Review Article

Geographical, ethnic, and genetic differences in pancreatic cancer predisposition

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Abstract: Pancreatic cancer remains a leading cause of cancer-related mortality worldwide. Treatment outcomes remain largely dismal despite significant medical advancements. This lends urgency to the need to understand its risk factors in order to guide early detection and improve outcomes. There are both modifiable and non-modifiable risk factors, the more established of such being that of age, smoking, obesity, diabetes mellitus (DM), alcohol and certain genetic predisposition syndromes with underlying germline mutations. Some genetic predisposition syndromes such as *BRCA1/2*, *PALB2*, *ATM*, and *CDKN2A* are well-established, arising from germline mutations that result in carcinogenesis through mechanisms such as cell injury, dysregulation of cell growth, dysfunctional DNA repair, and disruption of cell mobility and adhesion. There is also a significant proportion of familial pancreatic cancer (FPC) for which the underlying predisposing genetic mechanism is not yet understood. Nuances have emerged in the ethnic and geographical differences of pancreatic cancer predisposition, and these may be attributed to differences in lifestyle, standard of living, socioeconomic factors, and genetics. This review describes in detail the factors contributing to pancreatic cancer with focus on ethnic and geographical differences and hereditary genetic syndromes. Greater insight into the interplay of these factors can guide clinicians and healthcare authorities in addressing modifiable risk factors, implementing measures for early detection in high-risk individuals, initiating early treatment of pancreatic cancer, and directing future research towards existing knowledge deficits, in order to improve survival outcomes.

Keywords: Pancreas malignancy; risk factors; epidemiology; germline mutations

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Background

Pancreatic ductal adenocarcinoma (PDAC) consists of 85–90% of pancreatic neoplasms and is the most common histologic subtype. Globally, there has been an increasing burden of PDAC (1) over the years—this is expected to continue with a shift in lifestyle habits, ageing populations, and improved diagnostic tools. Despite medical advancements, PDAC is often diagnosed late with locally advanced, unresectable, or metastatic disease with

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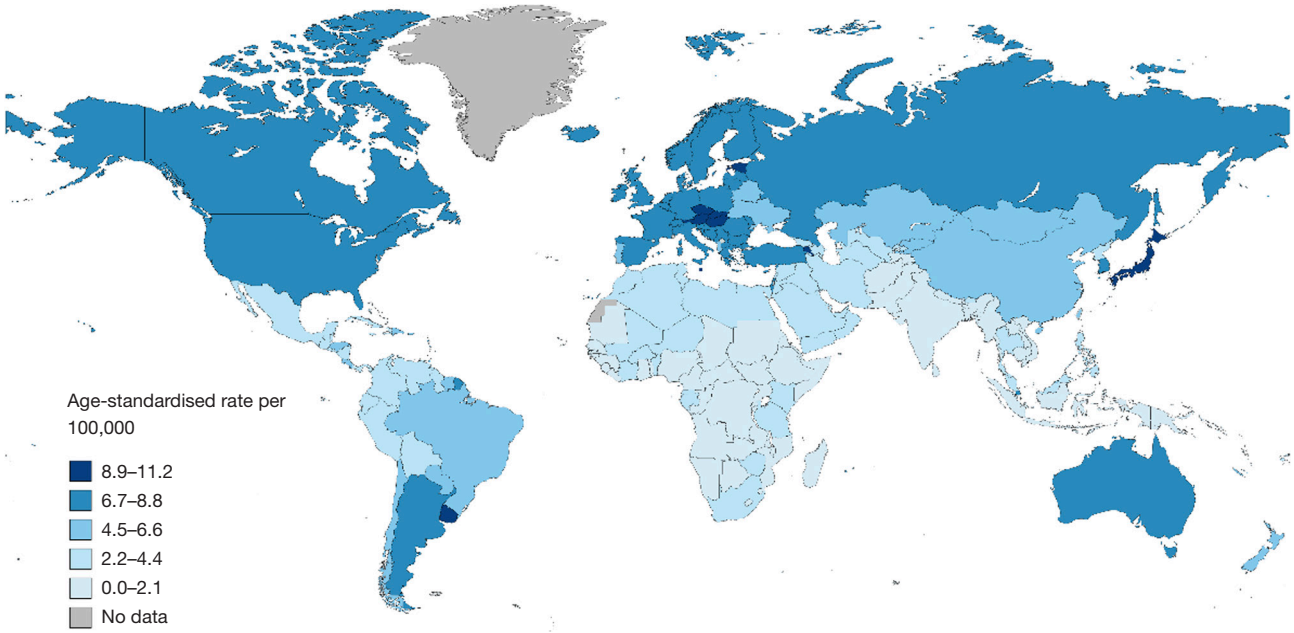

Figure 1 Estimated age-standardised incidence rates of PDAC in 2020 according to regions [data retrieved from GLOBOCAN 2020 (2)]. PDAC, pancreatic ductal adenocarcinoma.

poor clinical outcomes. It remains the seventh leading cause of worldwide cancer-related deaths (2) in 2020. An understanding of risk factors for PDAC is crucial for early detection and treatment.

Predisposition to PDAC can be attributed to modifiable and non-modifiable risk factors, including genetic factors. Ethnicity and geography affect the prevalence and significance of each risk factor and should be taken into consideration for effective screening and prevention programmes.

This review aims to describe the differences in ethnic and geographical distribution of PDAC and provide a comprehensive overview of the modifiable and non-modifiable risk factors and genetic predisposition syndromes for PDAC. It will highlight recent findings of interest, point out gaps in understanding, and suggest potential ways forward to improve screening and outcomes for patients with PDAC.

Incidence and mortality

Geography

Worldwide, high-income regions such as Europe, North America, Australia/New Zealand and Japan have higher incidence of PDAC ranging from 7.9 to 9.9 per 100,000 people (*Figures 1*,*2*). Conversely, low-income regions of Africa, Central America and South Asia have the lowest incidence at 1.5 to 4.6 per 100,000 people (2). This difference can be due to increased prevalence of risk factors associated with higher incomes such as alcohol use, obesity and diabetes, as well as ageing populations (1). This could also be confounded by the scarcity of high-quality data in low-income regions due to reduced access to advanced diagnostic tools and imaging, thus potentially causing a discrepancy in actual epidemiology.

Ethnicity

Within a geographic region, there is a difference in the incidence of PDAC amongst different ethnic groups. In the United States, many studies have identified a higher incidence of PDAC in non-Hispanic African populations compared to non-Hispanic European populations (3,4). Despite lower income levels amongst non-Hispanic Africans compared to non-Hispanic Europeans, differences in diet and lifestyle lead to higher rates of PDAC risk factors such as smoking, diabetes and obesity (5) in the non-Hispanic African group. However, a study done by Huang *et al.* (6) showed that non-Hispanic Africans had a 20% greater risk of PDAC compared to non-Hispanic Europeans even after adjusting for dietary and lifestyle differences, thus alluding

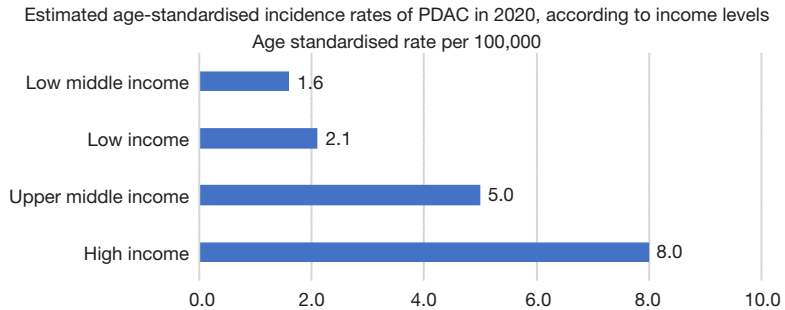

Figure 2 Estimated age-standardised incidence rate of PDAC in 2020 according to income levels [data retrieved from GLOBOCAN 2020 (2)]. PDAC, pancreatic ductal adenocarcinoma.

to other factors at play. One such factor could be that of biological differences that cause varying susceptibility to developing PDAC—research suggests that the non-Hispanic Africans are slower at metabolizing carcinogens from tobacco (7), and that PDAC in non-Hispanic Africans have increased K-ras mutations (8).

Socioeconomic factors also result in poorer overall survival for non-Hispanic Africans—a recent study has also showed that non-Hispanic Africans with PDAC had lower education and income level compared to non-Hispanic Europeans, and this correlated with more advanced stage at diagnosis, a lower likelihood of receiving treatment, and a longer time to commencement of treatment (9).

There have been fewer studies examining the rate of PDAC in other ethnic minorities, such as in Hispanic and Asian populations (6). In one US-based study, Asian populations had lower rates of smoking and obesity compared with other ethnic groups, which may contribute to their lower pancreatic cancer rates. Asian populations also have a higher survival rate compared to non-Asian populations (10), and there can be genetic factors behind this. Secreted protein acidic and rich in cysteine (SPARC), a protein that has been found to independently predict for poor disease-free survival and overall survival for patients with PDAC, was found by a recent study to have a lower stromal expression in Japanese patients and could be a potential factor contributing to better outcomes in this Asian population (11,12).

Trends

Incidence of PDAC has been on a gradual uptrend, with cases rising from 460,000 worldwide in 2018 to 496,000 in 2020 (2). Both the incidence and mortality of PDAC are expected to rise, and this likely has to do with its associated risk factors—ageing populations, lifestyle changes such as smoking, reduced physical activity and consumption of calorie-rich food (13). Improved diagnostic tools and technology, especially in developing regions, are also detecting more cases that would have otherwise been missed. PDAC has been projected to surpass breast cancer as the third leading cause of cancer death by 2025 (14). Comparing the incidence of PDAC from 2018 to 2020, the global distribution of proportion of newly diagnosed PDAC remains similar.

Risk factors (*Table 1*)

Smoking

Smoking is a notable risk factor for PDAC. Multiple studies have shown that there is an association between smoking and increased risk of death from PDAC, up to two times higher in smokers compared to non-smokers (15,16). The estimated attributable fraction of PDAC deaths due to smoking is 11–32% (25). Of note, the risk of PDAC decreases upon cessation of smoking—with a 30% risk reduction for pancreatic cancer with more than 10 years of cessation.

A systematic analysis in 2019 found that regions with the highest prevalence of smoking were that of Europe, Asia and Oceania, while the lowest prevalence of smoking were in Latin America and Sub-Saharan Africa (26). This distribution correlates well with the geographic distribution of PDAC, suggesting that smoking is indeed a strong independent risk factor.

Obesity and physical inactivity

There is a robust causal association between increasing

Table 1 Risk factors associated with increased risk of PDAC

Risk factor	Relative risk of PDAC	Geographical regions and ethnic groups with higher prevalence
Smoking	2 (15,16)	Central Europe, Western Europe and Southern Latin America amongst females, and Southeast/East Asian and Oceania amongst males
Obesity and physical inactivity	1.72 (17)	Americas, Europe
Heavy alcohol consumption	1.15–1.6 (18-20)	Russia, Europe; East Asia: *ALDH2*2* allele*
Ageing population	–	Europe, North America, East Asia
Male gender	1.39 (2)	–
Diabetes mellitus	1.82 (21)	North America, Russia, Asia (China, India, South-east Asia)
Chronic pancreatitis	Up to 16.16 (22)	Non-Hispanic Africans

* East Asians have a higher prevalence of the *ALDH2*2* allele, which is associated with inefficient enzyme metabolism of acetaldehyde, a metabolite of ethanol, and is associated with a higher risk of developing PDAC (23,24). PDAC, pancreatic ductal adenocarcinoma.

body mass index (BMI) and PDAC risk [relative risk (RR) 1.72] (17). Overweight or obese individuals develop PDAC at a younger age, and have a lower overall survival rate (27). On the other hand, physical activity is inversely associated with risk of PDAC among individuals with a BMI of more than 25 kg/m^2 (RR 0.59) (28). The global prevalence of obesity has doubled since 1980 (29)—as society gets increasingly re-engineered to minimize movement, sedentary lifestyles become easier to adopt and this poses an increasing health risk (30).

In a study that analyzed the epidemiology of obesity from 1980 to 2015 (29), the Americas and Europe emerged with the highest rates of obesity and Southeast Asia and West Pacific with the lowest, correlating closely with the pattern of incidence of PDAC. However, there were discrepancies such as countries like Austria and Japan, which had below-average obesity rates but high PDAC rates (2,31). These discrepancies could be due to other contributing risk factors such as higher alcohol consumption (32,33) and an ageing population (34) in these countries.

Alcohol

There is conflicting evidence regarding the association of alcohol intake and risk of PDAC. Several studies have shown that heavy alcohol consumption was associated with a 1.15 to 1.6 times increased risk of PDAC (18-20), but there is a lack of evidence to determine the association between low-to-moderate alcohol intake and PDAC. Liquor has been associated with PDAC more so than other types of alcohol. Increased alcohol consumption is also an established risk factor of pancreatitis (35), which in turn is a risk factor for PDAC.

Globally, the average per capita alcohol consumption has increased over the past two decades, with the lowest amount occurring in the Middle East and Northern Africa, and the highest in Russia and Europe. Interestingly, there is a decreasing trend of overall alcohol consumption in Europe and Russia and an increasing one in the Western Pacific and Southeast Asia regions, which is not in tandem with the trend in incidence of PDAC, suggesting again other confounding factors. In East Asian countries, 30–50% of the population carry the *ALDH2*2* allele, which is associated with inefficient enzyme metabolism of acetaldehyde, a metabolite of ethanol. Individuals carrying the *ALDH2*2* allele were found to have a higher risk of developing alcohol-related cancers such as pancreatic, oesophageal and liver cancer (23,24), suggesting that alcohol consumption may play a more significant role in PDAC development in the East Asian population.

Age

Pancreatic cancer incidence increases with age, with 90% of newly diagnosed patients aged 55 years and above (36), and the highest incidence of PDAC reported in people over 70 years old (37). It is estimated that the proportion of the world's population over 60 years will double from 11% in 2015 to 22% in 2050 (38). Many aging populations around the world also have high PDAC rates—for example, Japan had the highest proportion of elderly aged 65 and above (28%), and the third highest

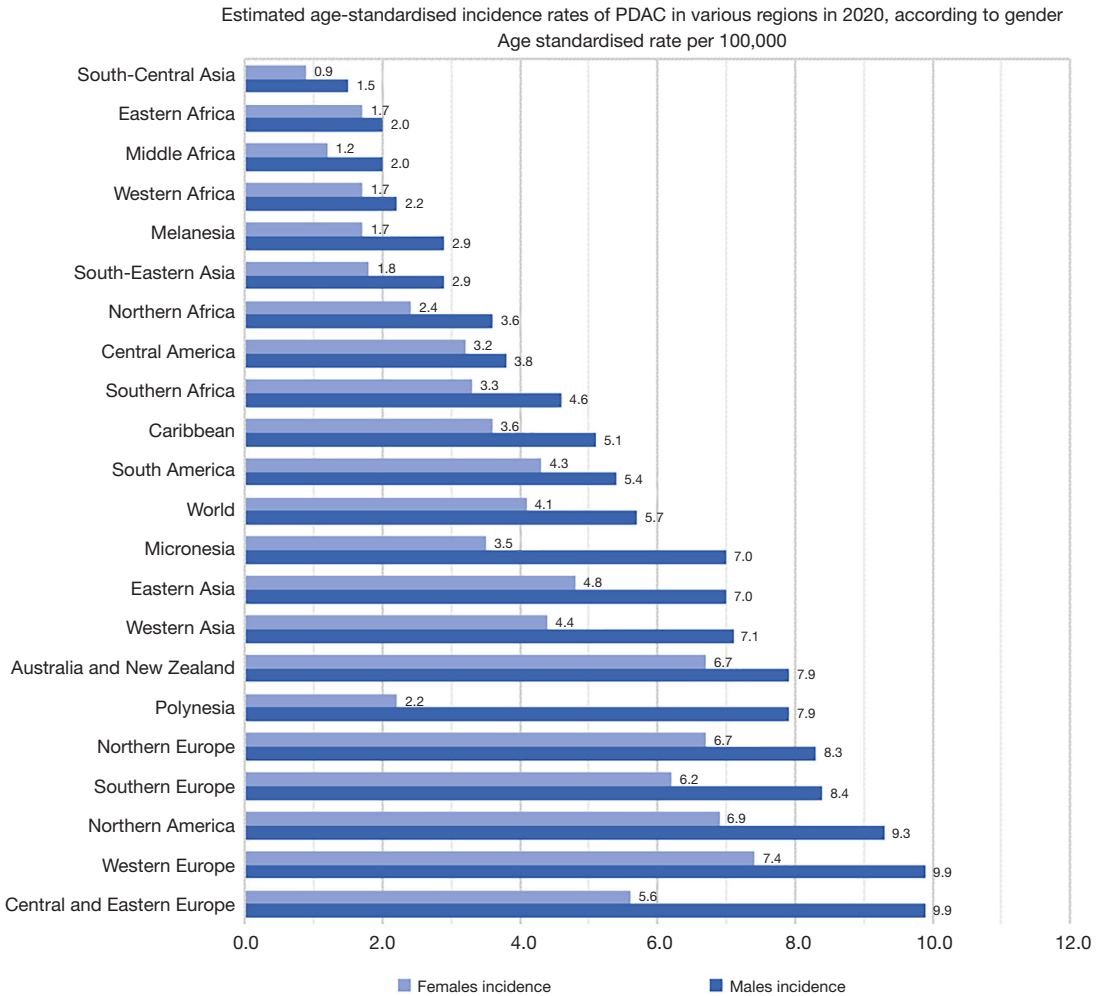

Figure 3 Estimated age-standardised incidence rate of PDAC in various regions in 2020, according to gender [data retrieved from GLOBOCAN 2020 (2)]. PDAC, pancreatic ductal adenocarcinoma.

incidence of PDAC (9.9 per 100,000 people) in 2020. Other countries like Germany, Malta and Hungary, with fast aging populations (20% and above) also had a high incidence of PDAC (8.8 per 100,000 people and above). Geographically, aging populations are concentrated in the regions of Europe, North America and Eastern Asia, which coincides with the geographical distribution of high PDAC incidence (2,39).

Gender

PDAC is more commonly found in males than females—this is consistent across various regions (*Figure 3*). The worldwide incidence of PDAC in 2020 is 5.7 per 100,000 for males and 4.1 per 100,000 for females (2). While the disparity could be attributed to differences in lifestyle factors, especially that of higher rates of smoking in men compared to women, there are intrinsic biological differences between the genders. Several studies suggest that the female sex hormone estrogen decreases pancreatic cancer growth (40-42), and a study using The Cancer Genome Atlas (TCGA) data has also revealed that there are distinct molecular differences between male and female patients across a broad range of cancer types (43). Another study found that Kaiso, a bi-modal transcription factor regulating gene expression, predicts for more aggressive pancreatic cancer when found in male versus female patients' tumor samples (44).

Diabetes mellitus (DM)

DM is a well-established risk factor for PDAC. There is a bidirectional relationship between DM and PDAC. One meta-analysis revealed an odds ratio (OR) of 1.82 for PDAC in individuals with type 2 DM (21). Newly diagnosed diabetics are also at 50% higher risk of developing PDAC compared to those with long-standing diabetes (45), possibly due to DM being one of the early manifestations of PDAC. Furthermore, the mortality rate of diabetics is twice as high compared to non-diabetics. DM can be the first presentation, and complication of PDAC (46).

North America, South-east Asia, Russia and some Asian countries like China and India have the highest prevalence of DM correlating with lifestyle and dietary factors, whereas Europe and Oceania have a lower prevalence (47). This distribution differs from that of global PDAC incidence, in which Europe and Oceania had higher incidence of PDAC than South-east Asia, China and India.

Pancreatitis

Chronic pancreatitis is a strong risk factor for PDAC, due to progressive inflammation and fibrosis. Rijkers *et al.* reported that whilst patients with a first episode of acute pancreatitis had a 0.4% risk of developing PDAC, this risk increased 9-fold for patients who progress to chronic pancreatitis (48). This risk increases in the first 5 years after diagnosis of chronic pancreatitis, thereafter decreases, suggesting that the initial few years of diagnosis are crucial for close follow up (49).

Lew *et al.* (50) found that 0.78% of patients admitted for chronic pancreatitis in a United States-based population also had PDAC. Blacks, men, age 40–59, and being overweight were significantly associated with chronic pancreatitis. Interesting, non-Hispanic Africans had a higher risk for chronic pancreatitis which did not translate into having a higher association of chronic pancreatitis with PDAC. Patients who were found to have both chronic pancreatitis and PDAC were predominantly non-Hispanic Europeans who were overweight and of older age. This correlated with higher incomes, better chances of getting insured and higher rates of being admitted to large urban teaching hospitals in the non-Hispanic European population.

With regards to the etiology of chronic pancreatitis, Wilcox *et al.* (51) reported that non-Hispanic Africans were twice as likely as non-Hispanic Europeans to be diagnosed with chronic pancreatitis attributed to alcohol or smoking, while genetic, idiopathic and autoimmune etiologies were more significant in non-Hispanic Europeans. Non-Hispanic Africans also had a longer duration of disease (8.6 versus 6.97 years) and significantly higher frequencies of severe and consistent pain, disability, and advanced pancreatic morphological changes, demonstrating different degrees of access to healthcare according to ethnicity.

Genetics

Approximately 10% to 15% of PDAC has a familial and/or underlying genetic predisposition, of which familial pancreatic cancer (FPC) constitutes 7% and those with known genetic predisposition syndromes constitute 3% (52) (*Table 2*). The most frequent genetic alterations are of *BRCA2*, *PALB2*, *ATM*, and *CDKN2A*, with less common alterations including *BRCA1*, *APC*, *MLH1*, *MSH2*, *MSH6*, *PMS2* and *PRSS1*. Of the patients with PDAC without significant family history, 5–8% are carriers of a germline mutation that predisposes to PDAC (64,65), explaining the trend and importance of multigene panel testing in patients diagnosed with FPC regardless of age or family history (22). In contrast, FPC is defined by PDAC developing in the context of a strong family history without a known causative germline pathogenic variant (PV) (66).

With time, germline PV may result in carcinogenesis due to the mechanisms of cell injury, dysregulation of cell growth, dysfunctional DNA repair, and disruption of cell mobility and adhesion.

Cell injury

Hereditary pancreatitis accounts for a very small fraction of PDAC but is associated with a markedly increased risk of PDAC (53), as chronic inflammation leads to accelerated mutation accumulation and clonal expansion. Increasingly more germline PV have been implicated in hereditary pancreatitis that progress into PDAC, the most well-studied being *PRSS1*, *SPINK1*, and *CFTR* alterations. Affected individuals develop chronic pancreatitis before the age of 20 and lifetime risk of PDAC is 25% to 44%, with a RR of 87 for developing PDAC (53,67).

PRSS1

PRSS1 on chromosome 7q35 is encoded by the cationic trypsinogen gene. Gain-of-function *PRSS1* variants are associated with autosomal dominant (AD) hereditary pancreatitis, with variable penetrance rates of 40–93%

Table 2 Hereditary syndromes associated with increased risk of PDAC

Gene	Relative risk of PDAC	Chromosome	Syndrome associated with increased risk of PDAC	Typical inheritance pattern	Phenotype
PRSS1	87 (53)	7q35	Hereditary pancreatitis	Autosomal dominant	Pancreatitis
SPINK1		5q32	Hereditary pancreatitis	Autosomal dominant	Pancreatitis
CFTR		7q31.2	Cystic fibrosis	Autosomal recessive	Pancreatitis, sinopulmonary disease, cirrhosis, infertility
TP53	7.3 (54)	17p13.1	Li-Fraumeni syndrome	Autosomal dominant	Breast cancer, soft tissue sarcomas, osteosarcomas, adrenocortical carcinoma, central nervous system tumors
ATM	2.41 (55)	11q22	Hereditary breast and ovarian cancer syndrome	Autosomal dominant	Multiple and early-onset breast and ovarian cancers Pancreas, prostate, melanoma and gastric cancer
CDKN2A	38 (56)	9p21	Familial atypical multiple mole melanoma	Autosomal dominant	Multiple atypical naevi progressing to melanoma Breast, lung and endometrial cancer
STK11	132 (57)	19p13.3	Peutz-Jeghers syndrome	Autosomal dominant	Gastrointestinal hamartomatous polyps, mucocutaneous pigmentation Breast, colon, pancreatic, stomach, ovarian cancer
BRCA1, BRCA2	3.1 (58), 3.51–4.1 (59,60), up to 21.7 (61)	17q12-21; 13q12-13	Hereditary breast and ovarian cancer syndrome	Autosomal dominant	Multiple and early-onset breast and ovarian cancers Pancreas, prostate, melanoma and gastric cancer
PALB2	6 (62)	16p12.2	Hereditary breast and ovarian cancer syndrome	Autosomal dominant	Multiple and early-onset breast and ovarian cancers Pancreas, prostate, melanoma and gastric cancer
MLH1, MSH2, MSH6, PMS2	8.6 (63)	3p21.3, 2p22-p21, 2p16, 7p22	Hereditary non-polyposis colorectal cancer aka Lynch syndrome	Autosomal dominant	Colorectal cancer, extra-colorectal cancers—pancreatic, endometrial, ovarian, stomach, bile duct, small bowel, pancreatic, ureter and renal pelvis cancer Muir-Torre syndrome: skin cancer (sebaceous tumors) Turcot syndrome: central nervous system tumors

PDAC, pancreatic ductal adenocarcinoma.

depending on variant (68-70). *PRSS1*-related hereditary pancreatitis has a prevalence of up to 12.4% in populations with chronic pancreatitis (71).

SPINK1

SPINK1 on chromosome 5q32 codes for serine peptidase inhibitor Kazal type 1. It is upregulated with inflammation to protect the pancreas from autodigestion by trypsin and other pancreatic enzymes. *SPINK1* germline mutation related-pancreatitis is associated with 12 times higher rate of PDAC than patients with idiopathic pancreatitis (72).

CFTR

CFTR on chromosome 7q31.2 codes for the cystic fibrosis transmembrane conductance regulator protein. Mutations in *CFTR* cause classic cystic fibrosis, an autosomal recessive disorder in which chloride and bicarbonate conductance is impaired, resulting in viscous fluid secretion in organs

leading to sinopulmonary disease, cirrhosis, and infertility. In the pancreas, this causes retained trypsin and hence pancreatic inflammation. Heterozygous *CFTR* carriers also have an increased risk of recurrent acute and chronic pancreatitis. A study by Hamoir *et al.* (73) reported that those with *CFTR*-related chronic pancreatitis had a standardized incidence ratio (SIR) of 26.5 for PDAC.

The *CFTR* PVs occur most commonly in Europe, North America and Australia amongst European populations, but is rare amongst Asian populations (74). Its incidence likely remains underreported in regions such as Latin and South America, India and Africa due to lack of registries.

Cell growth

TP53

Tumor protein p53 (*TP53*) on chromosome 17p13.1 codes for a tumor suppressor that regulates cell proliferation, DNA repair and apoptosis in response to cellular stress. Mutations in *TP53* cause Li-Fraumeni syndrome, an AD disorder characterized by high risk for cancer—often multiple and at early age (75). The most common tumors in children are osteosarcoma, adrenocortical carcinoma, central nervous system tumors, and soft tissue sarcoma, and in adults breast cancer in women and soft tissue sarcoma (76). Ruijs *et al.* estimated that the *TP53* mutation concurs a RR of 7.3 for PDAC (54).

ATM

ATM on chromosome 11q22 codes for a protein kinase that regulates cell proliferation and detects DNA damage (77). Biallelic loss-of-function mutations of *ATM* result in Ataxia-telangiectasia (AT), a rare autosomal recessive disorder characterized by progressive ataxia, telangiectasias, immune deficiency, and increased risk of malignancies—particularly leukemias and lymphomas (78). Instead of having classic manifestations of AT, heterozygote carriers of the *ATM* mutation are at increased risk for coronary heart disease and solid organ malignancies, particularly that of breast and pancreatic cancer (79). In a study of 4,607 *ATM* PV carriers, carriers were at moderate-to-high risk for PDAC (OR 4.21) (55). A United Kingdom study of 1,160 individuals estimated that heterozygous carriers of *ATM* mutation have a RR of 2.41 for developing PDAC (80). *ATM* is a well-established breast cancer susceptibility gene, with heterozygote carriers having more than twice the risk of the average population of developing breast cancer and a cumulative lifetime breast cancer incidence of 20–40% (81). Mutations in *ATM* should be considered in patients with PDAC that have a family history of breast cancer.

CDKN2A

CDKN2A on chromosome 9p21 codes for proteins $p16^{INK4A}$ and $p14^{ARF}$. Germline *CDKN2A* mutations are usually missense or nonsense variants (82), permitting inappropriate progression through the cell cycle. Prevalence of *CDKN2A* mutations in the general population is low at about 0.05% (83). Familial atypical multiple mole melanoma (FAMMM) is an AD condition associated with *CDKN2A* mutations, but with incomplete penetrance and variable expressivity. It is characterized by multiple atypical naevi progressing to melanoma (84), and increased risk for internal malignancies such as head and neck and esophageal squamous cell carcinomas, non-small cell lung cancers and pancreatic cancer (85). *CDKN2A*-associated FAMMM is associated with an elevated risk of developing PDAC, RR 13–22 (56), with variants affecting $p16^{INK4A}$ more frequently observed with pancreatic cancer compared to $p14^{ARF}$ (86).

Germline *CDKN2A* mutations are more prevalent in families in Europe, North America, and Australia (82), and in Dutch populations a *CDKN2A* mutation variant known as p16-Lieden is known to carry a particularly higher risk of PDAC, with a cumulative risk of 17% at 75 years of age (87).

STK11

STK11 (also known as *LKB1*) on chromosome 19p13.3 codes for a kinase that regulates AMP-activated protein kinase family members, which control multiple cellular processes including cell polarity, metabolism, and apoptosis (88). Mutations in *STK11* cause Peutz-Jeghers syndrome (PJS), an AD disorder characterized by gastrointestinal hamartomatous polyps and mucocutaneous pigmentation. Individuals with PJS have elevated cancer risks, most commonly that of breast and colon cancer, followed by pancreatic, stomach and ovarian cancer. The cumulative risk of developing any cancer and specifically PDAC at 70 years of age is 85% and 11% respectively, with a RR of 132 of developing PDAC (89).

DNA repair

BRCA1 and BRCA2

BRCA1 and *BRCA2* on chromosome 17q12-21 and 13q12-13 are DNA damage repair genes which code for proteins that function in homologous recombination repair

(90,91). *BRCA1* also functions in DNA damage signalling, chromatin remodelling, and transcriptional regulation. Mutations in *BRCA1/2* can cause hereditary breast and ovarian cancer syndrome (HBOC), one of the more common referrals for cancer genetic testing (92). HBOC is an AD syndrome characterized by multiple and early-onset breast and ovarian cancers, and increased risk for other cancers such as pancreas, prostate and melanoma. The incidence of germline *BRCA1/2* PVs in PDAC is 5–9% (93). *BRCA2* is the most frequently mutated gene (6–19%) in patients with PDAC associated with germline mutations even in the absence of breast cancer (59). *BRCA2* mutation confers a RR of 3.51–4.1 (59,60) for PDAC, with Mersch *et al.* even reporting an increased risk of PDAC up to 21.7 folds (61). On the other hand, *BRCA1* mutation carriers have a lower predilection for pancreatic malignancy (59,61), with RR of 3.1 (58).

BRCA1/2 founder mutations have been identified in groups of Ashkenazi Jews, French Canadians, Hispanics, and African Americans, and in the geographical regions of Netherlands, Sweden, Hungary, Iceland, Italy, France, South Africa, Pakistan and Asia (94). An analysis of the POLO trial cohort revealed that 5.9% of people with previously unknown *BRCA* status had a newly identified *BRCA* mutation, with rates highest in the United States, France, and Israel at 9.5%, 7.6%, and 7.4%, respectively (95). The highest rate of newly identified *BRCA* mutation prevalence was observed in African American patients (10.7%), although this could have been confounded by a small population size and potential disparities in uptake of genetic testing. Biallelic mutations cause Fanconi anemia (96), a syndrome characterized by bone marrow failure, predisposition to malignancy particularly that of acute myeloid leukemia, and physical abnormalities including short stature, microcephaly, developmental delay, café-au-lait skin lesions, and malformations belonging to the VACTERL-H association.

PALB2

PALB2 on chromosome 16p12.2 encodes a protein that contributes to the cellular machinery for DNA repair by homologous recombination (97). Heterozygous mutations in carriers are significantly associated with breast cancers at an OR of 3.1 to 9.2 (98), which is comparable with that of *BRCA1/2*. Among the breast cancer susceptibility genes like *BRCA1/2*, *PALB2* is also considered a high penetrance gene for breast cancer. Several studies have found that *PALB2*-mutated breast cancers are associated with aggressive features, such as higher rates of triple-negative phenotype, advanced disease stage, and higher Ki67 level (99). While the prevalence of *PALB2* variants is not high, there is emerging evidence supporting *PALB2* as a susceptibility gene for PDAC (100). *PALB2* mutation confers a 6-fold increased PDAC risk (62), with a significantly earlier mean age of onset (101).

MLH1, MSH2, MSH6, PMS2, EPCAM

Mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM* maintain genomic integrity by correcting base substitution and small insertion-deletion mismatches during DNA replication. Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is an AD condition caused by mutations in the MMR genes, or deletion in the EPCAM gene resulting in silencing of the downstream *MSH2* (102). Cancer develops according to the two-hit hypothesis, when the first allele is affected by the germline mutation and the second allele is inactivated by a somatic mutation, resulting in defective DNA repair and microsatellite instability. Affected individuals have an increased risk of colorectal cancer and other malignancies such as pancreatic, endometrial, ovarian, gastric, bile duct, small bowel, ureter and genitourinary cancers. The variants Muir-Torre syndrome and Turcot syndrome predispose to sebaceous tumors and central nervous system tumors (glioblastomas and astrocytomas) respectively (63,103). Kastrinos *et al.* described an increased PDAC risk by 8.6-fold and a cumulative PDAC risk of 3.7% at 70 years of age for individuals with HNPCC (63). There is recent evidence linking this increased risk of PDAC in HNPCC particularly with *MLH1* PV carriers (104)—Møller *et al.* observed the cumulative incidence of PDAC to be 6.2% by 75 years of age in *MLH1* PV carriers, compared to 0.5%, 1.4% and 0% for *MSH2*, *MSH6* and *PMS2* respectively.

Founder mutations of MMR genes have been found in Finland, Iceland, Ashkenazi Jews, French Canadian and Amish populations (105).

Cell mobility and adhesion

APC

APC on chromosome 5q21–22 codes for a tumor suppressor that helps to control cell proliferation, stabilize microtubules, and mediate cell migration and adhesion (106). PVs cause Familial adenomatous polyposis (FAP), an AD syndrome classically characterized by the development of hundreds to thousands of colorectal

adenomas, typically by late adolescence, which inevitably progress to colon cancer without intervention. FAP is also associated with extracolonic tumors including hepatoblastoma, duodenal, thyroid, bile duct and brain adenocarcinoma. While FAP has historically been thought of as a predisposing condition for PDAC (107), the incidence of classical exocrine PDAC in this population has likely been overreported in literature and we now know that the association of *APC* mutations with PDAC is not strong (108).

FPC

FPC is defined as families with two or more first-degree relatives with PDAC in the absence of a known PDAC-associated hereditary syndrome (22). It consists of 7% of PDACs (66), suggesting that there is much more to be discovered about the genetic, epigenetic, and environmental factors that contribute to the development of PDAC. European registries have observed an anticipation phenomenon in FPC (109), and every year there have been more discoveries of potential predisposing germline PVs for PDAC.

Large-scale population-based genome-wide association studies have identified common variants in several genomic regions associated with PDAC risk, particularly in the European (110-112), Chinese (113) and Japanese (114,115) populations. These variants individually have a small effect on PDAC risk, but each additional copy of a risk allele is associated with a 10–30% increase in the risk of PDAC and the cumulative effects can be significant. Studies are underway to better understand the mechanisms underlying carcinogenesis and to increase the diversity of genomic studies of PDAC.

The International Cancer of the Pancreas Screening (CAPS) Consortium (116) has put forth consensus guidelines recommending that in addition to individuals with known germline mutations in susceptibility genes, individuals who are FPC kindred should also undergo pancreatic surveillance to detect early pancreatic cancer and its high-grade precursors. This criterion is met by having at least one first-degree relative with pancreatic cancer who in turn also has a first-degree relative with pancreatic cancer. A 2015 systematic review by Lu *et al.* (117) found that PDAC screening in individuals with FPC resulted in a higher curative resection rate (60% versus 25%) and longer median survival time (14.5 versus 4 months) compared with the control group. Canto *et al.* observed that most PDACs detected during surveillance of high-risk individuals with FPC were resectable (9 out of 10), and 85% of these patients survived for 3 years (118). This is in contrast to the general population that typically present late, with only 15% to 20% of patients being candidates for pancreatectomy (119).

Conclusions

In this review, we have examined and summarized the geographical, ethnic and genetic factors that predispose to PDAC carcinogenesis. Incidence of PDAC has been on an uptrend worldwide, with high-income regions such as Europe, North America, Australia/New Zealand and Japan and ethnicities such as the African population experiencing higher incidence rates of PDAC. This is a result of an interplay between varying prevalence and trends of certain established risk factors—including diabetes, obesity, aging, smoking, alcohol consumption and chronic pancreatitis. Genetic factors also play an important role in PDAC predisposition, including germline PDAC, familial basis, and epigenetics involvement. With increasing uptake of large-scale population-based genome-wide association studies, future efforts of research could be directed to identifying more predisposing genetic mutations and understanding their ethnic and geographical variations, as the knowledge base on this is at present still scarce. Early detection and treatment of PDAC results in significantly better outcomes yet the majority currently are only detected at a late and advanced stage. Future studies should consider detailed evaluation of interethnic, environmental, behavioural and genetic data to further elucidate discrepancies between different populations. From there, a better understanding of nuances pertaining to PDAC predisposition will allow more effective and efficient measures for individualised and prompt detection and treatment of PDAC, to improve outcomes for patients with PDAC.

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Footnote

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