019
- [53] Tirkes T, Dasyam AK, Shah ZK, Fogel EL (2021) Role of standardized reporting and novel imaging markers in chronic pancreatitis. *Curr Opin Gastroenterol* [Internet. 2021, 37:512-9. 10.1097/MOG.0000000000000766
- [54] UK-EDI (2023) [Internet]. Org.uk. [cited 2023 May 20]. Available from. (2023). <https://lctc.org.uk/affiliates/ukedi/>.
- [55] Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. (2011) Pancreatic cancer. *Lancet* [Internet. 2011, 378:607-20.
- [56] Wang F, Herrington M, Larsson J, Permert J: (2003) The relationship between diabetes and pancreatic cancer. *Mol Cancer*. 2003, 6:4. 10.1186/1476-4598-2-4
- [57] Walker EJ, Ko AH, Holly EA, Bracci PM (2015) Metformin use among type 2 diabetics and risk of pancreatic cancer in a clinic-based case-control study. *Int J Cancer*. 2015, 136:646-53. 10.1002/ijc.29120
- [58] Wakasugi H, Funakoshi A, Iguchi H (2001) Clinical observations of pancreatic diabetes caused by pancreatic carcinoma, and survival period. *Int J Clin Oncol*. 2001, 6:50-4. 10.1007/pl00012080
- [59] Yuan C, Babic A, Khalaf N, et al. (2020) Diabetes, weight change, and pancreatic cancer risk. *JAMA Oncology*. 2020, 6:202948. 10.1001/jamaoncol.2020.2948
- [60] Zhao Z, Liu W (2020) Pancreatic cancer: a review of risk factors, diagnosis, and treatment. *Technol Cancer Res Treat*. 2020, 19:10.1177/1533033820962117
- [61] Zhou C, Qian W, Li J, et al. (2019) High glucose microenvironment accelerates tumour growth via SREBP1-autophagy axis in pancreatic cancer. *J Exp Clin Cancer Res*. 2019, 38:302. 10.1186/s13046-019-1288-7