

CHRONIC PANCREATITIS: COMPREHENSIVE ANALYSIS OF EPIDEMIOLOGICAL TRENDS, DISEASE EVOLUTION AND CLINICAL OUTCOMES

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DEDICATION

This thesis is dedicated to my mother, Gloria Alexis for her unwavering love and support.

DECLARATION

The work presented in this thesis was conducted by the author whilst in registered postgraduate candidature, unless otherwise acknowledged.

Shauntelle K Quammie

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"It takes a village to raise a child" – African Proverb

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SCIENTIFIC CONTRIBUTIONS

PUBLICATIONS

1. **Quammie S**, Rashid A, Munyal R, Nicholson ES, Clarke C, Venkatachalapathy SV, Crooks C, Aithal GP, Aravinthan AD. Chronic Pancreatitis: A Case Ascertainment Study. *Frontline Gastroenterology* 2025;16: 300-307. DOI: 10.1136/flgastro-2024-102786
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ABSTRACT

BACKGRUOND

Chronic pancreatitis (CP) is a progressive fibro-inflammatory disease characterised by irreversible pancreatic damage, chronic abdominal pain and loss of exocrine and endocrine function. Despite its significant morbidity and mortality, CP remains challenging to diagnose, particularly in early disease, due to heterogeneous clinical presentations and limitations of individual diagnostic modalities. Consequently, the true burden and broader clinical impact of CP are likely underestimated.

METHODS

This thesis employed a multi-method approach to comprehensively evaluate CP. A stringent, pragmatic, multi-source case ascertainment strategy was developed and applied within a UK tertiary centre to accurately identify patients with CP in routine clinical practice, addressing recognised diagnostic heterogeneity. This enabled robust estimation of incidence and prevalence. A systematic review and meta-analysis examined the association between CP and extra-pancreatic cancers. These findings were complemented by longitudinal cohort studies evaluating site-specific cancer risk, temporal patterns of cancer development and associated risk factors. Additional analyses assessed non-cancer comorbidities, pancreatic surgery and mortality. Finally, the burden and clinical significance of multi-organ fibrosis were examined to explore systemic involvement in CP.

RESULTS

From a screening cohort of 24,271 individuals undergoing pancreas-related investigations or treatment, 1,003 patients met stringent diagnostic criteria for CP. Reliance on single diagnostic modalities would have substantially underestimated disease burden. The median age at diagnosis was 65 years (IQR 50 – 76), with a male predominance (65.4%). The incidence of CP diagnosis increased by a mean of 4.1% per year over the study period, ranging from 8.5 to 13.8 per 100,000 population, while point prevalence rose progressively to 53.6 per 100,000 by the end of follow-up.

Systematic review and meta-analysis demonstrated a significantly increased risk of extra-pancreatic malignancies in patients with CP, extending beyond the established association with pancreatic cancer. Cohort analyses confirmed an expanding cancer spectrum, with increased frequencies of both pancreatic and extra-pancreatic cancers. Smoking and alcohol exposure were strongly associated with cancer risk, and cancers occurred after variable latency following CP diagnosis, highlighting prolonged vulnerability over the disease course.

Non-cancer comorbidities were highly prevalent and accumulated with disease duration. Pancreatogenic diabetes developed in a substantial proportion of patients, alongside cardiovascular and metabolic comorbidities. A proportion of patients required pancreatic surgery for pain or complications. Mortality was high and exceeded that expected in the general population, driven by both malignant and non-malignant complications of CP.

Evidence of fibrosis affecting organs beyond the pancreas was frequently identified. These findings support the concept of CP as a systemic fibro-inflammatory condition rather than an isolated pancreatic disorder.

CONCLUSION

This thesis demonstrates that CP is a diagnostically challenging, multisystem disease associated with increasing incidence, substantial cancer risk, high comorbidity burden and premature mortality. Stringent case ascertainment is essential to accurately identify affected patients. Holistic, long-term clinical management strategies are required to address the full spectrum of disease burden and improve outcomes

CHAPTER 1: INTRODUCTION

ANATOMY OF THE PANCREAS

The pancreas is a retroperitoneal gland that lies across the upper abdomen, crossing the bodies of the L1 and L2 vertebrae. It is divided into 3 parts: head, body and tail. The head is an expanded portion which lies within the C shaped loop of the duodenum and the tail extends across the abdomen to the hilum of the spleen. The pancreas contains a main duct, called the pancreatic duct which begins in the tail of the pancreas and runs the entire length of the organ and eventually enters the duodenum through the greater papilla [1].

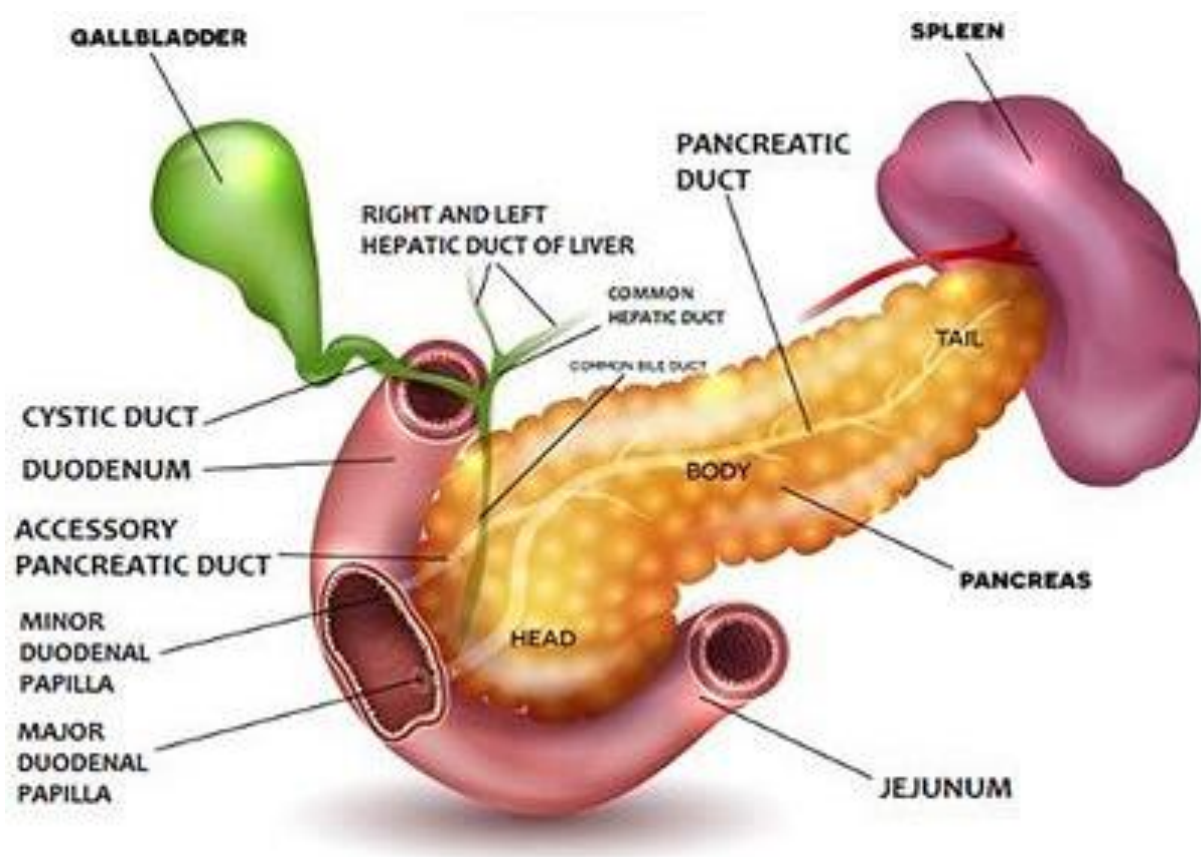


Figure 1.1 – General diagram of the human pancreas [2]

Embryology

Organogenesis is preceded by a process called gastrulation. During gastrulation, the embryo is transformed from a single layered epithelial cell to a trilaminar germinal disc (endoderm, mesoderm and ectoderm); this occurs during the third week of gestation [3]. The endoderm then develops into the foregut and hindgut. The foregut endoderm develops into the dorsal and ventral pancreatic ducts

between days 26 and 31 of development [4]. The ventral bud forms the uncinate process of the pancreas and part of the head of the pancreas while the rest of the pancreas is formed from the dorsal bud [5-7].

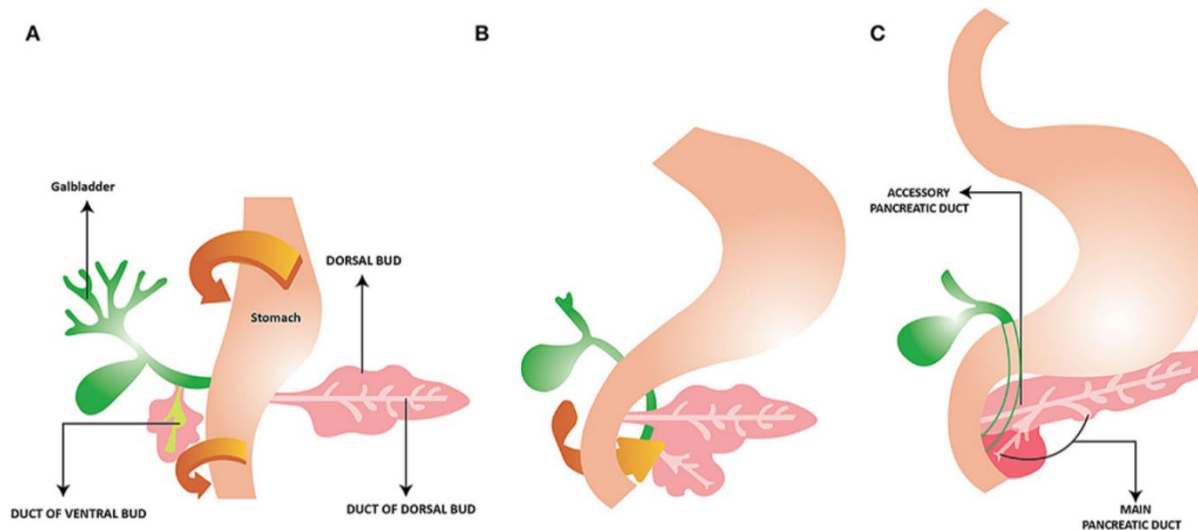


Figure 1.2 – Development of the Pancreas: A) Rotation of the ventral bud with the stomach and duodenum to the right B) The ventral and dorsal bud fuse together C) The main pancreatic duct exiting via the ventral bud to the duodenum [8]

Blood Supply and Venous Drainage

The pancreas receives its blood supply from the splenic, gastroduodenal, and superior mesenteric arteries. [9] The head and neck of the pancreas are supplied by two pancreaticoduodenal arterial arcades; one anterior and one posterior, and each arcade is fed by the superior and inferior pancreaticoduodenal arteries. The arcades lie between the convex periphery of the pancreatic head and the concave inner margin of the duodenum. The superior pancreaticoduodenal arteries are branches of the gastroduodenal artery which in turn is a branch of the common hepatic artery. The body and tail of the pancreas are supplied by multiple branches of the splenic artery.

The head and neck of the pancreas drain into the superior and inferior pancreaticoduodenal veins. The inferior pancreaticoduodenal veins drain into the superior mesenteric vein. The left pancreas drains into the splenic vein. Eventually, the entire venous drainage enters the portal vein [10].

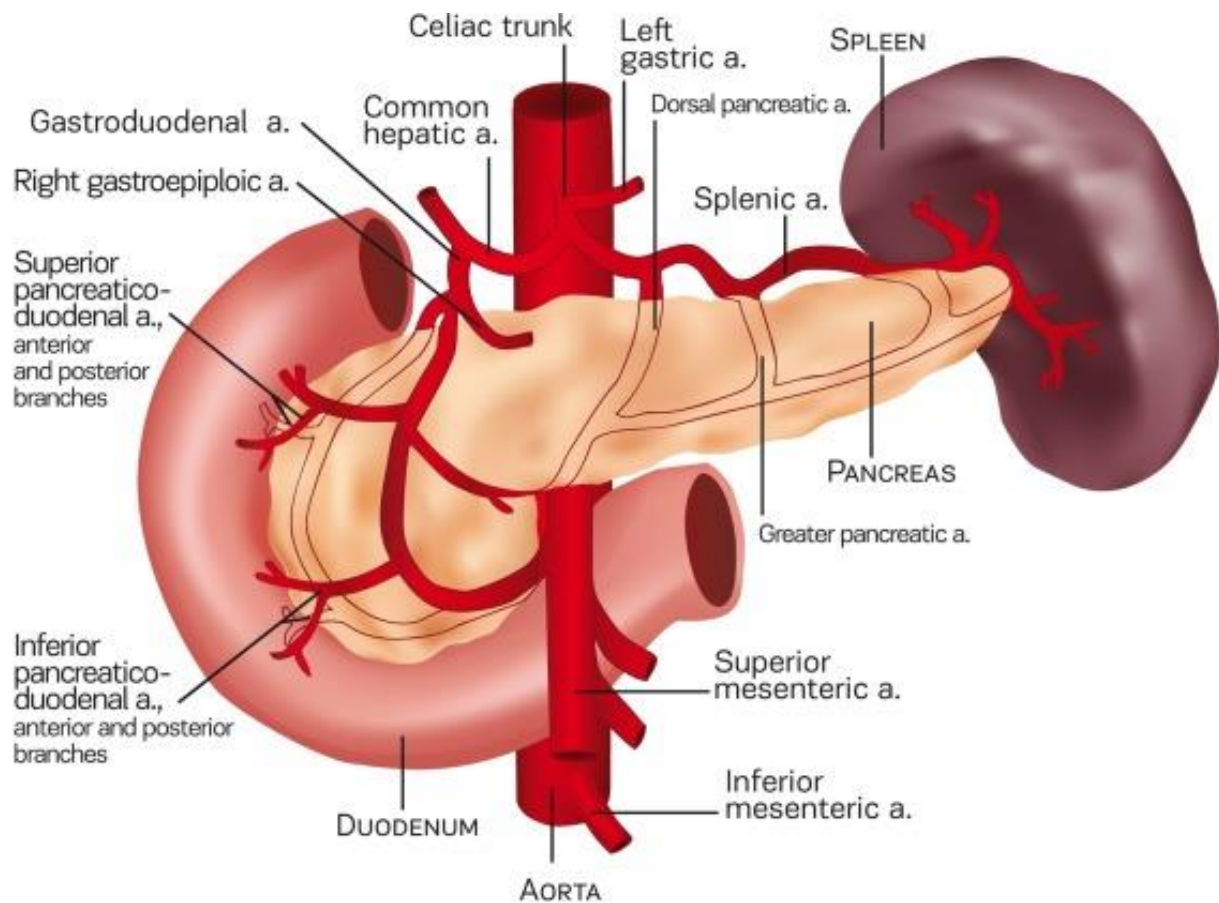


Figure 1.3 – Pancreas and its arterial vasculature [11]

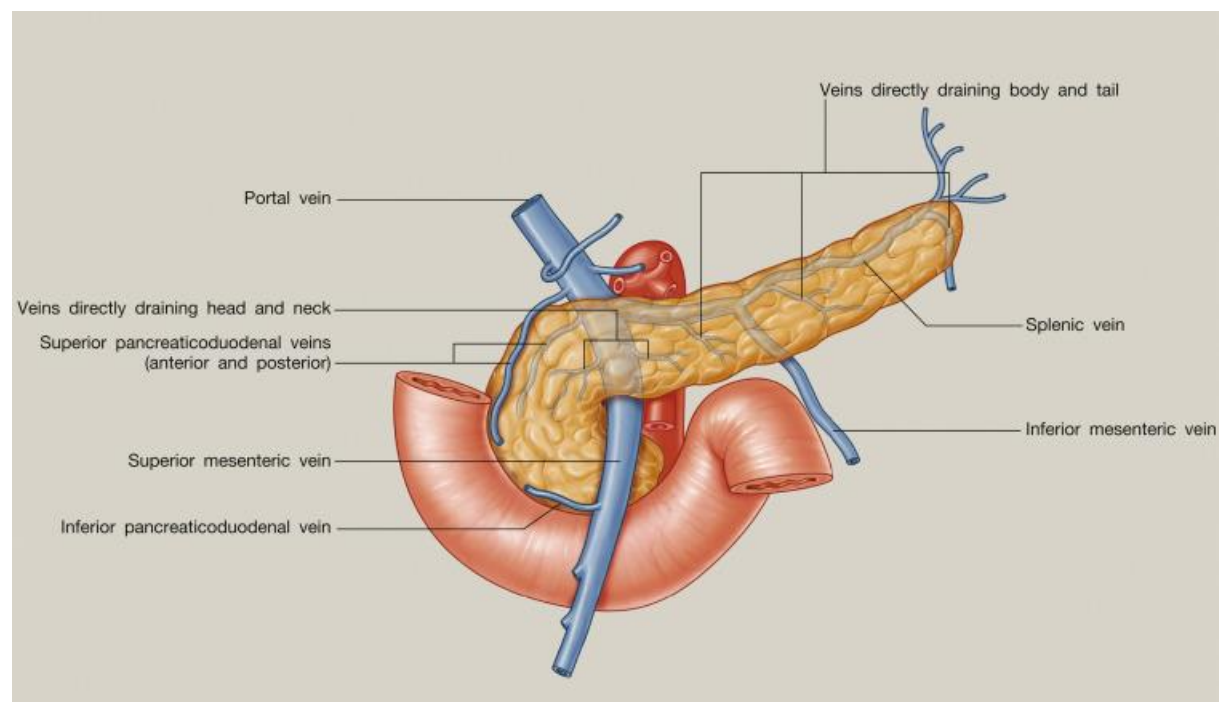


Figure – 1.4 – Venous drainage of the pancreas [1]

Lymphatic System

Lymphatic vessels draining the pancreas accompany the pancreatic arteries. The body and tail of the pancreas drain into the retro pancreatic nodes. The upper half of the head and neck drains into the coeliac lymph nodes while the lower half of the head drains into the superior mesenteric nodes [1].

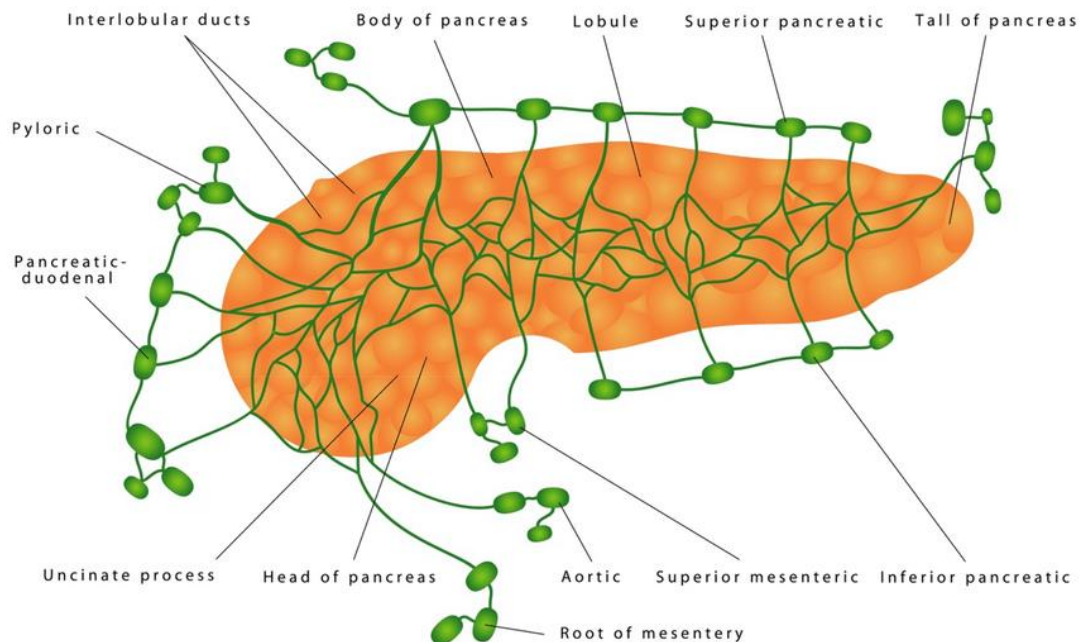


Figure – 1.5 – Lymphatic drainage of the pancreas [12]

Neural Network

The primary nerves supplying the pancreas are the vagus and the splanchnic nerves each carrying both efferent and afferent component [13]. The parasympathetic fibres arise from the posterior vagal trunk and are secretomotor [13]. Sympathetic innervation is via the T6 – T10 thoracic splanchnic nerves and the coeliac plexus [13].

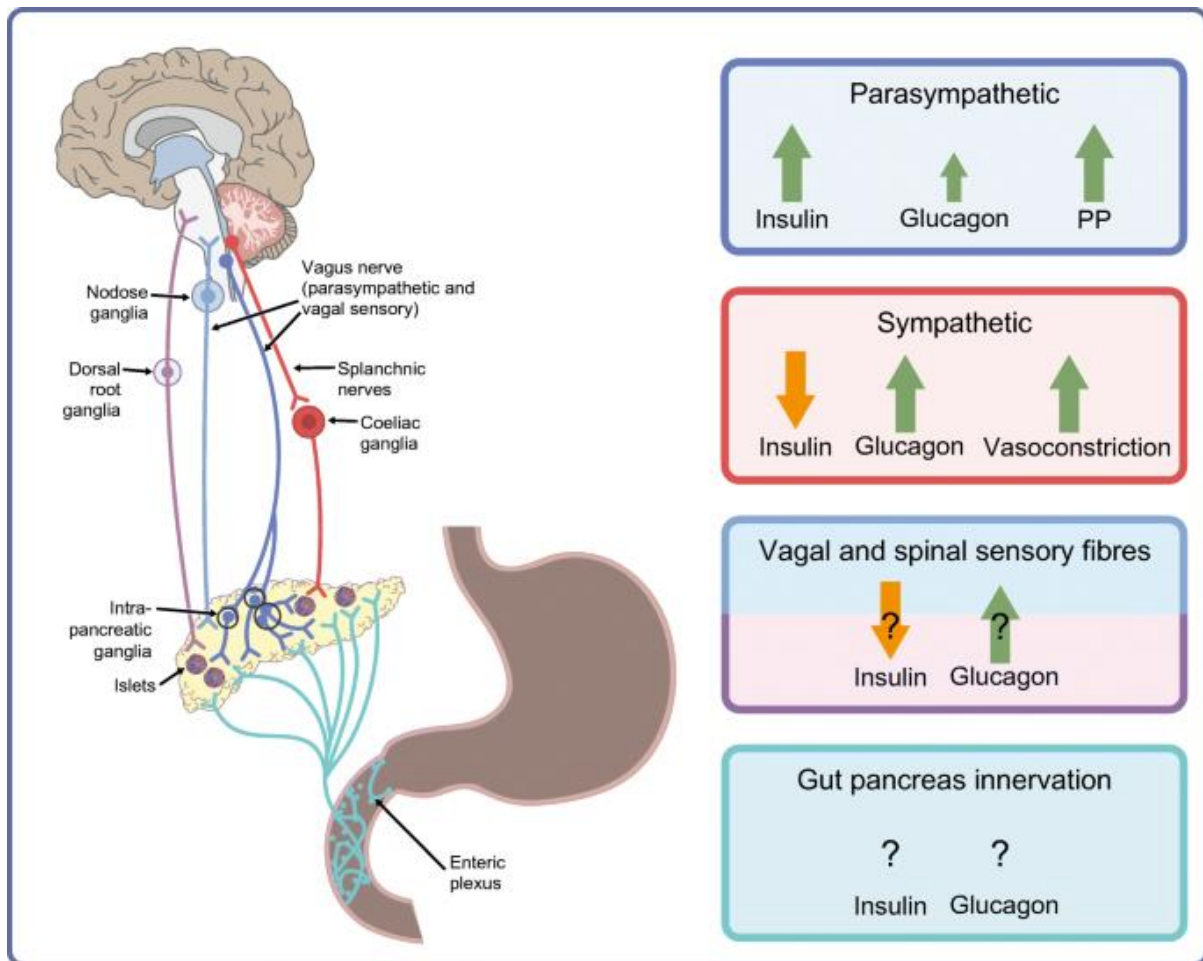


Figure 1.6 – Graphical Abstract of the effects of pancreatic innervation on islet function [14]

PHYSIOLOGY OF THE PANCREAS

80% of the pancreas is made up of exocrine pancreatic tissue and the remainder of endocrine tissue. Histologically, the exocrine system consists of lobules composed of numerous acini lined with epithelial cells which contain zymogen granules. The zymogen granules are secretory vesicles which release trypsinogen, chymotrypsinogen, procarboxypeptidase, amylase and lipase for food digestion [2].

Trypsinogen is a serine proteinase and the inactive precursor of trypsin [15]. Trypsinogen is activated by membrane bound enteropeptidase, which is located on the brush border of the duodenum and the jejunum mucosa, by cleavage of the N- terminal activation peptide located on the trypsinogen surface [16]. Trypsinogen can also be autoactivated by trypsin in a protein-to-protein interaction whereby active trypsin can activate trypsinogen by cleaving off its activation peptide [16]. Trypsin hydrolyses protein molecules into peptides and amino acids [17]. Chymotrypsinogen is the precursor to the serine protease, chymotrypsin and is converted to its active form by trypsin. Chymotrypsin aids in digesting protein. Procarboxypeptidase is also converted to its active carboxypeptidase by trypsin.

Carboxypeptidase degrades proteins by removing C-terminal amino acids from proteins and peptides [18]. Amylase aids in digestion of carbohydrates by cleaving α -1,4 glycosidic bonds in starch and glycogen to form maltose, maltotriose and dextrans [19]. Lipase catalyses the hydrolysis reaction and breaks down ester bonds of lipids and fats and convert this into fatty acids, glycerol, and other alcohols [20]. The epithelial cells lining the pancreatic ducts secrete fluid and bicarbonate that render the duodenal lumen pH alkaline [2].

The endocrine system consists of islets of Langerhans, which are interspersed among the acinar glands. There are three major cell types within the islets. These are the alpha cells which produce glucagon, beta cells which produce insulin and delta cells which produce somatostatin [21].

Glucose homeostasis depends largely on balanced secretion of glucagon and insulin from the Islets of Langerhans. In response to a meal, high plasma glucose stimulates the pancreas to release insulin. Insulin promotes glucose uptake, stimulates formation of glycogen from glucose (glycogenesis) in the liver and muscle and suppresses glucagon secretion. Alternatively, when plasma glucose levels fall low, the pancreas releases glucagon which promotes breakdown of glycogen to glucose (glycogenolysis), promotes glucose synthesis (gluconeogenesis) and inhibits glycogen formation (glycogenesis) [22]. Somatostatin is a paracrine inhibitor of both insulin and glucagon secretion [23]. Nevertheless the cellular regulation of somatostatin is poorly understood as it comprises only 5% of the islet cells [24].

DISEASES OF THE PANCREAS

Most common non-malignant diseases of pancreas are acute pancreatitis (AP) and chronic pancreatitis (CP). Acute Pancreatitis (AP) is defined as inflammation of the pancreas that is associated with systemic inflammatory response syndrome (SIRS) [25]. Alcohol and gallstones account for about 70 – 80% of AP cases [26]. A systematic review and meta-analysis conducted in 2016 showed that AP had a pooled global incidence of 34 per 100,000 person-years in high income countries [27]. The diagnosis is based on upper abdominal pain, elevated serum amylase or lipase or both at least three times the upper limit of normal, and imaging findings consistent with acute pancreatitis [28, 29]. The majority of AP presentations are mild and self- limiting. However, about 20% of patients develop moderate or severe AP with necrosis of the pancreatic tissue and/or organ failure with a mortality rate of 20% - 40% [30]. Approximately 20% of patients develop recurrent AP [31]. Nearly 10% of patients with AP and 36% with recurrent AP develop CP [32].

CP is described in detail below.

CHRONIC PANCREATITIS

CP is an irreversible condition of the pancreas characterized by chronic progressive pancreatic inflammation, fibrosis and scarring ultimately resulting in loss of both exocrine (acinar cells) and endocrine (islet cells) function [33, 34]. It is most commonly caused by alcohol and smoking [35]. In the Western world, 60-90% of cases of CP are caused by alcohol [36, 37], while smoking is associated with 93% of cases of CP [38]. Smoking has also been shown to independently increase the risk of developing CP by a factor of 2.5 [39].

Globally, the annual prevalence of CP ranged from 41.8 to 163 per 100,000 persons from 2011 to 2016, with an annual incidence of 4.1 to 12.8 per 100,000 person-years from 2015 to 2021 [40-43]. It causes debilitating abdominal pain leading to a reduced quality of life [44-46], and is associated with the development of diabetes mellitus, osteoporosis, and pancreatic cancer [47-50].

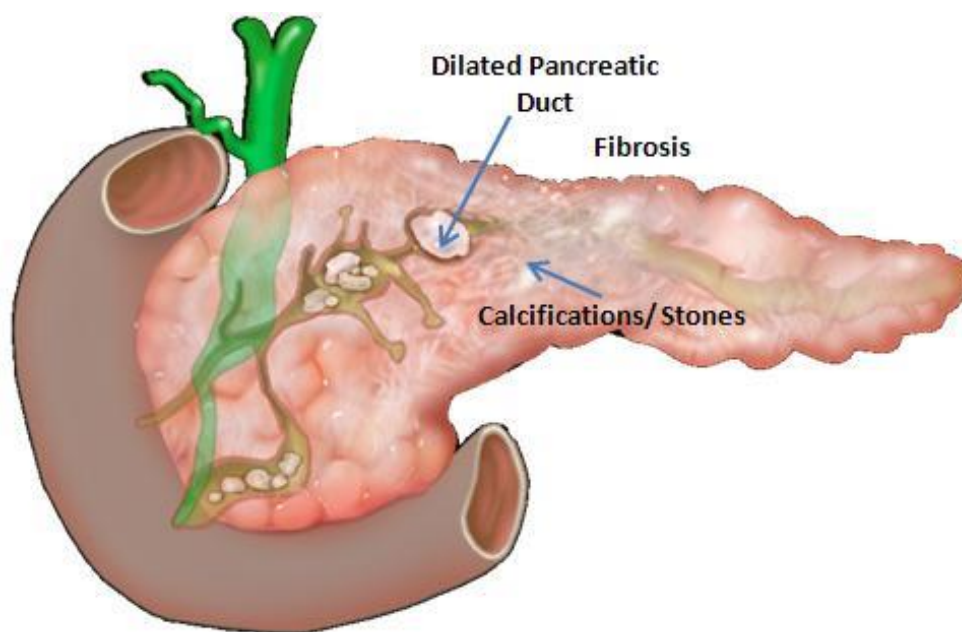


Figure 1.7 – Structural features of chronic pancreatitis. Adapted from Gorelick F, Pandol, SJ, Topazian M. Pancreatic physiology, pathophysiology, acute and chronic pancreatitis. Gastrointestinal Teaching Project, American Gastroenterological Association 2003.

Causes of Chronic Pancreatitis

A wide range of risk factors are associated with the development of CP. The TIGAR- O classification encompasses the majority of known causes of CP. This was initially proposed by Etemab and Whitcomb in 2001 in which CP was classified based on the following risk factors: Toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis and obstructive [51].

Table 1.1 – TIGAR-O Classification of CP V1 (ETEMAD AND WHITCOMB, 2001) [51]

Toxic Metabolic
Alcohol Tobacco Smoking Hypercalcemia - Hyperparathyroidism Hyperlipidemia (rare and controversial) Chronic renal failure Medications - Phenacetin abuse (possibly from chronic renal insufficiency) Toxins - Organotin compounds
Idiopathic
Early onset Late Onset Tropical - Tropical Calcific pancreatitis - Fibrocalculous pancreatic diabetes Other
Genetic
Autosomal Dominant - Cationic trypsinogen (Codon 29 and 122 mutations) Autosomal Recessive/ modifier genes - CFTR mutations - SPINK1 mutations - Cationic trypsinogen (Codon 16, 22, 23 mutations) - A1- Antitrypsin deficiency (possible)
Autoimmune
Isolated Autoimmune chronic pancreatitis Syndromic Autoimmune chronic pancreatitis - Sjögren syndrome- associated chronic pancreatitis - Inflammatory bowel disease- associated chronic pancreatitis - Primary biliary cirrhosis- associated chronic pancreatitis
Recurrent and severe acute pancreatitis
Postnecrotic (severe acute pancreatitis) Recurrent acute pancreatitis Vascular diseases/ ischemic Post- irradiation
Obstructive
Pancreatic Divisum Sphinter of Oddi disorders (controversial) Duct Obstruction (eg tumor) Preampullary duodenal wall cysts Posttraumatic pancreatic duct scars

Alcohol

Alcohol is an established risk factor for CP accounting for 60%-90% of cases in developed countries [37]. The pancreas metabolizes ethanol via oxidative and non-oxidative pathways [52, 53]. The oxidative pathway is catalysed by alcohol dehydrogenase (ADH) and cytochrome P₄₅₀ 2E1 (CYP 2E1) resulting in the production of acetaldehyde and reactive oxygen species (ROS) [54]. ADH and CYP 2E1 are both expressed in the pancreas; and CYP 2E1 has been shown to increase in production during chronic alcohol consumption [55]. At intoxicating levels of alcohol consumption, the rate of pancreatic ethanol oxidation approaches that of hepatic ethanol oxidation [54]. The non oxidative pathway of ethanol metabolism is catalysed by a group of enzymes known as fatty acid ethyl ester (FAEE) synthases to form FAEEs. [56] Although FAEE synthase are present in both the pancreas and the liver, FAEE synthase activity in the pancreas is 3.5 to 10 times higher than the liver [57]. Acetaldehyde has been shown to induce morphological and biochemical changes in the exocrine cells of the pancreas in rats [58]. Additionally, it activates pancreatic stellate cells resulting in increased extracellular matrix and subsequent fibrogenesis within the pancreas [59-63].

FAEEs have been shown to increase pancreatic lysosomal fragility [64]. ROS damage cellular lipid membranes through peroxidation leading to increased fragility of lysosomes and zymogen granules, followed by autodigestion, mast- cell degranulation, platelet aggregation and subsequently inflammatory damage eventually leading to activation of pancreatic stellate cells and fibrosis [63, 65, 66].

The risk of developing alcohol-induced CP is proportional to the duration of alcohol consumption and daily alcohol consumption, with a minimum of 6 – 12 years of heavy drinking (>80 grams of ethanol per day) being required to cause symptomatic CP [67]. Despite this, only 5% of patients with alcohol use disorder develop CP and up to 5-10% are found to have CP on autopsy [68-70].

Smoking

Tobacco smoking is an independent risk factor and confers a 2- to 3- fold increased risk of developing CP [39, 71]. Nicotine induces widespread changes in the pancreatic exocrine function affecting acinar cells and ductal epithelial cells [72, 73]. It has also been shown to induce morphological changes such as an increase in extracellular matrix and a decrease in the number of acinar structures [74]. Cigarette smoking is associated with development of pancreatic calcifications, pancreatic stones, pancreatic pseudocyst, steatorrhea and progression of alcoholic CP [75-77].

Hypercalcemia

Hypercalcemia leads to calcium deposition in the pancreatic duct and subsequently to the intrapancreatic conversion of trypsinogen to trypsin causing pancreatic autodigestion [78]. Pancreatic autodigestion results in AP. Recurrent episodes of AP can progress to CP by causing repeated inflammation, cytokine release, and pancreatic stellate cell activation, which in turn stimulates myofibroblast activation and subsequent fibrotic tissue deposition within the pancreas [79]. Additionally, trypsin activates protease activated receptor-2 (PAR-2) which is located in high densities on the luminal surfaces of pancreatic acinar cells and duct cells [80]. Rat pancreatic stellate cells have been shown to express PAR-2 and activation of PAR2 causes pancreatic stellate cells to produce increased collagen with subsequent replacement of normal tissues [81]. The increased collagen production drives pancreatic fibrosis, which is the defining feature of CP [82].

Hyperlipidaemia

Excess triglycerides are hydrolysed by lipase in the vascular bed of the pancreas to produce free fatty acids (FFA) [83]. Excess FFA accumulate due to limitation of albumin to bind the excess of FFA. The excess FFA aggregate into micellar structures with detergent properties [83]. This micellar structure is toxic to platelets, vascular endothelial cells and acinar cells leading to ischemia and acidosis [84]. Acidosis leads to activation of trypsinogen which triggers acute pancreatitis [85, 86]. FFA also increases ROS production and leads to vascular endothelial dysfunction [84, 87]. Additionally, elevated levels of chylomicrons, the largest among lipoproteins, leads to an increase in plasma viscosity. This elevated plasma viscosity causes capillary blockage and ischemia which enhances acidosis and eventually leads to acute pancreatitis. [84-86] Recurrent acute pancreatitis in turn leads to the development of CP [31, 88]. A triglyceride level of ≥ 1000 mg/dl (11.3 mmol/l) is associated with an increased risk of developing pancreatitis [89, 90].

Genetic

Autosomal Dominant

Codon 122 Mutation

The R122H is an amino acid substitution on the cationic trypsinogen gene where arginine is replaced with histidine at position 122 [91]. The pancreas secretes trypsinogen in three isoforms which are encoded by different genes: cationic trypsinogen PRSS1, anionic trypsinogen PRSS2 and mesotrypsinogen PRSS3 [92]. Cationic trypsinogen makes up two thirds of total trypsinogen while anionic trypsinogen makes up rest [93]. Trypsinogen is activated and converted to trypsin in the duodenum brush border protease, enteropeptidase. Cleavage of the Arg 122- Val 123 autolytic peptide bond on trypsin degrades and inactivates trypsin [94]. The R122H cationic trypsin mutation

destroys the Arg₁₂₂ autolytic site [95]. Premature activation of trypsin culminates in acinar cell death via apoptosis and digestion of the acinar cell by trypsin and other proteases [96].

Codon 29 Mutation

This is a missense mutation which occurs on cationic trypsinogen gene where there is a single nucleotide substitution of asparaginase to isoleucine at position 29 in exon 2 [91]. This mutation increases autoactivation resulting in significantly higher levels of trypsin [97] and leads to CP.

Autosomal Recessive

Cystic Fibrosis transmembrane conductance regulator Mutations

Cystic Fibrosis transmembrane conductance regulator (CFTR) is expressed in the apical plasma membrane of secretory epithelia in the airways, pancreas, intestine, reproductive organs and exocrine glands [98]. CFTR gene mutation leads to impaired protein folding, plasma membrane expression, function and stability of CFTR [98], and causes cystic fibrosis.

When the CFTR protein is functioning, there is an increase in the volume of alkaline fluid which allows the highly concentrated proteins secreted by the acinar cells as digestive enzymes to remain in a soluble state. However, in Cystic Fibrosis, where the CFTR proteins are either absent or reduced, there is impairment of transport of bicarbonate and chloride across the ducts ultimately resulting in decreased intraluminal pH, reduced volume and hyperconcentration of macromolecules [99, 100]. These changes eventually lead to cystic fibrosis patients having a low flow of secretions with a high protein concentration which precipitate in the duct causing obstruction and damage [101]. This obstruction in the acini leads to acini injury and destruction, resulting in inflammation, fibrosis and fatty replacement in the pancreas [102, 103]. Inflammation and fibrosis of the pancreas ultimately lead to CP [104].

SPINK mutations

Serine protease inhibitor kazal type 1 (SPINK 1) is a trypsin inhibitor synthesised and secreted by acinar cells [105]. SPINK prevents premature activation of trypsinogen thereby preventing autodigestion of the pancreas [106]. It inhibits up to 20% of trypsin activity by binding to the catalytic site [80]. There are many mutations in the SPINK gene but the N₃₄S is the most common missense mutation where there is a substitution of asparaginase by serine at codon 34 [80, 107]. These mutations whether autosomal dominant or recessive do not inherently cause CP on their own but

may act as disease modifiers by lowering the threshold for initiating pancreatitis caused by other genetic and/ or environmental factors [108].

Alpha 1 Antitrypsin Deficiency

Alpha 1 antitrypsin (A₁AT) inhibitor is a prototypical member of serine proteinase inhibitor the SERPIN) family of protease inhibitors [109]. Approximately 80% of AAT is produced by hepatocytes but some additional quantity is also produced by monocytes, macrophages, pancreas, lung alveolar cells, enterocytes, endothelium and some cancers [110-114].

In addition to neutrophil elastase, A₁AT inhibitor neutralizes/ inhibits proteinase 3, myeloperoxidase, cathepsin G and alpha defensins from neutrophils, chymase and tryptase from mast cells, trypsin, chymotrypsin and elastase from pancreas, granzyme B from T lymphocytes, circulating kallikrein 7 and 14 and the coagulation cascade serine proteases plasmin, thrombin, urokinase and factor Xa [109, 115, 116].

There are conflicting results regarding the association of A₁AT inhibitor deficiency as a risk factor for the development of CP with some studies reporting an association while others not [117-119]. Due to the inherent nature of A₁AT to inhibit the proteolytic enzymes trypsin, chymotrypsin and elastase and subsequent pancreatic autodigestion, theoretically, A₁AT inhibitor should be able to prevent the development of pancreatitis. However, Witt et al showed that A₁AT inhibitor deficiency was not related to the pathogenesis of idiopathic or hereditary CP [118]. This contradicts the findings by Novis et al, who reported an increased frequency of PiMZ phenotype in patients with CP [119]. However, this study was limited by abdominal radiographs being the mode of diagnosis of CP in some cases [119].

Autoimmune

Autoimmune Pancreatitis

Autoimmune pancreatitis (AIP) is a form of CP characterised by specific histological features, elevation of serum IgG₄ levels and/ or tissue infiltration of IgG₄ plasma cells with a predictable response to steroid therapy [120]. AIP is rare and the true incidence and prevalence is not well established [121]. The pathogenesis of AIP is characterized by genetic, environmental and immunological factors [121].

The genes, DRB1*0405-DQB1*0401 and ABCF1 are associated with increased susceptibility to AIP in Japanese patients [122]. Expression of cytotoxic T lymphocyte antigen 4 (CTLA 4; CD 152) on

activated memory T cells and CD4⁺CD25⁺ regulatory T cells have also been shown to increase susceptibility to AIP in Taiwanese and Japanese populations [123, 124].

Several antibodies have also been implicated in the development of AIP. These include serum antinuclear antibody, pancreatic secretory trypsin inhibitor, antilactoferrin and carbonic anhydrase II antibody [125-127].

Two types of types of AIP have been described namely, type 1 and type 2. These are differentiated by age of onset, organ/ systemic involvement, histopathological findings and presence of IgG4 positive cells [128]. Typical histological findings of type 1 AIP include lymphoplasmacytic sclerosing pancreatitis, periductal lymphoplasmacytic infiltrate without granulocytic infiltration, obliterative phlebitis, storiform fibrosis and abundant (>10 cells/hpf) IgG4 positive cells [129]. Type 2 AIP is typically characterised by granulocytic infiltration of duct wall with or without granulocytic acinar inflammation, lymphoplasmacytic acinar infiltrate and absent or scant (0-10 cells/hpf) IgG4 positive cells [129]. Type 1 is a systemic disease affecting the pancreas, bile ducts, kidneys, salivary glands, retroperitoneum, and is usually seen in middle-aged men. On the contrary, type 2 only affects the pancreas and is usually seen in younger patients [35].

AIP is hypothesised to progress to CP by causing pancreatic head swelling during the acute phase, which progresses to long standing narrowing of both Wirsung's and Santorini's ducts with subsequent pancreatic juice stasis in the pancreatic duct. This results in increased intra-pancreatic duct pressure which ultimately causes severe calcification and pancreatic atrophy [130].

Sjogren associated chronic pancreatitis

Sjogren's syndrome is a chronic autoimmune condition characterised by lymphoplasmacytic infiltration, with a predilection for exocrine glands, primarily the salivary and lacrimal glands [131]. It has been shown to be associated with the development of type 1 AIP, which is characterised by elevated IgG4 levels and organ fibrosis [132]. Sjogren's syndrome primarily contributes to CP via autoimmunity, owing to the presence of a shared antigen on pancreatic ductal cells, which is also expressed on salivary and lacrimal glands [133]. This results in the generation of common antibodies in patients with both Sjogren's syndrome and CP, which are not observed in CP due to other aetiologies [133]. Consequently, lymphocytic infiltration of the pancreas occurs, leading to chronic inflammation, activation of pancreatic stellate cells, and the release of pro-fibrotic cytokines [134]. The activated pancreatic stellate cells secrete excessive collagen, which replaces normal pancreatic tissue with fibrotic tissue, ultimately resulting in CP [134].

Clinical Manifestations of Chronic Pancreatitis

Abdominal Pain

Abdominal pain is the most common (90%) presenting symptom of CP [135]. The pathogenesis of pain is multifactorial including mechanical (intraductal pressure/obstruction), inflammatory, malabsorptive and neuropathic/neurogenic changes within the pancreas and/or surrounding organs [136].

Ductal hypertension results from pancreatic duct obstruction, strictures and/or peripancreatic fibrosis as well as ischemia from a stricture or compartment syndrome which may trigger the onset of abdominal pain [137-140]. However, pancreatic duct pressures do not correlate with severity of the abdominal pain and pancreatic duct stenting does not always lead to pain [141]. Pain relief has been noted after surgical procedures such as resection and drainage, pylorus preserving Whipple's and Frey procedures [142, 143].

Rat models of CP had elevated levels of calcitonin gene related peptide, substance P, brain-derived neurotrophic factor which have been shown to stimulate pain [144-146]. Inflammation has also been implicated in the pathogenesis of pain in CP and is mediated by fractalkine, CX₃CR₁, pancreatic mast cells, GAP-43 and other cytokines and chemokines [147-149].

As a result of the release of growth factors and cytokines by the inflamed pancreas, pancreatic nerve hypertrophy and increased neural density occur, which correlate with pain severity. These neuropathic changes seem to enhance and generate neuropathic pain [150]. There is also an increase in neuronal expression of genes that increase sensitisation to pain such as TRPV₁, TRPA₁, TRPV₄ and PAR 2 [151-154].

Additionally, patients with CP have alterations in central processing of pain. Microstructural changes of the brain have been identified in patients with pain-related to CP [155]. Cortical areas involved in pain processing have reduced thickness in patients with CP [156]. In rat models of CP, astrocytes and spinal microglia are activated and participate in the initiation of pain [157, 158].

Other causes of pain in CP include complications of CP such as pseudocysts, bile duct or duodenal obstruction or a secondary pancreatic cancer [35].

Pancreatic Exocrine Insufficiency Symptoms

Exocrine insufficiency occurs due to failure of digestive enzymes reaching the intestines for digestion of meals to meet nutritional and metabolic requirements [159]. Pancreatic exocrine insufficiency develops in 35–50% of patients with CP around 10–15 years after clinical onset, progressing to 70–80% as the disease advances [160]. This is associated with development of steatorrhea, diarrhoea, weight loss, flatulence and abdominal pain [161]. Steatorrhea refers to the development of large

volume, foul smelling stools which occurs due to increased fat in the stools from inadequate delivery of both lipase and bicarbonate [161]. The acidic environment further inactivates the remaining lipase that may be present and precipitates bile salts, worsening fat absorption. It is a late presentation of CP and is more common during the second decade after the onset of CP [162]. Steatorrhea tends to occur when there is a 90% loss of pancreatic exocrine function [163]. Male gender, presence of diabetes, excess alcohol consumption and pancreaticoduodenectomy have been shown to be associated with steatorrhea in patients with CP [164].

The gastrointestinal effects such as bloating, borborygmi, flatulence and osmotic diarrhoea occur as a result of microbial digestion of unabsorbed nutrients [159]. Weight loss in patients with CP is multifactorial – due to loss of exocrine function, insulin deficiency and food aversion secondary to pain [165].

Non-Cancer Disease Associations of Chronic Pancreatitis

Diabetes Mellitus

Endocrine dysfunction of CP is complex and is due to impaired production of insulin, insulin resistance or a combination of both [166]. Pancreatogenic diabetes mellitus (DM) is also known as type 3c DM [167]. Approximately 40%-60% of patients with CP develop pancreatogenic DM [168]. The risk of DM is increased with progression of the disease and calcifications [169, 170]. Approximately 50% of patients develop pancreatogenic DM after 10 years of CP diagnosis whereas 83% develop pancreatogenic DM after 25 years [171]. Pancreatogenic DM is difficult to control and is frequently associated with brittle diabetes [172]. This is largely due to the loss and function of islet cell mass causing loss of insulin, glucagon and pancreatic polypeptide ultimately culminating in large fluctuations in blood glucose [172].

Patients with CP are at high risk of insulin deficiency. The changes that occur in CP include beta cell dysfunction and destruction [173]. Beta cell dysfunction occurs early in the course of CP before the onset of clinical DM [173]. It occurs due to chronic inflammation and cytokine release which causes deranged signalling mechanism ultimately resulting in beta cell dysfunction [173]. Beta cell volume and pancreas volume are also decreased by 29% and 21%, respectively in patients with CP due to extensive fibrosis of the pancreas which destroys the islet cells [174]. The inflammatory process also contributes to the development of DM through cytokine-induced islet cell destruction [175].

Further, hepatic insulin resistance has been demonstrated in patients with CP [176]. The cause of this is multifactorial, but pancreatic polypeptide has been shown to play a key role as administration of pancreatic polypeptide improves glucose tolerance and increases insulin receptor activity in hepatocytes [177]. Pancreatic polypeptide is an endogenous peptide secreted by F cells of the islets

of Langerhans [178]. Pancreatic polypeptide also participates in glucose regulation by sensitising the liver to the action of insulin by increasing the number of insulin receptors on the hepatocytes [179]. Further, the decreased expression of high affinity insulin receptors on the hepatocytes in CP likely contributes to hepatic insulin resistance [177]. Pancreatic polypeptide also decreases the expression of resistin hormone which participates in glucose metabolism by inducing insulin resistance [180]. Patients with CP tend to have elevated resistin levels which contributes to the ongoing vicious cycle [181].

Osteopenia and Osteoporosis

CP is associated with an increased risk of developing osteopenia and osteoporosis with a subsequent increased risk of fractures [182, 183]. As a result of maldigestion and malabsorption of fat, fat soluble vitamins A, D, E and K are also malabsorbed [50]. Insufficient vitamin D leads to demineralisation as vitamin D deficiency results in decreased calcium absorption with subsequent bone resorption releasing of calcium from bones [184]. This eventually culminates in osteopenia, osteoporosis and osteomalacia [184].

Cardiovascular Diseases

CP is associated with an increased risk of cardiovascular events such as stroke, myocardial infarction and peripheral vascular disease [185-189]. CP is associated with increase in inflammatory cells such as neutrophils and macrophages with release of cytokines such as IL6, IL10, TNF α , TGF β , PDGF and the chemokine monocyte chemoattractant protein 1 [190].

IL 6 is a pro-atherogenic cytokine that is increased in unstable angina and is considered as an independent risk factor for the development of coronary artery disease [191]. TNF α is elevated in advanced heart failure and remains elevated among post myocardial infarction patients at increased risk of recurrent coronary events [192]. The chronic inflammation generated in CP activates immune cells to promote atherosclerotic lesions precipitating acute coronary syndrome [193].

Cancer Associations of Chronic Pancreatitis

Pancreatic Cancer

CP is a risk factor for development of pancreatic cancer with a risk factor that is 80 times higher than the general population [47, 194]. The risk tends to increase with increased duration of the disease [47]. The cumulative risk of developing pancreatic cancer in alcoholic CP is 2% after 5 years and 4% after 15 to 20 years. The cumulative risk in hereditary pancreatitis is 10%, 19% and 53.5% at the age

of 50, 60 and 75 years, respectively in patients with PRSS1 mutation, and 12% with SPINK1 mutation at 60 years of age [194-197].

CP is characterized by destruction of acinar cells which activates inflammatory cells such as macrophages and granulocytes which in turn secrete proinflammatory cytokines and chemokines. These subsequently activate pancreatic stellate cells to cause CP [198]. Activated pancreatic stellate cells produce IL 4, IL 5, IL 6, IL 10, IL 13, IL 1 β , TNF α , TGF 1 β , PDGF-BB [60, 199, 200].

Interleukin 4 (IL4) is a T helper 2 cytokine which regulates cell proliferation, apoptosis and immunity [201]. IL4 levels are higher in patients with pancreatic cancer compared to controls and it is shown to cause growth of pancreatic cancer cells [202, 203]. CP is associated with elevated IL6, and it is over expressed in pancreatic ductal adenocarcinoma [204]. IL6 is associated with increased tumour cell migration and metastases [205]. IL 13 has been proven to promote pancreatic tumorigenesis [206].

Oxidative stress with the generation of ROS and activation of inflammatory pathways are also implicated in the progression of CP to pancreatic cancer [195]. ROS, generated during the pathogenesis of CP [195], induce acinar cell necrosis and fibrosis subsequently modifying nucleic acids, lipids and proteins resulting in DNA fragmentation, membrane disintegration and protein misfolding [195]. These changes induced by ROS together with activation of cytokines and chemokines induce epithelial cell damage and increased proliferation [195].

Inflammatory mediators such as NF- κ b and STAT3 generate sustained oxidative injury which induces acinar cell injury [207]. These mediators are essential for the development and progression of pancreatic cancer [208, 209]. The inflammatory milieu induces ductal metaplasia which is a precursor to pancreatic cancer [207]. STAT3 is also an oncogene and is involved in the pathogenesis of pancreatic cancer by enhancing cell proliferation, survival, angiogenesis and metastasis by inducing the expression of vascular endothelial growth factor and matrix metalloproteinase 3 and 9 [210].

Extra Pancreatic Cancer

Studies suggest an increased risk of head and neck cancer in a Taiwanese population with CP [211]. However, a rigorous systematic review has not been performed to investigate the frequency of extra pancreatic cancers in patients with CP.

Complications of Chronic Pancreatitis

Pseudocysts

A pseudocyst is a fluid collection within the pancreas or peripancreatic tissues, characterised by a well-defined inflammatory wall and the absence of solid material [29]. It arises from disruption of the

pancreatic duct or its branches, leading to the extravasation of pancreatic enzymes into the parenchyma [29]. Approximately 40% of patients with CP develop pseudocysts [212]. These are more common in males than females and typically develop between the fourth and sixth decades of life [213]. Between 34% and 68% are located in the head of the pancreas [214].

Clinical presentation ranges from asymptomatic cases to symptoms such as abdominal pain, early satiety, upper gastrointestinal bleeding, nausea, and vomiting [215]. While 9% to 60% of pseudocysts secondary to CP resolve spontaneously, others may develop complications, including infection, haemorrhage, and rupture [216-219].

Management is multifactorial and includes conservative treatment, imaging-guided percutaneous drainage, endoscopic drainage, and surgical drainage [220]. Conservative management is generally reserved for asymptomatic patients, while drainage procedures are indicated for symptomatic pseudocysts or those complicated by infection, gastric outlet obstruction, or biliary obstruction [216].

Gastrointestinal Obstruction

Intestinal obstruction occurs in approximately 1% of patients with CP [221]. It is most commonly due to compression by pseudocysts or fibrotic changes in the head of the pancreas, with the duodenum being the most frequently affected site [222].

Gastric outlet obstruction in CP usually arises from compression by pseudocysts [223]. The preferred management of choice is endoscopic drainage of the pseudocyst [224].

Bile duct Strictures and Obstructive Jaundice

Bile duct strictures in CP result from recurrent inflammatory episodes, leading to periductal fibrosis. Their development is influenced by the anatomical relationship between the bile duct and the head of the pancreas [225, 226]. They occur in 3% to 46% of patients with CP and may present asymptotically or with deranged liver function tests, abdominal pain, jaundice, or cholangitis [227].

Obstructive jaundice develops in approximately 30% of patients with CP [225]. It is caused by biliary obstruction or, less commonly, by hepatocellular disease. The prognosis is generally favourable with respect to jaundice resolution, pain control, and overall survival [228, 229]. Endoscopic retrograde cholangiopancreatography with stent placement is the preferred treatment for bile duct strictures [230].

Splenic Vein Thrombosis

Splenic vein thrombosis occurs in approximately 22% of patients with CP [231]. The splenic vein lies posterior to the pancreas and is susceptible to thrombosis due to repeated fibroinflammatory

processes, cellular infiltration, and pancreatic oedema [232]. Clinical presentation is variable and includes incidental detection, gastrointestinal bleeding, abdominal pain, or splenomegaly [232].

Pseudoaneurysm

Pseudoaneurysm develops in 4% to 10% of patients with CP and is associated with a mortality rate of 15% to 40% following rupture [233]. It arises due to enzymatic digestion of pancreatic, peripancreatic, or adjacent arteries by pancreatic enzymes [234]. The most commonly affected arteries include the splenic, gastroduodenal, pancreaticoduodenal, and hepatic arteries [235]. Presentation typically involves major gastrointestinal bleeding in the event of rupture [236].

Pancreatic Haemosuccus

Pancreatic haemosuccus is a rare form of pseudoaneurysm, characterised by bleeding from the ampulla of Vater via the pancreatic duct [237]. It is associated with life-threatening haemorrhage [238], and usually presents with abdominal pain, upper gastrointestinal bleeding, and elevated serum amylase levels [239].

Diagnosis of Chronic Pancreatitis

Several different modalities are used to diagnose CP and this in itself has created a diagnostic dilemma [240]. Early changes of CP are missed on imaging, which can only detect advanced disease [240, 241]. The diagnosis of early CP is challenging as there are only subtle to no changes in pancreatic morphology on imaging and it may overlap other disorders [242-244].

The Japan Pancreas society developed a set of criteria to diagnose CP in 1971 which has since been updated [245, 246]. However, the criteria are more suitable for diagnosing advanced disease rather than early disease [246, 247].

Common methods for diagnosing CP include histology, imaging, and endoscopy.

Histology

Histology is considered the gold standard for diagnosing CP; however, biopsies are not routinely performed for diagnostic purposes due to technical challenges of obtaining tissue and availability of safer and non-invasive methods of diagnosis [248]. Thus histological confirmation is usually reserved for surgical specimens (e.g., tissue from pancreatectomy) [249]. Histological findings diagnostic of CP are perilobular and intralobular fibrosis, infiltration of inflammatory cells such as lymphocytes, macrophages and plasma cells, loss of acinar cells, distorted ducts and intraductal calcification [250]; however, routine use of histological diagnosis is limited by the lack of a consensus around grading [251].

Imaging

Computed Tomography

CT is considered the best initial investigation to diagnose CP, to exclude other extra-pancreatic pathology such as mass or gastrointestinal malignancy which may be mistaken for CP and to identify complications of CP such as pseudocyst, biliary or duodenal obstruction and splenic venous thrombosis [248, 252]. However, it is limited by its ability to detect only advanced disease [248, 252]. Classical CT findings suggestive of CP include dilated pancreatic duct, pancreatic atrophy and pancreatic calcification [240, 248]. The most commonly used CT classification for CP is the Cambridge Classification: grade 0, normal main pancreatic duct and side branches; grade 1 (equivocal), normal main pancreatic duct with fewer than three abnormal side branches; grade 2 (mild), normal main pancreatic duct with three or more abnormal side branches; grade 3 (moderate), abnormal main pancreatic duct with more than three abnormal side branches; and grade 4 (severe), abnormal main pancreatic duct with duct obstruction, a large cavity >10 mm, filling defects, and severe dilatation or irregularity [253]. Contrast-enhanced CT is usually the first investigation of choice to investigate the pancreas [252], as this provides better imaging resolution of the pancreas [252].

Magnetic Resonance Imaging

MRI is more sensitive than CT and is emerging as the investigation of choice in patients with equivocal or borderline CT results [254-256]. MRI and magnetic resonance cholangiopancreatography (MRCP) together allow for excellent visualization of the pancreatic duct and can reveal parenchymal and ductal changes consistent with CP [252, 257]. However, they are not ideal for visualisation of the side branches [258]. The addition of secretin to MRCP provides better visualisation of the main pancreatic duct and side branches as well as duodenal filling which allows estimation of pancreatic exocrine function [258-260]. Secretin is a 27 amino acid polypeptide hormone secreted by the duodenal mucosa in response to luminal acid usually after a meal [261]. It stimulates pancreatic secretion of bicarbonate-rich fluid and increase tone of sphincter of Oddi which causes distension of the pancreatic duct [262].

MRI parenchymal changes suggestive of CP include pancreatic atrophy, irregular contour of head or body, heterogeneous parenchyma, depressed T1 signal and delayed gadolinium enhancement after administration [257]. MRI ductal changes suggestive of CP include calculi, main pancreatic duct dilation, side branch dilation and irregular duct contour [257].

Abdominal Ultrasonography

Abdominal Ultrasonography (US) is commonly used as the first investigative modality in the work up of abdominal diseases and presentation of abdominal pain [263]. However, use of abdominal US in diagnosing CP is constrained by the retroperitoneal location of the pancreas and overlying structures [263], which limit its sensitivity to approximately 70 – 80% [264, 265].

Endoscopic Ultrasound

Endoscopic ultrasound (EUS) is the most sensitive tool for detecting early and minimal structural changes associated with CP [240]. EUS has been used to diagnose and assess severity of CP since 1986 [266, 267]. However, there are limitations to using EUS as a diagnostic tool. Minimal or mild parenchymal and ductal findings have 'poor specificity' resulting in overdiagnosis of CP [268]. Additionally, there is significant interobserver variability with EUS [269, 270]. EUS is an operator dependent test and is subject to individual bias in measuring each criterion [268]. There was also the lack of standardisation in establishing the CP diagnosis prior to the development of the Rosemont criteria in 2007 at an international congress meeting attended by internationally recognized endosonographers from North America and Japan [270]. They anonymously voted on terminology, establishment of a rank order and categorisation of criteria for CP into major and minor [270].

Table 1.2 – The Rosemont criteria and classification for EUS-based diagnosis of CP [271]

Major A criteria	Hyperechoic features with shadowing
	Main pancreatic duct calcifications
Major B criteria	Lobularity with honeycombing
Minor Criteria	Lobularity without honeycombing
	Hyperechoic features without shadowing
	Pseudocysts
	Stranding
	Irregular main pancreatic duct
	Main pancreatic duct dilatation
	≥3 dilated duct branches
	Hyperechoic main pancreatic duct wall
Consensus EUS-based criteria consistent with definitive chronic pancreatitis	
1. Two Major A criteria OR	
2. One Major A and Major B criteria OR	
3. One Major A and three or more minor criteria	
Consensus EUS-based criteria suggestive of chronic pancreatitis	
1. One Major A and less than three minor criteria OR	
2. One Major B and three or more minor criteria OR	
3. Five or more minor criteria	

Faecal Elastase

Elastase is a proteolytic enzyme secreted by the exocrine pancreas [272]. Faecal elastase is a test that measures pancreatic exocrine insufficiency (PEI) but is not interchangeable with a diagnosis of CP [273]. There are many conditions which can cause a low faecal elastase without CP such as pancreatic tumours including cystic disease, pancreatic resection, pancreatic atrophy, acute pancreatitis, spurious result due to watery diarrhoea, diabetes mellitus, bile acid diarrhoea, irritable bowel syndrome, inflammatory bowel disease, small bowel bacterial overgrowth, HIV infection and antiviral drugs, rheumatological disorders and chronic kidney disease [161, 273, 274]. A faecal elastase <200µg/g is considered an abnormal value in most laboratories that is consistent with pancreatic exocrine insufficiency [273]. However, some patients with CP may have a normal faecal elastase if there is adequate remaining parenchymal cell volume and they are exocrine sufficient [273].

Abdominal X-ray

Coarse calcifications in the epigastric region projecting over the pancreas are a recognised abdominal X-ray feature of CP. However, the sensitivity of AXR is as low as 30% in diagnosing CP [275]. Whilst these calcifications are sensitive, they are not specific and have to be differentiated from calcifications of other organs, tissues or vascular structures.

Management of Chronic Pancreatitis

Pain Management

Pain management in CP requires a multidisciplinary approach, incorporating lifestyle modifications, pharmacological therapy, endoscopic interventions, and surgery. Pain assessment in CP can be reliably performed using validated tools such as the Brief Pain Inventory and the McGill Pain Questionnaire [276-278].

Lifestyle Modification

Alcohol cessation is associated with a reduction in pain, and patients with CP are strongly advised to abstain from alcohol consumption [279, 280]. Although smoking cessation slows disease progression, it has not been conclusively shown to reduce pain levels [281].

Low fat Elemental Diet

An elemental diet is a hypoallergenic, easily digestible nutritional formulation composed of monosaccharides (e.g. dextrose, glucose, maltose), saccharide polymers (e.g. maltodextrins), amino acids, medium-chain triglycerides, trace elements, and vitamins [282]. These formulations require

minimal pancreatic function for digestion as they contain amino acids instead of intact proteins and minimal fat, yet they offer complete nutritional support with favourable safety and efficacy profiles [282]. Elemental diets allow for rapid absorption and high nutritional efficacy; however, their use is limited by poor palatability, leading to low patient compliance. In addition, they are costly and require specialist preparation due to the complexity of production and mixing [282]. A prospective multicentre study by Kataoka et al. demonstrated a significant reduction in abdominal pain after 12 weeks of consuming a low-fat elemental diet with meals in patients with painful CP [283]. Similarly, 88% of patients in a Japanese cohort reported pain relief after an 8-week course of a low-fat elemental diet combined with dietary fat restriction [284].

Antioxidants

Patients with CP typically have reduced antioxidant levels [285]. A Cochrane systematic review of 12 randomised controlled trials, six of which were double-blinded and placebo-controlled encompassing 585 participants, found that antioxidant therapy was associated with a reduction in pain intensity, as measured on a visual analogue scale, after 1 to 6 months of treatment. However, the proportion of participants who became pain-free was not statistically significant. In addition, 16% of patients receiving antioxidants experienced adverse events that led to treatment discontinuation [286]. Further well-designed clinical trials are needed to determine the efficacy and safety of antioxidant therapy in the management of pain in CP.

Analgesics

Non-Opioid Analgesia

These include paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs).

Paracetamol inhibits the COX-2 pathway of prostaglandin synthesis *in vivo* and weakly inhibits COX-1 and COX-2 *in vitro* [287, 288]. Prostaglandins mediate inflammation by increasing blood flow and microvascular permeability and contribute to pain via their effects on peripheral sensory neurons and central pathways in the spinal cord and brain [289]. Although paracetamol has a favourable safety profile at therapeutic doses, it is generally inadequate as monotherapy for pain in CP [290]. This may be due to lower serum concentrations observed in CP patients after oral or intravenous administration, alongside increased glucuronidation, potentially reducing its effectiveness [291].

NSAIDs exert their effect by inhibiting COX-1 and COX-2, thereby suppressing prostaglandin synthesis [292]. However, their use in CP is limited by their gastrointestinal side effect profile, including ulceration, bleeding, and perforation. CP patients may be particularly susceptible due to increased gastric acid secretion [292-295].

Opioid Analgesia

Opioids bind to μ , δ , or κ receptors coupled to G_i proteins, modulating pain via multiple mechanisms: inhibition of N-type voltage-gated calcium channels, activation of potassium channels, and inhibition of adenylyl cyclase, leading to reduced cyclic adenosine monophosphate (cAMP) levels [296]. The μ receptor is primarily associated with nociception and analgesia, whereas δ and κ receptor activation contributes to antinociceptive effects at spinal and supraspinal levels [296]. Opioids are classified as weak or strong based on pharmacodynamic characteristics such as potency and efficacy [297]. Weak opioids include codeine, while strong opioids include morphine, pethidine, and buprenorphine [297]. However, long-term opioid use is limited by tolerance, dependence, addiction, and opioid-induced hyperalgesia—a paradoxical increase in pain sensitivity [298-300].

Adjuvant Drugs – Pregabalin

Pregabalin is approved for epilepsy and neuropathic pain [301]. It provides analgesia by binding to the $\alpha_2\delta_1$ and $\alpha_2\delta_2$ subunits of voltage-gated calcium channels [302]. Limited studies support its use for pain relief in CP, although more robust evidence is needed [303, 304].

Adjuvant Drugs – Amitriptyline

Amitriptyline is a tricyclic antidepressant that inhibits the reuptake of noradrenaline and serotonin at presynaptic terminals and is commonly used for neuropathic pain [305, 306]. In CP, where allodynia and hyperalgesia are often present, amitriptyline may be used as an adjunct to analgesics [307].

Adjuvant Drugs – S-Ketamine

S-Ketamine is an N-methyl-D-aspartate receptor antagonist [308]. Small-scale studies suggest it may increase pressure pain thresholds (PPT), but data remain limited [308]. The RESET trial, which aimed to assess its efficacy in CP, was terminated prematurely [309]. Further high-quality trials are required [308].

EUS-guided coeliac plexus neurolysis

Coeliac Plexus Neurolysis (CPN) was first described in 1914 by Kappis using percutaneous anatomical landmarks [310]. In 1996, Wiersema introduced EUS-guided CPN, which proved effective in managing pain in patients with abdominal malignancies [311]. Neurolytic agents used include 50%–100% ethanol (more commonly) and 3%–20% phenol, both typically administered with a local anaesthetic such as bupivacaine or lidocaine [312]. Ethanol causes irreversible neural destruction, though it is painful and requires concurrent anaesthetic administration. Phenol also causes neural damage and has an immediate anaesthetic effect [312].

A systematic review and meta-analysis by Chan et al. demonstrated pain relief in 64% of CP patients following EUS-CPN [313]. However, the relief is typically temporary, lasting on average 12 weeks, though it can range from 4 weeks to 1 year, and the procedure often needs to be repeated [314, 315]. Notably, around 40% of patients do not experience any pain relief [315].

Extracorporeal Shock wave lithotripsy

Extracorporeal Shock Wave Lithotripsy (ESWL) is indicated for painful CP caused by large pancreatic duct (PD) calculi (>5 mm) in the head or body of the pancreas that are not amenable to standard endotherapy [316]. ESWL fragments the stones into smaller pieces (<3 mm), which are then removed via endoscopic retrograde cholangiopancreatography (ERCP) [316]. Complete ductal clearance is achieved in 75% of cases [317, 318].

ESWL is generally safe, though complications such as bleeding, bowel perforation, infection, perirenal haematoma, biliary obstruction, splenic rupture, and liver trauma have been reported [319, 320]. Post-procedure pancreatitis occurs in ~4% and cholangitis in ~0.5% [319, 320], although most complications are rare and anecdotal. Pain relief is reported in 70%–85% of patients, with reduced analgesic use and fewer hospitalisations [317, 319].

Surgery

Surgery is considered in patients with persistent, disabling abdominal pain unresponsive to medical and endoscopic treatment [321, 322]. Surgical procedures are tailored to the underlying anatomical cause of pain [321] and typically involve pancreatic duct decompression, pancreatic parenchymal resection, or a combination of both [323].

Pancreatic Enzyme Replacement Therapy

Pancreatic enzyme replacement therapy (PERT) is the cornerstone treatment of CP [324]. PERT is usually derived from porcine and is a mixture of the digestive enzymes amylase, lipase and protease [324, 325]. The main mechanism of PERT is to simulate the normal physiologic response of the exocrine pancreas to meals by ingestion during or just after meals [326]. PERT is usually initiated in CP patients with progressive weight loss and steatorrhea especially those who secrete more than 15g of faecal fat per day [327, 328]. It has been suggested that 50000 Units per meal of lipase is required to eliminate steatorrhea [326]. PERT has also been indicated as beneficial in patients with idiopathic or small duct CP who suffer from pain that is unresponsive to other measures [329]. PERT in addition to improving fat and protein absorption also improves abdominal pain and flatulence [330-332] .

Pancreatic enzyme replacement therapy (PERT) is available in various formulations, including non-enteric-coated preparations (powder, granules, capsules), enteric-coated tablets, enteric-coated microspheres, and enteric-coated microtablets [326]. When administered orally,

PERT is not fully absorbed because it is degraded by gastric acid and inactivated by the acidic pH of the duodenum. Enteric coating protects PERT from gastric acid, allowing it to reach the intestine intact [326, 333, 334]. The enteric coating is acid-resistant and is designed to stay intact in an acidic environment and to release its content when the pH is between 5.5 to 5.5 in the duodenum for digestion [329].

However, the intraduodenal pH of CP patients is shown to be acidic as a consequence of increased gastric acid production and impaired secretion of bicarbonate from affected pancreatic epithelial cells [294, 335]. This acidic environment inactivates the pancrelipase [336]. Acid suppression drugs such as H₂ receptor antagonist or proton pump inhibitors increases the pH resulting in improved lipolytic activity, prevention of precipitation of bile acids and increased fat absorption [336].

Porcine pancreatic enzymes are the standard of care and the two forms commonly used are pancreatin and pancrelipase [329]. Consumption of these is against the beliefs of some religious group [329], and patients with porcine allergy also do not have another treatment option. Alternative preparations using bovine have been proposed as a replacement. However, bovine enzymes are not used in many countries as their lipase activity is 75% lower than that of porcine enzymes, increasing pill burden to potentially achieve the same effect as a lower dose of porcine enzyme [324]. Additionally, there are also other potential risks that limit its use such as contamination with transmittable pathogens with increased distribution of foot and mouth disease and bovine spongiform encephalopathy [324].

The adverse effects associated with PERT include abdominal pain, nausea, bloating, headache and dizziness [337]. A rare side effect, fibrosing colonopathy characterized by extensive submucosal fibrosis resulting in narrowed colonic lumen causing colonic obstruction [338], has been reported in patients who consume high strength PERT [338, 339]. It was first reported in children with cystic fibrosis in Liverpool who received high strength pancreatic enzymes [340]. It has also been reported in adults taking large doses of pancreatic enzymes [341, 342]. Due to this, high doses of enzymes (e.g., >75000 units/meal for adults and >25000/ meal for children) are not recommended [343, 344].

Management of Vitamin Deficiencies

Patients with CP are at increased risk of malnutrition due to pancreatic enzyme insufficiency, alcohol excess, smoking, abdominal pain, diabetes mellitus, and poor dietary intake [345]. Micronutrient deficiencies such as vitamin B₁₂, folic acid, vitamins A, D, E, zinc, selenium, and iron can result from pancreatic enzyme insufficiency [345, 346]. Malnourished individuals, identified through clinical symptoms, functional impairment, anthropometric data, and biochemical markers, should be advised to consume high-protein, high-energy foods across 5 to 6 small meals per day [347]. Routine

assessment for vitamin and micronutrient deficiencies including fat-soluble vitamins (A, D, E, K), water-soluble vitamins (thiamine, B12, folate), and minerals (selenium, magnesium, iron, zinc) is recommended. Any deficiencies should be corrected through appropriate supplementation [347].

Elimination of the aetiology

Although eliminating the underlying cause of CP does not reverse existing structural damage, it is essential for slowing disease progression [280, 348]. Pancreatic function may continue to decline even after alcohol cessation, but the deterioration is slower and less severe compared to those who continue drinking [280, 348]. Therefore, cessation of alcohol and smoking should be strongly encouraged at every opportunity, as both are well-established contributors to disease progression in CP [280, 348, 349].

Chronic pancreatitis and Quality of Life

CP significantly impairs quality of life [46], with patients reporting lower scores in general health perception, physical functioning, role-physical, and vitality domains of the SF-36 quality of life questionnaire [45]. Contributing factors include the severity of abdominal pain, low body weight, recurrent disease relapses, and unemployment [45].

Socio-Economic Impact of Chronic pancreatitis

CP leads to frequent hospitalisations and represents a substantial economic burden. A 2014 systematic review estimated that CP accounts for approximately 12,000 hospital admissions annually in the United Kingdom, at a cost of £55.8 million [171]. Between 40% and 60% of CP patients develop endocrine insufficiency, adding an additional £45–£90 million per year to NHS costs [171]. The total economic burden of CP including management of exocrine and endocrine insufficiency, enzyme replacement therapy, hospital admissions, interventional procedures, and pain control is estimated at approximately £285.3 million annually [171, 350]. Furthermore, around 50% of patients with CP undergo surgery for pain or complications [351, 352], with approximately 700 CP-related surgical procedures performed annually in the UK [171].

THESIS RATIONALE

CP was selected as the focus of this thesis because it remains a largely neglected condition and is frequently misdiagnosed. Furthermore, there is a scarcity of studies examining the development of comorbidities, cancers, and mortality in this patient population. Existing studies are limited: some are over three decades old, and many employ inconsistent diagnostic methods for CP, reducing their relevance and practical applicability today.

Knowledge Gaps

- Comprehensive evaluations of the benefits and limitations of investigations used to suggest or diagnose CP are not readily available.
- While CP is known to increase the risk of pancreatic cancer, the relationship between CP and extra-pancreatic malignancies has not been adequately investigated.
- Outcome studies assessing comorbidities, cancer incidence, and mortality in CP patients are outdated and often rely on diagnostic methods that are no longer considered reliable or reproducible.

Thesis Aims

This thesis aims to identify the most reliable methods for diagnosing CP, determine the incidence and prevalence of CP in Greater Nottingham, assess the association between CP and extra-pancreatic cancers, as well as the development of comorbidities, evaluate the major causes of mortality in CP patients and compare patients with CP alone and those with CP complicated by multi-organ fibrosis.

CHAPTER 2: CHRONIC PANCREATITIS CASE ASCERTAINMENT

ABSTRACT

BACKGROUND

CP is a debilitating condition characterized by chronic inflammation and fibrosis of the pancreas. The population burden of CP is poorly understood. Therefore, we used a broad pragmatic approach to estimate the burden of CP amongst a patient population undergoing investigations at a tertiary university hospital in the UK.

METHOD

All adult patients who, during the 9 year study period (2006 – 2014), underwent abdominal CT or MR imaging or abdominal X-Ray or EUS or faecal elastase testing or received a prescription for pancreatin, or a recorded primary or comorbid ICD diagnosis of CP were screened (screening cohort) for inclusion in this study. Through applying the well-recognised CT, MRI, and EUS criteria to the screening cohort, patients with CP were identified (study cohort). Incidence of diagnosis and point prevalence of CP were calculated with confidence intervals, and the change in incidence modelled using Poisson regression.

RESULTS

A total of 24,271 cases were included in the screening cohort. A total of 1,003 patients who met the diagnostic criteria for CP were included in the study cohort. The median age of diagnosis was 65 (IQR 50–76); majority were males (n=656, 65.4%); and of European ancestry (n=884, 88.1%). The annual incidence of diagnosis increased by a mean of 4.1% per year (95%CI 0.5–7.8%; p=0.03) over the study period ranging from 8.5 to 13.8 per 100,000 general population. The point prevalence increased over the study period reaching 53.6 (95%CI 48.3 – 59.4) per 100,000 population at the end of the study period.

CONCLUSION

This study provides a clear method of pragmatically identifying patients with CP in a clinical setting. The incidence of CP diagnosis in patients undergoing investigations in hospital increased gradually in Greater Nottingham.

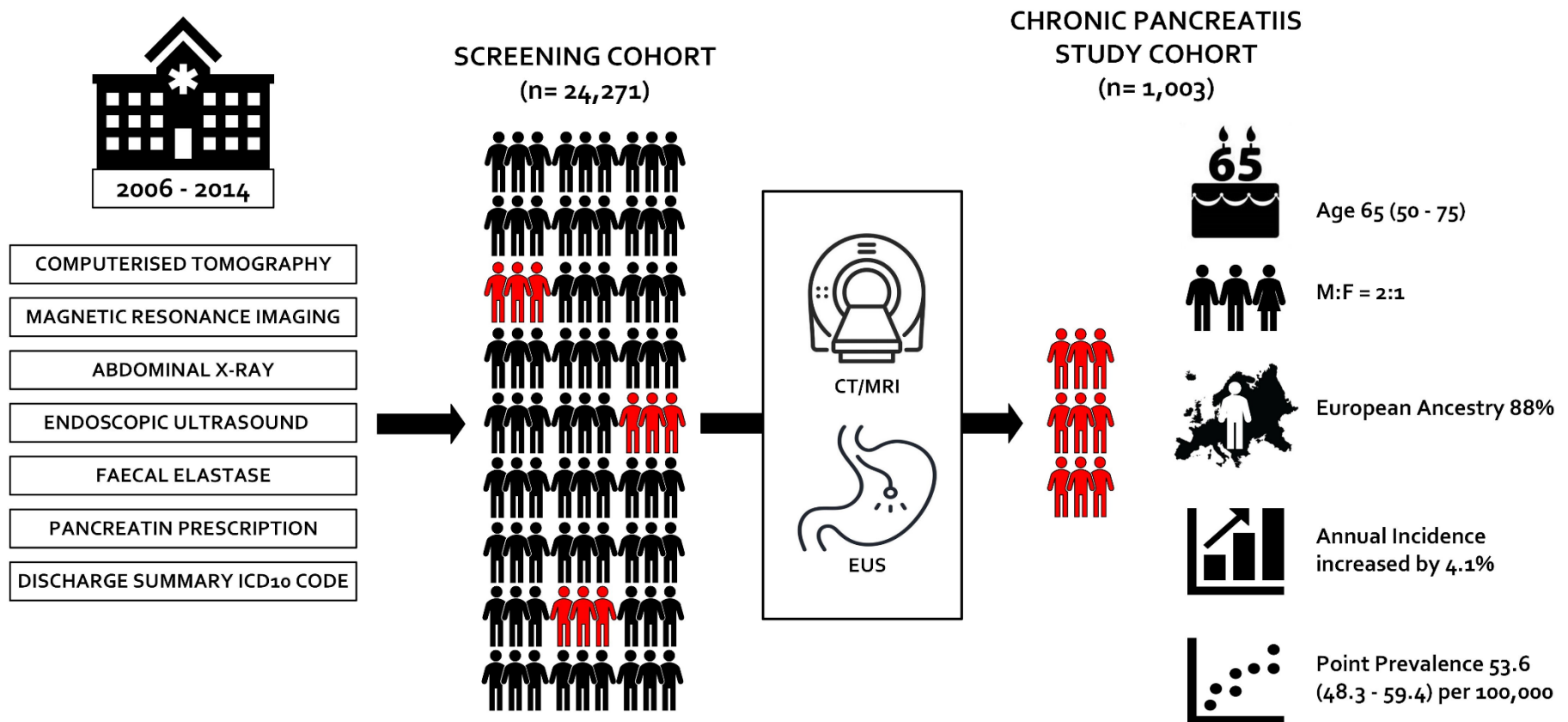


Figure 2.1 – Graphical abstract illustrating the development of the Screening Cohort through a multi-source case ascertainment method and the establishment of the Study Cohort using well-defined CT, MRI, and EUS diagnostic criteria for CP. It also highlights the key demographic characteristics of the Study Cohort.

INTRODUCTION

CP is a chronic progressive irreversible disorder characterised by inflammation and fibrosis of the pancreas [242]. The eventual clinical manifestations of this persistent pathological response to pancreatic parenchymal injury culminate in a range of clinical manifestations from no symptoms, especially in early stages, to exocrine and/or endocrine insufficiency, cancer and death [34].

CP is associated with debilitating chronic abdominal pain induced by obstructive, inflammatory, malabsorptive or neurogenic changes in the pancreas [353]. The endocrine and exocrine insufficiency manifestations include diabetes mellitus, metabolic bone diseases (osteopenia and osteoporosis), malnutrition and steatorrhea, all of which are associated with reduced quality of life [271, 354, 355]. Further, 4%-5% of patients with CP develop pancreatic adenocarcinoma over their lifetime [48, 196, 356].

The prevalence of CP in the UK is estimated to be 163 per 100,000 population, while the incidence is shown to have increased from 5.9 per year in 2001–2005 to 12.8 per year per 100,000 population in 2016–2020 based on a UK biobank study [357]. A 25-year population-based Danish nationwide study estimated the point prevalence and incidence of CP to be 153.9 per 100,000 population in 2016 and 12.5 per 100,000 person years, respectively [43]. The overall global incidence of CP is estimated to be 9.62 (95% CI 7.86–11.78) per 100 000 person-years [27]. However, these values may not reflect the true prevalence and incidence, due to difficult and opportunistic nature of the diagnosis of CP [240]. Traditionally, CP is diagnosed using computed tomography (CT) or magnetic resonance imaging (MRI). However, a wide variety of other modalities are also used in day-to-day clinical practice to diagnose CP. The lack of a rigorous criteria that encompasses various diagnostic tests, has led to a diagnostic dilemma [240]. For example, early changes of CP may not be present or may be overlooked on imaging [240, 241]. Imaging findings such as pancreatic duct dilatation and atrophy can occur in other pancreatic pathologies and may be misinterpreted as CP changes [248]. Endoscopic ultrasonography (EUS) findings are subject to interobserver variability and lack of specificity in early disease[358] . Further, a low faecal elastase, which is sometimes used as a sole diagnostic test of CP, can be a consequence of wide variety of unrelated medical conditions such as pancreatic head malignancy, microscopic colitis, coeliac disease and bile salt malabsorption [161, 359]. Histology remains the gold standard for diagnosing CP, however the process of obtaining tissue for diagnosis is associated with significant complications, some of which are life threatening [248]. The lack of standardisation in establishing the diagnosis of CP, has led to patients being diagnosed with CP based on symptoms alone or inaccurate interpretation of investigations [240]. Identifying those with CP is vital for managing symptoms and service development. Patients with CP are likely to be symptomatic [354, 355] and referred for investigations. Therefore, we used a broad pragmatic

approach to estimate the burden of CP amongst a patient population undergoing investigations at a tertiary University Hospital in the UK.

METHODS

Patient Selection and Data Collection

A retrospective analysis was undertaken in Nottingham University Hospital, a tertiary centre, to identify patients with CP. All adult patients (≥ 18 years) who, between 01 January 2006 and 31 December 2014, had (1) CT or MR imaging or abdominal X-Ray (AXR) and/or (2) EUS and/or (3) faecal elastase testing and/or (4) received a prescription for pancreatin and/or (5) an admission to NUH with a recorded primary or comorbid diagnosis of CP (ICD-10-CM Diagnosis Code K86.0 or K86.1) were screened for inclusion in this study. To ensure completeness of data, the case record of every patient included in the study cohort was searched manually beyond the study period that was used for patient selection. The study was ethically approved by Health Research Authority and Health and Care Research Wales (22/WA/0074).

Search and Diagnostic Criteria

Imaging modalities such as CT, MRI and AXR, EUS, faecal elastase levels, pancreatin prescription and discharge summaries were used to create a screening cohort (Figure 2.2). Cases included in the screening cohort were scrutinised systematically with below described CT, MRI, and EUS diagnostic criteria to create the CP study cohort (Figure 2.2). Two investigators (SQ and AR) reviewed all cases included in the screening cohort independently for diagnostic features of CP. Third investigator (ADA) over saw the process and resolved any conflicts.

CT and MRI

Reports of all abdominal CT and MRI scans performed during the study period were searched for the following terminologies: pancreatitis; atrophy; atrophic; calcification; pseudocyst; pancreatic calcification; calcific; pancreatic duct; main duct. Scan reports that were identified to have even one of above search terminologies were included in the screening cohort. The reports of those included into the screening cohort were then read in full to identify diagnostic features of CP. The complete list of types of CT and MRI scans that were screened are listed in the Table 2.1.

Based on previous literature [360, 361], any of the following radiological features were considered diagnostic of CP: (1) parenchymal or intraductal calcification; (2) pancreatic atrophy; (3) pancreatic duct dilatation; (4) pancreatic duct strictures; (5) irregular or beaded pancreatic duct; and (6)

pseudocyst. Calcification of any form (e.g., punctate, dystrophic, flecks and foci) was included. CT or MRI scans with the following findings were excluded: age-related pancreatic atrophy; pancreatic duct dilatation in patients with pancreatic cancer, calcifications in patients with the intrapapillary mucinous neoplasms (IPMN), solid pseudopapillary tumours, neuroendocrine tumours, serous cystic neoplasm, mucinous cystic neoplasm, acinar cell carcinoma and calcified pancreatic metastases.

Table 2.1 – The list of types of CT and MRI scans that were screened

CT Scans (n=17,047)	CT Abdomen CT Abdomen/Pelvis CT Chest/Abdomen CT Chest/Abdomen/Pelvis CT Neck/Chest/Abdomen CT Neck/Chest/Abdomen/Pelvis CT Pelvis CT Pancreas CT Renal CT Adrenal CT Colonoscopy CT Urogram CT Angiogram Unspecified or Aorta/Abdominal/Renal CT Guided Biopsy/Aspiration/Drainage CT Guided Nephrostomy CT Liver CT Spine Lumbar/Whole CT Maximum Intensity Projection CT Sinogram
MRI Scans (n=4,208)	MRI Whole Body MRI Abdomen MRI Abdomen with Contrast MRI Pancreas MRI Liver with Gadolinium MRI Liver with Hepatobiliary Contrast MRI Liver with Contrast MRI Liver and Spleen MRCP MRCP with Contrast MRCP and Secretin MRI Adrenal Both MRI Small Bowel MRI Spine Whole with Gadolinium MRI Spine Whole MRI Spine Whole with Contrast MRI Spine Lumbar/Sacral with Gadolinium MRI Spine Thoracolumbar MRA Aorta Whole MRA Aorta Abdominal MRA Aorta Thoracic MRA Renal and Visceral MRV Venogram MRV Inferior Vena Cava MRI Cardiac Rest Perfusion

Endoscopic Ultrasound

Reports of all EUS performed during the study period were reviewed for features of CP. Rosemont criteria (see table 1.2) were used for the confirmation of CP on EUS. All cases deemed definitive CP and probable CP based on Rosemont criteria were included into the study cohort.

Other Modalities

Reports of all AXR performed during the study period were reviewed for features of CP. Calcification in the epigastric region, was considered adequate to be included in the screening cohort. Similarly, all patients who received prescription for pancreatin during the study period and those who were had a recorded primary or comorbid diagnosis of CP (ICD-10-CM Diagnosis Code K86.0 and K86.1) on discharge summary during the study period were also included in the screening cohort. Similarly, all faecal elastase test results during the study period were reviewed and those with less than 200µg/g were included in the screening cohort.

The case notes and electronic notes of those included in the screening cohort were searched for above mentioned CT, MRI, or EUS confirmatory criteria of CP. Those with AXR findings alone or pancreatin prescription alone or diagnostic code of CP alone or faecal elastase less than 200µg/g alone (i.e., without any supporting diagnostic features on CT, MRI or EUS) were not included in the study cohort.

Case Definitions

Alcohol use was defined as current or previous alcohol consumption of more than 14 units per week for both men and women. Current or previous tobacco smoking, irrespective of the quantity or duration, was considered a history of smoking.

Data Presentation

All data are shown as median (interquartile range) if continuous or number (percentage) if categorical, unless otherwise stated.

STUDY AREA AND DENOMINATOR POPULATION

The annual population of Greater Nottingham was derived from the Office for National Statistics (ONS) for the years 2006 to 2014. The population for a particular year is estimated on 30 June of that particular year by the ONS. These midyear population estimations were used as the denominator populations to calculate the annual incidence of diagnosis and point prevalence of CP.

Estimation of Annual Incidence of Diagnosis and Point Prevalence

Only patients with confirmed CP from within Greater Nottingham were included in the estimation of annual incidence of diagnosis and point prevalence. Annual incidence of diagnosis was defined as the number of new cases of CP diagnosed over the preceding 12 months to 30 June of a particular year expressed as a rate in the general population of that year. For the year 2006 only, the analysis was limited to 6 months with newly diagnosed cases between 1 January 2006 to 30 June 2006. Point prevalence was defined as the total number of CP patients who were alive on 30 June of a particular year expressed as the proportion of the general population of that year.

The incidence of diagnosis and point prevalence and their respective 95% confidence intervals (95%CI) were calculated using Poisson test in R (Version 4.3.2). The change in incidence of diagnosis with respective 95%CI were calculated using Poisson regression in R (Version 4.3.2). The year 2006 was not included in the Poisson regression analysis as the number of CP cases were available only for the latter 6 months, and not the entire preceding year.

RESULTS

Demographics and Clinical Characteristics

A total of 24,271 cases were included in the screening cohort from individual sources (CT, MRI, EUS, faecal elastase, AXR, issue of pancreatin prescription and discharge summary ICD codes). Based on the CT, MRI, and EUS criteria for confirmation of CP a total of 1,003 patients were included in the study cohort (Figure 2.2).

Of the overall study cohort (n=1,003), nearly two thirds were male (n=656, 65.4%); the median age at diagnosis was 65 years (IQR 50 – 76); majority were of European ethnicity (n=884, 88.1%). Of the 1,003 patients in the overall study cohort, only 678 were residents of Greater Nottingham. The most common risk factors associated with the development of CP in this cohort were smoking (current or ex-smoking; n=524, 52.2%) and alcohol (n=388, 38.7%). Demographics and clinical characteristics are summarised in table 2.2.

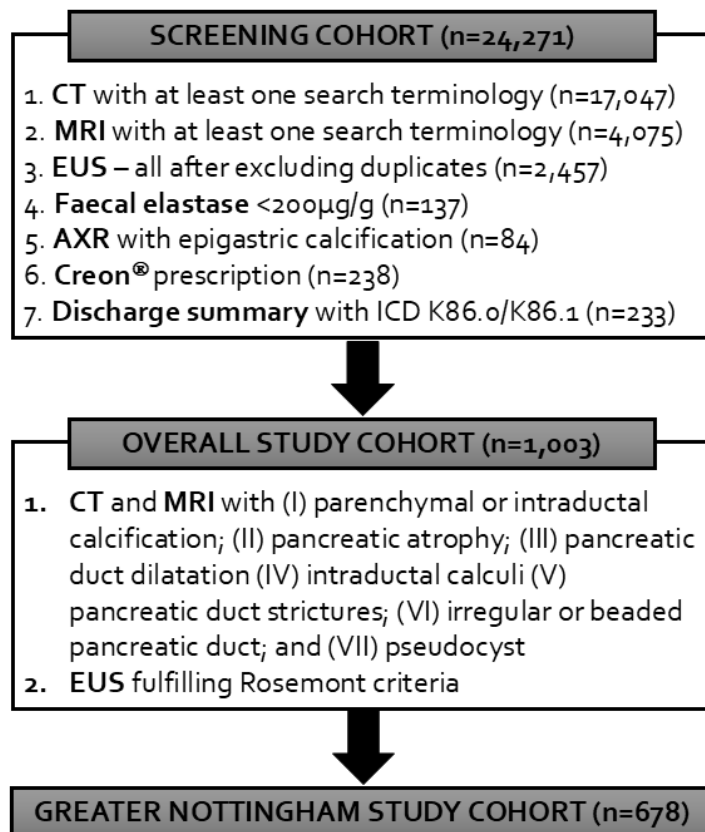


Figure 2.2 – Screening Cohort, Overall Study Cohort and Greater Nottingham Study Cohort. The figure illustrates the selection of participants for the study. The Screening Cohort was initially identified based on CT, MRI, EUS, abdominal X-ray features, faecal elastase levels, Creon prescription records, and discharge summaries. The Screening Cohort was further refined by evaluating only CT, MRI, and EUS features to identify cases with CP.

Table 2.2 – Clinical and demographic characteristics of patients diagnosed with CP

		All Confirmed Chronic Pancreatitis (n=1,003) median (IQR) / number (%)
Age at diagnosis		65 (50 – 76)
Male sex		656 (65.4%)
Ethnicity	European	884 (88.1%)
	African	14 (1.4%)
	South Asian	11 (1.1%)
	East/Southeast	1 (0.1%)
	Unknown	91 (9.1%)
Smoking	Current	477 (47.6%)
	Ex	47 (4.7%)
	Never	121 (12.1%)
	Unknown	358 (35.7%)
History of alcohol excess		388 (38.7%)
Diagnostic modality*	CT	872 (86.9%)
	MRI	108 (10.8%)
	EUS	160 (16.0%)

*since 179 patients with chronic pancreatitis were confirmed of the diagnosis using more than one modality, the total number and percentate will be higher than the study cohort of 1,003 and 100%. Abbreviations: CT computerised tomography. MRI magnetic resonance imaging, EUS endoscopic ultrasonography.

CP was confirmed in 876 (87.2%) patients using one modality – 754 (75.2%) patients using CT alone, 78 (7.8%) patients using EUS alone and 44 (4.4%) using MRI alone. In 117 patients (11.7%) CP was confirmed using two modalities; and in 10 patients (1.0%) CP was confirmed using three modalities (Figure 2.3).

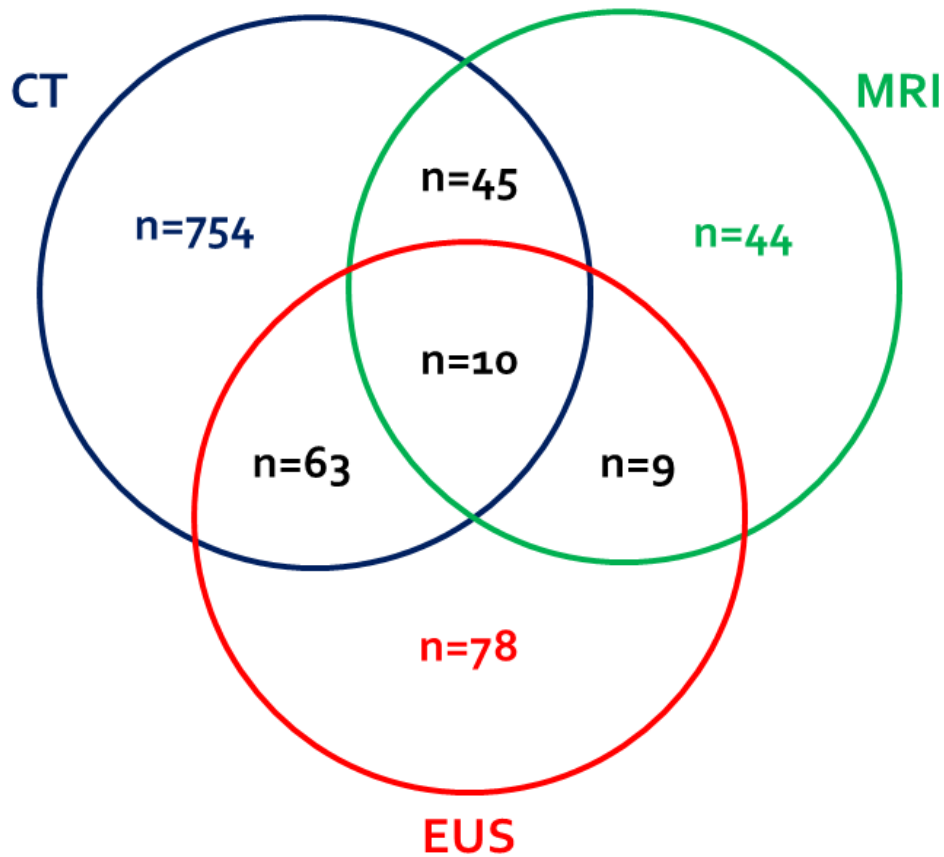


Figure 2.3 – Venn diagram showing the distribution of confirmation of CP based on diagnostic modalities CT, MRI and EUS.

Outcomes of Other Modalities

A total of 84 AXRs were included in the screening cohort based on the presence of calcification in the epigastric region. Of which only 57 (67.9%) were confirmed to have diagnostic features of CP on CT and/or MRI and/or EUS.

Similarly, 233 patients were identified and included in the screening cohort based on primary, secondary or comorbidity ICD code of K86.0 and K86.1. Of which, only 123 (52.8%) were confirmed to have CP on CT and/or MRI and/or EUS.

Further, based on pancreatin prescription, 238 patients were initially included in the screening cohort. Of which, only 115 (48.3%) were confirmed to have diagnostic features of CP on CT and/or MRI and/or EUS.

Of the 137 patients identified to have faecal elastase less than 200µg/g, only 63 (46.0%) were confirmed to have diagnostic features of CP on CT and/or MRI and/or EUS.

Annual Incidence of Diagnosis and Point Prevalence of Chronic Pancreatitis

During the study period, the annual incidence of CP among residents of Greater Nottingham (n=678) increased from 8.5 per 100,000 general population in 2007 to 13.8 per 100,000 general population in 2013. The incidence of CP diagnosis increased by a mean of 4.1% (95%CI 0.5 – 7.8) per year (Table 2, Figure 3) that was statistically significant (p=0.03). The point prevalence of CP increased by a mean of 16.8% per year (95%CI 15.1 – 18.6) reaching 53.6 per 100,000 general population at the end of study period (Table 2.3 and Figure 2.4).

Table 2.3 – Yearly Incidence of Diagnosis and Point Prevalence of CP

Year	General Population	New CP Cases	Total Number of CP Cases	Incidence (per 100,000) with 95%CI	Prevalence (per 100,000) with 95%CI
2006*	644903	21*	75*	3.3 (2.0 – 5.0) *	11.6 (9.1 – 14.6) *
2007	647571	55	117	8.5 (6.4 – 11.1)	18.1 (14.9 – 21.7)
2008	651966	62	160	9.5 (7.3 – 12.2)	24.5 (20.9 – 28.7)
2009	658028	71	206	10.8 (8.4 – 13.6)	31.3 (27.2 – 35.9)
2010	664843	63	235	9.5 (7.3 – 12.1)	35.3 (31.0 – 40.2)
2011	670751	73	272	10.9 (8.5 – 13.7)	40.6 (35.9 – 45.7)
2012	676809	64	300	9.5 (7.3 – 12.1)	44.3 (39.5 – 49.6)
2013	682412	94	340	13.8 (11.1 – 16.9)	49.8 (44.7 – 55.4)
2014	688521	75	369	10.9 (8.6 – 13.7)	53.6 (48.3 – 59.4)

Incidence of diagnosis was defined as the number of new cases of CP diagnosed over the preceding 12 months to 30 June of a particular year expressed as a proportion of the general population of that year. *Data for the year 2006 only included the newly diagnosed cases of CP between 1 January 2006 to 30 June 2006. Point prevalence was defined as the total number of CP patients who were alive on 30 June of a particular year expressed as the proportion of the general population of that year. **Abbreviations:** CP chronic pancreatitis; CI confidence interval.

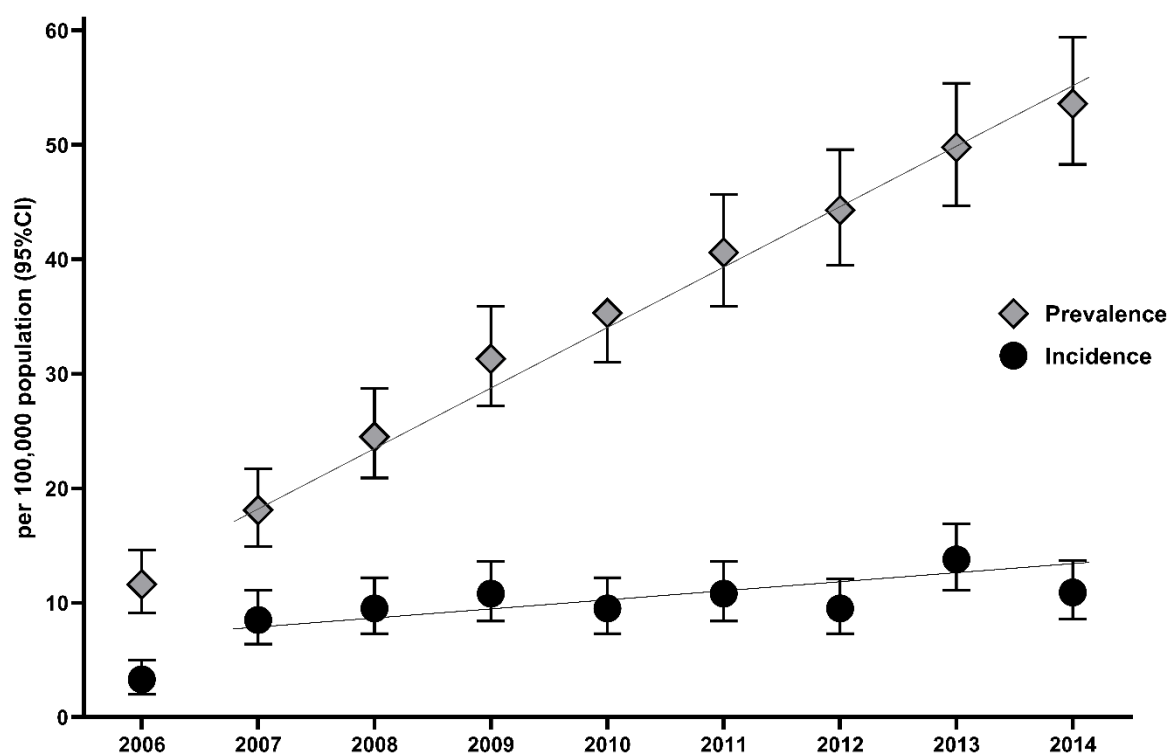


Figure 2.4 – Trend of yearly incidence and prevalence of chronic pancreatitis in Greater Nottingham from 2006 to 2014.

DISCUSSION

This study utilised multisource case ascertainment to provide a clear method of identifying patients with CP in a clinical setting. Using well established diagnostic criteria in three different modalities in a systematic approach this study has ascertained CP cases from a large data set. Even though multiple modalities were used to initially to establish a screening cohort, only three specific modalities, namely CT, MRI, and EUS, were chosen to confirm the diagnosis of CP, based on their availability, sensitivity and ability to detect changes of CP. The incidence of diagnosis of CP in Greater Nottingham increased over the study period.

In line with previous literature, CP was common in middle-aged men in this study [41, 42, 362, 363]. CP was also more common in those with European ancestry in this study mirroring the makeup of the general population of a Western country [363, 364]. Unsurprisingly history of smoking and excess alcohol was common in patients with CP in this and previous studies [41, 42, 363]. While oxidative and non-oxidative metabolism of ethanol are said to activate pancreatic stellate cells and lead to the development of CP [58, 59, 61, 62], nicotine has been shown to cause widespread changes in the pancreatic exocrine function affecting acinar cells and ductal epithelial cells, increase extracellular matrix and a decrease in the number of acinar structures [72-74]. Evidence also suggests an interplay

between smoking and alcohol consumption in the development of CP, and smoking seems to accelerate alcohol-induced CP progression [75, 76].

CT was the most common modality of identifying patients with and confirming the diagnosis of CP. This may be due to CT being a common cross-sectional radiological modality used widely in both acute and chronic clinical settings [Diagnostic Imaging Dataset Statistical Release, version 1, 18 May 2023, NHS England]. It is also likely due to CT being a reliable method of assessing pancreatic morphology [240] [252]. CT is a sensitive modality for detecting parenchymal changes associated with advanced CP such as parenchymal and ductal calcifications with sensitivity reaching as high as 90% [365, 366]. This makes CT a valuable primary diagnostic tool in diagnosing CP [240].

Unlike advanced CP, which is detected easily on CT imaging, detection of early stage CP is challenging as the classical parenchymal changes are not readily visible on CT [360, 365, 367]. In such instances EUS appears superior to CT [240]. EUS has the advantage of being able to detect early and subtle changes of CP that are not visible on CT [368]. EUS has been shown to have a sensitivity of 84% and a specificity of 100% of diagnosing CP compared to the gold standard histopathological diagnosis [369]. However, EUS is not without its diagnostic pitfalls – in the above study, of the 256 patients who met any EUS criteria of CP, only 159 (62%) fulfilled the benchmark Rosemont's EUS criteria of CP [268]. Such discrepancy has also been demonstrated in other studies [370]. Further, the use of more stringent Rosemont's criteria has also been shown to improve the interobserver agreement in diagnosing CP [370, 371]. Other EUS diagnostic criteria appear to vary widely depending on institutions and operators [372].

Similarly, MRI is also a sensitive modality in the diagnosis of early stage CP as it can detect initial parenchymal and ductal changes associated with CP and can exclude other diagnoses such as IPMN, which may be misdiagnosed as CP [373, 374]. Further, a study has shown that the diagnostic yield of MRI or MRCP can be improved by using secretin-enhanced MRI to detect early stage changes of CP [375].

Faecal elastase is an enzyme-linked immunosorbent assay that specifically measures pancreatic elastase-1. Low faecal elastase is not specific to CP, as the levels are reduced in a wide variety of conditions including but not limited to pancreatic tumours, pancreatic resection, acute pancreatitis, coeliac disease, bile acid diarrhoea, small bowel bacterial overgrowth and genetic conditions such as cystic fibrosis and Shwachman-Diamond syndrome [161, 273]. Age-related low faecal elastase levels in the absence of any gastrointestinal disease or surgery have also been reported in elderly adults [376] and has to be considered when interpreting faecal elastase levels. Corroborating the above mentioned caveats of faecal elastase interpretation, a recent study of 182 patients with pancreatic

exocrine insufficiency as confirmed by low faecal elastase demonstrated that only 11.5% had CP [377]. In line with the literature, faecal elastase had the lowest positive predictive value in our study.

The additional investigations which aided screening cohort included AXR. Coarse calcifications in the epigastric region projecting over the pancreas are a recognised AXR feature of CP. However, the sensitivity of AXR is as low as 30% in diagnosing CP [275]. Whilst these calcifications are specific, they have to be differentiated from calcifications of other organs, tissues or vascular structures. These limited the use of AXR as a sole diagnostic tool in determining CP, and thus it was only used as a screening modality in this study. Similarly, prescription of pancreatin and the discharge summaries with ICD codes K86.0 and K86.1 were only used as screening modalities due to the inherent low sensitivity and specificity [161, 378, 379].

This study provides an insight into the clinical incidence and prevalence of CP in a UK population and will be instrumental in organising and improving regional CP services in the National Health Service (NHS). This indicates a potential impact on the NHS and the urgent need of specialist regional CP services more promptly. The reported figures of incidence and prevalence of CP of this study are in keeping with previously reported figures from a multi-ethnic Western [380-382] and a more mono-ethnic Eastern [40, 41] countries. However, a UK biobank based cohort study reports a significantly higher prevalence rate of 163 per 100,000 population [357]. The likely reasons for the significant difference in prevalence between the two studies can be attributed to a number of factors. Firstly, individuals diagnosed with CP prior to our study commencement in 2016 were only included if they had a hospital episode during the 9-year study period, potentially resulting in an underestimation of CP prevalence in Greater Nottinghamshire. Secondly, while our study relied on meticulous clinical data, the identification of CP patients in the UK Biobank study was solely based on reported diagnoses without verification through appropriate investigations. Notably, in our study, almost half of those identified with an ICD-10 code for CP did not exhibit any CP features on CT, MRI, or EUS examinations. This underscores the inadequacy of relying solely on ICD-10 coding for identifying CP patients, a practice that likely led to an overestimation of CP prevalence in the aforementioned UK Biobank study.

This study has its own strengths and limitations. Though this is the largest study to date, it is entirely reasonable to consider the inherent biases of this being a single centre study as a major limitation and thus can only be generalised with caution. Further, given that CT was the most common modality to detect CP in this study and CT is less sensitive at detecting early stage CP changes, it is likely that the study cohort is biased towards detecting those with clinically relevant CP. In addition, as mentioned above, it is highly likely that the study duration of 9 years is relatively short, and this would have impacted the estimation of point prevalence estimate of this study. However, it is unclear, from

the current or previous studies, what the optimal study duration should be to estimate the 'true' prevalence of CP with certainty, especially given that the incidence of CP is also increasing.

This study illustrates the use of CT, MRI and EUS in identifying patient with CP in a clinical setting. CT seems to be the most reliable modality that identifies the majority of patient with CP. It is crucial that rigorous diagnostic criteria are applied in the diagnosis of CP for better understanding of the disease and avoid harm to the patients from unnecessary disease labelling and treatment.

CHAPTER 3: CHRONIC PANCREATITIS AND EXTRA PANCREATIC CANCERS: A SYSTEMATIC REVIEW AND META-ANALYSIS

ABSTRACT

Introduction

CP is a known risk factor for pancreatic cancer; however, its association to extra pancreatic (EP) cancers remains inadequately explored. The aim of this systematic review is to investigate the evidence for CP as a risk factor for developing EP cancers.

Method

Electronic search was conducted on Ovid Medline, EMBASE and Scopus from inception to 27th January 2024 to identify patients with CP who developed EP cancers. Prevalence and incidence of each cancer were calculated where possible from the reported numbers. A random effects meta-analysis was used to pool prevalence, incidence and hazard ratios (HR) of each EP cancer. Heterogeneity was assessed using I^2 . PROSPERO registration: CRD42024543050.

Results

Sixteen (16) studies consisting of 117,163 CP patients met the eligibility criteria. 4015 (3.4%) patients developed 4019 EP cancers. The overall annual prevalence and incidence of EP cancers were 7962 (95%CI 5044- 10880) per 100,000 CP patients and 1039 (95%CI 649-1663) per 100,000 person years. Lung cancer had the highest annual prevalence – (1540 (95% CI 667-2413) per 100,000 CP patients) and incidence (260 (95%CI 120-390) per 100,000 person years). The pooled HR were 1.31 (95% CI 1.03 – 1.66) and 1.58 (95% CI 1.27- 1.98) for adjusted lung cancer and crude liver cancer in patients with CP compared to patients without CP, respectively.

Conclusion

Patients with CP have an increased risk of developing EP cancers compared to patients without CP, in particular lung and liver cancer which had the highest relative risk. Shared risk factor modifications, such as smoking cessation and alcohol reduction, could lower the risk of common EP cancers. Further, implementing non-invasive screening measures may aid in early diagnosis in this high-risk group.

INTRODUCTION

CP is a progressive condition marked by irreversible changes in the pancreas, often driven by genetic or environmental factors [34]. Globally, the incidence of CP ranges from 4.1 to 12.8 per 100,000 individuals, with prevalence between 41.8 and 163 per 100,000 [40-43, 357]. CP is well known for its association with both exocrine and endocrine insufficiency, as well as an elevated risk of pancreatic cancer [47, 383]. However, the potential link between CP and the risk of extra-pancreatic (EP) cancers is less understood [195].

Some studies suggest an increased prevalence of EP cancers among CP patients, though this association remains unconfirmed [384, 385]. It is also unclear whether CP itself is an independent risk factor for EP cancers, given that the primary risk factors for CP—alcohol consumption and smoking—are also known contributors to various EP cancers [71, 384].

In vivo studies have demonstrated that CP is intrinsically associated with increased levels of inflammatory mediators, such as IL4, IL5, IL6, IL8, IL10, IL13, IL1 β , TNF α , and TGF β 1 [59, 386-388]. These cytokines have been implicated in various aspects of tumorigenesis. They regulate various processes such as tumour growth, metastasis, immune response, and angiogenesis. For instance, IL-4, IL-6, and IL-8 are directly involved in promoting tumour progression in cancers like liver, colon, and breast [389-400]. Other interleukins, such as IL-10 and IL-13, are connected to genetic predispositions that affect cancer risk [401-403]. IL1 β is linked to tumour progression and metastasis, with an increased risk of lung cancer [404, 405]. Both TNF α and TGF- β are associated with a wide range of cancers, including breast, gastric, pancreatic, ovarian, endometrial, prostate, bladder, colorectal, oral, liver cancers, leukaemia, and lymphoma [406-409]. These findings suggest a possible causal relationship between CP and EP cancers, warranting further investigation.

Despite advancements in medical science, cancer continues to pose a significant global health challenge [410, 411]. In 2020 alone, there were nearly 20 million new cancer cases worldwide, resulting in over 9.7 million deaths [410, 411]. Given the high incidence and mortality rates of cancer, it is crucial to explore whether CP increases the risk of developing EP cancers. Confirming such a correlation could lead to the implementation of targeted cancer screening programs for patients with CP. The aim of this systematic review is to evaluate the evidence on whether CP is associated with increased risk of EP cancers.

METHODS

This systematic review was carried out following the PRISMA guidelines, the MOOSE reporting guidelines and the Cochrane Handbook for Systematic Reviews [412]. The review was registered with PROSPERO (CRD42024543050). Relevant observational studies on the topic were included in the analysis.

Search Strategy

A comprehensive search using MEDLINE via Ovid SP (January 1946 to January 27, 2024) and Embase via Ovid SP (January 1974 to January 27, 2024) was conducted. A search strategy was designed with assistance of a librarian experienced in systematic reviews. The detailed search strategies for MEDLINE and Embase are provided in Supplementary Material 1. In addition, searches were also performed on Scopus, Cochrane Controlled Register of Trials and Open Grey databases. To identify further relevant studies, the reference lists of the included papers were also reviewed.

The search strategy for MEDLINE and Embase included terms such as: exp Neoplasms OR (cancer* or neoplas* or malignanc* or tum*r*) OR exp Carcinoma OR exp Sarcoma OR exp Multiple Myeloma OR leukaemia* OR exp Lymphoma OR (carcinoma* or sarcoma* or myeloma* or leukaemia* or lymphoma*) AND "chronic pancreatitis".

For Scopus, the Cochrane Central Register of Controlled Trials, and OpenGrey, the same search terms were used, with the search restricted to English-language publications, specific subject areas (medicine, biochemistry, genetics, molecular biology, pharmacology, toxicology, pharmaceuticals, health professions, immunology and microbiology, multidisciplinary sciences, chemistry, neuroscience, nursing, and agricultural and biological sciences), and document types (articles, letters, editorials, and conference papers).

Eligibility Criteria

Inclusion and exclusion criteria were defined using the PICO framework. The study population comprised patients with confirmed CP, diagnosed by any method. The comparator group consisted of individuals without CP. The primary outcome of interest was the occurrence of extra-pancreatic (EP) cancers following the development of CP. Cross-sectional and observational studies, as well as abstracts that met the inclusion criteria and reported the desired outcome, were included. Only articles published in English were considered. Review articles, systematic reviews, case reports, case series, and editorials were excluded from the analysis. Studies on groove pancreatitis, AIP types 1 and 2, and animal studies were also excluded. All studies aimed to investigate the association between CP and cancer.

Outcomes

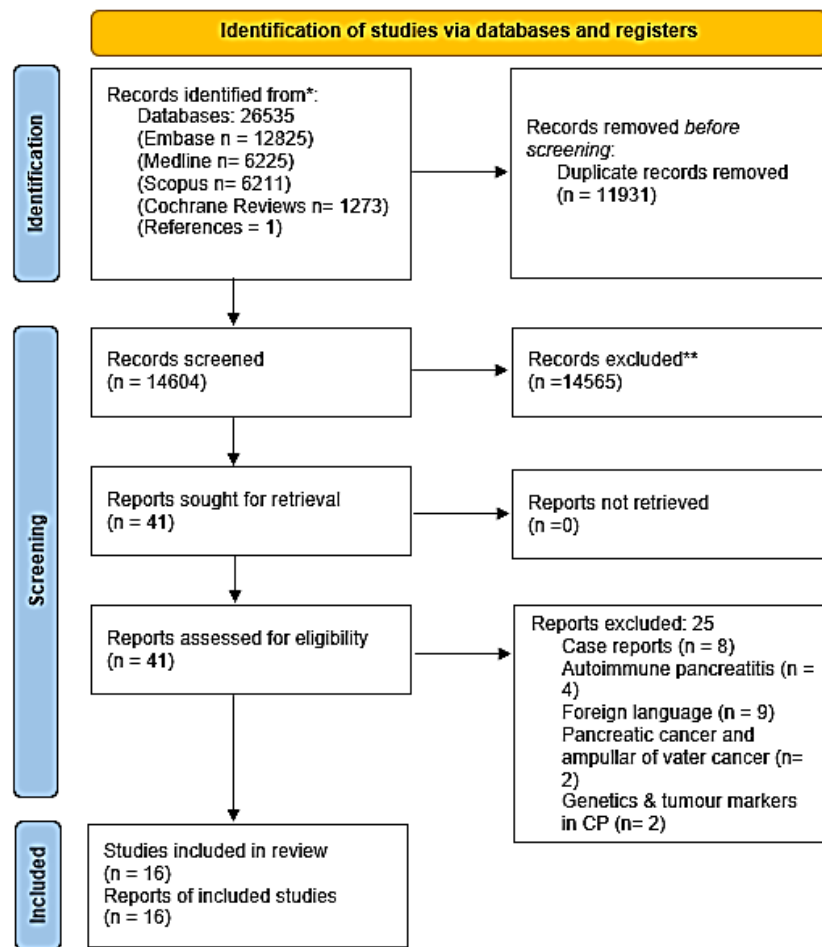
The primary outcome was the occurrence of EP cancers following a diagnosis of CP. Secondary outcomes included the prevalence of specific EP cancers.

Screening and Data Extraction

Two reviewers (Shauntelle Quammie, SQ and Abdulsalam Aliyu, AA) independently screened the title and abstract for eligibility, removed duplicate entries, and record reviewers' decisions using Rayyan-QRCI systematic review software and Microsoft Excel. Third reviewer (Aloysious D Aravinthan, ADA) over saw the process and resolved any conflicts (flow diagram, figure 3.1).

The following data were extracted: first author, year of publication (study ID), study design, setting, study size, number of males and females, assessment period, mean age of diagnosis of CP, mean age of the population, aetiology of CP, ethnicity, method of diagnosing CP, method of confirmation of extra pancreatic cancer, number of extra pancreatic cancers and location, time taken to develop extra pancreatic cancer from diagnosis of CP (if applicable), duration of follow-up, adjustment variables, overall cancer outcome risk and individual cancer outcome risk. For studies that compared results to a control group cancer registry, details of the database or cancer registry were included. In studies with propensity matching, the propensity ratio and control size were also included.

Figure 3.1 – Prisma 2020 Flow Diagram



Quality Assessment

Quality and risk of bias assessment for included studies was carried out using Critical Appraisal Skills Programme (CASP) tool.

Data Synthesis and Statistical Analysis

The results were presented in a narrative review. Studies were categorized based on the following criteria: outcomes of EP cancers only, outcomes compared to controls based on propensity matching, and outcomes compared to cancer registries.

The prevalence and incidence per 100,000 person years for both combined EP cancers and for each individual cancer were calculated from the raw numbers where available using `escalc` from the `metafor` package in R [413]. For studies that did not report person-years, the number of patients with CP multiplied by the mean follow-up period was used to estimate person-years. Forest plots were then constructed for incidence, prevalence and reported HRs for each cancer, and the heterogeneity

between studies was assessed using the I^2 statistic. For studies that showed significant outliers in the forest plot for incidence and prevalence and studies identified as low quality according to the CASP checklist, second and third plots were created excluding those studies for comparison.

For studies with heterogeneity between 80% and 90%, meta-regression was performed using the moderator argument of the *rma* function in the *metafor* package in R (version 4.3.2). Adjustments were made for the following covariates: year of publication, study quality, country, study size, study duration, and sex for incidence rates and prevalence. The covariate associated with high heterogeneity was then adjusted to assess its effect on the individual incidence and prevalence of specific cancers.

Depending on the heterogeneity among studies, a random-effects model was then fitted to pool incidence, prevalence and hazard ratios (HR) for each cancer using the restricted maximum likelihood (REML) estimation. Pooled HRs were calculated as either unadjusted or adjusted for age, sex, and Charlson Comorbidity Index depending on the estimates available. Knapp-Hartung adjustments were applied to calculate confidence intervals around the pooled effect, and the generic inverse variance (DerSimonian-Laird) method was used to calculate pooled hazard ratios (HR) for each cancer. All statistical analyses were performed using the *metafor* package in R version 4.3.2 [413].

RESULTS

Study Selection

After screening 26,535 titles and abstracts, 41 full papers were selected for retrieval. Of these, 25 were excluded, leaving 16 papers for final analysis. All retrieved papers were reviewed. The 25 excluded studies were dismissed due to issues such as type of pancreatitis, publication in a foreign language, focus on pancreatic cancer, or incorrect study design. Refer to the flow chart in figure 3.1 for details.

Study Characteristics

A total of 16 studies were included in the final analysis [163, 211, 351, 384, 385, 414-425]. Among these, 15 were full papers, and 1 was an abstract [415]. All studies were observational; eight were identified as retrospective and one as prospective. One study was conducted across multiple centres (Switzerland, Germany, USA, Italy, Sweden and Denmark) [424]. Additionally, three studies were conducted in Italy, three in Denmark, two each in the USA and Taiwan, and one each in Germany, Japan, the United Kingdom, Korea, and Switzerland. The periods of assessment ranged from 1946 to 2020, with follow-up durations ranging from 3 to 36 years (tables 3.1, 3.2 and 3.3).

Patient Characteristics

A total of 16 studies evaluated 117,163 patients, of whom 69,434 (59%) were males. One study did not report the proportion of males [384]. Of the studies that reported aetiologies of CP, alcohol was identified as a major cause in 31,297 patients (31.6%) [351, 384, 385, 414, 415, 417, 419-425] while smoking was reported as a cause in 40,725 patients (47.2%) [415, 417, 420, 422, 424, 425]. Only 1 study identified both alcohol and smoking as contributing factors in 119 out of 170 patients (70%) [425]. 5 studies reported genetic risk factors, which accounted for 26 out of 1,479 patients (1.8%) [351, 419, 421-423]. Of these, only 1 study specified cystic fibrosis as the genetic risk factor, while the others referred to hereditary or familial predisposition [423]. 3 studies did not provide information on aetiology [211, 416, 418]. Of the studies that reported age, the weighted mean age of patients was 50.5 ± 14.4 years [211, 384, 385, 414, 417, 418, 420-425]. Ethnicity was reported in only 2 studies [415, 423] with the majority being Caucasians (52,953 of 72,093; 73.5%).

Table 3.1 – Characteristics of included studies (outcomes only)

Study ID	Country	Assessment Period	Aetiology of CP	Study Size (Males)	EP Cancers	EP Cancer Locations	Mean Age	Follow up
Kamisawa 2007	Japan	1970-2004	Alcohol (135, 79.4%) Smoking (134, 78.8%)	170 (153)	24 (14.1%)	Stomach (9, 5.3%) Oesophagus (4, 2.4%) Colon (3, 1.8%) Lung (2, 1.2%) Acute leukaemia (2, 1.2%) Biliary (1, 0.6%) Duodenal (1, 0.6%) Bladder (1, 0.6%) Prostate (1, 0.6%)		Alcoholic CP: 5.5±5.4 yrs (mean) Non-alcoholic CP: 4.2±4.0 yrs (mean)
Lankisch 1993	Germany	-	Alcohol (230, 69%), primary hyperparathyroidism (5, 2%) Idiopathic (95, 28%) Hereditary (5, 2%)	335 (260)	13 (3.9%)	Upper respiratory tract (2, 0.6%) Colon (3, 0.9%) Urogenital tract (2, 0.6%) Primary hepatic (1, 0.3%) Breast (1, 0.3%) Malignant melanoma (1, 0.3%) Glioblastoma (1, 0.3%) Thyroid (1, 0.3%) Leukaemia (1, 0.3%)	-	9.8 yrs (median) 11.3±8.3 yrs (mean)
Lowenfels 1994	Switzerland Germany USA Italy Sweden Denmark (multicentre)	1946-1992	Alcohol (1515, 75.2%) Smoking (1351, 67.0%)	2015 (1598)	159 (7.9%)	Mouth, pharynx, larynx, oesophagus (32, 1.6%) Stomach, intestines, liver, gallbladder, and other GI tumours (24, 1.2%) Lung (24, 1.2%) Breast Female reproductive (4, 0.2%) Kidney Prostate Bladder Testis (16, 0.8%) All other sites (36, 1.8%) Site not specified (12, 0.6%)	46±13	7.4±6.2 yrs (mean)
Thuluvath 2003	USA	1979-1989	Alcohol (127, 66%), Pancreas divisum (11, 6%) Hyperlipidaemia (8, 4%) Cystic fibrosis (2, 1%) Familial (1, <1%) Duodenal abnormality (1, <1%) Trauma (3, 1%) Unknown (40, 21%)	193 (125)	9 patients; 1 patient had 2 cancers (10 cancers, 4.7%)	Lungs (2, 1.0%) Larynx (1, 0.5%) Prostate (1, 0.5%) Cervix (1, 0.5%) Skin (1, 0.5%) Kidney (1, 0.5%) Stomach (1, 0.5%) Endometrial (1, 0.5%) Bone (1, 0.5%)	39.2	10.1 (1-28) yrs (mean)

Table 3.2 – Characteristics of included studies (Propensity Matching)

Study ID	Setting	Assessment Period	Aetiology CP	Study Size (male)	EP cancer	Control size (male)	EP cancer in control	EP cancer (location-study grp)	Mean Age	Follow up
Bang 2014	Denmark	1995-2010	Alcohol (6306, 52.7%)	11972 (7961)	1112 (9.3%)	119720 (79613)	9201 (7.7%)	Oesophagus (55, 0.5%) Stomach (40, 0.3%) Small intestine (10, 0.08%) Colon (98, 0.8%) Liver (45, 0.4%) Lungs (119, 1.0%) Haematological (119, 1.0%) Melanoma (27, 0.2%)	54.5±14	6.0 yrs (mean)
Chen 2019	Taiwan	2000-2011	-	11237 (9354)	213 (1.9%)	11237 (9378)	180 (1.6%)	Head & Neck (213, 1.9%)	48.8±15.3	4.87 ±3.30 yrs (mean)
Dahabra 2020	USA	2015-2020	Alcohol (18940, 26.3%) Smoking (33040, 46.0%)	71900 (36350)	1179 (1.6%)	39043820 (17272430)	171793 (0.4%)	Colorectal (1179, 1.6%)	-	5 yrs (mean)
Goldacre 2008	UK	1963-1999	-	1496 (823)	108 (7.2%)	599308 (335612)	25464 (4.2%)	Oral cavity, pharynx, lip (5, 0.3%) Oesophagus (1, 0.07%) Stomach (6, 0.4%) Colon (13, 0.9%) Rectum (4, 0.3%) Liver (6, 0.4%)	-	36 yrs (mean)

								Lung (27, 1.8%) Breast (6, 0.4%) Uterus (1, 0.07%) Ovary (4, 0.3%) Prostate (4, 0.3%) Kidney (3, 0.2%) Bladder (4, 0.3%) Malignant melanoma (1, 0.07%) Other skin cancers (9, 0.6%), Malignant brain (1, 0.07%) Non-Hodgkin lymphoma (6, 0.4%) Multiple myeloma (2, 0.1%) Leukaemia (1, 0.07%) Myeloid leukaemia (1, 0.07%)		
Han 2022	South Korea	2002-2010	Alcohol (2897, 26.6%) Smoking (5410, 49.6%)	10899 (7947)	662 (6.1%)	32697 (23841)	1817 (5.6%)	Lip, oral cavity & pharynx (17, 0.2%) Oesophagus (19, 0.2%) Stomach (102, 0.9%) Colon & rectum (61, 0.6%) Liver (68, 0.6%) Gallbladder & biliary tract (34, 0.3%) Larynx (8, 0.07%) Lung (102, 0.9%) Breast (23, 0.2%) Cervix uteri (6, 0.06%) Corpus uteri (1, 0.009%) Ovary (3, 0.03%)	-	8-16 years (mean)

								Prostate (69, 0.6%) Testis (0) Kidney (13, 0.1%) Bladder (22, 0.2%) Brain (5, 0.05%) Thyroid gland (34, 0.3%) Hodgkin lymphoma (1, 0.009%) Non-Hodgkin lymphoma (4, 0.04%) Multiple myeloma & malignant plasma cell neoplasm (8, 0.07%) Leukaemia (14, 0.1%) Others (48, 0.4%)		
Hsieh 2023	Taiwan	2000-2017	-	5394 (3674)	379 (7.0%)	21576 (14700)	1093 (5.1%)	Liver (72, 1.3%) Breast (6, 0.1%) Lung (30, 0.6%) Thyroid (7, 0.1%) Colorectal (34, 0.6%) Kidney & bladder (15, 0.3%) Prostate (12, 0.2%) Stomach (14, 0.3%) Other & nasopharyngeal (189, 3.5%)	49.71±14.96	3.27±1.72 yrs (mean)

Table 3.3 – Characteristics of included studies (cancer registry comparison)

Study ID	Setting	Assessment Period	Cancer Registry	Aetiology of CP	Study size (male)	EP cancers	EP cancer (location)	SIR	Mean Age	Follow up
Ammann 1980	Switzerland	1963	Eidgenössisches Statistisches Amt, Bern 1969- 1972 Registre Genevois des Tumeurs, Geneva 1970-1973	Alcohol (165, 67.1%) Idiopathic (65, 26.4%) Rare causes (16, 6.5%)	246 (209)	21 (8.5%)	Oral cavity (6, 2.4%) Larynx (3, 1.2%) Lung (8, 3.3%) Stomach (2, 0.8%) Rectum/colon (2, 0.8%)	Lung cancer: 5-5.3 Oral cavity & larynx: 9	-	Non-calcifying CP 8.0±6.5 yrs (mean) calcifying CP 9.8±5.5 yrs (mean)
Hansen 1995	Denmark	1969-1989	Danish Cancer Society	Alcohol (136, 75.1%)	181	14 patients (3 types of cancer)- 17 cancers in total	Lung (4, 2.2%) Larynx (1, 0.6%) Cavum oris (2, 1.1%) Tongue (1, 0.6%) Oesophagus (1, 0.6%) Breast (1, 0.6%) Uterus (1, 0.6%) Prostate (1, 0.6%) Testis (1, 0.6%) CML (1, 0.6%) Lymphoma (1, 0.6%) Metastasis unknown primary (2, 1.1%)	SIR 2.43 (P<0.001)	57.8	26 yrs (mean)
Pedersen 1982	Denmark	1970-1977	Danish Cancer Society	Alcohol (45, 70.3%), idiopathic (14, 21.9%), hyperparathyroidism (3, 4.7%), hereditary (2, 3.1%)	64 (51)	7 (10.9%)	Oral cavity (1, 1.6%) Oesophagus (1, 1.6%) Stomach (1, 1.6%) Testes (2, 3.1%) Leukaemia (2, 3.1%)	-	-	4 yrs (mean)
Pedrazzoli 2008	Italy	1970-1999	Veneto Cancer Registry Database	Alcohol (167, 98.2%),	174 (152)	47 (27.6%)	Lung (22, 12.9%) Oral, pharynx, larynx (8, 4.7%)	SIR (oral cavity, pharynx,	45±10.2	16.7 ± 0.8 years (mean)

				Smoking (161, 94.7%)			Oesophagus (2, 1.2%) Kidney (2, 1.2%) Colon (2, 1.2%) Liver (2, 1.2%) Breast (1, 0.6%) Stomach (1, 0.6%) Mediastinum (1, 0.6%) Prostate (1, 0.6%) Melanoma (1, 0.6%) CML (1, 0.6%) Squamous cancer auricle (1, 0.6%) Liver metastasis from unknown primary (2, 1.2%)	oesophagus, larynx, lung): 0.37 (95% CI 0.26-0.53)		
Rocca 1987	Italy	1970-1984	Piemonte Region Cancer Registry	Alcohol (108, 62.8%), Idiopathic (38, 22.1%), Biliary (19, 11.0%), Familial (5, 2.9%), Hormonal (2, 1.2%)	172 (147)	21 (12.2%)	Lung (5, 2.9%) Liver (3, 1.7%) Stomach (2, 1.2%) Rectum (1, 0.6%) Colon (1, 0.6%) Bladder (1, 0.6%) Tongue (1, 0.6%) Lip (1, 0.6%) Larynx (2, 1.2%) Skin (1, 0.6%) Breast (1, 0.6%) Bone (2, 1.2%)	SIR: 37.2	50	14 yrs (mean)
Talamini 1999	Italy	1971-1995	Tumor Registry of the Lombardy Region	Alcohol (526, 73.6%), Obstructive (88, 12.3%), Familial (11, 1.5%), Idiopathic (90, 12.6%), Smoking (629, 88%)	715 (630)	47 (6.6%)	Lung (15, 2.1%) Stomach (6, 0.8%) Oral cavity (5, 0.7%) Oesophagus (4, 0.6%) Colorectal (3, 0.4%) Pharynx (2, 0.3%) Larynx (2, 0.3%) Skin (2, 0.3%) Multiple myeloma (2, 0.3%) Lymphoma (1, 0.1%)	SIR: 1.5 (95% CI 1.1 – 2.0), Smokers: SIR 1.7 (95% CI 1.24- 2.27) Non-Smokers: 0.49 (95% CI 0.05-1.77)	40.8±11.4	10 (1-25) yrs (median)

							Brain (1, 0.1%) Liver (1, 0.1%) Biliary tract (1, 0.1%) Mesenchymal retroperitoneal (1, 0.1%) Bladder (1, 0.1%)			
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Quality Assessment

The quality of the studies was assessed using Critical Appraisal Skills Programme (CASP) [426]. The key areas of concern included the identification of confounding factors, as some studies did not specify the aetiology of CP or provide a comprehensive list of aetiologies [211, 414, 416, 418]. Additionally, the mode of diagnosing EP cancers was not stated in many studies [351, 415, 420-425, 427] (table 3.4).

Studies were regarded as low quality if they had high or unclear risk of bias to the first 2 questions in the CASP checklist [426]. The studies which fulfilled these criteria were Ammann 1980, Lankisch 1993 and Pedersen 1982 [351, 385, 427].

With the exclusion of these studies, a modest increase in the incidence and prevalence of all cancers and individual cancers was identified (tables 3.5 and 3.6). The change in hazard ratio could not be determined as these individual studies did not assess hazard ratios.

Table 3.4 – Risk of bias of included studies using CASP checklist

Study ID	Address focused issue	Cohort recruited in acceptable way	Exposure to minimise bias	Outcome to minimise bias	Confounding factors identified	Confounding factors considered in design	Follow up complete enough	Follow up long enough	Results of study	How Precise are results	Can results be applied to local population	Do results fit with other evidence	Implications for the study for practice
Ammann 1980	low	Unclear	Unclear	Low	Low	High	Low	Low	Low	Unclear	Unclear	Low	Low
Bang 2014	Low	Low	Low	Low	High	High	Low	Low	Low	Unclear	Low	Low	Low
Chen 2019	Low	Low	Low	Low	High	High	Low	Low	Low	Low	Low	Low	Low
Dahabra 2020	Low	Low	Unclear	Unclear	Low	Low	Unclear	Unclear	Low	Low	Unclear	Unclear	Low
Goldacre 2008	Low	Low	Low	Low	High	High	Low	Unclear	Low	Low	Low	Low	Low
Han 2022	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Hansen 1995	Low	Low	Low	Unclear	Low	Low	Low	Low	Low	Unclear	Unclear	Low	Low
Hsieh 2023	Low	Low	Low	Low	High	High	Low	High	Low	Low	Low	Low	Low
Kamisawa 2007	Low	Low	Low	Unclear	Low	Low	Unclear	Low	Low	Low	Low	Low	Low
Lankisch 1993	Low	Unclear	Low	Unclear	Unclear	High	Low	Low	High	Unclear	High	Unclear	Low
Lowenfels 1994	Low	Low	Low	Unclear	Low	Low	Unclear	Low	Low	Low	Unclear	Low	Low
Pedersen 1982	Unclear	Unclear	Low	Unclear	Low	High	High	Low	High	Unclear	Unclear	Low	Low
Pedrazzoli 2008	Low	Low	Low	Unclear	High	High	Low	Low	Low	Low	High	High	Unclear
Rocca 1987	Low	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear	Low	Low	Low
Talamini 1999	Low	Low	Low	Unclear	High	High	Low	Low	Low	Low	Low	Low	Low
Thuluvath 2003	Low	Low	Low	Unclear	Low	Low	High	Low	High	Unclear	Unclear	Unclear	Low

Mode of Diagnosis of CP

All studies employed a range of methods for diagnosing CP. 6 studies relied solely on diagnoses coded in routine health record systems to identify patients with CP, using ICD-7, ICD-8, ICD-9, ICD-10 & SNOMED CT code [211, 414-418]. The remaining studies used a various diagnostic approach, including imaging, endoscopic retrograde cholangiopancreatography (ERCP), abnormal secretin stimulation tests, and measurement of amylase or lipase levels, along with clinical symptoms. Symptoms commonly used for diagnosis included pancreatic abdominal pain radiating to the back, a history of recurrent pancreatitis, and steatorrhea [351, 384, 419, 421-425]. Diagnostic tests included pathological secretin, faecal fat, reduction of duodenal amylase and lipase after a test meal.

Imaging results considered confirmatory for CP included: Abdominal X-ray showing calcifications; Ultrasound revealing pancreatic stones, pancreatic calcifications, dilated or irregular main pancreatic duct (PD), and hyperechogenic and heterogeneous pancreatic parenchyma; and Computed Tomography revealing pancreatic stones, pancreatic calcifications, dilated or irregular main PD and cysts. ERCP findings that confirmed CP included abnormalities in the main duct or its branches, irregular dilatation in PD branches, a Cambridge classification score ≥ 3 , stricture of PD and intraductal stones. Histological examination was used as an adjunct in six studies [384, 419-421, 423, 425]. 3 studies combined symptoms, secretin stimulation, faecal fat analysis, imaging and ERCP for diagnosis. [351, 422, 424]. Another 3 studies used a combination of imaging, ERCP, secretin test and histology [421, 423, 425]. 2 studies integrated symptoms, reduced amylase and lipase levels, imaging, ERCP and histology [384, 419]. 1 study identified patients through histology and surgical exploration alone [420].

Mode of Diagnosis of EP Cancers

5 studies relied solely on coding systems for EP cancer identification [211, 414, 416-418], while 3 studies used histology exclusively for confirmation [384, 385, 421]. 8 studies did not specify the method used to diagnose EP cancers [351, 415, 419, 420, 422-425].

EP Cancers

Among the 117,163 patients included in the 16 studies, 4015 (3.4%) developed a total of 4019 (3.4%) EP cancers. Lowenfels et al combined individual cancer outcomes into GI cancers, upper respiratory tract cancers, but excluded lung cancers [424]. This prevented objective interpretation of each individual cancer data such as oesophagus, breast etc since their outcomes were combined with other cancers [424]. Therefore, for lung cancer, the total denominator used was 4,019; but for other individual cancers a total denominator of 3,860 was used.

The most frequently reported EP cancers were colorectal (1404, 36.4%), lung (371, 9.2%), and cancers of the larynx, pharynx, oral cavity, including head and neck and ear (285, 7.4%). Other common EP cancers included liver (198, 5.1%), stomach (184, 4.8%), haematological malignancies including leukaemia, lymphoma, and myeloma (167, 4.3%), prostate (89, 2.3%), oesophagus (87, 2.3%) and kidney & bladder (63, 1.6%).

Additional EP cancers identified included skin cancers, including malignant melanoma (43, 1.1%), thyroid (42, 1.1%), breast (39, 1.0%) and gallbladder & biliary tract (36, 0.9%).

Cancers occurring in smaller proportions (≤ 11 patients each) included duodenum (11, 0.3%), brain including glioblastoma (8, 0.2%), ovary and cervix (7, 0.2%) each, metastasis of unknown primary (4, 0.1%), uterus, bone and testis (3, 0.08% each). Urogenital cancers were reported in 2 cases (0.05%) and endometrial, mesenchymal retroperitoneum and mediastinal cancers each contributed 1 case (0.03%).

Cancers that were not specified or were combined in a way that prevented determination of individual proportions accounted for 361 cases (9.0%).

Outcomes

Four studies reported outcomes of EP cancers without comparing them to a general population [351, 423-425]. The estimated incidence of EP cancers in patients with CP ranged from 4% to 14.1%. The follow-up duration varied from 1 to 28 years (table 2).

Six studies compared the outcomes of extra pancreatic (EP) cancers in CP patients to propensity matching cohort [211, 414-418]. Among the 112,898 CP patients in these studies, 3,653 (3.2%) developed EP cancers. In the propensity-matched cohort of 39, 828,358 patients, 209,548 (0.5%) developed EP cancers. The follow-up duration of these studies ranged from 3 to 16 years (table 3).

A further six studies compared the outcomes of EP cancers to data from cancer registries [384, 385, 419-422]. In four of these studies, the SIR of EP cancers in CP patients ranged from 1.5 to 37.2 per 100,000. One study reported an SIR of 0.37 [420], and another study was excluded because its overall SIR included pancreatic cancer [419]. The follow-up duration ranged from 1 to 36 years (table 4).

Incidence and prevalence of EP cancers

The overall incidence of EP cancers across all studies was 1,039 (95%CI 649-1663) per 100,000 person years of patients with CP. This incidence decreased to 834 (95%CI 549-1281) per 100,000 person years after excluding Kamisawa et al and Rocca et al., as these studies were significant outliers in the forest plot.

The EP cancers with the highest incidence in CP patients were lung 260 (95%CI 120-390), colorectal 110 (95% CI 66-184), stomach 107 (95%CI 40-290) and oesophagus 109 (95%CI 24-486) per 100, 000 person years.

Conversely, the cancers with the lowest incidence were thyroid cancer 18 (95%CI 3-122), breast cancer 29 (95%CI 6-144), prostate cancer 39 (95%CI 14-111) and kidney & bladder 47 (95%CI 24-94) per 100,000 person years. See table 5 and figure 2.

The overall annual prevalence of EP cancers across all studies was 7962 (95%CI 5044- 10880) per 100, 000.

The most prevalent cancers per 100,000 were lung 1,540 (95%CI 667- 2,413), upper respiratory tract 1,280 (95%CI 498-2,062), and colorectal cancer 908 (95% CI 622-1,195). The least prevalent cancers per 100,000 were breast cancer 191 (95%CI 92-290), thyroid cancer 227 (95%CI -50 – 554) and kidney & bladder 279 (95%CI 158-400) (table 6 and figure 3).

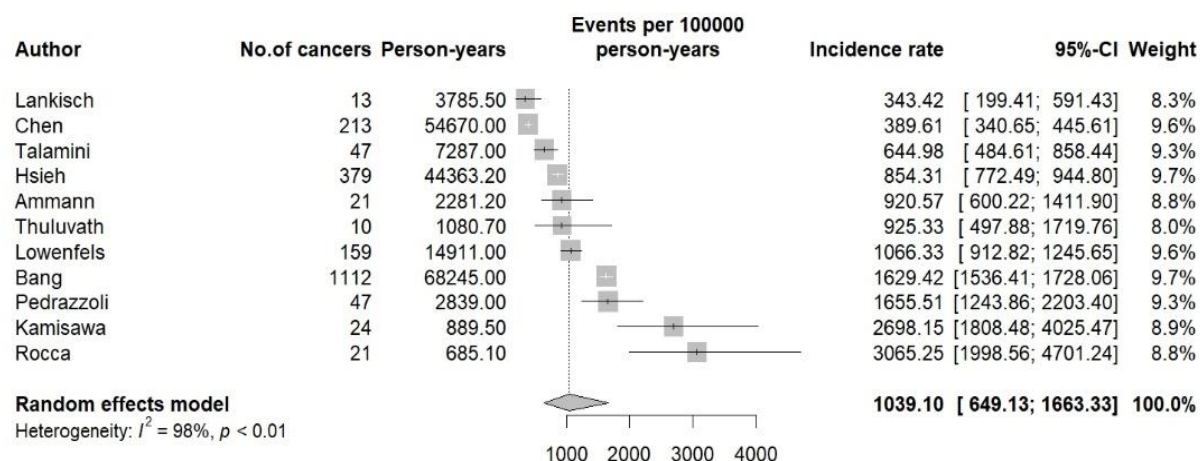
Table 3.5 – Incidence of Cancers

Cancer	Incidence (per 100,000 person- years)	95% CI (per 100,000 person- years)	I ²	P value of I ²
All cancers	1039	649-1663	98%	<0.01
All cancers (Kamisawa et al & Rocca et al excluded)	834	549-1281	98%	<0.01
All cancers (excluding low quality studies) *	1175	703-1966	98%	<0.01
Breast	29	6-144	43%	0.16
Breast (excluding low quality studies) *	33	2-650	61%	0.07
Colorectal	110	66-184	61%	0.01
Colorectal (Kamisawa et al & Rocca excluded)	92	59-143	62%	0.02
Colorectal (excluding low quality studies) *	117	55-251	71%	<0.01
Colorectal (adj. for size of study population)	111	45-272	46%	0.09
Kidney & Bladder	47	24-94	6%	0.38
Liver	88	26-292	87%	<0.01
Liver (Rocca et al excluded)	69	23-208	88%	<0.01
Liver (excluding low quality studies) *	102	25-414	89%	<0.01
Liver (adj. for country)	70	15-337	71%	0.008
Lung	260	120-390	97%	<0.0001
Lung (Rocca et al & Pedrazzoli et al excluded)	180	111-293	81%	<0.01
Lung (excluding low quality studies) *	244	124-481	92%	<0.01
Oesophagus	109	24-486	75%	<0.01
Oesophagus (Kamisawa et al excluded)	78	58-105	0%	0.75
Prostate	39	14-111	1%	0.38
Stomach	107	40-290	91%	<0.01
Stomach (Kamisawa et al excluded)	65	36-118	46%	0.09
Stomach (excluding low quality studies) *	110	34-356	92%	<0.01
Stomach (adj. for study quality)	64	31-133	53%	0.06
Thyroid	18	3-122	0%	0.67

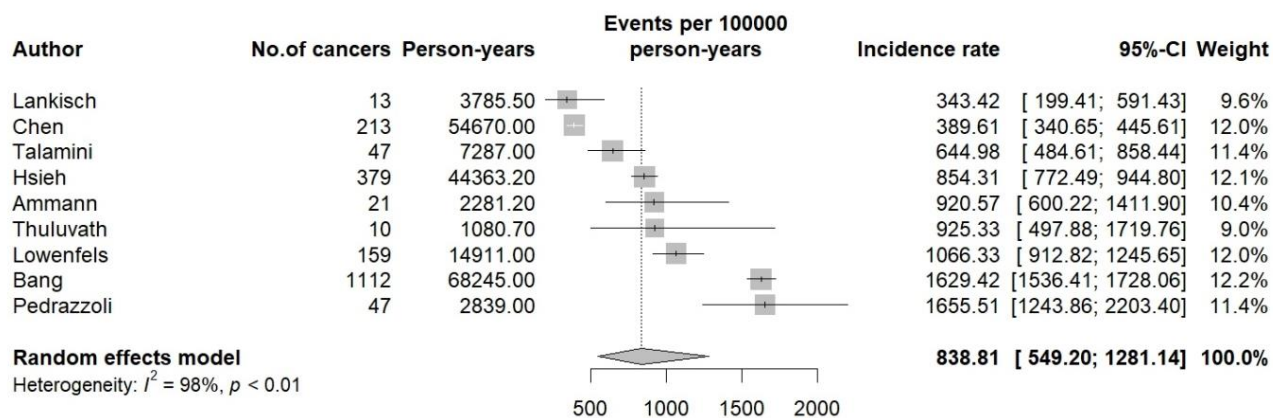
*Low quality studies- includes Ammann 1980, Lankisch 1993 & Pedersen 1982

Figure 3.2 – Incidence Rates of Cancers in Patients with Chronic Pancreatitis

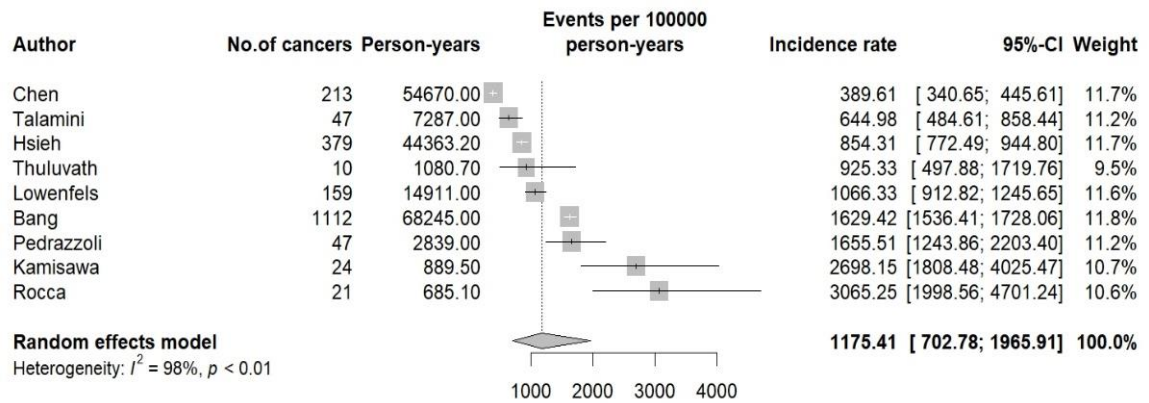
3.2.1 All cancers



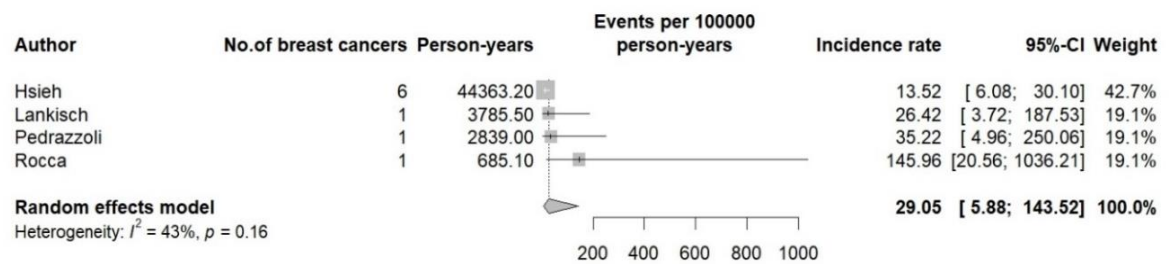
Kamisawa & Rocca excluded



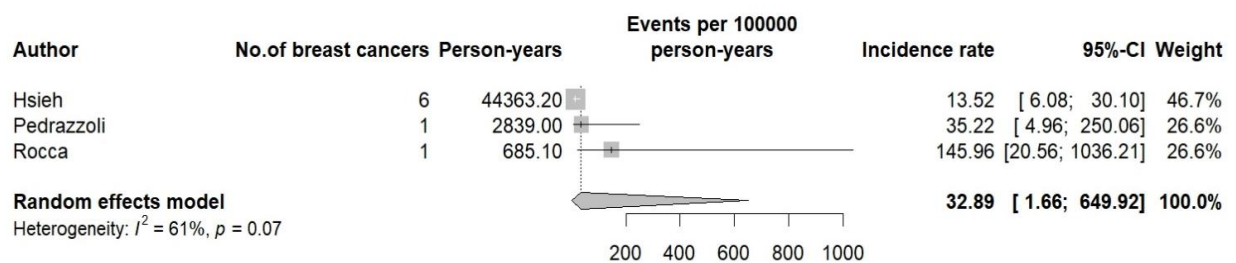
Low quality studies excluded



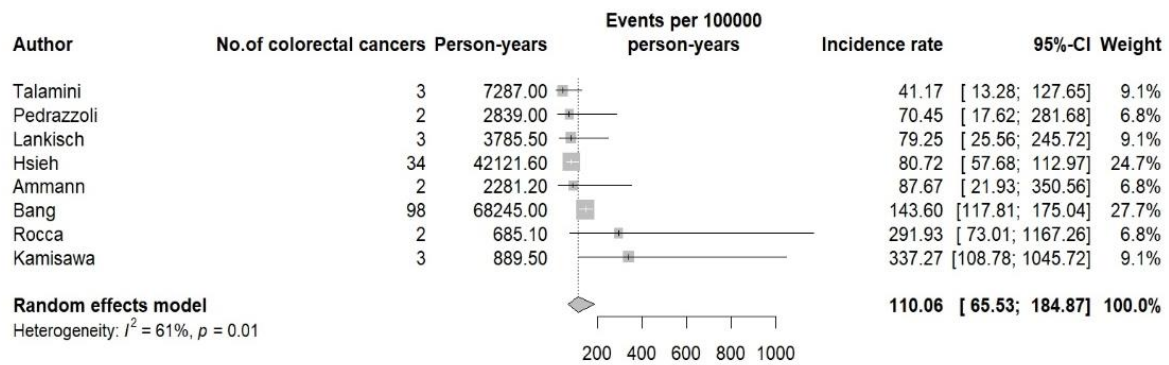
3.2.2 Breast



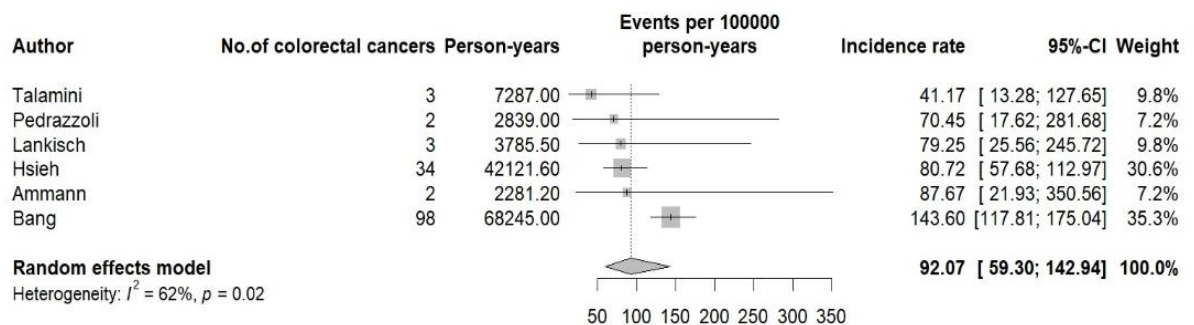
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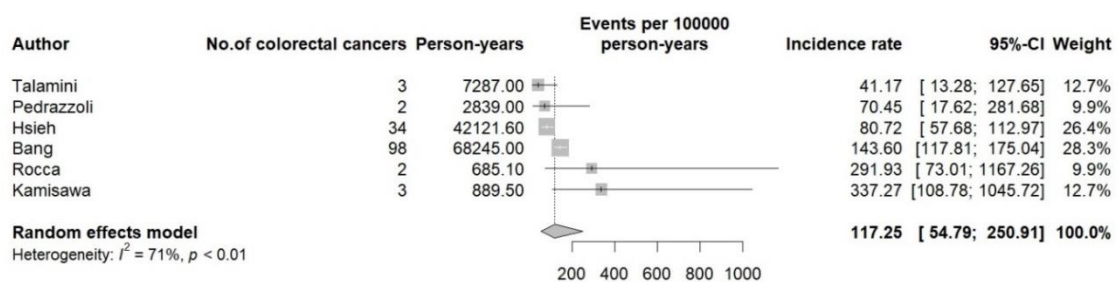
3.3-3 Colorectal



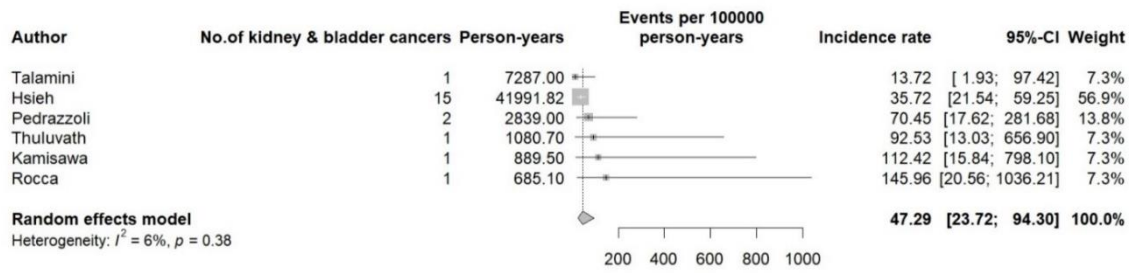
Kamisawa & Rocca excluded



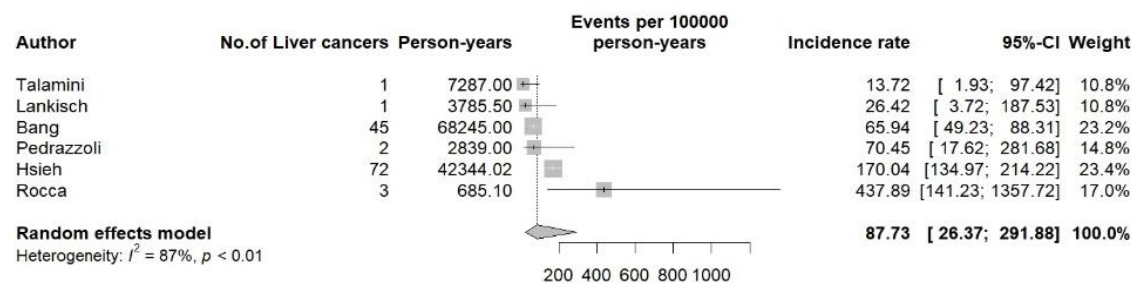
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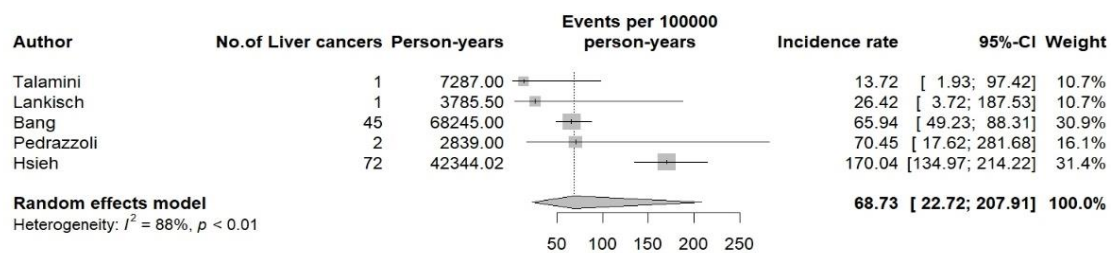
3.2.4 Kidney & Bladder



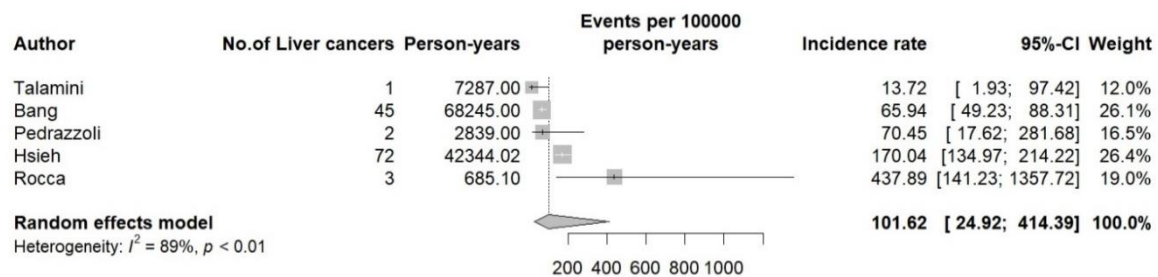
3.2.5 Liver



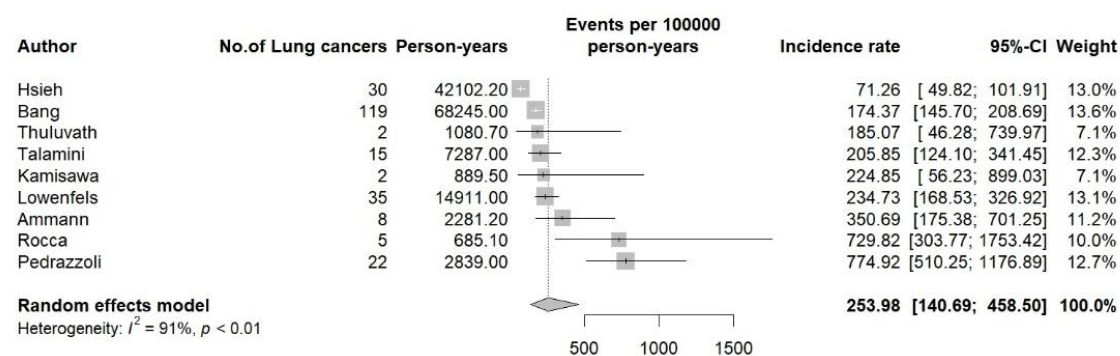
Rocca excluded



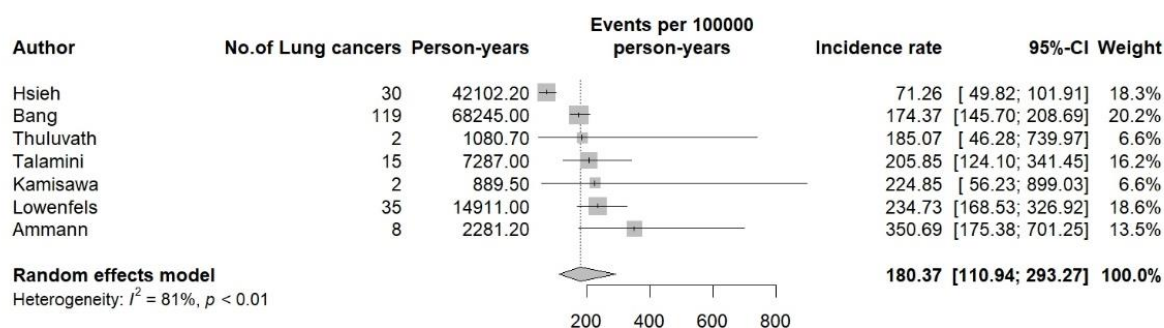
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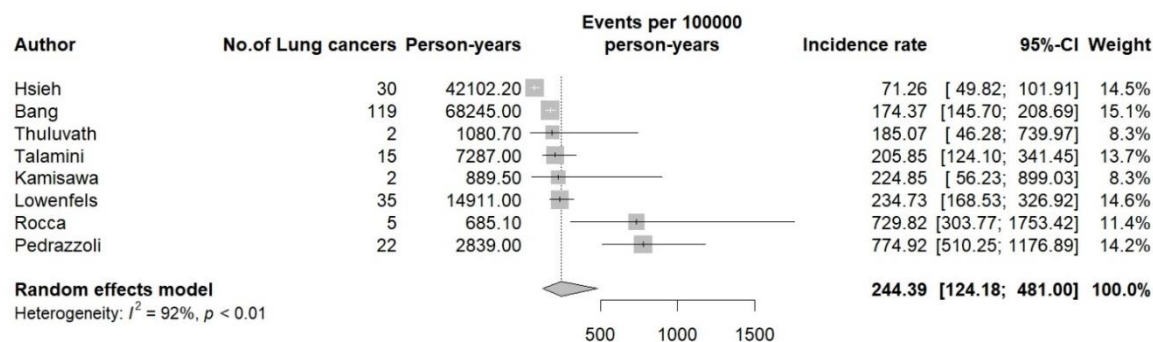
3.2.6 Lung



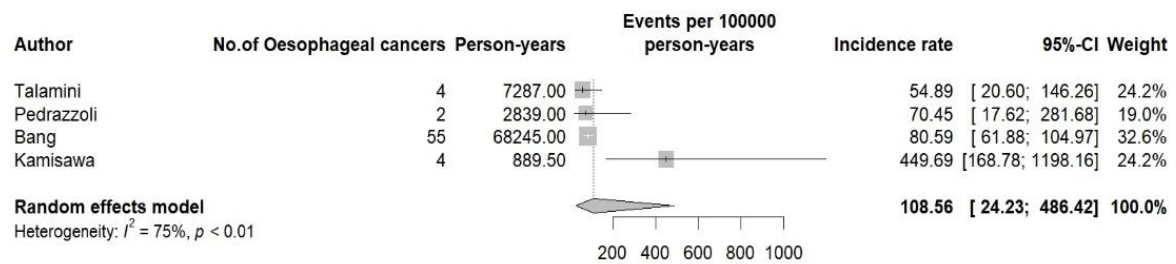
Rocca & Pedrazzoli excluded



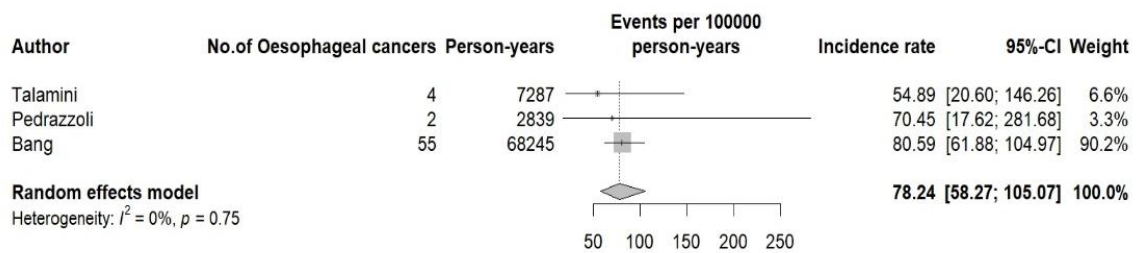
Low quality studies excluded



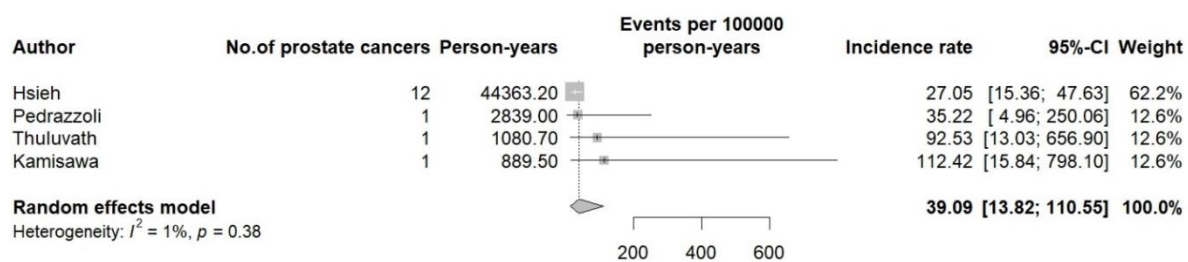
3.2.7 Oesophagus



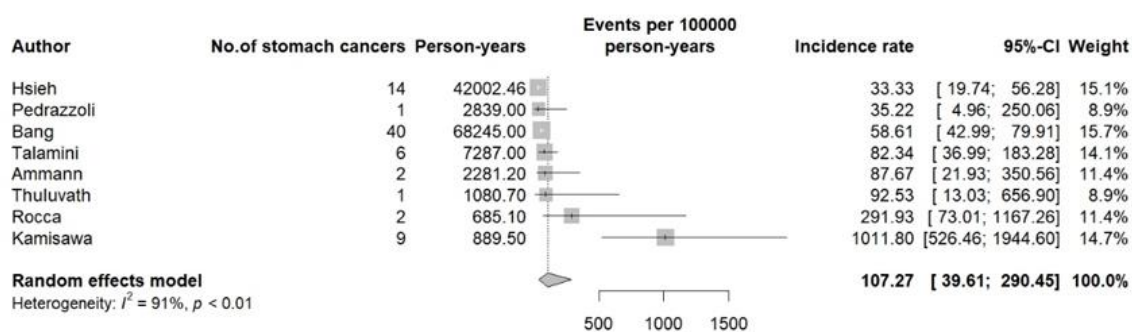
Kamisawa excluded



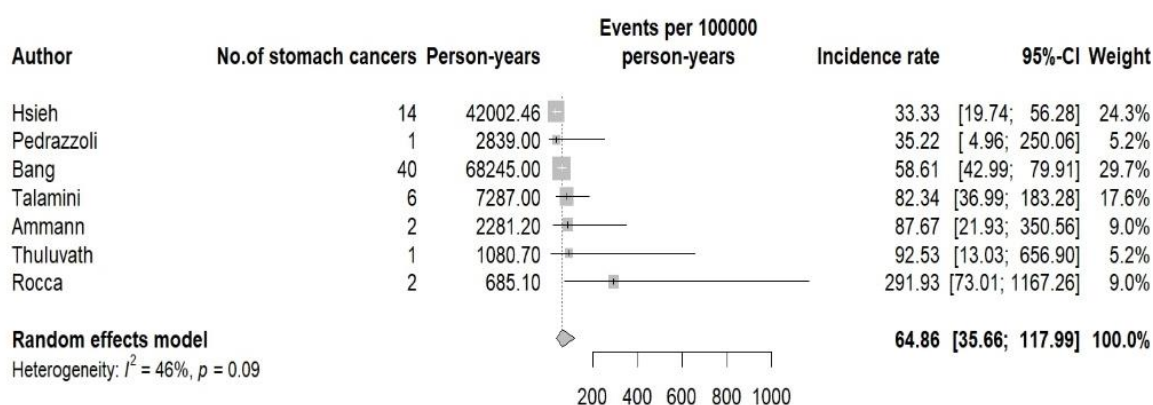
3.2.8 Prostate



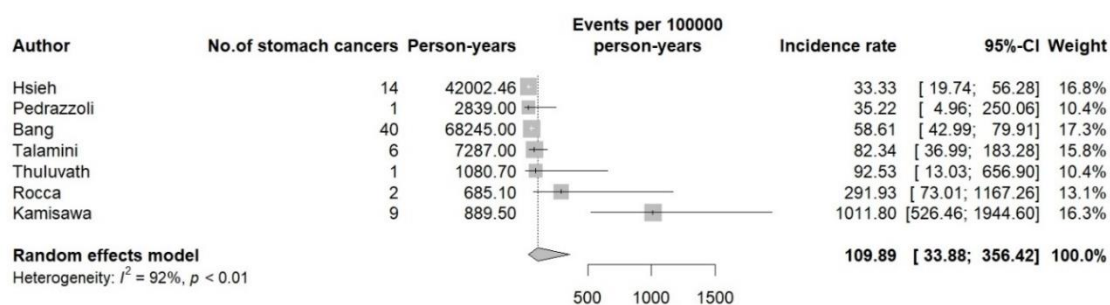
3.2.9 Stomach



Kamisawa excluded



Low quality studies excluded



3.2.10 Thyroid

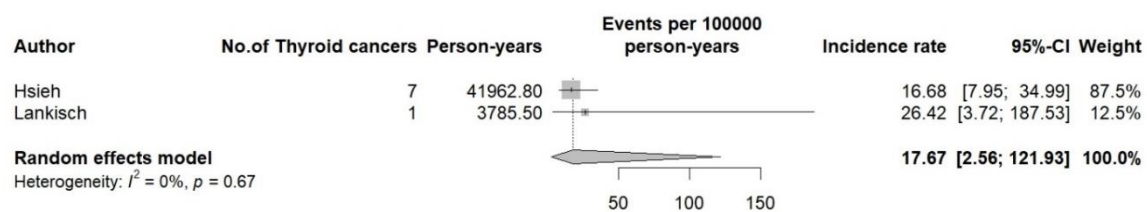


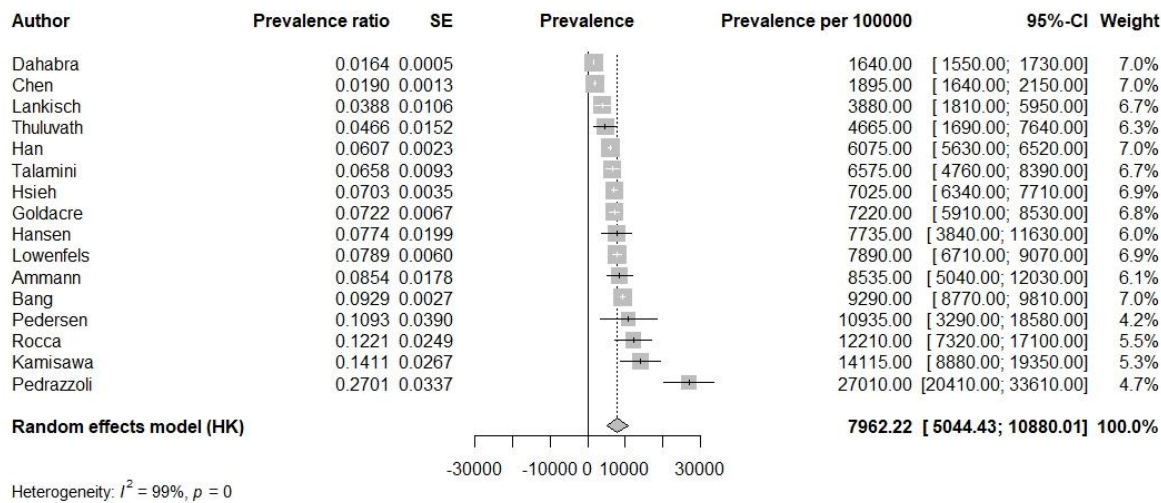
Table 3.6 – Prevalence of Cancers

Cancer	Prevalence (per 100, 000)	Prevalence (95% CI per 100, 000)	I ²	P value of I ²
All Cancers	7962	5044 - 10880	99%	0
All Cancers (Pedrazzoli et al excluded)	6749	4928- 8571	99%	0
All Cancers (low quality studies excluded) *	8193	4573-11812	99%	0
Breast	191	92-290	2%	0.41
Breast (low quality studies excluded) *	188	75-302	16%	0.31
Colorectal	908	622- 1195	96%	<0.01
Colorectal (low quality studies excluded) *	921	572-1269	97%	<0.01
Colorectal (adj. for country)	810	670-950	0%	0.6
Colorectal (adj. for study quality)	750	580-910	21%	0.3
Gallbladder & Biliary Tract	283	46-521	0%	0.44
Haematological Malignancy	600	3303-896	87%	<0.01
Haematological Malignancy (Pedersen et al excluded)	579	297-861	88%	<0.01
Haematological Malignancy (low quality studies excluded) *	617	302-933	90%	<0.01
Kidney & Bladder	279	158- 400	35%	0.15
Liver	587	201-973	85%	<0.01
Liver (low quality studies excluded) *	630	181-1078	87%	<0.01
Liver (adj. for country)	350	100-610	61%	0.4
Lung	1540	667-2413	83%	<0.01
Lung (Pedrazzoli et al excluded)	1350	888-1812	76%	<0.01
Lung (low quality studies excluded) *	1418	581-2254	83%	<0.01
Lung (adj. for year of publication)	1840	1350-2330	0%	0.8
Lung (adj. for sex)	2180	1120-3230	30%	0.3
Oesophagus	307	52-562	76%	<0.01
Oesophagus (low quality studies excluded) *	312	24-600	79%	<0.01
Prostate	416	237-595	66%	<0.01
Skin	350	177-522	0%	0.50
Skin (low quality studies excluded) *	367	155-578	6%	0.38
Stomach	583	260-907	80%	<0.01
Stomach (Kamisawa et al excluded)	544	327-762	79%	<0.01
Stomach (low quality studies excluded) *	562	194-930	84%	<0.01
Thyroid	227	-50-504	68%	0.04
Thyroid (low quality studies excluded) *	222	-954-1397	84%	<0.01
Upper Respiratory Tract	1280	498-2062	94%	<0.01
Upper Respiratory Tract (low quality studies excluded) *	1221	279-2164	96%	<0.01
Upper Respiratory Tract (adj. for sex)	1920	1670-2170	0%	0.5

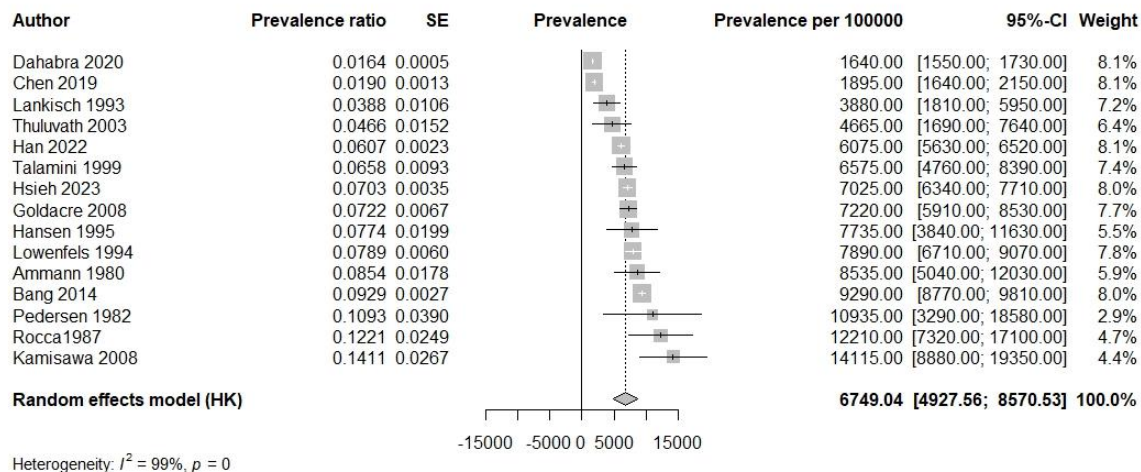
*Low quality studies- includes Ammann 1980, Lankisch 1993 & Pedersen 1982

Figure 3.3 Prevalence of Cancers in Patients with Chronic Pancreatitis

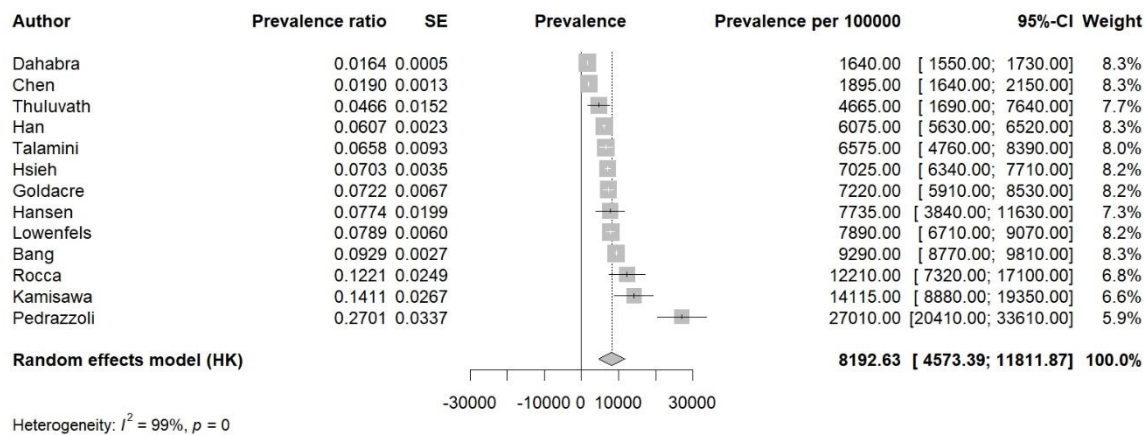
3.3.1 All Cancers



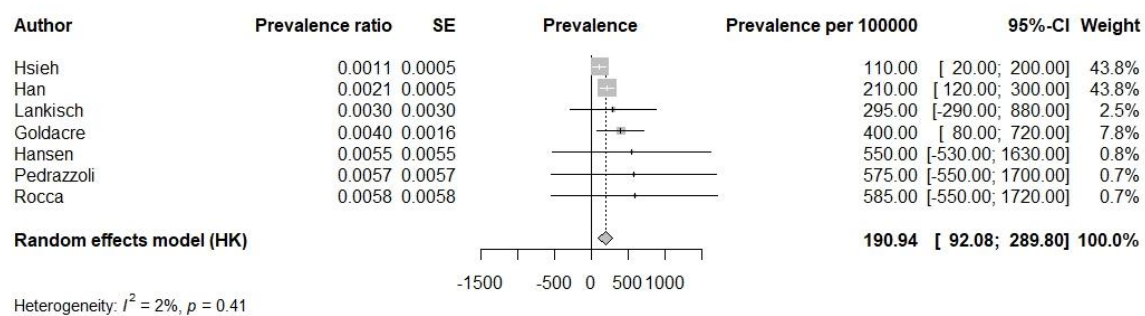
Pedrazzoli et al excluded



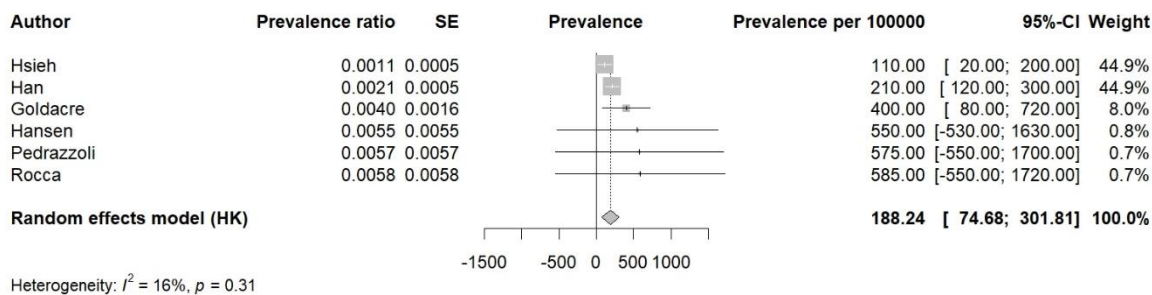
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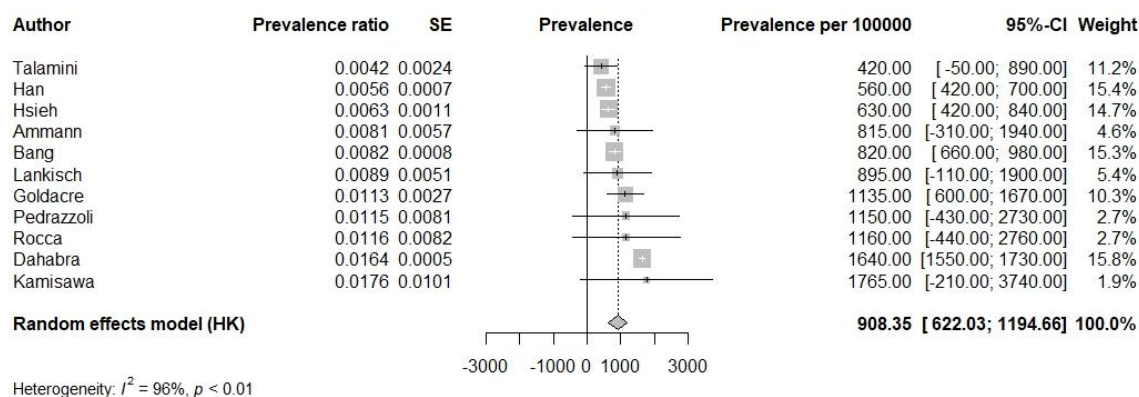
3.3.2 Breast



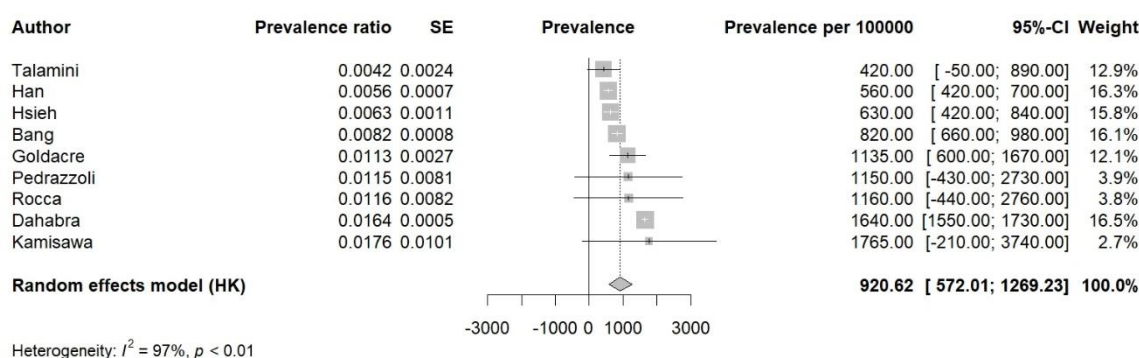
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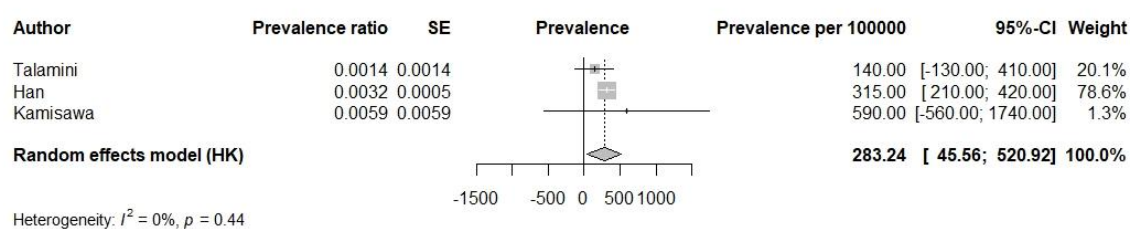
3.3.3 Colorectal



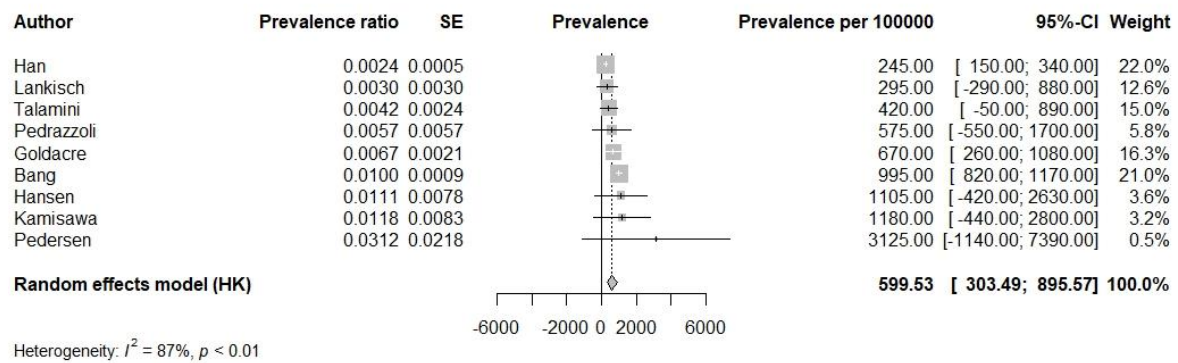
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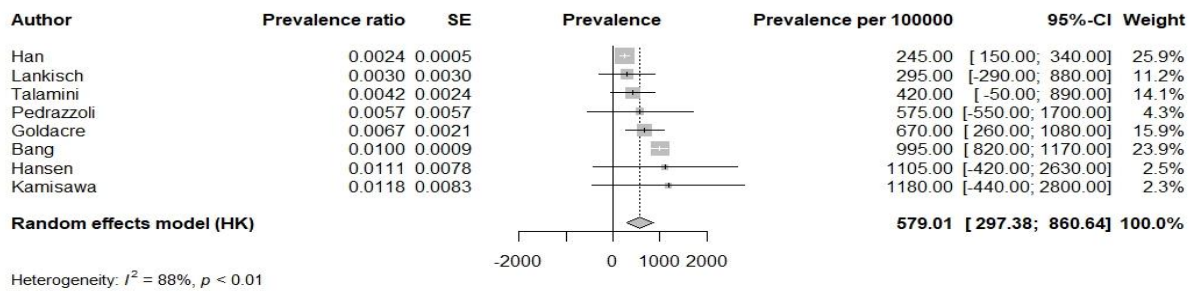
3.3.4 Gallbladder & Biliary Tract cancer



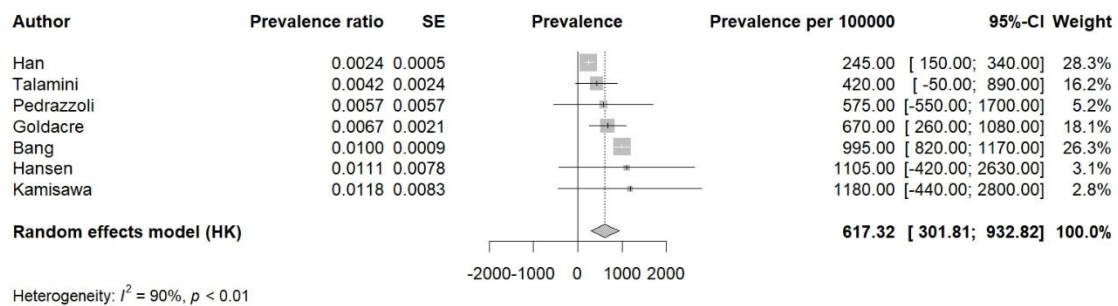
3.3.5 Haematological Malignancy



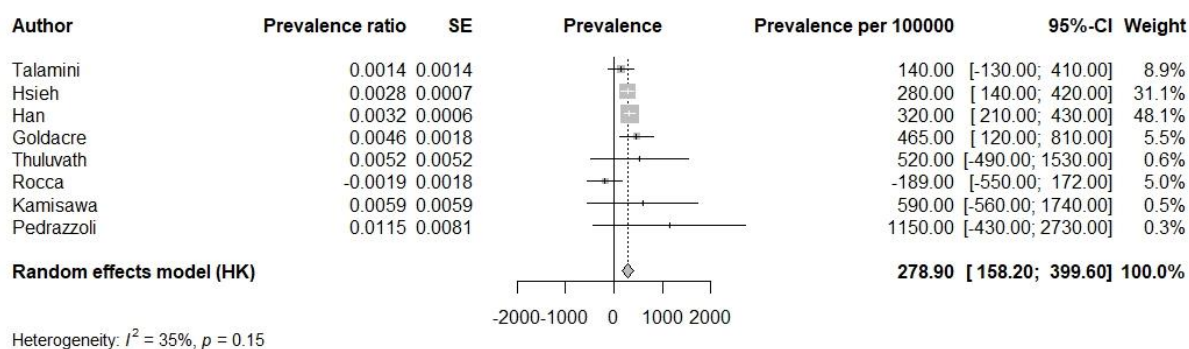
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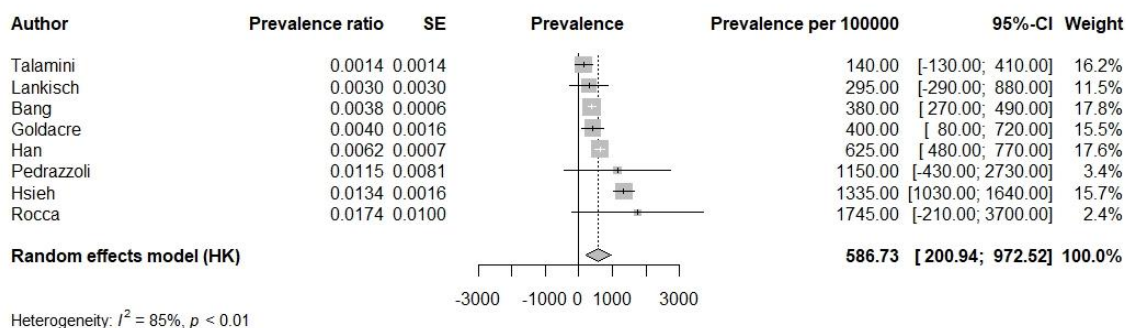
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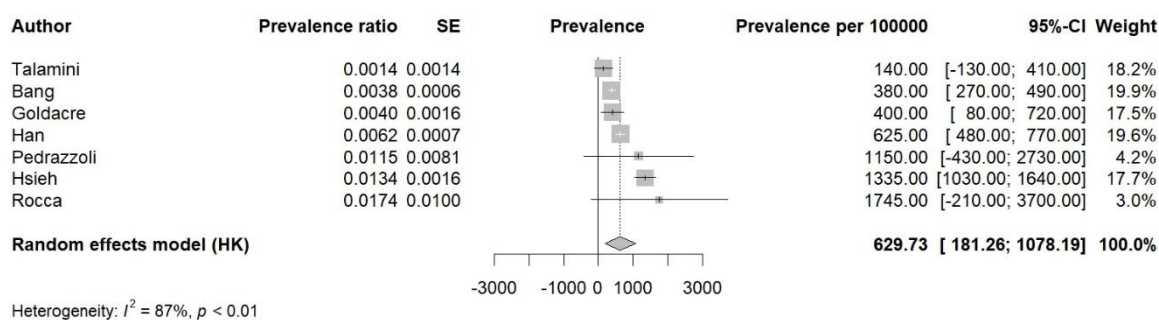
3.3.6 Kidney & Bladder



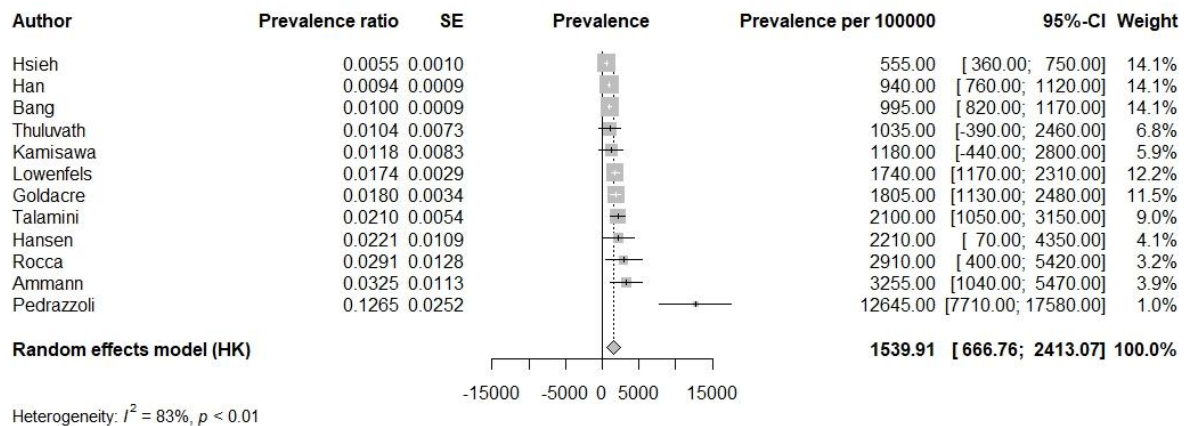
3.3.7 Liver



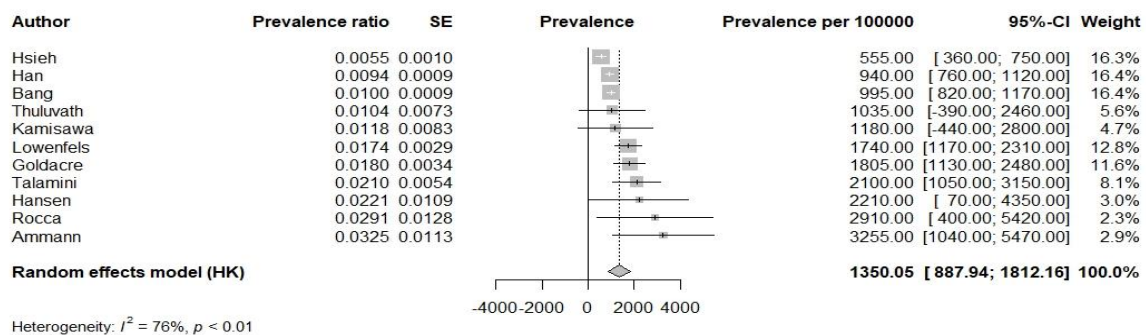
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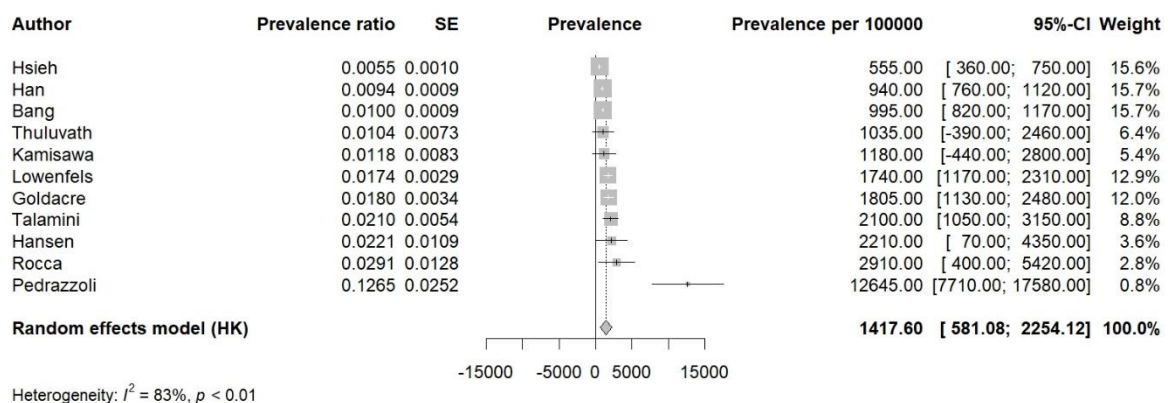
3.3.8 Lung



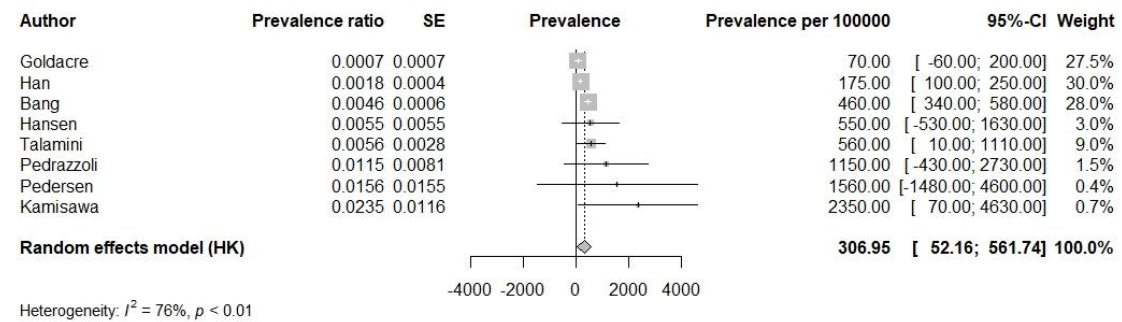
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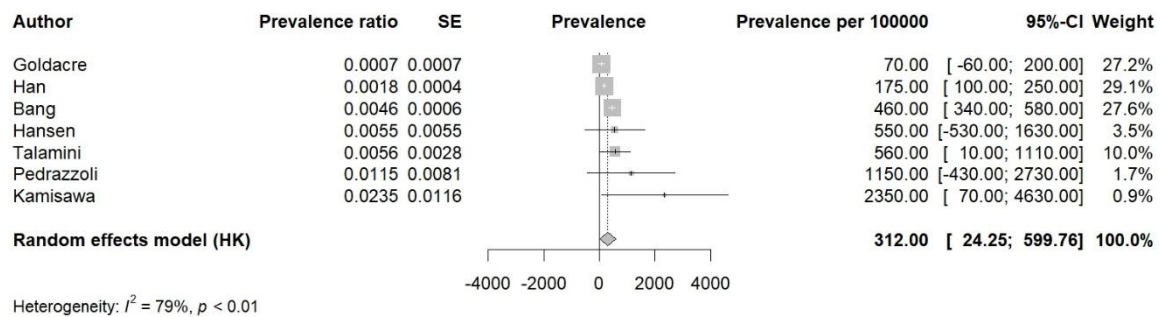
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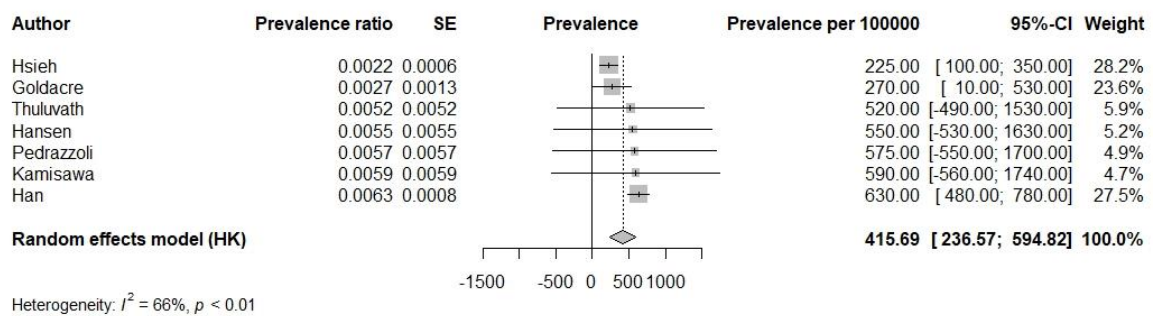
3.3.9 Oesophagus



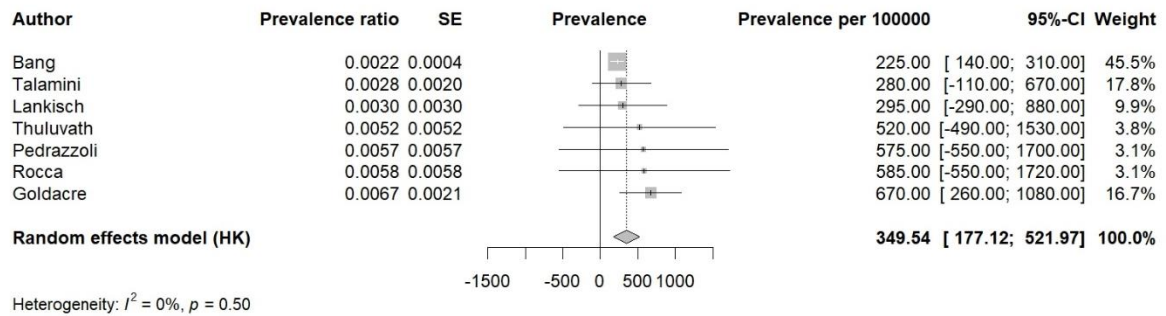
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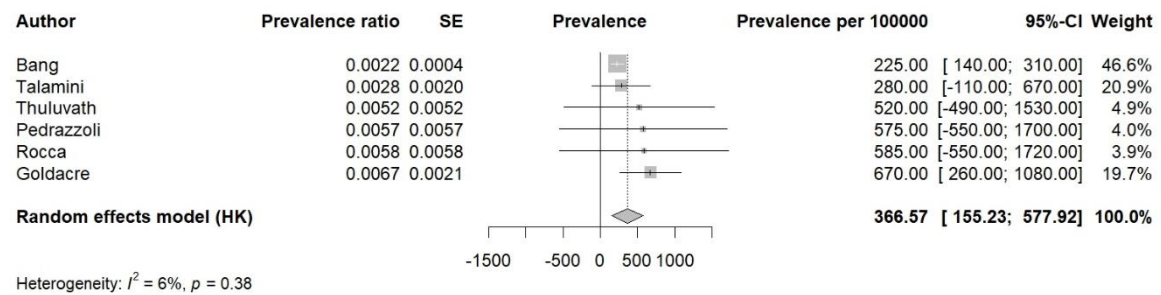
3.3.10 Prostate



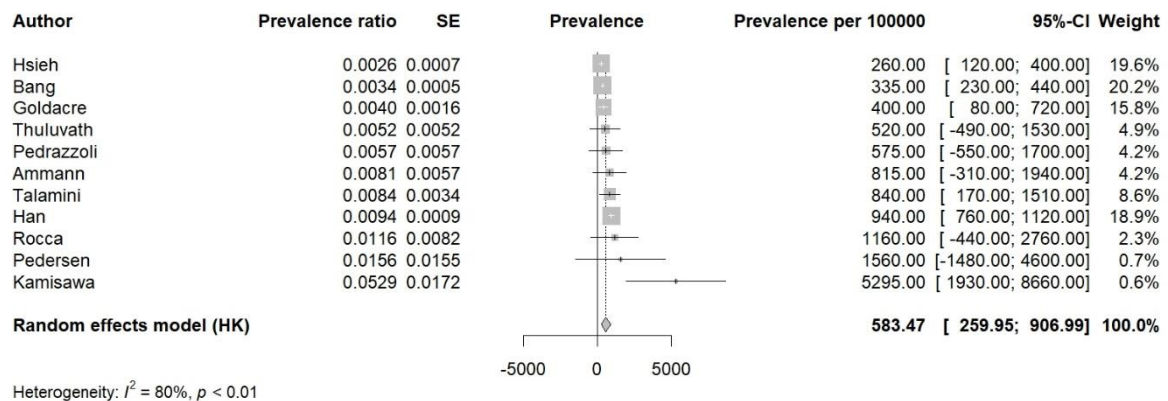
3.3.11 Skin



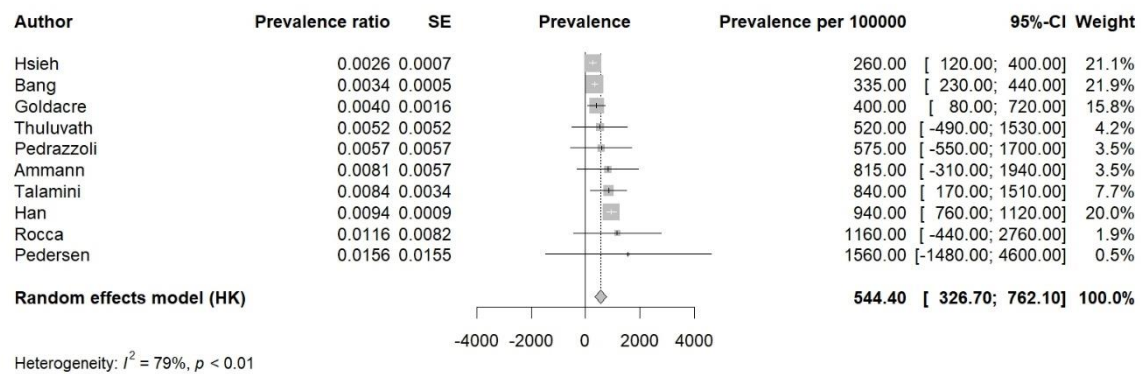
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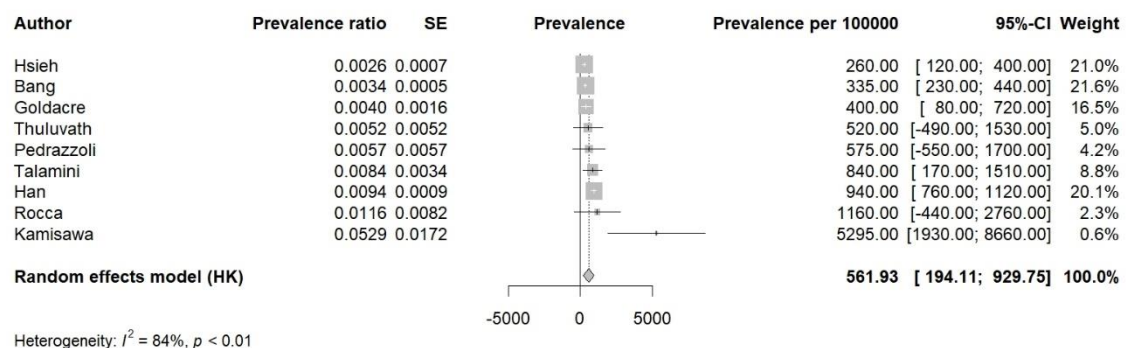
3.3.12 Stomach



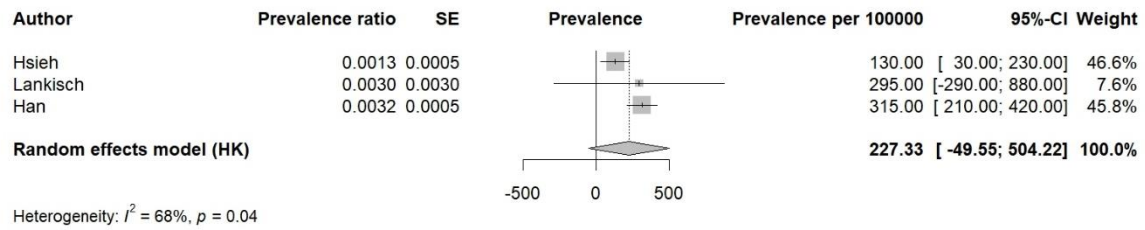
Kamisawa et al excluded



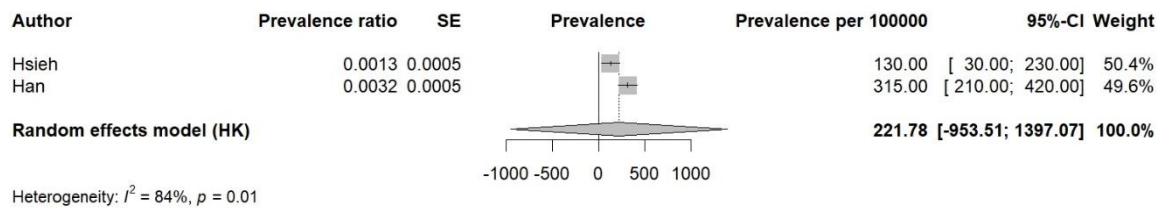
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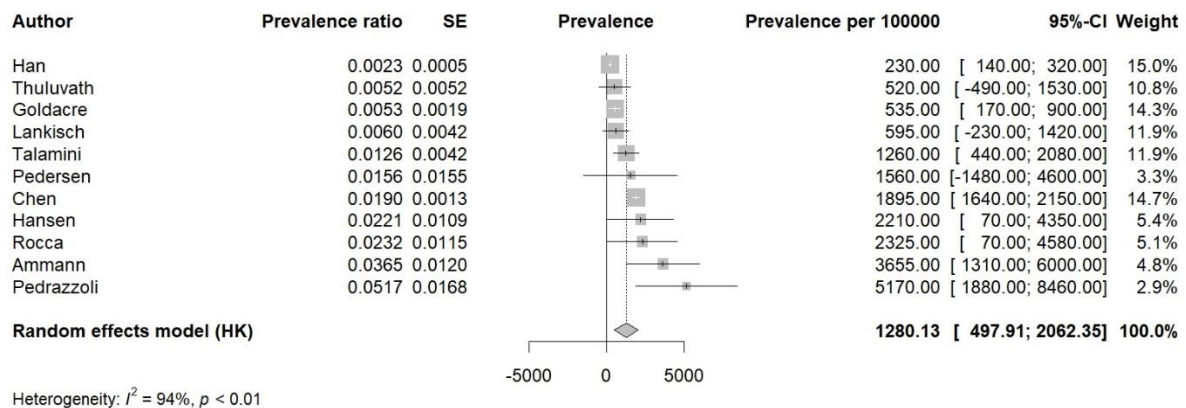
3.3.13 Thyroid



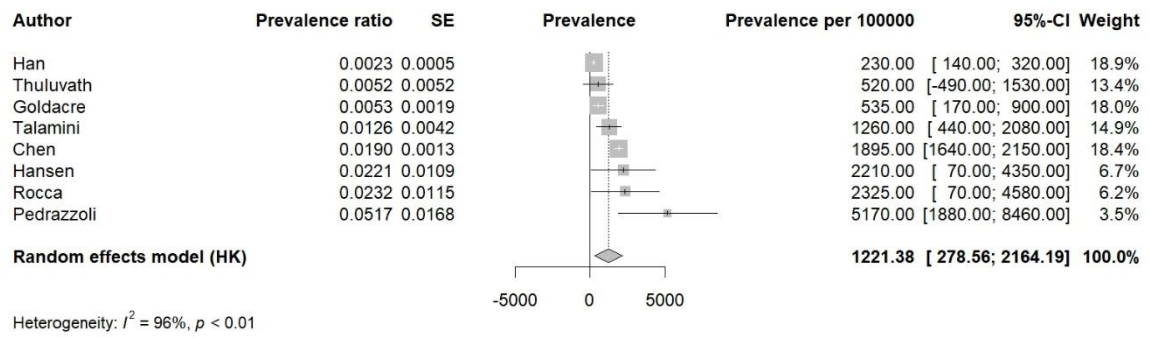
low quality studies excluded



3.3.14 Upper Respiratory tract



low quality studies excluded



Meta Analysis

6 studies reported SIR but focused on different types of cancers including pancreatic cancer, making it impossible to compute an overall SIR.

For the meta-analysis of the HR, 3 comparable cohort studies were included in the plots [414, 417, 418]. A fourth cohort study (Goldacre et al [416]) was only included in a secondary analysis as it utilised risk ratio instead of hazard ratio, only included acute hospital admissions, utilised an unmatched reference cohort, and was not contemporary (started in 1963). In contrast, Han et al [417], Bang et al [414] and Hsieh et al [418] had all reported on hazard ratios and used propensity matching. Dahabra et al [415] was also excluded as it did not state a follow up period and used odds ratios, and Chen et al. [211] was excluded as it was too restrictive reporting only head and neck cancer. One study separated outcomes by sex, so these results were included separately.

The pooled hazard ratios for 9 cancers were estimated, including both crude and adjusted values where available. Among these 9 cancers there were 6 cancers – lung, liver, stomach, oesophagus, kidney and bladder and breast – that exhibited increased hazard ratios, ranging from 1.12 to 2.18. Of these, only two cancers showed statistically significant hazard ratios: lung cancer (adjusted for age, sex, and Charlson comorbidity index) with a hazard ratio of 1.31 (p-value = 0.04) and liver cancer (unadjusted) with a hazard ratio of 1.58 (p-value = 0.01). Two cancers demonstrated decreased hazard ratios in CP patients. These were colorectal cancer (with adjusted and unadjusted hazard ratios of 0.73 and 0.81, respectively) and thyroid cancer (with an unadjusted hazard ratio of 0.83 and an adjusted hazard ratio of 1.00). However, none of these decreased hazard ratios were statistically significant (table 3.7, figure 4).

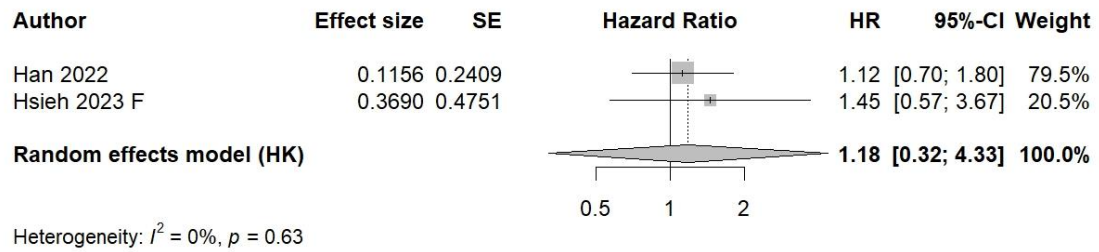
Table 3.7 – Hazard Ratio for Cancers

Cancer	Overall HR	HR (95% CI)	P value	Heterogeneity (I ²)	P value of I ²
Breast (crude)	1.18	0.32-4.33	0.35	0.00%	0.63
Breast (adjusted)	1.18	0.32-4.36	0.35	0.00%	0.63
Breast (adjusted with Goldacre)	1.07	0.55-2.11	0.69	0.00%	0.52
Colorectal (crude)	0.81	0.44-1.48	0.27	27.7%	0.25
Colorectal (adjusted)	0.73	0.51-1.04	0.07	31.4%	0.22
Colorectal (adjusted with Goldacre)	0.82	0.57-1.16	0.20	53.0%	0.06
Kidney & Bladder (crude)	1.17	0.82-1.66	0.26	0.00%	0.72
Kidney & Bladder (adjusted)	1.18	0.88-1.60	0.17	0.00%	0.81
Kidney & Bladder (adjusted with Goldacre)	1.13	0.88-1.45	0.26	0.00%	0.87
Liver Cancer (crude)	1.58	1.27-1.98	0.01	0.00%	0.76
Liver Cancer (adjusted)	1.54	0.97-2.43	0.06	53.4%	0.09
Liver Cancer (adjusted with Goldacre)	1.78	0.97-3.25	0.06	70.2%	<0.01
Lung Cancer (crude)	1.41	0.93-2.12	0.07	0.00%	0.41
Lung Cancer (adjusted)	1.31	1.03-1.66	0.04	0.00%	0.40
Lung Cancer (adjusted with Goldacre)	1.40	0.99-1.99	0.05	55.0%	0.06
Oesophagus (adjusted))	2.18	0.003-1570.1	0.37	83.1%	0.01
Oesophagus (adjusted with Goldacre)	1.55	0.06-37.59	0.60	78.5%	<0.01
Prostate (crude)	1.01	0.29-3.53	0.92	0.00%	0.45
Prostate (adjusted)	1.00	0.21-4.75	0.99	0.00%	0.35
Prostate (adjusted with Goldacre)	0.94	0.50-1.78	0.73	10.0%	0.33
Stomach (crude)	1.36	0.45-4.15	0.35	58.2%	0.09
Stomach (adjusted)	1.12	0.69-1.83	0.51	34.9%	0.2
Stomach (adjusted with Goldacre)	1.11	0.79-1.55	0.45	19.3%	0.29
Thyroid (crude)	0.83	0.39-1.79	0.41	0.00%	0.39
Thyroid (adjusted)	1.00	0.56-1.78	0.99	0.00%	0.62

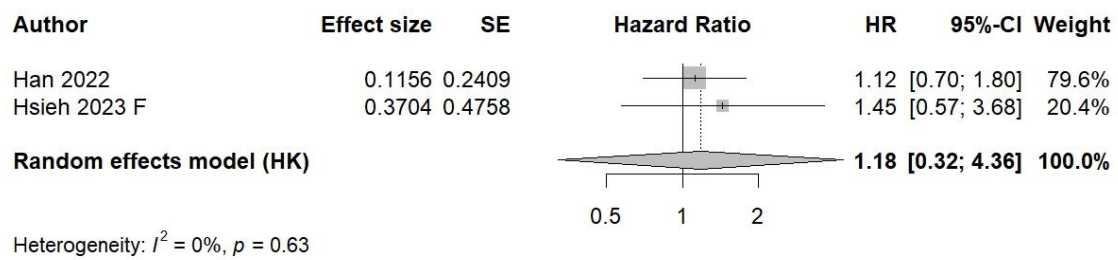
Figure 3.4 – Hazard Ratios of Cancers in Patients with Chronic Pancreatitis

3.4.1 Breast Cancer

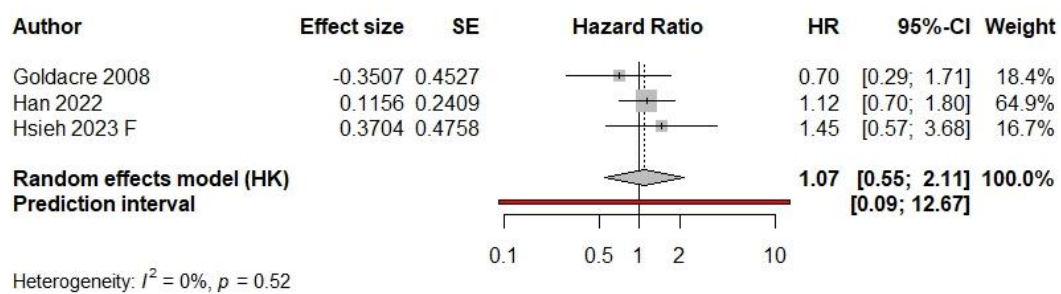
Crude



Adjusted

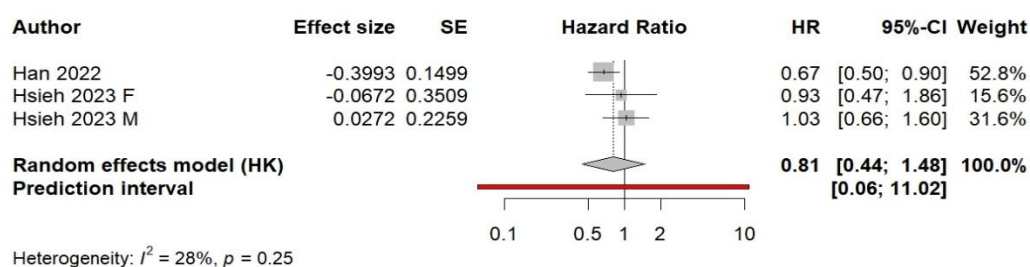


Adjusted (with Goldacre)

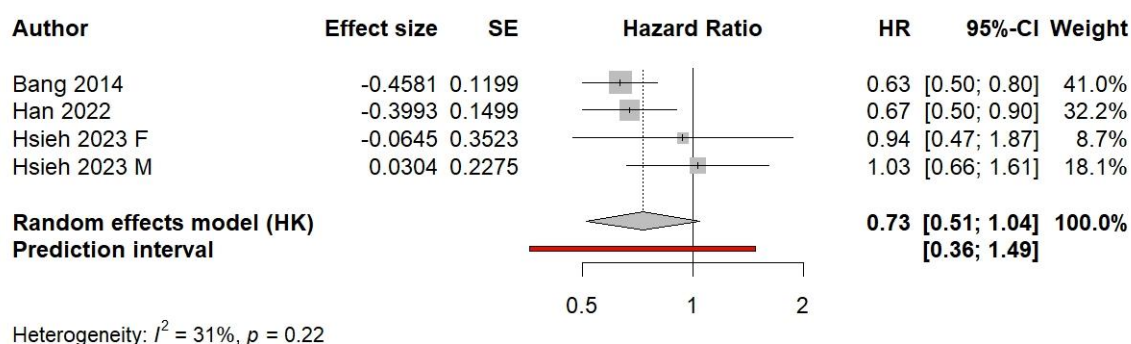


3.4.2 Colorectal Cancer

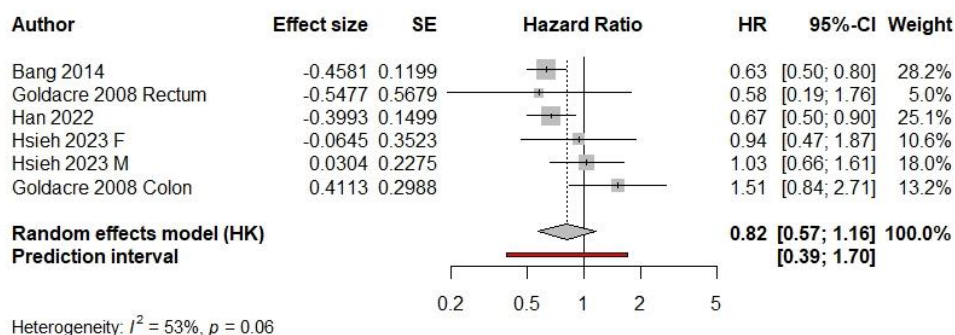
Crude



Adjusted

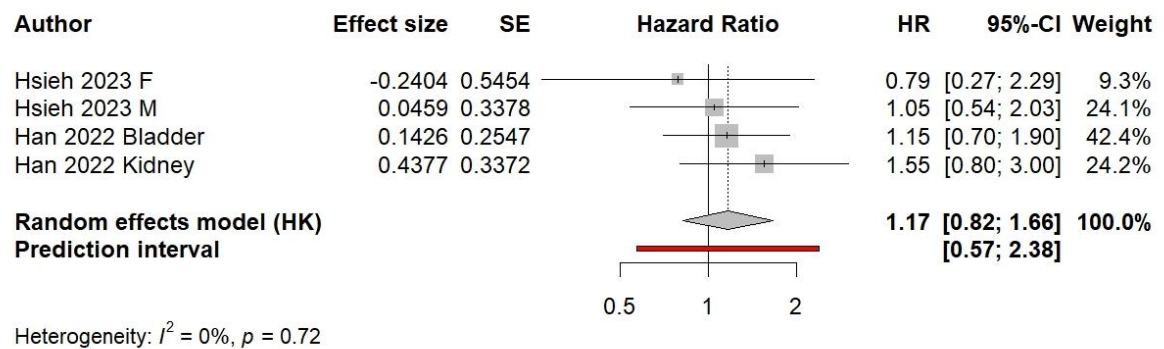


Adjusted (with Goldacre)

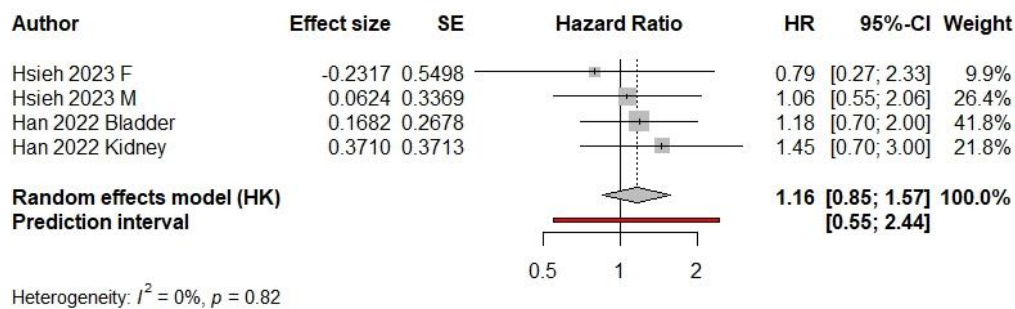


3.4.3 Kidney & Bladder

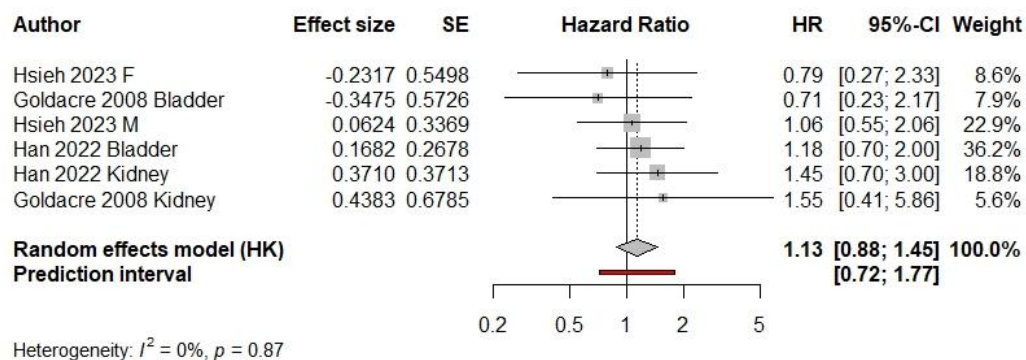
Crude



Adjusted

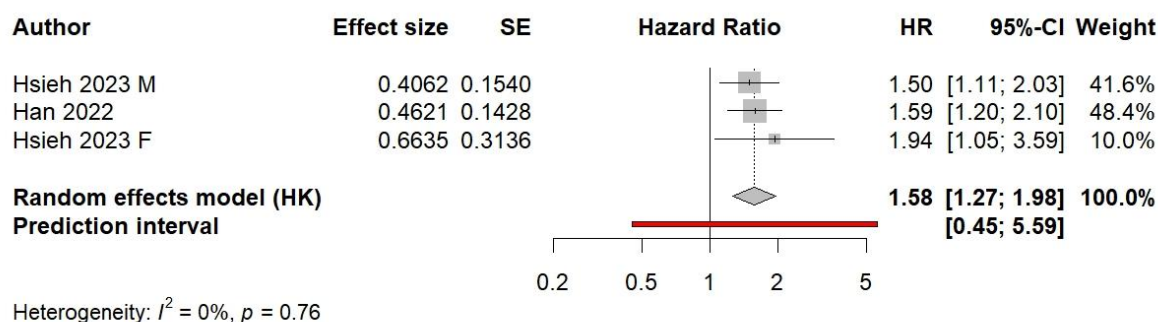


Adjusted (with Goldacre)

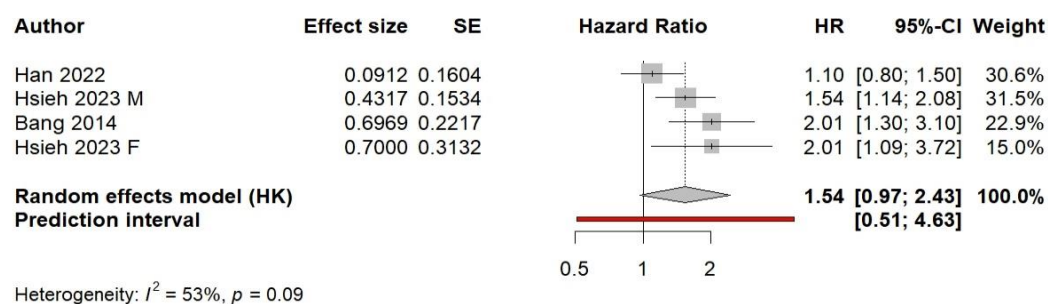


3.4.4 Liver

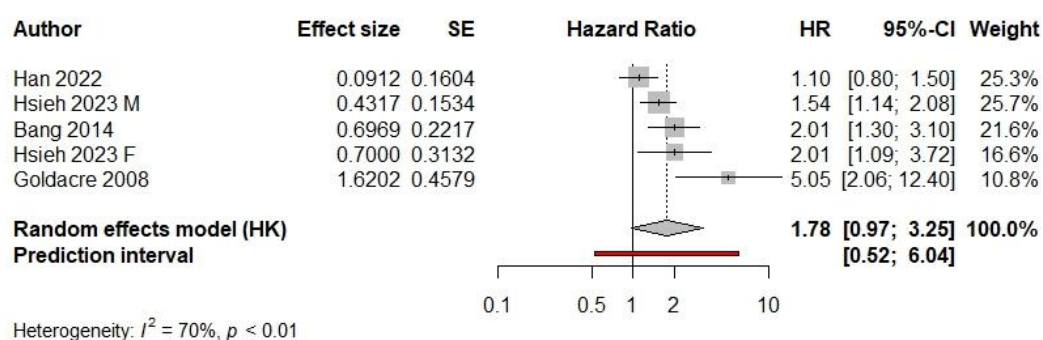
Crude



Adjusted

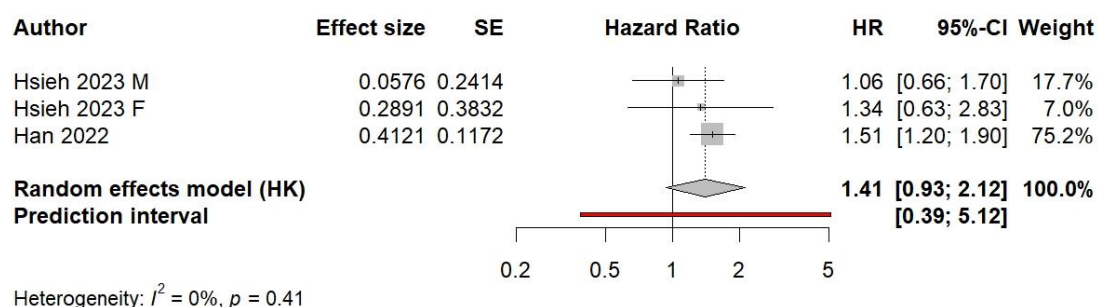


Adjusted (with Goldacre)

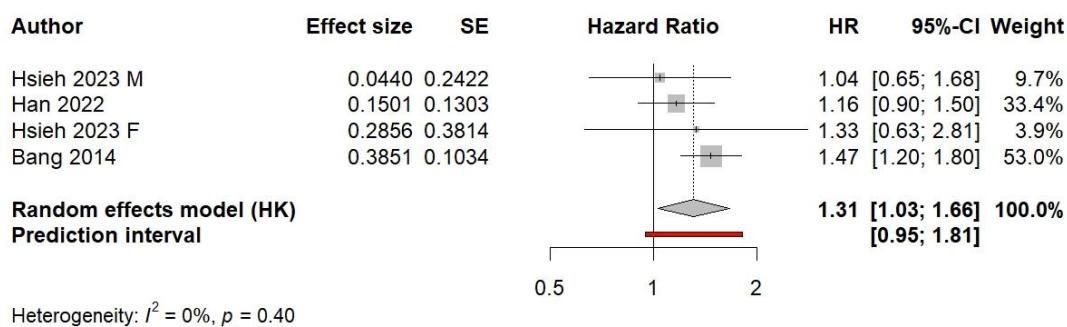


3.4.5 Lung Cancer

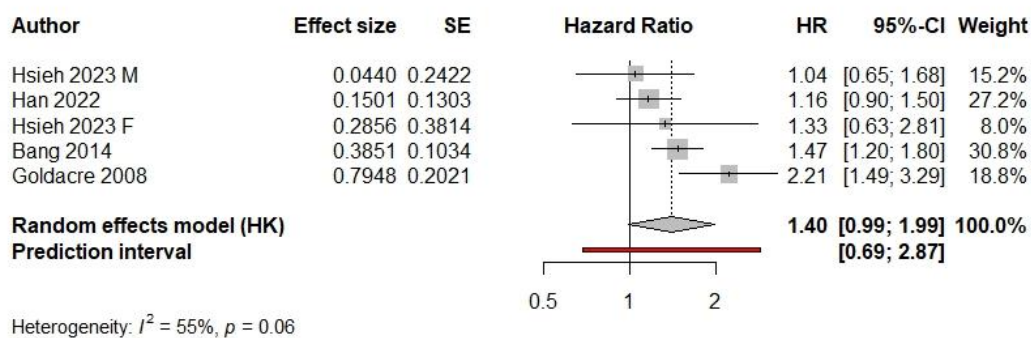
Crude



Adjusted

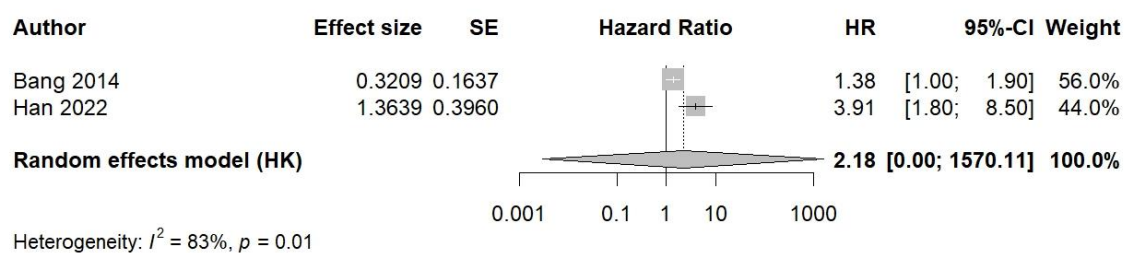


Adjusted (with Goldacre)

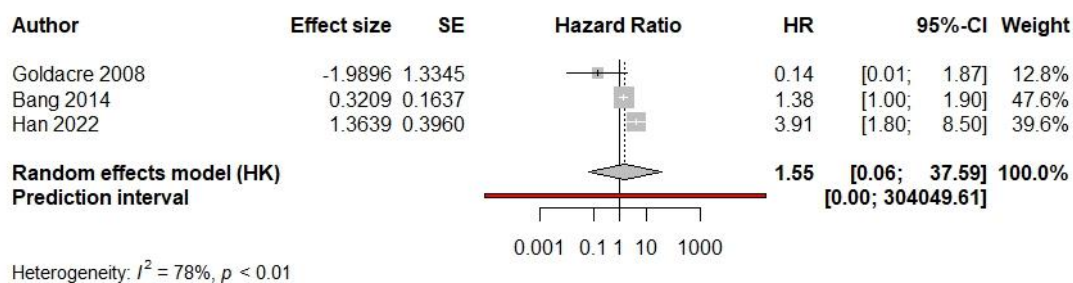


3.4.6 Oesophagus

Adjusted

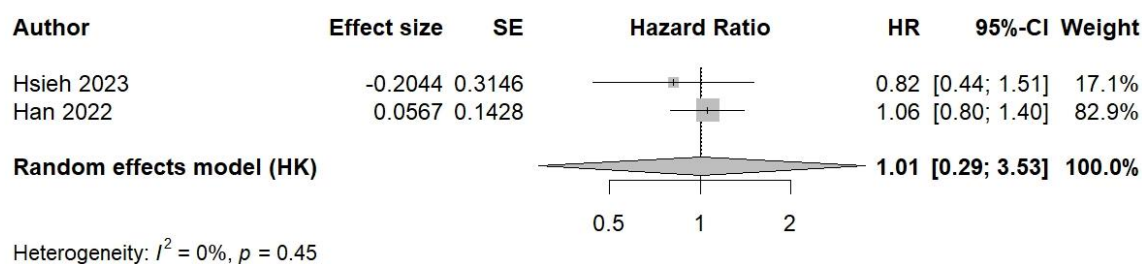


Adjusted (with Goldacre)

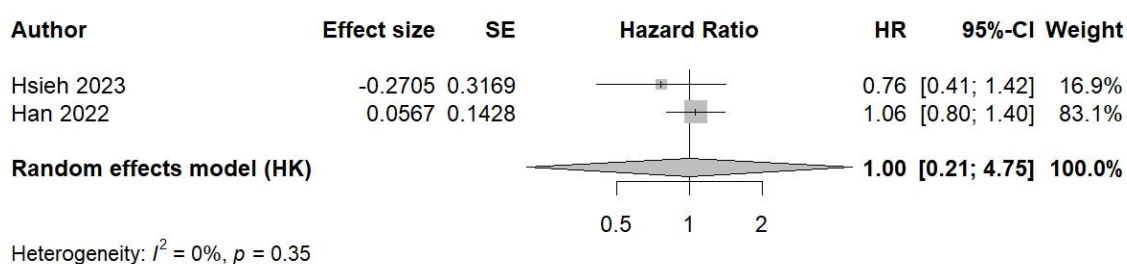


3.4.7 Prostate

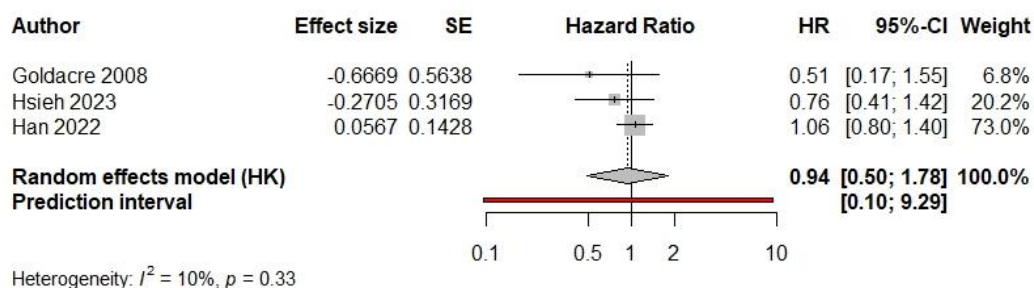
Crude



Adjusted

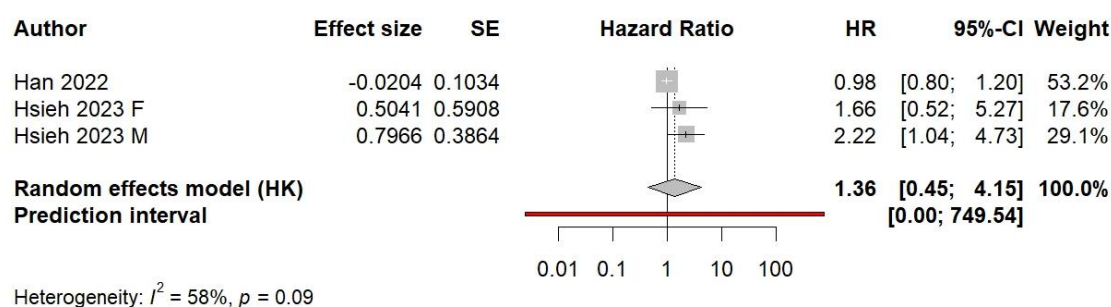


Adjusted (with Goldacre)

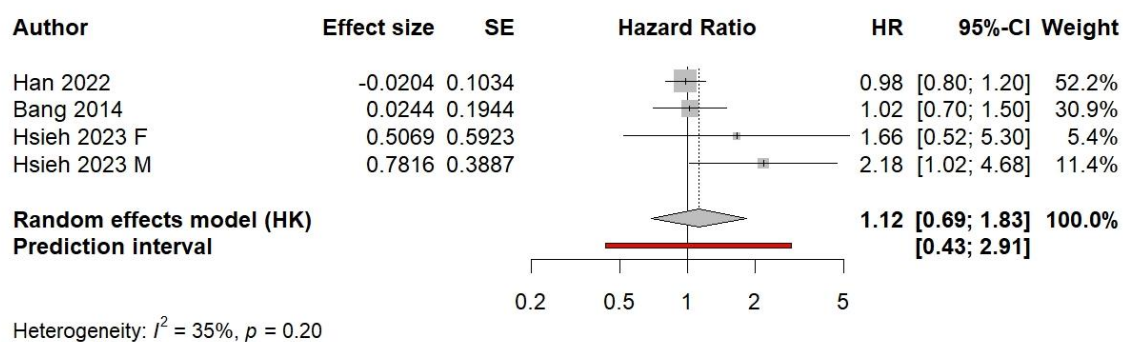


3.4.8 Stomach

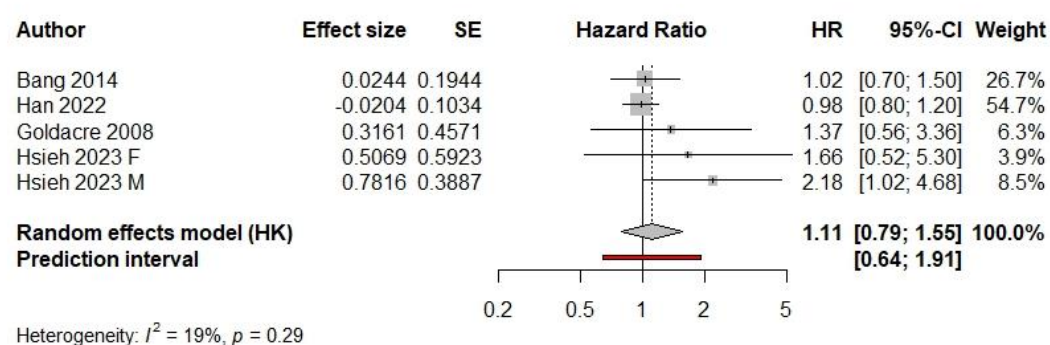
Crude



Adjusted

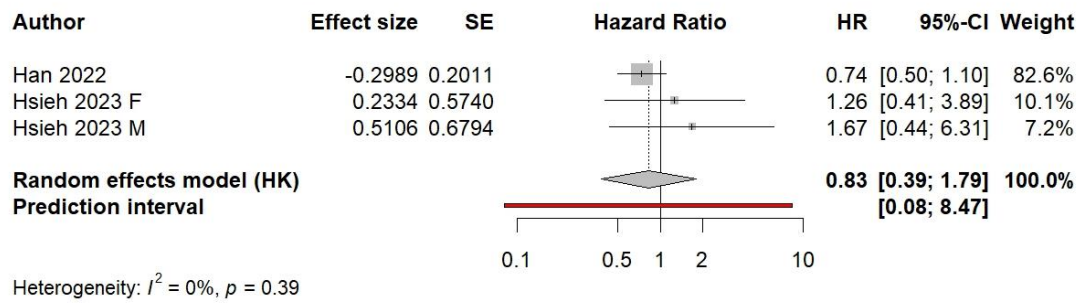


Adjusted (with Goldacre)

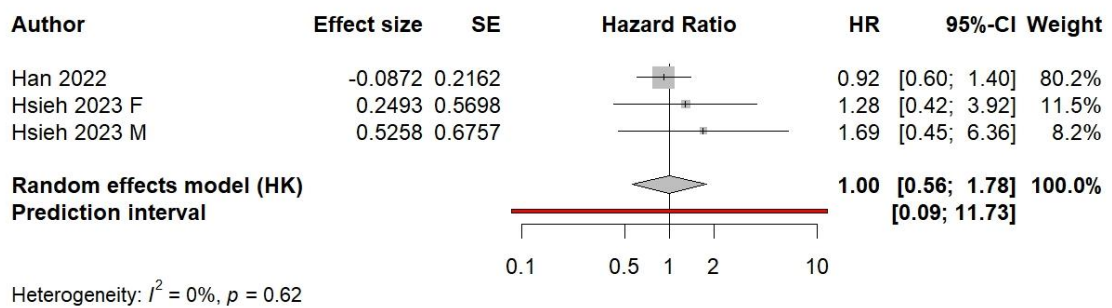


3.4.9 Thyroid

Crude



Adjusted



Meta Regression

Incidence

The meta-regression analysis identified a positive association between colorectal cancer incidence and smaller study size, European countries, and liver cancer incidence. Additionally, a positive association was observed between medium-quality studies and stomach cancer incidence (Table 3.8a-3.8e).

Table 3.8: Meta regression for incidence

Table 3.8a – Meta Regression for overall cancer incidence

Variable	I ² (residual heterogeneity/ unaccounted variability)	R ² (amt of heterogeneity accounted for)	Tests of moderator (QM)	Tests of moderator p value
Country	99.04%	0.00%	0.12	0.94
Quality of Study	98.30%	0.00%	1.31	0.52
Year of publication	98.95%	0.00%	2.38	0.30
Size	98.80%	0.00%	0.39	0.82
Sex	98.55%	0.00%	0.95	0.62

Table 3.8b – Meta regression for colorectal cancer incidence

Variable	I ² (residual heterogeneity/ unaccounted variability)	R ² (amt of heterogeneity accounted for)	Tests of moderator (QM)	Tests of moderator p value
Country	52.98%	0.00%	0.0001	0.99
Quality of Study	75.46%	0.00%	1.55	0.46
Year of publication	44.78%	51.29%	2.7	0.26
Size	12.06%	69.89%	6.11	0.047
Sex	43.91%	53.07%	2.34	0.31

Subgroup analysis for colorectal cancer incidence

Variable	Incidence (per 100,000 person years)	95% CI	I ²	P value for I ²
<1000 patients	111	45-272	46%	0.09

Table 3.8c – Meta regression for liver cancer incidence

Variable	I ² (residual heterogeneity/ unaccounted variability)	R ² (amt of heterogeneity accounted for)	Tests of moderator (QM)	Tests of moderator p value
Country	81.32%	54.17%	5.59	0.02
Quality of Study	92.75%	0.00%	0.54	0.46
Year of publication	83.39%	44.77%	5.34	0.07
Size	79.62%	0.00%	2.72	0.26
Sex	89.65%	4.82%	2.71	0.26

Subgroup analysis for liver cancer incidence

Variable	Incidence (per 100,000 person years)	95% CI	I ²	P value for I ²
European Countries only	70	15-337	71%	0.008

Table 3.8d – Meta regression for lung cancer incidence

Variable	I ² (residual heterogeneity/ unaccounted variability)	R ² (amt of heterogeneity accounted for)	Tests of moderator (QM)	Tests of moderator p value
Country	90.23%	0.00%	1.67	0.43
Quality of Study	97.68%	0.00%	0.15	0.93
Year of publication	96.73%	0.00%	1.10	0.58
Size	86.78%	0.00%	2.09	0.35
Sex	95.12%	9.61%	2.70	0.26

Table 3.8e – Meta Regression for stomach cancer incidence

Variable	I ² (residual heterogeneity/ unaccounted variability)	R ² (amt of heterogeneity accounted for)	Tests of moderator (QM)	Tests of moderator p value
Country	96.65%	0.00%	0.53	0.77
Quality of Study	16.27%	99.75%	8.54	0.01
Year of publication	99.31%	0.00%	0.07	0.96
Size	92.69%	0.00%	0.39	0.82
Sex	99.15%	0.00%	0.46	0.80

Incidence rate for stomach cancer

Variable	Incidence (per 100,000 person years)	95%CI	I ²	P value of I ²
Medium quality studies only	64	31-133	53%	0.06

Prevalence

The meta regression analysis revealed a positive correlation between colorectal cancer prevalence and European countries, as well as medium-quality studies. Furthermore, a positive correlation was found between European countries and liver cancer prevalence, the year of publication and sex in relation to lung cancer prevalence, and sex in relation to upper respiratory tract cancer prevalence (Table 3.9a-3.9f).

Table 3.9: Meta regression for prevalence

Table 3.9a – Meta Regression prevalence of all cancers

Variable	I ² (residual heterogeneity/ unaccounted variability)	R ² (amt of heterogeneity accounted for)	Tests of moderator (QM)	Tests of moderator p value
Country	98.88%	9.09%	3.34	0.19
Quality of Study	98.97%	0.00%	1.55	0.46
Year of publication	99.73%	0.00%	0.87	0.65
Size	99.71%	0.00%	3.09	0.38
Sex	99.22%	22.47%	7.09	0.03

Prevalence for sex M:F ratios

Variable	Prevalence per 100,000	95% CI	I ²	P value of I ²
M: F (4-6 :1)	7660	3890- 11430	96%	<0.0001
M: F (7-9 :1)	15570	3940- 27200	95%	<0.0001

Table 3.9b – Meta Regression for prevalence of colorectal cancer

Variable	I ² (residual heterogeneity/ unaccounted variability)	R ² (amt of heterogeneity accounted for)	Tests of moderator (QM)	Tests of moderator p value
Country	0.00%	100%	218.6	<0.0001
Quality of Study	18.31%	92.21%	48.35	<0.0001
Year of publication	91.82%	0.00%	0.95	0.62
Size	91.35%	0.00%	0.31	0.86
Sex	93.59%	0.00%	0.19	0.91

Prevalence for colorectal cancer

Variable	Prevalence (per 100,000)	95%CI	I ²	P value of I ²
European Countries only	810	670-950	0%	0.6
Medium quality studies only	750	580-910	21%	0.3

Table 3.9c – Meta Regression for prevalence of haematological malignancy

Variable	I ² (residual heterogeneity/ unaccounted variability)	R ² (amt of heterogeneity accounted for)	Tests of moderator (QM)	Tests of moderator p value
Country	35.23%	63.59%	2.78	0.10
Quality of Study	46.03%	40.39%	2.20	0.33
Year of publication	84.02%	0.00%	1.62	0.44
Size	81.45%	9.47%	1.46	0.69
Sex	85.70%	0.00%	1.32	0.52

Table 3.9d – Meta Regression for prevalence of liver cancer

Variable	I ² (residual heterogeneity/ unaccounted variability)	R ² (amt of heterogeneity accounted for)	Tests of moderator (QM)	Tests of moderator p value
Country	72.53%	55.82%	5.30	0.02
Quality of Study	91.05%	0.00%	0.32	0.85
Year of publication	89.79%	18.78%	3.25	0.20
Size	90.04%	0.00%	1.32	0.52
Sex	91.46%	0.48%	1.72	0.42

Prevalence for liver cancer adjusted for European countries only

Variable	Prevalence per 100,000	95% CI	I ²	P value of I ²
European countries only	350	100-610	61%	0.4

Table 3.9e – Meta Regression for prevalence of lung cancer

Variable	I ² (residual heterogeneity/ unaccounted variability)	R ² (amt of heterogeneity accounted for)	Tests of moderator (QM)	Tests of moderator p value
Country	83.77%	36.76%	5.68	0.06
Quality of Study	88.24%	4.89%	2.58	0.27
Year of publication	79.61%	69.94%	8.18	0.02
Size	88.26%	11.92%	4.43	0.11
Sex	87.69%	44.34%	6.30	0.04

Prevalence rates for lung cancer adjusted for year of publication and sex

Variable	Prevalence (per 100,000)	95%CI	I ²	P value of I ²
Year of publication 2000- 2023	2010	20-4000	99%	<0.0001
Year of publication 1990- 1999	1840	1350-2330	0%	0.8
M: F (4-6:1)	2180	1120-3230	30%	0.3

Table 3.9f – Meta Regression for prevalence of upper respiratory tract cancer

Variable	I ² (residual heterogeneity/ unaccounted variability)	R ² (amt of heterogeneity accounted for)	Tests of moderator (QM)	Tests of moderator p value
Country	94.66%	0.00%	1.08	0.58
Quality of Study	74.80%	0.00%	1.63	0.65
Year of publication	92.40%	15.45%	2.99	0.22
Size	95.40%	0.00%	1.22	0.75
Sex	23.02%	95.37%	41.17	<0.0001

Prevalence rates for upper respiratory tract cancers adjusted for sex

Variable	Prevalence	95%CI	I ²	P value for I ²
Sex M: F (4-6: 1)	1920	1670-2170	0%	0.5

DISCUSSION

This systematic review and meta-analysis shows that patients with CP face a significantly elevated risk of developing EP cancers, with a 58% higher risk for liver cancer and a 31% higher risk for lung cancer compared to the general population. Notably, no cancer type exhibited a statistically significant decreased risk among these patients. The most prevalent cancers in individuals with CP were similar to those observed in the general population; lung, upper respiratory tract, and colorectal cancers, while breast, thyroid, kidney, and bladder cancers were the least prevalent. The cancers with the highest incidence rates were lung, colorectal, and oesophageal cancers, whereas thyroid, breast, and prostate cancers showed the lowest incidence rates. Unfortunately, due to insufficient documentation in most studies, the time to development of these extra-pancreatic cancers could not be assessed.

Lung and liver cancer share common risk factors with CP. For example, alcohol and smoking. It is well established that cirrhosis significantly increases the risk of developing liver cancer, with annual incidence ranging between 1% to 8% [428]. The primary causes of cirrhosis vary by region but generally include excess alcohol consumption (40%-78%), chronic viral hepatitis (41%) and metabolic associated steatotic liver disease (26%) [429-431]. Similarly, alcohol is the predominant risk factor for CP, contributing to approximately 40%–70% of cases worldwide [432]. This shared risk factor may partially explain the elevated risk of liver cancer in patients with CP. Supporting this, Pace et al. demonstrated a strong correlation between cirrhosis and CP, as well as pancreatic fibrosis, in individuals with prolonged alcohol consumption [433]. Additionally, increased alcohol consumption also induces gut dysbiosis with subsequent increased bacterial overgrowth resulting in translocation of bacteria into the liver causing liver cancer [434, 435]. While alcohol is a well-documented risk factor for both cirrhosis and CP, genetic factors may also contribute to the development of multi-organ fibrosis, though this hypothesis requires further investigation [436].

Similarly, smoking is a well-established independent risk factor for the development of CP [437, 438]. It triggers morphological changes in the pancreas, including increased extracellular matrix, infiltration of inflammatory cells, loss of acinar structures, and upregulation of digestive enzymes such as trypsinogen and chymotrypsin, ultimately leading to CP [74]. Smoking is also responsible for 90% of lung cancer cases, the leading cause of cancer-related deaths worldwide [410] [439]. Given this shared risk factor, it is not surprising that patients with CP also have an elevated risk of developing lung cancer. This systematic review confirms this association, revealing that patients with CP have a 31% higher risk of developing lung cancer. Furthermore, lung cancer had the highest incidence and

prevalence among all EP cancers in CP patients, ranging from 180 to 260 per 100,000 for incidence and 1,350 to 1,540 per 100,000 for prevalence.

In this study, the cancers with the highest prevalence were lung, upper respiratory tract, colorectal, haematological (including multiple myeloma, leukaemia, and lymphoma), liver, and stomach cancers. The cancers with the highest incidence included lung, colorectal, oesophageal, stomach, and liver cancers. This pattern closely mirrors global cancer incidence trends, where the most common cancers are lung, breast, colorectal, prostate, stomach, and liver cancers [440]. As previously noted, the primary risk factors for CP – smoking and alcohol consumption—are also major contributors to cancer development [441]. Tobacco, in particular, contains over 62 carcinogens that promote cancer by altering the expression of genes involved in tumour suppression and activation, growth signalling pathways, apoptosis, angiogenesis, and telomerase activity, all of which contribute to tumorigenesis [442, 443].

Similarly, alcohol contributes to cancer development primarily through the production of acetaldehyde, a genotoxic and carcinogenic compound. It also generates reactive oxygen species, leading to mutations in genes involved in tumourigenesis [444]. Further, alcohol creates a pro-inflammatory environment characterised by elevated levels of TNF α , IL1, IL6, IL8, and NF κ B, which perpetuates a cycle of reactive oxygen species and chemokine- and cytokine-induced carcinogenesis [445, 446]. Alcohol also disrupts retinoid metabolism, a key regulator against carcinogenesis; lower retinoid levels have been linked to an increased risk of head and neck cancers [446]. Additionally, oral microbiota metabolize alcohol into acetaldehyde, resulting in higher concentrations of this carcinogen in saliva, which increases the risk of oral cavity cancers [444]. Therefore, it is not surprising to observe a strong association between excessive alcohol consumption and oesophageal, colorectal, liver, breast, and oral cavity cancers [440], which may partially explain some of our findings.

The overall cancer rates in Goldacre et al [416] were twice the overall cancer rates in Bang et al [414], Han et al [417] and Hsieh et al [418], and this is likely due to the incorporation of pancreatic cancer in this overall analysis in Goldacre et al [416]. However, the results of the secondary meta-analysis including Goldacre et al [416] were similar to the results obtained using the initial 3 studies [414, 417, 418] due to its low weighting from small numbers of events.

This study has several limitations. Some studies relied on ICD coding to identify patients with CP, which can be prone to inaccuracies due to mislabelling and misidentification. Additionally, most studies did not track the time between CP diagnosis and the development of EP cancers, making it difficult to determine the optimal timing for cancer surveillance. Six studies used propensity score matching, which can introduce bias by excluding unmatched patients and potentially including

patients who are not exact matches [447]. However, when applied correctly, propensity score matching generally balances measured covariates effectively [447]. The overall hazard ratio was calculated from only three studies that used the same effect size and assessed similar cancers. This limitation may have led to an underestimation of cancer outcomes, as many studies were excluded from the analysis, and to a potential overestimation of other cancers. Despite this, the calculation of prevalence and incidence provided valuable insights into the cancers with higher rates in CP patients, as it included most studies in the analysis. Additionally, some studies did not report person-years or provide sufficient data to calculate them, which may have resulted in an underestimation of the incidence of certain cancers.

In conclusion, this systematic review confirms that CP significantly increases the risk of developing EP cancers, with the greatest relative risk identified for liver and lung cancers compared to patients without CP. The underlying mechanisms are likely multifactorial, involving the combined effects of smoking and alcohol. Implementing smoking cessation and alcohol reduction strategies can not only alleviate the burden of CP but also potentially lower the risk of EP cancers in this population. Additionally, incorporating simple, non-invasive screening measures – such as an annual faecal immunochemical test for early colon cancer detection, annual chest X-rays or low-dose CT scans for early lung cancer detection and abdominal ultrasounds for hepatocellular carcinoma surveillance – could be valuable preventive strategies for this high-risk group.

CHAPTER 4: CHRONIC PANCREATITIS AND EXTRA PANCREATIC CANCERS

ABSTRACT

INTRODUCTION

CP is driven by smoking, excessive alcohol use, and chronic inflammation – all known contributors to carcinogenesis. However, its association with malignancies beyond the pancreas remains underexplored. This study aimed to assess the frequency and spectrum of cancers in patients with CP.

METHOD:

A retrospective cohort study was conducted at Nottingham University Hospitals of patients diagnosed with CP between 1 January 2006 and 31 December 2014, identified through a multisource case ascertainment strategy. Cancer frequencies were assessed in patients residing within Greater Nottingham. Age-adjusted standardised incidence ratios (SIRs) were calculated using national cancer incidence data from England as the reference population. Statistical analyses were performed using R (version 4.3.3).

RESULTS:

Of the 1,003 CP patients identified, 678 resided in Greater Nottingham (median age at diagnosis 68 years (IQR 53–79); 66% male; 92% Caucasians. The median follow-up period was 7.3 years (IQR 2.8–11.6). Compared to the general population, patients with CP demonstrated significantly higher SIRs for upper respiratory tract (12.4; 95%CI 6.6–21.1; $p < 0.0001$), pancreatic (10.8; 95%CI 6.2–17.6; $p < 0.0001$), liver (8.8; 95%CI 2.4–22.6; $p < 0.0001$), lung (5.6; 95%CI 4.0–7.7; $p < 0.0001$), renal tract (4.8; 95%CI 2.7–7.9; $p < 0.0001$) oesophageal (4.8; 95%CI 1.8–10.4; $p = 0.0001$) and colorectal (2.5; 95%CI 1.4–4.2; $p = 0.0009$) cancers.

CONCLUSION:

CP confers a markedly elevated risk of both pancreatic and extra-pancreatic cancers. These findings hypothesise that CP might be a high-risk state for malignancy that could warrant proactive, risk-based cancer surveillance in this vulnerable population.

INTRODUCTION

CP is a progressive and irreversible fibroinflammatory disease of the pancreas, characterised by persistent inflammation and fibrosis that lead to damage of the acinar, islet, and ductal cells [355, 448]. The global prevalence ranges from 53 to 163 per 100,000 individuals, with an annual incidence of 10 to 12.5 per 100,000 person-years [43, 357, 448, 449]. Alcohol and tobacco use are the predominant risk factors in both the development and progression of CP [68, 73], alongside a pro-inflammatory state driven by cytokine production [450, 451]. Importantly, CP is recognised as a precursor lesion to pancreatic cancer, with a reported cumulative risk of 4% over 15 to 20 years [195, 452].

In addition to pancreatic cancer [47, 195], several studies suggest that patients with CP may also be at increased risk of developing extra-pancreatic malignancies [211, 385, 414-416, 418, 422]. This broader cancer risk is thought to arise from shared aetiological factors particularly smoking, alcohol consumption, and chronic inflammation, which act individually and synergistically. The chronic inflammatory environment in CP contributes to a pro-oncogenic milieu, but the role of CP as an independent risk factor for EP cancers remains incompletely understood [453, 454].

Inflammatory mediators implicated in CP pathogenesis such as interleukin 6 (IL6), interleukin 8 (IL8), transforming growth factor β (TGF β), tumour necrosis factor α (TNF α), and nuclear factor κ B (NF κ B) are also known to promote tumour development and metastasis [390, 393, 395, 406, 455]. For instance, IL6, produced by pancreatic stellate cells and macrophages in alcoholic CP [456], has been linked to a range of malignancies including breast, lung, ovarian, and head and neck cancers [456-463]. Similarly, IL-8 promotes angiogenesis and metastasis [464], has been associated with colorectal, lung, and pancreatic cancers [464, 465].

Additional mechanisms such as oxidative stress, alcohol-mediated DNA damage, and tobacco-induced genetic mutations further support a plausible link between CP and cancer development [466-468]. These observations raise the possibility that CP may predispose individuals to a broader spectrum of cancers beyond the pancreas. This study aims to investigate the frequency of cancer in individuals with CP and assess whether CP is associated with an increased risk of developing extra-pancreatic malignancies.

METHODS

PATIENT SELECTION AND DATA COLLECTION

A retrospective study was conducted at Nottingham University Hospitals NHS Trust, covering the period from 1 January 2006 to 31 December 2014. Patients with CP were identified through multisource case ascertainment and confirmed using stringent diagnostic criteria based on computed tomography, magnetic resonance imaging, and endoscopic ultrasound findings, as described previously in Chapter 2. Ethical approval for the study was granted by the Health Research Authority and Health and Care Research Wales (reference: 22/WA/0074) and by the Confidentiality Advisory Group (22/CAG/0065).

STUDY COHORT

The study cohort comprised patients with CP identified through multisource case ascertainment who were resident within the Greater Nottingham area. This geographical boundary was selected to ensure accuracy and completeness of follow-up and outcome data, as Nottingham University Hospitals NHS Trust primarily serves this population.

For comparative purposes, cancer incidence in this cohort was compared with national cancer data from England in 2017, which represented the midpoint of the follow-up period.

ALCOHOL & SMOKING HISTORY

Alcohol use was defined as current or past consumption exceeding 14 units per week, in accordance with UK guidelines, for both men and women. A history of smoking was recorded if there was any current or past tobacco use, regardless of quantity or duration. These data were obtained from clinic letters and hospital admission notes within the Trust, accessed via electronic records.

CANCERS

All Cancers: Details of all cancers that were diagnosed after the CP diagnosis were collected. Cancer diagnoses were identified via the Cancer Centre at Nottingham University Hospitals NHS Trust. All cancers were coded using ICD-10 and SNOMED classification systems. For completeness, diagnoses

were cross verified using individual case notes and confirmed by histopathology and/or imaging reports, where available.

For cancers affecting fewer than five patients, the number was recorded as <5 to preserve anonymity and prevent potential identification.

Cancers of Interest: A subset of cancers was selected for calculating standardised incidence ratios (SIRs) and incidence rates. These comprised: (1) the ten most common cancers in males or females in the UK during 2017–2019, and (2) the ten cancers with the highest mortality in the UK during the same period. This resulted in a total of 14 cancer types, namely: upper respiratory tract cancers, pancreatic cancers, liver cancers, lung cancers, oesophageal cancers, renal tract cancers, colorectal cancers, breast cancers, Hodgkin lymphoma, malignant melanoma, multiple myeloma, non-Hodgkin lymphoma, prostate cancers, and stomach cancers.

High Frequency Cancers: The evaluation of associations between smoking, alcohol use, and sex with cancer outcomes was restricted to cancer types with ten or more recorded cases.

Additionally, a subgroup analysis was also conducted for cancers diagnosed at least 18 weeks after the diagnosis of CP. This time threshold was chosen in alignment with the NHS 18-week referral-to-treatment standard for non-urgent care, allowing for clearer temporal separation between the diagnoses of CP and cancer.

STATISTICAL ANALYSIS AND DATA PRESENTATION

Continuous variables are presented as median with interquartile range (IQR), and categorical variables as number and percentage, unless otherwise stated.

SIRs were calculated for each cancer type by comparing the number of observed cancer cases within the study cohort to the expected number based on cancer incidence in the general population of England in 2017, adjusted for age and sex. This was performed using the `sir_exp` function in R (version 4.3.3), with national cancer and population data obtained from NHS Digital. Cox regression analysis was used to assess the association between smoking, alcohol use, and sex with cancer outcomes among patients with CP. Cox regression was performed only for cancer types with a frequency of ten or more cases. Incidence rates were estimated using the `epi.conf` function from the EpiR package. A

p-value of <0.05 was considered statistically significant. All statistical analyses were conducted using R (version 4.3.3).

RESULTS

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

A total of 1,003 CP patients were identified through multisource case ascertainment. Of these, 678 resided within Greater Nottingham. The median follow-up period was 7.3 years (IQR 2.8–11.6). The cohort was predominantly male (n=450; 66.4%) and of Caucasian ethnicity (n=625; 92.2%). The median age at CP diagnosis was 68 years (IQR 53–79). A history of alcohol consumption and smoking was reported in 279 (41%) and 366 (54%) patients, respectively (Table 4.1).

Table 4.1: Demographic and clinical characteristics of patients with CP included in the analysis (Study Cohort)

Parameters	Study Cohort (n=678) median (IQR) or number (%)
Age at diagnosis (year)	68 (53–79)
Male sex	450 (66%)
Ethnicity	
Caucasian	625 (92%)
Black	14 (2.1%)
Asian	8 (1.2%)
Mixed	<5 (<0.7%)
Unknown	29 (4.3%)
Risk factors for chronic pancreatitis	
Smoking	366 (54.0%)
Alcohol	279 (41.2%)
Alcohol & smoking combined	194 (28.6%)
Hyperlipidaemia	19 (2.8%)
Idiopathic	5 (0.7%)
Hypercalcemia	<5 (<0.7%)
Recurrent acute pancreatitis	<5 (<0.7%)
Unknown	204 (30%)

CANCERS

A total of 151 cancers, diagnosed after CP diagnosis, were included in the analysis. The most frequent were the lung (n=37, 25%), pancreas (n=16, 11%), renal tract (n=15, 10%), colorectal (n=14, 9%), upper respiratory tract (n=13, 9%), haematological (n=11, 7%) prostate (n=9, 6%), oesophagus (n=6, 4%), and gallbladder and bile duct (n=5, 3%) cancers (Table 4.2).

Table 4.2: All cancers observed in the study cohort, with frequencies by sex, smoking and alcohol use

Cancer Types	Total Number (Males/Females)	Smoking alone	Alcohol alone	Smoking & Alcohol together
Lung	37 (24/13)	19	<5	14
Pancreas	16 (9/7)	<5	<5	<5
Renal tract†	15 (15/0)	7	<5	5
Colorectal	14 (9/5)	<5	<5	<5
Upper respiratory tract*	13	<5	<5	10
Prostate	9 (9/0)	<5	<5	<5
Oesophagus	6	<5	<5	<5
Gallbladder & bile duct	5 (<5, <5)	<5	<5	<5
Breast	<5 (<5, <5)	<5	<5	<5
Liver	<5 (<5, <5)	<5	<5	<5
Mesothelioma	<5 (<5, <5)	<5	<5	<5
Malignant melanoma	<5 (<5, <5)	<5	<5	<5
Non-Hodgkin lymphoma	<5 (<5, <5)	<5	<5	<5
Multiple myeloma	<5 (<5, <5)	<5	<5	<5
Myelodysplasia	<5 (<5, <5)	<5	<5	<5
Hodgkin lymphoma	<5 (<5, <5)	<5	<5	<5
Acute leukaemia	<5 (<5, <5)	<5	<5	<5
Chronic leukaemia	<5 (<5, <5)	<5	<5	<5
Ovary	<5 (<5, <5)	<5	<5	<5
Anal	<5 (<5, <5)	<5	<5	<5
Stomach	<5 (<5, <5)	<5	<5	<5
Ampulla	<5 (<5, <5)	<5	<5	<5
Endometrium	<5 (<5, <5)	<5	<5	<5
Small bowel	<5 (<5, <5)	<5	<5	<5
Other††	<5 (<5, <5)	<5	<5	<5
All	151 (107/44)	56	13	44

*Upper respiratory tract includes uvula, soft palate, tonsil, tongue, mandible, lip, nasal cavity, nostril, oral cavity, larynx, trachea

†Renal tract cancers include renal, renal pelvis, ureter and bladder cancers.

†† Other cancers include glial tumour, cancers of unknown primary, haemangioendothelioma, and sarcomas.

SITE-SPECIFIC CANCER FREQUENCIES

Patients with CP demonstrated significantly elevated SIR for upper respiratory tract (12.4; 95% CI: 6.6–21.1), pancreatic (10.8; 95% CI: 6.2–17.6), liver (8.8; 95% CI: 2.4–22.6), lung (5.6; 95% CI: 4.0–7.7), oesophageal (4.8; 95% CI: 1.8–10.4), renal tract (4.8; 95% CI: 2.7–7.9), and colorectal (2.5; 95% CI: 1.4–4.2) cancers (Table 4.3A). When restricting the analysis to cancers diagnosed more than 18 weeks after the diagnosis of CP, SIRs remained significantly elevated for upper respiratory tract (9.5; 95% CI: 4.6–17.5), renal tract (4.2; 95% CI: 2.2–7.1), pancreatic (4.1; 95% CI: 1.5–8.8), oesophageal (4.0; 95% CI: 1.3–9.4), and lung (3.3; 95% CI: 2.1–5.0) cancers (Table 4.3B).

Table 4.3A: Standardised Incidence Ratios (SIR) of cancers of interest diagnosed after chronic pancreatitis diagnosis in patients from Greater Nottingham compared to the general population of England

Cancer Types	Person years	SIR	95% CI	p value
Upper respiratory tract*	3723	12.4	6.6–21.1	<0.0001
Pancreas	3750	10.8	6.2–17.6	<0.0001
Liver	3766	8.8	2.4–22.6	<0.0001
Lung	3713	5.6	4.0–7.7	<0.0001
Oesophagus	3765	4.8	1.8–10.4	0.0001
Renal tract†	4090	4.8	2.7–7.9	<0.0001
Colorectal	3713	2.5	1.4–4.2	0.0009
Breast	3753	0.6	0.2–1.6	0.5
Hodgkin lymphoma	3756	7.2	0.2–39.9	0.3
Malignant melanoma	3759	1.6	0.3–4.6	0.7
Multiple myeloma	3762	2.5	0.3–9.0	0.4
Non-Hodgkin lymphoma	3758	1.6	0.3–4.6	0.7
Prostate	2466	1.0	0.5–1.9	0.9
Stomach	3768	1.2	0.03–6.4	0.7

Table 4.3B: Standardised Incidence Ratios (SIR) of cancers of interest diagnosed more than 18 weeks after chronic pancreatitis diagnosis in patients from Greater Nottingham compared to the general population of England

Cancer Types	Person years	SIR	95% CI	p value
Upper respiratory tract*	3719	9.5	4.6–17.5	<0.0001
Pancreas	3748	4.1	1.5–8.8	0.0009
Liver	3751	2.2	0.1–12.4	0.9
Lung	3725	3.3	2.1–5.0	<0.0001
Oesophagus	3749	4.0	1.3–9.4	0.004
Renal tract†	4078	4.2	2.2–7.1	<0.0001
Colorectal	3719	1.6	0.7–3.0	0.2
Breast	3736	0.6	0.2–1.6	0.5
Hodgkin Lymphoma	3749	7.2	0.2–40	0.3
Malignant melanoma	3742	1.6	0.3–4.6	0.7
Multiple myeloma	3749	1.3	0.03–7.0	0.7
Non-Hodgkin lymphoma	3741	1.6	0.3–4.6	0.7
Prostate	2456	1.0	0.5–1.9	0.9
Stomach	3751	1.2	0.03–6.5	0.7

*Upper respiratory tract includes uvula, soft palate, tonsil, tongue, mandible, lip, nasal cavity, nostril, oral cavity, larynx, trachea

†Renal tract cancers include renal, renal pelvis, ureter and bladder cancers.

The cancers with the highest incidence rates (per 100,000 person-years) were lung (9832; 95%CI 586–1146), pancreatic (357; 95%CI 204–579), renal tract (336; 95%CI: 188–554), colorectal (315; 95%CI 172–528), prostate (298; 95%CI 136–566), and upper respiratory tract cancer (292; 95%CI 155–499) (Table

4.4A). Among cancers diagnosed more than 18 weeks after the diagnosis of CP, the highest incidence rates were observed for lung (493; 95%CI 309–747), renal tract (292; 95%CI 156–500), upper respiratory tract (224; 95%CI 108–412), and colorectal (202; 95%CI 92–384) (Table 4.4B).

Table 4.4A: Incidence rates of cancers of interest diagnosed after chronic pancreatitis diagnosis in patients from Greater Nottingham

Cancer Types	Incidence Rate (per 100,000 person years)	95% CI
Lung	832	586–1,146
Pancreas	357	204–579
Renal tract†	336	188–554
Colorectal	315	172–528
Upper Respiratory Tract*	292	155–499
Prostate	298	136–566
Oesophagus	133	49–290
Breast	89	24–228
Liver	89	24–228
Malignant Melanoma	67	14–195
Non-Hodgkin Lymphoma	67	14–195
Multiple Myeloma	44	5–161
Hodgkin Lymphoma	22	1–124
Stomach	22	1–124

Table 4.4B: Incidence rates of cancers of interest diagnosed more than 18 weeks after chronic pancreatitis diagnosis in patients from Greater Nottingham

Cancer Types	Incidence Rate (per 100,000 person years)	95% CI
Lung	493	309–747
Renal tract†	292	156–500
Upper Respiratory Tract*	224	108–412
Colorectal	202	92–384
Prostate	299	137–568
Pancreas	134	49–291
Oesophagus	112	36–260
Breast	89	24–229
Malignant Melanoma	67	14–196
Non-Hodgkin Lymphoma	67	14–196
Hodgkin Lymphoma	22	1–124
Liver	22	1–124
Multiple Myeloma	22	1–124
Stomach	22	1–124

*Upper respiratory tract includes uvula, soft palate, tonsil, tongue, mandible, lip, nasal cavity, nostril, oral cavity, larynx, trachea

†Renal tract cancers include renal, renal pelvis, ureter and bladder cancers.

RISK FACTORS FOR CANCERS

Cox regression analysis among patients with CP showed that smoking was associated with a seven-fold increased risk of developing lung cancer. None of the other factors assessed, including alcohol consumption and sex, were associated with a statistically significant risk (Table 4.5A).

Among cancers diagnosed more than 18 weeks after the diagnosis of CP, smoking remained associated with a seven-fold increased risk of lung cancer. Male sex was associated with a 90% increased risk; however, this did not reach statistical significance (Table 4.5B).

TIME TO CANCER DEVELOPMENT

Patients with CP developed lung cancer after a median interval of 3.9 years (IQR 3.0–6.0) from CP diagnosis, at a median age of 76 years (IQR 65–78). The most common aetiological factor was smoking, present in 86% of cases, followed by alcohol in 59%, with both smoking and alcohol reported in 50% of cases.

Renal tract cancer developed after a median of 4.5 years (IQR 1.3–7.2) from CP diagnosis, at a median age of 70 years (IQR 58–81). Smoking was the predominant aetiology, identified in 77% of cases. Alcohol was implicated in 38%, with both smoking and alcohol contributing to 38%. A potential risk factor could not be identified in 23% of cases.

Similarly, upper respiratory tract cancers occurred after a median of 8.4 years (IQR 2.9–13.1) following CP diagnosis, at a median age of 60 years (IQR 53–73). Alcohol was the most common risk factor, present in 100% of cases. Smoking was implicated in 70%, and both alcohol and smoking were involved in 70% of cases (Table 4.6).

Table 4.5A: Cox regression analysis of sex, smoking and alcohol association with common cancers diagnosed after chronic pancreatitis diagnosis (only for cancer types with a frequency of ten or more cases)

Cancer	Male Sex HR (95%CI)	p value	Smoking HR (95%CI)	p value	Alcohol HR (95%CI)	p value
Lung	0.8 (0.3–2.4)	0.7	6.7 (2.4–18.9)	0.0003	0.5 (0.1–1.6)	0.2
Renal Tract†	Na	na	3.1 (0.9–11.0)	0.08	0.5 (0.2–1.4)	0.2
Upper Respiratory Tract*	1.5 (0.4–5.3)	0.6	2.6 (0.7–9.6)	0.1	na	na
Colorectal	0.9 (0.5–1.8)	0.8	0.5 (0.2–1.5)	0.2	0.8 (0.4–1.5)	0.4
Pancreas	0.6 (0.2–1.7)	0.4	0.6 (0.2–1.7)	0.4	0.4 (0.1–1.3)	0.2

Table 4.5B: Cox regression analysis of sex, smoking and alcohol association with common cancers diagnosed more than 18 weeks after chronic pancreatitis diagnosis (only for cancer types with a frequency of ten or more cases)

Cancer	Male Sex HR (95%CI)	p value	Smoking HR (95%CI)	p value	Alcohol HR (95%CI)	p value
Lung	0.7 (0.3–1.7)	0.4	6.6 (1.5–28.3)	0.01	1.6 (0.6–4.0)	0.4
Renal Tract†	Na	na	2.6 (0.7–9.3)	0.2	0.6 (0.2–1.8)	0.3
Upper Respiratory Tract*	1.7 (0.4–7.9)	0.5	1.8 (0.5–7.0)	0.4	na	na

*Upper respiratory tract includes uvula, soft palate, tonsil, tongue, mandible, lip, nasal cavity, nostril, oral cavity, larynx, trachea. Alcohol was a risk factor in all patients who developed upper respiratory tract cancer; therefore, a hazard ratio could not be calculated

†Renal tract cancers include renal, renal pelvis, ureter and bladder cancers. Renal tract cancers occurred exclusively in male patients; therefore, a hazard ratio could not be calculated.

Table 4.6: Cancers of interest diagnosed more than 18 weeks after chronic pancreatitis diagnosis, with corresponding time to cancer development

Cancer Types	Number of Cases (n=576)	Age at CP Diagnosis Median (IQR)	Age at Cancer Diagnosis Median (IQR)	Time to Cancer Development in Years Median (IQR)
Lung	22	71 (56–77)	76 (65–78)	3.9(3.0–6.6)
Renal tract†	13	68 (53–78)	70 (58–81)	4.5 (1.3–7.2)
Upper Respiratory tract*	10	50 (46–63)	60 (53–73)	8.4 (2.9–13.1)
Colorectal	9	68 (49–78)	74(62–85)	6.0(0.5–9.8)
Prostate	9	76 (65–81)	78 (67–87)	2.3 (1.7–4.8)
Pancreas	6	60 (50–73)	62 (61–74)	1.5 (1.0–3.6)
Oesophagus	5	65 (61–79)	72 (67–85)	6.3(4.2–7.5)
Breast	<5	62 (58–73)	67 (65–78)	5.5(3.4–8.5)
Malignant Melanoma	<5	80 (47–86)	86 (59–94)	8.2 (5.7–12.0)
Non-Hodgkin lymphoma	<5	65 (62–73)	67 (65–80)	3.0 (1.9–7.1)

*Upper respiratory tract includes uvula, soft palate, tonsil, tongue, mandible, lip, nasal cavity, nostril, oral cavity, larynx, trachea

†Renal tract cancers include renal, renal pelvis, ureter and bladder cancers.

DISCUSSION

This study comprehensively characterises the spectrum and risk of multiple cancers in a well-defined cohort of patients with CP, demonstrating significantly elevated risks of site-specific cancers compared to the general population. Unlike prior studies that have predominantly focused on pancreatic cancer alone, this analysis highlights the broad range of malignancies associated with CP and quantifies their relative incidence and standardized incidence ratios within a predominantly Caucasian Western population. By integrating detailed aetiological data on smoking and alcohol exposure, this study elucidates important modifiable risk factors driving cancer risk in CP, providing novel insights with potential clinical implications for cancer surveillance and prevention strategies in this vulnerable group.

Compared to the general population in England, patients with CP exhibited significantly higher risks of developing upper respiratory tract, pancreatic, liver, lung, oesophageal, renal tract, and colorectal cancers. Incidence rates within the CP cohort broadly reflected these associations. These findings corroborate the recent systematic review and meta-analysis on the extra-pancreatic cancer incidence in CP patients [469].

All patients who developed upper respiratory tract cancers consumed alcohol. Smoking was associated with a seven-fold increase in the risk of lung cancer. Smoking alone was the most common aetiological factor among CP patients who developed cancer, followed by combined smoking and alcohol use. The association between CP and upper respiratory tract and oesophageal cancers is likely mediated by alcohol, a recognised risk factor for both CP and cancers of the upper aerodigestive tract [470]. Alcohol's carcinogenic effects include suppression of salivary defence mechanisms, increased generation of acetaldehyde, induction of cytochrome P450 2E1, and promotion of mucosal damage leading to metaplastic change [471-473]. Genetic susceptibility may further modulate this risk, with polymorphisms such as the ADH1C1 allele, common in East Asian and Caucasian populations [474, 475], linked to both CP and oropharyngeal/laryngeal cancers [476-479]. These findings are consistent with reports from other populations, including Korean and Danish cohorts [414, 417]. Tobacco exposure may further amplify this risk through additional mechanisms, such as alteration of oral microbiota and promotion of local acetaldehyde accumulation [480].

The observed increase in pancreatic cancer risk among patients with CP reinforces existing evidence [47, 383, 414]. The chronic inflammatory milieu in CP drives acinar-to-ductal metaplasia and promotes oncogenic mutations, particularly in the KRAS gene [481]. A pro-tumourigenic

microenvironment is established through sustained activation of pancreatic stellate cells and secretion of inflammatory cytokines, including IL1, IL6, IL8, TNF α , and TGF β [482-484]. Similarly, genetic factors are also associated with the development of CP and eventually PC [485]. Inherited risk also plays a role; PRSS1 mutations, for example, are associated with premature trypsin activation and a markedly elevated cumulative risk of pancreatic cancer [486]. SPINK1 mutations have also been implicated, though results are variable [487-489]. Other emerging genetic links, including polymorphisms in GGT1, merit further study [490, 491].

The increased risk of liver cancer observed in this cohort may reflect shared aetiologies between CP and chronic liver injury, including alcohol and tobacco use, both of which contribute to oxidative stress and inflammation [433, 492, 493]. These exposures promote hepatic injury through the generation of acetaldehyde and reactive oxygen species, and through the upregulation of interleukin-6, a cytokine also elevated in CP [456, 493-498]. The contribution of advanced fibrosis, associated with CP and smoking, to hepatocarcinogenesis is also a plausible pathway [492, 499, 500]. These observations are supported by earlier studies reporting elevated liver cancer incidence among CP patients [418].

Lung cancer was the most frequently diagnosed malignancy in the CP cohort, which is consistent with previous literature [385, 414, 416, 420, 425]. The high prevalence of smoking in this subgroup likely explains much of the increased risk, as smoking is a well-established driver of lung carcinogenesis through the formation of DNA adducts and promotion of oncogenic mutations such as KRAS and TP53 [501-503]. Chronic inflammation associated with CP may contribute further, with cytokines such as IL6 and IL8 playing a role in tumour development and progression [504-506].

Renal tract cancers occurred more frequently in men and were significantly associated with CP. Although smoking was the predominant aetiological factor in this group, the associated increase in cancer risk did not reach statistical significance. Tobacco-derived nitrosamines, particularly NNK, are known to induce DNA damage linked to renal malignancy [507, 508]. In contrast, alcohol consumption has been inversely associated with renal cancer risk [509], and interestingly, none of the affected patients in this study had alcohol as the sole CP aetiology. Dysregulation of the mTOR signalling pathway, which plays a role in both renal carcinogenesis [510-512] and the activation of pancreatic stellate cells in CP [513], may represent a shared biological mechanism.

Colorectal cancer risk was also increased in the CP cohort, which aligns with previous data [415]. This association may be attributable to overlapping lifestyle risk factors, including smoking, alcohol use, and obesity [514, 515]. IL8, overexpressed in CP and known to promote tumour proliferation and metastasis in colorectal cancer [516, 517], is a plausible mechanistic link.

This study has important limitations. It was retrospective and conducted at a single centre, introducing the potential for selection bias. However, cancer diagnoses were rigorously validated through detailed chart reviews and cross-referencing with national cancer registry data, enhancing the reliability of the findings. Although comparisons with the general population were standardised for age and sex, other differences could not be accounted for. For example, the predominantly Caucasian study population may limit the generalisability of the results to more ethnically diverse populations. Patients diagnosed with CP may also have undergone more frequent imaging than the general population, increasing the likelihood of incidental cancer detection. This is particularly relevant for cancers with relatively good survival, such as prostate cancer. However, the cancers most strongly associated with CP typically have poor survival if left untreated, making it unlikely that many such cases would remain undiagnosed in the comparator population. Additionally, patients being investigated for suspected cancer symptoms are more likely to undergo abdominal imaging, which may incidentally lead to a diagnosis of CP. To assess the potential impact of this, sensitivity analyses excluding cases in which cancer was diagnosed within 18 weeks of CP diagnosis were performed; the associations persisted, with only slight attenuation.

In conclusion, this study provides compelling evidence that CP is associated with a substantially increased risk of developing several malignancies, including lung, renal tract, upper respiratory tract, pancreas, oesophageal and colorectal cancer. These findings highlight the important role of shared risk factors, particularly tobacco and alcohol use, but also raise the possibility that CP itself may represent a high risk state for cancer development. While larger population based studies adjusted for shared risk factors are needed to confirm these associations, there may be a case for considering targeted cancer surveillance in this vulnerable population.

CHAPTER 5: NON-CANCER COMORBIDITIES AND MORTALITY IN CHRONIC PANCREATITIS

ABSTRACT

BACKGROUND

CP is a progressive fibroinflammatory disease associated with increased comorbidity and mortality. This study aimed to characterise the natural history of CP by assessing comorbidity prevalence and mortality in a CP cohort.

METHOD

A retrospective study was performed at Nottingham University Hospitals NHS Trust, including patients diagnosed with CP between 1 January 2006 and 31 December 2014. Comorbidity prevalence was compared with national data from England in 2022 to calculate standardised prevalence ratios (SPRs). Similarly, standardised mortality ratios (SMRs) were also evaluated.

RESULTS

Of the 1,003 patients with CP, 678 who resided within the Greater Nottingham area were included in the study cohort. The overall median follow-up was 5.7 years (IQR 1.2–10.6). Compared with the general population, CP patients had significantly elevated SPRs for heart failure (3.0; 95%CI 2.3–3.8), ischaemic heart disease (2.4; 95%CI 2.0–2.8), atrial fibrillation (1.9; 95%CI 1.5–2.3) and cerebrovascular disease (1.4; 95%CI 1.0–1.8). The cumulative incidence at 20 years of diabetes mellitus, chronic liver disease and chronic kidney disease were 12%, 11% and 11%, respectively. Cardiovascular SPRs remained significantly raised at the end of follow-up. During follow-up, 495 patients (73%) died, with median survival of 5.7 years (95%CI 4.8–6.4). The overall SMR of CP patients was significantly increased (2.3; 95%CI 2.1–2.6; $p < 0.0001$) compared with the general population. Leading causes of death were malignancy (27%), infections (22%) and cardiovascular disease (6.9%).

CONCLUSION

CP is associated with increased risk of multiple comorbidities and elevated mortality. Enhanced surveillance and early intervention strategies may help prevent or delay the onset of these associated conditions.

INTRODUCTION

The global burden of CP is increasing, with a reported 20% rise in prevalence and an associated 80% increase in mortality over the past two to three decades [43, 518, 519]. CP is a progressive fibroinflammatory disease that impairs both the endocrine and exocrine functions of the pancreas [35]. Due to endocrine involvement, between 45% and 90% of patients with CP develop diabetes mellitus (DM) approximately 20 to 50 years after diagnosis, and CP is recognised as an established risk factor for DM [169, 170, 520].

CP has also been linked to an increased risk of osteopathy, with 25% to 66% of patients developing osteoporosis or osteopenia. This is thought to result from malabsorption, chronic inflammation, and potentially other yet unidentified mechanisms [182, 356]. However, the frequency of other comorbidities in patients with CP remains unclear. This represents an important gap in the field of Pancreatology and warrants further investigation to establish whether CP is an independent risk factor for a broader range of systemic conditions [189, 357].

In addition, although CP is associated with increased mortality, existing studies are limited by small sample sizes, outdated cohorts, inconsistent definitions of CP, and a restricted number of study centres that do not reflect the global or national burden of the disease [414, 521-523]. Further research is therefore required to examine mortality patterns in patients with CP, particularly to explore whether such patients may benefit from targeted screening for associated conditions [522-524]. Similarly, studies exploring the natural history of CP are limited and often date back more than two decades, with smaller cohorts that may not represent current clinical patterns [69, 525, 526].

The aim of this study is to evaluate the natural history of CP by investigating associated non-cancer comorbidities and mortality in a contemporary cohort of patients with CP.

METHODS

PATIENT SELECTION AND DATA COLLECTION

A retrospective analysis was conducted at Nottingham University Hospitals NHS Trust, a high-volume tertiary centre, to identify adult patients diagnosed with CP between 1 January 2006 and 31 December 2014. Case ascertainment was performed using multiple data sources, and CP diagnoses were confirmed according to established CT, MRI, and EUS criteria, as described previously in Chapter 2. Data were extracted in May 2023 from electronic health records, including clinic letters, hospital admission records for all patients, and GP health records where available. Manual chart review was also performed to ensure accuracy, with the end of follow-up defined at the time of extraction. The study was approved by the Health Research Authority (HRA) and Health and Care Research Wales (22/WA/0074), as well as by the Confidentiality Advisory Group (22/CAG/0065).

STUDY COHORT

The cohort included individuals diagnosed with CP who were identified using multiple data sources and were residents of the Greater Nottingham area. This geographical region was chosen to maximise the accuracy and completeness of follow-up and outcome data, as it falls predominantly within the catchment area of Nottingham University Hospitals NHS Trust (NUH).

COMORBIDITIES OF INTEREST AND NATURAL HISTORY

Non-cancer comorbidities were selected based on the twenty most prevalent conditions nationally, according to data from the Office for National Statistics (England) covering the period from March 2017 to March 2020. These included ischaemic heart disease (IHD), heart failure, cerebrovascular disease, atrial fibrillation, hypertension, chronic liver disease (CLD), diabetes mellitus (DM), osteoporosis/osteopenia, chronic kidney disease (CKD) and dementia (including Alzheimer's disease) [527]. All comorbidities were identified through ICD-10 coding and confirmed via electronic records. Surgical interventions related to complications of CP were also recorded as part of the disease burden. For conditions with fewer than five cases, values were recorded as "<5" to preserve anonymity.

The prevalence of these comorbidities at the time of CP diagnosis was evaluated using standardised prevalence ratios (SPRs). Cumulative incidence of comorbidities developing after the diagnosis of CP, along with SPRs at the end of follow-up, was then assessed to characterise the natural history of comorbidity development in this patient cohort.

ALCOHOL & SMOKING HISTORY

Alcohol exposure was defined as current or previous consumption >14 units/week. Any history of tobacco use was documented, with smoking burden recorded in pack-years. These data were obtained from clinic letters and hospital admission notes within the Trust, accessed via electronic records.

MORTALITY

Causes of death were obtained from electronic health records at NUH, based on the diagnoses listed on the death certificate. A subgroup analysis was conducted excluding patients who died within 18 weeks of their CP diagnosis, in order to explore potential causality by removing co morbidities that were diagnosed as part of the same tests performed to diagnose CP.

OUTCOMES

The primary outcomes were to evaluate the natural history of comorbidity development and to assess mortality in patients with CP. This included evaluating the prevalence and incidence of comorbidities (including surgical interventions related to CP), overall mortality, and causes of death. These outcomes were selected to provide a comprehensive understanding of the long-term clinical course, disease burden, and survival outcomes associated with CP.

STATISTICAL ANALYSIS AND DATA PRESENTATION

Continuous variables are presented as median (interquartile range), and categorical variables as number (percentage), unless otherwise stated. Prevalence of each comorbidity in the study cohort was compared with age-stratified national data for England, sourced from the 2022 Health Surveys for hypertension and CKD, the 2023–2024 National Diabetes Audit, and the 2022–2023 disease-specific registers for IHD, stroke/TIA, heart failure, and atrial fibrillation. Prevalence of CLD was obtained from the Global Burden of Disease data (2022).

Standardised prevalence ratios (SPRs), adjusted for age and sex where possible, were calculated using the *epiR* package [528]. Cumulative incidence was estimated using *cmprsk* and was adjusted for competing risk of death [529].

Kaplan–Meier curves and median survival were generated using the survival package. The age-adjusted standardised mortality ratio (SMR) was calculated using popEpi [530] comparing observed deaths in the CP cohort to the general population of England in 2022. A p-value <0.05 was considered statistically significant. All analyses were conducted using R (version 4.3.3).

RESULTS

CLINICAL CHARACTERISTICS

A total of 1,003 patients with CP were identified, of whom 678 resided within the Greater Nottingham area and were included in the study cohort. The median age at diagnosis was 68 years (IQR 53–79). The majority of patients were male (n = 450; 66.4%) and of European ancestry (n = 625; 92.2%) (Table 1). The median follow-up was 5.7 years (IQR 1.2–10.6).

The most frequently observed comorbidities at the time of diagnosis of CP were hypertension (n=240; 35.4%), DM (n=204; 30.1%), IHD (n=146; 21.5%), depression (n=85, 12.5%), CKD (n=80; 11.8%), atrial fibrillation (n=79; 11.7%), CLD (n=76; 11.2%), heart failure (n=63, 9.3%), cerebrovascular disease (n=53; 7.8%) and osteoporosis/osteopenia (n=50; 7.4%) (Table 5.1).

Table 5.1: Demographic and Clinical Characteristics of the Study Cohort (n=678)

Parameters	Median (IQR) or Number (%)
Age at diagnosis (years)	68 (53–79)
Male sex	450 (66.4%)
Ethnic Origin	
European	625 (92.2%)
African	14 (2.1%)
Asian	8 (1.2%)
Mixed	<5 (<1%)
Unknown	29 (4.3%)
Comorbidities at diagnosis	
Hypertension	240 (35.4%)
DM	204 (30.1%)
IHD	146 (21.5%)
CKD	80 (11.8%)
Atrial Fibrillation	79 (11.7%)
CLD	76 (11.2%)
Heart Failure	63 (9.3%)
Cerebrovascular disease	53 (7.8%)
Osteoporosis/ osteopenia	50 (7.4%)
Dementia	44 (6.5%)

Abbreviations: CLD chronic liver disease; CKD chronic kidney disease; DM diabetes mellitus; IHD ischaemic heart disease

NATURAL HISTORY OF COMORBIDITIES

Compared with national data for England, patients with CP had significantly increased SPRs for heart failure [3.0 (95%CI 2.3–3.8); $p<0.0001$], for IHD [2.4 (95%CI 2.0–2.8); $p<0.0001$], for atrial fibrillation

[1.9 (95%CI 1.5–2.3); $p < 0.0001$] and for cerebrovascular disease [1.4 (95%CI 1.0–1.8); $p = 0.02$], but not for DM [1.0 (95%CI 0.8–1.1); $p = 0.7$] at the time of CP diagnosis (Table 5.2).

Table 5.2: Age-adjusted Standardized Prevalence Ratios (SPRs) of comorbidities at CP diagnosis and at end of follow-up

Comorbidities	SPRs at CP diagnosis (95%CI)	p value	SPRs at end of follow-up (95%CI)	p value
Heart Failure	3.0 (2.3–3.8)	<0.0001	3.8 (3.0–4.7)	<0.0001
IHD	2.4 (2.0–2.8)	<0.0001	2.6 (2.2–3.0)	<0.0001
Atrial Fibrillation	1.9 (1.5–2.3)	<0.0001	2.6 (2.2–3.2)	<0.0001
Cerebrovascular Disease	1.4 (1.0–1.8)	0.02	2.5 (2.0–3.0)	<0.0001
DM	1.0 (0.8–1.1)	0.7	1.3 (1.1–1.4)	0.0001
CKD	0.7 (0.5–0.8)	<0.0001	1.1 (1.0–1.4)	0.1
CLD	0.7 (0.6–0.9)	0.004	1.4 (1.2–1.7)	<0.0001
Hypertension	0.7 (0.6–0.8)	<0.0001	0.9 (0.8–1.0)	0.009

SPRs were not calculated for dementia or osteoporosis/osteopenia due to the absence of national prevalence data

The cumulative incidence of comorbidities developing 10 and 20 years after CP diagnosis was as follows: DM 8.3% and 12%, CLD 8.9% and 11%, CKD 7.2% and 11%, osteoporosis/osteopenia 6% and 8.8%, cerebrovascular disease 5.3% and 6.9%, hypertension 4.2% and 6.7%, atrial fibrillation 3.6% and 5.5%, dementia 2.1% and 3.8%, heart failure 1.7% and 2.5%, and IHD 1.5% and 2.2% (Table 5.3; Figures 5.1).

Table 5.3: Cumulative incidence of comorbidities after CP diagnosis

Comorbidities	Years since CP diagnosis			
	5	10	15	20
DM	6.1% (4.4–8.0)	8.3% (6.4–11.0)	10% (8.1–13.0)	12% (9.2–16.0)
CLD	6.1% (4.4–8.0)	8.9% (6.9–11.0)	9.9% (7.7–12.0)	11.0% (8.1–15.0)
CKD	4.6% (3.2–6.3)	7.2% (5.4–9.3)	8.6% (6.5–11.0)	11.0% (7.8–14.0)
Osteoporosis/Osteopenia	3.7% (2.5–5.3)	6.0% (4.3–7.9)	8.3% (6.2–11.0)	8.8% (6.5–12.0)
Cerebrovascular Disease	3.0% (1.9–4.4)	5.3% (3.8–7.2)	6.9% (4.9–9.2)	6.9% (4.9–9.2)
Hypertension	1.9% (1.1–3.2)	4.2% (2.8–5.9)	5.7% (4.0–7.9)	6.7% (4.3–9.7)
Atrial fibrillation	1.5% (0.8–2.6)	3.6% (2.4–5.2)	5.0% (3.5–7.0)	5.5% (3.7–7.7)
Dementia	1.0% (0.5–2.0)	2.1% (1.2–3.4)	2.5% (1.5–4.0)	3.8% (1.6–7.5)
Heart Failure	0.7% (0.3–1.6)	1.7% (0.9–2.9)	2.5% (1.4–4.2)	2.5% (1.4–4.2)
IHD	0.7% (0.3–1.7)	1.5% (0.8–2.6)	2.2% (1.1–3.8)	2.2% (1.1–3.8)

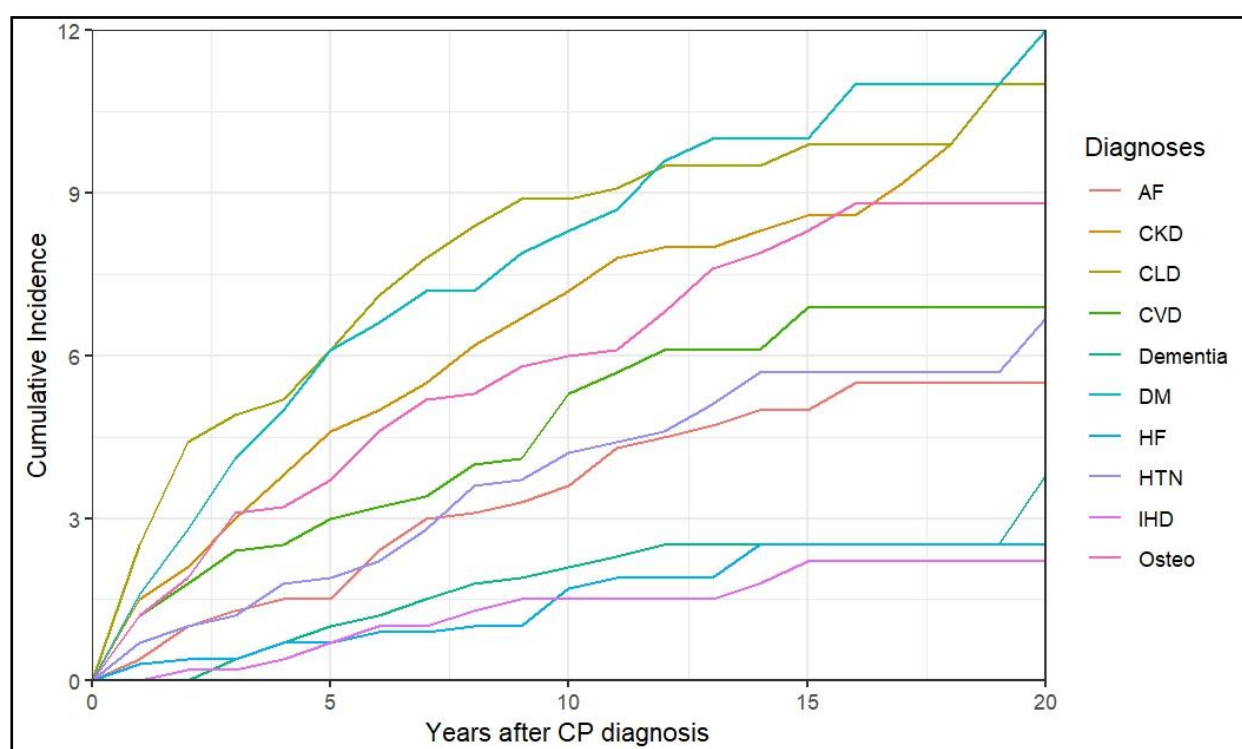


Figure 5.1. Cumulative incidence of comorbidities at 5, 10, 15, and 20 years following a diagnosis of chronic pancreatitis

At the end of follow-up, patients with CP had significantly increased SPRs for heart failure [3.8 (95%CI 3.0–4.7); $p < 0.0001$], for IHD [2.6 (95%CI 2.2–3.0); $p < 0.0001$], for atrial fibrillation [2.6 (95%CI 2.2–3.2); $p < 0.0001$] and for cerebrovascular disease [2.5 (95%CI 2.0–3.0); $p < 0.0001$], for CLD [1.4 (95%CI 1.2–1.7); $p < 0.0001$] at the end of follow-up, compared with national data for England (Table 5.2).

PANCREATIC SURGERY

A total of 40 patients (5.9%) underwent pancreatic surgery for complications related to CP, with a median time to surgery of 2.9 years (IQR 1.1–4.9) from diagnosis. The incidence rate of surgery for CP-related complications was 10 per 1,000 person-years. The most common indication was intractable abdominal pain ($n=17$; 42.5%). The most frequently performed surgical procedure was distal pancreatectomy with splenectomy ($n=17$; 42.5%) (Tables 5.4).

Table 5.4: Indications for and Types of Pancreatic Surgery in CP Patients

Indications for pancreatic surgery	Total (n=40) Number (%)
Intractable abdominal pain	25 (62.5%)
Strictures (bile duct, duodenal stricture, pancreatic duct)	7 (17.5%)
Malignancy or suspicion of malignancy	<5
Abscess	<5
Unknown	<5

Types of pancreatic Surgery	Total (n=40) Number (%)
Distal Pancreatectomy & splenectomy	17 (42.5%)
Roux en y lateral pancreaticojejunostomy	10 (25.0%)
Roux en y hepaticojejunostomy	5 (12.5%)
Frey Procedure	<5
Roux-en-Y enteroenterostomy with bypass gastrojejunostomy	<5
Pancreatectomy	<5

NOTE: For indications and types of surgery involving fewer than five patients, the number was recorded as <5 to preserve anonymity and prevent potential identification patients

MORTALITY

Following a diagnosis of CP, 495 patients (73%) died during follow-up (Figure 5.2). Median survival from diagnosis was 5.7 years (95%CI 4.8–6.4). The leading causes of death were malignancy (n=134, 27.1%), infections (n=110, 22.2%), and cardiovascular disease (n=34, 6.9%) (Table 5.5). The overall SMR for patients with CP was 2.3 (95% CI 2.1–2.6; $p < 0.0001$) over 4,588 person-years of follow-up, compared with the general population of England. The SMR was highest among those diagnosed at a younger age, declining gradually with increasing age at CP diagnosis (Tables 5.6A).

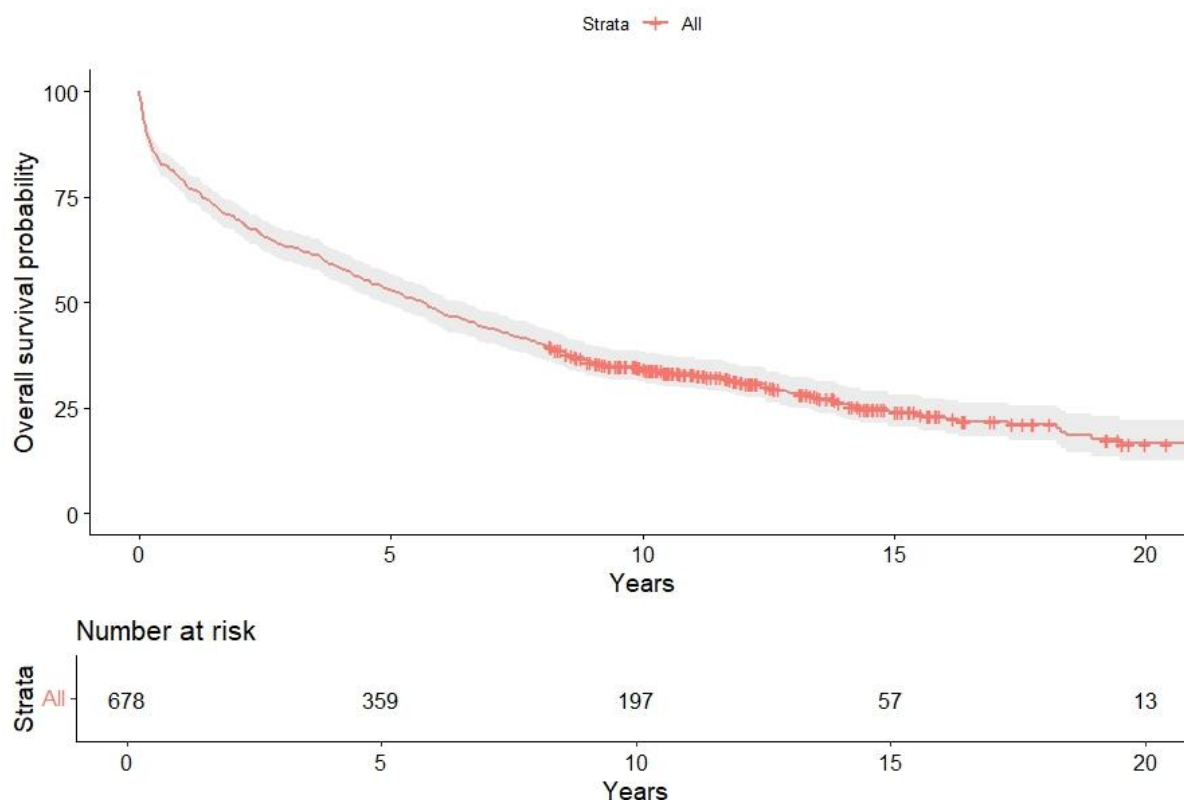


Figure 5.2. Kaplan–Meier curve showing overall survival probabilities in patients with chronic pancreatitis

In a subgroup analysis excluding patients who died within 18 weeks of CP diagnosis, 575 patients were included. During follow-up, 391 (68%) died. Median survival in this subgroup was 7.3 years (95%CI 6.5–8.3). The leading causes of death were malignancy (n=100; 26%) and infection (n=89; 23%), consistent with the overall cohort. The overall SMR was 1.9 (95%CI 1.7–2.1; $p < 0.0001$) over 4,490 person-years of follow-up, compared with the general population of England. As in the overall cohort, the SMR was highest in those diagnosed at a younger age, with a progressive decline in SMR observed with increasing age at diagnosis (Table 5.6B).

TABLE 5.5: Primary Causes of Death in CP Patients

Causes of Death	Number (%)
Malignancy	134 (27.1%)
Lung	32
Pancreas	18
Oesophagus	13
Colorectal	13
Renal Tract	10
Infection	110 (22.2%)
Pneumonia	80
Urosepsis	15
Covid Pneumonitis	6
Cholangitis/ Biliary sepsis	5
Cardiovascular Disease	34 (6.9%)
Congestive Cardiac Failure	15
Ischemic Heart Disease	12
Liver Disease - End Stage Liver disease	24 (4.9%)
Acute Abdomen	28 (5.7%)
Ischemic Colitis	9
Perforation	8
Respiratory	13 (2.6%)
COPD exacerbation	9
Others	151 (30.5%)
Unknown	110
Frailty	6

Table 5.6A: Standardised Mortality Ratio (SMR) in the CP cohort compared with the population of England in 2022, by age category

Age Category	Person Years	SMR (95% CI)	p value
30-34	10.1	817.0 (265.3 – 1906.5)	<0.0001
35-39	56.0	178.8 (81.8- 339.4)	<0.0001
40-44	203.5	38.6 (19.2- 69.0)	<0.0001
45-49	299.3	23.5 (13.2-38.8)	<0.0001
50-54	301.8	19.2 (11.5-29.9)	<0.0001
55-59	415.2	12.2 (7.9-18.1)	<0.0001
60-64	509.3	10.2 (7.3-14.0)	<0.0001
65-69	367.8	10.2 (7.5-13.7)	<0.0001
70-74	489.8	6.6 (5.1-8.5)	<0.0001
75-79	568.8	3.3 (2.5-4.2)	<0.0001
80-84	474.3	2.8 (2.2-3.5)	<0.0001
85-89	507.0	1.6 (1.3-2.0)	<0.0001
90-99	384.9	0.5 (0.4-0.7)	<0.0001
Overall	4588	2.3 (2.1- 2.6)	<0.0001

Table 5.6B: Standardised Mortality Ratio (SMR) in the CP cohort (excluding deaths within 18 weeks) compared with the population of England in 2022, by age category

Age Category	Person Years	SMR (95% CI)	p value
30-34	9.98	661.4 (180.2 – 1693.4)	<0.0001
35-39	55.62	140.0 (56.3 – 288.5)	<0.0001
40-44	119.12	65.9 (32.9 – 117.8)	<0.0001
45-49	299.10	20.4 (10.9 – 34.9)	<0.0001
50-54	301.49	16.1 (9.2 – 26.2)	<0.0001
55-59	414.20	8.8 (5.2 – 14.0)	<0.0001
60-64	507.94	8.1 (5.5 – 11.5)	<0.0001
65-69	367.01	8.0 (5.6 – 11.1)	<0.0001
70-74	488.26	5.3 (4.0 – 7.1)	<0.0001
75-79	567.35	2.6 (1.9 – 3.5)	<0.0001
80-84	472.46	2.2 (1.7 – 2.8)	<0.0001
85-89	503.65	1.2 (0.9 – 1.5)	0.3
90-99	384.29	0.5 (0.3 – 0.6)	<0.0001
Overall	4490.0	1.9 (1.7 – 2.1)	<0.0001

DISCUSSION

This study provides a comprehensive evaluation of the natural history of CP, focusing on the burden of non-cancer comorbidities and mortality within a large, contemporary cohort. Patients with CP exhibited significantly higher standardized prevalence ratios of cardiovascular comorbidities, including IHD, heart failure, atrial fibrillation, and cerebrovascular disease, as well as CLD, CKD and DM, when compared to the general population of England adjusted for age. Importantly, CP was also associated with a two-fold increased risk of death, largely driven by cancer and infections.

The association between CP and cardiovascular disease is biologically plausible and likely mediated by systemic inflammation. CP induces a pro-inflammatory state, characterised by elevated levels of cytokines such as tumour necrosis factor- α , interleukin-6, and interleukin-8, along with endothelial adhesion molecules like P-selectin and ICAM-1 [531-533]. These factors contribute to the formation and destabilisation of atherosclerotic plaques, which can precipitate cardiovascular events [533]. This mechanism may also explain the increased SPRs for IHD, HF, and CVD observed in this study, consistent with prior findings [187, 188, 534].

A novel finding in this study was the potential link between CP and heart failure, possibly via pancreatic exocrine insufficiency. Prior work has demonstrated reduced faecal elastase levels in patients with heart failure, suggestive of subclinical pancreatic exocrine insufficiency, which improved with pancreatic enzyme replacement therapy [535, 536]. Reduced pancreatic perfusion in heart failure may partly explain this observation [537-539], raising the possibility that CP could occasionally be a sequela rather than a cause of heart failure [535, 539]. Similarly, this study confirmed an increased risk of atrial fibrillation in patients with CP, potentially driven by cardiac remodelling associated with chronic alcohol use and systemic inflammatory spillover from pancreatic inflammation [540-543].

While alcohol is a well-established risk factor for both CP and CLD, only a minority of heavy drinkers develop either condition [36, 544, 545], suggesting the involvement of additional pathogenic mechanisms. CP may contribute to hepatic injury through pathways such as bacterial translocation, intestinal barrier disruption, and cytokine-mediated hepatic fibrosis [433, 546]. In this study, the prevalence and cumulative incidence of CLD were significantly elevated in patients with CP, consistent with previous findings—most notably, a population-based study by Chand et al., which reported a 5- to 9-fold increased risk of cirrhosis and liver disease among individuals with CP [547].

Diabetes is a well-established complication of CP, arising from chronic inflammation and progressive beta-cell dysfunction [48, 49, 173, 548]. Type 3c DM has a lifetime prevalence of 25–80% in patients with CP, with a cumulative incidence of 58% six years after CP diagnosis [549, 550]. These patients typically require higher insulin doses and exhibit poorer glycaemic control [551]. Notably, although DM had the highest cumulative incidence of all comorbidities in this cohort, the observed rates (8.3% at 10 years; 12.0% at 20 years) were lower than previously reported figures of 15–26% and up to 40% over comparable time intervals [49, 548]. This discrepancy may reflect competing mortality risks or represent a genuine regional variation in disease trajectory.

Surgical intervention for CP was required in only 6% of patients, considerably lower than historical estimates ranging from 40% to 75% [552, 553]. This lower rate may be attributable to the shorter follow-up period or increased reliance on minimally invasive or endoscopic therapies [49]. Consistent with previous studies [322, 553–555], the most common indication for surgery was intractable abdominal pain, with distal pancreatectomy and splenectomy being the most frequently performed procedure.

Mortality was substantial in this cohort, with 73% of patients dying over a median follow-up of 5.7 years. The leading causes of death were malignancy and infection. The age-adjusted standardised mortality ratio was more than twice that of the general population, aligning with existing literature [414, 420, 523]. The increased susceptibility to infection and malignancy in CP may be explained by immune dysregulation. CP has been associated with impaired innate and adaptive immunity, including reduced numbers and functional activity of natural killer (NK) cells, cytotoxic T lymphocytes (CD8+), and CD25+ regulatory T cells [556–560]. This immunosuppressed state may predispose patients to opportunistic infections. In parallel, chronic oxidative stress and inflammation, often exacerbated by alcohol use and smoking, are thought to contribute to carcinogenesis in CP [469]. In this population, the median age at diagnosis of CP was higher than reported in previous studies, which may explain the greater proportion of deaths observed over a shorter period.

This study has strengths and limitations. It represents one of the largest single-centre cohorts of CP patients, systematically identified from a well-defined geographical region. Comprehensive case ascertainment strategies minimised selection bias [561], and data accuracy was enhanced through manual chart review and multiple-source validation. The use of national comparator data further allowed for robust benchmarking of comorbidity and mortality rates. However, certain limitations should be acknowledged. The retrospective design introduces potential for misclassification and

missing data. The comparison with the general population was adjusted solely for age, as this was the only variable available. Furthermore, the CP cohort consisted predominantly of individuals of Caucasian descent, which limits the generalisability of the findings to other ethnic groups and populations. Although diagnoses were carefully verified and patients diagnosed only at death were excluded, diagnostic accuracy may still be affected by variability in documentation. To mitigate this, a sensitivity analysis excluding patients who died within 18 weeks of diagnosis was conducted and yielded consistent mortality outcomes. Additionally, underreporting of alcohol and tobacco use may have introduced bias, potentially leading to an underestimation of the aetiological role of these factors in CP and their associated outcomes. Finally, the relatively short median follow-up and high mortality rate may have limited the ability to capture the full cumulative incidence of comorbidities with longer latency, such as DM and osteoporosis.

In conclusion, this study provides important insights into the long-term clinical trajectory of patients with CP. CP is associated with significantly increased risks of cardiovascular disease, diabetes, CLD, and premature death, particularly from cancer and infection. These findings underscore the importance of routine screening for high-risk comorbidities and highlight the potential value of preventative strategies, including vaccination and early metabolic or cardiovascular intervention. Future prospective studies are needed to further delineate these relationships and identify opportunities for improved management of this high-risk population.

CHAPTER 6: MULTI-ORGAN FIBROSIS IN PATIENTS WITH CHRONIC PANCREATITIS

ABSTRACT

BACKGROUND

CP is occasionally associated with fibrosis in other organs, although not all patients develop such complications. This study aimed to determine whether routine clinical parameters can identify CP patients at risk of extra-pancreatic organ fibrosis.

METHODS

A prospective study was undertaken at Nottingham University Hospitals, where patients with CP were identified through multi-source case ascertainment. Participants were categorised into two cohorts: CP only and CP with additional organ fibrosis. All patients underwent blood tests, imaging, and physiological assessments. Group differences were analysed using the Mann–Whitney U test, with statistical analyses performed in R (version 4.3.3).

RESULTS

Compared with patients with CP only, those with additional organ fibrosis were more likely to have diabetes mellitus. They also had significantly higher diastolic blood pressure, baseline HbA_{1c}, serum IgG, and IgM.

CONCLUSION

These findings suggest that patients with CP may be predisposed to additional organ fibrosis through immune-mediated mechanisms and metabolic factors. Larger multicentre studies are needed to validate these associations and to determine whether biochemical and immunological markers can serve as predictors of additional organ fibrosis in CP.

INTRODUCTION

Multiorgan fibrosis, defined as excessive deposition of extracellular matrix components in two or more organs, accounts for approximately 45% of all deaths [436]. Its aetiology is multifactorial, involving genetic predisposition, autoimmunity, environmental irritants/toxins, ageing, persistent infections, and yet unidentified factors [562, 563].

In organ fibrosis, elevated cytokine production activates myofibroblasts, leading to increased synthesis of collagen and fibronectin and deposition of other extracellular proteins [564, 565], while inhibiting enzymes that degrade extracellular matrix [566]. Collectively, these processes drive the accumulation of extracellular matrix (ECM), which serves as the substrate for fibrosis [567].

CP is a progressive fibroinflammatory disease, most commonly associated with alcohol consumption, smoking, and a complex interplay of environmental and genetic factors [35]. Exposure to these predisposing factors stimulates pancreatic cells to release cytokines, which in turn activate pancreatic stellate cells, ultimately driving pancreatic fibrosis [568, 569]. Patients with CP may be predisposed to fibrosis in other organs, driven by genetic susceptibility, overlapping risk factors, systemic inflammation, and potentially autoimmune mechanisms [570, 571]. However, some patients with CP never develop multiorgan fibrosis [546, 572].

Given the high mortality associated with multiorgan fibrosis, it is clinically important to identify CP patients at greatest risk. This study therefore aimed to determine whether the development of fibrosis in other organs among patients with CP can be predicted using routine clinical investigations.

METHODS

PATIENT SELECTION

Patients with CP were identified using strict criteria based on computed tomography, magnetic resonance imaging, and endoscopic ultrasound findings, as described previously in Chapter 2. Only patients diagnosed with CP prior to 31 December 2022 were eligible, to ensure a minimum of two years' follow-up. Patients were contacted to participate, and only those who provided written consent and attended the study visit were included. Ethical approval was obtained from the Health Research Authority and Health and Care Research Wales (HCRW) (reference: 23/NW/0161).

STUDY COHORT

The study comprised two cohorts, namely patients with CP only and those with CP and additional organ fibrosis. The CP only cohort comprised individuals with CP alone, whereas the CP with organ fibrosis cohort included patients with CP plus any of the major organ fibroses (defined below).

ORGAN FIBROSIS

Major organ fibrosis of interest – chronic liver disease (CLD), chronic kidney disease (CKD), inflammatory bowel disease (IBD), and pulmonary fibrosis – was selected in line with the “Defining mechanisms shared across multiorgan fibrosis to prevent the development of long-term multimorbidity” (DEMISTIFI) consortium. These conditions were identified using ICD-10 and SNOMED classification systems, and diagnoses were verified through electronic patient records.

COMORBIDITIES AND CANCERS

Comorbidities were selected from the ten most prevalent conditions nationally and included ischaemic heart disease, heart failure, atrial fibrillation, hypertension, cerebrovascular disease, diabetes mellitus, dementia, and osteoporosis/osteopenia. CLD and CKD were excluded, as they were used to define the study cohorts. All cancers diagnosed following CP diagnosis were recorded.

DATA COLLECTION

Laboratory investigations included haematological, renal and liver tests, lipid profiles, and immunological parameters. Radiological findings consistent with CP were also recorded. Clinical

measurements comprised blood pressure, grip strength, body mass index (BMI), mid-arm, waist, and hip circumferences, together with demographic data. These parameters were selected because they are routinely assessed in clinical practice and are easily accessible.

Data were collected at two time points. Baseline data were defined as results obtained at the time of CP diagnosis, providing the initial clinical and biochemical profile for each patient. End of follow-up data were defined as results collected at the time of study recruitment, reflecting each patient's status after a minimum of two years' follow-up. Clinical measurements, including anthropometric indices and blood pressure were recorded only at the end of follow-up.

CASE DEFINITIONS

Alcohol was considered a cause of CP only if intake was ≥ 14 units per week at the time of CP diagnosis. Any history of smoking was recorded. Patients were classified as idiopathic if no cause was identified.

OUTCOMES

The primary outcome was to assess for any statistical differences in the above-listed variables between the two cohorts.

STATISTICAL ANALYSIS

Continuous variables are presented as median with interquartile range, and categorical variables as number with percentage. Differences between cohorts were assessed using the Wilcoxon (Mann-Whitney) test. All analyses were conducted using R (version 4.3.3).

RESULTS

CLINICAL CHARACTERISTICS

A total of 50 patients were included in the study cohort. The majority of patients were male ($n = 32$, 64%) and of Caucasian ancestry ($n=49$, 98%). The predominant aetiologies of CP were alcohol consumption ($n=42$, 84%), smoking ($n=37$, 74%), and recurrent acute pancreatitis ($n=14$, 28%). The most common clinical presentations were abdominal pain ($n=39$, 78%), weight loss ($n=16$, 32%), and steatorrhoea ($n=15$, 30%). In addition, 66% ($n=33$) of patients had a Hospital Anxiety and Depression Scale (HADS) score of 11 or more (Table 6.1). The overall median follow-up was 10.5 (IQR 8.1 – 13.3) years (IQR).

Of the study cohort, 26 patients had CP only, while 24 had CP with additional organ fibrosis. The median follow-up period was 10.8 years (IQR 7.0 – 13.2) for patients with CP only and 10.0 years (IQR 8.2 – 13.7) for those with CP and additional organ fibrosis. Among the 24 patients with CP and additional organ fibrosis, 22 had one additional organ affected and two had two additional organs affected. CLD was the most frequent manifestation ($n = 21$), followed by CKD ($n = 5$). Two patients had both CLD and CKD.

Table 6.1: Demographic and clinical parameters of the Study Cohort

Parameters	Study Cohort (n=50)	CP Only Group (n=26)	CP with Additional Organ Fibrosis (n=24)	P value
Age at CP diagnosis (Years)	50 (39–58)	51 (46–59)	48 (38–56)	0.32
Male Sex	32 (64.0%)	17 (65.4%)	15 (62.5%)	0.84
Caucasian Ancestry	49 (98.0%)	25 (96.2%)	24 (100%)	-
History of Smoking	37 (74.0%)	20 (76.9%)	17 (70.8%)	0.64
History of excess alcohol	46 (92.0%)	24 (92.3%)	22 (91.7%)	0.95
Smoking and Alcohol	35 (70.0%)	18 (66.2%)	17 (70.8%)	0.91
Recurrent AP (≥ 2 episodes)	14 (28.0%)	6 (23.1%)	8 (33.3%)	0.43
Presentation				
Abdominal pain	39 (78.0%)	21 (80.8%)	18 (75.0%)	0.64
Weight loss	16 (32.0%)	9 (34.6%)	7 (29.2%)	0.69
Steatorrhoea	15 (30.0%)	6 (23.1%)	9 (37.5%)	0.28
HADS Score				
0 – 7	10 (20.0%)	7 (26.9%)	2 (12.5%)	0.21
8 – 10	5 (10.0%)	4 (15.4%)	1 (4.2%)	0.19
≥ 11	33 (66.0%)	13 (50.0%)	20 (83.3%)	0.05

Abbreviations: AP acute pancreatitis; CP chronic pancreatitis; HADS Hospital Anxiety and Depression Scale

INVESTIGATIONS

Investigations at the time of CP diagnosis, revealed that patients with CP and additional organ fibrosis had higher HbA_{1c} values [47.5 (IQR 42.3–66.0), $p = 0.002$] compared with those with CP only (Table 6.2).

Table 6.2: Laboratory parameters at the time of CP diagnosis

Parameters	Study Cohort (n=50)	CP Only Group (n=26)	CP with Additional Organ Fibrosis (n=24)	p value
Haemoglobin	137.5 (127.0–147.8)	136.5 (127.5–148.5)	138.5 (126.0–145.8)	0.79
White Cell Count	8.5 (6.6–11.9)	8.8 (6.7–11.0)	8.4 (6.7–12.7)	0.63
Platelets	268 (202–350)	278 (204–382)	254 (192–332)	0.49
Serum Sodium	138 (137–140)	139 (137–140)	138 (136–140)	0.49
Serum Potassium	4.4 (4.0–4.6)	4.5 (4.0–4.7)	4.3 (4.0–4.5)	0.26
Urea	3.8 (3.1–4.7)	3.9 (3.1–4.7)	3.7 (3.0–4.6)	0.73
Creatinine	69 (60–79)	67 (62–78)	70 (59–80)	0.57
Bilirubin	9.5 (7.0–13.0)	9.0 (7.0–12.8)	11.5 (7.8–13.0)	0.50
Albumin	39 (35–41)	38 (35–40)	39 (35–42)	0.55
ALT	23 (16–42)	23 (18–40)	24 (16–40)	0.91
ALP	90 (73–121)	84 (72–114)	91 (75–124)	0.56
HbA _{1c}	43.5 (39.0–53.3)	40.5 (38.0–44.5)	47.5 (42.3–66.0)	0.002
Vitamin D	40.0 (28.5–60.0)	46.0 (32.5–74.5)	37.5 (22.0–49.3)	0.12
Serum Calcium	2.4 (2.3–2.4)	2.4 (2.3–2.4)	2.4 (2.3–2.4)	0.70
Serum Ferritin	120.0 (66.0–257.0)	162.0 (44.0–298.0)	102.0 (70.5–196.5)	0.68
C reactive protein	6.0 (5.0–41.3)	5.0 (5.0–29.0)	8.0 (5.0–60.5)	0.59
TSH	1.9 (1.2–3.0)	2.0 (1.1–3.5)	1.9 (1.5–2.7)	0.95
Total Cholesterol	4.2 (3.6–5.3)	4.2 (3.9–5.5)	4.2 (3.1–4.9)	0.33
Triglyceride	1.5 (1.0–2.2)	1.2 (1.1–2.3)	1.5 (1.0–1.9)	0.88
LDL Cholesterol	2.1 (1.8–3.3)	2.4 (2.1–3.3)	2.0 (1.5–2.8)	0.26
HDL Cholesterol	1.2 (1.0–1.5)	1.3 (1.1–1.5)	1.2 (1.0–1.5)	0.62

Abbreviations: ALP alkaline phosphatase; ALT alanine aminotransferase; HbA_{1c} glycated haemoglobin; HDL high-density lipoprotein; LDL low-density lipoprotein; TSH thyroid stimulating hormone.

At the end of follow-up, patients with CP and additional organ fibrosis had higher diastolic blood pressure [78.5 (IQR 69.5 – 87.3) Vs 71.5 (IQR 66.5 – 74.8), $p=0.04$], and lower serum sodium levels [137.0 (IQR 135.0 – 139.0) Vs 139.0 (IQR 136.3–140.0), $p = 0.04$] (Table 6.3). Further, patients with CP and additional organ fibrosis had significantly higher serum immunoglobulin G [9.60 (IQR 8.90 – 11.60) Vs 10.85 (IQR 9.53–13.4), $p<0.0001$] and immunoglobulin M [0.80 (IQR 0.60 – 1.00) Vs 1.30 (IQR 0.90 – 1.60), $p = 0.01$] compared with patients with CP only (Table 6.3).

Table 6.3: Clinical and laboratory parameters at the end of follow-up

Parameters	Study Cohort (n=50)	CP Only Group (n=26)	CP with Additional Organ Fibrosis (n=24)	p value
Systolic BP	139.0 (124.5–145.8)	137.0 (122.5–141.5)	141.0 (131.5–153.5)	0.12
Diastolic BP	73.0 (68.0–81.8)	71.5 (66.5–74.8)	78.5 (69.5–87.3)	0.04
Grip Strength	18.8 (13.1–25.7)	19.1 (13.7–26.6)	18.7 (11.4–23.6)	0.54
BMI	24.7 (22.3–28.7)	24.5 (21.3–26.5)	26.3 (23.1–29.2)	0.19
Midarm Circumference	30.0 (26.5–31.4)	30.0 (26.6–31.9)	30.0 (26.5–31.0)	0.91
Waist Circumference	96.0 (87.1–104.0)	93.0 (83.3–100.0)	97.8 (93.1–105.0)	0.05
Hip Circumference	100.5 (93.6–104.8)	98.5 (90.8–104.0)	102.3 (98.0–106.5)	0.16
Waist/Hip Ratio	0.95 (0.89–1.00)	0.94 (0.90–0.98)	0.99 (0.89–1.02)	0.23
Haemoglobin	131.0 (116.5–141.5)	136.0 (118.8–143.0)	126.5 (115.5–135.3)	0.18
White Cell Count	8.4 (5.3–10.4)	7.0 (4.8–9.3)	8.6 (7.5–10.9)	0.11
Platelets	249 (198–326)	248 (171–303)	253 (209–335)	0.52
Serum Sodium	138 (136–139)	139 (136–140)	137 (135–139)	0.04
Serum Potassium	4.5 (4.2–4.7)	4.5 (4.0–4.7)	4.5 (4.3–4.6)	0.26
Urea	4.2 (3.3–5.3)	4.2 (3.3–4.8)	4.4 (3.5–7.2)	0.17
Creatinine	68 (57–78)	65 (56–78)	71 (60–80)	0.19
Bilirubin	8.5 (7.0–12.0)	8.5 (6.3–11.8)	8.5 (7.0–12.3)	0.85
Albumin	40 (35–43)	41 (39–43)	39 (34–42)	0.06
ALT	26 (20–33)	27 (23–31)	23 (15–54)	0.30
ALP	101 (76–121)	85 (72–120)	103 (85–122)	0.14
HbA1c	45.0 (39.3–61.3)	46.0 (37.0–53.8)	44.0 (41.0–70.3)	0.17
Vitamin D	65.0 (49.0–98.5)	65.0 (52.0–105.0)	64.5 (44.0–90.3)	0.85
Serum Calcium	2.4 (2.3–2.5)	2.4 (2.3–2.5)	2.3 (2.3–2.4)	0.53
Serum Ferritin	127.0 (51.0–235.0)	123.0 (51.0–257.0)	129.0 (83.3–206.0)	0.86
C reactive protein	4.0 (1.0–15.0)	3.0 (1.0–12.8)	5.0 (3.5–15.0)	0.22
TSH	1.8 (1.2–2.4)	1.9 (1.4–2.1)	1.4 (1.1–2.5)	0.39
Total Cholesterol	4.1 (3.3–4.9)	4.4 (3.6–5.0)	3.8 (3.3–4.8)	0.52
Triglyceride	1.4 (0.8–2.2)	1.5 (0.7–2.3)	1.3 (0.9–1.7)	0.87
LDL Cholesterol	2.0 (1.7–2.8)	2.5 (1.9–3.1)	1.8 (1.7–2.3)	0.07
HDL Cholesterol	1.3 (1.0–1.5)	1.2 (1.0–1.5)	1.3 (1.0–1.5)	0.89
Immunoglobulin A	2.5 (2.1–3.5)	2.4 (2.0–3.1)	2.6 (2.2–3.8)	0.41
Immunoglobulin G	10.7 (9.0–11.8)	9.6 (8.9–11.6)	10.9 (9.5–13.4)	<0.0001
Immunoglobulin M	0.9 (0.7–1.5)	0.8 (0.6–1.0)	1.3 (0.9–1.6)	0.01

Abbreviations: BMI body mass index; BP blood pressure; ALP alkaline phosphatase; ALT alanine aminotransferase; HbA1c glycated haemoglobin; HDL high-density lipoprotein; LDL low-density lipoprotein; TSH thyroid stimulating hormone

NON-CANCER COMORBIDITIES

At the time of CP diagnosis, the most common comorbidities among patients with CP only were diabetes mellitus (n=5, 19.2%), hypertension (n<5, <20.0%), ischaemic heart disease (n<5, <20.0%), and osteopenia/osteoporosis (n<5, <20.0%). Among patients with CP and additional organ fibrosis, the most frequent comorbidities were diabetes mellitus (n=7, 30.4%), hypertension (n=7, 30.4%),

cerebrovascular disease (n<5, <20.0%), ischaemic heart disease (n<5, <20.0%), and osteopenia/osteoporosis (n<5, <20.0%).

At the end of follow-up, the prevalence of comorbidities in patients with CP only was diabetes mellitus (n=13, 50.0%), hypertension (n=8, 30.8%), ischaemic heart disease (n=9, 34.6%), and osteopenia/osteoporosis (n=6, 23.1%). For patients with CP and additional organ fibrosis, comorbidities included diabetes mellitus (n=19, 79.2%), hypertension (n=7, 29.2%), ischaemic heart disease (n=8, 33.3%), osteopenia/osteoporosis (n = 6, 25.0%) and cerebrovascular disease (n<5, <20.0%).

At the end of follow-up, patients with CP and additional organ fibrosis were significantly more likely to have diabetes mellitus compared with those with CP only (p=0.03).

Seven patients (14%) underwent surgery for complications of CP, most commonly for abdominal pain (n = 6, 12%) (Table 6.4).

Table 6.4: Comorbidities at the time of CP diagnosis and at the end of follow-up

Parameters	Study Cohort (n=50)	CP Only Group (n=26)	CP with Additional Organ Fibrosis (n=24)	p value
At CP diagnosis				
DM	12 (24.0%)	5 (19.2%)	7 (30.4%)	-
Hypertension	11 (22.0%)	<5 (<20.0%)	7 (30.4%)	-
IHD	<5 (<20.0%)	<5 (<20%)	<5 (<20%)	-
CVD	<5 (<20.0%)	<5 (<20%)	<5 (<20%)	-
Osteopenia/porosis	<5 (<20.0%)	<5 (<20%)	<5 (<20%)	-
At the end of follow-up				
DM	32 (64.0%)	13 (50.0%)	19 (79.2%)	0.03
Hypertension	15 (30.0%)	8 (30.8%)	7 (29.2%)	0.91
IHD	17 (34.0%)	9 (34.6%)	8 (33.3%)	0.93
CVA	<5 (<20.0%)	<5 (<20%)	<5 (<20%)	-
Osteopenia/porosis	12 (24.0%)	6 (23.1%)	6 (25.0%)	0.89
Pancreatic Surgery Indications				
Abdominal pain	6 (12.0%)	<5 (<20%)	<5 (<20%)	-
Pancreatic cancer	<5 (<20%)	<5 (20%)	<5 (<20%)	-

CANCERS

By the end of follow-up, patients with CP alone developed six cancers – colorectal, pancreatic, parotid, neuroendocrine, and haematological, whereas those with CP and additional organ fibrosis developed two cancers, adrenal and lung (p=0.07).

DISCUSSION

This study demonstrated minor differences between patients with CP alone and those with CP and additional organ fibrosis. While diastolic BP, serum IgG and IgM, serum sodium, and HbA1c showed statistically significant differences, all values were within the normal range, except for HbA1c. Further, diabetes mellitus was more prevalent among patients with additional organ fibrosis.

Although overall blood pressure was higher in patients with CP and additional organ fibrosis, only diastolic blood pressure reached statistical significance. Nevertheless, despite this, diastolic blood pressure remained within the normal range in both groups. Diastolic dysfunction is known to be associated with increased cardiac fibrosis and serves as an early marker of future cardiovascular disease, including atrial fibrillation and myocardial infarction [573, 574]. It would be worthwhile to investigate this in a larger cohort, where a true statistical difference might be detected, potentially identifying patients who could benefit from early cardiovascular screening and risk stratification.

Diabetes mellitus is a well-established driver of macrovascular and microvascular complications [575]. In this cohort, patients with additional organ fibrosis not only had a higher prevalence of diabetes but also exhibited persistently higher HbA1c values, indicating poorer glycaemic control. Hyperglycaemia promotes fibrogenesis through multiple mechanisms, including oxidative stress, fibroblast proliferation, activation of the renin–angiotensin–aldosterone system (RAAS), and increased deposition of extracellular matrix proteins such as collagen I, collagen III, transforming growth factor- β , and fibronectin [576-578]. Elevated HbA1c has also been associated with additional organ fibrosis in prior studies [579-581] raising the possibility that HbA1c may serve not only as a biomarker of diabetes but also as a marker of systemic fibrotic risk.

Although patients with CP and additional organ fibrosis had slightly lower serum sodium than those with CP alone, values in both groups remained within the normal range. However, hyponatremia is a well-recognised predictor of poor prognosis in chronic conditions, including liver and kidney disease [582, 583]. Patients with chronic liver disease and chronic kidney disease are predisposed to hyponatraemia due to splanchnic vasodilatation and renin–angiotensin–aldosterone system activation as disease progresses [584]. Given the small cohort and the overall normal serum sodium values, it remains unclear whether a true association exists. This is therefore another finding that warrants further investigation in a larger cohort with longer follow-up.

Similarly, although serum immunoglobulin A and G levels were higher in patients with CP and additional organ fibrosis, values remained within the normal range in both groups. IgG₄-related disease is a recognised fibro-inflammatory condition involving multiple organs [585], but it is often diagnostically challenging given its overlap with malignancy, asthma, and other autoimmune disorders [585-589]. None of the patients in this study had IgG₄-related disease or autoimmune comorbidity. Elevated IgG has been implicated in fibrosis through activation of the TGF- β /SMAD signalling pathway [590]. These suggestive findings warrant further investigation in larger patient cohorts to determine whether a potential association exists.

This study has limitations. It was conducted in a single centre with a relatively small cohort, predominantly of Caucasian descent, which may limit generalisability. Recruitment was also challenging, as many CP patients declined participation. Nonetheless, some of the results are consistent with prior work, while others are novel and hypothesis-generating. These findings therefore provide a platform for larger multicentre studies to validate the role of HbA_{1c}, sodium, and immunoglobulin profiles as predictors of additional organ fibrosis in CP.

In conclusion, this study supports the concept that a subset of patients with CP are predisposed to developing additional organ fibrosis. Biochemical, haematological, and immunological markers such as HbA_{1c}, sodium, IgG, and IgM may act as early predictors. These findings should be investigated in a larger patient cohort to determine whether true associations exist. If confirmed, identifying such markers in clinical practice could enable earlier intervention to delay or prevent the development of additional organ fibrosis in patients with CP.

CHAPTER 7: OVERALL DISCUSSION

CP is a progressive, irreversible and debilitating fibroinflammatory disease of the pancreas, caused by a complex interplay of smoking, alcohol, genetic predisposition and environmental factors [35]. It is characterised by persistent abdominal pain and by the development of both endocrine and exocrine pancreatic insufficiency [591]. Despite an estimated prevalence of 163 per 100,000 and an incidence rate of 12.8 per 100,000 based on UK Biobank data [357], CP remains a relatively neglected disease, often overshadowed by other comorbidities prevalent in this patient population within clinical practice and research communities. In Nottingham, for example, while hepatology and gastroenterology services are well established, dedicated provision for pancreatology has historically been limited, with only the recent establishment of a dedicated CP clinic. This disparity highlights the relative lack of attention given to CP despite its substantial burden.

A major barrier to progress is the diagnostic dilemma. The clinical presentation of CP varies widely, from asymptomatic disease to abdominal pain, malnutrition and weight loss [240]. Early-stage CP is especially difficult to identify because characteristic imaging features are often absent, and many commonly used diagnostic tests lack both sensitivity and specificity. For instance, abdominal X-ray detects calcifications with poor accuracy and may be confounded by vascular calcification [275], while low faecal elastase is non-specific, occurring in conditions such as coeliac disease and inflammatory bowel disease [12, 13], and is absent in up to half of CP patients [161, 592]. Although pancreatic histology is the diagnostic gold standard, it is invasive and carries significant risks [16, 17]. Advanced imaging such as CT, MRI and endoscopic ultrasound (EUS) offer better diagnostic yield, but are resource intensive. Consequently, CP has suffered from inconsistent case definition, both clinically and in research, limiting the quality of natural history data available [351, 526, 593, 594].

To address these diagnostic challenges, the first part of this thesis developed a pragmatic case ascertainment approach. A broad screening cohort was generated from multiple sources—including imaging, faecal elastase, discharge summaries and medication records—before applying stringent CT, MRI and EUS diagnostic criteria to establish a robust study cohort of 1,003 patients. Importantly, symptomatology was excluded as a diagnostic criterion, recognising that asymptomatic CP patients remain at risk of complications such as diabetes and pancreatic cancer, analogous to the risks borne by asymptomatic patients with cirrhosis [595].

From this well-defined cohort, the incidence and prevalence of CP in Greater Nottingham were calculated. The incidence increased from 8.5 per 100,000 in 2007 to 13.8 per 100,000 in 2013, with a

mean annual rise of 4.1% (95% CI 0.5–7.8; $p=0.03$). The point prevalence rose sharply, reaching 53.6 per 100,000 by the end of the study period. These findings confirm CP as an increasingly common condition in Nottingham, with implications for future healthcare planning.

CP is an established risk factor for pancreatic cancer, with cumulative risks of 2% at 5 years and 4% at 15–20 years [47, 195]. However, its relationship with EP malignancies has been less well explored. To address this, a systematic review and meta-analysis were conducted, incorporating 16 studies and over 117,000 CP patients. This showed that CP patients had significantly elevated risks of certain EP cancers, most notably lung cancer (HR 1.31, 95% CI 1.03–1.66) and liver cancer (HR 1.58, 95% CI 1.27–1.98).

These findings likely reflect both shared risk factors (smoking, alcohol) and the pro-inflammatory milieu of CP. The review highlighted that CP patients may warrant screening not only for pancreatic cancer but also for selected EP cancers. Nonetheless, limitations included heterogeneity in CP definitions, with diagnostic methods ranging from coding-based approaches to imaging and functional testing, underscoring the need for better-standardised studies.

To test these findings in a well-defined population, cancer incidence was evaluated in the Nottingham CP cohort. After excluding patients from outside the Greater Nottingham catchment, 678 patients were followed for a median of 7.3 years. Compared with national cancer incidence data, CP patients demonstrated markedly elevated risks of several cancers – upper respiratory tract (SIR 12.4), pancreatic (SIR 10.8), liver (SIR 8.8), lung (SIR 5.6), renal tract (SIR 4.8), oesophageal (SIR 4.8) and colorectal (SIR 2.5).

To account for possible reverse causation, analyses were repeated excluding cancers diagnosed within 18 weeks of CP diagnosis. While some associations weakened (notably for liver and colorectal cancers), most remained robust, reinforcing the likelihood of a true biological relationship. These findings suggest that CP is a high-risk state for multiple malignancies and provide a rationale for considering targeted cancer surveillance in this vulnerable group.

Beyond cancer, CP was associated with an excess burden of cardiovascular and metabolic comorbidities. Standardised prevalence ratios were significantly elevated for heart failure (3.0), IHD (2.4), atrial fibrillation (1.9) and cerebrovascular disease (1.4). At 20 years, the cumulative incidence of diabetes mellitus, chronic liver disease and chronic kidney disease was 12%, 11% and 11%, respectively.

Mortality was strikingly high – 73% of patients died during follow-up, with a median survival duration of just 5.7 years, and an overall standardised mortality ratio of 2.3 compared with the general

population. The leading causes of death were malignancy (27%), infection (22%) and cardiovascular disease (6.9%). These findings reinforce the importance of comprehensive surveillance in CP patients, not only for cancer but also for cardiovascular and infectious complications, to mitigate premature mortality.

A final small prospective study explored the phenomenon of multi-organ fibrosis, recognising that only a proportion of heavy alcohol users develop CP or CLD, and that CP rarely coexists with other fibrotic disorders [36, 545, 546, 596]. Although minor differences between variables reached statistical significance, values largely remained within the normal range. While these findings may help generate hypotheses, they cannot currently be used as definitive markers of fibrosis. However, this study highlights the potential value of routine clinical and biochemical markers as low-cost predictors of multi-organ fibrosis – an approach particularly relevant for resource-limited settings. Larger multicentre studies are needed to validate these associations and to identify potential targets for prevention or treatment.

This thesis provides a comprehensive analyses of CP in the UK to date, combining robust case ascertainment with systematic review, cohort analyses and exploratory prospective work. The findings highlight CP as a condition of growing prevalence, associated with markedly increased risks of cancer, cardiovascular disease and mortality. Future research should aim to (1) expand case ascertainment methods to larger, multicentre cohorts, (2) refine cancer surveillance strategies in CP, informed by risk stratification, (3) investigate mechanisms of multi-organ fibrosis, ideally through international collaboration using standardised definitions and (4) explore whether inexpensive, routine biomarkers can predict progression and comorbidity in CP, thus enabling earlier intervention.

Ultimately, patients with CP deserve the same level of clinical and research attention as those with CLD or cardiovascular diseases. By addressing the gaps identified in this thesis, it may be possible to improve survival, quality of life and long-term outcomes in this neglected but important disease.

REFERENCES

1. Mahadevan, V., *Anatomy of the pancreas and spleen*. Surgery, 2019. **37**(6): p. 297-301.
2. Karpinska, M. and M. Czauderna, *Pancreas-Its Functions, Disorders, and Physiological Impact on the Mammals' Organism*. Front Physiol, 2022. **13**: p. 807632.
3. Muhr, J., T.C. Arbor, and K.M. Ackerman, *Embryology, Gastrulation*, in StatPearls. 2024: Treasure Island (FL).
4. Mehta, V., et al., *Development of the human pancreas and its exocrine function*. Front Pediatr, 2022. **10**: p. 909648.
5. Pan, F.C. and M. Brissova, *Pancreas development in humans*. Curr Opin Endocrinol Diabetes Obes, 2014. **21**(2): p. 77-82.
6. O'Rahilly, R. and F. Muller, *Developmental stages in human embryos: revised and new measurements*. Cells Tissues Organs, 2010. **192**(2): p. 73-84.
7. Gittes, G.K., *Developmental biology of the pancreas: a comprehensive review*. Dev Biol, 2009. **326**(1): p. 4-35.
8. Ojo, A.S., *Pancreatic Duct Variations and the Risk of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis*. Cureus, 2020. **12**(9): p. e10445.
9. Kulenovic, A. and A. Sarac-Hadzihalilovic, *Blood vessels distribution in body and tail of pancreas- a comparative study of age related variation*. Bosn J Basic Med Sci, 2010. **10**(2): p. 89-93.
10. Mourad, N., et al., *The venous drainage of the pancreas*. Surg Radiol Anat, 1994. **16**(1): p. 37-45.
11. Henry, B.M., et al., *Development of the human pancreas and its vasculature - An integrated review covering anatomical, embryological, histological, and molecular aspects*. Ann Anat, 2019. **221**: p. 115-124.
12. Leong, S.P., et al., *The lymphatic system and sentinel lymph nodes: conduit for cancer metastasis*. Clin Exp Metastasis, 2022. **39**(1): p. 139-157.
13. Love, J.A., E. Yi, and T.G. Smith, *Autonomic pathways regulating pancreatic exocrine secretion*. Auton Neurosci, 2007. **133**(1): p. 19-34.
14. Hampton, R.F., M. Jimenez-Gonzalez, and S.A. Stanley, *Unravelling innervation of pancreatic islets*. Diabetologia, 2022. **65**(7): p. 1069-1084.
15. Paju, A., et al., *Expression and characterization of trypsinogen produced in the human male genital tract*. Am J Pathol, 2000. **157**(6): p. 2011-21.

16. Buettner, K., et al., *Protein surface charge of trypsinogen changes its activation pattern*. BMC Biotechnol, 2014. **14**: p. 109.
17. Vertiprakhov, V.G. and N.V. Ovchinnikova, *The activity of trypsin in the pancreatic juice and blood of poultry increases simultaneously in the postprandial period*. Front Physiol, 2022. **13**: p. 874664.
18. Sapio, M.R. and L.D. Fricker, *Carboxypeptidases in disease: insights from peptidomic studies*. Proteomics Clin Appl, 2014. **8**(5-6): p. 327-37.
19. Ishikawa, K., et al., *Substrate recognition at the binding site in mammalian pancreatic alpha-amylases*. Biochemistry, 1993. **32**(24): p. 6259-65.
20. Natalia B. Melani, E.B.T., Edgar Silveira, *Lipases: From production to Applications*. Separation & Purification Reviews, 2020. **49**: p. 143-158.
21. Moede, T., I.B. Leibiger, and P.O. Berggren, *Alpha cell regulation of beta cell function*. Diabetologia, 2020. **63**(10): p. 2064-2075.
22. Haedersdal, S., et al., *The Role of Glucagon in the Pathophysiology and Treatment of Type 2 Diabetes*. Mayo Clin Proc, 2018. **93**(2): p. 217-239.
23. Cejvan, K., D.H. Coy, and S. Efendic, *Intra-islet somatostatin regulates glucagon release via type 2 somatostatin receptors in rats*. Diabetes, 2003. **52**(5): p. 1176-81.
24. Brissova, M., et al., *Assessment of human pancreatic islet architecture and composition by laser scanning confocal microscopy*. J Histochem Cytochem, 2005. **53**(9): p. 1087-97.
25. Chatila, A.T., M. Bilal, and P. Guturu, *Evaluation and management of acute pancreatitis*. World J Clin Cases, 2019. **7**(9): p. 1006-1020.
26. Wang, G.J., et al., *Acute pancreatitis: etiology and common pathogenesis*. World J Gastroenterol, 2009. **15**(12): p. 1427-30.
27. Xiao, A.Y., et al., *Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies*. Lancet Gastroenterol Hepatol, 2016. **1**(1): p. 45-55.
28. Working Group, I.A.P.A.P.A.A.P.G., *IAP/APA evidence-based guidelines for the management of acute pancreatitis*. Pancreatology, 2013. **13**(4 Suppl 2): p. e1-15.
29. Banks, P.A., et al., *Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus*. Gut, 2013. **62**(1): p. 102-11.
30. Schepers, N.J., et al., *Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis*. Gut, 2019. **68**(6): p. 1044-1051.
31. Ahmed Ali, U., et al., *Risk of Recurrent Pancreatitis and Progression to Chronic Pancreatitis After a First Episode of Acute Pancreatitis*. Clin Gastroenterol Hepatol, 2016. **14**(5): p. 738-46.

32. Sankaran, S.J., et al., *Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis*. Gastroenterology, 2015. **149**(6): p. 1490-1500 e1.
33. Muniraj, T., et al., *Chronic pancreatitis, a comprehensive review and update. Part I: epidemiology, etiology, risk factors, genetics, pathophysiology, and clinical features*. Dis Mon, 2014. **60**(12): p. 530-50.
34. Singh, V.K., D. Yadav, and P.K. Garg, *Diagnosis and Management of Chronic Pancreatitis: A Review*. JAMA, 2019. **322**(24): p. 2422-2434.
35. Pham, A. and C. Forsmark, *Chronic pancreatitis: review and update of etiology, risk factors, and management*. F1000Res, 2018. **7**.
36. Vonlaufen, A., et al., *Alcoholic pancreatitis: A tale of spirits and bacteria*. World J Gastrointest Pathophysiol, 2014. **5**(2): p. 82-90.
37. Dufour, M.C. and M.D. Adamson, *The epidemiology of alcohol-induced pancreatitis*. Pancreas, 2003. **27**(4): p. 286-90.
38. Aune, D., et al., *Tobacco smoking and the risk of pancreatitis: A systematic review and meta-analysis of prospective studies*. Pancreatology, 2019. **19**(8): p. 1009-1022.
39. Andriulli, A., et al., *Smoking as a cofactor for causation of chronic pancreatitis: a meta-analysis*. Pancreas, 2010. **39**(8): p. 1205-10.
40. Cai, Q.Y., et al., *Incidence, prevalence, and comorbidities of chronic pancreatitis: A 7-year population-based study*. World J Gastroenterol, 2023. **29**(30): p. 4671-4684.
41. Hirota, M., et al., *The seventh nationwide epidemiological survey for chronic pancreatitis in Japan: clinical significance of smoking habit in Japanese patients*. Pancreatology, 2014. **14**(6): p. 490-6.
42. Yadav, D., et al., *Incidence, prevalence, and survival of chronic pancreatitis: a population-based study*. Am J Gastroenterol, 2011. **106**(12): p. 2192-9.
43. Olesen, S.S., et al., *Time trends in incidence and prevalence of chronic pancreatitis: A 25-year population-based nationwide study*. United European Gastroenterol J, 2021. **9**(1): p. 82-90.
44. Maatman, T.K. and N.J. Zyromski, *Chronic Pancreatitis*. Curr Probl Surg, 2021. **58**(3): p. 100858.
45. Mokrowiecka, A., D. Pinkowski, and E. Malecka-Panas, *Assessment of quality of life in patients with chronic pancreatitis*. Med Sci Monit, 2011. **17**(10): p. CR583-8.
46. Fitzsimmons, D., et al., *Symptoms and quality of life in chronic pancreatitis assessed by structured interview and the EORTC QLQ-C30 and QLQ-PAN26*. Am J Gastroenterol, 2005. **100**(4): p. 918-26.

47. Gandhi, S., et al., *Chronic Pancreatitis Is a Risk Factor for Pancreatic Cancer, and Incidence Increases With Duration of Disease: A Systematic Review and Meta-analysis*. Clin Transl Gastroenterol, 2022. **13**(3): p. e00463.
48. Bellin, M.D., et al., *Patient and Disease Characteristics Associated With the Presence of Diabetes Mellitus in Adults With Chronic Pancreatitis in the United States*. Am J Gastroenterol, 2017. **112**(9): p. 1457-1465.
49. Goodarzi, M.O., et al., *Diabetes in chronic pancreatitis: risk factors and natural history*. Curr Opin Gastroenterol, 2021. **37**(5): p. 526-531.
50. Duggan, S.N., et al., *Patients with chronic pancreatitis are at increased risk for osteoporosis*. Pancreas, 2012. **41**(7): p. 1119-24.
51. Etemad, B. and D.C. Whitcomb, *Chronic pancreatitis: diagnosis, classification, and new genetic developments*. Gastroenterology, 2001. **120**(3): p. 682-707.
52. Vonlaufen, A., et al., *Role of alcohol metabolism in chronic pancreatitis*. Alcohol Res Health, 2007. **30**(1): p. 48-54.
53. Gukovskaya, A.S., et al., *Ethanol metabolism and transcription factor activation in pancreatic acinar cells in rats*. Gastroenterology, 2002. **122**(1): p. 106-18.
54. Haber, P.S., et al., *Metabolism of ethanol by rat pancreatic acinar cells*. J Lab Clin Med, 1998. **132**(4): p. 294-302.
55. Norton, I.D., et al., *Cytochrome P₄₅₀2E1 is present in rat pancreas and is induced by chronic ethanol administration*. Gut, 1998. **42**(3): p. 426-30.
56. Laposata, M., *Fatty acid ethyl esters: ethanol metabolites which mediate ethanol-induced organ damage and serve as markers of ethanol intake*. Prog Lipid Res, 1998. **37**(5): p. 307-16.
57. Wilson, J.S. and M.V. Apte, *Role of alcohol metabolism in alcoholic pancreatitis*. Pancreas, 2003. **27**(4): p. 311-5.
58. Majumdar, A.P., et al., *Morphological and biochemical changes of the pancreas in rats treated with acetaldehyde*. Am J Physiol, 1986. **250**(5 Pt 1): p. G598-606.
59. McCarroll, J.A., et al., *Pancreatic stellate cell activation by ethanol and acetaldehyde: is it mediated by the mitogen-activated protein kinase signaling pathway?* Pancreas, 2003. **27**(2): p. 150-60.
60. Apte, M.V., et al., *Pancreatic stellate cells are activated by proinflammatory cytokines: implications for pancreatic fibrogenesis*. Gut, 1999. **44**(4): p. 534-41.
61. Bynigeri, R.R., et al., *Pancreatic stellate cell: Pandora's box for pancreatic disease biology*. World J Gastroenterol, 2017. **23**(3): p. 382-405.

62. Wu, Y., et al., *Targeting pancreatic stellate cells in chronic pancreatitis: Focus on therapeutic drugs and natural compounds*. Front Pharmacol, 2022. **13**: p. 1042651.
63. Apte, M.V. and J.S. Wilson, *Stellate cell activation in alcoholic pancreatitis*. Pancreas, 2003. **27**(4): p. 316-20.
64. Haber, P.S., et al., *Fatty acid ethyl esters increase rat pancreatic lysosomal fragility*. J Lab Clin Med, 1993. **121**(6): p. 759-64.
65. Stevens, T., D.L. Conwell, and G. Zuccaro, *Pathogenesis of chronic pancreatitis: an evidence-based review of past theories and recent developments*. Am J Gastroenterol, 2004. **99**(11): p. 2256-70.
66. Xia, D., et al., *NADPH oxidase 1 mediates caerulein-induced pancreatic fibrosis in chronic pancreatitis*. Free Radic Biol Med, 2020. **147**: p. 139-149.
67. Strate, T., et al., *Pathogenesis and the natural course of chronic pancreatitis*. Eur J Gastroenterol Hepatol, 2002. **14**(9): p. 929-34.
68. Schenker, S. and R. Montalvo, *Alcohol and the pancreas*. Recent Dev Alcohol, 1998. **14**: p. 41-65.
69. Ammann, R.W., *The natural history of alcoholic chronic pancreatitis*. Intern Med, 2001. **40**(5): p. 368-75.
70. Strate, T., et al., *Chronic pancreatitis: etiology, pathogenesis, diagnosis, and treatment*. Int J Colorectal Dis, 2003. **18**(2): p. 97-106.
71. Hansen, S.E.J., B.G. Nordestgaard, and A. Langsted, *Smoking as the most important risk factor for chronic pancreatitis in the general population*. Eur J Epidemiol, 2023. **38**(1): p. 95-107.
72. Chowdhury, P., P.L. Rayford, and L.W. Chang, *Pathophysiological effects of nicotine on the pancreas*. Proc Soc Exp Biol Med, 1998. **218**(3): p. 168-73.
73. Chowdhury, P. and P.L. Rayford, *Smoking and pancreatic disorders*. Eur J Gastroenterol Hepatol, 2000. **12**(8): p. 869-77.
74. Wittel, U.A., et al., *Chronic pancreatic inflammation induced by environmental tobacco smoke inhalation in rats*. Am J Gastroenterol, 2006. **101**(1): p. 148-59.
75. Maisonneuve, P., et al., *Cigarette smoking accelerates progression of alcoholic chronic pancreatitis*. Gut, 2005. **54**(4): p. 510-4.
76. Cavallini, G., et al., *Effect of alcohol and smoking on pancreatic lithogenesis in the course of chronic pancreatitis*. Pancreas, 1994. **9**(1): p. 42-6.
77. Hao, L., et al., *Clinical characteristics of smoking-related chronic pancreatitis*. Front Cell Infect Microbiol, 2022. **12**: p. 939910.

78. Abdullah, M., *Pancreatitis in primary hyperparathyroidism*. Med J Malaysia, 2003. **58**(4): p. 600-3.
79. Danis, F. and E. Kudu, *Recurrent acute pancreatitis and primary hyperparathyroidism in patients presenting to the emergency department: Diagnostic challenges*. World J Clin Cases, 2025. **13**(17): p. 100741.
80. Hirota, M., M. Ohmuraya, and H. Baba, *The role of trypsin, trypsin inhibitor, and trypsin receptor in the onset and aggravation of pancreatitis*. J Gastroenterol, 2006. **41**(9): p. 832-6.
81. Hrabak, P., et al., *Pancreatic stellate cells - rising stars in pancreatic pathologies*. Physiol Res, 2021. **70**(Suppl4): p. S597-S616.
82. Wang, Z., S. Dong, and W. Zhou, *Pancreatic stellate cells: Key players in pancreatic health and diseases (Review)*. Mol Med Rep, 2024. **30**(1).
83. Qiu, M., et al., *Comprehensive review on the pathogenesis of hypertriglyceridaemia-associated acute pancreatitis*. Ann Med, 2023. **55**(2): p. 2265939.
84. Zhang, M., et al., *Hypertriglyceridemia may contribute to stroke and pancreatitis: A case report and review of the literature*. Front Endocrinol (Lausanne), 2022. **13**: p. 960343.
85. Ewald, N., P.D. Hardt, and H.U. Kloer, *Severe hypertriglyceridemia and pancreatitis: presentation and management*. Curr Opin Lipidol, 2009. **20**(6): p. 497-504.
86. Yadav, D. and C.S. Pitchumoni, *Issues in hyperlipidemic pancreatitis*. J Clin Gastroenterol, 2003. **36**(1): p. 54-62.
87. Nakamura, T., et al., *Improvement of endothelial dysfunction is mediated through reduction of remnant lipoprotein after statin therapy in patients with coronary artery disease*. J Cardiol, 2020. **75**(3): p. 270-274.
88. Yamamiya, A., et al., *The Risk Factors for Progression to Chronic Pancreatitis in Patients with Past-History of Acute Pancreatitis: A Retrospective Analysis Based on Mechanistic Definition*. J Clin Med, 2022. **11**(8).
89. Garg, R. and T. Rustagi, *Management of Hypertriglyceridemia Induced Acute Pancreatitis*. Biomed Res Int, 2018. **2018**: p. 4721357.
90. Tenner, S., et al., *American College of Gastroenterology guideline: management of acute pancreatitis*. Am J Gastroenterol, 2013. **108**(9): p. 1400-15; 1416.
91. Chen, J.M. and C. Ferec, *Molecular basis of hereditary pancreatitis*. Eur J Hum Genet, 2000. **8**(7): p. 473-9.
92. Szmola, R., Z. Kukor, and M. Sahin-Toth, *Human mesotrypsin is a unique digestive protease specialized for the degradation of trypsin inhibitors*. J Biol Chem, 2003. **278**(49): p. 48580-9.

93. Guy, O., et al., *Two human trypsinogens. Purification, molecular properties, and N-terminal sequences*. Biochemistry, 1978. **17**(9): p. 1669-75.
94. Szmola, R. and M. Sahin-Toth, *Chymotrypsin C (caldecrin) promotes degradation of human cationic trypsin: identity with Rinderknecht's enzyme Y*. Proc Natl Acad Sci U S A, 2007. **104**(27): p. 11227-32.
95. Whitcomb, D.C., et al., *Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene*. Nat Genet, 1996. **14**(2): p. 141-5.
96. Ji, B., et al., *Intracellular trypsin induces pancreatic acinar cell death but not NF-kappaB activation*. J Biol Chem, 2009. **284**(26): p. 17488-98.
97. Szabo, A. and M. Sahin-Toth, *Increased activation of hereditary pancreatitis-associated human cationic trypsinogen mutants in presence of chymotrypsin C*. J Biol Chem, 2012. **287**(24): p. 20701-10.
98. Riordan, J.R., *CFTR function and prospects for therapy*. Annu Rev Biochem, 2008. **77**: p. 701-26.
99. Kopelman, H., et al., *Impaired chloride secretion, as well as bicarbonate secretion, underlies the fluid secretory defect in the cystic fibrosis pancreas*. Gastroenterology, 1988. **95**(2): p. 349-55.
100. Kopelman, H., et al., *Pancreatic fluid secretion and protein hyperconcentration in cystic fibrosis*. N Engl J Med, 1985. **312**(6): p. 329-34.
101. Wilschanski, M. and I. Novak, *The cystic fibrosis of exocrine pancreas*. Cold Spring Harb Perspect Med, 2013. **3**(5): p. a009746.
102. Imrie, J.R., D.G. Fagan, and J.M. Sturgess, *Quantitative evaluation of the development of the exocrine pancreas in cystic fibrosis and control infants*. Am J Pathol, 1979. **95**(3): p. 697-708.
103. Meyerholz, D.K., et al., *Pathology of gastrointestinal organs in a porcine model of cystic fibrosis*. Am J Pathol, 2010. **176**(3): p. 1377-89.
104. Milano, R.V., et al., *Pancreatitis in cystic fibrosis: Presentation, medical and surgical management, and the impact of modulator therapies*. Pediatr Pulmonol, 2024. **59 Suppl 1**: p. S53-S60.
105. Ravi Kanth, V. and D. Nageshwar Reddy, *Genetics of acute and chronic pancreatitis: An update*. World J Gastrointest Pathophysiol, 2014. **5**(4): p. 427-37.
106. Graf, R., et al., *The bifunctional rat pancreatic secretory trypsin inhibitor/monitor peptide provides protection against premature activation of pancreatic juice*. Pancreatology, 2003. **3**(3): p. 195-206.
107. Drenth, J.P., R. te Morsche, and J.B. Jansen, *Mutations in serine protease inhibitor Kazal type 1 are strongly associated with chronic pancreatitis*. Gut, 2002. **50**(5): p. 687-92.

108. Pfutzer, R.H., et al., *SPINK1/PSTI polymorphisms act as disease modifiers in familial and idiopathic chronic pancreatitis*. Gastroenterology, 2000. **119**(3): p. 615-23.
109. Janciauskiene, S.M., et al., *The discovery of alpha1-antitrypsin and its role in health and disease*. Respir Med, 2011. **105**(8): p. 1129-39.
110. Perlmutter, D.H., et al., *The cellular defect in alpha 1-proteinase inhibitor (alpha 1-PI) deficiency is expressed in human monocytes and in Xenopus oocytes injected with human liver mRNA*. Proc Natl Acad Sci U S A, 1985. **82**(20): p. 6918-21.
111. Ray, M.B., et al., *Alpha-1-antitrypsin immunoreactivity in gastric carcinoid*. Histopathology, 1982. **6**(3): p. 289-97.
112. Geboes, K., et al., *Morphological identification of alpha-1-antitrypsin in the human small intestine*. Histopathology, 1982. **6**(1): p. 55-60.
113. Boskovic, G. and S.S. Twining, *Local control of alpha1-proteinase inhibitor levels: regulation of alpha1-proteinase inhibitor in the human cornea by growth factors and cytokines*. Biochim Biophys Acta, 1998. **1403**(1): p. 37-46.
114. Higashiyama, M., et al., *An evaluation of the prognostic significance of alpha-1-antitrypsin expression in adenocarcinomas of the lung: an immunohistochemical analysis*. Br J Cancer, 1992. **65**(2): p. 300-2.
115. Holmes, M., et al., *Characterization of the intracellular mechanism causing the alpha-1-antitrypsin Nullgranite falls deficiency state*. Am Rev Respir Dis, 1989. **140**(6): p. 1662-7.
116. Bergin, D.A., et al., *alpha-1 Antitrypsin regulates human neutrophil chemotaxis induced by soluble immune complexes and IL-8*. J Clin Invest, 2010. **120**(12): p. 4236-50.
117. Mihas, A.A. and B.I. Hirschowitz, *Alpha-antitrypsin and chronic pancreatitis*. Lancet, 1976. **2**(7993): p. 1032-3.
118. Witt, H., et al., *Alpha1-antitrypsin genotypes in patients with chronic pancreatitis*. Scand J Gastroenterol, 2002. **37**(3): p. 356-9.
119. Novis, B.H., et al., *Chronic pancreatitis and alpha-1-antitrypsin*. Lancet, 1975. **2**(7938): p. 748-9.
120. Hart, P.A., et al., *Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis*. Gut, 2013. **62**(12): p. 1771-6.
121. Blaho, M., et al., *Autoimmune pancreatitis - An ongoing challenge*. Adv Med Sci, 2020. **65**(2): p. 403-408.
122. Ota, M., et al., *Two critical genes (HLA-DRB1 and ABCF1) in the HLA region are associated with the susceptibility to autoimmune pancreatitis*. Immunogenetics, 2007. **59**(1): p. 45-52.

123. Chang, M.C., et al., *T-cell regulatory gene CTLA-4 polymorphism/haplotype association with autoimmune pancreatitis*. Clin Chem, 2007. **53**(9): p. 1700-5.
124. Umemura, T., et al., *Association of autoimmune pancreatitis with cytotoxic T-lymphocyte antigen 4 gene polymorphisms in Japanese patients*. Am J Gastroenterol, 2008. **103**(3): p. 588-94.
125. Uchida, K., et al., *Clinical analysis of autoimmune-related pancreatitis*. Am J Gastroenterol, 2000. **95**(10): p. 2788-94.
126. Okazaki, K., et al., *Autoimmune-related pancreatitis is associated with autoantibodies and a Th1/Th2-type cellular immune response*. Gastroenterology, 2000. **118**(3): p. 573-81.
127. Asada, M., et al., *Identification of a novel autoantibody against pancreatic secretory trypsin inhibitor in patients with autoimmune pancreatitis*. Pancreas, 2006. **33**(1): p. 20-6.
128. Zen, Y., *Type 2 Autoimmune Pancreatitis: Consensus and Controversies*. Gut Liver, 2022. **16**(3): p. 357-365.
129. Okazaki, K., et al., *Recent advances in the concept and diagnosis of autoimmune pancreatitis and IgG4-related disease*. J Gastroenterol, 2011. **46**(3): p. 277-88.
130. Maruyama, M., et al., *Autoimmune pancreatitis can develop into chronic pancreatitis*. Orphanet J Rare Dis, 2014. **9**: p. 77.
131. Zhao, T., et al., *A comprehensive review of Sjogren's syndrome: Classification criteria, risk factors, and signaling pathways*. Heliyon, 2024. **10**(17): p. e36220.
132. Nista, E.C., et al., *Autoimmune Pancreatitis: From Pathogenesis to Treatment*. Int J Mol Sci, 2022. **23**(20).
133. Ludwig, H., et al., *Antibodies to pancreatic duct cells in Sjogren's syndrome and rheumatoid arthritis*. Gut, 1977. **18**(4): p. 311-5.
134. Li, S.Y., et al., *Autoimmune pancreatitis characterized by predominant CD8+ T lymphocyte infiltration*. World J Gastroenterol, 2011. **17**(41): p. 4635-9.
135. Thompson, B.S., et al., *Prodromal Signs and Symptoms of Chronic Pancreatitis: A Systematic Review*. J Clin Gastroenterol, 2022. **56**(1): p. e1-e10.
136. Drewes, A.M., et al., *Assessment of pain associated with chronic pancreatitis: An international consensus guideline*. Pancreatology, 2021. **21**(7): p. 1256-1284.
137. Ebbehøj, N., et al., *Pancreatic tissue pressure and pain in chronic pancreatitis*. Pancreas, 1986. **1**(6): p. 556-8.
138. Ebbehøj, N., et al., *Pancreatic tissue fluid pressure in chronic pancreatitis. Relation to pain, morphology, and function*. Scand J Gastroenterol, 1990. **25**(10): p. 1046-51.

139. Karanjia, N.D. and H.A. Reber, *The cause and management of the pain of chronic pancreatitis*. Gastroenterol Clin North Am, 1990. **19**(4): p. 895-904.
140. Karanjia, N.D., et al., *Compartment syndrome in experimental chronic obstructive pancreatitis: effect of decompressing the main pancreatic duct*. Br J Surg, 1994. **81**(2): p. 259-64.
141. Renou, C., et al., *Endoscopic treatment of the main pancreatic duct: correlations among morphology, manometry, and clinical follow-up*. Int J Pancreatol, 2000. **27**(2): p. 143-9.
142. Strate, T., et al., *Resection vs drainage in treatment of chronic pancreatitis: long-term results of a randomized trial*. Gastroenterology, 2008. **134**(5): p. 1406-11.
143. Dite, P., et al., *A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis*. Endoscopy, 2003. **35**(7): p. 553-8.
144. Winston, J.H., et al., *Molecular and behavioral changes in nociception in a novel rat model of chronic pancreatitis for the study of pain*. Pain, 2005. **117**(1-2): p. 214-22.
145. Hughes, M.S., et al., *Brain-derived neurotrophic factor is upregulated in rats with chronic pancreatitis and mediates pain behavior*. Pancreas, 2011. **40**(4): p. 551-6.
146. Liu, L., M. Shenoy, and P.J. Pasricha, *Substance P and calcitonin gene related peptide mediate pain in chronic pancreatitis and their expression is driven by nerve growth factor*. JOP, 2011. **12**(4): p. 389-94.
147. Ceyhan, G.O., et al., *Neural fractalkine expression is closely linked to pain and pancreatic neuritis in human chronic pancreatitis*. Lab Invest, 2009. **89**(3): p. 347-61.
148. Di Sebastiano, P., et al., *Immune cell infiltration and growth-associated protein 43 expression correlate with pain in chronic pancreatitis*. Gastroenterology, 1997. **112**(5): p. 1648-55.
149. Hoogerwerf, W.A., et al., *The role of mast cells in the pathogenesis of pain in chronic pancreatitis*. BMC Gastroenterol, 2005. **5**: p. 8.
150. Ceyhan, G.O., et al., *Pancreatic neuropathy and neuropathic pain--a comprehensive pathomorphological study of 546 cases*. Gastroenterology, 2009. **136**(1): p. 177-186 e1.
151. Xu, G.Y., et al., *Transient receptor potential vanilloid 1 mediates hyperalgesia and is up-regulated in rats with chronic pancreatitis*. Gastroenterology, 2007. **133**(4): p. 1282-92.
152. Ceppa, E., et al., *Transient receptor potential ion channels V4 and A1 contribute to pancreatitis pain in mice*. Am J Physiol Gastrointest Liver Physiol, 2010. **299**(3): p. G556-71.
153. Kawabata, A., et al., *Suppression of pancreatitis-related allodynia/hyperalgesia by proteinase-activated receptor-2 in mice*. Br J Pharmacol, 2006. **148**(1): p. 54-60.
154. Schwartz, E.S., et al., *Synergistic role of TRPV1 and TRPA1 in pancreatic pain and inflammation*. Gastroenterology, 2011. **140**(4): p. 1283-1291 e1-2.

155. Frokjaer, J.B., et al., *Altered brain microstructure assessed by diffusion tensor imaging in patients with chronic pancreatitis*. Gut, 2011. **60**(11): p. 1554-62.
156. Frokjaer, J.B., et al., *Reduced cortical thickness of brain areas involved in pain processing in patients with chronic pancreatitis*. Clin Gastroenterol Hepatol, 2012. **10**(4): p. 434-8 e1.
157. Liu, P.Y., et al., *Spinal microglia initiate and maintain hyperalgesia in a rat model of chronic pancreatitis*. Gastroenterology, 2012. **142**(1): p. 165-173 e2.
158. Feng, Q.X., et al., *Astrocytic activation in thoracic spinal cord contributes to persistent pain in rat model of chronic pancreatitis*. Neuroscience, 2010. **167**(2): p. 501-9.
159. Whitcomb, D.C., A.M. Buchner, and C.E. Forsmark, *AGA Clinical Practice Update on the Epidemiology, Evaluation, and Management of Exocrine Pancreatic Insufficiency: Expert Review*. Gastroenterology, 2023. **165**(5): p. 1292-1301.
160. Levy, P., et al., *Epidemiology of chronic pancreatitis: burden of the disease and consequences*. United European Gastroenterol J, 2014. **2**(5): p. 345-54.
161. Kunovsky, L., et al., *Causes of Exocrine Pancreatic Insufficiency Other Than Chronic Pancreatitis*. J Clin Med, 2021. **10**(24).
162. Ammann, R.W., et al., *Course and outcome of chronic pancreatitis. Longitudinal study of a mixed medical-surgical series of 245 patients*. Gastroenterology, 1984. **86**(5 Pt 1): p. 820-8.
163. DiMagno, E.P., V.L. Go, and W.H. Summerskill, *Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency*. N Engl J Med, 1973. **288**(16): p. 813-5.
164. Li, B.R., et al., *Risk Factors for Steatorrhea in Chronic Pancreatitis: A Cohort of 2,153 Patients*. Sci Rep, 2016. **6**: p. 21381.
165. Cohen, S.M. and T.S. Kent, *Etiology, Diagnosis, and Modern Management of Chronic Pancreatitis: A Systematic Review*. JAMA Surg, 2023. **158**(6): p. 652-661.
166. Cavallini, G., et al., *Diabetes in chronic alcoholic pancreatitis. Role of residual beta cell function and insulin resistance*. Dig Dis Sci, 1993. **38**(3): p. 497-501.
167. American Diabetes, A., *Diagnosis and classification of diabetes mellitus*. Diabetes Care, 2014. **37 Suppl 1**: p. S81-90.
168. Choudhuri, G., C.P. Lakshmi, and A. Goel, *Pancreatic diabetes*. Trop Gastroenterol, 2009. **30**(2): p. 71-5.
169. Wang, W., et al., *Occurrence of and risk factors for diabetes mellitus in Chinese patients with chronic pancreatitis*. Pancreas, 2011. **40**(2): p. 206-12.
170. Malka, D., et al., *Risk factors for diabetes mellitus in chronic pancreatitis*. Gastroenterology, 2000. **119**(5): p. 1324-32.

171. Hall, T.C., et al., *The socio-economic impact of chronic pancreatitis: a systematic review*. J Eval Clin Pract, 2014. **20**(3): p. 203-7.
172. Singh, A., et al., *Post-pancreatitis diabetes mellitus: insight on optimal management with nutrition and lifestyle approaches*. Ann Med, 2022. **54**(1): p. 1776-1786.
173. Sasikala, M., et al., *beta-Cell dysfunction in chronic pancreatitis*. Dig Dis Sci, 2012. **57**(7): p. 1764-72.
174. Schrader, H., et al., *Reduced pancreatic volume and beta-cell area in patients with chronic pancreatitis*. Gastroenterology, 2009. **136**(2): p. 513-22.
175. Andersson, A.K., M. Flodstrom, and S. Sandler, *Cytokine-induced inhibition of insulin release from mouse pancreatic beta-cells deficient in inducible nitric oxide synthase*. Biochem Biophys Res Commun, 2001. **281**(2): p. 396-403.
176. Seymour, N.E., et al., *In vitro hepatic insulin resistance in chronic pancreatitis in the rat*. J Surg Res, 1989. **46**(5): p. 450-6.
177. Seymour, N.E., et al., *Alterations in hepatocyte insulin binding in chronic pancreatitis: effects of pancreatic polypeptide*. Am J Surg, 1995. **169**(1): p. 105-9; discussion 110.
178. Lonovics, J., et al., *Pancreatic polypeptide. A review*. Arch Surg, 1981. **116**(10): p. 1256-64.
179. Seymour, N.E., A.R. Volpert, and D.K. Andersen, *Regulation of hepatic insulin receptors by pancreatic polypeptide in fasting and feeding*. J Surg Res, 1996. **65**(1): p. 1-4.
180. Acquarone, E., et al., *Resistin: A reappraisal*. Mech Ageing Dev, 2019. **178**: p. 46-63.
181. Adrych, K., et al., *Increased serum resistin concentration in patients with chronic pancreatitis: possible cause of pancreatic fibrosis*. J Clin Gastroenterol, 2009. **43**(1): p. 63-8.
182. Koh, A., et al., *Risk of osteopaenia, osteoporosis and osteoporotic fractures in patients with chronic pancreatitis: A systematic review and meta-analysis*. Clin Nutr, 2023. **42**(7): p. 1086-1094.
183. Parhiala, M., et al., *Osteoporosis and sarcopenia are common and insufficiently diagnosed among chronic pancreatitis patients*. BMC Gastroenterol, 2023. **23**(1): p. 124.
184. Lips, P., *Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications*. Endocr Rev, 2001. **22**(4): p. 477-501.
185. de la Iglesia, D., et al., *Pancreatic exocrine insufficiency and cardiovascular risk in patients with chronic pancreatitis: A prospective, longitudinal cohort study*. J Gastroenterol Hepatol, 2019. **34**(1): p. 277-283.
186. Nikolic, S., et al., *Chronic pancreatitis and the heart disease: Still terra incognita?* World J Gastroenterol, 2019. **25**(44): p. 6561-6570.

187. Desai, A., et al., *Chronic Pancreatitis and Risk of Atherosclerotic Cardiovascular Disease: A US Cohort Propensity-Matched Study*. *Pancreas*, 2023. **52**(1): p. e21-e28.
188. Hsu, M.T., C.L. Lin, and W.S. Chung, *Increased Risk of Acute Coronary Syndrome in Patients With Chronic Pancreatitis: A Nationwide Cohort Analysis*. *Medicine (Baltimore)*, 2016. **95**(20): p. e3451.
189. Wong, T.S., et al., *Chronic Pancreatitis Correlates With Increased Risk of Cerebrovascular Disease: A Retrospective Population-Based Cohort Study in Taiwan*. *Medicine (Baltimore)*, 2016. **95**(15): p. e3266.
190. Habtezion, A., *Inflammation in acute and chronic pancreatitis*. *Curr Opin Gastroenterol*, 2015. **31**(5): p. 395-9.
191. Biasucci, L.M., et al., *Increasing levels of interleukin (IL)-1Ra and IL-6 during the first 2 days of hospitalization in unstable angina are associated with increased risk of in-hospital coronary events*. *Circulation*, 1999. **99**(16): p. 2079-84.
192. Ridker, P.M., et al., *Elevation of tumor necrosis factor-alpha and increased risk of recurrent coronary events after myocardial infarction*. *Circulation*, 2000. **101**(18): p. 2149-53.
193. Hansson, G.K., *Inflammation, atherosclerosis, and coronary artery disease*. *N Engl J Med*, 2005. **352**(16): p. 1685-95.
194. Rebours, V., et al., *The natural history of hereditary pancreatitis: a national series*. *Gut*, 2009. **58**(1): p. 97-103.
195. Le Cosquer, G., et al., *Pancreatic Cancer in Chronic Pancreatitis: Pathogenesis and Diagnostic Approach*. *Cancers (Basel)*, 2023. **15**(3).
196. Lowenfels, A.B., et al., *Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group*. *N Engl J Med*, 1993. **328**(20): p. 1433-7.
197. Lowenfels, A.B., et al., *Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group*. *J Natl Cancer Inst*, 1997. **89**(6): p. 442-6.
198. Zhang, H., et al., *IL-6 trans-signaling promotes pancreatitis-associated lung injury and lethality*. *J Clin Invest*, 2013. **123**(3): p. 1019-31.
199. Xue, J., et al., *Alternatively activated macrophages promote pancreatic fibrosis in chronic pancreatitis*. *Nat Commun*, 2015. **6**: p. 7158.
200. Masamune, A. and T. Shimosegawa, *Signal transduction in pancreatic stellate cells*. *J Gastroenterol*, 2009. **44**(4): p. 249-60.
201. Gadani, S.P., et al., *IL-4 in the brain: a cytokine to remember*. *J Immunol*, 2012. **189**(9): p. 4213-9.

202. Yako, Y.Y., et al., *Inflammatory cytokines and angiogenic factors as potential biomarkers in South African pancreatic ductal adenocarcinoma patients: A preliminary report*. Pancreatology, 2017. **17**(3): p. 438-444.
203. Prokopchuk, O., et al., *Interleukin-4 enhances proliferation of human pancreatic cancer cells: evidence for autocrine and paracrine actions*. Br J Cancer, 2005. **92**(5): p. 921-8.
204. Bellone, G., et al., *Cytokine expression profile in human pancreatic carcinoma cells and in surgical specimens: implications for survival*. Cancer Immunol Immunother, 2006. **55**(6): p. 684-98.
205. Razidlo, G.L., K.M. Burton, and M.A. McNiven, *Interleukin-6 promotes pancreatic cancer cell migration by rapidly activating the small GTPase CDC42*. J Biol Chem, 2018. **293**(28): p. 11143-11153.
206. Liou, G.Y., et al., *The Presence of Interleukin-13 at Pancreatic ADM/PanIN Lesions Alters Macrophage Populations and Mediates Pancreatic Tumorigenesis*. Cell Rep, 2017. **19**(7): p. 1322-1333.
207. Pinho, A.V., L. Chantrill, and I. Rooman, *Chronic pancreatitis: a path to pancreatic cancer*. Cancer Lett, 2014. **345**(2): p. 203-9.
208. Collins, M.A., et al., *Oncogenic Kras is required for both the initiation and maintenance of pancreatic cancer in mice*. J Clin Invest, 2012. **122**(2): p. 639-53.
209. Muller-Decker, K., et al., *Preinvasive duct-derived neoplasms in pancreas of keratin 5-promoter cyclooxygenase-2 transgenic mice*. Gastroenterology, 2006. **130**(7): p. 2165-78.
210. Al-Hetty, H., et al., *STAT3 signaling in pancreatic ductal adenocarcinoma: a candidate therapeutic target*. Pathol Res Pract, 2023. **245**: p. 154425.
211. Chen, C.H., et al., *Risk of head and neck cancer after chronic pancreatitis*. Ann Transl Med, 2020. **8**(5): p. 213.
212. Grace, P.A. and R.C. Williamson, *Modern management of pancreatic pseudocysts*. Br J Surg, 1993. **80**(5): p. 573-81.
213. Lillemoe, K.D. and C.J. Yeo, *Management of complications of pancreatitis*. Curr Probl Surg, 1998. **35**(1): p. 1-98.
214. Gouyon, B., et al., *Predictive factors in the outcome of pseudocysts complicating alcoholic chronic pancreatitis*. Gut, 1997. **41**(6): p. 821-5.
215. Pan, G., et al., *Classification and Management of Pancreatic Pseudocysts*. Medicine (Baltimore), 2015. **94**(24): p. e960.
216. Habashi, S. and P.V. Draganov, *Pancreatic pseudocyst*. World J Gastroenterol, 2009. **15**(1): p. 38-47.

217. Barthet, M., et al., *Management of cysts and pseudocysts complicating chronic pancreatitis. A retrospective study of 143 patients*. Gastroenterol Clin Biol, 1993. **17**(4): p. 270-6.
218. Bourliere, M. and H. Sarles, *Pancreatic cysts and pseudocysts associated with acute and chronic pancreatitis*. Dig Dis Sci, 1989. **34**(3): p. 343-8.
219. Mehta, R., et al., *Natural course of asymptomatic pancreatic pseudocyst: a prospective study*. Indian J Gastroenterol, 2004. **23**(4): p. 140-2.
220. Koo, J.G., et al., *Pancreatic pseudocyst: The past, the present, and the future*. World J Gastrointest Surg, 2024. **16**(7): p. 1986-2002.
221. Vijungco, J.D. and R.A. Prinz, *Management of biliary and duodenal complications of chronic pancreatitis*. World J Surg, 2003. **27**(11): p. 1258-70.
222. Ramsey, M.L., D.L. Conwell, and P.A. Hart, *Complications of Chronic Pancreatitis*. Dig Dis Sci, 2017. **62**(7): p. 1745-1750.
223. Aranha, G.V., et al., *Gastric outlet and duodenal obstruction from inflammatory pancreatic disease*. Arch Surg, 1984. **119**(7): p. 833-5.
224. Zhang, Y., et al., *Successful Resolution of Gastric Outlet Obstruction Caused by Pancreatic Pseudocyst or Walled-Off Necrosis After Acute Pancreatitis: The Role of Percutaneous Catheter Drainage*. Pancreas, 2015. **44**(8): p. 1290-5.
225. Sarles, H. and J. Sahel, *Cholestasis and lesions of the biliary tract in chronic pancreatitis*. Gut, 1978. **19**(9): p. 851-7.
226. Hollinshead, W.H., *The lower part of the common bile duct: a review*. Surg Clin North Am, 1957. **37**(4): p. 939-52.
227. Abdallah, A.A., J.E. Krige, and P.C. Bornman, *Biliary tract obstruction in chronic pancreatitis*. HPB (Oxford), 2007. **9**(6): p. 421-8.
228. McCollum, W.B. and P.H. Jordan, *Obstructive jaundice in patients with pancreatitis without associated biliary tract disease*. Ann Surg, 1975. **182**(2): p. 116-20.
229. Hollands, M.J. and J.M. Little, *Obstructive jaundice in chronic pancreatitis*. HPB Surg, 1989. **1**(4): p. 263-70.
230. Paranandi, B. and K.W. Oppong, *Biliary strictures: endoscopic assessment and management*. Frontline Gastroenterol, 2017. **8**(2): p. 133-137.
231. Agarwal, A.K., et al., *Significance of splenic vein thrombosis in chronic pancreatitis*. Am J Surg, 2008. **196**(2): p. 149-54.
232. Sakorafas, G.H. and A.G. Tsiotou, *Splenic-vein thrombosis complicating chronic pancreatitis*. Scand J Gastroenterol, 1999. **34**(12): p. 1171-7.

233. Armstrong, E.M., et al., *Ultrasound guided thrombin injection to treat a pseudoaneurysm secondary to chronic pancreatitis*. Eur J Vasc Endovasc Surg, 2003. **26**(4): p. 448-9.
234. Chiang, K.C., T.H. Chen, and J.T. Hsu, *Management of chronic pancreatitis complicated with a bleeding pseudoaneurysm*. World J Gastroenterol, 2014. **20**(43): p. 16132-7.
235. Balachandra, S. and A.K. Siriwardena, *Systematic appraisal of the management of the major vascular complications of pancreatitis*. Am J Surg, 2005. **190**(3): p. 489-95.
236. Hsu, J.T., et al., *Management and outcome of bleeding pseudoaneurysm associated with chronic pancreatitis*. BMC Gastroenterol, 2006. **6**: p. 3.
237. Sandblom, P., *Gastrointestinal hemorrhage through the pancreatic duct*. Ann Surg, 1970. **171**(1): p. 61-6.
238. Mandaliya, R., et al., *Hemosuccus Pancreaticus: A Mysterious Cause of Gastrointestinal Bleeding*. Gastroenterology Res, 2014. **7**(1): p. 32-37.
239. Sakorafas, G.H., et al., *Hemosuccus pancreaticus complicating chronic pancreatitis: an obscure cause of upper gastrointestinal bleeding*. Langenbecks Arch Surg, 2000. **385**(2): p. 124-8.
240. Duggan, S.N., et al., *Chronic pancreatitis: A diagnostic dilemma*. World J Gastroenterol, 2016. **22**(7): p. 2304-13.
241. Busireddy, K.K., et al., *Pancreatitis-imaging approach*. World J Gastrointest Pathophysiol, 2014. **5**(3): p. 252-70.
242. Whitcomb, D.C., et al., *Chronic pancreatitis: An international draft consensus proposal for a new mechanistic definition*. Pancreatology, 2016. **16**(2): p. 218-24.
243. Sheel, A.R.G., et al., *The diagnostic value of Rosemont and Japanese diagnostic criteria for 'indeterminate', 'suggestive', 'possible' and 'early' chronic pancreatitis*. Pancreatology, 2018. **18**(7): p. 774-784.
244. Whitcomb, D.C., et al., *International consensus statements on early chronic Pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with The International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, PancreasFest Working Group and European Pancreatic Club*. Pancreatology, 2018. **18**(5): p. 516-527.
245. Homma, T., H. Harada, and M. Koizumi, *Diagnostic criteria for chronic pancreatitis by the Japan Pancreas Society*. Pancreas, 1997. **15**(1): p. 14-5.
246. Shimosegawa, T., et al., *The revised Japanese clinical diagnostic criteria for chronic pancreatitis*. J Gastroenterol, 2010. **45**(6): p. 584-91.
247. Otsuki, M., *Chronic pancreatitis. The problems of diagnostic criteria*. Pancreatology, 2004. **4**(1): p. 28-41.

248. Anaizi, A., P.A. Hart, and D.L. Conwell, *Diagnosing Chronic Pancreatitis*. Dig Dis Sci, 2017. **62**(7): p. 1713-1720.
249. Iglesias-Garcia, J., et al., *Histological evaluation of chronic pancreatitis by endoscopic ultrasound-guided fine needle biopsy*. Gut, 2006. **55**(11): p. 1661-2.
250. Kloppel, G. and B. Maillet, *Pathology of acute and chronic pancreatitis*. Pancreas, 1993. **8**(6): p. 659-70.
251. Sze, K.C., et al., *Current options for the diagnosis of chronic pancreatitis*. Expert Rev Mol Diagn, 2014. **14**(2): p. 199-215.
252. Conwell, D.L. and B.U. Wu, *Chronic pancreatitis: making the diagnosis*. Clin Gastroenterol Hepatol, 2012. **10**(10): p. 1088-95.
253. Hafezi-Nejad, N., et al., *Surgical approaches to chronic pancreatitis: indications and imaging findings*. Abdom Radiol (NY), 2016. **41**(10): p. 1980-96.
254. Sica, G.T., et al., *Comparison of endoscopic retrograde cholangiopancreatography with MR cholangiopancreatography in patients with pancreatitis*. Radiology, 1999. **210**(3): p. 605-10.
255. Zhang, X.M., et al., *Suspected early or mild chronic pancreatitis: enhancement patterns on gadolinium chelate dynamic MRI. Magnetic resonance imaging*. J Magn Reson Imaging, 2003. **17**(1): p. 86-94.
256. Balci, N.C., et al., *Magnetic resonance imaging in pancreatitis*. Top Magn Reson Imaging, 2009. **20**(1): p. 25-30.
257. Conwell, D.L., et al., *American Pancreatic Association Practice Guidelines in Chronic Pancreatitis: evidence-based report on diagnostic guidelines*. Pancreas, 2014. **43**(8): p. 1143-62.
258. Cappeliez, O., et al., *Chronic pancreatitis: evaluation of pancreatic exocrine function with MR pancreatography after secretin stimulation*. Radiology, 2000. **215**(2): p. 358-64.
259. Tirkes, T., et al., *Secretin-enhanced MR cholangiopancreatography: spectrum of findings*. Radiographics, 2013. **33**(7): p. 1889-906.
260. Balci, N.C., et al., *Suspected chronic pancreatitis with normal MRCP: findings on MRI in correlation with secretin MRCP*. J Magn Reson Imaging, 2008. **27**(1): p. 125-31.
261. Chey, W.Y. and T.M. Chang, *Secretin, 100 years later*. J Gastroenterol, 2003. **38**(11): p. 1025-35.
262. Tirkes, T., et al., *Imaging of the pancreas with secretin enhancement*. Top Magn Reson Imaging, 2009. **20**(1): p. 19-24.
263. Dimcevski, G., et al., *Ultrasonography in diagnosing chronic pancreatitis: new aspects*. World J Gastroenterol, 2013. **19**(42): p. 7247-57.
264. Bolondi, L., et al., *Sonography of chronic pancreatitis*. Radiol Clin North Am, 1989. **27**(4): p. 815-33.

265. Foley, W.D., et al., *Computed tomography, ultrasonography, and endoscopic retrograde cholangiopancreatography in the diagnosis of pancreatic disease: a comparative study*. Gastrointest Radiol, 1980. **5**(1): p. 29-35.
266. Sivak, M.V. and A. Kaufman, *Endoscopic ultrasonography in the differential diagnosis of pancreatic disease. A preliminary report*. Scand J Gastroenterol Suppl, 1986. **123**: p. 130-4.
267. Lees, W.R., *Endoscopic ultrasonography of chronic pancreatitis and pancreatic pseudocysts*. Scand J Gastroenterol Suppl, 1986. **123**: p. 123-9.
268. Stevens, T. and M.A. Parsi, *Endoscopic ultrasound for the diagnosis of chronic pancreatitis*. World J Gastroenterol, 2010. **16**(23): p. 2841-50.
269. Wallace, M.B., et al., *The reliability of EUS for the diagnosis of chronic pancreatitis: interobserver agreement among experienced endosonographers*. Gastrointest Endosc, 2001. **53**(3): p. 294-9.
270. Catalano, M.F., et al., *EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification*. Gastrointest Endosc, 2009. **69**(7): p. 1251-61.
271. Beyer, G., et al., *Chronic pancreatitis*. Lancet, 2020. **396**(10249): p. 499-512.
272. Sziegoleit, A., *A novel proteinase from human pancreas*. Biochem J, 1984. **219**(3): p. 735-42.
273. Lam, K.W. and J. Leeds, *How to manage: patient with a low faecal elastase*. Frontline Gastroenterol, 2021. **12**(1): p. 67-73.
274. Phillips, M.E., et al., *Consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines*. BMJ Open Gastroenterol, 2021. **8**(1).
275. Perez-Johnston, R., N.I. Sainani, and D.V. Sahani, *Imaging of chronic pancreatitis (including groove and autoimmune pancreatitis)*. Radiol Clin North Am, 2012. **50**(3): p. 447-66.
276. Tan, G., et al., *Validation of the Brief Pain Inventory for chronic nonmalignant pain*. J Pain, 2004. **5**(2): p. 133-7.
277. Cleeland, C.S. and K.M. Ryan, *Pain assessment: global use of the Brief Pain Inventory*. Ann Acad Med Singap, 1994. **23**(2): p. 129-38.
278. Seicean, A., et al., *Pain in chronic pancreatitis: assessment and relief through treatment*. Rom J Gastroenterol, 2004. **13**(1): p. 9-15.
279. de las Heras, G., et al., *Drinking habits and pain in chronic pancreatitis*. J Clin Gastroenterol, 1995. **20**(1): p. 33-6.
280. Strum, W.B., *Abstinence in alcoholic chronic pancreatitis. Effect on pain and outcome*. J Clin Gastroenterol, 1995. **20**(1): p. 37-41.
281. Jeon, C.Y., et al., *Lifetime smoking history and cohort-based smoking prevalence in chronic pancreatitis*. Pancreatology, 2021.

282. Nasser, J., et al., *Elemental Diet as a Therapeutic Modality: A Comprehensive Review*. Dig Dis Sci, 2024. **69**(9): p. 3344-3360.
283. Kataoka, K., et al., *Effects of oral ingestion of the elemental diet in patients with painful chronic pancreatitis in the real-life setting in Japan*. Pancreas, 2014. **43**(3): p. 451-7.
284. Ikeura, T., et al., *Beneficial Effect of Low-Fat Elemental Diet Therapy on Pain in Chronic Pancreatitis*. Int J Chronic Dis, 2014. **2014**: p. 862091.
285. Morris-Stiff, G.J., et al., *The antioxidant profiles of patients with recurrent acute and chronic pancreatitis*. Am J Gastroenterol, 1999. **94**(8): p. 2135-40.
286. Ahmed Ali, U., et al., *Antioxidants for pain in chronic pancreatitis*. Cochrane Database Syst Rev, 2014. **2014**(8): p. CD008945.
287. Graham, G.G. and K.F. Scott, *Mechanism of action of paracetamol*. Am J Ther, 2005. **12**(1): p. 46-55.
288. Ayoub, S.S., *Paracetamol (acetaminophen): A familiar drug with an unexplained mechanism of action*. Temperature (Austin), 2021. **8**(4): p. 351-371.
289. Funk, C.D., *Prostaglandins and leukotrienes: advances in eicosanoid biology*. Science, 2001. **294**(5548): p. 1871-5.
290. Singh, V.K. and A.M. Drewes, *Medical Management of Pain in Chronic Pancreatitis*. Dig Dis Sci, 2017. **62**(7): p. 1721-1728.
291. Siepsiak, M., et al., *Pharmacokinetics of paracetamol in patients with chronic pancreatitis*. Pharmacol Rep, 2016. **68**(4): p. 733-6.
292. Wongrakpanich, S., et al., *A Comprehensive Review of Non-Steroidal Anti-Inflammatory Drug Use in The Elderly*. Aging Dis, 2018. **9**(1): p. 143-150.
293. Tai, F.W.D. and M.E. McAlindon, *Non-steroidal anti-inflammatory drugs and the gastrointestinal tract*. Clin Med (Lond), 2021. **21**(2): p. 131-134.
294. Sato, T., et al., *Gastric acid secretion and serum gastrin levels in chronic pancreatitis*. Gastroenterol Jpn, 1981. **16**(2): p. 93-9.
295. Vantini, I., et al., *Duodenal ulcer in chronic relapsing pancreatitis*. Digestion, 1982. **24**(1): p. 23-8.
296. Bovill, J.G., *Mechanisms of actions of opioids and non-steroidal anti-inflammatory drugs*. Eur J Anaesthesiol Suppl, 1997. **15**: p. 9-15.
297. Crush, J., et al., *Misappropriation of the 1986 WHO analgesic ladder: the pitfalls of labelling opioids as weak or strong*. Br J Anaesth, 2022. **129**(2): p. 137-142.
298. Angst, M.S. and J.D. Clark, *Opioid-induced hyperalgesia: a qualitative systematic review*. Anesthesiology, 2006. **104**(3): p. 570-87.

299. Chen, L., et al., *Altered quantitative sensory testing outcome in subjects with opioid therapy*. Pain, 2009. **143**(1-2): p. 65-70.
300. The Lancet Regional, H.-A., *Opioid crisis: addiction, overprescription, and insufficient primary prevention*. Lancet Reg Health Am, 2023. **23**: p. 100557.
301. Freynhagen, R., et al., *Pregabalin for neuropathic pain in primary care settings: recommendations for dosing and titration*. Postgrad Med, 2021. **133**(1): p. 1-9.
302. Alles, S.R.A., S.M. Cain, and T.P. Snutch, *Pregabalin as a Pain Therapeutic: Beyond Calcium Channels*. Front Cell Neurosci, 2020. **14**: p. 83.
303. Olesen, S.S., et al., *Pregabalin reduces pain in patients with chronic pancreatitis in a randomized, controlled trial*. Gastroenterology, 2011. **141**(2): p. 536-43.
304. Bouwense, S.A., et al., *Effects of pregabalin on central sensitization in patients with chronic pancreatitis in a randomized, controlled trial*. PLoS One, 2012. **7**(8): p. e42096.
305. Lawson, K., *A Brief Review of the Pharmacology of Amitriptyline and Clinical Outcomes in Treating Fibromyalgia*. Biomedicines, 2017. **5**(2).
306. Sindrup, S.H., et al., *Antidepressants in the treatment of neuropathic pain*. Basic Clin Pharmacol Toxicol, 2005. **96**(6): p. 399-409.
307. Goulden, M.R., *The pain of chronic pancreatitis: a persistent clinical challenge*. Br J Pain, 2013. **7**(1): p. 8-22.
308. Bouwense, S.A., et al., *S-ketamine modulates hyperalgesia in patients with chronic pancreatitis pain*. Reg Anesth Pain Med, 2011. **36**(3): p. 303-7.
309. Juel, J., et al., *Study protocol for a randomised, double-blinded, placebo-controlled, clinical trial of S-ketamine for pain treatment in patients with chronic pancreatitis (RESET trial)*. BMJ Open, 2015. **5**(3): p. e007087.
310. Kappis, M., *Experiences with local anesthesia in abdominal surgery*. Verh Dtsch Ges Circ, 1914.
311. Wiersema, M.J. and L.M. Wiersema, *Endosonography-guided celiac plexus neurolysis*. Gastrointest Endosc, 1996. **44**(6): p. 656-62.
312. Cornman-Homonoff, J., et al., *Celiac Plexus Block and Neurolysis in the Management of Chronic Upper Abdominal Pain*. Semin Intervent Radiol, 2017. **34**(4): p. 376-386.
313. Chan, L.K.M., et al., *A Systematic Review and Meta-Analysis of The Efficacy of Endoscopic Ultrasound Guided Celiac Plexus Blocks for Chronic Pancreatitis Pain*. J Pain Palliat Care Pharmacother, 2025: p. 1-12.
314. Gress, F., et al., *A prospective randomized comparison of endoscopic ultrasound- and computed tomography-guided celiac plexus block for managing chronic pancreatitis pain*. Am J Gastroenterol, 1999. **94**(4): p. 900-5.

315. Gress, F., *Endoscopic ultrasound-guided celiac plexus neurolysis*. Gastroenterol Hepatol (NY), 2007. **3**(4): p. 279-81.
316. Tandan, M. and D.N. Reddy, *Extracorporeal shock wave lithotripsy for pancreatic and large common bile duct stones*. World J Gastroenterol, 2011. **17**(39): p. 4365-71.
317. Tandan, M., et al., *Extracorporeal shock wave lithotripsy and endotherapy for pancreatic calculi- a large single center experience*. Indian J Gastroenterol, 2010. **29**(4): p. 143-8.
318. Costamagna, G., et al., *Extracorporeal shock wave lithotripsy of pancreatic stones in chronic pancreatitis: immediate and medium-term results*. Gastrointest Endosc, 1997. **46**(3): p. 231-6.
319. Tandan, M., et al., *ESWL for large pancreatic calculi: Report of over 5000 patients*. Pancreatology, 2019. **19**(7): p. 916-921.
320. van Huijgevoort, N.C.M., et al., *Success of extracorporeal shock wave lithotripsy and ERCP in symptomatic pancreatic duct stones: a systematic review and meta-analysis*. Endosc Int Open, 2020. **8**(8): p. E1070-E1085.
321. van der Gaag, N.A., et al., *Functional and medical outcomes after tailored surgery for pain due to chronic pancreatitis*. Ann Surg, 2012. **255**(4): p. 763-70.
322. van Veldhuisen, C.L., et al., *Surgery for chronic pancreatitis across Europe (ESCPA): prospective multicentre study*. Br J Surg, 2025. **112**(4).
323. Bouwense, S.A.W., et al., *Surgery in Chronic Pancreatitis: Indication, Timing and Procedures*. Visc Med, 2019. **35**(2): p. 110-118.
324. Layer, P. and J. Keller, *Lipase supplementation therapy: standards, alternatives, and perspectives*. Pancreas, 2003. **26**(1): p. 1-7.
325. Gan, C., et al., *Efficacy and safety of pancreatic enzyme replacement therapy on exocrine pancreatic insufficiency: a meta-analysis*. Oncotarget, 2017. **8**(55): p. 94920-94931.
326. Imrie, C.W., et al., *Review article: enzyme supplementation in cystic fibrosis, chronic pancreatitis, pancreatic and periampullary cancer*. Aliment Pharmacol Ther, 2010. **32** Suppl 1: p. 1-25.
327. Fieker, A., J. Philpott, and M. Armand, *Enzyme replacement therapy for pancreatic insufficiency: present and future*. Clin Exp Gastroenterol, 2011. **4**: p. 55-73.
328. Bruno, M.J., et al., *Maldigestion associated with exocrine pancreatic insufficiency: implications of gastrointestinal physiology and properties of enzyme preparations for a cause-related and patient-tailored treatment*. Am J Gastroenterol, 1995. **90**(9): p. 1383-93.
329. Krishnamurthy, D.M., et al., *Delayed release pancrelipase for treatment of pancreatic exocrine insufficiency associated with chronic pancreatitis*. Ther Clin Risk Manag, 2009. **5**(3): p. 507-20.

330. Taylor, J.R., et al., *Systematic review: efficacy and safety of pancreatic enzyme supplements for exocrine pancreatic insufficiency*. Aliment Pharmacol Ther, 2010. **31**(1): p. 57-72.
331. Whitcomb, D.C., et al., *Pancrelipase delayed-release capsules (CREON) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: A double-blind randomized trial*. Am J Gastroenterol, 2010. **105**(10): p. 2276-86.
332. de la Iglesia-Garcia, D., et al., *Efficacy of pancreatic enzyme replacement therapy in chronic pancreatitis: systematic review and meta-analysis*. Gut, 2017. **66**(8): p. 1354-1355.
333. Layer, P., V.L. Go, and E.P. DiMagno, *Fate of pancreatic enzymes during small intestinal aboral transit in humans*. Am J Physiol, 1986. **251**(4 Pt 1): p. G475-80.
334. DiMagno, E.P., et al., *Fate of orally ingested enzymes in pancreatic insufficiency. Comparison of two dosage schedules*. N Engl J Med, 1977. **296**(23): p. 1318-22.
335. Elliott, D.W., *Effect of lost pancreatic juice on gastric acid and peptic ulcer*. Am J Surg, 1974. **127**(6): p. 658-62.
336. DiMagno, E.P., *Gastric acid suppression and treatment of severe exocrine pancreatic insufficiency*. Best Pract Res Clin Gastroenterol, 2001. **15**(3): p. 477-86.
337. Nakajima, K., et al., *Pancrelipase: an evidence-based review of its use for treating pancreatic exocrine insufficiency*. Core Evid, 2012. **7**: p. 77-91.
338. Dodge, J.A., *Fibrosing colonopathy: recent advances*. J R Soc Med, 1996. **89 Suppl 27**(Suppl 27): p. 19-23.
339. FitzSimmons, S.C., et al., *High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis*. N Engl J Med, 1997. **336**(18): p. 1283-9.
340. Smyth, R.L., et al., *Strictures of ascending colon in cystic fibrosis and high-strength pancreatic enzymes*. Lancet, 1994. **343**(8889): p. 85-6.
341. Bansi, D.S., et al., *Fibrosing colonopathy in an adult owing to over use of pancreatic enzyme supplements*. Gut, 2000. **46**(2): p. 283-5.
342. Brett, A.S. and E.H. Mack, *Fibrosing colonopathy in adults with cystic fibrosis*. AJR Am J Roentgenol, 2008. **190**(1): p. W73.
343. Dhanasekaran, R. and P.P. Toskes, *Pancrelipase for pancreatic disorders: An update*. Drugs Today (Barc), 2010. **46**(11): p. 855-66.
344. Shlieout, G., et al., *Administration of CREON(R) pancrelipase pellets via gastrostomy tube is feasible with no loss of gastric resistance or lipase activity: an in vitro study*. Clin Drug Investig, 2011. **31**(7): p. e1-7.
345. Duggan, S.N., et al., *The prevalence of malnutrition and fat-soluble vitamin deficiencies in chronic pancreatitis*. Nutr Clin Pract, 2014. **29**(3): p. 348-54.

346. Sikkens, E.C., et al., *The prevalence of fat-soluble vitamin deficiencies and a decreased bone mass in patients with chronic pancreatitis*. *Pancreatology*, 2013. **13**(3): p. 238-42.
347. Arvanitakis, M., et al., *ESPEN practical guideline on clinical nutrition in acute and chronic pancreatitis*. *Clin Nutr*, 2024. **43**(2): p. 395-412.
348. Gullo, L., L. Barbara, and G. Labo, *Effect of cessation of alcohol use on the course of pancreatic dysfunction in alcoholic pancreatitis*. *Gastroenterology*, 1988. **95**(4): p. 1063-8.
349. Alexandre, M., et al., *The emerging role of smoking in the development of pancreatitis*. *Pancreatology*, 2011. **11**(5): p. 469-74.
350. Jupp, J., D. Fine, and C.D. Johnson, *The epidemiology and socioeconomic impact of chronic pancreatitis*. *Best Pract Res Clin Gastroenterol*, 2010. **24**(3): p. 219-31.
351. Lankisch, P.G., et al., *Natural course in chronic pancreatitis. Pain, exocrine and endocrine pancreatic insufficiency and prognosis of the disease*. *Digestion*, 1993. **54**(3): p. 148-55.
352. Mullady, D.K., et al., *Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: a prospective cohort study*. *Gut*, 2011. **60**(1): p. 77-84.
353. Anderson, M.A., et al., *Mechanism, assessment and management of pain in chronic pancreatitis: Recommendations of a multidisciplinary study group*. *Pancreatology*, 2016. **16**(1): p. 83-94.
354. Braganza, J.M., et al., *Chronic pancreatitis*. *Lancet*, 2011. **377**(9772): p. 1184-97.
355. Majumder, S. and S.T. Chari, *Chronic pancreatitis*. *Lancet*, 2016. **387**(10031): p. 1957-66.
356. Duggan, S.N., et al., *High prevalence of osteoporosis in patients with chronic pancreatitis: a systematic review and meta-analysis*. *Clin Gastroenterol Hepatol*, 2014. **12**(2): p. 219-28.
357. Spagnolo, D.M., et al., *Acute and Chronic Pancreatitis Disease Prevalence, Classification, and Comorbidities: A Cohort Study of the UK BioBank*. *Clin Transl Gastroenterol*, 2022. **13**(1): p. e00455.
358. Rizk, M.K. and H. Gerke, *Utility of endoscopic ultrasound in pancreatitis: a review*. *World J Gastroenterol*, 2007. **13**(47): p. 6321-6.
359. Singh, V.K., et al., *Less common etiologies of exocrine pancreatic insufficiency*. *World J Gastroenterol*, 2017. **23**(39): p. 7059-7076.
360. Kamat, R., P. Gupta, and S. Rana, *Imaging in chronic pancreatitis: State of the art review*. *Indian J Radiol Imaging*, 2019. **29**(2): p. 201-210.
361. Tirkes, T., et al., *Reporting Standards for Chronic Pancreatitis by Using CT, MRI, and MR Cholangiopancreatography: The Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer*. *Radiology*, 2019. **290**(1): p. 207-215.

362. Vujasinovic, M., et al., *Risk of Developing Pancreatic Cancer in Patients with Chronic Pancreatitis*. J Clin Med, 2020. **9**(11).
363. Conwell, D.L., et al., *Validation of Demographics, Etiology, and Risk Factors for Chronic Pancreatitis in the USA: A Report of the North American Pancreas Study (NAPS) Group*. Dig Dis Sci, 2017. **62**(8): p. 2133-2140.
364. Wilcox, C.M., et al., *Racial Differences in the Clinical Profile, Causes, and Outcome of Chronic Pancreatitis*. Am J Gastroenterol, 2016. **111**(10): p. 1488-1496.
365. Choueiri, N.E., et al., *Advanced imaging of chronic pancreatitis*. Curr Gastroenterol Rep, 2010. **12**(2): p. 114-20.
366. Sinha, A., et al., *Abdominal CT predictors of fibrosis in patients with chronic pancreatitis undergoing surgery*. Eur Radiol, 2015. **25**(5): p. 1339-46.
367. Yamashita, Y., R. Ashida, and M. Kitano, *Imaging of Fibrosis in Chronic Pancreatitis*. Front Physiol, 2021. **12**: p. 800516.
368. Morris-Stiff, G., et al., *Endoscopic ultrasound reliably identifies chronic pancreatitis when other imaging modalities have been non-diagnostic*. JOP, 2009. **10**(3): p. 280-3.
369. Albashir, S., et al., *Endoscopic ultrasound, secretin endoscopic pancreatic function test, and histology: correlation in chronic pancreatitis*. Am J Gastroenterol, 2010. **105**(11): p. 2498-503.
370. Stevens, T., et al., *Multicenter comparison of the interobserver agreement of standard EUS scoring and Rosemont classification scoring for diagnosis of chronic pancreatitis*. Gastrointest Endosc, 2010. **71**(3): p. 519-26.
371. Kalmin, B., et al., *Conventional versus Rosemont endoscopic ultrasound criteria for chronic pancreatitis: comparing interobserver reliability and intertest agreement*. Can J Gastroenterol, 2011. **25**(5): p. 261-4.
372. D'Souza, S.L., et al., *EUS Diagnostic Criteria for Chronic Pancreatitis: A Comparison of Conventional Versus Rosemont Criteria*. Dig Dis Sci, 2015. **60**(12): p. 3782-7.
373. Tirkes, T., *Chronic Pancreatitis: What the Clinician Wants to Know from MR Imaging*. Magn Reson Imaging Clin N Am, 2018. **26**(3): p. 451-461.
374. Tirkes, T., et al., *Detection of exocrine dysfunction by MRI in patients with early chronic pancreatitis*. Abdom Radiol (NY), 2017. **42**(2): p. 544-551.
375. Lohr, J.M., et al., *United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU)*. United European Gastroenterol J, 2017. **5**(2): p. 153-199.
376. Herzig, K.H., et al., *Fecal pancreatic elastase-1 levels in older individuals without known gastrointestinal diseases or diabetes mellitus*. BMC Geriatr, 2011. **11**: p. 4.

377. Shandro, B.M., et al., *The investigation and management of pancreatic exocrine insufficiency: A retrospective cohort study*. Clin Med (Lond), 2020. **20**(6): p. 535-540.
378. Reddy, N.G., S. Nangia, and M.J. DiMagno, *The Chronic Pancreatitis International Classification of Diseases, Ninth Revision, Clinical Modification Code 577.1 Is Inaccurate Compared With Criterion-Standard Clinical Diagnostic Scoring Systems*. Pancreas, 2016. **45**(9): p. 1276-1281.
379. Brennan, G.T. and M.W. Saif, *Pancreatic Enzyme Replacement Therapy: A Concise Review*. JOP, 2019. **20**(5): p. 121-125.
380. Dominguez-Munoz, J.E., et al., *A Spanish multicenter study to estimate the prevalence and incidence of chronic pancreatitis and its complications*. Rev Esp Enferm Dig, 2014. **106**(4): p. 239-45.
381. Capurso, G., et al., *Prevalence of chronic pancreatitis: Results of a primary care physician-based population study*. Dig Liver Dis, 2017. **49**(5): p. 535-539.
382. Machicado, J.D., et al., *Period prevalence of chronic pancreatitis diagnosis from 2001-2013 in the commercially insured population of the United States*. Pancreatology, 2019. **19**(6): p. 813-818.
383. Kirkegard, J., F.V. Mortensen, and D. Cronin-Fenton, *Chronic Pancreatitis and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis*. Am J Gastroenterol, 2017. **112**(9): p. 1366-1372.
384. Hansen, T.H., et al., *Chronic pancreatitis and extrapancreatic cancer: a retrospective study among 181 patients with chronic pancreatitis*. Int J Pancreatol, 1995. **18**(3): p. 235-9.
385. Ammann, R.W., et al., *High incidence of extrapancreatic carcinoma in chronic pancreatitis*. Scand J Gastroenterol, 1980. **15**(4): p. 395-9.
386. Miron, N., et al., *Proinflammatory cytokines: an insight into pancreatic oncogenesis*. Roum Arch Microbiol Immunol, 2010. **69**(4): p. 183-9.
387. Sandstrom, A., et al., *Serum proteome profiling of pancreatitis using recombinant antibody microarrays reveals disease-associated biomarker signatures*. Proteomics Clin Appl, 2012. **6**(9-10): p. 486-96.
388. Sri Manjari, K., et al., *A single-nucleotide polymorphism in tumor necrosis factor-alpha (-308 G/A) as a biomarker in chronic pancreatitis*. Gene, 2014. **539**(2): p. 186-9.
389. Kwasniak, K., et al., *Scientific reports concerning the impact of interleukin 4, interleukin 10 and transforming growth factor beta on cancer cells*. Cent Eur J Immunol, 2019. **44**(2): p. 190-200.

390. Joshi, B.H., et al., *Interleukin-4 receptor alpha overexpression in human bladder cancer correlates with the pathological grade and stage of the disease*. *Cancer Med*, 2014. **3**(6): p. 1615-28.
391. Rahaman, S.O., M.A. Vogelbaum, and S.J. Haque, *Aberrant Stat3 signaling by interleukin-4 in malignant glioma cells: involvement of IL-13Ralphaz*. *Cancer Res*, 2005. **65**(7): p. 2956-63.
392. Murata, T., N.I. Obiri, and R.K. Puri, *Human ovarian-carcinoma cell lines express IL-4 and IL-13 receptors: comparison between IL-4- and IL-13-induced signal transduction*. *Int J Cancer*, 1997. **70**(2): p. 230-40.
393. Kawakami, M., et al., *Interleukin 4 receptor on human lung cancer: a molecular target for cytotoxin therapy*. *Clin Cancer Res*, 2002. **8**(11): p. 3503-11.
394. Venmar, K.T., et al., *IL4 receptor alpha mediates enhanced glucose and glutamine metabolism to support breast cancer growth*. *Biochim Biophys Acta*, 2015. **1853**(5): p. 1219-28.
395. Koller, F.L., et al., *Epithelial interleukin-4 receptor expression promotes colon tumor growth*. *Carcinogenesis*, 2010. **31**(6): p. 1010-7.
396. Xu, J., et al., *IL-6/STAT3 Is a Promising Therapeutic Target for Hepatocellular Carcinoma*. *Front Oncol*, 2021. **11**: p. 760971.
397. Ghoshal, S., B.C. Fuchs, and K.K. Tanabe, *STAT3 is a key transcriptional regulator of cancer stem cell marker CD133 in HCC*. *Hepatobiliary Surg Nutr*, 2016. **5**(3): p. 201-3.
398. Zheng, X., et al., *IL-6/STAT3 axis initiated CAFs via up-regulating TIMP-1 which was attenuated by acetylation of STAT3 induced by PCAF in HCC microenvironment*. *Cell Signal*, 2016. **28**(9): p. 1314-1324.
399. Lee, Y.S., et al., *Interleukin-8 and its receptor CXCR2 in the tumour microenvironment promote colon cancer growth, progression and metastasis*. *Br J Cancer*, 2012. **106**(11): p. 1833-41.
400. Chen, L.C., et al., *Alteration of gene expression in normal-appearing colon mucosa of APC(min) mice and human cancer patients*. *Cancer Res*, 2004. **64**(10): p. 3694-700.
401. Sheikhpour, E., et al., *A Survey on the Role of Interleukin-10 in Breast Cancer: A Narrative*. *Rep Biochem Mol Biol*, 2018. **7**(1): p. 30-37.
402. Walczak, A., et al., *Association of -1112 c/t promoter region polymorphism of the interleukin 13 gene with occurrence of colorectal cancer*. *Pol Przegl Chir*, 2011. **83**(1): p. 27-31.
403. Gunter, M.J., et al., *Inflammation-related gene polymorphisms and colorectal adenoma*. *Cancer Epidemiol Biomarkers Prev*, 2006. **15**(6): p. 1126-31.
404. Landvik, N.E., et al., *A specific interleukin-1B haplotype correlates with high levels of IL1B mRNA in the lung and increased risk of non-small cell lung cancer*. *Carcinogenesis*, 2009. **30**(7): p. 1186-92.

405. Nakao, S., et al., *Infiltration of COX-2-expressing macrophages is a prerequisite for IL-1 beta-induced neovascularization and tumor growth*. J Clin Invest, 2005. **115**(11): p. 2979-91.
406. Brierly, G., et al., *Tumour Necrosis Factor Alpha (TNF-alpha) and Oral Squamous Cell Carcinoma*. Cancers (Basel), 2023. **15**(6).
407. Sheen, Y.Y., et al., *Targeting the Transforming Growth Factor-beta Signaling in Cancer Therapy*. Biomol Ther (Seoul), 2013. **21**(5): p. 323-31.
408. Zhao, B. and Y.G. Chen, *Regulation of TGF-beta Signal Transduction*. Scientifica (Cairo), 2014. **2014**: p. 874065.
409. Villalba, M., et al., *Role of TGF-beta in metastatic colon cancer: it is finally time for targeted therapy*. Cell Tissue Res, 2017. **370**(1): p. 29-39.
410. Sung, H., et al., *Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries*. CA Cancer J Clin, 2021. **71**(3): p. 209-249.
411. Deo, S.V.S., J. Sharma, and S. Kumar, *GLOBOCAN 2020 Report on Global Cancer Burden: Challenges and Opportunities for Surgical Oncologists*. Ann Surg Oncol, 2022. **29**(11): p. 6497-6500.
412. Page, M.J., et al., *The PRISMA 2020 statement: an updated guideline for reporting systematic reviews*. BMJ, 2021. **372**: p. n71.
413. Viechtbauer, W., *Conducting meta-analyses in {R} with the {metafor} package*. Journal of Statistical Software, 2010. **36**: p. 1-48.
414. Bang, U.C., et al., *Mortality, cancer, and comorbidities associated with chronic pancreatitis: a Danish nationwide matched-cohort study*. Gastroenterology, 2014. **146**(4): p. 989-94.
415. Dahabra, L., et al., *Soo47 Chronic Pancreatitis as a Possible Risk Factor for Colorectal Cancer: A Large Population Data Analysis*. Official journal of the American College of Gastroenterology | ACG, 2020. **115**: p. S23.
416. Goldacre, M.J., et al., *Liver cirrhosis, other liver diseases, pancreatitis and subsequent cancer: record linkage study*. Eur J Gastroenterol Hepatol, 2008. **20**(5): p. 384-92.
417. Han, M., T.P.T. Tran, and J.K. Oh, *Chronic pancreatitis and cancer risk in a matched cohort study using national claims data in South Korea*. Sci Rep, 2022. **12**(1): p. 5545.
418. Hsieh, C.C., et al., *The Impact of Chronic Pancreatitis on the Occurrences of Human Cancers: Real-World Data*. J Clin Med, 2023. **12**(15).
419. Thorsgaard Pedersen, N., et al., *Chronic pancreatitis in Copenhagen. A retrospective study of 64 consecutive patients*. Scand J Gastroenterol, 1982. **17**(7): p. 925-31.
420. Pedrazzoli, S., et al., *Survival rates and cause of death in 174 patients with chronic pancreatitis*. J Gastrointest Surg, 2008. **12**(11): p. 1930-7.

421. Rocca, G., et al., *Increased incidence of cancer in chronic pancreatitis*. J Clin Gastroenterol, 1987. **9**(2): p. 175-9.
422. Talamini, G., et al., *Incidence of cancer in the course of chronic pancreatitis*. Am J Gastroenterol, 1999. **94**(5): p. 1253-60.
423. Thuluvath, P.J., et al., *Chronic pancreatitis. Long-term pain relief with or without surgery, cancer risk, and mortality*. J Clin Gastroenterol, 2003. **36**(2): p. 159-65.
424. Lowenfels, A.B., et al., *Prognosis of chronic pancreatitis: an international multicenter study. International Pancreatitis Study Group*. Am J Gastroenterol, 1994. **89**(9): p. 1467-71.
425. Kamisawa, T., et al., *The incidence of pancreatic and extrapancreatic cancers in Japanese patients with chronic pancreatitis*. Hepatogastroenterology, 2007. **54**(77): p. 1579-81.
426. *Critical Appraisal Skills Programme. CASP (Cohort Study)*. 2018.
427. Pedersen, N., et al., *Alcohol modulates circulating levels of interleukin-6 and monocyte chemoattractant protein-1 in chronic pancreatitis*. Scand J Gastroenterol, 2004. **39**(3): p. 277-82.
428. Ioannou, G.N., et al., *Incidence and predictors of hepatocellular carcinoma in patients with cirrhosis*. Clin Gastroenterol Hepatol, 2007. **5**(8): p. 938-45, 945 e1-4.
429. Huang, D.Q., et al., *Global epidemiology of cirrhosis - aetiology, trends and predictions*. Nat Rev Gastroenterol Hepatol, 2023. **20**(6): p. 388-398.
430. Alberts, C.J., et al., *Worldwide prevalence of hepatitis B virus and hepatitis C virus among patients with cirrhosis at country, region, and global levels: a systematic review*. Lancet Gastroenterol Hepatol, 2022. **7**(8): p. 724-735.
431. Tapper, E.B. and N.D. Parikh, *Diagnosis and Management of Cirrhosis and Its Complications: A Review*. JAMA, 2023. **329**(18): p. 1589-1602.
432. Herreros-Villanueva, M., et al., *Alcohol consumption on pancreatic diseases*. World J Gastroenterol, 2013. **19**(5): p. 638-47.
433. Pace, A., et al., *Pancreas and liver injury are associated in individuals with increased alcohol consumption*. Clin Gastroenterol Hepatol, 2009. **7**(11): p. 1241-6.
434. Rossi, M., et al., *Colorectal Cancer and Alcohol Consumption-Populations to Molecules*. Cancers (Basel), 2018. **10**(2).
435. Molina, P.E., et al., *Focus on: Alcohol and the immune system*. Alcohol Res Health, 2010. **33**(1-2): p. 97-108.
436. Wenzke, K.E., et al., *Identifying common genes and networks in multi-organ fibrosis*. AMIA Jt Summits Transl Sci Proc, 2012. **2012**: p. 106-15.

437. Talamini, G., et al., *Alcohol and smoking as risk factors in chronic pancreatitis and pancreatic cancer*. Dig Dis Sci, 1999. **44**(7): p. 1303-11.
438. Yadav, D. and D.C. Whitcomb, *The role of alcohol and smoking in pancreatitis*. Nat Rev Gastroenterol Hepatol, 2010. **7**(3): p. 131-45.
439. de Groot, P.M., et al., *The epidemiology of lung cancer*. Transl Lung Cancer Res, 2018. **7**(3): p. 220-233.
440. Bray, F., et al., *Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries*. CA Cancer J Clin, 2024. **74**(3): p. 229-263.
441. Sasco, A.J., M.B. Secretan, and K. Straif, *Tobacco smoking and cancer: a brief review of recent epidemiological evidence*. Lung Cancer, 2004. **45 Suppl 2**: p. S3-9.
442. Hecht, S.S., *Cigarette smoking: cancer risks, carcinogens, and mechanisms*. Langenbecks Arch Surg, 2006. **391**(6): p. 603-13.
443. Nooshinfar, E., et al., *The Molecular Mechanisms of Tobacco in Cancer Pathogenesis*. Int J Cancer Manag, 2017. **10**(1): p. e7902.
444. Seitz, H.K. and F. Stickel, *Molecular mechanisms of alcohol-mediated carcinogenesis*. Nat Rev Cancer, 2007. **7**(8): p. 599-612.
445. Linhart, K., H. Bartsch, and H.K. Seitz, *The role of reactive oxygen species (ROS) and cytochrome P-450 2E1 in the generation of carcinogenic etheno-DNA adducts*. Redox Biol, 2014. **3**: p. 56-62.
446. Ratna, A. and P. Mandrekar, *Alcohol and Cancer: Mechanisms and Therapies*. Biomolecules, 2017. **7**(3).
447. Medaglio, D., A.J. Stephens-Shields, and C.E. Leonard, *Research and scholarly methods: Propensity scores*. J Am Coll Clin Pharm, 2022. **5**(4): p. 467-475.
448. Thierens, N., et al., *Chronic pancreatitis*. Lancet, 2025. **404**(10471): p. 2605-2618.
449. Shauntelle Quammie, A.R., Rahul Munyal, Edward S Nicholson, Christopher Clarke, Suresh V Venkatachalapathy, Colin J Crooks, Guruprasad P Aithal, Aloysious D Aravinthan *Chronic pancreatitis: a case ascertainment study*. Frontline Gastroenterol, 2025. **16**: p. 300-307.
450. Manohar, M., et al., *Pathogenic mechanisms of pancreatitis*. World J Gastrointest Pharmacol Ther, 2017. **8**(1): p. 10-25.
451. Hagn-Meincke, R., et al., *Circulating immune signatures in chronic pancreatitis with and without preceding acute pancreatitis: A pilot study*. Pancreatology, 2024. **24**(3): p. 384-393.
452. Kong, X., et al., *Chronic Pancreatitis and Pancreatic Cancer*. Gastrointest Tumors, 2014. **1**(3): p. 123-34.

453. Cote, G.A., et al., *Alcohol and smoking as risk factors in an epidemiology study of patients with chronic pancreatitis*. Clin Gastroenterol Hepatol, 2011. **9**(3): p. 266-73; quiz e27.
454. Shadhu, K. and C. Xi, *Inflammation and pancreatic cancer: An updated review*. Saudi J Gastroenterol, 2019. **25**(1): p. 3-13.
455. Rayet, B. and C. Gelinas, *Aberrant rel/nfkb genes and activity in human cancer*. Oncogene, 1999. **18**(49): p. 6938-47.
456. Zheng, M., et al., *Interleukin-6 participates in human pancreatic stellate cell activation and collagen I production via TGF-beta1/Smad pathway*. Cytokine, 2021. **143**: p. 155536.
457. Stanam, A., et al., *Upregulated interleukin-6 expression contributes to erlotinib resistance in head and neck squamous cell carcinoma*. Mol Oncol, 2015. **9**(7): p. 1371-83.
458. Abulaiti, A., et al., *Interaction between non-small-cell lung cancer cells and fibroblasts via enhancement of TGF-beta signaling by IL-6*. Lung Cancer, 2013. **82**(2): p. 204-13.
459. Chang, Q., et al., *The IL-6/JAK/Stat3 feed-forward loop drives tumorigenesis and metastasis*. Neoplasia, 2013. **15**(7): p. 848-62.
460. Manore, S.G., et al., *IL-6/JAK/STAT3 Signaling in Breast Cancer Metastasis: Biology and Treatment*. Front Oncol, 2022. **12**: p. 866014.
461. Szulc-Kielbik, I., et al., *The implication of IL-6 in the invasiveness and chemoresistance of ovarian cancer cells. Systematic review of its potential role as a biomarker in ovarian cancer patients*. Biochim Biophys Acta Rev Cancer, 2021. **1876**(2): p. 188639.
462. Browning, L., et al., *IL-6 and ovarian cancer: inflammatory cytokines in promotion of metastasis*. Cancer Manag Res, 2018. **10**: p. 6685-6693.
463. Jobe, N.P., et al., *Simultaneous blocking of IL-6 and IL-8 is sufficient to fully inhibit CAF-induced human melanoma cell invasiveness*. Histochem Cell Biol, 2016. **146**(2): p. 205-17.
464. Meier, C. and A. Brieger, *The role of IL-8 in cancer development and its impact on immunotherapy resistance*. Eur J Cancer, 2025. **218**: p. 115267.
465. Rafaqat, S., et al., *Interleukins: pathophysiological role in acute pancreatitis*. Arch Med Sci, 2024. **20**(1): p. 138-156.
466. Vineis, P., et al., *Tobacco and cancer: recent epidemiological evidence*. J Natl Cancer Inst, 2004. **96**(2): p. 99-106.
467. Rumgay, H., et al., *Alcohol and Cancer: Epidemiology and Biological Mechanisms*. Nutrients, 2021. **13**(9).
468. Verlaan, M., et al., *Assessment of oxidative stress in chronic pancreatitis patients*. World J Gastroenterol, 2006. **12**(35): p. 5705-10.

469. Quammie, S., et al., *Chronic pancreatitis and extra pancreatic cancers- A systematic review and meta analysis*. Pancreatology, 2025. **25**(4): p. 516-527.
470. Bagnardi, V., et al., *Alcohol consumption and the risk of cancer: a meta-analysis*. Alcohol Res Health, 2001. **25**(4): p. 263-70.
471. Maier, H., et al., *The effect of chronic ethanol consumption on salivary gland morphology and function in the rat*. Alcohol Clin Exp Res, 1986. **10**(4): p. 425-7.
472. Helander, A. and K. Lindahl-Kiessling, *Increased frequency of acetaldehyde-induced sister-chromatid exchanges in human lymphocytes treated with an aldehyde dehydrogenase inhibitor*. Mutat Res, 1991. **264**(3): p. 103-7.
473. Seitz, H.K., G. Poschl, and U.A. Simanowski, *Alcohol and cancer*. Recent Dev Alcohol, 1998. **14**: p. 67-95.
474. Asakage, T., et al., *Genetic polymorphisms of alcohol and aldehyde dehydrogenases, and drinking, smoking and diet in Japanese men with oral and pharyngeal squamous cell carcinoma*. Carcinogenesis, 2007. **28**(4): p. 865-74.
475. Bosron, W.F., T. Ehrig, and T.K. Li, *Genetic factors in alcohol metabolism and alcoholism*. Semin Liver Dis, 1993. **13**(2): p. 126-35.
476. Fang, F., et al., *Association between alcohol dehydrogenase 1C gene *1/*2 polymorphism and pancreatitis risk: a meta-analysis*. Genet Mol Res, 2015. **14**(4): p. 15267-75.
477. Coutelle, C., et al., *Laryngeal and oropharyngeal cancer, and alcohol dehydrogenase 3 and glutathione S-transferase M1 polymorphisms*. Hum Genet, 1997. **99**(3): p. 319-25.
478. Harty, L.C., et al., *Alcohol dehydrogenase 3 genotype and risk of oral cavity and pharyngeal cancers*. J Natl Cancer Inst, 1997. **89**(22): p. 1698-705.
479. Visapaa, J.P., et al., *Increased cancer risk in heavy drinkers with the alcohol dehydrogenase 1C*1 allele, possibly due to salivary acetaldehyde*. Gut, 2004. **53**(6): p. 871-6.
480. Salaspuro, M.P., *Acetaldehyde, microbes, and cancer of the digestive tract*. Crit Rev Clin Lab Sci, 2003. **40**(2): p. 183-208.
481. Kolodecik, T., et al., *Risk factors for pancreatic cancer: underlying mechanisms and potential targets*. Front Physiol, 2013. **4**: p. 415.
482. Bachem, M.G., et al., *Pancreatic carcinoma cells induce fibrosis by stimulating proliferation and matrix synthesis of stellate cells*. Gastroenterology, 2005. **128**(4): p. 907-21.
483. Hwang, R.F., et al., *Cancer-associated stromal fibroblasts promote pancreatic tumor progression*. Cancer Res, 2008. **68**(3): p. 918-26.
484. Erkan, M., et al., *The role of stroma in pancreatic cancer: diagnostic and therapeutic implications*. Nat Rev Gastroenterol Hepatol, 2012. **9**(8): p. 454-67.

485. Whitcomb, D.C., *Genetics of alcoholic and nonalcoholic pancreatitis*. Curr Opin Gastroenterol, 2012. **28**(5): p. 501-6.
486. Rosendahl, J., et al., *Hereditary chronic pancreatitis*. Orphanet J Rare Dis, 2007. **2**: p. 1.
487. Witt, H., et al., *Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis*. Nat Genet, 2000. **25**(2): p. 213-6.
488. Muller, N., et al., *Natural history of SPINK1 germline mutation related-pancreatitis*. EBioMedicine, 2019. **48**: p. 581-591.
489. Cazacu, I.M., et al., *Pancreatitis-Associated Genes and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis*. Pancreas, 2018. **47**(9): p. 1078-1086.
490. Brand, H., et al., *Variation in the gamma-glutamyltransferase 1 gene and risk of chronic pancreatitis*. Pancreas, 2013. **42**(5): p. 836-40.
491. Liao, W., et al., *Circulating gamma-glutamyl transpeptidase and risk of pancreatic cancer: A prospective cohort study in the UK Biobank*. Cancer Med, 2023. **12**(7): p. 7877-7887.
492. Zein, C.O., et al., *Smoking and severity of hepatic fibrosis in nonalcoholic fatty liver disease*. J Hepatol, 2011. **54**(4): p. 753-9.
493. Aleksandrova, K., et al., *Inflammatory and metabolic biomarkers and risk of liver and biliary tract cancer*. Hepatology, 2014. **60**(3): p. 858-71.
494. Hyun, J., et al., *Pathophysiological Aspects of Alcohol Metabolism in the Liver*. Int J Mol Sci, 2021. **22**(11).
495. Seitz, H.K. and F. Stickel, *Acetaldehyde as an underestimated risk factor for cancer development: role of genetics in ethanol metabolism*. Genes Nutr, 2010. **5**(2): p. 121-8.
496. Seitz, H.K. and P. Becker, *Alcohol metabolism and cancer risk*. Alcohol Res Health, 2007. **30**(1): p. 38-41, 44-7.
497. Aggarwal, V., et al., *Role of Reactive Oxygen Species in Cancer Progression: Molecular Mechanisms and Recent Advancements*. Biomolecules, 2019. **9**(11).
498. Waris, G. and H. Ahsan, *Reactive oxygen species: role in the development of cancer and various chronic conditions*. J Carcinog, 2006. **5**: p. 14.
499. Kleiner, D.E., et al., *Association of Histologic Disease Activity With Progression of Nonalcoholic Fatty Liver Disease*. JAMA Netw Open, 2019. **2**(10): p. e1912565.
500. Tanaka, K., et al., *Cigarette smoking and liver cancer risk: an evaluation based on a systematic review of epidemiologic evidence among Japanese*. Jpn J Clin Oncol, 2006. **36**(7): p. 445-56.
501. Walser, T., et al., *Smoking and lung cancer: the role of inflammation*. Proc Am Thorac Soc, 2008. **5**(8): p. 811-5.
502. Hecht, S.S., *Lung carcinogenesis by tobacco smoke*. Int J Cancer, 2012. **131**(12): p. 2724-32.

503. Takahashi, H., et al., *Tobacco smoke promotes lung tumorigenesis by triggering IKKbeta- and JNK1-dependent inflammation*. *Cancer Cell*, 2010. **17**(1): p. 89-97.
504. Poulsen, V.V., et al., *Circulating Biomarkers Involved in the Development of and Progression to Chronic Pancreatitis-A Literature Review*. *Biomolecules*, 2024. **14**(2).
505. Garon, E.B., J. Chih-Hsin Yang, and S.M. Dubinett, *The Role of Interleukin 1beta in the Pathogenesis of Lung Cancer*. *JTO Clin Res Rep*, 2020. **1**(1): p. 1000001.
506. Pine, S.R., et al., *Increased levels of circulating interleukin 6, interleukin 8, C-reactive protein, and risk of lung cancer*. *J Natl Cancer Inst*, 2011. **103**(14): p. 1112-22.
507. Clague, J., et al., *Sensitivity to NNKOAc is associated with renal cancer risk*. *Carcinogenesis*, 2009. **30**(4): p. 706-10.
508. Li, Y. and S.S. Hecht, *Metabolic Activation and DNA Interactions of Carcinogenic N-Nitrosamines to Which Humans Are Commonly Exposed*. *Int J Mol Sci*, 2022. **23**(9).
509. Scelo, G. and T.L. Larose, *Epidemiology and Risk Factors for Kidney Cancer*. *J Clin Oncol*, 2018. **36**(36): p. JCO2018791905.
510. van der Mij, J.C., et al., *Novel drugs that target the metabolic reprogramming in renal cell cancer*. *Cancer Metab*, 2016. **4**: p. 14.
511. Sato, Y., et al., *Integrated molecular analysis of clear-cell renal cell carcinoma*. *Nat Genet*, 2013. **45**(8): p. 860-7.
512. Voss, M.H., et al., *Tumor genetic analyses of patients with metastatic renal cell carcinoma and extended benefit from mTOR inhibitor therapy*. *Clin Cancer Res*, 2014. **20**(7): p. 1955-64.
513. Elghazi, L., et al., *Role of nutrients and mTOR signaling in the regulation of pancreatic progenitors development*. *Mol Metab*, 2017. **6**(6): p. 560-573.
514. Chan, A.T. and E.L. Giovannucci, *Primary prevention of colorectal cancer*. *Gastroenterology*, 2010. **138**(6): p. 2029-2043 e10.
515. Carr, P.R., et al., *Estimation of Absolute Risk of Colorectal Cancer Based on Healthy Lifestyle, Genetic Risk, and Colonoscopy Status in a Population-Based Study*. *Gastroenterology*, 2020. **159**(1): p. 129-138 e9.
516. Di Sebastiano, P., et al., *Expression of interleukin 8 (IL-8) and substance P in human chronic pancreatitis*. *Gut*, 2000. **47**(3): p. 423-8.
517. Najdaghi, S., S. Razi, and N. Rezaei, *An overview of the role of interleukin-8 in colorectal cancer*. *Cytokine*, 2020. **135**: p. 155205.
518. Li, T., et al., *Global and regional burden of pancreatitis: epidemiological trends, risk factors, and projections to 2050 from the global burden of disease study 2021*. *BMC Gastroenterol*, 2024. **24**(1): p. 398.

519. Jiang, W., et al., *Age-period-cohort analysis of pancreatitis epidemiological trends from 1990 to 2019 and forecasts for 2044: a systematic analysis from the Global Burden of Disease Study 2019*. Front Public Health, 2023. **11**: p. 1118888.
520. Pan, J., et al., *Risk Factors for Diabetes Mellitus in Chronic Pancreatitis: A Cohort of 2,011 Patients*. Medicine (Baltimore), 2016. **95**(14): p. e3251.
521. Oh, T.K. and I.A. Song, *Five-year mortality trends associated with chronic pancreatitis in South Korea: A population based cohort study*. Pancreatology, 2020. **20**(5): p. 828-833.
522. Levy, P., et al., *Mortality factors associated with chronic pancreatitis. Unidimensional and multidimensional analysis of a medical-surgical series of 240 patients*. Gastroenterology, 1989. **96**(4): p. 1165-72.
523. Nojgaard, C., et al., *Danish patients with chronic pancreatitis have a four-fold higher mortality rate than the Danish population*. Clin Gastroenterol Hepatol, 2010. **8**(4): p. 384-90.
524. Wilson, G.C., et al., *Long-Term Survival Outcomes after Operative Management of Chronic Pancreatitis: Two Decades of Experience*. J Am Coll Surg, 2023. **236**(4): p. 601-610.
525. Liyen Cartelle, A., et al., *Natural History, Clinical Characteristics, and Outcomes in Idiopathic Chronic Pancreatitis*. Gastro Hep Adv, 2023. **2**(4): p. 449-453.
526. Ahmed, A., et al., *Natural history, clinical characteristics, outcomes, and long-term follow-up of pain-free chronic pancreatitis*. Gastroenterol Rep (Oxf), 2023. **11**: p. goad024.
527. Statistics, O.o.N. *Deaths registered in England and Wales: 2022*. 2023 [cited 2023 15/12/2023].
528. Stevenson M, S.E., *epiR: Tools for the Analysis of Epidemiological Data. R package version 2.0.85*. 2025.
529. B, G., *cmprsk: Subdistribution Analysis of Competing Risks. R package version 2.2-12*. 2024.
530. Miettinen J, R.M., *popEpi: Functions for Epidemiological Analysis using Population Data_. R package version 0.4.13*. 2025.
531. Yu, J.H. and H. Kim, *Oxidative stress and inflammatory signaling in cerulein pancreatitis*. World J Gastroenterol, 2014. **20**(46): p. 17324-9.
532. Bhardwaj, P. and R.K. Yadav, *Chronic pancreatitis: role of oxidative stress and antioxidants*. Free Radic Res, 2013. **47**(11): p. 941-9.
533. Frak, W., et al., *Pathophysiology of Cardiovascular Diseases: New Insights into Molecular Mechanisms of Atherosclerosis, Arterial Hypertension, and Coronary Artery Disease*. Biomedicines, 2022. **10**(8).
534. Sung, L.C., et al., *Risk of acute atherosclerotic cardiovascular disease in patients with acute and chronic pancreatitis*. Sci Rep, 2021. **11**(1): p. 20907.

535. Xia, T., X. Chai, and J. Shen, *Pancreatic exocrine insufficiency in patients with chronic heart failure and its possible association with appetite loss*. PLoS One, 2017. **12**(11): p. e0187804.
536. Ozcan, M., et al., *Evaluation of malnutrition with blood ghrelin and fecal elastase levels in acute decompensated heart failure patients*. Turk Kardiyol Dern Ars, 2015. **43**(2): p. 131-7.
537. Warshaw, A.L. and P.J. O'Hara, *Susceptibility of the pancreas to ischemic injury in shock*. Ann Surg, 1978. **188**(2): p. 197-201.
538. Reilly, P.M., et al., *Hemodynamics of pancreatic ischemia in cardiogenic shock in pigs*. Gastroenterology, 1997. **113**(3): p. 938-45.
539. Dams, O.C., et al., *Heart Failure and Pancreas Exocrine Insufficiency: Pathophysiological Mechanisms and Clinical Point of View*. J Clin Med, 2022. **11**(14).
540. Saulea, A., S. Costin, and V. Rotari, *Heart ultrastructure in experimental acute pancreatitis*. Rom J Physiol, 1997. **34**(1-4): p. 35-44.
541. Kanaian, A.S., et al., *[Combined pathology of the pancreas and myocardium in myocardial infarction and acute destructive pancreatitis]*. Arkh Patol, 1996. **58**(5): p. 56-61.
542. Brunner, S., et al., *Alcohol consumption, sinus tachycardia, and cardiac arrhythmias at the Munich Oktoberfest: results from the Munich Beer Related Electrocardiogram Workup Study (MunichBREW)*. Eur Heart J, 2017. **38**(27): p. 2100-2106.
543. Voskoboinik, A., et al., *Alcohol and Atrial Fibrillation: A Sobering Review*. J Am Coll Cardiol, 2016. **68**(23): p. 2567-2576.
544. Zorniak, M., et al., *What Do We Currently Know about the Pathophysiology of Alcoholic Pancreatitis: A Brief Review*. Visc Med, 2020. **36**(3): p. 182-190.
545. Aberg, F., et al., *Alcohol consumption and metabolic syndrome: Clinical and epidemiological impact on liver disease*. J Hepatol, 2023. **78**(1): p. 191-206.
546. Angelini, G., et al., *Association of chronic alcoholic liver and pancreatic disease: a prospective study*. Am J Gastroenterol, 1985. **80**(12): p. 998-1003.
547. Chand, S.K., et al., *Frequency and risk factors for liver disease following pancreatitis: A population-based cohort study*. Dig Liver Dis, 2019. **51**(4): p. 551-558.
548. Dugic, A., et al., *Post-pancreatitis diabetes mellitus is common in chronic pancreatitis and is associated with adverse outcomes*. United European Gastroenterol J, 2023. **11**(1): p. 79-91.
549. Hart, P.A., et al., *Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer*. Lancet Gastroenterol Hepatol, 2016. **1**(3): p. 226-237.
550. Talukdar, R., et al., *Impact of ductal interventions on diabetes in patients with chronic pancreatitis*. J Gastroenterol Hepatol, 2021. **36**(5): p. 1226-1234.

551. Milani, I., et al., *The Challenge of Type 3c Diabetes: From Accurate Diagnosis to Effective Treatment*. JCEM Case Rep, 2025. **3**(7): p. 104109.
552. Skube, M.E. and G.J. Beilman, *Surgical treatment of pain in chronic pancreatitis*. Curr Opin Gastroenterol, 2018. **34**(5): p. 317-321.
553. Cavallini, G., et al., *Long-term follow-up of patients with chronic pancreatitis in Italy*. Scand J Gastroenterol, 1998. **33**(8): p. 880-9.
554. Strobel, O., M.W. Buchler, and J. Werner, *Surgical therapy of chronic pancreatitis: indications, techniques and results*. Int J Surg, 2009. **7**(4): p. 305-12.
555. Zafar, H.B., *Surgical Management of Chronic Pancreatitis: A Systemic Review*. Cureus, 2023. **15**(3): p. e35806.
556. Inman, K.S., A.A. Francis, and N.R. Murray, *Complex role for the immune system in initiation and progression of pancreatic cancer*. World J Gastroenterol, 2014. **20**(32): p. 11160-81.
557. Ockenga, J., et al., *Lymphocyte subsets and cellular immunity in patients with chronic pancreatitis*. Digestion, 2000. **62**(1): p. 14-21.
558. Shi, S., et al., *Innate Lymphoid Cells: Emerging Players in Pancreatic Disease*. Int J Mol Sci, 2022. **23**(7).
559. Sonika, U., et al., *Mechanism of Increased Intestinal Permeability in Acute Pancreatitis: Alteration in Tight Junction Proteins*. J Clin Gastroenterol, 2017. **51**(5): p. 461-466.
560. Wu, L., et al., *Gut microbiota interacts with inflammatory responses in acute pancreatitis*. Therap Adv Gastroenterol, 2023. **16**: p. 17562848231202133.
561. Quammie S, R.A., Munyal R, Nicholson ES, Clarke C, Venkatachalapathy SV, Crooks CJ, Aithal GP, Aravinthan AD *Chronic pancreatitis: a case ascertainment study*. Frontline Gastroenterol, 2025. **16**: p. 300-307.
562. Henderson, N.C., F. Rieder, and T.A. Wynn, *Fibrosis: from mechanisms to medicines*. Nature, 2020. **587**(7835): p. 555-566.
563. Lurje, I., et al., *Mechanisms of organ fibrosis: Emerging concepts and implications for novel treatment strategies*. Mol Aspects Med, 2023. **92**: p. 101191.
564. Liu, Y., et al., *The NLRP3 inflammasome in fibrosis and aging: The known unknowns*. Ageing Res Rev, 2022. **79**: p. 101638.
565. Wei, X., et al., *Gegen Qinlian pills alleviate carrageenan-induced thrombosis in mice model by regulating the HMGB1/NF-kappaB/NLRP3 signaling*. Phytomedicine, 2022. **100**: p. 154083.
566. Feng, Y., et al., *Runt-related transcription factors: from pathogenesis to therapeutic targets in multiple-organ fibrosis*. Front Cell Dev Biol, 2025. **13**: p. 1528645.

567. Herrera, J., C.A. Henke, and P.B. Bitterman, *Extracellular matrix as a driver of progressive fibrosis*. J Clin Invest, 2018. **128**(1): p. 45-53.
568. Mews, P., et al., *Pancreatic stellate cells respond to inflammatory cytokines: potential role in chronic pancreatitis*. Gut, 2002. **50**(4): p. 535-41.
569. Glaubitz, J., et al., *Immune response mechanisms in acute and chronic pancreatitis: strategies for therapeutic intervention*. Front Immunol, 2023. **14**: p. 1279539.
570. Aghdassi, A.A., et al., *Analysis of lifestyle factors in patients with concomitant chronic pancreatitis and liver cirrhosis*. Pancreatology, 2017. **17**(5): p. 698-705.
571. Lanzillotta, M., et al., *Update on Autoimmune Pancreatitis and IgG4-Related Disease*. United European Gastroenterol J, 2025. **13**(1): p. 107-115.
572. Aparisi, L., et al., *Does an association exist between chronic pancreatitis and liver cirrhosis in alcoholic subjects?* World J Gastroenterol, 2008. **14**(40): p. 6171-9.
573. Reed, A.L., et al., *Diastolic dysfunction is associated with cardiac fibrosis in the senescence-accelerated mouse*. Am J Physiol Heart Circ Physiol, 2011. **301**(3): p. H824-31.
574. Lewandowski, D., et al., *Relation of Left Ventricular Diastolic Function to Global Fibrosis Burden: Implications for Heart Failure Risk Stratification*. JACC Cardiovasc Imaging, 2023. **16**(6): p. 783-796.
575. Cade, W.T., *Diabetes-related microvascular and macrovascular diseases in the physical therapy setting*. Phys Ther, 2008. **88**(11): p. 1322-35.
576. Tang, M., et al., *High glucose promotes the production of collagen types I and III by cardiac fibroblasts through a pathway dependent on extracellular-signal-regulated kinase 1/2*. Mol Cell Biochem, 2007. **301**(1-2): p. 109-14.
577. Fiaschi, T., et al., *Hyperglycemia and angiotensin II cooperate to enhance collagen I deposition by cardiac fibroblasts through a ROS-STAT3-dependent mechanism*. Biochim Biophys Acta, 2014. **1843**(11): p. 2603-10.
578. Singh, V.P., K.M. Baker, and R. Kumar, *Activation of the intracellular renin-angiotensin system in cardiac fibroblasts by high glucose: role in extracellular matrix production*. Am J Physiol Heart Circ Physiol, 2008. **294**(4): p. H1675-84.
579. Miyake, T., et al., *Glycemic Control Is Associated with Histological Findings of Nonalcoholic Fatty Liver Disease*. Diabetes Metab J, 2024. **48**(3): p. 440-448.
580. Gao, Y., et al., *Evaluation of myocardial fibrosis in diabetes with cardiac magnetic resonance T1-mapping: Correlation with the high-level hemoglobin A1c*. Diabetes Res Clin Pract, 2019. **150**: p. 72-80.

581. Lee, Y.S., et al., *The value of glycated hemoglobin as predictor of organ dysfunction in patients with sepsis*. PLoS One, 2019. **14**(5): p. e0216397.
582. Corona, G., et al., *Correction: Hyponatremia Improvement Is Associated with a Reduced Risk of Mortality: Evidence from a Meta-Analysis*. PLoS One, 2016. **11**(3): p. e0152846.
583. Waikar, S.S., G.C. Curhan, and S.M. Brunelli, *Mortality associated with low serum sodium concentration in maintenance hemodialysis*. Am J Med, 2011. **124**(1): p. 77-84.
584. John, S. and P.J. Thuluvath, *Hyponatremia in cirrhosis: pathophysiology and management*. World J Gastroenterol, 2015. **21**(11): p. 3197-205.
585. Floreani, A., et al., *IgG4-related disease: Changing epidemiology and new thoughts on a multisystem disease*. J Transl Autoimmun, 2021. **4**: p. 100074.
586. Wallace, Z.S., et al., *IgG4-Related Disease: Clinical and Laboratory Features in One Hundred Twenty-Five Patients*. Arthritis Rheumatol, 2015. **67**(9): p. 2466-75.
587. Stone, J.H., Y. Zen, and V. Deshpande, *IgG4-related disease*. N Engl J Med, 2012. **366**(6): p. 539-51.
588. Kamisawa, T., et al., *IgG4-related disease*. Lancet, 2015. **385**(9976): p. 1460-71.
589. Ryu, J.H., et al., *Spectrum of Disorders Associated with Elevated Serum IgG4 Levels Encountered in Clinical Practice*. Int J Rheumatol, 2012. **2012**: p. 232960.
590. Yu, L., et al., *IgG is an aging factor that drives adipose tissue fibrosis and metabolic decline*. Cell Metab, 2024. **36**(4): p. 793-807 e5.
591. Witt, H., et al., *Chronic pancreatitis: challenges and advances in pathogenesis, genetics, diagnosis, and therapy*. Gastroenterology, 2007. **132**(4): p. 1557-73.
592. Erchinger, F., et al., *Exocrine pancreas insufficiency in chronic pancreatitis - Risk factors and associations with complications. A multicentre study of 1869 patients*. Pancreatology, 2022. **22**(3): p. 374-380.
593. Machicado, J.D., et al., *A population-based evaluation of the natural history of chronic pancreatitis*. Pancreatology, 2018. **18**(1): p. 39-45.
594. Tewatia, V., et al., *Natural History of Chronic Pancreatitis: A Systematic Review*. HPB, 2021. **23**: p. S895-S896.
595. Dhar, P., S. Kalghatgi, and V. Saraf, *Pancreatic cancer in chronic pancreatitis*. Indian J Surg Oncol, 2015. **6**(1): p. 57-62.
596. Lankisch, P.G., A.B. Lowenfels, and P. Maisonneuve, *What is the Risk of Alcoholic Pancreatitis in Heavy Drinkers?* Pancreas, 2002. **25**(4): p. 411-412.

LIST OF ABBREVIATIONS

A ₁ AT	Alpha 1 antitrypsin
ADH	Alcohol Dehydrogenase
AIP	Autoimmune Pancreatitis
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AP	Acute Pancreatitis
AXR	Abdominal X-ray
BMI	Body Mass Index
cAMP	cyclic adenosine- 3', 5' monophosphate
CASP	Critical Appraisal Skills Programme
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CI	Confidence Interval
CKD	Chronic Kidney Disease
CLD	Chronic Liver Disease
COX	Cyclooxygenase
CP	Chronic Pancreatitis
CPN	Coeliac Plexus Neurolysis
CT	Computerised Tomography
CTLA ₄	Cytotoxic T lymphocyte antigen 4
CVD	Cerebrovascular Disease
CX ₃ CR ₁	fractalkine Receptor
DM	Diabetes Mellitus
DNA	Deoxyribonucleic Acid
ECM	Extracellular Matrix
EP	Extra Pancreatic
ERCP	Endoscopic Retrograde Cholangiopancreatography
ESWL	Extra Corporeal Shock Wave Lithotripsy
EUS	Endoscopic Ultrasound

EUS-CPN	Endoscopic Ultrasound Coeliac Plexus Neurolysis
FAEE	Fatty Acid Ethyl Ester
FFA	Free fatty Acid
GGT	Gamma Glutamyl Transferase
HADS	Hospital Anxiety Depression Scale
HDL	High Density Lipoprotein
HF	Heart Failure
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IBD	Inflammatory Bowel Disease
ICD	International Classification of Diseases
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IHD	Ischemic Heart Disease
IL	Interleukin
IPMN	Intrapapillary Mucinous Neoplasms
IQR	Interquartile Range
LDL	Low Density Lipoprotein
MRA	Magnetic Resonance Angiography
MRCP	Magnetic Resonance Cholangiopancreatography
MRI	Magnetic Resonance Imaging
NF- κ b	Nuclear Factor Kappa B
NHS	National Health Service
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NUH	Nottingham University Hospitals NHS Trust
ONS	Office for National Statistics
PAR-2	Protease Activated Receptor-2
PD	Pancreatic Duct
PDGF	Platelet Derive Growth Factor
PEI	Pancreatic Exocrine Insufficiency
PICO	Patient Intervention Comparison Outcome
PPT	Pressure Pain Thresholds

RAAS	Renin Angiotensin Aldosterone System
ROS	Reactive Oxygen Species
SIR	Standardised Incidence Ratio
SMR	Standardised Mortality Ratio
SNOMED CT	Systematized Nomenclature of Medicine- Clinical Terms
SPINK ₁	Serine Protease Inhibitor Kazal-1
SPR	Standardised Prevalence Ratio
STAT ₃	Signal Transducer and Activator of Transcription 3
TGFβ	Transforming Growth Factor Beta
TIA	Transient Ischemic Attack
TNFα	Tumour Necrosis Factor Alpha
TSH	Thyroid Stimulating Hormone
US	Ultrasound

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