

Uniting Epidemiology and Experimental Models: Pancreatic Steatosis and Pancreatic Cancer



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Summary

Research from epidemiologic studies and experimental animal models provide insights into the role of pancreatic steatosis in the development of pancreatic cancer. Epidemiologic data demonstrate that pancreatic steatosis is widely prevalent and significantly associated with both development and progression of pancreatic cancer. By focusing on current experimental models, this review elucidates potential cellular mechanisms underlying not only the pathophysiology of pancreatic steatosis itself, but also the pathogenesis behind pancreatic steatosis's role in changing the tumour microenvironment and accelerating the development of pancreatic cancer. This review further explores the impact of bariatric surgery on pancreatic steatosis and pancreatic cancer. Synthesizing knowledge from both epidemiologic studies and experimental animal models, this review identifies gaps in current knowledge regarding pancreatic steatosis and its role in carcinogenesis and proposes future research directions to elucidate the possible mechanisms underlying other obesity-associated cancers.

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Introduction

Worldwide prevalence of obesity has nearly tripled between 1975 and 2016.¹ According to the World Health Organization (WHO), 650 million adults were obese worldwide in 2016.¹ Obesity, especially abdominal obesity, is linked with metabolic syndrome and insulin resistance and may cause fat accumulation in the liver (non-alcoholic fatty liver disease or NAFLD) and pancreas (non-alcoholic fatty pancreas disease or pancreatic steatosis).² Importantly, fatty pancreas is a risk factor for pancreatic cancer, a highly lethal disease that causes over 331,000 deaths/year and ranks as the 3rd leading cause of cancer-related death in the United States and the 7th leading cause of cancer-related death worldwide.^{3,4}

Following a review of the epidemiology, risk factors and diagnosis, and potential of pancreatic steatosis, this article examines current experimental models exploring the role of fatty pancreas in pancreatic cancer and potential underlying cellular mechanisms. This review centres on the currently accepted perspective of pancreatic steatosis, which holds that metabolic syndrome is a manifestation of pancreatic fat accumulation and

subsequent development of pancreatic cancer through numerous mechanisms.

The Burden of Pancreatic Steatosis

Estimates of fatty pancreas prevalence vary by population characteristics, and most population-based data come from Asia (Table 1). Different imaging modalities result in variable fat detection, described in Table 2. Steatosis measurement by radiographic imaging following same protocol as for liver steatosis has yet to be validated by histologic assessment. Regardless histologic assessment of pancreatic steatosis is associated with chronic cardiometabolic disorders.

Risk Factors of Pancreatic Steatosis

Intra-pancreatic fat deposition occurs through two mechanisms: 1) “fatty replacement” through acinar cell death and adipocyte replacement or 2) “fatty infiltration” or accumulation associated with obesity and/or metabolic syndrome.

Noxious risk factors for pancreatic acinar cell death and fatty replacement include alcohol abuse, chronic liver disease (including NAFLD, chronic hepatitis B, and cirrhosis), congenital diseases (such as cystic fibrosis, Shwachman-Bodian-Diamond syndrome, and Johanson-Blizzard syndrome), iron overload, malnutrition, medications (corticosteroids, gemcitabine,

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a)				
Study population	Cohort description	Prevalence	Diagnostic modality	Diagnostic threshold
Pooled population ¹	Based on a systematic review and meta-analysis of 12,675 individuals from South Korea, Italy, Indonesia, US, Turkey, and Taiwan	33%	EUS, US, CT, MRI	Variable
Taiwanese adults ²	Those who had undergone a health checkup at the Health Management Center of National Taiwan University Hospital (NTUH) between January 2009 and December 2009	16%	US	Increased echogenicity (% not specified) of the pancreatic body compared with the kidney, using hepatic echogenicity as an intermediary comparison between the kidney and pancreas echogenicities
Chinese adults ³	Those who attended the Ningbo Chinese Medical Hospital Affiliated to Zhejiang Chinese Medical University for medical examination or outpatient visit who responded to an advertisement from January 2015 to October 2017	11%	US	Pancreatic parenchymal echogenicity > 80%, compared with the spleen
Chinese adults ⁴	Those who had undergone a health checkup at the Health Examination Center of Shandong Provincial Hospital affiliated to Shandong University between January 2013 and December 2013	30.7%	US	Increased echogenicity (% not specified) of the pancreatic body compared with the kidney, using hepatic echogenicity as an intermediary comparison between the kidney and pancreas echogenicities
Indonesian adults ⁵	Those who had undergone medical check-up and abdominal ultrasound in Medistra Hospital, Jakarta between January and December 2013	35%	US	Increased echogenicity (% not specified) of the pancreatic body compared with the kidney or liver
U.S. hospitalized children ⁶	Patients 2 to 18 years old who had undergone abdominal CT in the emergency department or inpatient ward within a 1-year time span	10% (19% obese children, 8% nonobese children)	CT	A difference of –20 mean Hounsfield units between the pancreas and spleen
Egyptian obese children ⁷	Pre-pubertal Egyptian children with obesity	58%	US	Increased echogenicity (% not specified) of the pancreas compared with the kidney
Hong Kong Chinese obese adolescents with NAFLD ⁸	Post-pubertal Hong Kong Chinese adolescents aged 14–18 years with primary obesity and NAFLD attending the Obesity and Lipid Disorder Clinic in the Prince of Wales Hospital, Hong Kong who enrolled in a dietician-led lifestyle modification program to reduce NAFLD in obese adolescents	50%	MRE	Chemical shift encoded MRI—pancreas proton density fat fraction $\geq 5\%$
b)				
Comorbidity	RR	95% CI		
Metabolic syndrome	2.37	2.07–2.71		
NAFLD	2.67	2.00–3.56		
Diabetes	2.08	1.44–3.00		
Arterial hypertension	1.67	1.32–2.10		

Table 1: Prevalence of Pancreatic Steatosis and Risk of Metabolic Syndrome

a) Prevalence of pancreatic steatosis based on different study populations. B) Risk of metabolic syndrome in pancreatic steatosis. CT=computed tomography. EUS=endoscopic ultrasound. MRE=magnetic resonance enterography. MRI=magnetic resonance imaging. NAFLD=non-alcoholic fatty liver disease. US=ultrasound.

Diagnostic modalities	Visualization of pancreatic steatosis	Advantages	Limitations
Histological examination	Performed on pancreatic tissue samples from surgical resections, autopsies, or fine needle aspiration cytological biopsies	<ul style="list-style-type: none"> ■ Gold standard 	<ul style="list-style-type: none"> ■ Invasive, ■ Lack of standardized grading system ■ Risk of associated complications including pain, bleeding, and death
Imaging			
Transabdominal ultrasonography	Increased echogenicity of the pancreatic parenchyma as compared to that of the hepatic or renal parenchyma	<ul style="list-style-type: none"> ■ Quick ■ Inexpensive ■ Noninvasive 	<ul style="list-style-type: none"> ■ Operator dependence, ■ Difficult pancreatic visualization with excessive obesity ■ Confounding pancreatic hyperechogenicity due to fibrosis
Endoscopic ultrasound	Increased echogenicity of the pancreatic parenchyma as compared to that of the hepatic parenchyma, renal parenchyma, or retroperitoneal fat	<ul style="list-style-type: none"> ■ Excellent visualization ■ Allows for fine needle aspiration cytology 	<ul style="list-style-type: none"> ■ Invasive ■ Operator dependence ■ Confounding pancreatic hyperechogenicity due to fibrosis
Transient elastography	Evaluation of organ stiffness, though not widely used for pancreatic visualization	<ul style="list-style-type: none"> ■ Quick ■ Inexpensive ■ Noninvasive 	<ul style="list-style-type: none"> ■ Limited use due to the pancreas's retroperitoneal location and small size
Computed Tomography (CT)	Increased hypodensity compared to that of the spleen: <ul style="list-style-type: none"> ■ Pancreatic and splenic attenuation ■ Pancreas-to-spleen attenuation ratio ■ Fat/parenchyma ratio 	<ul style="list-style-type: none"> ■ Radiation exposure ■ Comparable to histological assessment 	<ul style="list-style-type: none"> ■ Ionizing radiation ■ Operator dependence ■ Contrast-enhanced CT scans can have focal fatty replacement exhibiting positive attenuation values that simulate a true mass
Magnetic Resonance Imaging (MRI)	Measurement of pancreatic fat fraction: <ul style="list-style-type: none"> ■ Use of the frequency shift between fat and water resonances to produce in- and opposed-phase images ■ Spectral-spatial excitation technique ■ Automated intra-subject registration-based segmentation ■ Dixon method ■ 3-D iterative decomposition with echo asymmetry and least squares estimation (IDEAL) 	<ul style="list-style-type: none"> ■ Noninvasive ■ High sensitivity ■ Comparable to histological or biochemical evaluation 	<ul style="list-style-type: none"> ■ Expensive

Table 2: Diagnosis of Pancreatic Steatosis

octreotide, and rosiglitazone), pancreatitis (acute and chronic), and viral infections with Reovirus.⁵ For instance, those with chronic pancreatitis show higher pancreatic fat fraction ($p < 0.001$) in mild (24%), moderate (23%), and severe (21%) chronic pancreatitis compared to those without chronic pancreatitis (15%).⁹ However, these conclusions are drawn from a cross-sectional study that cannot infer causality due to the inability to establish a temporal sequence (i.e. whether higher pancreatic fat fraction or chronic pancreatitis develops first).

Sedentary lifestyles with low exercise, obesogenic diets, metabolic syndrome, and differential storage of visceral fat increases risk of ectopic fat deposition in the organs.¹⁰ Compared to non-fatty pancreas, fatty pancreas diagnosed at autopsy or by diagnostic imaging is associated with higher levels of visceral fat, waist circumference, total cholesterol, triglyceride, high density lipoprotein, free fatty acid, and higher insulin resistance.¹¹⁻¹³ In particular, each one kg/m^2 BMI (OR 1.05, $p = 0.03$) and fatty liver (OR 3.61, $p < 0.01$) are independently associated with fatty pancreas on endoscopic

a) Mechanisms of pancreatic steatosis	
Cellular mechanisms	Molecule mechanisms
Imbalance in endoplasmic reticulum Proinflammatory environments <ul style="list-style-type: none"> • ↑ Triglycerides, free fatty acids, cholesterol, total fat • ↑ IL-1β, TNF-α, IL-6, TGF-β, α-SMA • ↓ IL-10 	Changes in core circadian genes <ul style="list-style-type: none"> • Phase shift in CLOCK, Per2, and REV-ERB-α • Decreased amplitude in Per2 and BMAL-1
b) Mechanisms of pancreatic steatosis leading to pancreatic cancer	
Cellular mechanisms	Molecule mechanisms
Adipokines such as adiponectin and leptin Proinflammatory cytokines/chemokines Stellate cell activation Supply of glutamine Impairment of cellular immunity	Impairment of cellular immunity ↑ Transcriptional upregulation of genes involved in... <ul style="list-style-type: none"> • Angiogenesis • Inflammation • Anti-apoptosis • Repression of interferon-inducible genes • Cell migration and invasion

Table 3: Cellular and Molecular Mechanisms of Pancreatic Steatosis and Pancreatic Cancer
 a) Cellular and molecular mechanisms of pancreatic steatosis. b) Cellular and molecular mechanisms of pancreatic steatosis. α -SMA= α -smooth muscle actin. BMAL-1=brain and muscle Arnt-like protein-1. CCK=cholecystokinin. CLOCK=clock circadian regulator. IL-1 β =interleukin-1 β . IL-6=interleukin-6. IL-10=interleukin-10. Per2=period circadian regulator 2. TNF- α =tumour necrosis factor- α . TNF β =tumour necrosis factor- β .

ultrasound (EUS).¹⁴ Pancreatic steatosis often predicts co-existence of NAFLD.¹⁵ In NAFLD patients, waist circumference is predictive for increased risk of fatty pancreas, and there is a statistically significant association between severe pancreatic steatosis on US and cardiometabolic factors including increased mesenteric fat, total cholesterol, elevated fasting glucose, serum lipase, and serum amylase.¹⁶

Pathogenesis of Pancreatic Steatosis

The pathogenesis of pancreatic steatosis remains poorly understood, but several mechanisms are hypothesized (Table 3a). In underlying pancreatic disease, pancreatic steatosis is attributed to adipocyte replacement of acinar cells. For example, those with cystic fibrosis develop precipitation of secretions that cause ductal obstruction and subsequent loss of acinar cells with fatty replacement.¹⁷ In those without underlying pancreatic disease, the prevailing view is that obesogenic diets and sedentary lifestyles lead to obesity that causes pancreatic ectopic fat deposition.³

It has been postulated that visceral or subcutaneous fat are storage areas that may either be impaired or reach capacity in obesity, thus causing adipocyte overflow into organs such as the pancreas. Individuals may be more susceptible to developing ectopic fat deposition, such as in lipodystrophy. Those with Berardinelli-Seip congenital lipodystrophy may accumulate ectopic or visceral fat even with moderate

weight gain due to lack of subcutaneous fat reserve.¹⁸

Subcutaneous abdominal adipose tissue may be protective against ectopic fat accumulation and metabolic derangements.¹⁹ In a longitudinal study of 76 Hispanic children and young adults, accumulation of subcutaneous abdominal adipose tissue is associated with metabolic and beta-cell function improvement, whereas visceral adipose tissue and hepatic fat fraction is significantly associated with declining metabolic and beta-cell function.¹⁹ Metabolically benign obesity in individuals with high subcutaneous fat but low ectopic and visceral fat has been described in the literature.²⁰ Conversely, transplantation of adipose tissue from wild type mice into the subcutaneous tissue of fatless mice significantly lowers intramuscular and intrahepatic triglyceride content.²¹

Obesity induces a proinflammatory environment that may lead to pancreatic steatosis. An experimental model with 30 leptin-deficient obese female mice and 30 lean controls found that the autopsied pancreata from obese mice have histologically increased fat with higher levels of triglycerides, free fatty acids, cholesterol, total fat, and proinflammatory cytokines including interleukin-1 β (IL-1 β) and tumour necrosis factor-alpha (TNF α) ($p < 0.05$).²² Furthermore, obesity impairs the spleen's ability to produce potent anti-inflammatory cytokines such as interleukin-10 (IL-10), which downregulates the release of proinflammatory mediators.²³ In high fat diet-induced obese mice, splenectomy

exacerbates inflammatory responses and pancreatic fat accumulation, especially in intralobular areas, whereas mice with IL-10 knockout who underwent splenectomy fail to develop splenectomy-induced fat accumulation.²³ Conversely, systemic administration of IL-10 decreases pancreatic fat accumulation in both wild type and IL-10 knockout mice.²³ Spleen-derived IL-10 may therefore protect against obesity-induced pancreatic steatosis. Numerous other cytokines may play roles in pancreatic fat infiltration but remain to be investigated.

Other experimental models illustrate that maternal obesity and obesogenic diets in the postnatal period can cause pancreatic steatosis through imbalance in circadian metabolic patterns or endoplasmic reticulum.^{24,25} Compared to the offspring of control mice weaned onto control chow, the offspring of obese mice weaned onto obesogenic diets have significantly increased pancreatic macrovesicular fat infiltration and triglycerides.²⁴ Increased pancreatic steatosis is accompanied by increased pancreatic mRNA expression of IL-6, TGF- β , α -SMA, TNF- α , and collagen and significant disruptions in biological clock-molecular core circadian genes including a phase shift in CLOCK, Per2, and REV-ERB- α and decreased amplitude in Per2 and BMAL1.²⁴ A transcriptional and translational negative feedback loop controls the heterodimer CLOCK and BMAL1 alongside regulatory accessory pathways including REV-ERB- α in order to encode circadian clock genes, such as Per2, that drive the daily rhythm of behaviour and physiology.²⁴ Maternal obesity and a postnatal obesogenic diet cause perturbations in core circadian genes that may thus induce hyperphagic behaviour and pancreatic steatosis in offspring. The pathogenesis of pancreatic steatosis induced by maternal and offspring obesogenic feeding has also been linked to stress-related alterations in the endoplasmic reticulum, such as the unfolded protein response (UPR).²⁵ A murine model found that maternal obesity, post-weaning obesogenic diets in their offspring, or both differentially activates three major UPR pathways that involve proapoptotic and autophagy-related markers and are regulated by the following endoplasmic reticulum transmembrane proteins: kinase RNA (PKR)-like ER kinase (PERK), inositol-requiring 1 alpha protein (IRE1a), and activating transcription factor 6 (ATF6).²⁵ Moreover, endoplasmic reticulum proteostasis is essential to pancreatic β -cells function, whose insulin secretion has been suggested to reduce NAFLD progression and may likewise contribute to pancreatic steatosis pathogenesis.²⁶ Contrarily, deletion of *Chop/Ddit3* in mice alleviates endoplasmic reticulum stress in pancreatic β -cells, improves insulin secretion, and protects against liver steatosis.²⁷

Despite these experimental models and proposed mechanisms, the pathogenesis of pancreatic steatosis necessitates elucidation and validation with future research studies.

Pancreatic Steatosis as a Risk Factor for Pancreatic Cancer

Previous research demonstrates correlations between ectopic fat deposition, especially NAFLD, and development of pancreatic cancer independent of obesity. In a study of 4,722 NAFLD subjects and 14,441 age- and sex-matched subjects, NAFLD is associated with higher risk of incident cancers (IRR=2.0, 95% CI 1.5, 2.9), while obesity is not (IRR=1.0, 95% CI 0.8, 1.4).²⁸ In particular, NAFLD is associated with pancreatic cancer (IRR=2.0, 95% CI 1.2, 3.3).²⁸ Given this precedent and the association between hepatic and pancreatic fat, pancreatic steatosis may be associated with pancreatic cancer development and progression, independent of BMI, a general measure of obesity.

Fatty pancreas is associated with the development of pre-malignant lesions. Based on CT, the number of pancreatic intraepithelial neoplasia (PanIN) lesions correlate with extent of pancreatic steatosis (extralobular ($p=0.01$) and intralobular ($p<0.0001$)) and intralobular fibrosis ($p=0.003$), and PanIN lesion number correlates with intravisceral fat ($p=0.02$).²⁹ Pancreatic fat content, as measured using CT pancreas-to-spleen attenuation ratio, is statistically significantly different between subjects with and without intraductal papillary mucinous neoplasms (IPMN, a premalignant lesion, $p=0.001$).³⁰

Aside from pre-malignant lesions, fatty pancreas is also associated with pancreatic carcinoma. A systematic review found that the pooled prevalence of intra-pancreatic fat deposition based on modern radiology or histology from 13 studies is 52% in cases with pre-malignant lesions or pancreatic cancer.³ Pancreatic steatosis has increased prevalence and severity in pancreatic carcinoma based on EUS and pancreatectomy specimens.³¹⁻³³ Pancreatectomy specimens from 68 pancreatic ductal adenocarcinoma (PDAC) cases exhibit higher ratios of positive change in fatty degeneration (72% vs 44%), inflammatory cell infiltration (14% vs 3%), and fibrosis (86% vs 42%) than controls without PDAC.³² There is no difference in degree of pancreatic steatosis before and after PDAC diagnosis on CT scans, suggesting that pancreatic steatosis, rather than resulting from cancer-associated inflammation, is a carcinogenic risk factor.³⁴ Furthermore, pancreatic fat content is significantly associated with cancer progression on MRI in low-risk branch duct IPMN.³⁰ Increased severity of pancreatic steatosis further correlates with increased risk of pancreatic cancer. In a study investigating 68 cases of histologically proven PDAC with non-contrast CT, risk of PDAC significantly increases with higher pancreatic fat quartiles, in which pancreatic fat is estimated by calculating pancreatic attenuation corrected to splenic attenuation.³⁴ Pancreatic steatosis is also an independent risk factor for pancreatic cancer. Fukuda et al found that low pancreatic CT density, a diagnostic parameter for the diagnosis of fatty pancreas, is an independent risk factor for PDAC (odds ratio 2.31; $p = 0.023$) based on

multivariate analysis including age, gender, diabetes mellitus, and smoking.³⁵ Among 162 patients who underwent EUS-FNA for pancreatic cancer diagnosis, fatty pancreas is the only significant risk factor for pancreatic malignancy (odds ratio: 18.027 [95% CI: 7.288–44.588]).³¹ Factors such as gender, age, chronic pancreatitis, and diabetes are not significant risk factors for pancreatic cancer.³¹ The collective evidence suggests that pancreatic steatosis is an independent risk factor for pancreatic cancer, and increased severity of pancreatic steatosis progressively correlates with increased cancer risk. The causal implications of these observational studies would be further supported by measurement of biomarkers that represent specific mechanistic pathways, such as ER stress and inflammation.

Cellular and Molecular Mechanisms of Pancreatic Steatosis Leading to Pancreatic Cancer

The pathogenesis and role of pancreatic steatosis in carcinogenesis and progression of pancreatic cancer revolve around the tumour microenvironment and inflammatory pathways (Table 3b). Regulating endocrine metabolism, adipocytes secrete adipokines, cytokines, and chemokines that accelerate development and progression of pancreatic neoplasia.³⁶ In a study analysing pancreatic steatosis from pancreatoduodenectomy specimens on histology, pancreatic steatosis, independent of obesity, has been linked to pancreatic cancer development and progression.³⁷ Given the scarcity of animal models focusing on pancreatic steatosis, rather than high fat diets, obesity, or visceral fat, as an independent risk factor for pancreatic cancer, the carcinogenic mechanism remains to be fully understood. Similar to hepatic steatosis advancing to non-alcoholic steatohepatitis, fibrosis, cirrhosis, and even hepatocellular carcinoma, pancreatic steatosis is hypothesized to undergo a comparable pathological process involving inflammation and fibrosis in pancreatic cancer.³⁸

Pancreatic steatosis gives rise to adipocytic secretion of adipokines such as adiponectin and leptin that promote carcinogenesis through induction of inflammation, cell proliferation and migration, and apoptosis antagonism.³⁹ Increased fat decreases adiponectin levels and increases leptin levels, both of which are associated with significantly higher risk of pancreatic cancer and more aggressive phenotypes.^{39,40} This increased cancer risk may be attributed to pro-oncogenic deregulation of the tumour microenvironment, as adiponectin promotes apoptosis and reduction of the availability of growth factors, such as basic fibroblast growth factor, heparin-binding epidermal growth factor-like growth factor, and platelet-derived growth factor B.³⁹ On the other hand, leptin activates JAK2 and causes phosphorylation of STAT3 leading to increased transcriptional upregulation of genes involved in angiogenesis, inflammation, anti-apoptosis, repression of interferon-

inducible genes, and cell migration and invasion.⁴¹ In a study involving rat pancreatic islets that are isolated and incubated with leptin under serum-deprived conditions, leptin suppresses apoptosis in isolated pancreatic islet cells and thus increases viable cell numbers.⁴² Pancreatic steatosis thus may increase risk of development and progression of pancreatic cancer through secretion of adipokines that stimulate inflammation, antagonize apoptosis, and promote cell proliferation and migration.

Alongside adipokine secretion, pancreatic steatosis gives rise to proinflammatory chemokines and cytokines that fuel the tumour microenvironment and promote pancreatic carcinogenesis through chronic low grade inflammation.⁴³ A murine model of high fat diet-induced pancreatic steatosis demonstrated that accumulation of visceral peri-pancreatic fat generates significantly increased inflammation in the pancreas with proinflammatory shifts in cytokine profiles that may contribute to the development of pancreatic cancer.⁴⁴ According to a systematic review, the levels of six cytokines, specifically interleukin[IL]-1 β , IL-6, IL-8, IL-10, vascular endothelial growth factor (VEGF), and transforming growth factor (TGF), are consistently increased and associated with severity in PDAC.⁴⁵ The levels of anti-inflammatory and immunosuppressive cytokines such as IL-10 may be an immune response to fight cancer, whereas the secretion of proinflammatory cytokines and chemokines promotes inflammation and cell transition. For instance, IL-6, a proinflammatory cytokine produced by cancer-associated fibroblasts and pancreatic cancer cell lines, stimulates epithelial to mesenchymal transition and tumour cell invasion and migration.⁴³ Proinflammatory signalling cascades in pancreatic fat tissue propel cell reprogramming toward fibrosis development. In co-cultures of murine 3T3L1 adipocytes and human pancreatic MiaPaCa2 cancer cells, pro-oncogenic WNT5a, a glycoprotein promoting proliferation, migration, and invasion of PDAC cells, induces pancreatic adipocytes to dedifferentiate and reprogram towards fibroblast-like cells.⁴⁶ Furthermore, a study on Syrian golden hamsters susceptible to *N*-nitrosobis(2-oxopropyl)amine (BOP)-induced pancreatic carcinogenesis found that BOP treatment induces severe, scattered pancreatic steatosis with increased production of cytokines and adipokines and shortens the developmental period of BOP-induced PDAC.^{37,47} These animal studies suggest that pancreatic adipocytes, when exposed to oncogenic stimuli, drive stellate cell activation and generate fibrosis that benefits the tumour microenvironment and accelerates cancer progression as an early event.⁴⁸ However, the molecular mechanisms underlying the role of stellate cell activation and fibrosis in pancreatic cancer remains unclear.

The tumour microenvironment has also been investigated as a pro-oncogenic mechanism of pancreatic

steatosis. As shown in oncogenic *Kras* murine models, obesity drives aberrant pancreatic islet expression of cholecystokinin, whose overexpression accelerates pancreatic ductal cancer development.⁴⁹ Apart from obesity-associated overexpression of pancreatic islet hormones, additional factors induced by pancreatic steatosis itself in the tumour microenvironment drive pancreatic carcinogenesis. In co-cultures of murine 3T3L1 adipocytes and cell lines derived from p53fl+/LSL-KrasG12D/Pdx1-Cre/YFP (PKCY) mice that are used to model PanIN and PDAC, adipocytes supply glutamine and stimulate precancerous and cancerous cell proliferation in the nutrient-poor tumour microenvironment.⁵⁰ Lack of adequate nutrients in the tumour microenvironment may also drive dysfunction of regulatory immune cells that normally promote apoptosis of developing pancreatic cancer cells. In a genetically engineered mouse model of PDAC and human tumour specimens, progressive accumulation of specific long-chain fatty acids in intrapancreatic CD8+ T cells leads to impaired mitochondrial function and enhanced intratumoral T cell survival and persistence.⁵¹ Failed apoptosis may generate a vicious positive feedback cycle in which surviving intrapancreatic CD8+ T cells down-regulate the very-long-chain acyl-CoA dehydrogenase enzyme and thereby aggravate accumulation of long-chain fatty acids that facilitate lipotoxicity.⁵¹ Lipotoxicity may be exacerbated through accumulation of lipophilic toxins such as persistent organic pollutants in pancreatic adipose tissue, thereby propagating pancreatic cancer development.⁵² Such mechanisms may explain in part the multifaceted role of pancreatic steatosis independent of obesity in the development of pancreatic cancer.

Incidence of Pancreatic Steatosis and Pancreatic Cancer after Bariatric Surgery

Reduction in pancreatic fat infiltration and improvement in pancreatic metabolism may account for decreased risk of pancreatic cancer among those who had undergone bariatric surgery. A large retrospective cohort study that included 22,198 subjects who had bariatric surgery and 66,427 nonsurgical subjects matched for age, gender, study site, body mass index, and Elixhauser comorbidity index found that those who underwent bariatric surgery have statistically significantly lower risk of pancreatic cancer (HR 0.46, 95% CI 0.22, 0.97, $p=0.04$) compared with matched nonsurgical patients.⁵³

Bariatric surgery effectively reduces pancreatic steatosis. Based on pre-operative and post-operative MRI evaluation, a prospective cohort study of 12 individuals with morbid obesity who underwent bariatric surgery found that pancreatic fat is significantly reduced at 12 months post-operatively, whereas abdominal white fat and hepatic fat are significantly reduced at 6 months

post-operatively.⁵⁴ Another prospective cohort study involving 20 obese patients who underwent bariatric surgery found that both pancreatic steatosis ($-43.8 \pm 7.0\%$) and hepatic steatosis ($-51.2 \pm 7.9\%$) are significantly reduced to lean levels on CT imaging.⁵⁵ As the losses in pancreatic and hepatic steatosis are not correlated, ectopic fat mobilization may be specific to each organ.⁵⁵ Of note, ectopic fat deposition in the liver is located mainly intracellularly, whereas fatty pancreas is heterogeneously characterized by both extracellular adipocyte infiltration of the pancreatic tissue and increased intracellular lipid accumulation.⁵⁶

Bariatric surgery not only reduces pancreatic fat, but also improves pancreatic metabolism and glucose homeostasis. A longitudinal prospective cohort study with 27 morbidly obese subjects demonstrated that bariatric surgery induces decreases in pancreatic fat volume, fatty acid uptake, and blood flow with 23% excess weight loss, though pancreatic fat-free volume remains unchanged on CT imaging.⁵⁷ In addition, six months after bariatric surgery, seven of ten patients have remission of diabetes, suggesting that decreased pancreatic steatosis causes favourable glucose homeostasis and β -cell function.⁵⁷ Corroborating this finding, another study demonstrated that 11 individuals who underwent Roux-en-Y gastric bypass develop subsequent higher insulin sensitivity and lower insulin and C-peptide levels post-operatively in the context of decreased overall pancreatic volume and pancreatic fat volume on MRI.⁵⁸

Improvements in pancreatic fat following bariatric surgery may be related to changes in glycerol, an essential metabolite for lipid accumulation and insulin secretion. A study on diet-induced obese rats demonstrated that sleeve gastrectomy is associated with upregulation of aquaporin-7 (AQP7), the main glycerol channel in β -cells, and normalization of increased levels of AQP12, an aquaporin implicated in pancreatic damage, in the rat pancreas.⁵⁹ These changes increase intracellular glycerol used for GLP-1-induced insulin release and likely account for the reduction in pancreatic steatosis, β -cell apoptosis, and insulin secretion following bariatric surgery.⁵⁹ Another study of 17 severely obese subjects who underwent laparoscopic biliopancreatic diversion with duodenal switch develop normalized whole-body glycerol turnover with associated lower HOMA-insulin resistance index three days after surgery.⁶⁰

Finally, bariatric surgery has been shown to be a potential treatment and preventative measure against pancreatic fibrosis and precancerous lesions, specifically acinar-ductal metaplasia. In an animal model including 63 male Wistar rats, there were less fibro-inflammatory islets ($p=0.0004$), fat infiltrates ($p=0.005$), and acino-ductal metaplasia ($p=0.05$) among rats fed with a high fat diet who underwent bariatric surgery as compared to rats who did not undergo bariatric surgery.⁶¹

Pancreatic Steatosis is Associated with Poorer Outcomes in Pancreatic Cancer

Alongside its implications in the development of premalignant lesions and pancreatic carcinoma, pancreatic steatosis promotes the spread of pancreatic cancer. In a case-control analysis on 42 subjects who underwent pancreatoduodenectomy for PDAC, lymph node-positive subjects have significantly more adipocytes in the pancreas than node-negative subjects (46.4 ± 8.7 versus 21.4 ± 4.8 , $p < 0.02$) based on surgical pathology specimens from the pancreatic neck.⁶² Furthermore, those with lymphatic metastases demonstrate a significantly lower CT attenuation of the pancreatic body and tail compared to those without lymphatic metastases (pancreatic body: 23 ± 9 Hounsfield units vs 35 ± 15 Hounsfield units; pancreatic tail: 21 ± 8 Hounsfield units vs 34 ± 15 Hounsfield units).⁶³ Moreover, those with lymphatic metastases with increased visceral fat (≥ 10 mm vs < 10 mm) exhibit poorer survival (7 ± 1 months vs 16 ± 2 months, $p < 0.01$).⁶³ In addition to lymphatic metastases, fat in the pancreatic tissues based on CT imaging and pancreatotomy or pancreatoduodenectomy specimens is associated with significantly higher risk of blood loss intraoperatively and the development of pancreatic fistula postoperatively.⁶⁴⁻⁶⁷ However, these findings may be confounded by increased severity of pancreatic cancer and its correlating increased damage to the tissues, which may result in acinar cell death and replacement with adipocytes.

Future Directions

There are not yet consensus guidelines on diagnosing or evaluating pancreatic steatosis. Animal studies may serve as a good proxy for determining the best methods and definitions for the diagnosis of pancreatic steatosis. Future preclinical and clinical research should focus on identifying biomarkers or proxies of pancreatic fat. Validated, multicentre trials should be conducted to evaluate the comparative accuracies of available modalities for diagnosing pancreatic steatosis and to standardize imaging thresholds. Furthermore, assessment scores grading the severity of pancreatic steatosis, inflammation, and fibrosis need to be developed to empower assessment of fibrosis impact on pancreatic cancer risk. The molecular mechanisms underlying pancreatic steatosis and its connections with pancreatic cancer necessitate further elucidation. Relationships between levels of pancreatic fat and adipokines, chemokines, or cytokines in animals with pro-oncogenic phenotypes may help determine pancreatic cancer risk. It is important to investigate the impact of stellate cell activation, splenectomy, spleen-derived IL-10, changes in circadian metabolic patterns (including CLOCK, Per2, REV-ERB- α , or BMAL-1), imbalance in endoplasmic reticulum (affecting 3 major unfolded

protein response pathways: kinase RNA (PKR)-like ER kinase (PERK), inositol-requiring 1 alpha protein (IRE1a), or activating transcription factor 6 (ATF6)), and nutrient provision in the tumour microenvironment on pancreatic cancer risk. Future studies should solidify the causal role of pancreatic steatosis on pancreatic cancer risk through rigorous epidemiologic investigation. Such investigation may involve conducting case-control studies with pre-diagnostically determined pancreatic fat to establish the temporal order of pancreatic fat and cancer, controlling for confounding factors including BMI through large natural history studies assessing pancreatic steatosis and pancreatic cancer risk independent of obesity, and determining the extent of steatosis that elevates pancreatic cancer risk through dose-response studies. There are currently ongoing longitudinal studies to investigate associations between serum biomarkers and imaging findings with incidence of pancreatic cancer.⁶⁸⁻⁷⁰ These studies will shed light on the value of measuring and monitoring pancreatic fat for pancreatic risk stratification. Identifying those with pancreatic steatosis who are most at risk of pancreatic cancer would empower targeted therapeutic intervention. Because both obesity and fatty pancreas are risk factors for pancreatic cancer, therapeutic interventions for pancreatic steatosis may be beneficial. Such interventions include dietary changes and increased exercise with a goal of reducing pancreatic steatosis. If these interventions fail to significantly reduce weight over time, more aggressive interventions such as bariatric surgery for those without contraindications may be considered. However, it remains to be explored whether decrease in pancreatic cancer after bariatric surgery is directly correlated with decreased pancreatic fat.

Conclusions

Given the rising global burden of obesity and its associated comorbidities, pancreatic steatosis is a prevalent, increasingly recognized condition that is often neglected in the medical field. Risk factors for fatty infiltration of the pancreas include obesity, metabolic syndrome, insulin resistance, and dyslipidaemia, all of which continue to be challenging to tackle with therapeutic options ranging from lifestyle changes to medications to bariatric surgery. Despite numerous imaging modalities capable of identifying fatty pancreas, there remains a lack of consensus guidelines for evaluating pancreatic steatosis. Pancreatic fat is significantly associated with development and progression of pancreatic cancer through molecular mechanisms involving inflammatory signalling pathways that aid the tumour microenvironment. Understanding and preventing the harmful impact of pancreatic fat infiltration will aid the prevention of pancreatic cancer and elucidate the pathogenesis underlying other obesity-associated cancers.

Outstanding Questions

Future research should focus on generating guidelines for the diagnosis and grading of pancreatic steatosis and fibrosis using different non-invasive modalities such as imaging, biomarkers, or a combination of both. In addition, future studies should investigate the molecular mechanisms underlying pancreatic steatosis and its role in the development of pancreatic cancer. Such mechanisms may revolve around the tumour microenvironment, inflammatory pathways, circadian rhythms, and imbalance in endoplasmic reticulum. The causal role of pancreatic steatosis on pancreatic cancer risk also needs to be solidified through rigorous epidemiologic investigation.

Search Strategy and Selection Criteria

A literature search was conducted on PubMed from 1975 through November of 2021 with the following terms: “fatty pancreas,” “pancreatic steatosis,” “pancreatic fat,” “NAFLD,” and any of the aforementioned terms combined with “bariatric surgery,” “gastric bypass,” “sleeve gastrectomy,” “pancreatic precancerous lesions,” “pancreatic ductal adenocarcinoma,” or “pancreatic cancer.” Additional papers were referenced through forward and/or backward citation of relevant search results. Only papers published in English were included. The final reference list was created based on relevance to this review’s broad scope.

Contributors

ET participated in the design of the study, interpreted the data, and drafted the manuscript. SP and CJ participated in the design of the study, interpreted the data, and critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

Declaration of interests

None

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