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REVIEW

Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes

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Abstract

This review aims to outline the most up-to-date knowledge of pancreatic adenocarcinoma risk, diagnostics, treatment and outcomes, while identifying gaps that aim to stimulate further research in this understudied malignancy. Pancreatic adenocarcinoma is a lethal condition with a rising incidence, predicted to become the second leading cause of cancer death in some regions. It often presents at an advanced stage, which contributes to poor five-year survival rates of 2%-9%, ranking firmly last amongst all cancer sites in terms of prognostic outcomes for patients. Better understanding of the risk factors and symptoms associated with this disease is essential to inform both health professionals and the general population of potential preventive and/or early detection measures. The identification of high-risk patients who could benefit from screening to detect pre-malignant conditions such as pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasms and mucinous cystic neoplasms is urgently required, however an acceptable screening test has yet to be identified. The management of pancreatic adenocarcinoma is evolving, with the introduction of new surgical techniques and medical therapies such as laparoscopic techniques and neo-adjuvant chemoradiotherapy, however this has only led to modest improvements in outcomes. The identification of novel biomarkers is desirable to move towards a precision medicine era, where pancreatic cancer therapy can be tailored to the individual patient, while unnecessary treatments that have negative consequences on quality of life could be prevented for others. Research efforts

must also focus on the development of new agents and delivery systems. Overall, considerable progress is required to reduce the burden associated with pancreatic cancer. Recent, renewed efforts to fund large consortia and research into pancreatic adenocarcinoma are welcomed, but further streams will be necessary to facilitate the momentum needed to bring breakthroughs seen for other cancer sites.

Key words: Pancreatic cancer; Pancreatic adenocarcinoma; Pancreatic cancer risk factors; Pancreatic cancer treatment

Core tip: The incidence of pancreatic adenocarcinoma is rising in the developed world and modifiable lifestyle factors such as alcohol and obesity may play an important role in this. The five-year survival from this disease is as low as 2% in some countries, despite improvement in surgical technique, chemotherapy regimens and the introduction of neo-adjuvant chemoradiotherapy. The poor outcomes are largely due to the late presentation of the disease and therefore the detection of early tumours or premalignant conditions is essential for treatment to be initiated early. The optimum screening test is however yet to be identified. Given the poor outcomes and current gaps in knowledge surrounding this malignant process, further research is essential to understand this disease better, enable early diagnosis and improve survival.

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INTRODUCTION

Pancreatic adenocarcinoma is a lethal condition with poor outcomes and an increasing incidence. This review presents the most up to date knowledge on the incidence, outcomes, risk factors, pathogenesis, diagnostics, investigated biomarkers and treatments available to pancreatic adenocarcinoma patients. This review focuses on pancreatic adenocarcinoma where possible, however in some places where the general term "pancreatic cancer" is used, it should be assumed that the majority of cases are pancreatic ductal adenocarcinomas.

INCIDENCE

Pancreatic cancer is ranked as the 14th most common cancer and the 7th highest cause of cancer mortality in the world. Globocan estimates revealed that there will be 458918 diagnoses and 432242 deaths from pancreatic cancer globally in 2018[1]. The incidence rates vary significantly between countries, as demonstrated in Figure 1. The highest age-standardised incidence is seen in Europe and North America, and the lowest in Africa and South Central Asia[2]. There is a general trend of higher incidence rates in developed countries compared to developing countries and this is supported by Wong *et al*[3] who demonstrated that in higher human development index countries there are higher incidences of pancreatic cancer in both males and females.

A major concern is that the incidence of pancreatic cancer is increasing in the Western world. One example of this is a study performed by Saad *et al*[4] using data from the United States Surveillance, Epidemiology, and End Results Program (SEER) which found that, between 1973 and 2014, the age-standardised incidence rates of pancreatic cancer have increased by 1.03% per year. This translates to pancreatic cancer being predicted to rise from being the 4th to the 2nd most common cause of cancer-related death in the United States by 2030[5,6].

The large disparities in pancreatic cancer incidence between countries also suggest that environmental factors play a significant role as risk factors for the disease, and these are discussed below.

RISK FACTORS

Due to the relatively low incidence and poor survival of pancreatic cancer, the risk factors associated with the development of this disease have historically been investigated using case-control studies. Unfortunately, these study designs do have weaknesses including selection bias and recall bias. Consortia pooling data from multiple cohort studies are needed to overcome sample size issues in prospective studies, and these have been published more frequently in recent years. The best available evidence is presented below in the sections divided into non-modifiable and modifiable risk factors and the evidence behind the latter is summarised in Table 1[7-26]. There is also some preliminary evidence that some of these lifestyle factors can influence survival, but this is an area that requires further research[7,8].

NON-MODIFIABLE RISK FACTORS

Age

Pancreatic cancer is typically a disease of the elderly. It is extremely rare for patients to be diagnosed before the age of 30, and 90% of newly diagnosed patients are aged over 55 years of age, with the majority in their 7th and 8th decade of life[9,10]. The age at which the incidence peaks varies between countries. In India, for example, there is a peak in incidence in patients in their sixth decade of life whereas the in the United States this is the seventh decade of life[9].

Sex

The worldwide incidence of pancreatic cancer is higher

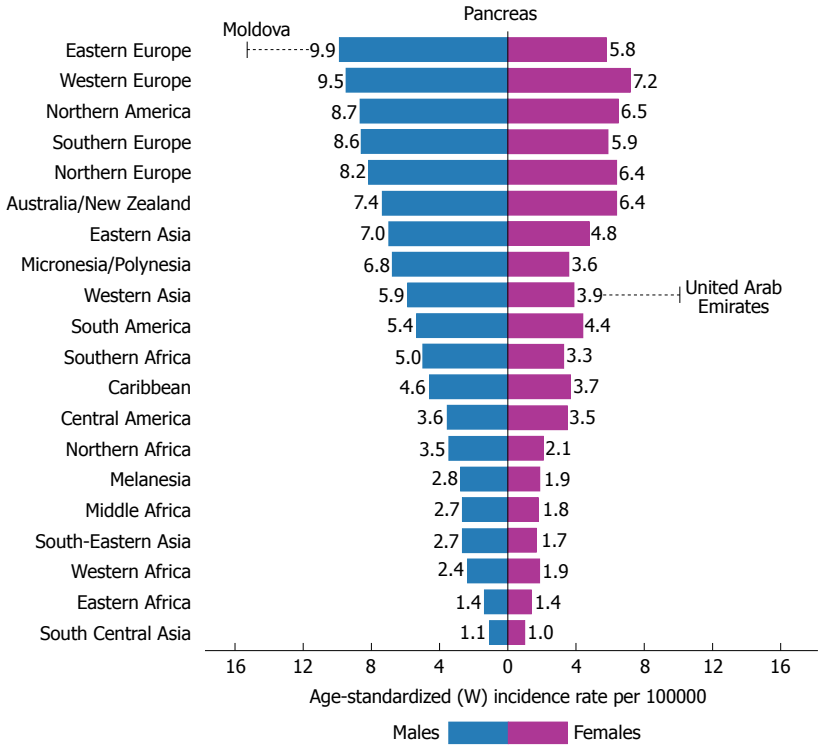

Figure 1 Diagram of incidence of pancreatic cancer in both sexes throughout the world Adapted from Globocan[1] 2018.

in males than females (Age-standardised rate 5.5 in males compared to 4.0 in females)[1]. This disparity appears to be greater in higher development index countries[7]. Despite the sex difference, a systematic review of 15 studies concluded that reproductive factors were not associated with pancreatic cancer in women[11]. These findings point towards differing exposures in environmental or genetic factors as alternative explanations for the male predominance.

Ethnicity

Within the United States, a 50%-90% increased risk of pancreatic cancer in African-Americans compared to Caucasians has been reported, while incidence rates are lowest in Pacific Islanders and Asian-Americans[9]. The higher incidence rates within the African-American population is proposed to be linked to a greater exposure to other risk factors for pancreatic cancer, such as cigarette smoking, alcohol consumption, elevated body mass index and higher incidence of diabetes[12], but there is also evidence for underlying genetic or gene environment interactions to explain at least some of the observed differences in incidence between ethnic groups[13,14].

Blood group

The risk of developing pancreatic adenocarcinoma has been shown to be associated with different ABO blood groups in several large epidemiological studies. Wolpin *et al*[15] combined data from the renowned United States Nurse Health Study and Health Professionals Follow-up Study, and found that compared to blood patients with blood group O, patients with blood group A (HR: 1.32, 95%CI: 1.02-1.72), AB (HR: 1.51, 95%CI: 1.02-2.23), or B (HR: 1.72, 95%CI: 1.25-2.38) were at a significantly higher risk of developing pancreatic adenocarcinoma. Results from the Pancreatic Cancer Cohort Consortium which combined data from 12 prospective cohort studies was in agreement with these findings[16]. The proposed mechanisms behind this include alterations in glycosyltransferase specificity and the host inflammatory state across the different ABO blood groups[15]

Gut Microbiota

Multiple studies have been performed examining the role of gut microbiota in pancreatic cancer. A systematic review by Memba *et al*[17] demonstrated that lower levels of *Neisseria elongate* and *Streptococcus mitis,* and higher levels of *Porphyromonas gingivalis* and *Granulicatella adiacens* are associated with an increased risk of pancreatic cancer. However, further studies are needed to validate these findings and also to establish if targeted treatment is a therapeutic possibility.

Family history and genetic susceptibility

Pancreatic cancer is considered to be familial if two or more first degree relatives have previously been diagnosed with the disease and accounts for 5%-10% of new cases[27]. Patients with familial risk factors have a nine times higher risk of developing pancreatic cancer than those with no family history, and this increases to a thirty-two times greater risk if three or more first degree relatives have been previously diagnosed[28]. A meta-analysis of nine studies has also reported that individuals

Table 1 Summary of modifiable risk factors associated with pancreatic cancer

Factor	Direction of association	Strength of association	Type of studies conducted	Related notable findings	Ref.
Smoking	Positive	Strong association; 74% increased risk in current smokers; 20% increased risk in former smokers	Case-control, cohort, nested case-control studies	Dose responsive; risk remains 10-20 yr following smoking cessation	[18-20]
Alcohol	Mixed between no association and positive	Various; 15%-43% increased risk in meta-analysis	Meta-analysis of cohort studies	Dose responsive; sex dependent; Increased risk in spirit drinkers; link with chronic pancreatitis which is a risk factor for pancreatic cancer	[9,21-24]
Obesity	Positive	10% increased risk for every 5 BMI units	Cohort studies	Link with Type 2 diabetes which is associated with increased risk of pancreatic cancer	[25]
Dietary factors	Variable	Non-significant positive association for red meat; 17% increased risk associated with 50 g/d of processed meat consumption compared to 20 g/d	Cohort studies	Overall consensus cannot be made and further research is required	[25]
Helicobacter pylori	Positive	45% increased risk	Meta-analysis of case-control studies	Significant publication bias and small numbers included therefore further studies are required	[26]

BMI: Body mass index.

with a family history of pancreatic cancer were only one first degree relative has been diagnosed with pancreatic cancer, still have an 80% increased risk of developing pancreatic adenocarcinoma (RR: 1.8, 95%CI: 1.48-2.12) compared with individuals with no reported family history[29].

This points towards a strong genetic susceptibility for pancreatic cancer in a subgroup of affected patients. In familial pancreatic cancer, the risk rises exponentially with the number of first degree relatives affected and BRCA2 and PALB are the most commonly implicated mutations in this cohort[2,9]. Specific syndromes are also associated with an increased risk of pancreatic cancer compared to the general population. These are summarised in Table 2[30,31].

Diabetes

Diabetes is a well-established risk factor for pancreatic cancer. Stevens *et al*[32] performed a meta-analysis which demonstrated that the risk of pancreatic cancer was twice that in patients with type one diabetes compared to those without this condition (RR: 2.00, 95%CI: 1.37-3.01). Another comprehensive meta-analysis of 36 studies also demonstrated a similar magnitude of increased risk of pancreatic cancer in patients with type-2 diabetes (OR: 1.82 95%CI: 1.66-1.89)[33]. However, it must be noted that although diabetes is a risk factor, pancreatic cancer can also manifest itself as new onset of diabetes. This has led to interest in HbA1c as a potential biomarker of early detection in pancreatic cancer[34].

MODIFIABLE RISK FACTORS

Smoking

Cigarette smoking is considered the most important modifiable risk factor in pancreatic cancer with multiple individual and combined studies demonstrating a strongly positive association. The Panc4 study combined data from 12 case-control studies of which there were 6507 cancer cases and 12890 controls. The results demonstrated a dose responsive significantly increased risk of pancreatic cancer in ever smokers[18]. A meta-analysis of 82 published studies found that there is a 74% increased risk of pancreatic cancer in current (OR: 1.74, 95%CI: 1.61-1.87) and a 20% increased risk in former smokers (OR: 1.20, 95%CI: 1.11-1.29) compared to never smokers[19]. This study also found that following smoking cessation the risk remains for at least 10 years[19] while others have shown it may take up to 20 years following smoking cessation for the risk to return to baseline[9]. The Pancreatic Cancer Cohort Consortium has reported similar findings, and also found the risk increased with both duration of smoking (> 50 years OR: 2.13, 95%CI: 1.25-3.62) and number of cigarettes smoked (> 30 cigarettes/d, OR: 1.75, 95%CI: 1.27-2.42)[20].

A novel area for future research remains unanswered in relation to e-cigarettes and pancreas health. E-cigarettes deliver heated nicotine, but fewer chemicals than tobacco smoking, and have generally been promoted as safer (but not necessarily safe) alternatives to traditional cigarettes[35]. New studies are required to determine the risk/benefit balance of e-cigarettes as an exposure with unknown carcinogenic potential, or as a helpful smoking cessation tool contributing to pancreatic cancer prevention[35].

Alcohol

Multiple studies have investigated the impact of alcohol consumption on the development of pancreatic cancer but thus far results have been mixed[9,21,22]. A pooled analysis of 14 cohort studies with 2187 cases of pancreatic cancer found an increased risk when patients consumed > 30 g of alcohol per day (RR: 1.22,

Table 2 Range of increased relative risk of pancreatic cancer associated with specific syndromes as summarised by Chen *et al*[30] and Del Chiaro *et al*[31]

Gene	Syndrome	Increase relative risk *vs* general population	
		Chen *et al*[30]	Del Chiaro *et al*[31]
BRCA2	Hereditary breast and ovarian cancer	2.2-5.9	
BRCA1		1.6-4.7	
STK11	Peutz-Jeghers syndrome	76.2-139.0	132.0
PRSS1	Hereditary pancreatitis	53-87	50-70
CDKN2A	Familial atypical multiple mole melanoma	14.8-80.0	34-39
MMR	Hereditary nonpolyposis colorectal cancer	0.0-10.7	4.7

95%CI: 1.03-1.45)[23]. The most recent meta-analysis found that low and moderate alcohol consumption was not associated with pancreatic cancer risk, however, in those with a high alcohol consumption there was a 15% increased risk of pancreatic cancer (RR: 1.15, 95%CI: 1.06-1.25; P = 0.001)[24]. This increased risk was strongest in heavy male drinkers and heavy drinkers of spirits[24].

Excessive alcohol consumption is also the main cause of chronic pancreatitis, which is a known risk factor for pancreatic cancer and therefore alcohol in this setting is a risk factor for pancreatic cancer[36].

Chronic pancreatitis

Chronic pancreatitis is a progressive inflammatory condition of the pancreas leading to fibrosis and loss of acinar and islet cells. Significant variety exists in the reported incidence of this disease, ranging from 2-14/100000 of the United States population[37]. Approximately 5% of these patients will develop pancreatic cancer a during their lifetime[38]. Pooled results from seven studies investigating chronic pancreatitis and found significantly 13-fold higher risk of pancreatic cancer (RR: 13.3, 95%CI: 6.1-28.9) in these patients, compared with the general population or controls[38]. The relatively low incidence and greater risk infers that of chronic pancreatitis patients could be a potential target group for pancreas cancer screening, if an effective test can be found and long latency period accounted for.

Obesity

The worldwide prevalence of obesity is increasing with an estimated 1.97 billion adults and 338 million children and adolescents categorised worldwide as overweight or obese in 2016[25]. The World Cancer Research Fund in the pancreatic cancer report from 2012 identified 23 studies which assessed for an association between a raised body mass index (BMI) and pancreatic cancer. Nineteen of these individual studies reported an increased risk of pancreatic cancer in obese patients and in the meta-analysis performed of these studies there was a 10% increased risk of pancreatic cancer for every 5 BMI units (RR: 1.10, 95%CI: 1.07-1.14) with no difference in outcomes between males and females[25].

Given the strength of the evidence linking obesity to pancreatic cancer, it is likely that the rising incidence of obesity is a major factor for the increasing incidence of pancreatic cancer in the developed world. There have been large public health campaigns around some of the other major lifestyle with a subsequent decrease in alcohol consumption and cigarette smoking. Similar campaigns need to focus on educating the public on the health risks associated with obesity.

Dietary factors

Table 3 provides a concise review of the impacts of diet and nutrition on the risk of pancreatic cancer according to the World Cancer Research Fund global report. There is limited suggestive evidence that red and processed meat consumption are association with pancreas cancer development. This is biologically plausible given that excessive consumption of red and processed meat has been shown to potentially cause DNA damage and the formation of carcinogens such as N-nitroso compounds[25]. Other dietary factors with limited suggestive evidence in pancreatic cancer aetiology include foods and beverages containing fructose, or foods containing saturated fatty acids; while no conclusions could be made with regards to other dietary exposures. This reflects the difficulties in nutritional epidemiology and appropriate study designs for investigating pancreatic cancer risk.

Infection

The relationship between several infections and pancreatic cancer has also been investigated, with increased risks observed in patients with *Helicobacter pylori* (*H-pylori*)[26] or hepatitis C infections[39]. Further studies are necessary to strengthen these findings[26]. The potential association for *H-pylori* raises interesting speculation about *H-pylori* eradication (intended to reduce gastric cancer risk) having potentially negative consequences for increasing pancreas cancer incidence, as has been noted for oesophageal adenocarcinoma trends[40].

Outcome

The worldwide 5-year survival rate for pancreatic cancer patients is approximately 6%, but this ranges from 2% to 9% in published literature[2,41,42]. Factors that impact on survival include age, sex, quality of healthcare available, presence of co-morbidities and lifestyle habits and some of these account for the difference in survival rates between countries. However, the main factor influencing

Table 3 Summary of impact of dietary factors, nutrition and physical activity on pancreatic cancer risk

	Diet, nutrition, physical activity and pancreatic cancer		
		Decreases risk	Increases risk
Strong evidence	Convincing		Body fatness
	Probable		Adult attained height
Limited evidence	Limited - suggestive		Red meat, Processed meat; alcoholic drinks (heavier drinking); foods and beverages containing fructose; foods containing saturated fatty acids
	Limited - no conclusion	Physical activity; fruits; vegetables; folate; fish; eggs; tea; soft drinks; coffee; carbohydrates; sucrose; glycaemic index; glycaemic load; total fat; monounsaturated fat; polyunsaturated fats; dietary cholesterol; vitamin C; and multivitamin/mineral supplements	
Strong evidence	Substantial effect on risk unlikely		

Adapted from World Cancer Research Fund Continuous Update Project[25].

disease outcome is the tumour stage at the time of diagnosis[43]. Unfortunately pancreatic cancer often presents late and only 20% of patients with pancreatic cancer have surgically resectable disease at time of presentation[2,43]. In patients who are able to undergo successful surgical resection, 5-year survival is quoted as 27% whereas if the patient has locally advanced or metastatic disease the median survival is six to eleven months and two and six months respectively[44]. Despite advances in surgical and medical treatment of pancreatic cancer there has been a minimal improvement in the 5-year survival rates. For example, population-based Northern Ireland cancer registry data revealed minimal improvements in five-year survival from 2.5% to 5.2% in cases diagnosed between 1993-1999 compared with 2005-2009[45]. The rising incidence and ongoing poor survival figures highlight the need to identify methods of screening patients at high risk, develop methods of early detection and improve both surgical and medical management of these patients.

PATHOLOGY OF PANCREATIC CANCER

Pancreatic adenocarcinoma and its variants account for 90% of all pancreatic carcinomas[46]. This section will briefly outline the pathology of pancreatic adenocarcinoma, its variants and precursor lesions. Non-ductal tumours such as acinar cell carcinomas and neuroendocrine neoplasms will not be discussed here and for this, readers are directed elsewhere[47].

Approximately 60%-70% of pancreatic adenocarcinomas arise in the head of the pancreas with the remainder being found in the body (15%) and tail (15%). At the time of diagnosis most pancreatic adenocarcinomas have already spread beyond the pancreas and nodal metastases are not uncommon[48].

Morphological variants of pancreatic adenocarcinoma, recognised in the World Health Organisation classification of pancreatic tumours have different histological features compared to conventional pancreatic adenocarcinomas. These variants also differ in terms of prognosis and may have a different molecular signature[49-52]. The main variants of pancreatic adenocarcinomas are presented in Table 4.

PATHOGENESIS

Pancreatic adenocarcinoma develops following a series of step-wise mutations from normal mucosa (Figure 2A) to specific precursor lesions and ultimately invasive malignancy[53]. The three best characterised precursors of this malignancy are pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN)[54]. Each of these has unique clinical, pathological and molecular characteristics.

PanIN

Pancreatic intraepithelial neoplasia is a non-invasive microscopic lesion that occurs in the small (usually less than 0.5 cm) pancreatic ducts. It has been proposed that PanIN may have a role in the development of localised pancreatitis and that the resultant epithelial injury and repair cycles may further propagate the neoplastic process[55]. These lesions were first categorised in 2001 and initially graded from 1-3, reflecting progressive neoplastic morphological changes[56]. More recently there has been a move to simplify the classification using a two-tiered system, with the suggestion that the historical grades of 1a/1b and 2 be classified as low grade PanIN (Figure 2B), and the original PanIN 3 revised to high grade (Figure 2C)[57].

A recent microsimulation model, using the original PanIN classification, has sought to shed further light on the natural history of these lesions. Based on this model, the authors estimate an overall chance of 1.5% for men and 1.3% for women progressing from PanIN 1 to detectable pancreatic adenocarcinoma over their lifetime[58]. It was also estimated that it will take 11.3 years for men and 12.3 years for women to transform from PanIN 3 to pancreatic adenocarcinoma[58]. This represents a possible window for screening prior to the development of invasive malignancy as will be discussed later.

IPMN

IPMNs are also well recognised as precursor lesions for pancreatic cancer[59]. They represent a broad group of pathology, being mainly classified as arising from the

Table 4 Summary of the different subtypes of pancreatic ductal adenocarcinoma[52]

Morphological Variant	Characteristics
Adenosquamous carcinoma	Significant components of ductal/glandular and squamous differentiation (at least 30%). Considered to have a worse prognosis than pancreatic adenocarcinoma.
Colloid/mucinous carcinoma	Production of copious amounts of extracellular stromal mucin. Most arise in association with intraductal papillary mucinous neoplasms; thought to have more favourable prognosis than pancreatic adenocarcinoma
Undifferentiated/anaplastic carcinoma	Minimal or no differentiation; highly atypical cells which may appear spindle shaped or sarcomatoid, often admixed with osteoclast-like giant cells. One of the most aggressive forms of pancreatic cancer with extremely poor survival rates
Signet ring cell carcinoma	Discohesive, singly invasive cells with intracytoplasmic mucin that may displace the nucleus. Similar tumours throughout the gastrointestinal tract. Very rare form of pancreatic cancer with prognosis similar to that of pancreatic adenocarcinoma
Medullary carcinoma	Syncytial arrangement of pleomorphic epithelial cells with associated intratumoral lymphoid infiltrate. Prognosis is slightly better than pancreatic adenocarcinoma
Hepatoid carcinoma	Morphological similarity to hepatocellular carcinoma. May produce bile. Very rare tumour with a poor prognosis similar to that of pancreatic adenocarcinoma

main pancreatic duct or one of the side branches. This distinction is important as the risk of malignancy is significantly different. For example, several studies found malignant cells, including carcinoma in situ, present in a mean of 70% of resected main duct IPMNs compared to a mean of 25% of side branch lesions that were removed[60].

Mucinous cyst neoplasms

Mucinous cyst neoplasms also represent premalignant lesions of the pancreas. They account for 25% of pancreatic cysts undergoing resection and are significantly more common in women[53]. A retrospective study of 163 patients undergoing pancreatic resection for MCN, found malignancy in 17.5% of the lesions removed[61].

Given that 1% of abdominal computed tomography (CT) scans will identify a cystic lesion of the pancreas, it is imperative that clear guidelines exist to ensure the appropriate management of these potentially premalignant abnormalities[53]. European[62] and international[63] consensus papers have recently been published and are an important point of reference for clinicians dealing with these lesions. However, there is a lack of high-quality population-based studies investigating all premalignant lesions of the pancreas and future work is needed to progress our understanding of aetiology, trends in incidence and factors affecting progression to malignancy. This is particularly urgent given the known rise in pancreatic cancer incidence, and that a diagnosis of PanIN and/or pancreatic cysts represents a potential opportunity for intervention and patient management to minimise this risk of progression. On the other hand, this must be balanced with better understanding of which patients could be considered low-risk, which could provide reassurance both to the patient and minimise unnecessary burden on healthcare systems.

Molecular understanding of pancreatic adenocarcinoma pathogenesis

PanIN is the most common precursor of pancreatic adenocarcinoma and this is supported by molecular studies that show that these lesions have genetic abnormalities that are common to adjacent pancreatic adenocarcinoma and the histological progression of PanIN parallels the accumulation of molecular abnormalities[46]. Lower grade PanIN lesions have mutations in the KRAS oncogene and exhibit telomere shortening, suggesting these are early changes on the pathway to invasive malignancy[64]. Mutations in p16, CDNK27, p53 and SMAD4 appear later and are present in higher grade PanIN and pancreatic adenocarcinoma. The rate of KRAS mutation also increases in relation to the grade of PanIN[53,65]. Abnormalities in notch signalling and sonic hedgehog pathways have also been implicated in pancreatic adenocarcinoma development and 80% of these mutations appear to be sporadic[9,43].

Recent genomic analysis identified 32 recurrently mutated genes in pancreatic adenocarcinoma and these were able to be stratified into four sub-groups namely squamous, pancreatic progenitor, immunogenic and aberrantly differentiated endocrine exocrine, each of which has a unique genomic signature which corresponded to histopathological findings and prognosis[66]. The squamous sub-type was associated with the adenosquamous histological variant of pancreatic adenocarcinoma and found to carry an independently poor prognosis. The pancreatic progenitor group highly expressed transcription factors involved in determining pancreatic cell lineage. Significant immune infiltration was found in the immunogenic tumours and the aberrantly differentiated endocrine exocrine tumours were associated with acinar cell carcinomas[66]. These findings shed further light on the complex and heterogenous nature of pancreatic cancer and may aid the development of more targeted, personalised therapy based on individual tumour biology.

Given that the majority of pancreatic tumours express androgen receptors (AR), the role of these in the pathogenesis of this disease has been an area of study for many years[67-69]. Some *in vitro* and mouse models have shown reduced cell line proliferation and tumour shrinkage with androgen receptor blockade[69]. However,

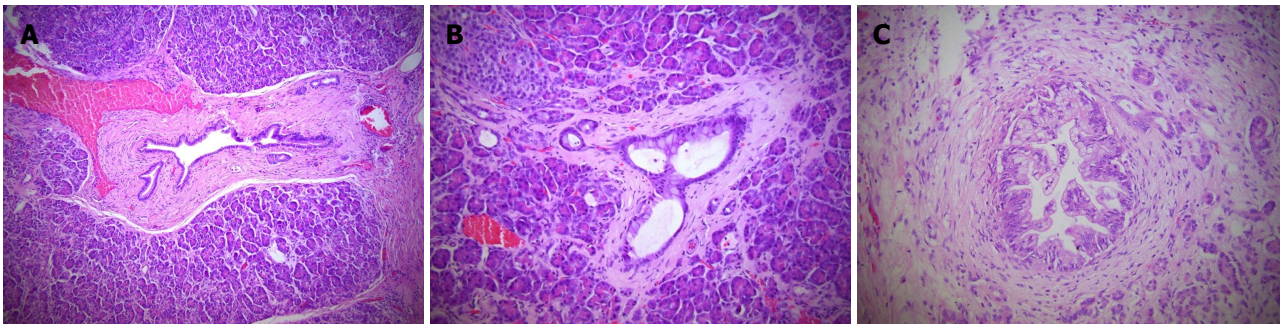

Figure 2 Pathogenesis. A: Normal duct; B: Low grade pancreatic intraepithelial neoplasia (PanIN); C: High grade PanIN.

there is discordance between studies regarding AR expression in pancreatic adenocarcinoma and its possible role in pathogenesis[70]. A retrospective cohort study of 60 patients who underwent pancreatic resection found that AR expression was not related to the grade of tumour or prognosis[70]. The relative lack of robust evidence prevents any current recommendation that therapies targeting AR be used in pancreatic adenocarcinoma and this is another area in need of further study[68,71].

DIAGNOSIS AND SCREENING

Pancreatic cancer poses a significant diagnostic challenge and the majority of cases present late, with either locally advanced or metastatic disease. The reasons for this are multi-factorial including the non-specific symptoms associated with the disease and the close proximity of major blood vessels which can be readily invaded by the tumour[72]. These factors mean that 80%-85% of tumours are not resectable at the time of presentation[43]. At present, surgical resection is the only potential cure for pancreatic cancer, although rates of recurrence are high with inevitably dismal rates of long-term survival.

Due to the low lifetime risk of pancreatic cancer (around 1%), population-based screening of unselected populations for this tumour is not recommended[31,73,74]. The International Cancer of the Pancreas Screening Consortium, recommends that individuals meeting the definition of familial pancreatic cancer (outlined in Table 2) are a potential target for screening[73]. There was disagreement as to when to begin screening of these high risk populations, with just over half of the consensus group voting that screening should begin at 50[73]. If a non-suspicious cyst is found, surveillance should be repeated every 6-12 mo. Solid lesions, not meeting the criteria for immediate resection, and main pancreatic duct strictures should have repeat imaging after three months[73].

Whilst a high-risk population for screening has been identified, the best diagnostic imaging modalities and lesions which should be targeted are less well defined[73]. Secretin enhanced magnetic resonant imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) have been shown to have a good to excellent concordance with endoscopic ultrasound (EUS) findings when used as a one-time screening modality and avoids the risk of ionising radiation[73]. However, EUS has a higher sensitivity for identifying solid pancreatic lesions, less than 2cm, when compared to CT and MRI[75]. EUS is also able to identify worrisome features in pancreatic cysts and can be combined with fine needle aspiration cytology to help further characterise these lesions[73]. Historically it was felt that PanIN could not be reliably identified on imaging[76]. There is, however, emerging evidence that it may be associated with lobulocentric atrophy producing similar appearances to chronic pancreatitis on EUS[55,77]. In the high risk population outlined by the International Cancer of the Pancreas Screening Consortium group, consensus was that a combination of EUS and MRI/MRCP are the recommended imaging modalities for screening in these individuals[73].

Whilst the appropriate population and imaging modality for screening has been outlined, equipoise still exists as to the appropriate management of any identified abnormalities and further study is needed. A recent meta-analysis of screening programs in populations at high risk of pancreatic cancer found higher rates of curative resection and longer median survival when compared to controls[78]. These findings are promising, although must be balanced against the issue of heightened anxiety in the screened population[78].

Whilst general population-based screening is not recommended, various awareness campaigns have been established to highlight the often vague symptoms of pancreatic cancer and encourage individuals to seek medical attention early. One study highlighted that many people who were ultimately diagnosed with pancreatic cancer were falsely reassured by the intermittent nature of their symptoms over the preceding months[79]. The relative rarity of pancreatic cancer also means that many primary care physicians will only see a case every few years on average. It is therefore imperative to maintain awareness among these professionals in order that those with relevant symptoms are investigated in a timely and appropriate fashion. A retrospective case-control study in primary care found that patients sought medical attention 18 times on average in the period preceding

their pancreatic cancer diagnosis[80].

BIOMARKERS FOR EARLY DETECTION

Investigation of potential biomarkers including liquid biopsy, to aid in screening, diagnosis, and treatment of pancreatic cancer has been an area of intense research. Efforts to detect biomarkers in blood, breath and pancreatic juice have all been investigated.

Serum cancer antigen 19-9 (CA 19-9) is the only marker approved by the United States Food and Drug Administration for use in the routine management of pancreatic cancer[81]. The low positive predictive value of CA19-9 means it has no role in mass screening of asymptomatic patients and is only appropriate to monitor response to treatment and as a marker of recurrent disease[82]. Mass spectrometry of tumour tissue metabolites found increased levels of specific metabolic by-products in early stage pancreatic adenocarcinoma when compared to controls in a recent study. There was, however, discordance between the levels identified from tumour tissue and plasma samples suggesting further study is required if a blood based biomarker is to be developed[74]. More recent studies into plasma-based metabolite panels have shown more promise in relation to the early diagnosis of pancreatic adenocarcinoma in the general population[83] and in those with chronic pancreatitis and a higher risk of pancreatic adenocarcinoma[84]. The high rate of genetic mutation associated with pancreatic adenocarcinoma has also led to the investigation of cell free DNA and tumour cells in systemic circulation as a screening or diagnostic test. Riva *et al*[84] found that, despite the high rates of KRAS mutation in pancreatic tumour tissue, concentrations of circulating tumour cells or cell free DNA did not have the required level of sensitivity or specificity to enable their use as screening tests.

Other non-invasive alternatives to blood have been investigated as mediums for early detection biomarker research, namely the increased concentration of volatile organic compounds (VOC) in exhaled air specific. A recent case-control study found raised levels of VOC in patients with pancreatic cancer compared to healthy controls with a sensitivity and specificity of 100% and 84% respectively[85]. This is another avenue of potential further study in the development of a non-invasive biomarker for pancreatic cancer.

The presence of DNA mutations in pancreatic juice has also been an area of study. Mutant P53 was found in the pancreatic juice of individuals with PanIN 2-3, intermediate and high grade IPMN and invasive malignancy[86]. When next generation sequencing techniques were used, pancreatic cancer was more likely to have mutated DNA found in pancreatic juice than healthy controls[76]. A small number of patients who eventually developed invasive malignancy had evidence of mutated DNA in pancreatic juice samples pre-dating any abnormalities identified on imaging[76].

Whilst the discovery of biomarkers for the diagnosis of pancreatic adenocarcinoma continues, a recent review concluded that a lack of validated and specific biomarker for this disease remains a major challenge[87].

TREATMENT

Surgical resection is the only treatment that offers a potential cure of pancreatic cancer and the addition of chemotherapy in the adjuvant setting has been shown to improve survival rates. There have been some optimistic results showing a further improvement in survival with the administration of chemo-radiotherapy in the neo-adjuvant setting but further work is needed to identify which group of patients will benefit the most. The most up-to-date evidence supporting these treatment options is presented below.

SURGICAL MANAGEMENT

Pancreatico-duodenectomy (Whipple's procedure), distal or total pancreatectomy are the surgical options for the resection of pancreatic cancer depending on the anatomical location of the tumour or tumours. Reorganisation of healthcare services and restriction of these procedures to high volume centres has improved outcomes as surgeons' expertise increases[20]. Innovations in technology and operative technique have sought to further reduce adverse outcomes and improve survival. The aim of surgical resection is to achieve an R0 resection as this is associated with a significantly improved survival compared to R1 resections[88]. Neo-adjuvant treatment and vascular resections have been employed in an attempt to increase the rate of microscopic clearance. There is ongoing debate as to what constitutes an R1 resection with the Union for International Cancer Control and College of American Pathologists defining it as microscopic evidence of cancer cells at the definite resection margin whereas the Royal College of Pathologists define it as tumour within 1mm of the resection margin[89].

Pre-operative biliary drainage

A significant proportion of patients with pancreatic cancer present with jaundice. This can have implications with regards to coagulopathy and increased peri-operative infective complications[90]. Traditionally, patients with obstructive jaundice would have this relieved prior to resection taking place.

A Cochrane review comparing the outcomes of five studies investigating pre-operative biliary drainage (4 *via* percutaneous transhepatic cholangiography and 1 using endoscopic retrograde cholangiopancreatography (ERCP) found no evidence for or against drainage, although the evidence was acknowledged to be poor[91]. However, a recent multi-centre randomised trial of ERCP and drainage *vs* immediate surgery found a higher rate of peri-operative complications in the drainage group[92]. This suggests that a select group of patients

may do better with expedited surgery rather than biliary decompression, followed by resection.

Anastomotic technique

A major source of morbidity following Whipple's procedure is leak from the pancreatic anastomosis and formation of a pancreatic fistula[93]. It is possible to reconstruct the alimentary tract following Whipple's by anastomosing the pancreatic remnant to the stomach or jejunum. A recent Cochrane review found no difference in outcome when these two techniques were compared to each other[94]. Variations in anastomotic technique have also been described but a recent meta-analysis failed to demonstrate reduced rates of pancreatic fistula with the "duct-to-mucosa" anastomosis *vs* the "invagination" technique[94].

Minimally invasive surgery

In line with other areas, interest has grown in minimally invasive techniques for pancreatic surgery. Laparoscopic distal pancreatectomy was the first minimally invasive pancreatic resection to be described. One meta-analysis found comparable morbidity and mortality between laparoscopic and open distal pancreatectomy, with reduced blood loss and length of stay in the minimally invasive group. There was no difference in the rate of positive resection margins[95]. A further meta-analysis stated that laparoscopic distal pancreatectomy was at least non-inferior to the open procedure, but lack of level one evidence meant that it could not be deemed superior[96].

Attempts have also been made to use robotic techniques to improve Whipple's procedure. When compared to open pancreatectomy, a meta-analysis of retrospective cohort studies found a lower complication rate and less margin involvement in the robotic group[97]. However, the lack of randomisation in these studies leaves them open to selection bias. Robotic surgery also requires a significant capital investment and no cost-effectiveness evaluations were included in any of the papers[98].

Vascular resection

The relationship between any pancreatic tumour and the surrounding vasculature is an important determinant of resectability[99]. Whilst it is often technically feasible, the benefit of resection of mesenteric and portal vessels invaded by tumour remains a controversial topic[99].

Meta-analysis of studies involving patients undergoing Whipple's procedure with or without major arterial resection found higher rates of peri-operative mortality and poor outcomes at year one and three in the group undergoing arterial reconstruction[100]. For this reason, invasion of the superior mesenteric artery or coeliac trunk remains a largely accepted contraindication to resection. Outcomes from venous resection, however, may be more promising. A meta-analysis of 22 retrospective cohort studies found no difference in perioperative morbidity, one or three-year survival in those undergoing resection of the portal or superior mesenteric vein when compared to those in whom no vascular intervention was undertaken. Unsurprisingly, there was an increased operative time and blood loss recorded in the venous resection group[101]. As stated previously, the lack of randomisation leaves these studies at risk of selection bias. However, combined pancreatectomy and venous resection may have a role in a select group of patients.

MEDICAL MANAGEMENT

Adjuvant treatment

The use of adjuvant chemotherapy was supported by the landmark randomised CONKO-001 study which compared adjuvant gemcitabine after complete surgical resection against surgery alone. This study demonstrated a significantly improved median disease free survival (13.4 mo *vs* 6.7 mo) and overall survival with a five year survival of 20.7% *vs* 10.4% and ten year survival of 12.2% *vs* 7.7%[102]. However, despite these promising results the median overall survival only improved from 20 to 23 mo ($P = 0.01$)[102]

Further studies have sought to identify the best chemotherapy regime. The ESPAC-3 trial demonstrated that gemcitabine was the chemotherapy agent of choice when compared to 5-fluorouracil[103]. Although survival outcomes were comparable in both groups, the latter was less well tolerated[103]. Due to the success of dual therapy of capecitabine and gemcitabine in both advanced and metastatic disease, Neoptolemos *et al*[103] performed the ESPAC-4 trial in patients with resected disease and found that the median overall survival was 28 mo (95%CI: 23.5-31.5) in dual therapy compared to 25.5 mo (22.7-27.9) in gemcitabine alone (HR: 0.82, 95%CI: 0.68-0.98; $P = 0.032$).

Other chemotherapy regime have been studied, for example, in the PRODIGE24/CCTG randomised clinical trial which compared the outcomes of gemcitabine or mFOLFIRONOX (a combination of oxaliplatin, irinotecan, and leucovorin) in patients with an R1 or R0 resection of pancreatic adenocarcinoma[104]. The results at a median follow up time of 33.6 mo have shown that administration of mFOLFIRONOX was associated with a significantly improved disease-free survival (21.6 mo *vs* 12.8 mo), and overall survival (54.4 mo *vs* 35 mo) compared to gemcitabine[105]. Administration of mFOLFIRONOX was associated with a significantly increased risk of complications although the only death that occurred was within the gemcitabine treatment group[105]. The current standard of care is guided by post-operative fitness and mFOLFIRONOX is used for very fit patients with tumours of the head, body and tail of the pancreas whereas in less fit patients dual therapy with gemcitabine and capecitabine is given[105]. Single agents (usually 5-Fu) are used for periampullary tumours as there is insufficient evidence for the same treatment as the previously mentioned tumours[106].

Neo-adjuvant treatment

Although there has been shown to be a survival benefit with adjuvant treatment, between 71% and 76% per cent of patients still relapse within two years up. Furthermore, due to complications associated with surgery up to 40% of patients are not suitable for progression to adjuvant therapy[105]. Such figures coupled with the success seen with neo-adjuvant treatment in several other cancers including rectal, oesophageal, and gastric cancer have led to the exploration of the impact of neo-adjuvant treatment in pancreatic cancer[107].

The theoretical advantage of neo-adjuvant therapy includes eliminating micro-metastases and shrinkage of the primary tumour and both these factors are associated with a decreased incidence of tumour recurrence[108]. However, patients receiving neo-adjuvant treatment may develop complications which can delay or prevent the progression to surgery and tumours may be unresponsive to the chemoradiotherapy leading to disease progression and previously resectable disease becoming unresectable. Furthermore, the administration of chemo radiotherapy induces fibrosis within the pancreas which can increase the complication rate associated with pancreatectomy[109].

Studies looking at the impact of neo-adjuvant treatment have been performed in patients with resectable or borderline resectable disease. The definition of resectable disease is in those patients who have no involvement of the superior mesenteric artery, coeliac axis, portal vein or superior mesenteric vein whereas the definition of borderline resectable disease is based on the degree of involvement of these major venous and arterial structures[110].

Multiple meta-analyses have been performed studying the impact of neoadjuvant treatment on survival in pancreatic adenocarcinoma. The most recent was by Versteijne *et al*[110] which included 38 studies with a combination of 3 randomised controlled trials, 9 phase one or phase two trials, 12 prospective cohort studies and 14 retrospective cohort studies. In intention-to-treat analysis there was a median overall survival of 18.8 mo in the neo-adjuvant group compared to 14.8 mo in the surgery first group. For those who actually underwent surgery the median survival time was 15 mo in the surgery-first group, compared to 26.1 mo in the neoadjuvant treated group. The overall resection rate was lower in the neoadjuvant group compared to those who had surgery first (66% *vs* 81.3%; $P < 0.001$) however the R0 resection rate was higher in patients who had neo-adjuvant treatment compared to those who had surgery first (86.8% *vs* 66.9%; $P < 0.001$)[111].

The ongoing Preopanc-1 trial is a Dutch study which recruited 246 patients with resectable or borderline resectable disease[112]. Patients were randomised to either immediate surgery or to pre-operative chemoradiotherapy followed by surgery. There was an increased rate of resection in the immediate surgery group (72%) compared to the group which received preoperative chemoradiotherapy (60%) although this did not reach a level of statistical significance. There was an improved survival in intention to treat analysis with 17.1 mo in the neoadjuvant group compared to 13.7 mo in the immediate surgery group although this did not reach statistical significance ($P = 0.07$) either. In patients who underwent an R0 or R1 resection there was a significantly improved overall survival in the neo-adjuvant group (42.2 mo *vs* 16.8 mo; $P < 0.001$) and there was also a significantly increased time until distant metastases ($P = 0.01$) and loco regional recurrence ($P = 0.002$)[112]. It should be noted that the evidence base for neo-adjuvant treatment in pancreatic cancer is based on phase two trials and meta-analysis while the results of phase three trials are awaited.

TREATMENT IN METASTATIC PATIENTS

The management of metastatic pancreatic cancer involves symptom control, management of jaundice and palliative chemotherapy with the preferred chemotherapy regime FOLFIRONOX (mFOLFIRINOX with 5-fluorouracil). Conroy *et al*[112] performed a multicentre, randomised trial in 48 French centres with patients receiving either gemcitabine or FOLFIRINOX within a week of enrolment. There were 171 patients within each group and intention to treat analysis was performed. The median overall survival in the FOLFIRONOX group was 11.1 mo (95%CI: 9.0-13.2) compared to 6.8 mo (95%CI: 5.5-7.6) in the gemcitabine group (HR: 0.57 95%CI: 0.45-0.73; $P < 0.001$). There was an increased incidence of adverse affects within the group receiving FOLFIRONOX however, this group concluded that FOLFIRONOX should be the treatment of choice in patients with metastatic disease[114].

FUTURE DIRECTIONS FOR PANCREATIC CANCER TREATMENT

The limitations of current treatment strategies in pancreatic cancer reinforces the need for new avenues of research to be explored, in order to achieve potential breakthroughs. Novel therapeutic modalities including oncolytic viral therapy and gene editing technology have been identified as promising in several pre-clinical and early phase clinical trials[114,115]. These therapeutic strategies have been recently reviewed by Rouanet *et al*[116], which provides an excellent overview of the current landscape of these experimental treatments.

SUMMARY AND FUTURE RESEARCH RECOMMENDATIONS

Pancreatic cancer is more common in developed countries, which may be attributed to lifestyle factors. Aetiology is still poorly understood, and further large, prospective studies are necessary to better understand risk factors associated with pancreatic cancer.

Patients with a risk of familial pancreatic ductal

adenocarcinoma are a potential target for screening. However, the optimum age, time interval at which screening should be performed or the best imaging technique is not agreed upon. Further retrospective and prospective studies which follow these patients with familial pancreatic cancer over time will help gain a better understanding of the course of this disease and enable the introduction of effective screening and treatment methods.

PanIN, IPMN and MCN are recognised precursors to pancreatic adenocarcinoma. Identifying patients with these lesions early, and developing an appropriate follow up programme will enable early treatment in high risk patients but also prevent unnecessary surgery in low risk lesions. This can be achieved by performing large retrospective and prospective studies which follow these patient groups over prolonged periods of time which will enable a better understanding of the disease process to be achieved. Furthermore, the risk factors associated with these pre-malignant conditions will be able to be identified, which opens the possibility of target populations being screened for these pre-malignant conditions.

The introduction of neo-adjuvant therapy has improved survival in some patients whereas others with previously resectable disease have developed unreseactable disease during the course of their treatment. Further randomised studies are essential to identify which patients will benefit most from this approach. The discovery of novel biomarkers may contribute to the decision-making process and enable precision medicine and therapy tailored to individual patients.

Surgical resection remains the mainstay of curative treatment of pancreatic cancer. Venous resection enables clear margins to be achieved but the survival benefit from this is not clear. Further retrospective studies identifying patients who have undergone this treatment and the outcomes associated with it will add to the evidence pool and help formulate future guidelines.

CONCLUSION

This review provides a comprehensive account of the epidemiology and management of pancreatic ductal adenocarcinoma. Significant gaps (as highlighted in the summary section above) remain in the understanding of this disease and treatment options although continually evolving continue to have limited success. There has been a recent drive to fund large consortia and specialist research into pancreatic ductal adenocarcinoma but there is much work to be done to enable similar breakthroughs as seen for other cancer sites.

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