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PANCREATITIS - DIABETES - PANCREATIC CANCER: Summary of an NIDDK-NCI Workshop

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Abstract

A workshop sponsored by the NIDDK and the NCI on “Pancreatitis-Diabetes-Pancreatic Cancer” focused on the risk factors of chronic pancreatitis (CP) and diabetes mellitus (DM) on the development of pancreatic ductal adenocarcinoma (PDAC). Sessions were held on a) an overview of the problem of PDAC, b) CP as a risk factor for PDAC, c) DM as a risk factor for PDAC, d) pancreatogenic, or type 3c DM (T3cDM), e) genomic associations of CP, DM, and PDAC, f) surveillance of high-risk populations and early detection of PDAC, and g) effects of DM treatment on PDAC. Recent data and current understandings of the mechanisms of CP- and DM-associated factors on PDAC development were discussed, and a detailed review of the possible risks of DM treatment on the development of PDAC was provided by representatives from academia, industry, and the Food and Drug Administration. The current status of possible biomarkers of PDAC and surveillance strategies for high-risk populations were discussed, and the gaps in knowledge and opportunities for further research were elucidated. A broad spectrum of expertise of the speakers and discussants provided an unusually productive workshop, the highlights of which are summarized in the accompanying article.

INTRODUCTION

To better understand the mechanisms and potential interconnections between pancreatitis, diabetes and pancreatic ductal adenocarcinoma (PDAC), the National Institute of Diabetes,

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Digestive & Kidney Disease (NIDDK) and the National Cancer Institute (NCI) cosponsored a workshop in Bethesda, Maryland, USA on June 12–13, 2013. The workshop was designed to bring together experts from academic institutions, industry and government agencies to present relevant data and perspectives on questions related to the risk and development of pancreatic cancer.

Twenty-seven presenters and seven discussants were joined by twenty-one poster presentations (a complete agenda and list of presenters is available as supplementary material at www.pancreasjournal/sdc). The workshop was dedicated to the memory of George S. Eisenbarth, MD, PhD, a visionary mentor and investigator in the field of diabetes who succumbed to pancreatic cancer in November 2012. The program included six sessions: (1) Statement of the Problem of PDAC, (2) Pancreatitis as a Rsk Factor for PDAC, (3) Diabetes as a Risk Factor for PDAC, (4) Pancreatogenic (Type 3c) Diabetes, (5) Surveillance of High-risk Populations and Early Detection of PDAC, and (6) Effects of DM Treatment on PDAC. In addition, the workshop included state of the art lectures on *Overview of PDAC* and on *Genomic Associations of Chronic Pancreatitis, Diabetes Mellitus, and PDAC*. The highpoints of each session are summarized below.

OVERVIEW OF THE PROBLEM

In contrast to dramatic declines in cancer-related deaths from other malignancies (i.e., lung and bronchus, breast, colorectal, and prostate cancer), progress in the management of PDAC has been slow and the incidence of deaths due to PDAC continues to rise [1]. The known risk factors for PDAC include tobacco exposure, longstanding diabetes, obesity, advanced age, exposure to benzenes, family history, and chronic pancreatitis (Table 1) [2]. It is generally believed that unless the cancer risk in a given population increases 8–10 fold over average risk, there is no cost-benefit advantage to screening. In selected syndromes such as familial pancreatic cancer, Peutz-Jeghers syndrome, familial atypical mole and melanoma syndrome, familial pancreatitis or in selected families with BRCA mutations, the risk does approach or exceed this threshold. In these circumstances, screening with either endoscopic ultrasound (EUS) or magnetic resonance imaging is justified [3].

On the molecular level, the driving oncogene for this malignancy appears to be KRAS [4]. In addition to activating mutations of this gene, other pathways are frequently suppressed, such as p16, p53, and DPC4. However, a family history is still more important than mutation screening for predicting the risk of PDAC. Precursor lesions for invasive disease include pancreatic intraepithelial neoplasms (PanINs) or benign tumors with malignant potential, such as intraductal-papillary mucinous neoplasms (IPMNs) or mucinous cystic neoplasms. Histologically, the invasive malignant lesion is dominated by an intense desmoplastic stroma, and the role of the stromal compartment is incompletely understood but thought to play a major role in the aggressive behavior of this malignancy. It has been suggested that the desmoplastic stroma may be a barrier to effective drug delivery. Although new chemotherapy regimens, such as FOLFIRINOX or gemcitabine plus nab-paclitaxel, have been introduced, these regimens are not free of toxicity and add little to long-term survival. For these reasons, a better understanding of the unique characteristics of PDAC is needed in order to improve early detection, treatment, and prevention.

CHRONIC PANCREATITIS (CP) AS A RISK FACTOR FOR PDAC

Understanding the common pathways for CP and PDAC may help to identify high risk patients and facilitate the development of effective screening tools. Epidemiologically, pancreatitis can be considered as a disease continuum: starting with an attack of acute pancreatitis (AP), leading to recurrent AP in some patients (about 20–30%), then

progression to CP in some (about 10%) and ultimately development of PDAC in a subset of CP patients [5]. Risk of progression from AP to CP seems to be higher in patients with a history of continuous tobacco smoking or alcohol drinking [5]. The precise risk factors and mechanisms involved with this progression have yet to be determined however.

One of the challenges in epidemiology studies of pancreatitis and/or diabetes with PDAC is reverse causality [6]. While long-standing CP clearly increases risk for PDAC, PDAC also causes AP and CP. Likewise, while long-standing diabetes increases risk for PDAC, PDAC itself causes glucose intolerance and diabetes as a paraneoplastic process. Thus, great care must be given in evaluating the timing, context and comparison groups in epidemiology and database studies of PDAC risk association and causality.

Environmental and genetic factors contribute to the risk for AP, CP and PDAC, with hereditary CP (HCP) clearly having the largest genetic contribution [6]. Familial studies and candidate gene testing have established *PRSS1, SPINK1, CTRC, CFTR, CASR* and *GGT1* as susceptibility loci for CP (PMID 20059346, 23462328). Recently, a large two-stage GWAS analysis identified and replicated *PRSS1-PR SS2* and X-linked *CLDN2* as susceptibility loci for CP [7]. The highest cancer risks have been observed in patients with hereditary pancreatitis—a rare genetic form of pancreatitis with mutations of the cationic trypsinogen gene (*PRSS1*) with an onset at an early age. In subjects with hereditary pancreatitis, the risk of PDAC is about 50 times greater than in the corresponding background population, and the lifetime risk of developing PDAC is about 70 percent [8], although the life-time risk in non-smokers with HP may be less than 20% [9].

The inflammatory milieu is important in both CP and PDAC, and there is evidence that this component may promote the epithelial-to-mesenchymal transition of pancreatic cells [10], which is a component of oncogenesis. In $KRAS^{G12D}$-engineered mice, PanIN lesions have been associated with acinar-to-ductal metaplasia (ADM) [11, 12], a condition where the phenotypic characteristics of the acinar cells are changed and cells express ductal markers such as CK19 and Sox9 [13, 14]. Inducing even one episode of acute pancreatitis in mice with $KRAS^{G12d}$ mutation may lead to feed-forward activation loops with persistent NF-κb activation (a pro-inflammatory, anti-apoptotic mediator), with a marked increase in PDAC development [15, 16]. These recent findings provide a possible mechanistic pathway between chronic inflammation and PDAC.

The Role of Stellate Cell Activation in PDAC

Pancreatic stellate cells (PSCs) constitute roughly 4% of all pancreatic cells and are thought of as specialized myofibroblasts that are regulated by autocrine and paracrine stimuli [17, 18]. PSCs promote tumor progression, metastasis and resistance to chemotherapy, and thus play a central role in PDAC (as well as CP). These specialized cells are now known to be activated by ethanol and its metabolites and by several factors that are upregulated during pancreatic injury including growth factors, cytokines and oxidant stress. Conditioned media from cultured PSCs can also alter apoptosis – the result being protection of pancreatic cancer cells from chemo-and radiation-induced apoptosis. Furthermore, the dense network of collagen and other matrix proteins may prevent circulating chemotherapeutic agents from reaching PDAC cells. Strategies are being developed to cirmumvent the protective barrier for PDAC cells that are generated by PSCs and improve delivery of therapeutic agents to the target.

Role of CCK in PDAC Development

The gastrointestinal peptide cholecystokinin (CCK) and the related peptide gastrin act on CCK receptors to regulate pancreatic digestive enzyme release, gastric acid stimulation, and

GI tract growth. CCK is released in response to dietary fat; epidemiologic studies show an increased incidence of CP in countries were fat consumption is high, and CCK blood levels have been reported to be elevated in patients with CP. CCK-B receptors are the primary receptor type detected in the normal human pancreas and are markedly over-expressed in pancreatic cancer [19]. CCK receptors have been identified on PSCs, and stimulation of these receptors produces collagen and fibrosis, features common to both CP and PDAC [20–22]. In animal models, CCK receptors have been recently described on very early PanINs in mice [23] and receptor blockade halts PanIN progression and reverses fibrosis. A splice variant in the CCK-B receptor known as CCK-C has been identified in human PDAC which results from a germline single nucleotide polymorphism (SNP) [24].

DIABETES AS A RISK FACTOR FOR PDAC

Obesity, diabetes mellitus, and glucose intolerance all have been associated with increased pancreatic cancer risk (Table 1). A study of 29,133 Finnish male smokers revealed that the presence of diabetes mellitus and, independently, elevated insulin concentrations both showed a significant 2-fold increased risk of the subsequent development of PDAC more than 10 years after baseline [25]. These results support the hypothesis that exposure to higher insulin concentrations and insulin resistance affects the risk of exocrine pancreatic cancer.

These epidemiologic findings support the laboratory observations that PDAC is characterized by a constituitive over-expression of insulin receptors and insulin-like growth factor receptors [26]. The trophic effects of these enhanced signaling systems are also the target for the interaction of metformin in PDAC [27], which has attracted much recent interest.

Combined chronic pancreatitis and diabetes risk on pancreatic cancer

A recent study from Taiwan indicated that the hazard ratio (HR) for subsequent PDAC in individuals with the combined factors of CP and diabetes was increased 33-fold over controls [28], but the forms of diabetes and CP were not further characterized. The ideal model to study this complex relationship is hereditary pancreatitis (HP), a rare autosomal dominant inheritance disease caused by a mutation of the PRSS1 gene. Pancreatic insufficiencies occur early, and the median age at onset of exocrine insufficiency and diabetes is 29 and 38 years, respectively. Almost all patients experience these complications during their life span. In HP patients, the cumulative risk of PDAC at 50, 60, and 75 years are 10 percent, 19 percent, and 54 percent, respectively [29]. HP is associated with a high relative and absolute risk of PDAC as compared to the general population (SIR: 87). While only 26% of patients in this French study developed diabetes mellitus, this complication was a major risk factor for PDAC within this cohort (RR 13, 95% CI 3–65) [9, 29]. It is reasonable to assume that diabetes is a risk factor for PDAC rather than just being a symptom in HP patients. However, it remains possible that diabetes is a surrogate marker for the severity of pancreatitis and thus the link to cancer is indirect.

In a separate study, pancreatic tissues from 43 patients with CP and 27 controls were examined by immunohistochemistry and quantitative morphometry. The pancreatic volumes were significantly reduced by about 20% in CP patients compared to controls, and beta-cell areas were 0.69 % ± 0.08 % in CP patients and 0.97 % ± 0.08 % in controls, whereas alpha-cell areas did not differ between the groups. The lack of increased beta-cell turnover in CP patients, despite an approximately 10-fold increase in the number of apoptotic acinar cells, suggests that the damage to the pancreas is highly specific for the exocrine compartment and affects the endocrine islets to a lesser extent [30]. However, recent reports suggest that beta-cell dysfunction develops in the early stages of CP while clinical diabetes manifests later,

when there is profound fibrosis. This suggests that endocrine deficiency in CP is multifactorial. Although the role of transcription factors (such as PDX-1, MafA, NeuroD) on beta-cell function is understood, alterations in these factors in CP have not been elucidated. Moreover, the role of PSCs on islet-cell function is still poorly understood. Hyperglycemia and endothelin 1 have been reported to induce PSC activation, but the role of PSC activation on islet-cell function remains unknown.

Role of PDX-1 in PDAC Development

Pancreatic duodenal homeobox 1 (PDX-1) is a master regulator of embryologic pancreatic growth and development, and regulates insulin expression and islet maintenance in the adult pancreas. However, it is also known that PDX-1 is an oncogenic transcription factor regulating PDAC. Therefore, PDX-1 is a potential therapeutic target in PDAC. Treatment with bifunctional human shRNA-PDX-1 significantly ablates human PDX-1-positive PDAC in SCID mice and prolongs survival, and a synthetic human insulin promoter drives expression of imaging genes in PDX-1-positive PDAC cell lines and tumors in mice [31]. Systemic delivery of the bifunctional shRNA(PDX-1) resulted in marked reduction of tumor volume and improved survival in a human pancreatic cancer xenograft mouse model [32]. PDX-1 therefore appears to be a critical mediator of growth in normal and neoplastic pancreatic tissue.

PANCREATOGENIC (TYPE 3c) DIABETES

Classification and prevalence of T3c diabetes mellitus (T3cDM)

T3cDM, also called pancreatogenic or apancreatic diabetes mellitus, and is a form of secondary or Type 3 diabetes mellitus as defined by the American Diabetes Association (ADA) and by the World Health Organization [33]. The exocrine pancreatic diseases underlying T3cDM include acute and chronic pancreatitis of any etiology, hemochromatosis, cystic fibrosis, fibrocalculous pancreatopathy, pancreatic trauma leading to loss of pancreatic tissue, pancreatectomy, pancreatic agenesis, and pancreatic cancer. The most common underlying disease is CP, accounting for about 75–80% of T3cDM patients [34]. Pancreatic carcinoma accounts for 8 % of all T3cDM according to a recent study, but T3cDM also frequently occurs after surgical treatment of benign or malignant disease. Detailed data on T3cDM prevalence is scarce, due to lack of research on the issue and difficulties with diabetes classifications [35].

Older studies estimated T3cDM to have a low prevalence of about 0.5–1.2 percent among all cases of diabetes in North America, but recent data suggest that T3cDM might be more common than generally believed. In Germany, Ewald et al investigated 1868 diabetic patients seen at an academic medical center [34]. After comprehensive evaluation, 9.2% of patients could be classified as T3cDM, using ADA criteria, of which 78% were also diagnosed with CP. Most T3cDM patients were initially misclassified as T2DM. The previous underestimation of the prevalence of T3cDM might be due to the fact that it has become easier to detect exocrine pancreatic pathology as imaging methods of the pancreas have improved, and noninvasive screening methods to quantify exocrine dysfunction, such as fecal elastase 1, are now widely available [35].

In contrast to T1DM or T2DM, the endocrinopathy in T3cDM is complex and complicated by additional comorbidities such as maldigestion of fats and proteins and malnutrition. Exocrine insufficiency, a deficiency of fat-soluble vitamins (especially vitamin D) and impairments of fat hydrolysis and incretin secretion are found very commonly in T3cDM [36]. Pancreatic enzyme replacement therapy is therefore required in virtually all patients with T3cDM [37].

Treatment of T3cDM

Seventy-five percent of T3cDM is due to chronic pancreatitis, which carries a high risk for pancreatic carcinoma. Insulin and insulin secretagogue treatment may increase the risk of malignancy, whereas metformin therapy may reduce it. Metformin should therefore be the first line of therapy, if tolerated, and continued if insulin treatment must be added for adequate glucose control [37].

In advanced T3cDM, insulin replacement therapy is the only efficacious treatment option, and patients should be treated using general insulin dosing and regimen guidelines for T2DM [38]. In T3cDM, blood glucose control may be labile due to loss of glucagon secretion, carbohydrate malabsorption, and/or inconsistent eating patterns due to pain and/or nausea. Insulin pump therapy should be considered for patients who are able to manage this form of treatment. In diabetes due to CP, therapy with insulin or insulin secretagogues (sulfonylurea and glinides) may be necessary. Because secretagogues can cause hypoglycemia, short-acting agents are preferred when meal ingestion is inconsistent. Adverse effects associated with thiazolidinediones and potential risks of incretin-based therapies (e.g. GLP-1 analogues and DPP-4 inhibitors) should preclude their use in T3cDM outside of the context of formal clinical trials. Because T3cDM has the same incidence of retinopathy as T2DM [39], surveillance for microvascular disease should be conducted as for T1DM and T2DM.

Discrimination of T3cDM from T2DM

T3cDM differs from T2DM not only by the loss of insulin from beta-cells but also of glucagon from alpha-cells and PP from PP- or F- cells, respectively. CP patients that have pre-existing risk factors for T2DM, such as obesity, may have further difficulties with glucose homeostasis, and a system for differentiating T3cDM from T2DM is needed. Ewald and Bretzel suggested the following criteria for diagnosing T3cDM [35]:

Proposed major criteria (all must be fulfilled):

- Presence of exocrine pancreatic insufficiency (according to monoclonal fecal elastase-1 test or direct function tests).
- Pathological pancreatic imaging (endoscopic ultrasound, MRI, CT).
- Absence of type 1 diabetes mellitus associated autoimmune markers

Minor criteria:

- Impaired beta cell function (e.g. HOMA-B, C-peptide/glucose ratio)
- No excessive insulin resistance (e.g. HOMA-IR)
- Impaired secretion of incretins (e.g. GLP-1)
- Low serum levels of lipid soluable vitamins (A, D, E, and K).

Despite these criteria, there is a degree of overlap between the different forms of diabetes because long-standing T1DM and T2DM are associated with exocrine pancreatic failure, and diabetics are at a higher risk for developing AP and/or CP. Furthermore, patients with previous episodes of pancreatitis may develop T1DM or T2DM independently of their exocrine pancreatic disease. The best discriminator of T3cDM from T2DM appears to be the PP response to nutrients [38].

PP is localized predominantly to islets in the ventral portion (head) of the pancreas and is promptly secreted in response to ingested nutrients. T3cDM secondary to cystic fibrosis, CP, pancreatic malignancy, or pancreatic resection is uniformly characterized by a deficiency in

the nutrient-stimulated release of PP. T2DM, on the other hand, is typically associated with an increase in basal and nutrient-stimulated levels of PP, and healthy elderly subjects with normal glucose tolerance also demonstrate elevations in basal and nutrient-stimulated levels of PP compared with younger subjects. Therefore, the discrimination of T3cDM from T2DM is based on the failure of plasma PP levels to increase after nutrient ingestion. Basal levels of PP in PP-deficient subjects are similar to basal levels in normal subjects, so a nutrient stimulus is required to confirm PP deficiency. Glucose ingestion is a relatively weak stimulus for PP release, whereas a mixed nutrient meal is a strong inducer of PP release. A standardized mixed-nutrient stimulus is 8 ounces of a liquid dietary supplement such as Boost® or Ensure®; peak levels of PP are seen within 30–60 min after ingestion.

Role of pancreatic polypeptide (PP) in T3cDM

Enhanced sensitivity to insulin administration, due to prevailing insulin deficiency, was a well-recognized consequence of pancreatogenic diabetes but it was not until euglycemic clamp studies were performed with glucose tracer methodology that isolated hepatic insulin resistance was discovered to coexist in the setting of increased peripheral insulin sensitivity in animal and then clinical studies of T3cDM [37]. Isolated hepatic insulin resistance has been documented in T3cDM due to CP, pancreatic resection, pancreatic cancer, and cystic fibrosis, and results in persistent, unsuppressed hepatic glucose production. PP deficiency has also been documented in CP [40], proximal or total pancreatectomy, and cystic fibrosis, so it was identified as a likely mediator of the hepatic defect. Acute administration of PP was found to have no effect on hepatic insulin sensitivity in normal or PP-deficient individuals; however, prolonged PP administration was found to reverse the hepatic insulin resistance in rats, dogs, and patients with T3cDM due to CP or pancreatic resection. Animal studies confirmed that PP deficiency results in diminished hepatic insulin receptor (IR) availability, and hepatic IR deficiency is reversed by prolonged PP administration [37]. In clinical studies, PP administration reversed hepatic insulin resistance in patients with CP or after proximal pancreatectomy, and resulted in improved glucose tolerance. Recently, a randomized, placebo-controlled study in T1DM and T3cDM patients found that PP administration enhanced insulin sensitivity and lowered the insulin requirements of these patients [41].

Mechanism(s) of pancreatic cancer-induced T3cDM

While long-standing diabetes mellitus (DM) modestly increases the risk of PDAC, PDAC also frequently causes DM. This “reverse causality” has greatly complicated epidemiologic studies of the relationship between the two diseases [42]. More than half of PDAC patients have DM or hyperglycemia, and the onset of DM typically occurs between 6 months and 36 months before PDAC diagnosis in 20–25 percent of patients. Furthermore, resection of the PDAC leads to amelioration of DM in roughly half of new-onset DM subjects [43]. This suggests that new-onset DM could be a biomarker of PDAC [44].

Hypotheses of how pancreatic cancer induces T3cDM

As in T2DM, beta cell dysfunction and peripheral insulin resistance are seen in PDAC-induced DM (PDAC-DM). However, in contrast to T2DM, onset and progression of glucose intolerance in PDAC-DM occur in the face of ongoing, often profound, weight loss. There are several hypotheses for how PDAC might cause DM, including progressive pancreatic tissue destruction due to the tumor growth, and metabolic consequences of cancer-related malnutrition. The most likely explanation for the frequent occurrence of DM in PDAC, however, is a paraneoplastic phenomenon caused by tumor-secreted products [45]. This notion is supported by laboratory findings that supernatants from PDAC cell lines inhibit insulin secretion.

One such possible mediator of beta-cell dysfunction in pancreatic cancer-induced diabetes is adrenomedullin, a pluripotent hormone with some homology to amylin, which is overexpressed in PDAC [46]. Adrenomedullin receptors are found on beta- cells and its expression is seen specifically in the F cells of the islets. Inhibition of insulin secretion was replicated by external addition of adrenomedullin and abrogated by its genetic knockdown. Similar effects were seen in orthotopic and subcutaneous in vivo tumor models using adrenomedullin-expressing PDAC cell lines [45]. These findings support the notion that adrenomedullin is a mediator of beta-cell dysfunction in PDAC. The cause(s) of insulin resistance and PDAC-DM-associated weight loss remains unclear, though these appear to be paraneoplastic phenomena as well [46].

GENOMIC ASSOCIATIONS OF CP, DM, AND PDAC

After several decades of research, a roster of genes has been identified for CP, DM, and PDAC (Table 1), all three of which share three characteristics: familial aggregation and familial clustering, which in are indicators of shared genetic and/or environmental etiologies; variation in age at diagnosis, which has been linked in some subsets of patients to familial risk; and a hereditary component as demonstrated by Mendelian segregation analyses. For all three, epidemiologic risk factors (e.g. sex, obesity [DM], alcohol intake [CP], and smoking [PDAC]) may interact with genetic factors.

Variants of approximately 30 genes have been found to confer genetic risk for DM, each with a modest effect (e.g. PPARG and KDNJ11, identified through the candidate gene approach; and TCF7L2, WFS1, HDF1B, FTO, CDKN2A, SLC20A8, among others, identified through association and GWAS approaches) [47–50]. Research to date suggests that susceptibility to DM is explained by a polygenic risk model, with each genetic variant having a small effect, and none of which significantly improve risk assessment over common risk factors such as age, sex, family history, BMI, and clinical measures [51].

Rather than a classic Mendelian disorder, recurrent AP and CP represent truly complex diseases with the interaction and synergism of multiple genetic and environmental factors, especially alcohol and smoking [52, 53]. However, much of the variability in susceptibility to recurrent AP and CP is now clearly shown to be related to genetic factors, with PRSS1, SPINK1, CTRC, CFTR, and CASR established as susceptibility loci for CP. Most recently, a large two-stage GWAS analysis by Whitcomb et al [7] identified and replicated PRSS1-PRSS2 and the X chromosome-linked CLDN2 as susceptibility loci, with the latter gene's variants potentially interacting with alcohol consumption.

Over the past decade, the efforts of the Pancreatic Cancer Genetic Epidemiology Consortium (PACGENE), Pancreatic Cancer Case-Control Consortium (PanC4), and PanScan have demonstrated that individuals with a family history of pancreatic cancer are at an increased risk of developing pancreatic cancer. Overall, case-control studies have estimated that the odds of having a family history of pancreatic cancer are 1.9- to 13-fold higher in pancreatic cancer patients compared with healthy controls. A recent pooled analysis of data from five cohort and one case-control study estimated the odds of pancreatic cancer to be 1.76 higher among individuals with one first-degree relative and 4.26 higher with two or more first-degree relatives with pancreatic cancer compared with those without a family history of pancreatic cancer [54, 55].

A number of susceptibility genes have been identified [56]. The most commonly mutated gene is BRCA2, with PALB2 the second most commonly mutated gene for hereditary pancreatic cancer[57]. Carrying a disease-associated mutation in CFTR is associated with a modest increase in risk for pancreatic cancer, with those affected generally diagnosed at a younger age, especially among smokers; interestingly, clinical evidence of antecedent

pancreatitis was uncommon among both carriers and noncarriers of CFTR mutations [58]. Next-generation sequencing studies indicate that inherited ATM mutations also play an important role in familial pancreatic cancer predisposition [59].

GWAS studies of sporadic cases of pancreatic cancer have implicated regions that harbor ABO, TERT, and CLPTM1L. The results are consistent with earlier epidemiologic evidence suggesting that people with blood group O may have a lower risk of pancreatic cancer than those with groups A or B [60]. Using GWAS data from 3,851 cases and 3,934 controls and a logistic regression model for genotype trend effect that was adjusted for study, age, sex, self-described ancestry, and five principal components, Petersen et al. identified eight SNPs that map to three loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. Two correlated SNPs, rs9543325 and rs9564966, map to a nongenic region on chromosome 13q22.1. Five SNPs on 1q32.1 map to NR5A2, and the strongest signal was at rs3790844. A single SNP, rs401681 maps to the CLPTM1L-TERT locus on 5p15.33, which is associated with multiple cancers [61]. Additional insights gained from pathway, candidate gene, and gene-environment studies are now possible.

SURVEILLANCE OF INDIVIDUALS WITH HIGH RISK OF PANCREATIC CANCER

Radiologic and cytogenetic detection of premalignant lesions

Management of patients at high risk for PDAC is important yet difficult because of uncertainties regarding the method and frequency of screening methods, as well as concerns about the potential harm from missing resectable and curable lesions compared to the risk of removing lesions with low-malignant potential. There have been numerous small screening studies performed in the US and Europe over the last decade [62–68] as well as ongoing studies of PDAC genetic epidemiology [69–71]. Target lesions for pancreatic screening include T1N0M0 margin-negative PDAC, high-grade dysplastic precursor lesions such as PanIN-3, and intraductal papillary mucinous neoplasia with high grade dysplasia. Screening and surveillance is also recommended for first-degree relatives (FDRs) of patients with PDAC in at least two FDRs, patients with Peutz-Jeghers syndrome, and carriers of mutations in familial PDAC susceptibility genes (p16, BRCA2, PALB2 and HNPCC-associated genes) with at least one affected FDR. Pancreatic lesions are more common in older individuals, so screening should generally be initiated at age 50 or 55 [69, 70, 72].

The initial screening test for cystic lesions should include endoscopic ultrasonography (EUS) and/or MRI/magnetic resonance cholangiopancreatography (MRCP) based upon the results of the CAPS3 trial that showed EUS and MRI/MRCP had similar accuracy at detecting pancreatic cysts that exceeded the sensitivity of CT scanning [71]. When PDAC is suspected, CT imaging using a pancreatic protocol is the best technique for evaluating solid lesions. Because of the risk of post-procedure pancreatitis, endoscopic retrograde cholangiopancreatography (ERCP) should only be used when there is a suspected neoplastic main duct lesion identified by EUS or MRI/MRCP.

Because PanIN lesions can only be identified reliably by histological analysis of pancreatic tissue, investigators have proposed several approaches to identify PanIN. One option involves performing pancreatic tail resections for patients with diffuse pancreatic imaging abnormalities and then proceeding to total pancreatectomy if PanIN-3 is detected [73, 74]. Other approaches are under investigation, including analysis of endoscopically-collected pancreatic fluid for markers of PanIN-3 [75, 76], and molecular imaging approaches [77].

Subjects with subcentimeter branch duct-IPMNs identified by screening are currently recommended to undergo surveillance annually or more often, depending on the size of the

lesion. For high risk subjects with unifocal cysts or one dominant cyst with disturbing features (mural nodule, duct dilatation, of several centimeters and increasing size), criteria for resection at many screening centers have evolved to be similar to the criteria used to manage sporadic lesions [78, 79]. There is no consensus on whether to perform partial or total pancreatectomy for suspicious lesions identified by screening. Patients who undergo a partial pancreatectomy are recommended to continue surveillance. Some centers will perform a completion total pancreatectomy if PanIN-3 is detected in the resection specimen rather than continue surveillance. Islet cell autotransplant after total pancreatectomy is not recommended for patients with high risk of developing PDAC because of concerns of reintroducing neoplastic cells into the patient's liver.

Biomarkers for pancreatic screening and lesion characterization

An obstacle to detecting small early-stage pancreatic cancers is that very small cancers may not produce a sufficient amount of material useful for a screening test. Improvements in diagnostic imaging are needed, such as molecular imaging tools that improve the discrimination of malignant cells from benign conditions such as plectin-based imaging [77].

A variety of molecular targets are under investigation for their diagnostic utility in PDAC. Although gene mutations are a major focus of biomarker efforts at early detection, other biomarkers are under investigation including proteins [80], modified proteins such as glycoproteins, miRNAs [81] and other non-coding RNAs. The tumor antigen, CA19-9 is a glycoprotein, and further investigation of glycosylation abnormalities and glycoprotein patterns may help identify diagnostic markers [82]. Furthermore, many individuals develop antibodies to mutated proteins, overexpressed proteins, or altered forms of proteins that arise during malignant progression of cancer, and these autoantibodies may be useful biomarkers [83].

The main clinical scenarios in which biomarkers are needed include the detection of asymptomatic T1N0M0 pancreatic cancers, the evaluation of pancreatic cysts, and the detection of PanINs. While EUS-guided fine needle aspiration of solid masses has a high cytological diagnostic yield, standard cytologic evaluation of pancreatic cyst fluid has limited value, due to the paucity of cellular material in early non-invasive lesions and the limited diagnostic utility of current marker tests. Sequencing IPMN cyst fluid DNA for somatic mutations in candidate genes has led to the identification of oncogenic GNAS mutations in 66% of IPMNs, and this approach is a focus of current investigation [84].

Cost-benefit analysis of screening and intervention in high-risk patients

The outcome measure of health services effectiveness is reported as quality-adjusted life years (QALY), which combines the quantity and quality of life into one single index. Quantity is defined as years of life, while quality is quantified through the concept of "utility," which incorporates a patient's preference for a specific state of health. Cost-effectiveness analysis is generally more useful when the diagnostic indications and tests and subsequent management is relatively agreed upon and standardized. Cost effectiveness analysis studies have been performed in the setting of screening asymptomatic members of familial pancreatic cancer kindreds, and illustrate that current knowledge gaps prevent cost-effectiveness determinations in pancreatic cancer screening [85].

Because no consensus guideline for clinical use exists, screening is typically done in association with research studies linked to a registry and with protocol-directed collection of blood, urine and/or pancreatic juice. Most academic centers recommend EUS every year starting at age 50 or 10 years younger than the earliest age of onset in patients who are first

degree relatives in familial pancreatic cancer syndromes, and first or second degree relatives in gene carriers for diseases associated with an increased risk of PDAC and hereditary pancreatitis. Other centers use MRI instead of EUS. The rationale is that MRI appears to have similar sensitivity for cystic lesions but because of volume averaging, small cancers may be missed, and cancers outside of dominant cysts may also be missed. The frequency and type of follow-up testing depends on the presence of high risk biomarkers and co-morbid conditions that may affect the decision for definitive treatment, such as total pancreatectomy

THE EFFECTS OF DIABETES TREATMENT ON PDAC

In addition to diet and exercise, commonly used drugs to treat T2DM include sulfonylureas, metformin, thiozolidinediones, alpha-glucosidase inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors. In addition, there are various forms of insulin, including insulin glargine, a long-acting recombinant insulin that exhibits an increased binding affinity toward the insulin- and insulin-like growth factor-1 receptors. While several studies have suggested that insulin glargine may increase slightly the risk of certain cancers, including possibly PDAC, other studies have failed to show such an association. Sulfonylureas, thiozolidinediones, and alpha-glucosidase inhibitors appear to have little or no effect on the risk of PDAC.

Metformin is a biguanide that acts principally to decrease hepatic glucose output. Several retrospective studies of diabetic patients and three case-control studies of patients with pancreatic cancer have reported that metformin use is associated with a reduced risk of PDAC [86]. It has also been reported that metformin use was associated with a longer overall survival time and lower mortality in patients with PDAC and DM, and that metformin may help reduce the risk for PDAC [87]. However, two cohort studies of diabetic patients did not confirm that metformin lowered the risk for pancreatic cancer. In view of the limitations of retrospective studies due to multiple potential biases, there is clearly a need for large scale studies to assess the effects of metformin as well as other glucose-lowering agents on the pancreas [88].

Mechanisms of action of incretins

GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are intestinal derived incretins which potentiate glucose-stimulated insulin secretion by the beta cell, inhibit glucagon release by the alpha cell, and promote beta cell growth and survival. GLP-1 acutely stimulates glucose-dependent insulin release through increased production of intra-cellular cAMP, and exerts chronic effects that prevent beta cell exhaustion by ensuring that insulin mRNA stability is increased and insulin stores are refilled. GLP-1 also upregulates PDX-1 expression and induces its translocation to the nucleus, leading to enhanced insulin gene transcription [89]. GLP-1 also acts to suppress beta-cell apoptosis. Thus, GLP-1 promotes beta cell proliferation, and beta-cell survival [90].

GLP-1 mimetics such as exendin-4 (exenatide) and liraglutide interact directly with the GLP-1 receptor, whereas DPP-4 inhibitors such as sitagliptin, saxagliptin, and linagliptin increase endogenous levels of GLP-1 by interfering with its DPP-4-mediated degradation. GLP-1 receptors are expressed on various cell types, including beta cells, pancreatic duct cells, pancreatic duct glands, acinar cells, and cells within PanIN lesions. Therefore, in addition to its effects on the beta cells, GLP-1 can exert trophic effects on these other cell types. For example, GLP-1 may promote mitogenic signaling in human pancreatic ductal cells by activating the GLP-1 receptors on these cells. These observations underscore the importance of assessing the potential role of GLP-1 receptor agonists in the human pancreas.

Results from a human pancreatic biobank study

To explore this issue, a recent study examined autopsy-obtained pancreata derived from 7 T2DM patients who had been treated with sitagliptin and one who had been treated with exenatide (a GLP-1 homologue) [91]. These pancreata were ~40 percent larger than pancreata from 12 donors with T2DM who had not been treated with incretin mimetics (control group). Cell proliferation and the frequency of PanIN lesions were increased in the incretin group compared with the control group. In addition, the incretin group exhibited alpha cell hyperplasia and glucagon-expressing microadenomas (3/8) and one pancreas harbored a glucagon-expressing neuroendocrine tumor (NET). By contrast, no glucagon-expressing microadenomas or NETs were present in the pancreata from the control group.

These alterations, combined with an increased number of PanIN lesions adjacent to ducts, could potentially contribute to obstruction-associated alterations and pancreatitis during long-term incretin mimetic therapy. However, the incretin mimetic group was on average 18 years older than the control group, which may have affected the results as the incidence of PanIN lesions increases with age. The increased size of the pancreata in the incretin-treated cohort remains unexplained, but the effect was primarily due to inclusion of two morbidly obese men (BMI > 40) and a severely obese woman (BMI > 35) in the incretin mimetic group. Also, the pancreas sizes were not controlled for sex (male pancreata tend to be larger) or visceral fat in the pancreas of obese subjects [92]. Additional clinical studies are therefore required to assess the consequences of incretin mimetic therapy on the pancreas, especially because a study with diabetic rats suggested that GLP-1 may cause pancreatic abnormalities including pancreatic ductal hyperplasia [93] and a study using a genetically engineered mouse model of pancreatic cancer in which oncogenic Kras is expressed revealed that 12 weeks of treatment with Exendin-4 led to accelerated PanIN and desmoplastic progression [94].

Industry perspective on pancreatitis and pancreatic cancer risk with liraglutide

Treatment of T2DM patients with liraglutide, a long-acting GLP-1 receptor agonist, have not shown any evidence of a risk of pancreatitis or PDAC. Studies in mice, rats, and cynomolgous monkeys did not reveal any hyperplasia, PanINs, metaplasia, or endocrine tumors. Similarly, studies in diabetic Zucker rats did not reveal any drug induced effects. In humans, in over 6,500 patients and greater than 5,000 patient-year exposures, there were two patients with pancreatic cancer after 152 and 7 days of therapy, respectively, and a third patient was diagnosed with pancreatic cancer prior to randomization. With respect to AP, there was a 1.8-fold increase in incidence per 1,000 patient-year exposure which approximated the range anticipated in a population of individuals with T2DM (0.55 to 1.37 cases per 1,000 patient-years). Interestingly, unrelated to therapy, lipase levels were increased in 20% of T2DM and fluctuated over time. Studies in mice, rats, and monkeys given high doses of liraglutide did not reveal any histological evidence for pancreatic inflammation or PanIN formation.

In humans, a causal relationship between liraglutide and AP or PDAC can neither be established nor excluded based on current data. However, prospective, controlled and independently adjudicated data are being collected from several ongoing clinical trials, including a large 9,000-patient cardiovascular outcome trial (LEADER®). Data from post-marketing safety surveillance and independently submitted reports to regulatory agencies over the last 3–4 years have not identified an association between liraglutide and pancreatic pathology. Two prospective epidemiological studies, based on a claims-database in the United States and a medical record database in the United Kingdom, are currently being conducted and will provide valuable additional information.

Industry perspective on pancreatitis and pancreatic cancer risk with sitagliptin

In studies with mice, rats, monkeys, and dogs, the DPP-IV inhibitor sitagliptin was not associated with any episodes of pancreatitis, gross alterations in the pancreas, or histomorphological changes in the pancreas. In humans, a *post hoc* analysis of reported adverse events of pancreatitis and pancreatic cancer was carried out using a pooled population of nearly 15,000 patients. Slightly more than half of these patients were randomized to receive sitagliptin (100 mg/day), for at least 12 weeks, with some patients receiving the drug for up to 2 years. To take into account potential differences between groups in relation to duration of exposure to treatment, reports of adverse events were expressed as exposure-adjusted incidence rates (numbers of patients with events per 100 patient-years). The mean duration of exposure was 284 days for the sitagliptin group and 264 days for the comparison group. For the composite endpoint of pancreatitis (which included the terms “pancreatitis” and “pancreatitis acute”), exposure-adjusted incidence rates were similar for both groups (0.08 and 0.09 events per 100 patient-years in the sitagliptin and comparator groups, respectively). A similar pattern was observed with an expanded composite which added the term “pancreatitis chronic”, with 0.13 and 0.09 events per 100 patient-years in the sitagliptin and comparison groups, respectively [95].

For the composite endpoint of pancreatic cancer (including the terms “adenocarcinoma of pancreas,” “pancreatic carcinoma,” and “pancreatic carcinoma metastatic”), the exposure-adjusted incidence rates were similar in the two treatment groups (0.05 and 0.06 events per 100 patient-years in the sitagliptin and comparison groups, respectively). These data from sitagliptin clinical trials are consistent with a published meta-analysis of clinical trials involving multiple DPP-4 inhibitors [96]. In view of the long latency period for the development of pancreatic cancer, data from longer term studies are required. Such data will be available from a sitagliptin cardiovascular outcomes study of over 14,000 patients (TECOS), and cardiovascular outcome studies with other DPP-4 inhibitors.

Pitfalls in studies of adverse drug effects

Given the large number of patients with T2DM who take anti-diabetes medications on a long-term basis, any protective or harmful effects of these medications on cancer risk, even at a relatively modest magnitude, could have significant public health implications. Ideally, one should conduct randomized controlled trials (RCTs) to assess drug risk. Because the sample size and follow-up duration are seldom sufficient for cancer outcomes in such studies, post-marketing surveillance is critical. This includes spontaneous adverse event reporting systems and formal phase IV studies. However, spontaneous reporting is subject to reporting bias and rarely guides practice. Post-marketing RCT may inform safety, but are only occasionally available. While observational studies involving large populations and extensive person-years of drug use are important phase IV studies, they are prone to various biases. These include confounding by indication, as in the case of the choice of anti-diabetes therapy being dictated by factors such as severity of diabetes. Smoking, diet, physical activity, compliance/adherence, and comorbidity status also need to be considered, since they may influence cancer risk. Another concern is protopathic bias, which occurs when treatment for the early symptoms or other consequences of a disease appears to cause the disease. This is usually associated with an inverse duration-response effect between the exposure and outcome, and is of concern when evaluating the association between diabetes medications and pancreatic cancer. For example, a reported association between short-term exposure to anti-diabetes medications and the risk of pancreatic cancer disappeared or was significantly decreased after longer duration of exposure. Incorporation of a lag-time in exposure definition helps to control for protopathic bias.

Time-related biases are common and give the incorrect appearance that a medication reduces the risk of developing the outcome of interest. They include immortal time bias in which treatment status involves a delay during which follow-up time is accrued, time-window bias in case-control studies due to differences in exposure opportunity time windows between cases and controls, and time-lag bias which occurs when different classes of diabetes treatments are prescribed at different stages of diabetes. It is therefore important to use appropriate statistical methods that minimize these biases.

FDA surveillance of adverse drug effects

Investigational drugs are subject to extensive non-clinical testing, including 6- to 9-month studies in rodents and non-rodents, and 2-year evaluation of carcinogenicity in rats and mice. Although pancreatic toxicity or pancreatic neoplasms have not been observed with incretin mimetics, carcinogenicity studies revealed that acinar and islet hyperplasia or hypertrophy, inflammation, and acinar atrophy, were occasionally present in treated animals. These changes were of minimal severity, and modest increases in either incidence or severity were observed only at the highest dose evaluated, which is several-fold higher than used in humans.

Because GLP-1-based therapeutics may exert adverse effects on the exocrine pancreas under pathophysiological conditions that predispose to pancreatitis, such as T2DM, the FDA issued a post-marketing requirement (PMR) on the sponsors of exenatide, liraglutide, and sitagliptin to conduct a pancreatic toxicology study in a rodent model of T2DM. Three such studies that met PMR criteria were submitted to the FDA for review, and none demonstrated a treatment-related adverse effect on exocrine histology or proliferation. FDA veterinary pathologists reexamined the histological slides from one of these studies and concluded that treatment could cause mild changes, such as peri-ductal inflammation, islet degeneration, and intraluminal concretions.

The FDA also initiated research into identifying an experimental model that would enable a comparative toxicological assessment of potential pancreatic toxicity for investigational GLP-1-based therapies currently under development. Chemically induced models of pancreatic injury, Zucker Diabetic Fatty rats, and mice fed a standard or high-fat diet have thus far been investigated. Mice fed a high-fat diet and administered exenatide displayed a time- and dose-dependent exacerbation of acinar cell hyperplasia, atrophy, fibrosis, and increased peri-ductal inflammation. The effect of exenatide was multi-focal and associated with histological changes of minimal to moderate severity, but not with any effects on animal morbidity or mortality. The FDA has continuously monitored the GLP-1-based therapies since initial approval of these two drug classes, and continued non-clinical investigation remains an important component of the FDA's efforts to clarify the potential pancreatic toxicity of the GLP-1-based therapies.

FDAs approach to addressing a pancreatic safety signal with incretin mimetics

The market share for incretin mimetics in T2DM therapy is roughly 10%, and there is insufficient information to characterize safety profiles for these drugs. Therefore, post-market safety and surveillance are crucial, and the FDA Adverse Event Reporting System (FAERS) is functioning well in this regard. While pharmacovigilance and pharmacoepidemiology are used by the FDA to address pancreatic safety signals, there is also concern regarding published studies that suffer from limited power and incomplete validation. Cases of acute pancreatitis (AP), including necrotizing and hemorrhagic pancreatitis in association with incretin therapy in T2DM, have been reported to AERS in the post-marketing setting, and a recent analysis of admissions for acute pancreatitis among diabetic subjects revealed an increased association with incretin-based therapies [97]. Safety

concerns regarding these drugs have therefore been the subject of multiple FDA reviews and labeling changes. Published data mining analyses of the publicly available AERS data raised concerns regarding the risk of acute pancreatitis, pancreatic cancer, and thyroid cancer in association with incretin mimetic therapy [98]. Limitations of AERS data include under-reporting, lack of an accurate population denominator, adequate control data, and inadequate clinical documentation. It is therefore not possible to calculate incidence rates and establish causality based on such data. The FDA has therefore issued safety communications and added information in the Important Limitations of Use subsection of the Indications and Usage Section, the Adverse Reactions, Post-marketing subsection, and the Patient Counseling Information Section to warn patients of the risk of acute pancreatitis. The FDA has also required the manufacturers to conduct epidemiological studies of pancreatic toxicity in order to confirm and quantify the potential association with GLP-1 therapies in T2DM, and that cases of pancreatitis and pancreatic cancer be reported as adverse events of special interest in large cardiovascular outcome trials that are required for the GLP-1 based therapies. The signal for medullary thyroid cancer, a rare form of thyroid cancer that has been observed in animal studies with long-acting GLP-1 agonists, is labeled in a Boxed Warning in all approved long-acting GLP-1 agonists (liraglutide and exenatide). Moreover, the FDA has required that all manufacturers of approved GLP-1 agonists participate in a Medullary Thyroid Cancer Registry as a post-marketing requirement. Importantly, to date, a causal link between GLP-1-based therapies and the risk of AP has not been established, and evaluation of the potential association between GLP-1-based therapies and pancreatitis and pancreatic and thyroid cancers will require adequately powered, long-term epidemiological studies.

GAPS AND OPPORTUNTIES FOR FURTHER RESEARCH

Gaps in our knowledge exist across the full spectrum of pancreatic cancer. The failure to diagnose PDAC at an early stage as well as an aggressive pattern of metastasis both contribute to the dismal outcomes with this disease. For this reason, continued emphasis should be placed on both early diagnosis and therapy. The major challenge for the future, given the incidence of this disease, is the development of strategies for early detection that focus on cost-effective and transportable tests to identify high-risk subjects..

Clinical Trials

Advancing the clinical care of patients with PDAC will require improving biorepositories and developing a roadmap to prioritize therapeutic targets in clinically relevant models. Therapeutic intervention in the adjuvant setting may be preferable to eliminate some of the challenges of drug development in the advanced disease setting [99]. The emphasis must therefore be on performing well-designed phase II studies with uniform sets of basic entry and evaluation criteria with survival as a primary endpoint. Patients with either metastatic or locally advanced PDAC must be studied separately [100].

Pancreatic Stellate Cell Studies

Despite the increasing recognition of the tumor microenvironment and tumor-stromal interactions as significant contributors to PDAC, there remain significant gaps in knowledge regarding the role of PSCs. The origin of PSCs is not clear, but some investigators have identified the bone marrow as a source of a proportion of PSCs found in the pancreas. Although many investigators have identified PSC-derived factors that promote PDAC, it is unclear which mechanisms are most critical to PDAC progression. Evidence suggests that PSCs play a role in metastasis, but the precise mechanisms are still lacking. The PDAC-associated stroma represents an attractive target for novel therapies, but recent attempts to inhibit the stroma to improve response to chemotherapy have failed in clinical trials.

Whether the stroma of PDAC is a rational target for novel therapies, and if so, what the best strategy is to inhibit the stroma, are issues yet to be resolved.

CCK receptor studies

Because CCK receptors are expressed by PSCs and responsible in part for collagen production [101], will treatment with CCK receptor antagonists stop or prevent fibrosis in patients with CP? Since CCK receptors are over-expressed in PDAC, could CCK receptor antagonists be a reasonable preventative therapy in high risk individuals? Are CCK signaling pathways reasonable potential targets for PDAC treatment? Do high fat diets stimulate endogenous CCK release, and subsequently stimulate growth of tumors via CCK receptors? What is the role of CCK in pancreatic regeneration, in cross-talk between cells in the developing pancreas, and in malignant transformation?

The role of CP in PDAC development

If future epidemiologic studies of CP are to proceed, the clinical definition of CP needs to be carefully defined (i.e., self-report vs. clinician diagnosis) and the actual prevalence of CP needs to be established. In general, pancreatitis is considered as three basic categories -- AP, recurrent AP, and CP – as part of a disease continuum. Further information is needed on the factors which determine progressing through such a continuum. Some microbes directly infect the pancreas, but it unclear what the role of microbial components play in CP and PDAC. The cellular origin of PDAC remains unclear, and the factors which mediate acinar to ductal metaplasia (ADM) and the early initiation of PanIN formation need further examination. ADM has been observed in CP as well; will a better understanding of ADM increase our success in screening and prevention of PDAC? Epidemiologic studies are needed to determine if CP patients who present with (Type 3c) diabetes should be screened and monitored for PDAC development. Can the specificity of screening be improved with multiple serial markers and tests (biomarkers, mutations, hyper-methylation in pancreatic juice, markers of activation of pancreatic stellate cells) and imaging (EUS, other imaging, targeted imaging, computer-aided diagnosis)? It seems reasonable to imagine that multiple biomarkers and imaging technologies may improve the predictive ability to identify high-risk CP patients, but which tests, and how many tests will be necessary? Will such screening approaches in high risk persons be cost-effective?

Pancreatic screening and markers of pancreatic neoplasia

There are numerous gaps in our understanding of the benefits and potential risks of pancreatic screening. Further research is needed to improve the risk stratification of subjects undergoing pancreatic screening, and to better identify non-genetic risk factors associated with PDAC. Continued screening of high risk individuals will generate better estimates of the prevalence of different grades of IPMNs and PanINs and invasive cancers for different genetic and familial backgrounds and other risk factors. This information is needed to determine what is the most appropriate age to initiate screening, and how often subjects should be screened. We also need to better understand the natural history of PanIN and IPMN lesions, and to develop biomarkers and molecular imaging methods to reliably detect high-grade pancreatic neoplasia and early-stage invasive cancer.

T3cDM Diagnosis and Treatment Implications

Further studies are needed to evaluate the pathophysiology of T3cDM caused by CP, PDAC, pancreatic resection and cystic fibrosis. Specific issues that require clarity include the best criteria for differentiating T3cDM from T2DM, an assessment of the incidence of T3cDM in PDAC and diabetic populations in general, and an assessment of the effect of various diabetic drug treatments on the subsequent risk of PDAC in T3cDM patients. Additional

studies are needed to establish a standard provocative agent for assessment of nutrient-stimulated hormone (e.g., GLP-1 and PP) release in diabetic subjects, so as to discriminate T3cDM from T2DM. Studies are also needed to determine how PP levels compare to other measures of beta-cell function and insulin sensitivity in the development of T3cDM, as well as the possible role of PP in the treatment of T3cDM. An evaluation of the long-term glycemic control and rate of diabetes-associated complications of T3cDM patients with early insulin treatment compared with oral therapy is also needed.

Diabetic Pharmacotherapy Associations with PDAC

Large consortium studies are needed to compare new-onset and long-duration diabetic populations to determine the effects of antidiabetic treatments on the risk of PDAC. A randomized trial of incretin and other antidiabetic agents in T2DM subjects is needed, with periodic imaging of pancreatic size, measurement of pancreatic enzyme and GLP-1 levels, and islet cell products such as chromogranin-A and glucagon. A multi-site survey of autopsy findings in diabetic subjects, similar in design to the recent study by Butler et al [91], should be conducted.

SUMMARY AND CONCLUSIONS

Several themes emerged from the workshop. First, the relationship between pancreatitis, diabetes and PDAC is complex, but complexity is confounded by reverse causality. CP can cause diabetes by destruction of the islets (Type 3c) resulting in the loss of glucagon and PP in addition to insulin, with a high risk of hypoglycemia. The risks of T3cDM and CP are additive in hereditary pancreatitis, but the specific PDAC risk of T3cDM in epidemiology studies is not known because it has not been specifically measured.

Recent reports in the medical literature and lay press have raised major concerns about the risk of PDAC in patients taking GLP-1 agonists or DPP-4 antagonists. The reports are primarily case-control studies using existing databases and a small report of autopsy findings [91]. The majority of the variation in case-control studies appeared to be related to the control groups. Patients with diabetes are at increased risk of PDAC regardless of treatment, and new onset diabetes in an older population may be a biomarker of occult cancer, thereby confounding outcome measures. Prospective, randomized control trials have not revealed any association between GLP-1 or DPP4 agents and PDAC, although the duration of treatment was limited. In addition, animal studies including over 18,000 animals using doses of GLP-1 agonists or DPP-4 antagonists that were many times higher than doses given to humans did not reveal any signal of either pancreatitis or PDAC, or premalignant lesions at rates higher than controls – and these findings were independently confirmed by studies done by the FDA. Finally, the relationship between anti-diabetic agents, PDAC and the public welfare are the responsibility of the FDA, and the presentations on the process of evaluating medical reports, public concerns, animal data and human trials are handled with vigilance and objectivity. To date, the FDA has not seen a convincing signal between the use of GLP-1 or DPP-4 agents and PDAC, but they continue to monitor new findings and carefully evaluate them.

The value of open exchange of ideas and information from multiple branches of medicine and academics, industry and government was obvious to all in attendance. It is anticipated that the foundations established by this Workshop will provide groundwork for many productive programs and projects that will optimize patient treatment and reduce suffering, especially the burden of disease caused by PDAC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Established risk factors for pancreatic ductal adenocarcinoma.

Table 1.	Risk Factor	OR, Confidence Interval*	Reference
Lifestyle	Smoking	1.75 CI 1.61–1.87	Iodice, 2008 [102]
	Alcohol (>4 drinks/day)	1.5	Lucenteforte, 2012 [103]
Occupational	Chlorinated hydrocarbons	1.4–4.4	Andreotti, 2012 [104]
	Polycyclic aromatic hydrocarbons (PAH)	1.5	Andreotti, 2012 [104]
Diet	n-nitroso containing foods	1.27 CI 1.09–1.48	Risch, 2012 [105]
	saturated fat/animal fat	1.5	Sanchez, 2012 [106]
Medical	**Pancreatitis**	**5.1** CI 3.5–7.3	Raimondi, 2010 [8]
	- **Chronic pancreatitis**	**13.3** CI 6.1–28.9	Raimondi, 2010 [8]
	- **Hereditary pancreatitis**	**69.9** CI 56.4–84.4	Raimondi, 2010 [8]
	Allergies	**0.73** CI: 0.64- 0.84	Olson, 2012 [107]
	Diabetes mellitus	1.5	Li, 2012 [87]
	Obesity	1.3	Bracci, 2012 [108]
	Non-type O blood groups	1.65 CI 1.30–2.09	Risch, 2012 [105]
Genetics	***BRCA2***	3.5 CI 1.87–6.58	Klein, 2012 [55]
	STK11/LKB1	132 CI 44–261	Klein, 2012 [55]
	PALB2	Familial**	Jones, 2012 [57]
	CDKN2A	12–38	Klein, 2012 [55]
	CFTR	5.3–6.6	Raimondi, 2009 [109]
	TP53	Familial**	Raimondi, 2009 [109]
	APC	4.46 CI 1.2–11.4	Raimondi, 2009 [109]
	Mismatch repair genes	0–8.6	Klein, 2012 [55]
	PALLD	Familial**	Pogue-Geile, 2006 [110]
	1q32.1 locus	0.77 CI 0.71–0.84	Petersen, 2010 [61]
	13q22.1 locus	1.26 CI 1.18–1.35	Petersen, 2010 [61]
	GGT1	1.86 CI 1.11–3.15	Diergaarde, 2010 [111]

Factors are classified by environmental, medical and genetic categories. Bold risk factors indicate very high risk or odds ratio (OR) for pancreatitis and familial cancer syndromes. Abbreviations in italics are standard gene symbols.

*Confidence intervals are given for meta-analyses.

**Risk for familial cancer is high, but not comparable to population-based studies.

References are from recent reviews or recent primary sources.