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Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors

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Abstract

Pancreatic cancer is a leading cause of cancer death worldwide and its global burden has more than doubled over the past 25 years. The highest incidence regions for pancreatic cancer include North America, Europe and Australia, and although much of this increase is due to ageing worldwide populations, there are key modifiable risk factors for pancreatic cancer such as cigarette smoking, obesity, diabetes and alcohol intake. The prevalence of these risk factors is increasing in many global regions, resulting in increasing age-adjusted incidence rates for pancreatic cancer, but the relative contribution from these risk factors varies globally due to variation in the underlying prevalence and prevention strategies. Inherited genetic factors, although not directly modifiable, are an important component of pancreatic cancer risk, and include pathogenic variants in hereditary cancer genes, genes associated with hereditary pancreatitis, as well as common variants identified in genome-wide association studies. Identification of the genetic changes that underlie pancreatic cancer not only provides insight into the aetiology of this cancer but also provides an opportunity to guide early detection strategies. The goal of this Review is to provide an up-to-date overview of the established modifiable and inherited risk factors for pancreatic cancer.

The global burden of pancreatic cancer has increased dramatically over the past few decades and is expected to continue to represent a leading cause of cancer-related mortality (see Surveillance, Epidemiology, and End Results Program (SEER))[1]. The shifting age structure of the global population, particularly in developing regions[2], as well as changes in established modifiable risk factors account for many of the observed trends. Genetic factors and modifiable exposures, either independently or acting jointly, play an important part in pancreatic cancer risk. As our ability to detect pancreatic cancer and its precursor lesions improves, understanding the underlying risk factors and their interactions will enable prevention efforts, including primary prevention strategies, to reduce exposures and to identify individuals most at risk of this often fatal cancer. This approach will help reduce the growing incidence of this disease. This Review outlines the current knowledge of established

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pancreatic cancer risk factors including lifestyle and disease-specific risks followed by inherited genetic risks. The underlying mechanisms of risk and risk factors with inconclusive associations with pancreatic cancer risk are not discussed.

Global trends in pancreatic cancer

The past two decades have seen a doubling in the global annual number of pancreatic cancers diagnosed. In 2017, there were 441,000 pancreatic cancers worldwide compared with 196,000 in 1990 (REF.[1]). Given that pancreatic cancer is a disease in which risk increases with age and rarely occurs before the age of 40 years[1], the shifting age structure of the global population together with improved diagnosis account for much of the increased incidence (number of cases in the population in a year) of pancreatic cancer, particularly in high-income nations[1]. Incidence rates in low-income nations have remained low, and there is a lack of high-quality data on mortality in these regions due to poor access to advanced imaging and expertise in pathology[1].

The risk of death from pancreatic cancer rises dramatically with age from <2 deaths per 100,000 person-years for individuals in the USA aged 35–39 years to >90 deaths per 100,000 person-years for individuals aged >80 years. As global health improves, resulting in lifespan increases, the overall incidence of pancreatic cancer is also likely to increase. An international report noted that in 2012, 8% of the global population was older than 65 years, the age group at highest risk of pancreatic cancer[2]. In the next 30 years, this proportion is expected to double to 16.7%, particularly in all regions in Asia, Australia, Europe, and many regions in Latin America[2], regions with the some of the highest age-standardized death rates of pancreatic cancer[1]. Even in Africa, where incidence rates of pancreatic cancer remain low, in part due to reduced access to care, the proportion of the population above age 65 years is projected to double in the next several decades[2]. Thus, the incidence of pancreatic cancer will continue to grow over the next few decades.

The increased prevalence of key risk factors, especially in high-income nations, is leading to increased age-adjusted incidence rates of pancreatic cancer[1,3] (number of cases in a population in a year standardized to the age distribution of a ‘standard’ population). The role of the changing prevalence of specific risk factors on age-adjusted incidence rates of pancreatic cancer risk is discussed later. Globally, age standardized incidence rates increased from 5.0 per 100,000 person-years in 1990 to 5.7 (5.6–5.8) per 100,000 person-years in 2017 (REF.[1]). As shown in FIG. 1, incidence is highest in North America, Europe and Argentina followed by East Asia and Australia[4–6]. In addition, in the USA, the 2017 age-adjusted incidence rates were higher in Black individuals (15.9 per 100,000 person-years) than white individuals (13.4 per 100,000 person years), SEER-defined Hispanic individuals (11.7 per 100,000 person-years) and Asian individuals (10.2 per 100,000 person-years) (see Related links). Although under-studied, the increased risk in Black individuals has been suggested to be primarily due to differences in the prevalence of the established risk factors such as smoking, high BMI and diabetes[7]. Additional studies are needed to understand differences in risk across racial and ethnic groups. Globally, incidence rates for pancreatic cancer tend to be somewhat higher in men than in women, particularly in those below the age of 75 years[1].

Survival rates for pancreatic cancer remain low, despite improvements in overall 5-year survival from <5% in the 1990s to as high as 9% in the USA and Europe in 2019 (REFS[8,9]). Low survival rates are, in part, attributed to the advanced stage at diagnosis in most cases, with only ~20% of patients presenting with early-stage, surgically resectable disease. Among patients who undergo surgical resection, the 5-year survival rate is ~15–25%[10] and in the USA the survival rate for stage 1A disease is >80%[11]. The majority of cancers in the pancreas are pancreatic ductal adenocarcinomas (>90%)[12], and the risk factor studies described in the following sections and summarized in TABLE 1 are focused on this tumour type.

Risk factors

Cigarette smoking.

Cigarette smoking is a well-established risk factor for pancreatic cancer[13–15]. A meta-analysis of the effect of smoking on the risk of pancreatic cancer found an odds ratio of 1.74 (95% CI 1.61–1.87) for current smokers compared with never smokers[12]. The risk is highest among those who smoke the greatest number of cigarettes per day, with smokers of more than 35 cigarettes per day having an odds ratio for pancreatic cancer of 3.0 (95% CI 2.2–4.1) compared with never smokers[12]. Quitting smoking results in a reduction of this risk, such that the odds ratio of pancreatic cancer in former smokers is 1.2 (95% CI 1.11–1.29) compared with never smokers[12]. Interestingly, the risk of pancreatic cancer in former smokers decreases as the years since cessation of smoking increases, such that 10–20 years after smoking cessation[14,15] the risk of pancreatic cancer in former smokers returns to that in never smokers. Although the majority of the studies in this meta-analysis were European, a pooled analysis of Japanese cohort studies demonstrated similar findings[16]. Large-scale studies have failed to show an association between passive smoking or parental smoking and pancreatic cancer risk in non-smoking individuals[17,18]. Some studies have found an increased risk of pancreatic cancer in non-cigarette smoking individuals who consume non-cigarette tobacco products, specifically cigars[19], but other studies have failed to detect an association in this group[20,21].

Over the past several decades there has been a decrease in the prevalence of cigarette smoking in much of Europe and North America[22]; however, prevalence rates in Asia (specifically, China and India)[23] and in other parts of the world remain high. In areas where smoking prevalence has decreased, so too has the fraction of pancreatic cancers attributable to smoking. The use of the population attributable risk (PAR; also known as population attributable fraction) is a useful metric to plan population interventional strategies as it denotes the amount by which risk will decrease if a risk factor is eliminated. By definition, as based upon effect size and prevalence of the risk factor in the population, it is population-specific and affected by temporal trends in prevalence and, therefore, not generalizable across populations. A summary of meta-analyses indicates that the PAR of pancreatic cancer due to smoking ranges across studies and across global regions from 11% to 32%[24], with a PAR of 13.6% (6.3–20.8%) reported in Italy, for example[25].

Diabetes mellitus.

Diabetes mellitus is both a risk factor for pancreatic cancer as well as a consequence of the cancer, with many patients with newly diagnosed pancreatic cancer reporting onset of diabetes or, among those with diabetes, a worsening of the disease. Long-standing diabetes (>3 years) has been associated with a 1.5–2.4-fold increased risk of pancreatic cancer[26–29]. Some studies have suggested that there might be no increase in risk among individuals diagnosed with diabetes of >15–20 years duration[29,30], whereas other studies have indicated that individuals with diabetes for 20 years or more[28] remain at an elevated risk of pancreatic cancer.

Many patients with pancreatic cancer report developing diabetes in the months preceding diagnosis and these patients with new-onset diabetes who undergo surgical resection of their pancreatic cancer often see their diabetes resolve after removal of the pancreatic cancer[31]. New-onset of diabetes might be indicative of an underlying pancreatic cancer. Focused studies of 2,122 individuals in the Mayo Clinic population initially indicated that up to 1% of patients with newly diagnosed diabetes develop pancreatic cancer within 3 years of their diabetes diagnosis[31]. However, larger studies conducted with the US Department of Veteran Affairs system have shown a lower risk of <0.3% for developing pancreatic cancer within 3 years of a diabetes diagnosis[32,33] compared with a risk of pancreatic cancer of ~0.11% in patients without diabetes. Ongoing efforts, including the US New-Onset Diabetes cohort (which aims to identify the subgroup with new-onset diabetes with underlying pancreatic cancer), are underway to improve the early detection of pancreatic cancer[34].

The prevalence of diabetes worldwide has increased considerably over the past several decades from 4.3% in 1980 to 9.0% in 2014 in men, and from 5.0% to 7.9% in women. The number of adults with diabetes in the world increased from 108 million in 1980 to 422 million in 2014 (REF.[35]). The increasing prevalence of diabetes is probably one reason why the age-adjusted incidence rates of pancreatic cancer are increasing in many nations despite a decreasing prevalence of cigarette smoking. In addition to a diagnosis of diabetes, biomarkers of diabetes risk have also been shown to be associated with pancreatic cancer risk, including fasting glucose, insulin and insulin resistance levels in both European and Chinese populations[36,37]. A nested case–control study of 466 matched pairs within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort demonstrated that patients with pancreatic cancer had higher levels of HbA_{1C}, a marker of excessive blood sugar used to diagnose diabetes, prior to their pancreatic cancer diagnosis than cancer-free controls[38].

Body mass index.

Increased weight or BMI has been shown to increase the risk of pancreatic cancer. In 2001, with data from 46,648 men and 117,041 women in the USA within the Health Professional follow-up study and Nurse's Health study, Michaud et al. reported a 1.72 (95% CI 1.19–2.4) relative risk of pancreatic cancer in individuals with a BMI of >30 kg/m^2 compared with individuals with a BMI of <23 kg/m^2 after controlling for the effects of age, smoking and diabetes[39]. A pooled analysis of 2,170 cases and 2,209 control individuals (restricted to never smokers) from 13 US and European prospective cohort studies compared the odds

ratios for pancreatic cancer in individuals with overweight (BMI 25–29.9 kg/m^2), obesity (BMI 30–34.9 kg/m^2) and severe obesity (BMI >35 kg/m^2) with those in individuals with normal weight and found odds ratios of 1.19 (95% CI 1.02–1.40), 1.25 (95% CI 1.02–1.55) and 1.62 (95% CI 1.19–2.21), respectively (trend test $P < 0.01$), controlling for the effects of age[40]. The fraction of pancreatic cancer attributable to an increased BMI will vary globally and longitudinally as the prevalence of obesity shifts. The global prevalence of obesity has tripled since 1975 (REF.[41]), which will probably lead to an increasing burden of pancreatic cancer. Thus, it is expected that rates of pancreatic cancer will increase with the increasing obesity rates.

The association between changes in BMI in adulthood and pancreatic cancer risk has also been examined. However, the findings have been inconsistent across studies, or replication studies have not been reported. A study of just over 500,000 individuals, of whom 2,122 developed pancreatic cancer, in the AARP (American Association of Retired Persons) cohort suggested that weight gain after age 50 years is associated with an increased risk of pancreatic cancer[42], with the hazard ratio increasing with increasing weight gain. A record linkage study of 293,209 individuals in the Danish population of whom 1,268 had pancreatic cancer suggested that BMI in early life is important, with high childhood BMI associated with an increased risk of pancreatic cancer before age 70 years[43]. Interestingly, in a study in 2020 of 112,818 women enrolled in the Nurse's Health study and 46,207 men in the Health Professionals Follow-up study (of whom 1,116 developed pancreatic cancer), weight loss in adulthood was associated with an increased risk of pancreatic cancer compared with individuals who gained or maintained weight. Pancreatic cancer risk increased with increasing weight loss, with a weight loss of >8 lb associated with an adjusted hazard ratio of 1.92 (95% CI 1.58–2.32). This risk was even higher in individuals who lost weight and had new onset of diabetes[44]. Although weight loss might be an indicator of early precancerous changes, a better understanding of how changes in weight in adulthood affect the risk of pancreatic cancer is needed.

Alcohol.

Although some studies have found an increased risk of pancreatic cancer among heavy drinkers of alcohol, other studies have not found a statistically significant association. A pooled analysis of data of 5,585 cases and 11,827 controls from the Pancreatic Cancer Case Control Consortium (PanC4) found a statistically significant increased risk (OR 1.6, 95% CI 1.2–2.2) of pancreatic cancer among heavy alcohol drinkers (nine or more drinks per day) compared with consumers of less than one drink per day[45]. Pooled case–control data nested within prospective cohorts in North America, Australia and Europe showed a relative risk of 1.22 (95% CI 1.03–1.45) of pancreatic cancer when comparing individuals who drank >30 g of alcohol per day to those who drank 0 g per day. There was no significant evidence of interaction by sex[46]. Analysis of the NIH-AARP Diet and Health study (of >430,000 individuals of whom 1,149 were diagnosed with pancreatic cancer) showed a relative risk of 1.45 (95% CI 1.17–1.80) of pancreatic cancer among consumers of more than three drinks per day[47]. A focused analysis of never smokers from the American Cancer Society Cancer Prevention Study II showed a relative risk of 1.32 (95% CI 1.10–1.57) of pancreatic cancer in individuals who consumed more than three liquor drinks

per day compared with non-drinkers[48]. Studies including 1,283 individuals who developed pancreatic cancer and 476,106 cancer-free participants within the EPIC cohort population also identified a significant association between heavy alcohol use and pancreatic cancer (HR 1.77, 95% CI 1.06–2.95) in men who consumed >60 g per day of alcohol compared with moderate drinkers (0.1–4.9 g per day), but the risk in women who drank >30 g per day was not significantly elevated[49]. In summary, evidence is growing that alcohol intake, particularly heavy alcohol intake, is associated with pancreatic cancer risk. As such, it is expected that the increasing prevalence of heavy alcohol use in some regions will translate to increased rates of pancreatic cancer. Notably, heavy alcohol consumption is associated with pancreatitis, an established risk factor for pancreatic cancer[50].

Pancreatitis.

Like diabetes, pancreatitis is a risk factor for pancreatic cancer as inflammation and damage resulting from pancreatitis can lead to the development of pancreatic cancer; however, pancreatitis can also develop as a result of an underlying pancreatic cancer[50]. A pooled analysis within the PanC4 consortium showed that 6% of patients with pancreatic cancer reported a history of pancreatitis compared with 1% of control individuals[51]. When examining this association by the duration of pancreatitis, a recent diagnosis of pancreatitis (<1 year) was associated with an odds ratio of 21.35 (95% CI 12.03–37.86) for pancreatic cancer[51], whereas individuals diagnosed with pancreatitis >2 years previously had an odds ratio for pancreatic cancer of 2.71 (95% CI 1.96–3.74)[51]. Similar results were found in a large nested population-based case–control study of pancreatitis from a Danish cancer registry. Unlike the PanC4 study, this study relied upon in-patient diagnosis of pancreatic cancer and compared 41,669 patients diagnosed with incident acute pancreatitis with 208,340 individuals from the general population without acute pancreatitis. The relative hazard of pancreatic cancer in individuals with acute pancreatitis was 19.28 (95% CI 14.62–25.41) within the 2 years following the pancreatitis diagnosis. Pancreatic cancer risk decreased with time since pancreatitis diagnosis but there continued to be an elevated adjusted relative hazard of 2.02 (95% CI 1.57–2.61) for pancreatic cancer in patients with pancreatitis followed beyond 5 years[52]. Fortunately, pancreatitis is relatively rare, being found in only 1% of controls in pooled case–control studies[51].

Allergy.

The role of the immune system in the development of pancreatic cancer is of increasing interest. Individuals with a personal history of allergies have been shown to be protected against pancreatic cancer with the underlying hypothesis that individuals with an active immune system might have increased antitumour immunity[53]. Studies have demonstrated that individuals with allergy have a decreased risk of cancer and improved survival compared to those without an allergy[53]. A 2005 meta-analysis of 14 studies demonstrated a relative risk of 0.83 (95% CI 0.68–0.80) for pancreatic cancer in individuals with a history of allergy compared to those without[53]. This protective effect was only observed among individuals with atopy and not among patients with asthma. A pooled analysis of data from the PanC4 consortium showed lower pancreatic cancer risk in individuals with a history of hay fever and animal allergies (OR 0.74 (95% CI 0.56–0.96) and 0.62 (95% CI 0.41–0.94), respectively)[54]. A similar result was found when examining 345 patients with pancreatic

cancer and 1,285 population controls matched for age and sex from the Ontario Cancer Registry[55]. Interestingly, the PanGenEU study of 1,297 patients with pancreatic cancer and 1,024 control individuals found a protective effect of both long-standing asthma (OR 0.39, 95% CI 0.24–0.64) and nasal allergies (OR 0.66, 95% CI 0.52–0.83)[56]. Although one can hypothesize that individuals with allergy might have a reduced risk of pancreatic cancer due to residual confounding of smoking, the protective effect of allergy seems to be even stronger in smokers than never smokers[53,55].

Role of the microbiota.

In the past decade there has been an increased interest in the role of the microbiota in pancreatic cancer risk. Notably, studies have examined the role of the microbiota, including the tumour microbiota, on survival and treatment response[57], but the focus in this Review is on associations between the microbiota and the risk of pancreatic cancer. A meta-analysis demonstrated that periodontal disease and tooth loss is associated with a 50–70% increased risk of pancreatic cancer[58]; the oral microbiota, particularly *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*, has been associated with future risk of pancreatic cancer in 361 individuals who developed pancreatic cancer and 371 matched controls from the American Cancer Society Cancer Prevention Study II and the National Cancer Institute Prostate, Lung, Colorectal and Ovarian Cancer Study[59]. This finding is supported by a study in 405 patients with pancreatic cancer and 416 matched controls in the EPIC cohort, which demonstrated that antigens to *P. gingivalis* in prediagnostic blood samples were more common among individuals who developed pancreatic cancer than in control individuals[60]. The mechanism underlying this association is unclear and questions remain as to whether it represented a direct causal correlation or whether it reflected a common underlying cause and was therefore not directly causal.

Infection with *Helicobacter pylori* has also been associated with pancreatic cancer in some studies. A meta-analysis found no overall association between *H. pylori* seropositivity and pancreatic cancer risk (OR 1.13, 95 % CI 0.86–1.50)[61]. However, there was some evidence that CagA-positive strains of *H. pylori* were associated with a low risk of pancreatic cancer (OR 0.78, 95% CI 0.67–0.91) and CagA-negative strains of *H. pylori* were associated with an increased risk of pancreatic cancer (OR 1.30, 95% CI 1.02–1.65)[61]. Further studies are needed to determine if inconsistency in the results was due to strain-specific associations and to understand the underlying mechanism.

Environmental and occupational causes

Numerous studies have investigated the relationship between environmental exposures and the risk of pancreatic cancer, often with inconsistent findings (reviewed elsewhere[62,63]). Accurate assessment of exposure to common environmental and occupational compounds is challenging, particularly in non-occupational settings, which often do not have detailed exposure measurements and rely on self-report[64]. Analysis of a large-scale case–control study including 2,092 patients with pancreatic cancer seen at the Mayo Clinic and 2,353 primary care Mayo Clinic patients as controls frequency-matched on the basis of age, race, sex and state or region of residence showed that patients with pancreatic cancer were more

often regularly exposed to pesticides (OR 1.21, 95% CI 1.02–1.44), asbestos (OR 1.54, 95% CI 1.23–1.92), benzene (OR 1.70, 95% CI 1.23–2.35) and chlorinated hydrocarbons (OR 1.63, 95% CI 1.32–2.02)[65]. However, this study was based on retrospective self-reported lifetime exposures and differential recall between cases and controls might have led to biased associations. A series of studies examined the association between reported occupational history exposure in 116 patients with pancreatic cancer in eastern Spain and the concentration of 12 trace elements in the toenails and organochlorine compounds in blood[66,67]. Correlations with pancreatic cancer were reported between several compounds and self-reported occupation. These studies did not have a control group and, as such, the association between occupational history and pancreatic cancer risk is unclear[66,67]. However, in a study including 118 patients with pancreatic cancer from the same Spanish population and 339 hospital-based controls, an association was found between the risk of pancreatic cancer and the levels of lead, nickel, selenium, cadmium and arsenic in toenail samples[68]. Further work is needed to understand the role of environmental exposure in pancreatic cancer risk.

Familial history of cancers

Inherited genetic factors also play an important part in pancreatic cancer risk. The first lines of evidence supporting a role for inherited factors in pancreatic cancer were case reports followed by observational studies. These studies demonstrated that having a close blood relative with pancreatic cancer is associated with a 1.5–13-fold increased risk of pancreatic cancer[69–78]. Prospective studies have demonstrated that first-degree relatives of patients with familial pancreatic cancer (individuals with at least two close family members with pancreatic cancer) have a 6.79-fold (95% CI 4.54–9.75) increased risk of pancreatic cancer[78]. Unlike other cancers in which individuals with a family history develop cancer at a younger age, there is, at most, a 6-year difference in the average age of pancreatic cancer among those with and without a family history[75,79–81]. Pancreatic cancer in families also clusters with other cancers. Increased risks of breast, ovarian, prostate, colon, bile duct and liver cancer[77,82,83] have all been reported among the relatives of patients with pancreatic cancer.

The pancreatic cancers that develop in patients with a family history of pancreatic cancer are quite similar to those that develop in individuals without a family history, as shown by a large-scale histopathological comparison that showed no statistically significant differences between familial and sporadic pancreatic cancers[84]. Furthermore, the somatic genetic mutational profile of pancreatic cancers that develop in those with a family history is also quite similar to that of apparently sporadic pancreatic cancers[79]. Although the cancers themselves are similar, patients with a family history of pancreatic cancer have a higher prevalence of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasia (IPMN) in the normal pancreas adjacent to their cancer than patients without a family history[85]. These studies suggest that the genetic basis of familial and sporadic pancreatic cancer is very similar; however, individuals with a family history are more likely to develop precursor lesions, some of which might progress to pancreatic cancer.

Inherited predisposition genes

The clustering of pancreatic cancer in families can be attributed to both shared environmental factors as well an underlying genetic predisposition. The proportion of pancreatic cancers due to inherited genetic factors (heritability) has been estimated to be 21.4–36%, with the higher estimates from family-based studies that might have better captured the contribution of rare genetic variation[86,87]. Over the past 15 years, as genomic technology has improved, both high-penetrance rare variants and low-penetrance common variants associated with an increased risk of pancreatic cancer have been identified[88–95]. However, the identified genetic changes explain only 20–25% of the heritability (4–5% of all pancreatic cancers)[86], leaving much that still needs to be learned. For the 20% of familial pancreatic cancers for which a causative mutation has been identified, knowledge of the precise genetic mutation can help guide therapeutic decisions for those who develop pancreatic cancer and prompt early detection screening choices for at-risk relatives. For example, early detection screening or clinical trials using imaging techniques might be used in patients who have a strong family history of pancreatic cancer and/or who carry germline pathogenic variants in established familial pancreatic cancer genes[96–100] (TABLE 2); furthermore, *BRCA2*-deficient or *PALB2*-deficient cancers have increased sensitivity to PARP inhibitors or mitomycin C[101–104], microsatellite instability-high pancreatic cancers can be treated with anti-PD1 immunotherapy[105], and patients with pancreatic cancer with a family history of breast, ovarian or pancreatic cancer have improved survival when treated with platinum-containing agents[106].

In the sections below, the associations between pancreatic cancer and specific syndromes or specific hereditary cancer genes (including the prevalence of pathogenic variants in these genes among patients with pancreatic cancer and the risk of pancreatic cancer among variant carriers) are discussed.

BRCA2.

Pathogenic variants in *BRCA2* account for the largest proportion of patients with pancreatic cancer found to have a high-risk genetic variant[107], with prevalence rates ranging from 1.4% to 7% in case series of unselected patients[108–111]. Prevalence rates are up to 16% among patients with a family history of pancreatic, ovarian or breast cancer (particularly cancer of early onset)[112–114]. Studies of the estimated lifetime risk of pancreatic cancer among *BRCA2* pathogenic variant carriers are limited to studies of families ascertained on a history of breast or ovarian cancer, which suggest a 3.5–5.8-fold increased risk of pancreatic cancer compared with individuals without pathogenic *BRCA2* variants[109,115,116].

BRCA1.

Individuals who carry deleterious mutations in *BRCA1* have also been shown to be at an increased risk of pancreatic cancer; however, studies of the prevalence and penetrance of *BRCA1* mutations have demonstrated that the risk is probably lower than that for *BRCA2* carriers. Estimates of the risk of pancreatic cancer in those with pathogenic variants in the *BRCA1* gene suggest a 2.7–4.1-fold higher risk compared with individuals without pathogenic *BRCA1* variants[109,116,117]. The prevalence of *BRCA1* pathogenic variants

in patients with pancreatic cancer unselected for family history range from 0.35% to 1.0%[109–111] and, as with *BRCA2*, prevalence rates are at least about twofold higher among patients with pancreatic cancer with a family history of pancreatic or ovarian cancer[107].

PALB2.

Pathogenic variants in the *PALB2* gene, encoding a binding partner of BRCA2, are also associated with an increased risk of pancreatic cancer. Although initial reports suggested that up to 3% of patients with a family history of pancreatic cancer carry pathogenic variants in *PALB2* (REF.[88]), subsequent studies suggested that the prevalence might be closer to 1% among those with a family history[107,118,119] and 0.2–0.4% in unselected patients[109–111].

ATM.

Pathogenic variants in the DNA repair gene *ATM* have also been associated with an increased risk of pancreatic cancer. The prevalence of *ATM* pathogenic variants is 0.5–2.3% in unselected patients with pancreatic cancer[109–111,120]. Among patients with pancreatic cancer with a family history of pancreatic cancer, the prevalence of pathogenic *ATM* variants is higher, ranging from 2.6% to 3.4%[89,90].

CDKN2A.

Pathogenic variants in the *CDKN2A* gene, first associated with an increased risk of melanoma, are also associated with an increased risk of pancreatic cancer, which is the second leading cause of cancer death in individuals with pathogenic *CDKN2A* variants[120]. Pathogenic variants in *CDKN2A* have been reported in <1% of unselected patients with pancreatic cancer and up to 2.5% of patients with a family history of pancreatic cancer[107]. Individuals with pathogenic variants in *CDKN2A* have a 12–38-fold increased risk of pancreatic cancer compared with individuals without pathogenic variants in *CDKN2A*[109,121] or a lifetime risk of pancreatic cancer of 17%[122,123]. Among individuals with a specific pathogenic variant in *CDKN2A* (the Leiden founder variant (c.225_243del19)) undergoing early detection screening for pancreatic cancer using MRI or magnetic resonance cholangiopancreatography, 7.3% were found to have pancreatic cancer[124].

Lynch syndrome.

Lynch syndrome is associated with an increased risk of colorectal, endometrial, stomach, breast and pancreatic cancer[125]. Pathogenic variants in *MLH1*, *MSH2*, *MSH6*, *PMS2* and *EPCAM* underlie Lynch syndrome. Individuals with Lynch syndrome have been shown to have a 3.68% (95% CI 1.45–5.88%) risk of pancreatic cancer by age 70 years which is 8.6-fold higher than in the general population[125]. Pathogenic variants in several genes associated with Lynch syndrome (such as *MLH1*, *MSH2* and *MSH6*) have been shown to be more common in patients with pancreatic cancer, but these variants are still uncommon, collectively occurring in ~0.5–1.0% of unselected patients with pancreatic cancer[109–111].

Peutz–Jeghers syndrome.

Individuals with Peutz–Jeghers syndrome, which is caused by pathogenic variants in the *STK11* gene, develop hamartomatous polyps of the gastrointestinal tract[126]. These individuals have a remarkably high risk of any cancer (40% by age 40 years and 76% by age 70 years[126]) and a remarkably high lifetime risk of pancreatic cancer (11–32%)[126–128].

Hereditary pancreatitis.

Pancreatitis, as discussed above, is a risk factor for pancreatic cancer and both common and rare genetic variants have been associated with an increased risk of pancreatitis and possible subsequent pancreatic cancer. The risk of developing pancreatic cancer is extremely high among individuals with hereditary pancreatitis (30–40% by age 70 years)[129,130] and it has been suggested that the age of onset of pancreatic cancer is about 20 years younger in smokers with hereditary pancreatitis than in non-smoking individuals with hereditary pancreatitis[130]. A proportion of patients with hereditary pancreatitis have inherited pathogenic variants in the *PRSS1* gene[131–133] as well as specific pathogenic variants in *CTFR* and *SPINK1*. However, unlike pathogenic variants in *PRSS1*, evidence supporting a role for *CFTR* and *SPINK1* variants in pancreatic cancer risk is limited[134,135]. In addition, one study has suggested that ER-stress-inducing variants in the pancreatic secretory enzyme genes *CPA1* and *CPB1* are more common in patients with pancreatic cancer, occurring in up to 1% of individuals with pancreatic cancer compared with <0.001% in population controls[90,136].

Common genetic variants.

In addition to pathogenic variants in the above-mentioned genes (which lead to a moderate-to-high lifetime risk of pancreatic cancer), large-scale population-based genome-wide association studies (GWAS) have identified common variants in several genomic regions as significantly associated with pancreatic cancer risk. In European ancestry populations, associated regions include 1q32.1 (*NR5A2*), 1p36.33 (*NOC2L*), 2p13.3 (*ETAA1*), 3q29 (*TP63*), 5p15.33 (*CLPTM1L, TERT*), 7p14.1 (*INHBA*), 8q21.11 (*HNF4G*) 8q24.21 (*MYC*), 9q34.2 (*ABO*), 13q12.2 (*PDX1*), 13q22.1 (*KLF5*), 16q23.1 (*BCAR1*), 17q12 (*HNF1B*), 17q25.1 (*LINC00673*), 18q21.32 (*GRP*) and 22q12.1 (*ZNRF*)[94,95,137,138]. GWAS have been conducted both in Chinese and Japanese populations, with five loci (21q21.3, 5p13.1, 21q22.3, 22q13.32 and 10q26.11) found to be associated with pancreatic cancer in the Chinese population, and six loci (6p25.3, 12p11.21, 7q36.2, 13q12.2, 13q221 and 16p12.3) found in the Japanese population[139–141]. Many of the loci are distinct and have not been replicated across ancestral populations. However, a GWAS in the Japanese population found evidence of replication ($P < 0.01$) for 1q36.33, 9q24.2, 13.q12.2, 17q24.2 and 13q22.1 (REF.[141]), which are loci first reported to be associated with pancreatic cancer in European populations[95]. Individually, these variants have only a small effect on pancreatic cancer risk but each additional copy of a risk allele is associated with a 10–30% increase in the risk of pancreatic cancer[95]. The effects of these common variants are similar in patients with pancreatic cancer with a family history of pancreatic cancer[142]. In addition, secondary analyses of GWAS data, focusing on pathway-based associations or transcriptome-wide associations, have suggested several other candidate regions requiring further replication and

follow-up[137,143]. Studies are underway to fully understand the mechanisms underlying both the primary and secondary associations and to increase the diversity of genomic studies of pancreatic cancer.

Pancreatic cancer screening

Currently, screening for pancreatic cancer is not recommended for the general population in the USA. However, individuals who have several close relatives with pancreatic cancer, individuals with a pathogenic variant in one of the high-risk pancreatic cancer susceptibility genes or individuals at high risk owing to a personal history of pancreatic cysts might consider screening[144]. The International Cancer of the Pancreas Screening Consortium have agreed that screening be conducted as part of a clinical trial, or if that is not possible, at a centre with experience in pancreatic cancer screening[145]. The consensus statements support screening using endoscopic ultrasonography (EUS) or MRI, with less support for CT scanning, which has lower sensitivity[145]. The results from EUS-based screening trials in both the USA and Europe have demonstrated that asymptomatic precursor lesions including IPMNs, as well as cancers, can be detected[146]. When compared with the US population Surveillance, Epidemiology, and End Results Program (SEER), there is an indication that the pancreatic cancers detected through screening are diagnosed at an earlier stage, yet additional work is needed to definitively show that early detection screening improves outcomes[11,124,146–148]. In addition, there is considerable effort underway to develop additional early detection screening tests and/or improve the ability of current technologies to identify early pancreatic cancer, for example with minimally invasive blood-based tests[149,150] and improved imaging through radiomics[151,152].

Conclusions

Pancreatic cancer is increasing, in part due to the ageing of the world’s population but also due to increases in the prevalence of modifiable pancreatic risk factors including obesity, diabetes and cigarette smoking. Population-based interventions such as smoking cessation, obesity prevention and weight loss studies can be implemented to reduce the burden of many diseases including pancreatic cancer. Inherited genetic changes also play a key part in pancreatic cancer risk; identifying high-risk individuals, together with improvements in screening technologies, might provide opportunities for earlier detection of a growing cause of cancer mortality.

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RELATED LINKS

National Cancer Institute. SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program: https://seer.cancer.gov/explorer/

Key points

- Smoking continues to be a leading cause of pancreatic cancer worldwide.
- Increasing rates of diabetes and obesity will probably result in increased rates of pancreatic cancer.
- Growing evidence indicates that high alcohol intake contributes to pancreatic cancer risk.
- Knowledge of inherited genetic factors in pancreatic cancer continues to grow and probably explains 22–33% of pancreatic cancer risk.

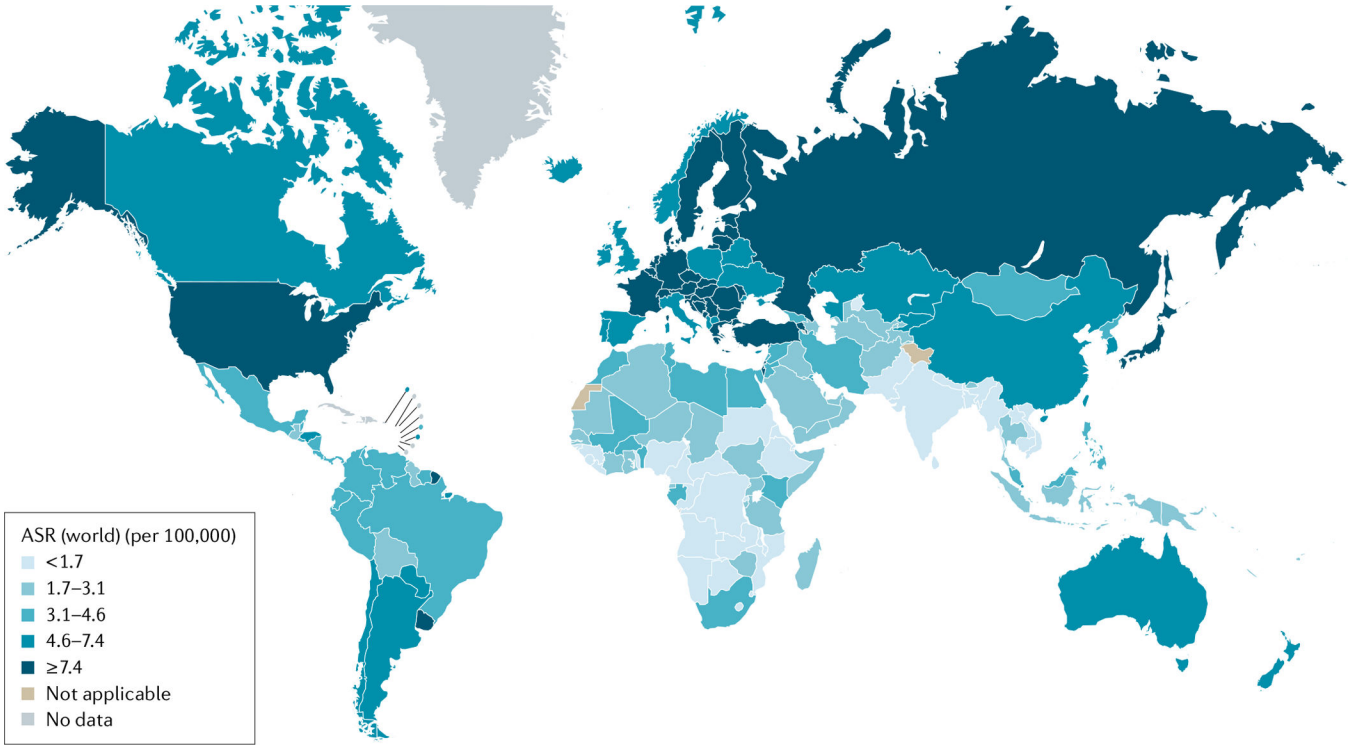

Fig. 1 |. Incidence of pancreatic cancer.

Age-standardized incidence rates (ASR) of pancreatic cancer across the globe in 2020. Figure adapted with permission from REF.[5], International Agency for Research on Cancer (accessed 14 April 2021).

Table 1 |

Pancreatic cancer risk factors

Risk factor	Associated risk of pancreatic cancer	Refs
Cigarette smoking	~1.7-fold increased risk compared with never smokers	13–16
Obesity	~1.6-fold increased risk in individuals with obesity compared with those with normal weight	39,40,42
Alcohol use	1.6-fold increased risk in those consuming >6 drinks per day compared with those consuming >1 drink per day	45–49
New-onset diabetes	<0.3–0.8% of patients with new-onset diabetes develop pancreatic ductal adenocarcinoma within 3 years of diabetes diagnosis	31–33
Long-standing diabetes	1.5–2-fold increased risk of pancreatic cancer for individuals with diabetes of >3 years in duration	26–30
Family history of pancreatic cancer	Twofold increased risk in individuals with a single family member with pancreatic cancer compared with the general population; sevenfold increased risk in individuals with multiple family members with pancreatic cancer compared with the general population	78
Pancreatitis	Twofold to threefold increased risk in individuals with long-standing chronic pancreatitis	50–52
Allergy	25% lower risk of developing pancreatic cancer	53–56

Table 2 |

High-risk pancreatic cancer inherited susceptibility genes

Gene	Prevalence in patients with pancreatic cancer (%)	Refs
BRCA2	2–7	107–116,120
PALB2	<0.5	88,107,118,119
BRCA1	0.6–2.2	107,109,110,116,117
ATM	2.3	89,90,109–111
STK11	<1	126–128
P16/CDKN2A	<1–2.5	121–124
PRSS1	<1	129–133
MLH1, MSH2, MSH6, PMS2	<1	109,125