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REVIEW

# Genetic and other risk factors for pancreatic ductal adenocarcinoma (PDAC)

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**Abstract**
Pancreatic ductal adenocarcinoma (PDAC) is often diagnosed at an advanced stage, resulting in poor prognosis and low 5-year survival rates. While early evidence suggests increased long-term survival in those with screen-detected resectable cancers, surveillance imaging is currently only recommended for individuals with a lifetime risk of PDAC ≥ 5%. Identification of risk factors for PDAC provides opportunities for early detection, risk reducing interventions, and targeted therapies, thus potentially improving patient outcomes. Here, we summarize modifiable and non-modifiable risk factors for PDAC. We review hereditary cancer syndromes associated with risk for PDAC and their implications for patients and their relatives. In addition, other biologically relevant pathways and environmental and lifestyle risk factors are discussed. Future work may focus on elucidating additional genetic, environmental, and lifestyle risk factors that may modify PDAC risk to continue to identify individuals at increased risk for PDAC who may benefit from surveillance and risk reducing interventions.

**Keywords** Pancreatic cancer · Cancer risk factors · Genetics · Cancer predisposition

## Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the tenth most common cancer diagnosed in the United States, with incidence increasing globally, especially in Western countries [1, 2]. Although the median age of diagnosis is 70 years, recent trends have shown increases in pancreatic cancer diagnoses among young individuals, particularly those assigned female at birth [3].

Pancreatic cancer is the third leading cause of cancer death in the U.S. with a 5-year survival rate of 12.5% [1]. Although survival is better for individuals presenting with early-stage disease, most individuals with PDAC are diagnosed at advanced stages. Improved understanding of the contribution of genetics and other factors in the pathogenesis of PDAC provide opportunities to advance early detection and treatment of pancreatic neoplasia.

Historically, the general presumption had been that PDAC is largely a sporadic, rather than hereditary, disease.

However, with advances in next generation sequencing technologies and expanded use of genomic profiling of tumor and germline DNA, germline pathogenic variants (GPVs) in a broad array of cancer susceptibility genes are identified in approximately 5–20% of PDAC patients, many of whom do not meet classic criteria for the corresponding hereditary cancer syndrome [4–8]. As genetic diagnoses have significant implications for management of PDAC patients and their family members, clinical guidelines in the U.S. recommend universal germline genetic testing for all individuals with PDAC [9, 10].

## Pathogenesis of pancreatic ductal adenocarcinoma (PDAC)

Chronic inflammation, immune response, genetic susceptibility, and behavioral risk factors contribute to risk for PDAC. Comprehensive genomic profiling classifies PDAC

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into distinct tumor subtypes characterized by dysregulation of specific molecular pathways (e.g. DNA damage repair, cell cycle regulation, TGF-beta signaling, chromatin regulation, and axonal guidance) which have implications for disease prognosis and response to treatment [11]. Pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasms (IPMNs), and mucinous cystic neoplasms (MCNs) are precursors to PDAC, however, only a small proportion of these lesions will acquire the specific somatic aberrations in oncogenes and tumor suppressor genes to transform into invasive PDAC [12]. Activating somatic mutations in *KRAS* are found in > 90% of PDAC tumors and are thought to be early drivers of PDAC [13, 14]. The tumor suppressor genes *CDKN2A*, *TP53*, and *SMAD4* are somatically mutated in 90%, 75%, and 50% of PDAC tumors, respectively [15]. Homologous recombination is essential to the repair of DNA double-stranded breaks and somatic mutations in the homologous recombination DNA damage repair (HR-DDR) pathway genes *ATM, BRCA1, BRCA2*, and *PALB2* are found in 10–20% of PDAC tumors [16, 17]. Up to 10% of individuals diagnosed with PDAC were born carriers of GPVs in *BRCA1* or *BRCA2*, with genetic predisposition to hereditary breast and ovarian cancer syndrome (HBOC) [4, 6]. PDAC patients who have alterations in HR-DDR genes in their germline and/or tumor DNA may benefit from targeted therapy with a poly ADP ribose polymerase (PARP) inhibitor, which has been shown to increase progression-free survival in patients with BRCA-mutated PDAC [18]. Specific genetic, environment, and lifestyle factors associated with risk for PDAC are discussed in detail below.

## Genetic susceptibility to pancreatic cancer

The lifetime risk to develop PDAC in the general population is 1.7% [1]. "Familial pancreatic cancer", which refers to families with two or more relatives with PDAC, accounts for a minority (< 10%) of cases. Approximately 5–10% of patients with PDAC have a first-degree relative with the same diagnosis and even in the absence of a known genetic GPV, individuals who have multiple family members diagnosed with PDAC are at increased risk [19–21]. Large cohort studies of individuals with familial pancreatic cancer have shown that the risk to develop PDAC is increased in individuals with a family history of PDAC (approximately two-fold for those with an affected first-degree relative), with even higher risk increases for those with two or more first-degree affected relatives [21, 22]. It has also been suggested that PDAC diagnoses occur at younger ages in these families [23]. The multi-site Pancreatic Cancer Genetic Epidemiology (PACGENE) Consortium, created in 2002 with the goal of identifying genetic risk factors in familial pancreatic cancer [23], identified germline alterations in highly penetrant cancer genes in only 1 in 10 of these familial pancreatic cancer families, with GPVs most commonly identified in *ATM, BRCA1, BRCA2, PALB2*, and *CDKN2A* [5, 24, 25]. The finding that prevalence of GPVs in "the usual suspects" is similar among familial PDAC and sporadic PDAC cases suggests other factors may contribute to familial PDAC, such as low-penetrance genetic variants, epigenetic changes, and shared environmental or lifestyle exposures [26].

Germline genetic testing in unselected patients with PDAC has identified GPVs in 5–20%, with GPVs most commonly identified in *ATM, BRCA1, BRCA2, CDKN2A, PALB2*, and *CHEK2* [4–8, 25, 27, 28]. Rates of GPVs and findings differ among studies, in part due to differences in clinic populations. For example, clinics with a high proportion of individuals with Ashkenazi Jewish ancestry report higher rates of *BRCA1* and *BRCA2* GPVs [7, 8], as well as higher rates of common low penetrance alleles such as *APC* I1307K, which is a well-known founder mutation in the Ashkenazi Jewish population. Certain variants in the *CHEK2* gene also appear to be overrepresented in oncology patient cohorts due to the high prevalence of GPVs in this gene among individuals with specific European ancestries; however, at this time, GPVs in *CHEK2* have not been established as a risk factor for PDAC [7, 29, 30]. Among early onset PDAC (diagnosed < 45 years) rates of GPVs appear to be higher, approximately 30%, with GPVs primarily occurring in the *BRCA1, BRCA2, PALB2, CDKN2A*, and *ATM* genes [31]. Given that rates of GPV detection in PDAC patients does not meaningfully differ based on whether or not there is a family history of PDAC, U.S.-based guidelines recommend that all individuals with a PDAC diagnosis undergo germline genetic testing due to the potential implication of a genetic diagnosis on the cancer treatment plan and the management of at risk family members [9, 10]. Clinicians in other countries, including Canada, Japan, and Israel, have suggested universal germline testing for PDAC, although barriers may exist to instituting this in practice [32, 33]. The European Society for Medical Oncologists (ESMO) does not currently recommend universal germline testing for patients with PDAC, but does acknowledge the potential value of targeted therapy based on germline findings [33, 34]. Expanded use of tumor mutation profiling in PDAC and other solid tumors provides opportunities not only to identify therapeutic targets, but also to offer germline testing to individuals whose tumors exhibit somatic variants in these genes of interest [35].

## Hereditary cancer syndromes associated with risk for PDAC (Table 1)

### Hereditary breast and ovarian cancer syndrome (HBOC) – BRCA1, BRCA2, PALB2

Pathogenic variants in the *BRCA1* and *BRCA2* genes, which are involved in the HR-DDR complex, cause the autosomal dominant condition hereditary breast and ovarian cancer syndrome (HBOC) and the autosomal recessive condition Fanconi anemia. The risk of developing PDAC is estimated at 4–5% in those with pathogenic variants in *BRCA1* and 5–8% in those with pathogenic variants in *BRCA2* [36, 37]. Pathogenic variants in these two genes make up the majority of germline findings in individuals with PDAC [38]. HBOC occurs in approximately 1/300-1/400 individuals, with a higher prevalence of about 1/40 in individuals with Ashkenazi Jewish ancestry [39]. Individuals with pathogenic variants in these genes are also at increased risk for breast (> 60% risk), ovarian (13–58% risk), and prostate (7–61% risk) cancers in addition to pancreatic cancer [9]. While some recommendations require a family history of PDAC for individuals with *BRCA1* or *BRCA2* pathogenic variants to qualify for pancreatic cancer screening, recent

**Table 1** Hereditary cancer syndromes associated with risk for PDAC

| Gene(s) | Hereditary cancer/risk syndrome (autosomal dominant) | Lifetime risk for PDAC | Population prevalence | Age to start screening |
|---|---|---|---|---|
| *ATM* | Cancer risk | 5–10% [9, 43] | 1 in 100 | • Age 50 (or 10 years younger than the earliest PDAC diagnosis in the family, whichever is earlier)<br>• Consider screening for all individuals or only in the setting of family history of PDAC [9, 36] |
| *BRCA1, BRCA2* | Hereditary breast and ovarian cancer syndrome (HBOC) | 4% (*BRCA1*) 5–8% (*BRCA2*) [36, 37] | 1 in 300 to 1 in 400 (1 in 40 with Ashkenazi Jewish Ancestry) | • Age 50 (or 10 years younger than the earliest PDAC diagnosis in the family, whichever is earlier) [36]<br>• Consider screening for all individuals or only in the setting of family history of PDAC [9] |
| *CDKN2A* | Familial atypical multiple mole melanoma syndrome (FAMMM) | > 15–20% [9, 37, 45] | Unknown | • Age 40 (or 10 years younger than the earliest PDAC diagnosis in the family, whichever is earlier)<br>• Screen all GPV carriers, even if no family history of PDAC [9, 36] |
| *MLH1, MSH2, MSH6, EPCAM* | Lynch syndrome (LS) | 4–6% [48, 49] | 1 in 279 | • Age 50 (or 10 years younger than the earliest PDAC diagnosis in the family, whichever is earlier).<br>• Consider screening only in setting of family history of PDAC [9, 36] |
| *PALB2* | Cancer risk | 2–5% [9] | Unknown | • Age 50 (or 10 years younger than the earliest PDAC diagnosis in the family, whichever is earlier) [36]<br>• Consider screening for all individuals or only in setting of family history of PDAC [9] |
| *PRSS1, SPINK1, CTRC, CPA1, CPB1* | Hereditary pancreatitis | 10–50% [57, 119] | Less than 1 in 100,000 | • Age 40 [36] (or 20 years after onset of pancreatitis, whichever is earlier) [9]<br>• Consider screening only for individuals with GPV and a clinical phenotype consistent with hereditary pancreatitis [9] |
| *STK11* | Peutz-Jeghers syndrome (PJS) | > 15% [9] | 1 in 25,000 to 1 in 300,000 | • Age 30–35 (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier) [9, 36]<br>• Screen all GPV carriers, even if no family history of PDAC |
| *TP53* | Li Fraumeni syndrome (LFS) | ~ 5% [9] | 1 in 5,000 to 1 in 20,000 | • Age 50 (or 10 years younger than the earliest PDAC diagnosis in the family, whichever is earlier)<br>• Screen individuals with a family history of PDAC [9] |

guidelines have recommended screening for all individuals whose lifetime risk for PDAC is estimated at ≥ 5%, and have suggested that all individuals with *BRCA1* or *BRCA2* GPVs should be offered PDAC screening regardless of family history [9, 36, 40]. As clinical trials have demonstrated that treatment with PARP inhibitors improves progression-free survival for PDAC patients with GPVs in *BRCA1* and *BRCA2*, the genetic diagnosis of HBOC has immediate implications for oncologic treatment [18, 41].

Pathogenic variants in *PALB2* (Partner and Localizer of *BRCA2*), another gene involved in HR-DDR, confer an increased risk for breast (41–60%) and ovarian (3–5%) cancer in addition to PDAC (2–5%) in the autosomal dominant setting [9]. *PALB2* GPVs are found in approximately 3–4% of familial PDAC cases and in about 1% of individuals with breast cancer, however, the general population incidence is unknown [42]. The impact of *PALB2* GPVs for PDAC treatment implications are less well-defined than for the more commonly mutated *BRCA1* and *BRCA2* genes. GPVs in *PALB2* are also implicated in autosomal recessive Fanconi anemia.

### ATM

*ATM* is also involved in HR-DDR and is considered a moderate risk cancer susceptibility gene. Biallelic GPVs in *ATM* are implicated in the autosomal recessive neurologic condition ataxia telangiectasia. GPVs in *ATM* are relatively common, with approximately 1–2% of individuals in the general population being monoallelic carriers of a GPV in *ATM*. Lifetime risk for PDAC has been estimated at 5–10% [9, 43]. In cohorts of PDAC patients undergoing germline sequencing, GPVs in *ATM* are identified in 1–3% of patients [43]. *ATM* GPV heterozygotes also have an increased lifetime risk for breast (20–30% risk) and ovarian (2–3% risk) cancers with emerging evidence for possible increase in prostate cancer risk [9]. Despite its involvement in HR-DDR, patients with *ATM* PGV and PDAC do not appear to have the same response to PARP inhibitor therapy as those with PGVs in *BRCA1* and *BRCA2* [41].

### Familial atypical multiple mole melanoma syndrome (FAMMM) – CDKN2A

Familial atypical multiple mole melanoma syndrome (FAMMM) is caused by GPVs in *CDKN2A*, a tumor suppressor gene involved in regulation of the cell cycle. Functioning *CDKN2A* genes assist in the cell division and apoptosis processes. *CDKN2A* inactivation is a well-known driver in PDAC development; somatic mutations in *CDKN2A* play a major role in pancreatic tumorigenesis and are found in 90% of PDAC tumors [15, 44]. PGVs in *CDKN2A* are associated with a > 15–20% lifetime risk for pancreatic cancer and 28–76% lifetime risk for melanoma [9, 37, 45]. GPVs in *CDKN2A* are identified in less than 1% of patients with PDAC, possibly because the incidence of GPVs in *CDKN2A* is lower than in genes such as *ATM, BRCA1/2*, and the mismatch repair genes [4–6, 46]. The Netherlands has a relatively high prevalence of FAMMM due to a *CDKN2A* founder mutation, and a Dutch cohort of 347 *CDKN2A* GPV carriers undergoing pancreatic imaging reported an incidence of PDAC of 20.7% by age 70, with 83.3% of these PDACs considered surgically resectable at the time of diagnosis [45]. The rate of *CDKN2A* GPVs may be higher in familial pancreatic cancer kindreds, with the prevalence estimated at 1.5-3% [9, 44]. The exact prevalence of FAMMM in the general population is unknown [47].

### Lynch syndrome – MLH1, MSH2, MSH6, PMS2, EPCAM

The DNA mismatch repair genes excise base pair mismatches during DNA replication, with dysfunction of DNA mismatch repair typically resulting in hypermutated tumors. GPVs in the DNA mismatch repair genes *MLH1, MSH2, MSH6, PMS2*, and *EPCAM* are implicated in Lynch syndrome, which is associated with increased risk for specific cancers including colorectal, endometrial, ovarian, and pancreatic cancer (*MLH1, MSH2, MSH6, EPCAM* only), among others. Lynch syndrome is relatively common and is estimated to affect 1 in 279 individuals in the general population. Cancer risk estimates vary widely based on the gene affected, but are highest for colorectal and endometrial carcinomas, with lifetime risks of 40–60%. Cumulative lifetime risk for PDAC is estimated at 4% [48], and may be stratified by the gene affected, with the highest risks being in individuals with GPVs in *MLH1* and *MSH2*, while individuals with GPVs in *PMS2* do not appear to be at increased risk compared to general population risk [49, 50]. GPVs associated with Lynch syndrome are identified in up to 1% of patients with PDAC [4–6].

A genetic diagnosis of Lynch syndrome can have implications for the oncologic treatment plan as immunotherapies (specifically immune checkpoint inhibitors) have shown promise in leveraging patients' immune systems to recognize unique cancer antigens in hypermutated tumors. Reports of individuals with microsatellite unstable and/or mismatch repair deficient PDAC showing response to immune checkpoint inhibitors suggest a possible role for this therapy for individuals with Lynch syndrome [51, 52]; however, variability in patient response emphasizes the need to determine which individuals may be more likely to respond favorably to immune-based PDAC treatments [53].

#### Peutz-Jeghers syndrome (PJS) – STK11

Peutz-Jeghers syndrome (PJS) is caused by pathogenic variants in *STK11* and is associated with increased risk for gastrointestinal hamartomatous polyps and increased lifetime risk for multiple types of cancer, including breast, gastrointestinal, and gynecologic tumors. Lifetime risk for pancreatic cancer is increased by > 10 fold (11–36%) with an average age of PDAC diagnosis of around 40 years [54]. Guidelines recommend pancreatic screening for individuals with PJS beginning at age 35–40 [9, 36, 54]. PJS is a rare condition; prevalence estimates range from 1/25,000–1/300,000 and *STK11* GPVs are identified in less than 1% of patients with PDAC [4, 5, 55, 56].

#### Li Fraumeni syndrome (LFS) – TP53

Li Fraumeni syndrome (LFS) is caused by pathogenic variants in the *TP53* tumor suppressor gene. Lifetime risks for cancer are > 80% for individuals with GPVs in *TP53*, and the associated tumor spectrum includes breast cancers, soft tissue sarcomas, osteosarcomas, central nervous system tumors, adrenal carcinomas, and gastrointestinal cancers. PDAC diagnoses appear to be overrepresented among LFS families, with the risk for PDAC estimated to be about 5% [9]. LFS is a rare condition and is identified in less than 1% of patients with PDAC and in 1 in 5,000 to 1 in 20,000 individuals in the general population [4–6].

### Hereditary pancreatitis – PRSS1, SPINK1, CASR, CFTR, CPA1, CTRC

Hereditary pancreatitis is inherited in an autosomal dominant manner, primarily due to GPVs in *PRSS1*, and most information about hereditary pancreatitis is derived from families with GPVs in this gene. Clinical presentation of this condition can vary greatly and published estimates of pancreatic cancer risk range from 10 to 70%, with more recent consensus suggesting risks may be on the lower end of this range [57]. Some guidelines support pancreatic cancer screening in individuals with *PRSS1* pathogenic variants after the age of 40 years; however other guidelines suggest surveillance only in those with a GPV in a gene associated with hereditary pancreatitis and a personal history consistent with pancreatitis, or were not able to reach a consensus on this recommendation [9, 36, 40].

### Familial adenomatous polyposis (FAP) – APC

Pathogenic variants in *APC*, a tumor suppressor gene, are associated with familial adenomatous polyposis (FAP), with affected individuals developing colorectal, duodenal, and ampullary adenomas which can undergo malignant transformation. While PDAC is not a common diagnosis in individuals with FAP, it can be difficult to distinguish between cancers of the ampulla and a primary pancreatic cancer. One study of 615 PDAC patients treated at a tertiary care center in New York City reported finding *APC* GPVs in 2.1% of cases; however, it is important to note that the *APC* I1307K variant accounted for all the reported *APC* GPVs, which could be explained by the high prevalence of individuals with Ashkenazi Jewish ancestry in this PDAC cohort [7]. APC I1307K is a common polymorphism in individuals in Ashkenazi Jewish ancestry (population prevalence of 1–2/100), is not associated with a classic FAP phenotype, and does not appear to confer increased risk for PDAC [58, 59].

## Unmeasured genetic factors

The fact that clinical genetic testing is uninformative for many families affected with familial pancreatic cancer has prompted search for novel genetic or epigenetic factors which might explain familial risk. GPVs in the *PALLD* gene were identified in affected members of a large familial pancreatic cancer family via linkage analysis and isolation of a susceptibility locus [60]. *PALLD* was suggested as a potential novel hereditary PDAC gene, however later studies have not replicated this finding in additional familial pancreatic cancer kindreds [61, 62]. Although *CDK4* interacts with *CDKN2A*, studies have not supported a role of *CDK4* in PDAC development [63, 64]. Whole exome and genome sequencing have been employed for the identification of candidate genes. Several genes identified via whole exome/genome studies in familial pancreatic cancer cohorts play a role in the HR-DDR pathway, including many in the Fanconi anemia complementation (FANC) group, a group of genes associated with Fanconi anemia to which *BRCA1* (also called *FANCS*), *BRCA2* (also called *FANCD1*) and *PALB2* (also called *FANCN*) belong. While evidence of autosomal dominant PDAC risk related to genes in this FANC group is limited outside of the *BRCA1, BRCA2*, and *PALB2* genes, several, including *ERCC4, FANCA, FANCC, FANCM, RAD51D*, and *XRCC2*, have been proposed as candidate genes based on whole exome/genome studies in familial pancreas cancer families [26, 65–68].

Large, genome-wide association studies (GWAS) have identified more than 20 single nucleotide polymorphisms (SNPs) related to pancreatic cancer risk [69]. These common SNPs are estimated to account for 13% of pancreatic cancer hereditability with those with fewer risk alleles having a below general population risk to develop pancreatic cancer and those with a greater number of risk alleles having a

higher risk of pancreatic cancer development [69]. While it has been suggested that polygenic risk scores (PRS), which take SNPs into account, might assist in identifying those with new-onset diabetes at highest risk to develop PDAC, PRS tests for PDAC are not clinically available and are limited by lack of racial and ethnic diversity of the cohorts with which these were developed [70].

An emerging area for potential genetic cancer risk is epigenetic changes that affect gene expression but do not affect the gene DNA sequence. It has been suggested that epigenetic changes including DNA methylation, chromatin remodeling factors, miRNAs, and histone post-translation modification may play a role in PDAC progression [71]. CpG methylation in *CDKN2A* has been identified in a significant number of patients with PDAC, further highlighting the significant role this gene plays in tumorigenesis [72]. Identification of epigenetic changes consistent with hypoxia in PDAC cancer cells supports a potential role for the hypoxia-inducible factor (HIF) genes in PDAC development [73]. Work is ongoing to determine the potential impact of epigenetic changes as diagnostic and prognostic markers as well as potential therapeutic targets [74].

## Other biologically relevant pathways

Associations between genes playing roles in multiple pathways and diseases have been suggested to contribute to PDAC development based on large GWAS studies. These include those related to maturity-onset diabetes of the young, regulation of beta-cell development, epidermal growth factor receptor transactivation in cardiac hypertrophy pathways, cellular response to UV, and multiple gastrointestinal tissues [75, 76]. In particular, multiple SNPs in the *HNF1A* and *HNF1B* genes (which are causative of maturity-onset diabetes of the young when an autosomal dominant GPV is present) have been linked to PDAC risk [75–77]. *HNF1A* and *HNF1B* have been noted as candidate genes for regulation of pancreatic differentiation and may play a role in tumor suppression in PDAC, with transcriptome analysis revealing a tumor suppression function for *HNF1A* and PDAC samples showing little to no *HNF1B* expression on immunohistochemistry [78–80].

Examination of the tumor microenvironment has revealed immunosuppression as a unifying characteristic across tumors, with metabolism and obesity, infection and inflammation, host immune state, host genetics, environmental factors, and microbiota all potentially contributing to this [81]. However, immunotherapy has had limited effect in controlling disease progression in PDAC, even for individuals with hypermutated microsatellite instable tumors [81].

Several population-based studies have also identified an increased risk for pancreatic cancer for individuals with blood groups A, AB, or B, although the mechanism by which blood type may influence risk is unknown [82]. It has been suggested that a genetic variant affecting cancer risk may be linked to the locus determining blood type [83]. GPV in genes related to pancreatic secretory enzymes may also be linked to pancreatic cancer development [84].

## Other factors impacting risk of PDAC

### Precursor lesions to PDAC

Precursor lesions for PDAC include intraductal papillary mucinous neoplasms (IPMNs), pancreatic intraepithelial neoplasia (PanIN), and mucinous cystic neoplasms (MCNs). Of these, progression to PDAC most commonly occurs in PanIN, of which > 90% of lesions have a somatic *KRAS* mutation [15]. PanIN are not detectable with current imaging modalities, and once a mass is identifiable by imaging, the progression to advanced disease occurs rapidly [85, 86]. Increased use of imaging has resulted in increased detection of incidental cystic lesions, with approximately 15% of individuals undergoing imaging of the pancreas having a cyst identified [87, 88]. Only a small number of these cystic lesions will progress to PDAC, and the size and characteristics of these pancreatic lesions dictate clinical management [87, 88].

### Smoking

Current cigarette smokers have an approximately 2-fold increase in PDAC risk compared to never smokers, with risk highest in those who smoke the highest number of cigarettes per day [2]. It has been suggested that smoking cessation can decrease risk; 10–20 years after smoking cessation the risk of PDAC may be similar to that of never smokers [2]. The global population attributable risk of PDAC due to smoking ranges from 11 to 32% [2].

### Pancreatitis (Acute vs. Chronic)

Individuals with chronic pancreatitis are at increased risk to develop pancreatic cancer due to inflammation of the pancreas, and pancreatic cancer has been reported both in individuals who are symptomatic and those with no known history of pancreatitis-related symptoms [57]. In cases of chronic pancreatitis, tissue damage occurs over decades, and it is though that the scope of tissue injury, fibrosis, inflammation, and cellular DNA damage may increase the risk for PDAC. For individuals with chronic pancreatitis, PDAC risk has been reported to be as high as 50–70%, although more recent reports estimate the risk as closer to 10%, and it has been suggested that genetic modifiers beyond known

genetic risk factors may contribute to risk [57]. In cases of acute pancreatitis, PDAC risk is highest within a year of the pancreatitis episode, as some cases of pancreatitis can be a manifestation of obstructive pancreatitis caused by a tumor [89]. For this reason, follow up pancreatic imaging is recommended after resolution of an episode of acute pancreatitis [90].

### Diabetes

Increased risk for pancreatic cancer has been described in individuals with new-onset and long-standing diabetes. The risk of pancreatic cancer in those with type II diabetes is approximately two times that of the general population, with significantly higher risk for cancer development within the first three years of diagnosis [91–93]. It has been suggested that in the case of new-onset diabetes and pancreatic cancer, the diabetes may be a symptom of the cancer rather than a cause; diabetes is more likely to resolve after pancreaticoduodenectomy in those with new-onset disease rather than a long-standing diagnosis [92]. Experimental studies in cell lines and animal models have also suggested that pancreatic cancer cells impair glucose metabolism via beta cell dysfunction and insulin resistance, supporting this theory [92, 94]. Due to the high incidence of diabetes in the population, it is not feasible to subject every individual with diabetes to pancreatic surveillance, however, work is ongoing to develop models for risk stratification to identify those most likely to develop pancreatic neoplasia who would benefit from surveillance [95]. The Consortium for the study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDCP), an NIH-funded prospective cohort study of 10,000 adults with new onset diabetes, aims to quantify the incidence of PDAC among individuals with new-onset diabetes, identify biomarkers for early detection of pancreatic neoplasia, and establish algorithms for clinical risk stratification and operationalizing pancreatic surveillance [96].

### Obesity

Multiple studies have found an associated between obesity and PDAC risk [97, 98]. It has been suggested that increasing rates of obesity may be linked to increasing incidence of PDAC [2]. For overweight individuals, physical activity may lower PDAC risk [97].

### Alcohol

A large prospective study identified a positive association between heavy alcohol consumption (~6 drinks/day) and pancreatic cancer development, although this relationship only reached statistical significance for individuals assigned male at birth [99]. This association was not observed in individuals with light-to-moderate alcohol consumption ($\leq$4 drinks/day) [100]. Alcohol use may compound the negative effects of other risk factors such as tobacco smoking and pancreatitis [101]. Alcohol may also cause direct damage to the pancreas through release of toxic metabolites like acetaldehyde into the bloodstream, and acetaldehyde has been shown to bind to DNA repair proteins and promote DNA damage [101].

### Nutrition

While associations between diet and PDAC have been suggested, randomized trials are needed to better evaluate this relationship due to confounding factors such as smoking and obesity [102]. High dietary intake of fruits, vegetables, and whole grains has been shown to reduce pancreatic cancer risk and a possible protective role of dietary folate consumption has also been suggested [102, 103]. Red meat and high-fat diets have been proposed as risk factors for PDAC [102].

### Environmental exposures

Exposure to chemicals used in common products may also contribute to PDAC risk. Exposures to arsenic, cadmium, and lead have been identified as risk factors for PDAC in a study which examined trace elements in toenail samples [101]. A case-control study also identified exposure to benzene, asbestos, and chlorinated hydrocarbons as risk factors for PDAC [104]. In vitro experiments on human cell lines and tissues show increased proliferation and DNA damage when exposed to Bis[2-ethylhexyl]phthalate (DEHP), a compound present in many plastics [101]. The expansion of pesticide use has been posited as an explanation for increasing PDAC rates; while exact relationships are complex to discern, pesticides may be a direct (oxidative stress, cell damage) or indirect (fatty pancreas, diabetes) cause of PDAC [105].

### Microbiome

The microbiome has more recently been implicated in PDAC, with potential roles in PDAC risk, tumorigenesis, impact on tumor microenvironment, and treatment response [106]. Dysbiosis of the gut microbiome has been associated with risks for cancer and other diseases, and higher alpha diversity of the microbiome has been used to differentiate PDAC patients with good prognosis from those with poor survival [107]. Intra-tumoral bacteria composition has been shown to affect host immune response toward cancers, as

well as metabolism of specific chemotherapeutic agents (e.g. gemcitabine) [108]. Experiments in mice with orthotopic PDAC tumors found that animals subjected to fecal microbiome transplants from patients with advanced PDAC developed larger tumors, while those receiving fecal transplants from PDAC long-term survivors developed smaller tumors [109]. Early work suggests that metabolites derived from the microbiome may drive cancer development and progression; further work is necessary to determine if there are specific microbial factors associated with risk for PDAC, and whether the microbiome might present potential therapeutic targets for PDAC treatment and/or prevention [110].

## Discussion and summary

Pancreatic cancer is among the deadliest cancers, with most individuals diagnosed at advanced stages of the disease. Screening offers opportunities for early detection; however, challenges remain in identifying individuals at increased risk for pancreatic neoplasia. Genetic susceptibility to cancer is implicated in approximately 1 in 10 PDAC cases and similar rates of GPV among unselected patients with PDAC and those meeting criteria for familial pancreatic cancer underscores the importance of offering germline genetic testing broadly [111]. Care delivery models which incorporate universal germline genetic testing for PDAC patients at point of care have demonstrated benefit for identifying individuals with GPVs who can benefit from targeted oncologic therapies [112–114]. Furthermore, offering germline genetic testing to relatives of patients with GPVs as well as relatives of PDAC patients who did not themselves undergo genetic testing is also high yield for identifying individuals at increased risk who would be eligible for pancreatic surveillance [115]. Although family history and genetics have been the primary criteria for assessing pancreatic cancer risk, recent modeling studies suggest that incorporating other individual characteristics, such as comorbidities, health behaviors, and longitudinal tracking of laboratory values through electronic medical records can improve the precision of risk stratification [116]. New-onset diabetes has emerged as a potential red flag, and machine learning algorithms capable of mining big data from electronic medical records propose to facilitate identification of patients who would benefit the most from high-risk screening/surveillance [116]. For individuals with a lifetime risk of PDAC $\geq$ 5%, surveillance using MRCP and EUS can detect some resectable neoplasms and improve survival [36] [36]. However, there is still work to be done to improve the sensitivity and specificity of current imaging and blood and/or tissue-based tests, and artificial intelligence applications in radiomics and biomarker discovery hold promise for improving detection of pancreatic neoplasia [117]. Real-world testing of risk stratification and surveillance strategies, through prospective follow up of large cohorts of individuals at increased risk for PDAC, including Cancer of the Pancreas Screening Study (CAPS), Pancreatic Cancer Early Detection (PRECEDE) Consortium, and CPDCP will pave the way for clinical implementation and dissemination [40, 96, 118].

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**Data availability** No datasets were generated or analysed during the current study.

## Declarations

**Competing interests** The authors declare no competing interests.

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