Published in final edited form as:

J Acad Nutr Diet. 2018 April ; 118(4): 555–567. doi:10.1016/j.jand.2017.07.005.

Diabetes Mellitus and Obesity as Risk Factors for Pancreatic Cancer

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Conflict of Interest disclosures: All authors declared no conflict of interest

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is still one of the deadliest types of cancer. The worldwide estimates of its incidence and mortality in the general population are 8 cases per 100,000 person-years and 7 deaths per 100,000 person-years, and they are significantly higher in the United States than the rest of the world. The incidence of this disease in the United States (US) is over 50,000 new cases in 2017. Indeed, total deaths due to PDAC are projected to increase dramatically to become the second leading cause of cancer-related deaths before 2030. Considering the failure to date to efficiently treat existing PDAC, increased effort should be undertaken to prevent this disease. A better understanding of the risk factors leading to PDAC development is of utmost importance to identify and formulate preventive strategies. Large epidemiological and cohort studies have identified risk factors for the development of PDAC, including obesity and type-2 diabetes mellitus (T2DM). This review highlights the current knowledge of obesity and T2DM as risk factors for PDAC development and progression, their interplay and underlying mechanisms, the relation to diet, as well as outlines research gaps and opportunities to address this deadly disease.

Keywords

Pancreatic cancer; obesity; type 2 diabetes mellitus; prevention; review

Introduction

It is estimated that about one third of cases of cancer, the second leading cause of death in the United States (US), are caused by dietary factors.[1,2] One of the deadliest types of cancer has been and still is pancreatic ductal adenocarcinoma (PDAC), the most common histologic

type of pancreatic cancer. The worldwide estimates of its incidence and mortality in the general population are eight cases per 100,000 person-years and seven deaths per 100,000 person-years, and they are significantly higher in the US than the rest of the world.[3] The projected incidence of this disease in the US is over 50,000 new cases in 2017 and it is currently the third leading cause of cancer mortality in both men and women.[2] Despite advances in understanding the biology of PDAC, molecularly targeted therapy (such as epidermal growth factor receptor inhibitors) has not translated into substantially improved prognosis. Indeed, total deaths due to PDAC are projected to increase considerably to become the second leading cause of cancer-related deaths before 2030.[4] Considering the failure to date to efficiently treat existing PDAC, increased effort should be undertaken to prevent this disease. Consequently, the focus of research has shifted gradually towards its prevention and interception, which encompasses halting transformed cells from becoming malignant cancers.[5–9] In this context, a better understanding of the risk factors leading to PDAC development is of great importance to identify and formulate preventive and interceptive strategies and to ultimately educate the public. Large epidemiological and cohort studies have identified risk factors for the development of PDAC,[10–13] including obesity and type-2 diabetes mellitus (T2DM). This review highlights the current knowledge of obesity and T2DM as risk factors for PDAC development and progression, their interplay and underlying mechanisms, the relation to dietary influences, as well as outlines research gaps and opportunities to address this deadly disease.

Epidemiology of obesity, diabetes mellitus, and pancreatic cancer

Obesity and Diabetes as Risk Factors for PDAC

T2DM and obesity are among the small number of known modifiable risk factors for PDAC. There is a complex relationship between T2DM and obesity as they often coexist, but independently increase the risk for developing PDAC. An association of PDAC with T2DM and obesity is strongly suggested when the geographic prevalence of all three diseases is examined (Figure 1). The epidemiologic support for and proposed mechanisms of increased risk for PDAC in both longstanding T2DM and new-onset DM have been previously reviewed,[14–17] so the connection with obesity is further emphasized here.

Epidemiological evidence from various study types has consistently shown that obesity is a dose-dependent risk factor for the development of PDAC.[18–24] In a population study of over 900,000 adults, a 52% increased death rate from all cancers was observed in men and a 62% increased death rate in women with a body mass index (BMI) greater than 40 kg/m^2 compared to normal weight controls.[21] The relative risk (RR) of PDAC for subjects with BMI > 40 kg/m^2 was 2.61 (95% CI, 1.3–5.4; P=.001) for men and 2.76 (95% CI, 1.74–4.36; P=.001) for women. Additionally, an increased BMI was associated with an increased risk of death from several other cancers (such as esophagus, liver, and colon)[25–27] in which DM is less prevalent supporting an independent role of obesity in cancer development. It is important to acknowledge that the effect size of obesity as a PDAC risk factor is likely diluted when only BMI is considered because the distribution of fat appears to also influence cancer risk. For example, an increased waist to hip ratio is associated with a greater than 70% increased risk of PDAC.[23]

Evidence from clinical studies shows that weight loss, induced by dietary restriction, exercise, or bariatric surgery, reduces the risk of cancer.[28–33] Adams et al reported that the incidence of obesity-related cancers decreased by 50% in 6,596 bariatric surgery patients compared to 9,442 obese controls followed for an average of 12.5 years.[31] Similarly, in the Swedish Obesity Subjects study involving 2,010 bariatric surgery patients and 2,037 un-operated controls, Sjöström et al reported that the overall mortality was reduced by 24% in the surgery cohort, but the number of deaths from individual cancers was too small to assess organ-specific effects.[29,33]

Interaction of Obesity with Diabetes and PDAC

Although many epidemiologic studies have been confounded by the frequent coexistence of T2DM in the obese groups, larger studies indicate that obesity confers a significant cancer risk independent of the presence of T2DM. For example, Jiao et al studied a pooled cohort of over 900,000 subjects in which there were 2,454 who developed PDAC.[34] The incidence of PDAC increased by 19% in the group with a BMI 30–35 kg/m^2, and was not affected by the presence of T2DM.

Studies probing the contribution of metabolic alterations associated with obesity have corroborated the risk and suggest that increased insulin levels due to the insulin resistance of obesity are an important factor. Stolzenberg-Solomon et al studied levels of glucose and insulin and measures of insulin resistance in 29,133 Finnish male smokers followed for almost two decades.[35] Fasting glucose, insulin levels, and insulin resistance (estimated with HOMA-IR) were positively associated with PDAC. Importantly, the RR of PDAC was 2.71 (95% CI, 1.19–6.18; P=.006) in subjects with the highest quartile of insulin resistance. As obesity is associated with insulin resistance in virtually all subjects, hyperinsulinemia is believed to have a causative role in PDAC tumorigenesis.[36] In an autopsy study, Butler et al evaluated the influence of DM and obesity on pancreatic duct cell proliferation determined by the expression of Ki67, a nuclear protein strictly associated with cellular proliferation.[37] Lean non-diabetic, obese non-diabetic, lean diabetic, and obese diabetic subjects demonstrated progressive increases in Ki67 expression, suggesting that obesity increased pancreatic duct cell proliferation, and the magnitude of this effect was further increased by the presence of T2DM. When hyperinsulinemia can no longer adequately compensate for the insulin resistance, persistent hyperglycemia results, and further increases the risk. In this way, both hyperinsulinemia and hyperglycemia are related factors which promote dysplasia and neoplasia in the pancreas.

Overview of mechanisms underlying the increased risk of PDAC by T2DM and obesity

A variety of overlapping and distinct mechanisms exist, by which T2DM and obesity can promote PDAC development. Patients with T2DM and the overwhelming majority of obese subjects are characterized by insulin resistance with ensuing hyperinsulinemia and high levels of insulin-like growth factor-1 (IGF-1),[38–45] which can act as potent growth-promoting factors. The effects of insulin and/or IGF-1 are mediated by binding to insulin receptors, IGF-1 receptors, and hybrid insulin/IGF-1 receptors with subsequent activation of

the PI3K signaling cascade.[46] Of note, insulin/IGF-1 receptors have been described to be expressed on human pancreatic cancer cells.[47] The importance of elevated insulin/IGF-1 levels in PDAC development is highlighted by the potential anti-tumor effects of metformin, an anti-diabetic drug that lowers circulating insulin/IGF-1 levels. Recent preclinical and clinical studies indicate that metformin use lowers the risk of PDAC, inhibits cancer cell growth, and improves survival of patients.[7,48–55] The observation that several clinical trials did not find a beneficial effect of metformin in patients with advanced PDAC[56–58] suggests a potential role of metformin more in the primary/secondary prevention and early interception settings.[59]

Obesity and T2DM are increasingly recognized as chronic, systemic, low-grade inflammatory conditions with elevations in reactive oxygen species, pro-inflammatory cytokines, adipokines, and eicosanoids.[40,41,45] This systemic and local inflammatory milieu may be conducive to tumor initiation and/or promotion.[60,61] The inflammatory microenvironment also is thought to be the major mechanism, by which chronic pancreatitis leads to PDAC development.[62–65] Targeting pancreatic inflammation by inhibiting cyclooxygenase activity, using aspirin, or targeted blockade of inflammatory cytokines has been shown to attenuate cancer development and/or growth.[66–71] Mouse models have demonstrated that obesity is associated with increased pancreatic inflammation, immune cell infiltration, and accelerated neoplasia.[72–74] Targeting obesity by caloric restriction decreased pancreatic inflammation and reduced PDAC incidence and progression.[75,76] Similarly, T2DM and accompanying hyperglycemia have been shown to lead to chronic inflammation and increased cancer risk,[77] while inhibition of inflammatory signaling pathways reduced PDAC growth in a diabetic animal model.[78] On a molecular level, a novel cross-talk between the inflammatory prostaglandin signaling pathway and mTORC-1, which is implicated in insulin resistance during obesity and T2DM, highlights the intricate cross-talk between obesity, T2DM, and inflammation.[79] There is recent evidence indicating the nuclear receptor PPAR-γ to be at the crossroads of obesity, T2DM, and PDAC by regulating metabolism, inflammation, insulin and adipokine production.[80] Dietary fish oil and omega-3 polyunsaturated fatty acids (PUFAs) have been shown in some laboratory and clinical studies to be correlated with a reduced PDAC incidence and decreased cancer growth,[81–86] while some reports showed no beneficial effects.[87] The Pancreatic Cancer 2012 Report of the Continuous Update Project (CUP) described a marginal correlation between total fat intake and PDAC risk, but no conclusions could be made for PUFAs.[88] Consumption of fish oil has been correlated with the prevention of obesity and the improvement of insulin resistance, non-alcoholic fatty liver disease, and cardiovascular disease.[89–94] Fish oil rich in omega-3 PUFAs has thereby been shown to promote an anti-inflammatory microenvironment by altering adipokine/cytokine production and attenuating pro-inflammatory immune cells.[95–98] Importantly, omega-3 PUFAs are known ligands of PPAR-γ, again placing this nuclear receptor in a central role orchestrating metabolism, inflammation, and cancer risk.

Chronic pancreatic inflammation is characterized by a desmoplastic (dense fibroblastic) reaction. Conflicting reports have described both a pro- and anti-tumorigenic role of desmoplasia (dense connective tissue).[99,100] Recent studies have highlighted the importance of pancreatic desmoplasia in the context of obesity-associated PDAC.[101] In addition, a

connection between hyperinsulinemia, pancreatic stellate cell activation, and islet fibrosis in a diet-induced obesity model of PDAC has been described.[102] Other mechanisms have been described, by which obesity can promote the development of cancers, including changes in autophagic processes, gastrointestinal peptide secretion, and gut microbiota.[39,43,45,103] A recent study reported that a membrane protein from a specific gut bacterium improved metabolism in obese and diabetic mice.[104] However, a current meta-analysis questioned whether there are specific microbiome-based markers that can be associated with human obesity.[105] This analysis reported that the ability to reliably classify individuals as obese solely on the basis of the composition of their microbiome was limited due to a lack of power to detect modest effect sizes.[105] It is therefore currently unclear whether obesity leads to significant changes in the gut microbiome with subsequent deleterious health effects. Overall, there are many possible mechanisms, by which obesity and T2DM can promote PDAC development and enhance risk factor-induced tumor formation, including changes in signaling and metabolic pathways and fibro-inflammatory processes.

The central role of adipose tissue in mediating the increased risk of PDAC by T2DM and obesity

During obesity, the white adipose tissue may become dysfunctional and fail to meet the storage capacity needed for the excess caloric intake. This may lead to deleterious sequelae, including inflammation, fibrosis, hypoxia, and dysregulated adipokine secretion (Figure 2).[106] This adaptive failure of adipose tissue may also result in ectopic fat deposition in other metabolically active tissues, e.g. liver, skeletal muscle, endocrine and exocrine pancreas, leading to progressive insulin resistance and T2DM.[106,107] Obesity-associated adipose tissue inflammation is characterized by an elevation of pro-inflammatory cytokines and adipokines, e.g. TNF-α, IL-1β, IL-6, MCP-1, leptin, and resistin, and a decrease in anti-inflammatory molecules, e.g. IL-10, adiponectin.[108] The inflammatory milieu in white adipose tissue during obesity is also characterized by profound immune cell changes. Adipose tissue macrophages (ATM) play a critical role in obesity-associated adipose tissue inflammation.[109–115] In the lean state, ATMs display an anti-inflammatory M_2-polarized phenotype, which is maintained by Th_2-type cytokines produced by other tissue-resident immune and stromal cells. During obesity, the adipose tissue is characterized by a reduction of anti-inflammatory immune cells and cytokines, a predominance of pro-inflammatory M_1-polarized macrophages, and an increase in Th_1-type cytokines. Inhibiting the pro-inflammatory macrophage phenotype has been demonstrated to improve obesity-associated metabolic dysfunctions.[116,117]

Adipose tissue inflammation is considered to significantly contribute to the development of obesity-associated cancers, including PDAC.[41,43,101,118,119] A recent report has demonstrated that in the conditional KrasG12D mouse model of PDAC diet-induced obesity induced robust inflammation in the visceral white adipose tissue with an increase in crown-like structures, histological features of adipose tissue inflammation (necrotic adipocytes surrounded by macrophages) and elevated levels of pro-inflammatory cytokines and adipokines.[120] This was associated with an acceleration of PDAC development.[120] Interestingly, the observed obesity-associated inflammatory changes in this model were

more robustly seen in mesenteric (peri-pancreatic) visceral adipose tissue than in other depots, emphasizing the importance of distinct anatomical locations of white adipose tissue.[120] This notion is supported by human studies showing a stronger correlation between visceral adiposity (in contrast to generalized whole body fat), metabolic dysfunction, and PDAC.[121–126]

Recent studies have highlighted the importance of adipokines in PDAC risk and progression. Elevated levels of leptin, which are commonly seen in obese patients (with or without T2DM), were found to be associated with an increased risk of PDAC.[127,128] Increased plasma concentrations of leptin were also detected in a diet-induced obesity model of PDAC,[72] whereas caloric restriction decreased circulating leptin levels, which was accompanied by a delay of PDAC development.[129] Experimental studies have linked leptin signaling to PDAC progression.[130–132] Fewer studies have focused on the role of adiponectin in PDAC but lower circulating adiponectin levels are correlated to an increased PDAC risk.[133–135]

Intra-pancreatic fat accumulation, termed non-alcoholic fatty pancreas disease (NAFPD), ranging from simple fat deposition to pancreatic inflammation and fibrosis, has been associated with other diseases of obesity.[107] A recent meta-analysis of clinical studies has shown that NAFPD may promote pancreatic endocrine dysfunction associated with insulin resistance and T2DM, and have links to the development of PDAC.[136–141] Taken together, the available literature strongly indicates an important role of dysfunctional white adipose tissue, including inflammation and ectopic fat deposition due to obesity on metabolic disorders and PDAC development.

Dietary factors and Pancreatic Ductal Adenocarcinoma

Dietary factors that may affect the risk for PDAC include carbohydrate intake, fat intake, meat, fish, fruits and vegetables.[12] It has been difficult to definitively establish risk factors because selection bias (e.g. studies limited to females only, or individuals of certain ethnicity only) complicates such investigations.[24] The other common problem with studies on dietary factors is recall bias, which is a particular concern in retrospective studies. Further, individual studies of various designs and questionable methodological quality are frequently evaluated by meta-analysis,[142] which may yield biased estimates. While more than 100 articles are published annually on dietary factors associated with risk of developing PDAC, we elected to present findings from the most robust individual epidemiological studies, i.e. prospective cohort studies conducted in a general population. PubMed was searched for articles published between January 1, 1990, and December 31, 2016. Only prospective, population-based, cohort studies that investigated dietary factors in relation to the development of PDAC are summarized below. Studies had to include adult individuals of both sexes living in a given geographic area. Studies were excluded if they were retrospective cohort, (nested) case-control, cross-sectional, or interventional studies or were not representative of the general population (e.g., insurance claims, tertiary setting only, cohorts limited to a particular ethnicity or occupation).

Carbohydrate intake

A prospective cohort study by Mueller et al.[143] followed up a total of 60,524 individuals in Singapore for 14 years (on average), of which 140 developed incident PDAC. In multivariate analysis, the authors found that individuals consuming ≥2 soft drinks/week had a statistically significant increased risk of PDAC (hazard ratio or HR, 1.87; 95% CI, 1.10–3.15) compared with individuals who did not consume soft drinks. No statistically significant association was found between juice consumption and PDAC risk. A prospective cohort study by Larsson et al.[144] followed a total of 77,797 individuals in Sweden for 7.2 years (on average), of which 131 developed incident PDAC. In multivariate analysis, the authors found significant associations between consumption of added sugar and soft drinks and risk of pancreatic cancer. The HRs for the highest compared with the lowest consumption categories were 1.95 (95% CI, 1.10–3.46; P = 0.03) for added sugar and 2.30 (95% CI, 1.35–3.92; P = 0.006) for soft drinks. However, there were no associations between consumption of fruit soups, or stewed fruit jam/marmalade, or sweets and PDAC risk. In a prospective cohort study by Bao et al.[145] a total of 487,922 individuals in the US were followed up for 7.2 years (on average), of which 1258 developed incident PDAC. In multivariate analysis, the authors found no statistically significant association between high intake of total added sugar or sugar-sweetened foods/beverages and PDAC risk. The median intakes for the lowest and highest quintiles of total added sugar intake were 12.6 (3 tsp/d) and 96.2 (22.9 tsp/d) g/d, respectively. A prospective cohort study by Jiao et al.[146] followed up a total of 482,362 individuals in the US for 7.2 years (on average), of which 1151 developed incident PDAC. In multivariate analysis, the authors found no statistically significant association between total or available carbohydrates or glycemic load/glycemic index and risk of pancreatic cancer. However, individuals with high free fructose intake were at a significantly higher risk of developing PDAC (highest compared with lowest quintile, RR, 1.29; 95% CI, 1.04–1.59; P = 0.004). Similarly, individuals with high free glucose intake were at a significantly higher risk of developing PDAC (RR, 1.35; 95% CI, 1.10–1.67; P = 0.005). These data are in agreement with another large meta-analysis describing a positive correlation between high fructose intake (but not total carbohydrates, glycemic index) and pancreatic cancer.[142] In another prospective cohort study by Patel et al.[147] a total of 124,907 individuals were followed up in the US for a maximum of nine years, of which 401 developed incident PDAC. In multivariate analysis, the authors found no statistically significant association between glycemic load/glycemic index or carbohydrate intake and PDAC risk. Finally, an important meta-analysis reported that high fructose intake is associated with an increased incidence of PDAC.[142]

Fat intake

A prospective cohort study by Thiebaut et al.[148] followed up a total of 525,473 individuals in the US for 6.3 years (on average), of which 1337 developed incident PDAC. In multivariate analysis, the authors found that the intakes of total fat (highest vs lowest quintile, HR, 1.23; 95% CI, 1.03–1.46; P = 0.03), saturated fat (HR, 1.36; 95% CI, 1.14–1.62; P = 0.001), and monounsaturated fat (HR, 1.22; 95% CI, 1.02–1.46; P = 0.05) were associated with statistically significant higher PDAC risks. The associations were strongest for saturated fat from animal food sources (HR, 1.43; 95% CI, 1.20–1.70; P < .001); specifically, intakes from red meat and dairy products.

Fish intake

A prospective cohort study by He et al.[85] followed up a total of 66,616 individuals in the US for 6.8 years (on average), of which 151 developed incident PDAC. In multivariate analysis, the authors found that long-chain (n-3) polyunsaturated fatty acids (LC-PUFAs) were associated with a statistically significant lower PDAC risk (HR, 0.62; 95% CI, 0.40–0.98; P = 0.04). Similarly, non-fried fish intake was associated with a statistically significant lower PDAC risk (HR, 0.55; 95% CI, 0.34–0.88; P = 0.04). Also, docosahexaenoic acid showed a greater inverse association with PDAC than eicosapentaenoic acid. However, no statistically significant associations were observed with fried fish and shellfish consumption.

Meat intake

A prospective cohort study by Stolzenberg-Solomon et al.[149] followed up a total of 537,302 individuals in the US for a maximum of five years, of which 831 developed incident PDAC. In multivariate analysis, the authors found total, red, and high-temperature cooked meat intake was significantly associated with PDAC among men (fifth versus first quintile: HR, 1.41, 95% CI, 1.08–1.83, P = 0.001; HR, 1.42, 95% CI, 1.05–1.91, P = 0.01; and HR, 1.52, 95% CI, 1.12–2.06, P = 0.005, respectively). However, no statistically significant associations were observed among women.

Fruits and vegetables

A prospective cohort study by Larsson et al.[150] followed up a total of 81,922 individuals in Sweden for 6.8 years (on average), of which 135 developed incident PDAC. In multivariate analysis, the authors found that cabbage consumption was associated with a statistically significant lower PDAC risk (≥1 serving/week versus never consumption: HR, 0.62; 95% CI, 0.39–0.99). However, the HR for the highest compared with the lowest category of intake was not statistically significant for total vegetables (HR, 1.08; 95% CI, 0.63–1.85). Similarly, the HR for the highest compared with the lowest category of intake was not statistically significant for total fruits (HR 1.10; 95% CI, 0.64–1.88). While some studies found no association between fruit and vegetable intake and PDAC, it is possible that measurement errors may obscure an association as one large cohort found an inverse association between vitamin C and carotenoids (as markers of fruit and vegetable intake) and PDAC risk.[151]

It is now well-established that metabolic pathways are altered in cancer.[152] However, it is less readily evident how chronic alterations in our system biology enhance cancer risk. Excessive caloric intake due to excessive dietary fat and red meat, sugar-containing soft drinks, and fructose can lead to an increasing prevalence of obesity of diabetes, and secondarily to a higher incidence of PDAC. However, there are likely also direct effects. Thus, high intake of sugars leads to elevated chronic elevation in insulin levels, excessive fat intake may cause abnormal lipid metabolism and promote reactive oxygen generation, whereas the chronic absence of green vegetables and fruits can lead to alterations in regulatory immune pathways and the microbiome. All these alterations can enhance cancer risk in the context of polymorphisms and genetic susceptibilities. An update of the current evidence on food, nutrition and physical activity relating to the prevention of pancreatic cancer has been published as part of the Continuous Update Project in 2012.[88] An improved

understanding of these alterations that precede neoplastic transformation in the pancreas would allow for the development of more precise preventive strategies.

Animal models of obesity and diabetes to study PDAC

Animal models that mimic aspects of diabetes, in particular, T2DM and obesity are important tools for the understanding of how these metabolic diseases can increase the risk of developing other diseases such as PDAC. The complexity of the processes involved with T2DM and obesity and the time it takes for individuals to develop PDAC makes it challenging to conduct longitudinal studies in humans focused on specific molecular mechanisms related to these diseases. Therefore, using animal models that recapitulate in part obesity and T2DM as surrogates are an option for researchers interested in understanding the molecular basis of these diseases. Unfortunately, animal models are imperfect and most do not recapitulate all features of human obesity and T2DM. The selection of the models used for pre-clinical studies depends on the research hypothesis and a detailed understanding of how the model was generated including its phenotype. Of the many models currently available, the diet-induced obesity (DIO) model is one of the most commonly used as well as genetically engineered mouse models (GEMM) for which pathways linked to the control of body weight and appetite signals are altered. Currently available mouse models to study obesity are comprehensively reviewed elsewhere.[153,154] Here we describe the models most commonly used to study these diseases as they relate to PDAC.

In the DIO model mice are fed a diet high in fats and calories that closely mimics what is commonly referred to as a Western-style diet, which contains 40–60% of energy derived from fats and is consumed *ad libitum.*[155] These diets have been used extensively in obesity research with great success[76,156] and recapitulate obesity-induced by diet in humans. The most commonly used mouse strain is C57BL/6, which is among the most sensitive to DIO and results in increased glucose levels. In this strain, males develop more severe obesity than females. Using this model injection of PDAC cells led to increased tumor burden in diet-induced obese mice.[132,157] A number of studies have tested these diets using GEMM that recapitulate the human stages of PDAC development, and shown an acceleration of the initiation and progression of PDAC and reduced survival.[72,74,76,120,158,159] Moreover, these studies have been able to identify the molecular mechanisms for which obesity increases the risk of developing PDAC, including an increase in inflammatory pathways.

Among the most commonly used GEMM of obesity and diabetes are those affecting the leptin pathway leading to hyperphagia, decreased energy expenditure, hyperglycemia, and insulin resistance. Mice with a single base spontaneous mutation in the obese (ob) gene (Lep^{ob}/Lep^{ob}) are not able to secrete leptin from adipose tissues.[160,161] These mice become obese and exogenous administration of leptin prevents obesity development and metabolic syndrome. Recently this model was used to study the effects of obesity-induced inflammation in PDAC where PDAC cell lines were injected orthotopically and an accelerated tumor growth was observed.[101] Another useful model is one, in which mice lack the leptin receptor ($LepR^{db}/LepR^{db}$)[162–164] due to a point mutation in a stop codon that shortens the intracellular domain and abolishes signaling. PDAC cells implanted

subcutaneously in this model developed larger tumors compared to lean mice.[165] However, the obesity and insulin-resistant phenotype observed in these mice is dependent upon the genetic background.[153] These mice are often used in T2DM studies, but do not recapitulate all aspects of human disease, such as pancreatic amyloid deposition.[153]

Despite marked similarities between mouse models and human disease, differences exist that need to be considered before designing animal experiments. Even though the mouse models of obesity and T2DM (in the context of PDAC) discussed here do not recapitulate all features seen in humans, they are still an invaluable resource to investigate important aspects of these diseases that can then be translated into humans. With obesity and obesity-related metabolic diseases representing a growing socioeconomic burden globally and PDAC being a relatively rare cancer, mouse models are needed to explore the molecular mechanisms that link these diseases.

Effect of T2DM and obesity on the pancreatic microenvironment - crosstalk between stellate cells and islets

PDAC presents a unique microenvironment for a cancer with a substantial desmoplastic response. The desmoplastic response is due to proliferation and production of extracellular matrix proteins by tumor-associated fibroblasts, which are activated pancreatic stellate cells (PaSCs). This desmoplasia or microenvironment contains immune cells, nerve cells, blood vessels and extracellular matrix (ECM) proteins and factors that regulate ECM production.[166] The identification of activated PaSCs as key participants in the desmoplastic microenvironment of PDAC was first made in 2004 by Apte et al.[167] They showed that the activated PaSCs, which contribute to the fibrosis of chronic pancreatitis,[168] were also present in PDAC. In their normal, inactive and non-pathologic state, PaSCs produce small amounts of ECM and are involved in tissue repair.[169] In both in human tissue and in mouse experimental models of PDAC activated PaSCs are present both in early intraepithelial neoplastic lesions (PanIN) as well as in advanced PDAC.[72,166,170] Related to obesity and diabetes, in a mouse model of high fat, high calorie diet there were increased activated PaSCs and fibrosis associated with the advancement of the tumor lesions.[72]

Regarding the effect of T2DM on PaSC function a recent publication examined the effects on insulin and glucose on PaSCs in mice and humans.[102] In this study, activated PaSC were observed both in the islets and the peri-islet exocrine tissue in both T2DM patients and in mice fed a high-fat, high-calorie diet. These findings were absent in control-fed animals. These findings support those of previous studies showing mild fibrosis in patients with T2DM which has been referred to as diabetes-associated exocrine pancreatopathy.[171] This study also found that PaSCs respond to high concentrations of both insulin and glucose with increased cell proliferation and ECM production. Further, the effects of insulin were mediated by insulin receptors and insulin-like growth factor receptors that were present on PaSCs and by Akt/mTOR downstream signaling. The study concluded that obesity and T2DM through effects on PaSCs can contribute to pancreatic fibrogenesis, desmoplasia and promotion of PDAC. Several other studies have demonstrated that islet macrophages, particularly M1-like macrophages, contribute to islet inflammation and beta-cell dysfunction

in T2DM.[172] Therefore, it is plausible that in T2DM multiple local cytokines secreted by islet macrophages and PaSCs modulate macrophage polarization, islet inflammation, and peri-islet fibrosis, all factors increasing T2DM pathology and the risk of PDAC.

There are studies designed to delineate mechanistic relationships between PaSCs, cancer cells and immune cells in PDAC.[166,173] In brief, these studies show that PDAC cells stimulate proliferation and migration of PaSC in culture, as well as their production of ECM components.[166,174] Secretions from pancreatic duct cells isolated from GEMM stimulate activation, proliferation and fibrogenic responses in isolated mouse PaSC[170] supporting the role of the cancer cell in regulating the PaSC responses in development.

A question that remains under debate is whether the activated PaSCs promote or retard cancer growth. Early studies showed that PaSCs stimulate cell proliferation; inhibit apoptosis; and promote migration as well as epithelial mesenchymal transition (EMT) in cancer cells.[166,175,176] Also, studies have shown that ECM proteins made by PaSCs are necessary to prevent apoptosis of cancer cells.[177–181] A recent study[182] using a chronic pancreatitis model where the tissue has similar characteristics to the desmoplasia of PDAC activated PaSCs secrete cytokines IL-4 and IL-13 promoting the transition of monocytes and macrophages to pro-tumor associated macrophages (TAMs). These macrophages are present in PanIN lesions and PDAC.[183] Furthermore, TAMs in PDAC are associated with poor outcomes as they inhibit normal immune surveillance.[184,185] Because TAMs secrete TGF-β, which promotes the activated state of PaSCs, a feed forward promotion of PaSC activation and TAM maintenance has been proposed for advancement of PDAC.[173]

There are recent reports[186,187] showing that genetic methods eliminating PaSCs or pharmacological targeting of the Sonic hedgehog pathway, which is known to promote PaSC function in a PDAC mouse model, increased invasive and undifferentiated tumors and decreased survival. These results have resulted in a consensus that PaSCs can have either PDAC promoting or inhibiting effects. Current work is directed toward understanding the molecular details of these differences which could lead to important therapeutic interventions.

Gaps in knowledge and research opportunities

Although the risk factors promoting PDAC development have been known for several decades their underlying molecular mechanisms and interactions have just recently begun to be explored. High quality epidemiological studies associate obesity with an elevated risk of PDAC. Nevertheless, it is currently unclear whether “metabolically healthy obesity” also carries an increased risk of PDAC. In addition, the beneficial effects of weight reduction and bariatric surgery on improving insulin resistance are known, but their role in decreasing PDAC incidence is still essentially unknown. Although the general pathways linking obesity and T2DM to PDAC have been described, including chronic tissue and systemic inflammation, cytokines/adipokines, hyperinsulinemia and elevated IGF-1, the exact molecular and signaling pathways and their intricate interaction are still underexplored. Adipose tissue plays a central role in obesity and T2DM. However, the precise contribution and molecular signals of different adipose tissue depots and possible sex differences on

PDAC development are not known. Several genetically engineered animal models are now available to study early PDAC development and risk factors and to investigate preventive strategies. Diet-induced obesity models are valuable tools to explore the role of obesity and metabolic disturbances in PDAC. However, very few studies exist that comprehensively investigate and compare the effects of individual nutritional components on PDAC development. It is currently unknown whether obesity experimentally induced by a high fat or high carbohydrate diet differs in increasing PDAC incidence or whether the simply increased caloric intake is the essential component. Altogether, given the high mortality of PDAC and expected increase in obesity and diabetes over the next few decades, efforts should be undertaken to mechanistically understand the link between obesity, diabetes, and PDAC. Preclinical animal models are available that will facilitate the study of these important interactions to advance our knowledge, so that the obesity- and diabetes-driven burden of PDAC can be curbed.

The Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC) is a multi-center program jointly sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases and the National Cancer Institute, which is pursuing a variety of studies to further identify mechanisms and biomarkers of PDAC in order to increase early detection of the disease and to inform intervention strategies.[188] CPDPC investigators are applying lessons learned from studies such as those described here to gain insights into the mechanisms by which diabetes and inflammation contribute to the incidence of PDAC.

Acknowledgments

Grant support: Research reported in this publication was supported by National Cancer Institute and National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under award numbers U01DK108300, U01DK108314, U01DK108323, U01DK108326, U01DK108327, P01CA163200, P01DK098108, R01CA075059. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Research Snapshot

Research Question

What is the current research status on the link between obesity, type 2 diabetes mellitus, dietary issues, and pancreatic cancer?

Key Findings

This narrative review describes a clear epidemiological association between obesity, type 2 diabetes mellitus and pancreatic cancer risk. Major pathophysiological mechanisms underlying this link, including inflammation and adipose tissue dysfunction, are discussed. Available animal models to study the impact of these risk factors on pancreatic cancer development are summarized, and research gaps and opportunities to advance the field presented.

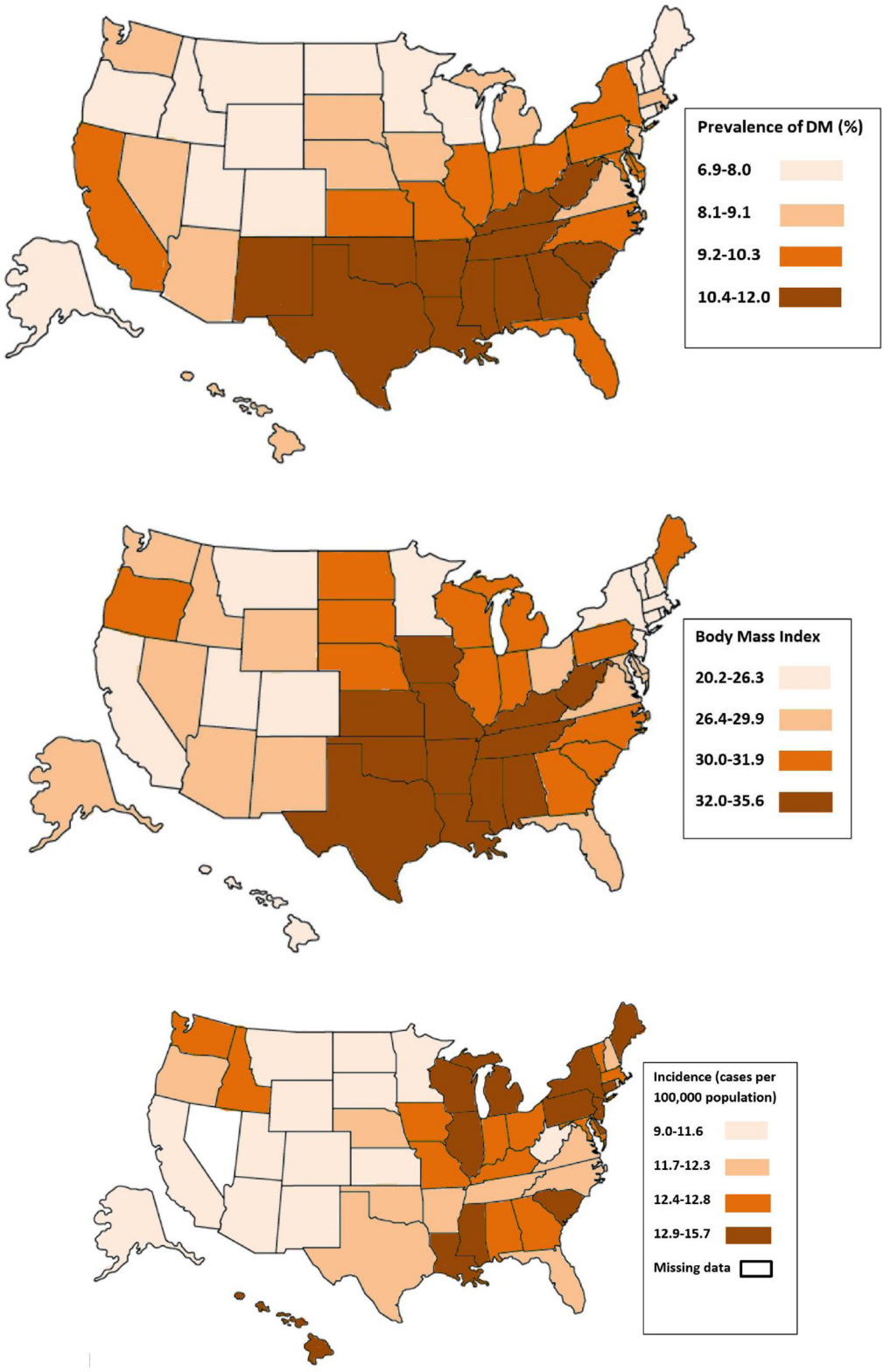

Figure 1. Prevalence of diabetes mellitus (DM), Prevalence of Obesity, and Incidence of Pancreatic Cancer

Figure 1A (Top): Prevalence of DM (in quartiles) 2014 (from http://www.cdc.gov/diabetes/data). Figure 1B (Middle): Prevalence of Obesity expressed as Body Mass Index (in quartiles) 2015 (from http://www.cdc.gov/obesity/data). Figure 1C (Bottom): Incidence of Pancreatic Cancer, age adjusted, all races (in quartiles) 2009–2013 (from http://statecancerprofiles.cancer.gov/data-topics/incidence.html).

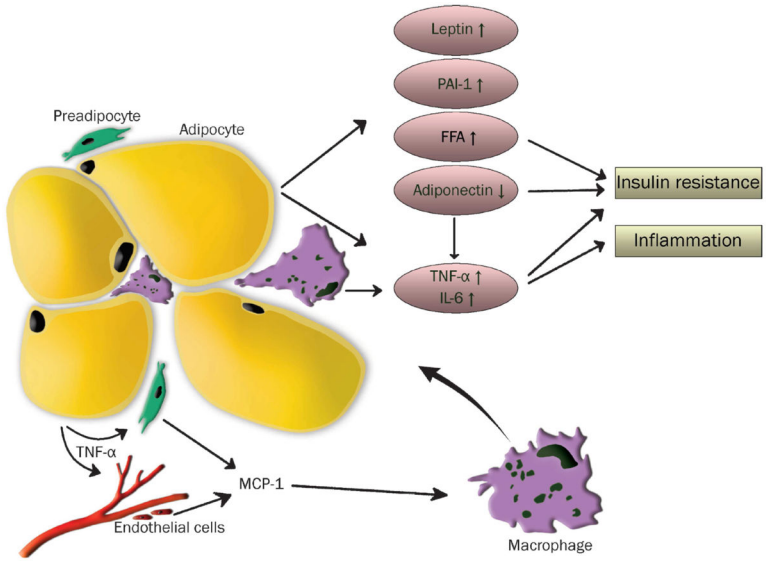

Figure 2. Adipose tissue dysfunction during obesity

Schematic overview of obesity-associated changes in white adipose tissue leading to hyperplasia/hypertrophy of adipocytes, recruitment and proliferation of immune cells, increased secretion of pro-inflammatory cytokines (e.g. TNF-α, IL-6) and adipokines (leptin), reduction of adiponectin, increase of free fatty acids (FFA), ultimately leading to insulin resistance and systemic and local inflammation (from van Kruijsdijk et al. Cancer Epidemiol Biomarkers Prev 2009; 18(10): 2569–78 with permission).

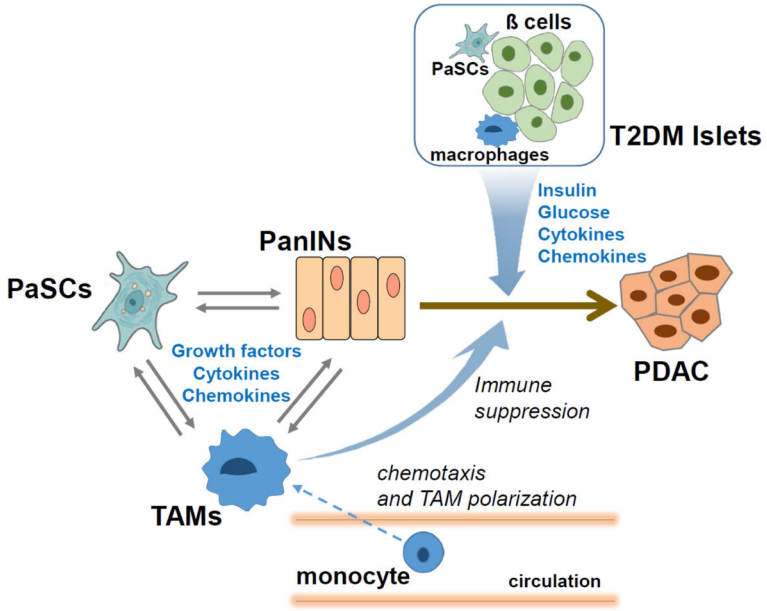

Figure 3. Promotion of PDAC by T2DM: Potential Role of Islet Factors

Illustration of the interplay and crosstalk between pancreatic pre-cancer (PanIN) and cancer (PDAC) cells, pancreatic stellate cells (PaSCs), immune cells (e.g. tumor-associated macrophages: TAMs), and islets.