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Review

Pancreatic Cancer: Epidemiology, Risk Factors, and Prevention

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Simple Summary

Pancreatic cancer remains one of the most lethal malignancies due to its silent progression and late diagnosis. The review outlines current knowledge on its epidemiology, highlighting variations across regions and populations, and identifies both modifiable and inherited risk factors. We discuss recent efforts in early detection, including biomarker development and imaging advances, as well as preventive strategies targeting high-risk individuals. A better understanding of these factors may help refine risk assessment, promote prevention, and improve survival outcomes in the future.

Abstract

Pancreatic cancer is one of the most lethal malignancies, with a 5-year survival rate of around 10%. This review aims to provide a comprehensive overview of the current understanding of the epidemiology, risk factors, and preventive measures of pancreatic cancer. The global incidence of pancreatic cancer is currently increasing, with significant regional variations. Developed countries exhibit higher incidence and mortality rates compared to developing countries. Several genetic and environmental risk factors have been identified, including BRCA1 and BRCA2 gene mutations, Lynch syndrome, smoking, obesity, and pesticide exposure. Primary prevention strategies focus on lifestyle modifications such as stopping smoking, maintaining a healthy weight, avoiding heavy alcohol consumption, and minimizing pesticide exposure. Secondary prevention focuses on improving early detection through advancements in imaging and the development of novel biomarkers, alongside the identification of molecular therapeutic targets to extend survival. Changes in the epidemiology of pancreatic cancer and the identification of new biomarkers could open roads for more accurate risk stratification, early detection, and more effective prevention strategies in pancreatic cancer.

Keywords: pancreatic cancer; epidemiology; prevention; risk factors

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1. Introduction

Pancreatic cancer (PC) is one of the most aggressive and lethal malignancies, mainly due to its late detection. Indeed, more than 80% of affected individuals are diagnosed in the advanced stage, resulting in a 5-year survival rate of 11%. Only 20 to 30% of patients are eligible for surgical resection at the time of diagnosis [1,2]. Recent therapeutic progress, particularly in neoadjuvant strategies, has allowed certain patients with initially unresectable PC to benefit from so-called conversion surgery. Evidence suggests that this approach can yield a median survival ranging from 26 to 56 months [3–6].

Over the last decades, the incidence rate of PC has risen progressively in several countries. It is estimated that by 2030, PC will be the third cause of cancer deaths in Europe, the second cause of cancer deaths in the United States, and probably the most frequent digestive malignancy [7–9].

PC typically originates in the ductal cells of the pancreas, and about 90% of PC are pancreatic ductal adenocarcinomas (PDACs). The progression from normal pancreatic duct cells to invasive cancer involves multiple genetic mutations and alterations in cellular pathways. More than 90% of PDACs harbor activating somatic mutations in the KRAS oncogene, a gene that plays a crucial role in cell signaling pathways that control cell growth and division. Somatic mutations in the tumor suppressor genes p16/CDKN2A, TP53, and SMAD4 are also found in 90%, 75%, and 50% of PC tumors, respectively [10].

The neoplastic precursor lesions for PDAC are pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (MCN). The latter two often present as incidental findings on cross-sectional imaging of pancreatic cysts and harbor an annual incident risk of malignancy of 0.25% with a prevalent malignant risk of 0.25% when the cyst is identified [11]. However, unlike PanIN, which is not visible on imaging modalities, only a small number of these cystic lesions progress from low- to high-grade epithelial lesions (around 12% at 15 years) [12].

Modifiable risk factors of PDAC are tobacco smoking, heavy alcohol drinking, obesity, type 2 diabetes, chronic pancreatitis, and pesticide exposure. Further, around 5 to 10% of PDACs are caused by genetic predispositions and inherited susceptibility.

Poor prognosis of PDAC primarily stems from the challenge of the timely diagnosis of PC, not to mention identifying the factors influencing neoplastic progression, lesions at risk of degeneration, and high-risk individuals with genetic variants. Indeed, the early detection of resectable neoplasms is the best strategy for improving PDAC survival and/or cure.

PC is a growing public health concern worldwide, known for its silent progression and poor prognosis. Despite advances in oncology, the overall survival remains low, mainly due to late-stage diagnosis and limited treatment options. This review aims to provide an overview of the current knowledge on PC, mostly epidemiology, as well as its risk factors. It also highlights recent advancements to provide a better understanding of prevention in these areas.

2. Epidemiology

PC ranks as the seventh leading cause of cancer-related deaths worldwide. According to the Global Cancer Observatory, approximately 495,773 new cases (262,865 males and 232,908 females) and 466,003 deaths (246,840 males and 219,163 females) were attributed to PC in 2020 [13]. The estimated lifetime risk of developing PDAC is approximately 1.7%.

Pancreatic cancer incidence shows marked global disparities, with significantly higher rates observed in countries with a very high or high Human Development Index (HDI) [14]. Indeed, if we compare age-standardized rates (ASR) among different countries, the incidence of PC was the highest in those with a very high HDI (ASR 7.7) as compared to those with a high (ASR 4.9), medium (ASR 2.5), or low HDI (ASR 1.8) (ASR 2.5) [14]. In the same proportion, the mortality is higher in the same configuration. Western Europe and North America report some of the highest incidence rates, with 8.5 and 8.0 cases per 100,000, respectively, while countries in Africa and South Asia show much lower rates at 1.3 cases per 100,000 inhabitants [13]. These variations in incidence rates are not completely understood but can probably be attributed to genetic predispositions, environmental exposures, and lifestyle factors as well as healthcare infrastructure and cancer registries. The influence of regional dietary habits, pollution, and access to medical care further complicates our understanding of these variations.

Demographic factors such as age, sex, race, and ethnicity are known to be non-modifiable risk factors for PC. Indeed, PC predominantly affects older adults, with a median age of around 70 years at diagnosis and a mean of 65 years in the United States. Interestingly, recent studies have highlighted a rising incidence in young women, especially those under 55, and even among women aged 15 to 34 [15]. GLOBACAN data from 184 countries indicate an increase in incidence among people over 50 years in 18 countries and younger populations in several others, including Canada, the Netherlands, and the UK [14].

Men are slightly more susceptible to pancreatic cancer than women, with a male-to-female ratio of 1.4:1 [14]. This trend is observed consistently across studies and regions [13,14,16]. This difference may partially be explained by men's higher rates of smoking and occupational exposure. However, hormonal differences and variations in lifestyle factors between sexes could also play a role.

Ethnic disparities, particularly in the U.S., show that African Americans have the highest incidence of PC, followed by White, Hispanic, and Asian populations [17,18]. This variation likely reflects a complex interplay of genetic susceptibility, comorbidities like diabetes and obesity, healthcare access, and environmental influences. Moreover, emerging evidence suggests potential differences in treatment response, such as neoadjuvant chemotherapy, which may indicate underlying variations in tumor biology across racial groups [16].

2.1. Genetic Predispositions and Inherited Susceptibility for Pancreatic Ductal Adenocarcinoma

Overall, 5 to 10% of patients with PDAC have a genetic component [14]. However, these numbers might be lower, since two prospective studies conducted in Europe found a prevalence of familial aggregation in only 2.7 and 1.9% of all PDAC patients [17–19]. The reason for this discrepancy may be that most previous studies relied on reported cancers rather than cancers confirmed by family medical records, which may entail considerable inaccurate reporting.

Furthermore, pathogenic germline variants occur in 5 to 20% of patients with PC [10,20,21]. However, half of these patients do not report any family history of PC and/or do not meet criteria for the hereditary syndrome.

Germline alterations most frequently involve genes implicated in homologous recombination DNA damage repair, notably BRCA2, BRCA1, and PALB2. In contrast, somatic alterations in BRCA2, PALB2, or ATM are observed in only 8% of PDAC cases and tend to be biallelic. New clinical guidelines now recommend universal genetic testing for all PDAC patients, regardless of family history, using a multigene panel [22].

An inherited predisposition toward developing PDAC occurs in three different scenarios: (1) hereditary cancer syndromes such as hereditary breast and ovarian cancer; (2) hereditary pancreatitis and cystic fibrosis; and finally, (3) familial PC, which accounts for approximately 75% of all inherited cancers. Table 1 shows the three different groups of inherited PC with their respective defective genes and the risk of developing PDAC by the age of 70 (Table 1).

Table 1. Three types of inherited pancreatic cancer.

	Defective Gene	PDAC Risk Up to Age 70
1. Hereditary cancer syndrome (20%)		
Peutz–Jeghers syndrome	STK11	36%

Table 1. *Cont.*

	Defective Gene	PDAC Risk Up to Age 70
Familial atypical multiple mole melanoma syndrome	CDKN2A	17%
Hereditary breast and ovarian cancer	BRCA1/2, PALB2	3–8%
Hereditary nonpolyposis colon cancer	MLH1, MSH2/6	<5%
Familial adenomatous polyposis	APC	<5%
2. Hereditary pancreatitis (5%)	PRSS1, SPINK1	40%
Cystic fibrosis	CFTR	<5%
3. Familial pancreatic cancer syndrome (75%)	BRCA2, PALB2, ATM, CDKN2A, CHEK2	>40%

2.1.1. Hereditary Cancer Syndrome

Individuals with Peutz–Jeghers syndrome, caused by pathogenic germline mutations in the STK11 gene, are at a significantly increased risk of developing multiple cancers, including pancreatic cancer. This syndrome, marked by characteristic hamartomatous gastrointestinal polyps and mucocutaneous pigmentation, confers one of the highest known lifetime risks for PC, estimated at up to 36%.

Familial atypical multiple mole melanoma syndrome is linked to mutations in the CDKN2A gene, a tumor suppressor gene that encodes the p16 protein. This condition is linked not only to melanoma but also to an elevated risk of PDAC, with estimated lifetime risks ranging between 16 and 20% for PDAC having been reported [23]. Because the syndrome may present subtly, sometimes without a known history of melanoma or the characteristic atypical nevi, it is likely to be underdiagnosed. A personal or family history of both melanoma and PDAC should raise clinical suspicion, even in the absence of typical skin lesions. Genetic counseling and regular dermatological examinations are recommended for affected individuals.

Mutations in BRCA1 and BRCA2 are known not only to be associated with breast and ovarian cancer but also to elevate the risk of PC. Individuals with BRCA2 mutations have a lifetime risk of 5 to 10% for PC and are identified in up to 7% of patients with PC. Guidelines on the surveillance of PC in carriers with BRCA1 and BRCA2 mutations diverge, with some proposing surveillance regardless of family history and others only for carriers with a family history of PC. Both germline and somatic alterations in BRCA1/2 carry therapeutic implications. In the POLO trial, patients with metastatic pancreatic cancer harboring germline BRCA mutations who received maintenance therapy with the PARP inhibitor, Olaparib, showed a significant improvement in progression-free survival after platinum-based chemotherapy [24]. This has led to the integration of BRCA testing into therapeutic decision-making for advanced PDAC, making it relevant not only for surveillance, family screening but also personalized treatment approaches. The ATM gene, also involved in the DNA repair pathway, is considered a cancer susceptibility gene of moderate risk, with carriers having a 5 to 10% risk of developing PDAC by the age of 80 years. Currently, surveillance should only be offered to carriers with a family history of PC.

Lynch syndrome, caused by pathogenic variants in mismatch repair genes such as MLH1, MSH2, MSH6, PMS2, and EPCAM, is associated with an increased risk of various

malignancies, including PC. Individuals carrying these mutations face a lifetime risk of PDAC estimated between 0.5 and 7%. Surveillance should be offered to carriers reporting a family history of PC [25].

The APC gene, a key tumor suppressor involved in colorectal tumorigenesis, is primarily linked to familial adenomatous polyposis (FAP), a condition predisposing to colorectal, duodenal, and periampullary neoplasms. Although less commonly associated with PC, pathogenic APC variants have been detected in approximately 2.1% of PDAC cases, particularly among individuals of Ashkenazi Jewish descent [26].

2.1.2. Hereditary Pancreatitis

Chronic pancreatitis is also a risk factor for developing pancreatic cancer, with a 40% lifetime risk of this cancer in patients with hereditary pancreatitis syndromes and a higher risk in cases of paternal inheritance of the disease and tobacco consumption. Hereditary pancreatitis is an autosomal dominant inherited disease caused by PRSS1, which encodes cationic trypsinogen. Few families have germline mutations in SPINK1, CTRC, CPA1, and CPB1, which encode the pancreatic digestive enzymes, and have a much lower risk of developing PDAC. Furthermore, mutations of the CFTR gene seen in cystic fibrosis increase the risk of PDAC by 5.3 [27].

2.1.3. Familial Pancreatic Cancer

Familial pancreatic cancer (FPC) includes individuals with at least two first-degree relatives with PDAC who do not fulfill the criteria for other hereditary cancer syndromes [18].

Inheritance is autosomal dominant in 58 to 80% of FPC families. The most recent European Registry of Hereditary Pancreatitis and Pancreatic Cancer and the German National Case Collection for Familial Pancreatic Carcinoma described autosomal dominant inheritance in 58% and 72% of patients, respectively.

In FPC kindreds, adults considered to be at a high risk include first-degree relatives of affected individuals or carriers of a predisposing germline mutation. FPC can be divided into two groups: (1) "pure" FPC families (37%) and (2) other types of cancer (63%). The three most common associated cancers are breast cancer (30%), colorectal cancer (11%), and melanoma (9.7%).

The National Familial Pancreas Tumor Registry estimated that the relative risk of developing PDAC in FPC families was elevated in individuals with three (32.0; 95% CI, 10.2–74.7), two (6.4; 95% CI, 1.8–16.4), or one (4.6; CI, 0.5–16.4) first-degree relative(s) with PC (10). Furthermore, this risk was higher in smokers than in non-smokers [28,29].

In the vast majority of FPC cases, estimated at around 90%, the underlying genetic defect remains unidentified. The most frequently identified genetic alterations in FPC are BRCA2 germline mutations (15–29%) [28,30]. A study of 3000 patients showed that 2 to 5% of patients with PDAC with no family history of this cancer harbored at least one known inherited PC-predisposing genetic alteration compared with 7 to 9% of patients with a positive family history. This finding led to updated recommendations from the American Society of Clinical Oncology and the National Comprehensive Cancer Network to consider germline testing for all patients diagnosed with PC in the early course of the disease [20,31,32].

2.2. Modifiable Risk Factors Associated with Pancreatic Ductal Adenocarcinoma

Several modifiable risk factors are associated with PC, including tobacco smoking, obesity, diabetes, chronic pancreatitis, and occupational exposure to certain chemicals (Table 2).

Table 2. Risk factors associated with pancreatic cancer.

Risk Factor	Description	Risk Increase (RR = Relative Risk/ OR = Odds Ratio)
Smoking	Smoking is the most significant modifiable risk	RR = 2–3
Alcohol consumption	High alcohol intake contributes to chronic pancreatitis, a known precursor of pancreatic cancer	RR = 1.2–1.5 (heavy drinking), 3.5 in men
Obesity	Obesity (BMI $\geq$ 30 kg/m^2) is associated with increased risk, especially abdominal obesity	RR = 1.1–1.7
Diabetes	Both long-standing diabetes and new-onset diabetes increase the risk of pancreatic cancer	RR = 2.4–15 depending on the year after diabetes onset
Chronic pancreatitis	Chronic inflammation, whether alcohol-related or hereditary, strongly increases the risk.	RR = 0.4–9
Exposure	Exposure to organic solvents and pesticides may increase the risk of cancer	OR = 0.9–1.4

2.2.1. Smoking

Several epidemiological studies have clearly established smoking as a risk factor for PC, accounting for approximately 11 to 32% of cases, with an average 2-fold increase in the risk of PC compared to non-smokers [33]. The risk increases with both smoking intensity and duration. Furthermore, one study showed that both smoking and genetic mutations were major risk factors for early-onset PC. Smoking is the strongest exogenous risk factor in familial pancreatic cancer, particularly in people under 50 years. Smoking increases the risk of PDAC by 2 to 3.7 times over the inherited predisposition and lowers the age of onset by about 10 years.

In this same context and based on the results of the Global Burden of Disease Study of 2017 [34], PC deaths worldwide were primarily attributable to smoking (25.9% in males, 16.1% in females). Regionally, the highest proportions of smoking-related PC mortality in males were observed in Eastern Europe (35.7%) and East Asia (31.3%), whereas among females, North America (29.3%) and Southern Latin America (27.6%) had the greatest burdens [34].

Nevertheless, the 2019 Global Burden of Disease Study shows a decrease in smoking prevalence among younger people, whereas the prevalence of PC has increased in this population [35]. The increasing trend observed may therefore be attributed to other risk factors.

According to the International Pancreatic Cancer Case–Control Consortium (Panc4) [36], the odds of developing PC were 1.2 for former smokers and 2.2 for current smokers compared to never-smokers. A clear dose–response relationship was observed, with individuals smoking over 35 cigarettes per day facing an odds ratio of 3.4. Similarly, prolonged tobacco use, up to 40 years, was associated with an elevated risk (OR 2.4). The burden of PC deaths attributed to smoking was most prominent among individuals aged 55 to 84. Smoking cessation remains the most effective strategy to reduce the risk,

with evidence showing that former smokers' risk approximates that of never-smokers after two decades [36]. However, recent epidemiological data on the evolution of tobacco-related cancer incidence is not in line with the PC incidence, thus making this hypothesis questionable or only partially explainable. This evolution raises questions about other understudied risk factors, and as a result, further research is required to address the precise impact of smoking on PC.

2.2.2. Alcohol Consumption

Heavy alcohol use (defined as binge drinking or drinking ≥3 drinks per day) is a risk factor for chronic pancreatitis, which in turn increases the risk of PC [37–39]. Discordant observations in the literature exist in terms of the dose and duration of alcohol exposure. In the study of Gupta et al., binge drinking (≥5 drinks per drinking episode or more than 70 g alcohol per episode) was associated with a 3.5-fold increased risk of PC in men but not in women [39]. This risk was positively associated with an increasing average number of alcoholic drinks consumed during binge drinking [39]. Multivariate analyses suggested that heavy drinkers who were current smokers may have a greater risk of PC compared to former or never-smokers [39]. In other studies, the association between alcohol and PC persisted even among non-smokers and former smokers [38–40]. In conclusion, while the role played by moderate alcohol consumption in PC is less clear, heavy drinking should be avoided to reduce the overall cancer risk.

2.2.3. Obesity and Physical Inactivity

Obesity, typically defined as a body mass index (BMI) $\geq$ 30 kg/m^2, and insufficient physical activity (<150 min of moderate or <75 min of vigorous exercise per week) are recognized contributors to PC risk. Several studies have shown a correlation between high BMI and the risk of PC. Obesity, particularly central obesity, increases the risk of PC by 1.72 [41]. The underlying mechanisms may include chronic inflammation, type 2 diabetes, insulin resistance causing hyperinsulinemia, and higher levels of insulin-like growth factors. One meta-analysis pooling data from seven large prospective cohorts found that, compared to individuals with a normal BMI, those classified as overweight had a 1.13-fold increased risk of PC, and those with obesity a 1.19-fold increase [42]. Regular physical activity helps maintain a healthy weight and may reduce the risk of PC by improving metabolic health and reducing inflammation. However, studies did not find that physical activity modifies the association between BMI and risk of PC [41,42]. Despite the relative modesty of individual risk, the rising global prevalence of obesity, especially among women, underscores its growing public health importance in the context of PC prevention.

2.2.4. Diabetes

Individuals with type 2 diabetes have an approximately 2.4-fold increased risk of developing PC compared to the general population [43–45]. In the first year after diabetes onset, this risk is significantly higher, up to 14–15-fold, and then decreases to 3-fold after the third year; for this reason, diabetes can be considered a potential early symptom of PC [46]. Although diabetes is believed to be secondary to the tumor-induced destruction of the pancreas or canalicular obstruction, some studies showed that it could be a secondary effect of glucose metabolism, such as insulin resistance, which explains why glucose levels return to normal after cancer resection in some individuals [47,48]. The relationship between diabetes and PC is complex, as they share risk factors like obesity and inflammation.

Regarding type 2 diabetes therapy, metformin significantly decreases the risk of PC, although this effect was not seen with other antidiabetics such as insulin or sulfonylurea [45,49].

2.2.5. Chronic Pancreatitis

Long-standing inflammation of the pancreas significantly increases the risk of PC. Indeed, not only is pancreatitis associated with PC as a risk factor, but it can also develop because of underlying PC. The strongest correlation between acute or chronic pancreatitis as a symptom of PC is observed in individuals aged 56–75 years. Similarly to diabetes, the strongest association occurs in the first two years after the diagnosis of pancreatitis, especially in patients between the ages of 61 and 70 years [50]. According to the Dutch pancreatitis study group, the likelihood of developing PC after an isolated episode of acute pancreatitis is relatively low (0.4%), but this risk increases dramatically by 9-fold if the disease progresses to its chronic form [51]. Given this elevated risk, post-acute pancreatitis patients are generally advised to undergo follow-up imaging to exclude underlying malignancy [52]. Moreover, chronic pancreatitis often coexists with other PC risk factors such as tobacco use, excessive alcohol intake, and genetic predispositions, compounding the overall risk.

2.2.6. Pesticide Exposure

Recent studies have suggested that exposure to certain pesticides may be linked to an increased risk of PC [53–55]. Organochlorine compounds include thousands of metabolism-resistant lipophilic substances that are stored in adipose tissue for long periods of time. Their residue can be measured, being designated as persistent organic pollutants. In the PESTIPAC study conducted by Brugel et al. in France, a country with extensive agricultural activity, the results showed a significantly higher concentration of organochlorine compounds, namely trans-nonachlor, cis-nonachlor, 4,4'-DDE, and Mirex, detected in the adipose tissue of patients with PC [56]. The same authors performed a nationwide ecological regression study between 2011 and 2021, highlighting several pesticides that could be linked to the increased incidence of PC. Spatial analyses showed that sulfur, mancozeb, and glyphosate were the three most toxic pesticides, with a significant correlation between exposure and risk of PC (0.9 to 1.4%). Furthermore, agricultural workers and individuals living in areas with high pesticide use are particularly at risk of PC, according to several French studies [54,56].

2.3. Preneoplastic Pancreatic Lesions

Pancreatic cystic lesions, such as IPMN or MCN, are often identified incidentally with cross-sectional imaging in elderly individuals and have a potential for malignancy. The prevalence of cystic lesions increases with age, affecting up to 20% of individuals over 80 years [57].

IPMNs are precancerous intraepithelial ductal lesions that develop from the epithelium of pancreatic ducts (main and/or secondary). The cystic component of IPMN features a mucinous-type epithelium that produces mucin. These lesions can affect patients of all ages but are most common in those aged 50–70 years, with a balanced sex ratio. The majority of IPMNs are located in the head of the pancreas (70%). There are three subtypes based on the type of pancreatic duct involved: the main pancreatic duct, branch ducts, or mixed form. As these lesions derive from mucinous columnar epithelium, carcinoembryonic antigen (CEA) levels are generally elevated. The connection with the main pancreatic duct explains the typically high levels of cystic amylase, while intracystic glucose levels are low. Two of the most frequent mutations identified in IPMN are GNAS and KRAS and can be detected in pancreatic cyst fluid obtained by endoscopic ultrasound-guided fine-needle aspiration. GNAS mutations are highly specific to IPMN and are detected in up to 66% of resected IPMN lesions. In contrast, KRAS mutations are more common but less specific. The presence of KRAS alone does not distinguish between benign and malignant lesions,

whereas the co-occurrence of KRAS and GNAS mutations may increase the likelihood of IPMN. Recent studies have also demonstrated the role of cell-free tumor DNA, circulating tumor cells, and exosomes in improving the diagnostic accuracy for pancreatic cystic lesions. These molecular tools contribute to the evolving strategy of non-invasive stratification, early detection, and monitoring of pancreatic preneoplastic conditions [58].

The malignant potential of IPMN depends on the pancreatic duct involved, its growth, the presence of mural nodules or solid components, and the presence of pancreatic atrophy. In the different recommendations for identifying high-risk IPMN lesions, algorithms take into consideration serum CEA and CA 19-9, cyst size, thickened/enhancing cyst wall and mural nodule, main pancreatic duct diameter, and presence of jaundice or pancreatitis. In such cases, the cystic lesion should be investigated by endoscopic ultrasound (EUS) and cyst aspiration (cytology, molecular analysis, CEA, amylase) if the individual is fit enough to undergo surgery [59–61].

Involvement of the main pancreatic duct carries a higher malignant potential compared to the branch ducts (62% vs. 30%) and requires surgical treatment [57]. A review of 99 studies involving a total of 9249 patients with IPMN reported a 42% incidence of high-grade dysplasia or cancer following surgical resection [62]. Management of IPMN involving secondary ducts varies. A recent study demonstrated that the risk of developing cancer from branch-duct IPMN increases with age and follow-up duration, with rates of 3.5% at 10 years and 12% at 15 years after the initial diagnosis [12]. Of note, half of cancers developed in non-cystic pancreatic parenchyma distant from the IPMN.

MCN is another precancerous lesion composed of a large columnar epithelium surrounded by an ovarian-type stroma, which distinguishes it from other mucinous neoplasms. Due to its cellular origin, it primarily affects middle-aged women and is usually located in the body and tail of the pancreas. The mucinous columnar cells can produce CEA, leading to generally high CEA levels, while the cystic glucose level remains low. Molecular analysis typically shows a KRAS gene mutation but not GNAS. Clinically, patients are often asymptomatic. Although the exact rate of malignant transformation is debated, it is considered high-risk, especially when the lesion is $\geq$40 mm in diameter; in this case, surgical resection is recommended.

3. Prevention

Preventing PC involves addressing modifiable risk factors and proposing personalized surveillance for high-risk individuals such as those with a family history of PC or known genetic mutations. Genetic counseling and testing can identify at-risk individuals who may benefit from enhanced surveillance. Public health policies should ensure that these services are accessible and affordable to all.

3.1. Lifestyle Changes

Quitting smoking and preventing obesity through regular physical activity are important measures to reduce the risk of PC. Public health campaigns should thus target smoking cessation and promoting active lifestyles. National educational programs should be implemented to guide the population in adopting a balanced diet with suggestions to eat local produce grown without pesticides. Indeed, healthy eating can significantly impact cancer prevention. Furthermore, limiting alcohol intake, especially heavy drinking, can reduce the risk of chronic pancreatitis and subsequent PC [63]. Public health campaigns should emphasize the risks associated with heavy alcohol consumption and provide support for individuals seeking to reduce their intake.

3.2. Screening and Imaging

Currently, no screening tool for the early detection of PC exists. Laboratory tests, including serum biomarkers such as carbohydrate antigen 19-9 (CA 19-9), are used in complement to imaging studies [64,65]. However, this marker has poor sensitivity and specificity [66]. Other biomarkers under investigation, including circulating tumor DNA, microRNAs, and exosomes, hold promise for improving early detection and monitoring treatment response [65,67].

In symptomatic patients, CA 19-9 has a sensitivity of approximately 70–80% and specificity of about 80–90% for PDAC [68]. However, it is important to keep in mind that approximately 5 to 10% of individuals cannot synthesize CA 19-9 antigens and are therefore regarded as Lewis a-b negative [69]. Hence, negative CA 19-9 test results do not necessarily exclude PDAC.

Advances in imaging technologies such as EUS and magnetic resonance imaging (MRI) are currently being investigated for their potential use in early detection. These techniques might be particularly beneficial for individuals at elevated risk, such as those with hereditary cancer syndrome, a family history of PC, or known preneoplastic pancreatic lesions. The development of non-invasive imaging methods could enhance early detection and improve survival rates.

3.3. Surveillance of Preneoplastic Pancreatic Lesions

Before initiating the surveillance of pancreatic cystic lesions, several patient characteristics should be considered, such as age, comorbidities, and personal wishes. The risks and benefits of the surveillance program should also be discussed with the patient. Indeed, due to the higher incidence of cystic pancreatic lesions with age, investigations such as EUS and cyst aspiration carry risks, not to mention the morbidity and mortality linked to pancreatic surgery, which stand at 20–40% and 1–3%, respectively. The surveillance rate depends on the guidelines. While the 2017 International Association of Pancreatology guidelines propose a different surveillance frequency based on the size of pancreatic cystic lesions, the 2015 American Gastroenterological Association and 2018 European guidelines do not take size differences into account [11,58,59]. The European guidelines recommend conducting surveillance at 6 and 12 months and then annually, including CA 19-9 measurements and MRI or EUS [59].

3.4. Surveillance of High-Risk Individuals and Patients with Known Genetic Mutations

The aim of PC surveillance is to detect and manage precursor lesions before they progress to invasive lesions, reducing both incidence and mortality of PC. It should aim to identify stage 1 PDAC or premalignant lesions with high-grade dysplasia, such as PanIN or IPMN. Factors that guide eligibility for surveillance include the patient's age, family history of PC, and the presence of pathogenic germline mutations. The degree of familial clustering, especially the number of first- and second-degree relatives with PC, is critical to assess the relative risk of developing PC. For example, individuals with two first-degree relatives diagnosed with PC have an estimated lifetime PDAC risk of about 8%. Furthermore, surveillance recommendations depend on the type of gene mutation, and currently, it is recommended for BRCA2, ATM, BRCA1, PALB2, CDKN2A, STK11, MLH1, and MSH2.

The American College of Gastroenterology conditionally recommends the annual screening of these high-risk FPC individuals using EUS and/or MRI starting at the age of 50 years or 10 years less than the earliest reported age of PDAC in the family if the patient is eligible for potential surgical treatment. Computed tomography should be performed on patients unable to undergo MRI or EUS. The preference for EUS and MRI is based on their superiority at detecting sub-centimeter pancreatic cysts and the avoidance of ionizing

radiation. Surveillance from age 40 is recommended for CDKN2A mutation carriers. The Cancer of the Pancreas Screening Consortium recommends screening individuals with a high risk of pancreatic carcinoma at expert multidisciplinary centers under research conditions. While this consortium agreed on surveillance modalities (EUS and/or MRI), they could not reach a consensus about the ages to initiate or stop surveillance.

Recent reviews have emphasized the importance of individualized surveillance algorithms based on the specific germline mutation, family history, age, and comorbidities. These decision-tree-based approaches help define optimal screening intervals, imaging modalities, and eligibility for early surgical evaluation in the context of premalignant lesions. Such structured algorithms aim to maximize early detection and adjust the surveillance in order to avoid unnecessary procedures in moderate-risk populations [70].

In addition, a large multicenter Dutch cohort demonstrated that structured surveillance of high-risk individuals led to earlier detection of PC and was associated with significantly improved overall survival, supporting the clinical benefit of such algorithms in appropriately selected patients [71].

Patients with only one relative with PDAC do not require surveillance, as the risk is the same for those without a family history. The average lifetime risk of developing PDAC is too low (about 1%) for population-based screening.

Of note, individuals who smoke tend to be diagnosed with PDAC at a younger age [72]. Furthermore, the median age of PDAC in individuals with hereditary pancreatitis due to the PRSS1 mutation occurs approximately 10 years earlier than in those without genetic predispositions. The recommended starting age of surveillance may vary in high-risk individuals without a family history. Surveillance of patients with Peutz–Jeghers syndrome should start at the age of 35 or 10 years before the age of the youngest relative with PC. For patients with hereditary pancreatitis, surveillance is recommended, with most experts agreeing on the age of 40 or 20 years after the first attack of pancreatitis, irrespective of genetic status.

The utility of CA 19-9 as a screening tool in individuals with inherited risk factors or a strong family history of PC has not been formally validated. It is generally accepted that this biomarker may offer diagnostic support in cases where there is already a heightened suspicion of PC, such as in the case of worrisome features on imaging. It should be used selectively in patients with specific clinical and radiologic indicators suggestive of malignancy.

Given that 0.4 to 0.8% of individuals over the age of 50 who develop new-onset diabetes are diagnosed with PC within 3 years, expert consensus supports additional diagnostic evaluation in high-risk patients presenting with recent diabetes onset.

Furthermore, as some germline mutations can induce cancers other than PDAC, experts recommend surveillance for other cancers according to the cancer family history and gene mutation status.

4. Current Therapeutic Strategies in PDAC

Despite advances in understanding the molecular pathogenesis of PDAC, effective therapeutic strategies remain limited, and outcomes continue to be poor. Indeed, chemotherapy remains the cornerstone of PDAC treatment. The two main first-line regimens for patients with advanced or metastatic disease are FOLFIRINOX (a combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) and gemcitabine-based combinations, such as gemcitabine plus nab-paclitaxel. FOLFIRINOX has shown superior efficacy in terms of overall survival compared to gemcitabine monotherapy but is often reserved for patients with good performance status due to its toxicity profile. Second-line therapy is less well defined but may include irinotecan in combination with 5-FU and leucovorin.

Targeted therapies have also emerged. For instance, small molecule kinase inhibitors (SMKIs) targeting KRAS or MEK are under investigation, although results have been limited so far. In patients with mismatch repair deficiency (dMMR) or microsatellite instability-high (MSI-H) tumors, immune checkpoint inhibitors such as pembrolizumab have shown promising results. However, this only represents a small minority of PDAC cases.

Furthermore, as discussed previously, patients with germline BRCA mutations may benefit from PARP inhibitors such as Olaparib, which has been approved as maintenance therapy in metastatic PDAC following response to platinum-based chemotherapy.

Finally, emerging therapies such as stromal remodeling agents, cancer vaccines, and adoptive T-cell therapies are being investigated in clinical trials. However, their integration into routine clinical practice remains limited. Overall, while modest progress has been made, therapeutic advances in PDAC remain limited due to the complex interplay of tumor heterogeneity, an immunosuppressive microenvironment, and resistance mechanisms [73–75].

5. Conclusions

In conclusion, PC remains a medical challenge and poses a significant public health risk due to its high mortality rate and late-stage diagnosis. A comprehensive understanding of its epidemiology and risk factors is crucial for prevention strategies. Modifiable factors, including smoking cessation and weight management, remain essential measures to reduce the risk of PC. Further studies are required to address both the genetic and environmental risk factors in order to reduce the incidence and improve the prognosis of this devastating disease.

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