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Advances in the epidemiology of pancreatic cancer: Trends, risk factors, screening, and prognosis

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ABSTRACT

Pancreatic cancer is a malignancy with poor prognosis and high mortality. The recent increase in pancreatic cancer incidence and mortality has resulted in an increased number of studies on its epidemiology. This comprehensive and systematic literature review summarizes the advances in the epidemiology of pancreatic cancer, including its epidemiological trends, risk factors, risk prediction models, screening modalities, and prognosis. The risk factors for pancreatic cancers can be categorized as those related to individual characteristics, lifestyle and environment, and disease status. Several prediction models for pancreatic cancer have been developed in populations with new-onset diabetes or a family history of pancreatic cancer; however, these models require further validation. Despite recent progress in pancreatic cancer screening, the quantity and quality of related studies are also unsatisfactory, especially with respect to the identification of high-risk populations and development of effective screening modality. Apart from the populations with familial genetic risk and those at a high risk of sporadic pancreatic cancer, risk factors such as new-onset diabetes may be a new direction for timely intervention. We hope this work will provide new ideas for further prevention and treatment of pancreatic cancer.

1. Introduction

Pancreatic cancer, a common malignant tumor, which frequently occurs as pancreatic adenocarcinoma, is characterized by poor prognosis, with an overall 5-year relative survival rate of approximately 10% [1]. Pancreatic neuroendocrine tumor, accounting for less than 5% of pancreatic cancer, has different characteristics and treatment methods compared to pancreatic adenocarcinoma [2], and is not the focus of the present review. Surgical resection at an early stage is currently the only effective treatment. Therefore, early diagnosis and timely surgical intervention are currently the only effective means to improve outcomes in pancreatic cancer patients. It is important to identify the related risk factors and populations that are at a high risk of pancreatic cancer, in addition to achieving early diagnosis based on clinical examinations or biomarkers. Recent decades have witnessed a series of advances in epidemiological and clinical research on pancreatic cancer [3–10]. This review summarizes the advances in research on pancreatic cancer in terms of its epidemiological trends, risk factors, risk prediction models, screening modalities, and prognosis, which may provide important references for the further prevention and treatment of pancreatic cancer.

2. Epidemiology of pancreatic cancer

According to the Global Cancer Observatory (GLOBOCAN) 2020 [11], an estimated 495,773 patients were newly diagnosed with pancreatic cancer in 2020 worldwide, ranking pancreatic cancer 12th among all malignant tumors. The global crude incidence rate was $6.4/10^5$, and the age-standardized incidence rate (ASR) was $4.9/10^5$. An estimated 466,003 deaths were attributed to pancreatic cancer in 2020, resulting in pancreatic cancer ranking 7th among all malignant tumors,

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with a crude mortality of 6.0/10^5 and an ASR of 4.5/10^5. The incidence and mortality (both crude and ASR) were higher in men than in women. Asia contributed the most to both the new diagnosed cases (47.1%) and cancer-related deaths (48.1%) worldwide. The incidence and mortality rates of different countries worldwide in 2020 are shown in Fig. 1.

An analysis of recent trends in pancreatic cancer in 48 countries by Huang et al. [7] showed significant increases in the incidence of pancreatic cancer in men in 14 countries (average annual percent changes [AAPCs], 8.85–0.41) and in women in 17 countries (AAPCs, 6.04–0.87). Similarly, increased mortality was observed in men in 8 countries (AAPCs, 4.20–0.55) and in women in 14 (AAPCs, 5.83–0.78) countries. An increase was also observed in individuals older than 50 years of age in 18 countries. Malta showed the fastest-growing incidence in women, with an AAPC of 6.04%. Iceland reported the most drastic increase in men, with an AAPC of 8.85%. In terms of mortality, the Philippines showed the most significant increase in both sexes, with AAPCs of 4.20% in men and 5.53% in women [7].

The human development index (HDI), calculated according to life expectancy, education level, and quality of life, is used to evaluate the state of national development. A higher HDI was associated with an increased incidence and mortality of pancreatic cancer [7]. In the US, pancreatic cancer is the 4th leading cause of death among all cancers [12] and is predicted to be the second leading cause of death by 2030 [13]. In EU countries, the incidence of pancreatic cancer ranks 8th among all malignant tumors, and the cancer-related death rate ranks 6th. The total incidence of pancreatic cancer is expected to increase by an estimated 30% by 2040 [14]. In China, there were an estimated 95,000 (crude incidence rate: 6.92/10^5) and 85,000 (crude mortality rate: 6.16/10^5) new cases and deaths, respectively, due to pancreatic cancer in 2015, ranking 10th and 6th among all malignant tumors in China, respectively [15].

Pancreatic cancer imposes a great burden on human health globally. There was a 2.1-fold increase in global disability-adjusted life years (DALYs) due to pancreatic cancer from 1990 to 2017, increasing from 4.4 million (95% confidence interval [CI]:4.3–4.5) to 9.1 million (95% CI, 8.9–9.3) [16]. In 2017, the DALY of pancreatic cancer in China was 1.89 million (DALY rate: 133.87/10^5), approximately three times the disease burden in 1990 [17].

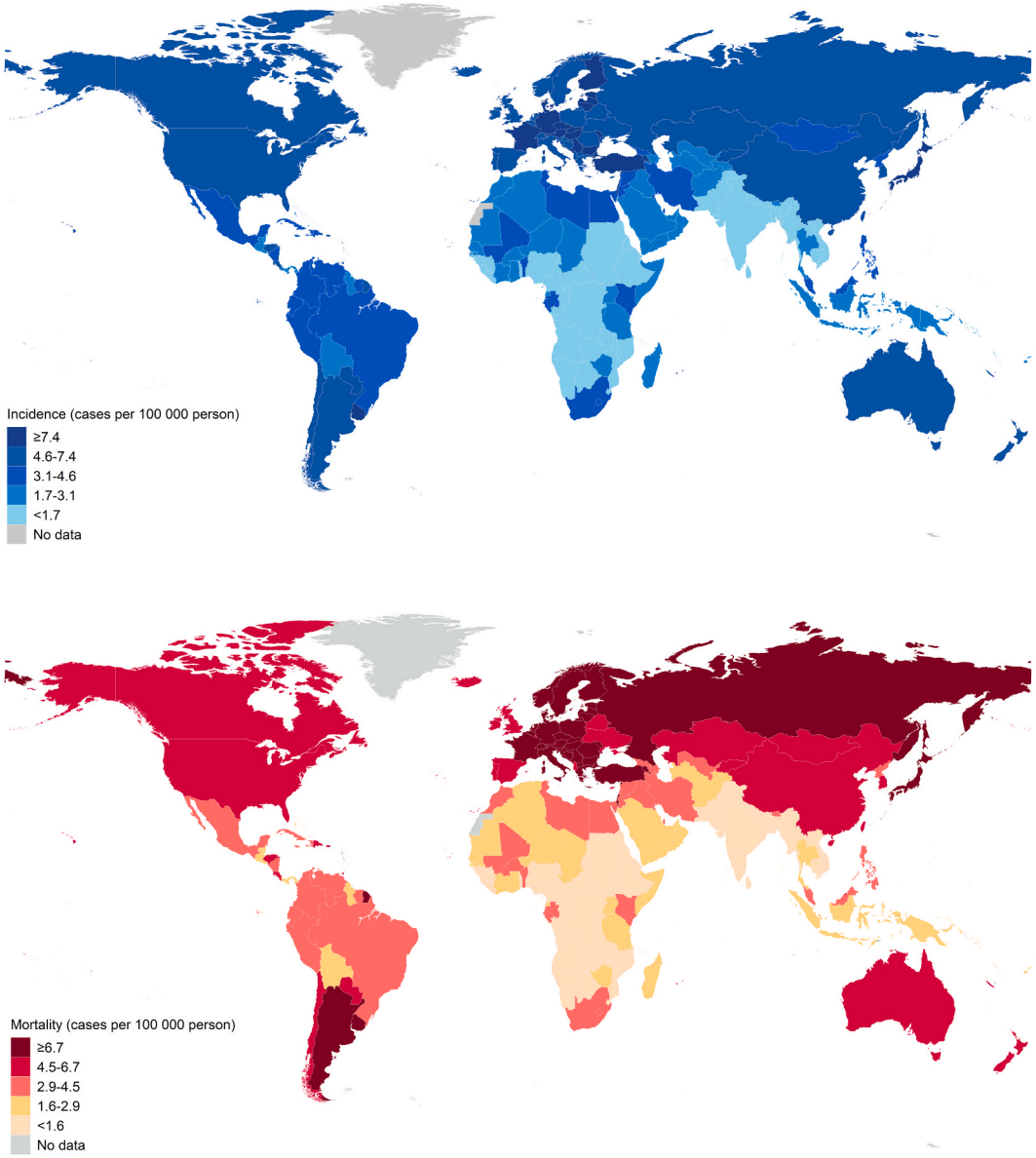

Fig. 1. Estimated age-standardized incidence rates (World) for pancreatic cancer in 2020, both sexes (the figure was mapped using published data from GLOBOCAN 2020).

3. Risk factors for pancreatic cancer

In general, the risk factors for pancreatic cancer can be categorized as those related to individual characteristics, lifestyle and environment, and disease status. Among them, the risk factors associated with individual characteristics mainly include age, sex, race, ABO blood group, family history, and genetic mutations. The risk factors related to lifestyle and environment include dietary habits, exposure to trace elements, smoking, drinking, physical activity, and obesity. The disease status aspect includes chronic pancreatitis, diabetes, infection, etc [18]. An overview of the risk and preventive factors for pancreatic cancer is shown in Table 1.

3.1. Individual characteristics

3.1.1. Age

Pancreatic cancer mainly occurs in elderly individuals. In the US, most patients are diagnosed with pancreatic cancer in later life, with a median age of 70 years at diagnosis, with only 10.6% of diagnoses being made in patients before the age of 55 years [1]. In China, both the incidence (ASR: $5.02/10^5$ in 2017) and mortality (ASR: $5.67/10^5$ in 2017) of pancreatic cancer were the highest in the population aged 85–90 years. The DALY was the highest in people aged 70–74 years in both 1990 and 2017 [17]. Pancreatic cancer may be associated with age-related pancreatic morphological and pathological changes such as telomere dysfunction [19].

3.1.2. Sex

The incidence of pancreatic cancer is generally higher in men than in women. The reported global incidence (ASR) in men was $5.7/10^5$ and $4.1/10^5$ in women. In Polynesia, the incidence (ASR) in men was approximately 3.6 times that in women (7.9/2.2). However, there were no significant sex differences in terms of mortality (ASR) [11]. In China, the incidence in men (crude: $7.67/10^5$; ASR: $5.06/10^5$) was also slightly higher than that in women (crude: $6.14/10^5$; ASR: $3.54/10^5$) [15].

Table 1
Overview of risk and preventive factors of pancreatic cancer.

Factors	Risk	References
Individual characteristics		
Age (older)	+++	[1,17]
Gene mutations	+++	[5,10,29,36]
Race (black)	++	[1,21,22]
Family history	+	[28]
Gender (male)	+	[11,15]
Blood group (A/B/AB)	+	[23–26]
Lifestyle and environment		
Exposure to iron, cadmium, arsenic and lead	++	[77–80]
High consumption of red and processed meat	+	[41,42]
Sugar-sweetened foods and drinks	+	[43–45]
Excessive alcohol consumption	+	[61,62]
Smoking	+	[64,65]
Obesity	+	[69,71]
Soy products	(+)	[53]
Exposure to selenium and nickel	(−)	[80]
Coffee	(−)	[47–50]
Vitamin D	(−)	[58,59]
Vegetables, fruits, nuts, whole grains	–	[54–57]
Physical activity	–	[66,67]
Aspirin use	–	[73,74]
Disease status		
Chronic pancreatitis	+++	[82]
Type II diabetes	++	[3]
Hepatitis B virus infection	++	[99]
Pancreatic cystic lesions	+	[86–94]
Helicobacter pylori infection	+	[100]

†: +++ = very strong risk increase (>3-fold) . ++ = strong risk increase (2∼3-fold). + =moderate risk increase (1∼2-fold).
- = risk reduction. Parentheses show probable but not fully established associations.

However, studies have not shown the protective effect of estrogen against pancreatic cancer [20]. Therefore, the causes and mechanisms of sex differences, which may be related to genetic and lifestyle differences between men and women, require further exploration.

3.1.3. Race and ethnicity

The risk of pancreatic cancer varies among ethnicities. According to the Surveillance, Epidemiology, and End Results (SEER) database (2013–2017), the ASR in males was the highest in black ($16.9/10^5$), followed by non-Hispanic ($15.2/10^5$) and white ($15.0/10^5$) populations, and the lowest in Asian/Pacific Islanders ($11.0/10^5$). In women, the highest incidence was also observed in the black ($14.1/10^5$), followed by non-Hispanic ($11.7/10^5$) and white ($11.6/10^5$) populations, while the lowest incidence was observed in American Indian/Alaska natives ($7.8/10^5$) [1]. Excess risk of pancreatic cancer among American black populations may be attributed to race-based differences in the metabolism of cigarette smoke, higher levels of cigarette smoking, high-calorie diets, heavy alcohol consumption, obesity, long-standing diabetes, and low-income level [21]. In addition, pancreatic cancer appears to be less aggressive and more survivable in Asian patients residing in the US than in non-Asians residing in the US [22].

3.1.4. Blood group

Individuals with blood types A, B, and AB are at a higher risk than those with blood type O. Compared to blood type O, the odds ratios (ORs) for pancreatic cancer in individuals with types A, AB, and B were 1.38 (95% CI: 1.18–1.62), 1.47 (95% CI, 1.07–2.02), and 1.53 (95% CI, 1.21–1.92), respectively [23]. This difference may be related to the single nucleotide polymorphism of ABO, rs505922, which causes a strong linkage disequilibrium in the O/non-O blood group alleles [24,25]. A pooled analysis of 24 studies on the association between ABO blood type and pancreatic cancer among cytotoxin-associated gene A (CagA)-endemic and CagA-nonendemic individuals showed that compared to group O, individuals with group A blood type in both CagA-nonendemic and CagA-endemic populations showed increased risks (OR_{pooled}, 1.40; 95% CI, 1.32–1.49). Meanwhile, group B (OR 1.38; 95% CI, 1.16–1.64) and AB (OR, 1.52; 95% CI, 1.24–1.85) were associated with higher risk only in non-endemic populations [26].

3.1.5. Family history and gene mutations

In addition, pancreatic cancer also shows familial characteristics. Approximately 5–10% of pancreatic cancer patients have a family history of pancreatic cancer [27]. A meta-analysis showed that people with a family history have a significantly increased risk of pancreatic cancer, with a relative risk (RR) of 1.80 (95% CI, 1.48–2.12) [28]. Gene mutations, including those of germ and somatic cells, and genetic syndrome are also associated with pancreatic cancer. Hereditary pancreatic cancer can present in the context of several hereditary syndromes, including Peutz-Jeghers syndrome (PJS), hereditary pancreatitis (HP), familial atypical multiple mole melanoma (FAMMM), hereditary breast and ovarian cancer syndrome (HBOC), Lynch syndrome (LS), and familial adenomatous polyposis (FAP) [29]. The most frequent genetic alterations are those in breast cancer gene 2 (*BRCA2*), partner and localizer of BRCA2 (*PALB2*), ataxia-telangiectasia-mutated (*ATM*), and *CDKN2A/p16*, and, less frequently, *BRCA1*, adenomatous polyposis coli (*APC*), MutL homolog 1 (*MLH1*), MutS homolog 2 (*MSH2*), *MSH6*, PMS1 homolog 2 (*PMS2*), serine protease 1 (*PRSS1*), and serine/threonine kinase 11 (*STK11*) [29].

Most of these hereditary syndromes associated with pancreatic cancer are inherited autosomal dominant gene mutations. PJS, with a mutation in *STK11* (also known as *LKB1*), is characterized by the presence of hamartomatous polyps on the gastrointestinal tract or mucosae. A meta-analysis showed a cumulative lifetime risk of pancreatic cancer of 36% in patients with PJS [30]. HP is characterized by chronic pancreatitis and recurrent acute pancreatitis, the causative genes of which include *PRSS1*, *SPINK1*, *PRSS2*, and chymotrypsin C (*CTRC*). The

cumulative risk of pancreatic cancer in patients with HP varies between 7.2% [31] and 53.5% [32]. FAMMM, also an autosomal dominant inherited syndrome but with incomplete penetrance, is characterized by multiple atypical nevi progressing to melanoma. Approximately 30%–40% cases of FAMMM syndrome are caused by germline mutations in *p16/CDKN2A* [33], and the cumulative risk of pancreatic cancer is as high as 17% [34]. HBOC is genetically caused by inactivating mutations in *BRCA1*, *BRCA2,* and *PALB2*. The reported mutation rates of these three gene were 0.59%, 1.95%, 0.40%, respectively [35]. *BRCA2* mutation carriers had a 21.7-fold increased risk of pancreatic cancer, compared to a 2- and 6-fold increase in risk of pancreatic cancer in *BRCA1* and *PALB2* mutation carriers, respectively [29,36]. LS, associated mainly with an increased risk of colorectal cancer, develops from germline mutations in mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*), with reported mutation rates of 0.5% in patients with pancreatic cancer [35]. Recent evidence has indicated an association between pancreatic cancer and LS mainly in patients carrying *MLH1* mutations, who showed an 8.6-fold increase in the risk of pancreatic cancer and a cumulative risk of 3.7% of developing pancreatic cancer 70 years of age [5,10]. FAP is associated with germline mutations in *APC*, with a cumulative risk of pancreatic cancer of 1.7% at 80 years of age [37]. Patients with other hereditary syndromes, such as Li-Fraumeni syndrome (LFS), associated with *TP53* mutations; ataxia telangiectasia (AT), associated *ATM* mutations; and cystic fibrosis (CF), associated with *CFTR* mutations, showed <5% lifetime cumulative risk of pancreatic cancer [38].

3.2. Lifestyle and environment

Lifestyle and environment are modifiable risk factors and important foci of disease prevention and health promotion strategies. A healthy lifestyle is an effective method for pancreatic cancer prevention and control [39]. As an important digestive organ, the pancreas participates in the digestion and metabolism of sugars, proteins, and lipids. Thus, diet plays an important role in the pathogenesis of pancreatic cancer.

3.2.1. Red meat and saturated fat

Red meat and saturated fat are proven risk factors for gastrointestinal tumors, such as colorectal cancer [40]. Moreover, excessive intake of red meat and saturated fat may also increase the risk of pancreatic cancer [41]. The "Diet, nutrition, physical activity, and pancreatic cancer" revised in 2018 [42] reported a non-significant association between per 100 g/d increases in red meat consumption and the risk of pancreatic cancer (RR, 1.14; 95% CI, 0.95–1.38). When stratified by sex, the RR of every 100 g/d increase in red meat consumption was significant in men (RR, 1.43; 95% CI, 1.40–1.86) but not significant in women (RR, 1.06; 95% CI, 0.86–1.30). Individuals who consumed processed meat showed a 17% increase in the risk of pancreatic cancer (RR, 1.17; 95% CI, 1.01–1.34), especially in men (RR, 1.21; 95% CI, 1.01–1.45), for every increase in intake of 50 g/day. When the intake of saturated fat increased by 10 g/d, the risk of pancreatic cancer increased by 11% (RR, 1.11; 95% CI, 1.01–1.21) [42].

3.2.2. Sugars, sugar-sweetened foods, and soft drinks

High intake of sugars, sugar-sweetened foods, or soft drinks also increase the risk of pancreatic cancer [43–45]. A pooled analysis of 14 cohort studies showed that the risk of pancreatic cancer was increased by 7% (RR, 1.07; 95% CI, 1.02–1.03) for the consumption of carbonated beverages with a daily sugar content of >175 g/day [45]. However, a recent study showed no significant correlation between sweet-beverage consumption and the risk of pancreatic cancer [46]. The association between coffee consumption and pancreatic cancer also remains controversial. A recent study showed that coffee intake was a protective factor for pancreatic cancer (moderate consumer >1 to <4 cups/day): hazard ratio (HR), 0.79; 95% CI, 0.64–0.99; heavy consumer (>4 cups/day): HR, 0.74; 95% CI, 0.57–0.95 [47]. However, the results of several published meta-analyses are contradictory and have not yielded a consistent conclusion [48–50]. Many experts believe that chronic pancreatitis might be a confounding factor in these studies; therefore, a high-quality meta-analysis is needed to clarify the relationship between coffee consumption and pancreatic cancer [51,52].

3.2.3. Other dietary factors

A recent large prospective cohort in Japan reported that soy products might increase the risk of pancreatic cancer, with an RR of 1.48 (95% CI, 1.15–1.92) [53], a finding that requires further confirmation. Vegetables, fruits, nuts, and whole-grain intake could reduce the risk of pancreatic cancer [54–57]. Meanwhile, the protective effect of vitamin D on pancreatic cancer remains controversial [58,59].

3.2.4. Alcohol

Population studies showed that alcohol consumption increased the risk of pancreatic cancer. The higher the alcohol consumption, the higher the risk of pancreatic cancer [60]. A meta-analysis showed that the risk of pancreatic cancer increased by 15% (RR, 1.15; 95% CI, 1.06–1.25) in heavy drinkers (average alcohol consumption ≥ 24 g/d), while the risk in heavy liquor drinkers was quite high (RR, 1.43; 95% CI, 1.17–1.74) [61]. In addition, alcohol consumption was negatively correlated with survival time after pancreatic cancer diagnosis. The results of cohort studies showed that every 10 g/day increase in alcohol intake increased the risk of death due to pancreatic cancer by 9% (HR, 1.09; 95% CI, 1.00–1.19) [62]. Animal experiments also confirmed that moderate drinking promoted pancreatic cancer progression in mice [63].

3.2.5. Smoking

Smoking is also closely associated with pancreatic cancer occurrence and development. The risks of pancreatic cancer in current (RR, 1.8; 95% CI, 1.7–1.9) and former (RR, 1.2; 95% CI, 1.1–1.2) smokers was significantly higher than that in non-smokers [64]. The higher the amount of smoking, the higher the risk of pancreatic cancer. Smoking more than 30 cigarettes a day results in an increase in RR to 2.2 (95% CI, 1.9–2.4); correspondingly, quitting smoking helped to prevent pancreatic cancer (RR, 0.6; 95% CI, 0.5–0.7) [64]. Smoking can also significantly increase the risk of death due to pancreatic cancer. The results of a large cohort study showed that current smokers had a 37% higher risk of pancreatic cancer than did non-smokers (RR, 1.37; 95% CI, 1.11–1.69), with even higher risks observed in heavy smokers (RR, 1.76; 95% CI, 1.23–2.51) [65].

3.2.6. Physical activity

Appropriate physical activity may have a protective effect against pancreatic cancer. A meta-analysis of 14 studies showed that people who performed at least 150 min of physical activity at a certain intensity every week have 15% reduced risk of pancreatic cancer (RR, 0.85; 95% CI, 0.78–0.93) [66]. Another meta-analysis including 30 different studies reported that physical activity risk estimates appeared to be more pronounced for consistent physical activity over time (RR, 0.86; 95% CI, 0.76–0.97) than for recent-past (RR, 0.95; 95% CI, 0.90–1.01) or distant-past (RR 0.95; 95% CI, 0.79–1.15) physical activity [67].

3.2.7. Overweight and obesity

Overweight and obesity, as a risk factor for multiple metabolic disorders, can also increase the risk of pancreatic cancer, the mechanisms of which may be associated with inflammation, microbiota, hormones, and high-fat diets [68]. A meta-analysis showed that obesity (body mass index [BMI] ≥30 kg/m^2) may increase the risk of pancreatic cancer by 34–36% (male RR, 1.36; 95% CI, 1.07–1.73; female RR, 1.34; 95% CI, 1.22–1.46) [69]; however, the prognosis of patients with pancreatic cancer was not affected [70]. At the same time, overweight and obesity in adolescence may have a long-term effect on the risk of pancreatic cancer. A study of 1.79 million Israeli adolescents followed for more

than 20 years showed that compared to normal weight (5th to <85th percentiles), obesity (≥95th percentile) was associated with an increased risk of pancreatic cancer among both men (HR, 3.67; 95% CI, 2.52–5.34) and women (HR, 4.07; 95% CI, 1.78–9.29), with an estimated population-attributable fraction due to overweight and obesity of 10.9% (95% CI, 6.1–15.6%) [71]. In addition, the results of a randomized controlled trial (RCT) also showed that a low-fat diet intervention reduced the risk of pancreatic cancer in overweight women (BMI ≥ 25 kg/m^2) (HR, 0.71; 95% CI, 0.53–0.96) [72].

3.2.8. Aspirin use

Aspirin is a nonsteroidal anti-inflammatory drug used primarily for the prevention and treatment of cardiovascular diseases; however, its preventive effect in pancreatic cancer also has been reported [73,74]. A study including 761 patients with pancreatic cancer and 794 healthy individuals showed that ever-regular use of aspirin was associated with a lower risk of pancreatic cancer (OR, 0.54; 95% CI, 0.40–0.73) and that the risk decreased by 8% with each cumulative year of use (OR_{trend}, 0.92; 95% CI, 0.87–0.97) [73]. A meta-analysis published in 2020 that included 15 original studies showed that aspirin use reduced the risk of pancreatic cancer, with a pooled RR of 0.78 (95% CI, 0.68–0.89) [74]. However, recent cohort studies reported non-significant results; for example, Natalia Khalaf et al. [75] and Risch et al. [76] both reported no significant association between aspirin use and the risk of pancreatic cancer.

3.2.9. Exposure to trace elements

Trace elements, such as iron and cadmium, are reportedly associated with an increased risk of pancreatic cancer. A prospective study showed an association between heme–iron and increased pancreatic cancer risk in female smokers, with an HR (per 1 mg/day increase) of 1.38 (95% CI, 1.10–1.74), which increased significantly to 2.5-fold (95% CI, 1.22–5.28) after calibration [77]. Urinary cadmium concentrations were also significantly associated with an increased risk of pancreatic cancer (2nd quartile OR, 3.34; 3rd, 5.58; 4th, 7.70; test for trend $p < 0.0001$) [78]. In addition, exposure to trace elements from the environment, such as arsenic (HR, 2.46; 95% CI, 1.09–5.58) [79] and lead (OR, 6.26; 95% CI, 2.71–14.47) may also increase pancreatic cancer risk [80]. Conversely, selenium and nickel concentrations were negatively associated with the risk of pancreatic cancer [80]; however, this association requires further verification.

3.3. Disease status

The occurrence and development of pancreatic cancer are related to chronic pancreatitis, pancreatic cystic lesions, type II diabetes, infection, and other diseases.

3.3.1. Chronic pancreatitis

Chronic pancreatitis is a pathological change in pancreatic tissue and is considered an important risk factor for pancreatic cancer [81]. A recent meta-analysis showed a 16-fold increased lifetime risk of pancreatic cancer in patients with chronic pancreatitis (RR, 16.16; 95% CI, 12.59–20.73) [82]. The main manifestations of chronic pancreatitis are the destruction of pancreatic acinar cells and pathological fibrosis. A series of inflammatory processes, supplemented by somatic cells and genetic mutations, increase the risk of pancreatic cancer. Patients with genetically determined idiopathic chronic pancreatitis have a higher risk of pancreatic cancer, while the risk of alcohol-related chronic pancreatitis may be much lower [83]. However, although there is a strong association between chronic pancreatitis and pancreatic cancer, less than 5% of patients develop pancreatic cancer [84].

3.3.2. Pancreatic cystic lesions

Pancreatic cystic lesions include pancreatic pseudocysts (PPC) and pancreatic cystic neoplasms (PCN), the latter of which are a heterogeneous group of pancreatic cysts, such as intraductal papillary mucinous neoplasms (IPMN), mucinous cystic neoplasms (MCN), serous cystic neoplasms (SCN), and other rare cystic lesions, among which IPMN is the most common. Among these, IPMN and MCN are regarded as precursors to pancreatic cancer [85]. The risk of advanced neoplasia in IPMN is increased predominantly by main duct involvement, with a mean frequency of 62% in resected specimens. Individuals with IPMN also have an increased risk (1–8%) of developing conventional pancreatic ductal adenocarcinoma (PDAC) elsewhere in the pancreas [86]. A 10–39% increased risk of advanced neoplasia has been reported in patients with resected MCN [87–92]. Up to 15% and 10% of patients with resected solid pseudopapillary neoplasms (SPN) and cystic neuroendocrine tumors (cNET) develop invasive cancer, respectively [93,94].

3.3.3. Type II diabetes

Type II diabetes, characterized by insulin resistance, insufficient secretion, and abnormal glucose metabolism, is also closely associated with pancreatic cancer. A meta-analysis showed a 2-fold increase in the risk of pancreatic cancer in patients with type II diabetes (RR, 1.94; 95% CI, 1.66–2.27) and that the relative risk of pancreatic cancer was negatively correlated with the duration of diabetes [95]. Moreover, the risk of pancreatic cancer increased more significantly when newly diagnosed diabetes patients experienced recent weight loss, with an HR as high as 6.75 (95% CI, 4.55–10.00) [3]. A meta-analysis also showed that every 0.56 mmol/L (10 mg/dL) increase in fasting blood glucose level was associated with a 14% increased risk of pancreatic cancer (95% CI, 1.06–1.22) [9]. However, damage to pancreatic tissue affects insulin secretion function, which in turn may cause diabetes, thus demonstrating the complex relationship between pancreatic cancer and diabetes.

3.3.4. Infection

Some microbial infections, such as hepatitis B virus and *Helicobacter pylori*, mainly those of the digestive tract, have been associated with an increased risk of pancreatic cancer [96–98]. The estimated adjusted ORs and 95% CIs for hepatitis B virus and hepatitis C virus were as follows: anti-HCV-positive, 0.9 (95% CI, 0.3–2.8); anti-HBc-positive, 2.5 (95% CI, 1.5–4.2); anti-HBc-positive/anti-HBs-positive, 2.3 (95% CI, 1.2–4.2); and anti-HBc-positive/anti-HBs-negative, 4 (95% CI, 1.4–11.1) [99]. Regarding *H. pylori* infection, compared to seronegative subjects, those positive for *H. pylori* or cytotoxin-associated gene-A-positive strains showed a significantly increased risk of pancreatic cancer (OR, 1.87; 95% CI, 1.05–3.34; OR, 2.01; 95% CI, 1.09–3.70, respectively) [100].

4. Pancreatic cancer risk prediction models

The risk prediction models for pancreatic cancer can help to identify high-risk individuals for further intervention. Table 2 summarizes relevant studies on pancreatic cancer risk models.

The PancPRO [101] was the first risk prediction model for FPC and provided mutation carrier probability and absolute risk for a specified age interval. It included 6134 individuals from 961 families to establish a model based on the Mendelian risk prediction approach. This model has a relatively satisfactory performance, with an area under the curve (AUC) of 0.75. The PancPRO scored families based on pedigree data and assigned a quantitative risk score to any family member depending on the age at diagnosis (or death) of the affected relatives.

Another two studies also developed risk prediction models for the general population [102,103]; however, the performances of these models were not satisfactory, with both AUCs <0.7. In recent years, several teams have established risk prediction models in patients with new-onset diabetes (NOD) [8,103–105], most of which performed well. Notably, the risk prediction model of pancreatic cancer for the NOD patients conducted by Ayush Sharma et al. [8] had the highest AUC (0.87). The model was also convenient to use because it included only three parameters: change in weight, change in blood glucose level, and

Table 2
Summary of studies on pancreatic cancer risk models.

Study Source	Study Population	Sample Size	Study Design	Predictive factors	Prediction approach	AUC
Aileen Baecker et al. [103], 2019	General population and NOD	88938	Case-control study	Race, presence of at least 1 claim for acute pancreatitis, chronic pancreatitis, diabetes mellitus, dyspepsia, gallbladder disease, any abdominal pain, weight loss, jaundice, influenza vaccination, depression, chest pain	Logistic regression model	0.683(general population); 0.735(NOD)
Ayush Sharma et al. [8], 2018	NOD	1561	Retrospective cohort study	Change in weight, change in blood glucose, age at DM onset	Logistic regression model	0.87
Xin Dong et al. [104], 2018	NOD	413	Matched case-control study	BMI, age of DM onset, HBV infection, TBIL, ALB, ALT, BUN, Cr, TC, TG, HDL, LDL, APO-A1, APO-B, WBC count, HB, PLT count, PT	Logistic regression model	0.82
Ben Boursi et al. [105], 2017	NOD	109385	Retrospective cohort study	Age, BMI, change in BMI, smoking, insulin, oral hypoglycemics (not metformin), metformin, PPIs, HbA1c, Hb, cholesterol, creatinine, alkaline phosphatase	Logistic regression model	0.82
Alison P. Klein et al. [102], 2013	General population	7018	Case-control study	Current smoking, heavy alcohol use, obesity, diabetes >3 years, family history of pancreatic cancer, O/ABO genotype, rs3790844 (chr1q32.1), rs401681 (5p15.33), rs9543325 (13q22.1)	Logistic regression model	0.58(only non-genetic factors); 0.57(only genetic factors); 0.61 (both non-genetic and genetic factors)
Wenyi Wang et al. [101], 2007	FPC	6134	Prospective cohort	Pedigree data, age of family members combined with knowledge of the genetic transmission of pancreatic cancer.	Mendelian Risk Prediction Model	0.75

‡:NOD, New-Onset Diabetes; DM, Diabetes Melitums; FPC, Familial Pancreatic Cancer; BMI, Body Mass Index; HBV, Hepatitis B Virus; TBIL, Total Bilirubin; ALB, Albumin; ALT, Alanine Aminotransferase; BUN, Burea Nitrogen; Cr, Creatinine; TC, Total Cholesterol; TG, Total Glycerin Three Greases; HDL, High-Density Lipoprotein ; LDL, Low-Density Lipoprotein; APO-A1, Apolipoprotein-A1; APO-B, Apolipoprotein-B; WBC, White Blood Cell; HB, Hemoglobin; PLT, Platelet; PT, Prothrombin Time; HbA1c, Glycated Hemoglobin.

age at diabetes onset. However, research regarding risk prediction models for pancreatic cancer remain unsatisfactory both in quantity and quality; thus, additional studies are required.

5. Early detection and screening

5.1. Early detection modalities and biomarkers

Due to the lack of typical clinical manifestations and effective diagnostic methods, most patients with pancreatic cancer are in an advanced stage when diagnosed, with a low resection probability and poor treatment effect. Therefore, appropriate early diagnosis and screening strategies are particularly important for the early identification of pancreatic cancer patients to increase surgical opportunities and provide earlier treatment. At present, the methods used for the early diagnosis of pancreatic cancer in the clinical setting mainly include computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS), endoscopic retrograde cholangiopancreatography (ERCP), and magnetic resonance cholangiopancreatography (MRCP) [106,107]; however, these methods are not sensitive enough to identify patients with early pancreatic cancer.

Biomarkers may play an important role in the early detection and screening of individuals at a high risk of pancreatic cancer. Many studies have explored potential biomarkers for the early-stage detection of pancreatic cancer, mainly including proteomic, metabolomic, genetic, or transcriptomic biomarkers [85]. Carbohydrate antigen 19–9 (CA19-9), carcinoembryonic antigen (CEA), and CA12-5 are the most commonly used biomarkers for pancreatic cancer in the clinical setting; however, their accuracy for the early diagnosis of pancreatic cancer is not satisfactory [4,108,109]. The sensitivity and specificity of CA19-9 in the diagnosis of symptomatic patients can reach 79–81%, and 82–90%, respectively [110]. Therefore, many teams are committed to exploring and developing new biomarkers for early diagnosis. Recently, liquid biopsy has shown promise as a research direction for screening biomarkers. Researchers have screened exosomes, miRNAs, proteins, lipid metabolites, and other early diagnostic biomarkers of pancreatic cancer from body fluids including blood, saliva, urine, and pancreatic juice, including lymphatic vessel endothelial hyaluronic acid receptor 1 (LYVE1), regenerating family member 1 beta (REG1B), and trefoil factor 1 (TFF1) protein levels in urine combined with CA19-9 in serum [111], and mucin 1 (MUC1) and MUC2 in pancreatic juice [112], etc [6,113,114]. Besides proteins, several RNA biomarkers also showed potential, including miR-1246 [115], miR-25 combined with CA19-9 [116], miR-1290 combined with CA19-9 [117], and ABHD11-AS1 combined with CA19-9 or CEA or CA125 [118]. In addition, CancerSEEK [119], which uses combined assays for genetic alterations and protein biomarkers, and neutrophil-to-lymphocyte ratio (NLR) [120] also showed relatively satisfactory performances. Detailed information of studies on these potential biomarkers is shown in Table 3.

5.2. Screening

Screening is an important method to detect patients with early pancreatic cancer. However, it is not recommended for the general population, mainly due to the low incidence of pancreatic cancer and the low screening benefit. In addition, the accuracy of available screening methods is not satisfactory and some may also have negative effects on human health, such as pain and anesthesia-related adverse reactions after EUS examination, acute pancreatitis, and even hospitalization after ERCP, as well as anxiety and psychological effects [107]. Regarding populations that are at a high of pancreatic cancer, many teams are still evaluating appropriate screening strategies. The International Federation of Pancreatic Screening (CAPS) published guidelines for pancreatic cancer screening in 2012 [121], recommending screening out for high-risk groups with a lifetime risk of pancreatic cancer of >5% or more than five times the RR. The definition of high-risk population mainly refers to the population with a strong family history or genetic predisposition, including familial pancreatic cancer (FPC), genetic syndrome (LS, PJS, and gene mutations (*p16*, *BRCA2*, *and PALB2*). EUS and MRI are the most accurate and non-invasive tools used for the early screening of pancreatic cancer. In recent years, the United States [122–126], the Netherlands [127], Denmark [128], Germany [129], Sweden [130], Canada [131], and other countries have conducted screening programs for pancreatic cancer in high-risk groups. They mainly enrolled

Table 3
Selected studies on potential biomarkers for early detection of pancreatic cancer, published between 2017 and 2021.

Study Source	Biomarkers panel	Sample size	Marker type	Sample	AUC
Debernardi et al. [111], 2020	LYVE1, REG1B, TFF1, and CA19-9	PC (n = 199); BHD (n = 208); HC (n = 183)	Protein	Urine (LYVE1, REG1B, TFF1); serum (CA19-9)	0.992 (PDAC stage I-II vs. HC); 0.919 (PDAC stage I-II vs. Benign)
Tanaka et al. [112], 2019	MUC1 and MUC2	193 studies, comprising 12297 patients	Protein	Pancreatic juice	0.85 (malignant vs. benign IPMN)
Lee et al. [113], 2018	CEMIP	PC (n = 324); HC (n = 49); PC I-II (n = 88)	Protein	Serum	0.94 (PDAC vs. benign disease and HC)
Kim et al. [114], 2017	THBS-2 and CA19-9	PC III-IV (n = 109); HC (n = 140); PC I (n = 16)	Protein	Plasma	0.97 (PDAC all stages vs. HC); 0.96 (PDAC I/II vs. HC)
Mellby et al. [6], 2018	29-protein biomarker panel	PC II (n = 132); PC III (n = 65); PC IV (n = 230); HC (n = 888)	Protein	Serum	0.96 (PDAC stage I-II vs. HC)
Ishige et al. [115], 2020	MiR-1246	PC (n = 41); HC (n = 30)	miRNA	Serum, urine and saliva	0.87 (serum, PDAC stage 0-IV vs. HC); 0.90 (urine, PDAC stage 0-IV vs. HC); 0.48 (saliva, PDAC stage 0-IV vs. HC)
Yu et al. [116], 2020	MiR-25 and CA19-9	PC (n = 80); HC (n = 90)	miRNA	Plasma	0.985 (PDAC stage I-IV vs. HC)
Tavano et al. [117], 2018	MiR-1290 and CA19-9	PC (n = 167); HC (n = 267)	miRNA	Plasma	0.956 (PDAC stage I-IV vs. HC)
Liu et al. [118], 2019	ABHD11-AS1 and CA19-9 or CEA or CA125	PC (n = 114); CP (n = 97); HC (n = 46)	lncRNA and protein	Plasma	0.982 (ABHD11-AS1+ CA19-9); 0.943 (ABHD11-AS1+ CEA); 0.914 (ABHD11-AS1+ CA125)
Cohen et al. [119], 2018	CancerSEEK	1005 cancer patients	DNA and proteins	Plasma	Sensitivity over 70% when specificity is over 99% (PDAC vs. HC)
Gemenetzis et al. [120], 2017	NLR	IPMN (n = 272)	Other	Serum	0.89 (non-invasive vs. invasive IPMN)

THBS2, Thrombospondin-2; PC, Pancreatic Cancer; HC, Healthy Controls; BHD, Benign Hepatobiliary Disease; CP, Chronic Pancreatitis; NLR, Neutrophil-to-Lymphocyte Ratio; CEMIP, Cell Migration-inducing hyaluronan Binding Protein.

individuals with a family history of pancreatic cancer and/or gene mutations and genetic syndromes. EUS and or MRI were the main examination methods, supplemented by CT, MRCP, and ERCP (details in Table 4).

For example, in 2006, Canto et al. performed a screening study [126] of 78 subjects with a family history of pancreatic cancer and PJS (the high-risk group) and 161 subjects in the control group. CT or ERCP combined with EUS was used for the examination. A total of 17 neoplastic-type lesions (21.8%) were detected in the high-risk group, compared to only one small cystic lesion (0.6%) in the control group. Finally, seven patients underwent surgical resection. Another screening study of 411 high-risk subjects with pancreatic cancer with a family history of pancreatic cancer and *CDKN2A/p16*, *BRCA1/2*, or *PALB2* mutations published by Vasen et al., in 2016 [129] reported a total of 14 cases of pancreatic cancer, 2 cases of suspected pancreatic cancer, and 140 cases of pancreatic cystic lesions detected by MRI/MRCP combined with EUS, with a diagnosed yield of pancreatic cancer of 7.3%. Among these, 12 cases of pancreatic cancer were detected in the *CDKN2A/p16* mutation group, with a resection rate of 75% and a 5-year survival rate of 24%, which was significantly higher than that of sporadic pancreatic cancer and symptomatic pancreatic cancer patients with the *CDKN2A/p16* gene [132]. Precursor lesions were much more frequent in patients with FPC (52.4%) than in *CDKN2A/p16-Leiden* mutation carriers, while the yield of pancreatic cancer was very low (0.9%) [129].

Despite the focus on the high-risk population with FPC and genetic predisposition, some researchers have also proposed screening for populations at a high risk of sporadic pancreatic cancer based on risk enrichment due to new-onset diabetes, weight change, and other risk factors [8,133]. However, related research and evidence are limited. More studies are needed to identify populations that are at a high risk of pancreatic cancer and further support screening for pancreatic cancer.

6. Prognosis

The 5-year survival rate has improved slightly worldwide with the continuous development of treatment technology for pancreatic cancer. According to the SEER database, the overall 5-year relative survival rate during 2011–2017 was 10.8% in the US [1], compared to 14.3% in Australia, 11.4% in Canada, 9.88% in Norway, 9.59% in Denmark, and 7.93% in the United Kingdom in 2014 [134], and 7.2% in China during 2012–2015 [135].

The prognosis of patients with pancreatic cancer is not only related to tumor characteristics such as size, invasion site, molecular typing, TNM stage but is also affected by patient status and treatment. In the US, approximately half of the patients had distant-stage disease, with a 5-year relative survival rate of only 2.9%, while 11% of patients had localized-stage tumors and a 5-year relative survival rate of 39.4% [1]. Bailey et al. [136] defined four pancreatic cancer subtypes, viz., squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine exocrine, while Collisson et al., in 2011 [137] defined three subtypes, viz., classical, quasi-mesenchymal (QM-PDA), and exocrine-like type. Among these, the squamous, QM-PDA, and basal-like subtypes were associated with poor prognosis [136,137]. Several biomarkers predicting patient prognosis have been reported in recent years. For example, the presence of mutated *KRAS* [138], *ATM* and *TP53* [139], and protein arginine methyltransferase 1 (*PRMT1*) [140] was correlated with worse prognosis. Wang et al., in 2019 [141] reported SCAMP1, HCP5, MAL2, and LINC00511 as key long non-coding RNAs (lncRNAs) predicting prognosis. Yokoyama et al., in 2020 [142] also reported that mucins (MUC) played crucial roles in carcinogenesis and tumor invasion in pancreatic cancers and also developed a machine-learning prognosis prediction model. However, high-quality clinical studies with large samples are still needed for further verification in this field.

7. Summary and future perspectives

As a malignant tumor with poor prognosis, improving the overall survival rate of pancreatic cancer is a major challenge. In recent years, the incidence of pancreatic cancer has been rising worldwide, especially in younger individuals. Elucidating the underlying mechanism of the tumorigenesis of pancreatic cancer, effective control of risk factors, and implementation of effective early screening and detection techniques may help to reduce disease burden. The risk factors for pancreatic cancer mainly include those related to individual characteristics, lifestyle behaviors, environment, and disease status. These provide a certain direction for the etiological prevention and screening of pancreatic cancer. However, additional study of the causal relationships is required.

Table 4
Results of selected prospective pancreatic cancer screening studies.

Study Source	Recruitment Period	Country	Eligible for inclusion	No. of Participants screened	Age, Mean (SD) [Range], y	Screening Methodology	Lesions detected	Management
Barnes et al. [122], 2018	2012–2017	USA	FPC; PJS; gene panels including *APC, ATM, BMPR1A, BRCA1, BRCA2, CDKN2A, CDK4, EPCAM, FANCC, MLH1, MSH2, MSH6, NF1, PALB2, PALLD, PMS2, SMAD4, STK11, TP53*	65	56 (14) [NR]	MRI; EUS after positive in MRI	28 patients with lesions by MRI; 9 of 28 were detected by EUS	–
Gangi et al. [123], 2018	2007–2017	USA	FPC; PJS; HP; FAMMM; *BRCA2* mutation	58	60 (NR) [NR]	EUS	15 Hyperechoic foci;8 Fat stranding; 5 Lobularity; 3 Hyperechoic main pancreatic duct; 2 Calcifications; 1 Pancreatic ductal dilation	Positive subjects get further FNA
Harinck et al. [127], 2016	2006–2013	Netherlands	FPC; PJS; mutation of *CDKN2A, BRCA1, BRCA2, p53*	139 at baseline;	51.1 (9.7) [20-73]	EUS and MRI	Baseline:135 at the 2nd round; 2 solid lesions, 9 cysts ≥10 mm; 2nd round:12 solid lesions in 8 individuals were detected	Interval 3 or 6 months; Standard FU at 12 months; 12 lesions in 8 individuals were detected after 12 months (2nd round)
Joergensen et al. [128], 2016	2006–2014	Denmark	FPC; mutation of *PRSS1*	71	51.1 (NR) [26–72]	EUS	2 PDAC	Surgical resection (n = 2)
Vasen et al. [129], 2016	2002–2009	Germany	FPC; mutation of *CDKN2A, p16, BRCA1/2, PALB2*	*CDKN2A*:178 FPC: 214 *BRCA1/2* or *PALB2*:19	CDKN2A:56 (NR) [37–75] FPC::48.2 (NR) [27–81] BRCA1/2 or PALB2:52.6 (NR) [25–70]	EUS and MRI/MRCP	*CDKN2A*: PDAC (n = 13), cystic lesion (n = 26); FPC: suspected PDAC (n = 3), cystic lesion (n = 112); *BRCA1/2* or *PALB2*: PDAC (n = 1), cystic lesion (n = 2)	Surgical resection (n = 31); surveillance
Del Chiaro et al. [130], 2015	2010–2013	Sweden	FPC; PJS; mutation of *BRCA2, BRCA1/p16*	40	49.9 (NR) [23–76]	MRI; EUS after positive in MRI	PDAC (n = 2); branch duct (BD) IPMN(n = 9); mixed-type IPMN (n = 3); main duct IPMN in (n = 2)	Surgical resection (n = 5); surveillance
Al-Sukhni et al. [131], 2012	2003–2011	Canada	FPC; PJS or HP; mutation of *p16, STK11, BRCA2, BRCA1*	262	54 (NR) [22–89]	MRI	3 PDAC; 15 BD IPMNs; 65 simple pancreatic cysts; 22 mildly dilated main pancreatic ducts	Surgery or surveillance
Canto et al. [124], 2012	2006–2009	USA	FPC; PJS; FBOC	216	56.1 (NR) [28–79]	EUS and CT and MRI/MRCP	3 solid lesions; 84 cystic lesions; 5 isolated dilated main pancreatic ductother surveillance	5 Surgically-Treated
Ludwig et al. [125], 2011	2002–2009	USA	FPC; mutation of *BRCA*	109	54 (11.4) [33–86]	MRCP or CT for those unwilling to undergo MRCP	9 significant lesions	6 surgical resection; all under surveillance
Canto et al. [126], 2006	2001–2004	USA	FPC; PJS	High-risk: 78 Controls: 161	High-risk: 52 (NR) [32–77] Controls: 54 (NR) [30–80]	High-risk: EUS and CT; Controls: EUS and/or ERCP	High-risk: neoplastic-type lesions (n = 17); Controls: a small cyst (n = 1)	7 surgical resection; 9 surveillance; 1 FNA

§: FPC, Familial Pancreatic Cancer; FNA, Fine-Needle Aspiration; FAMMM, Familial-Atypical Multiple Mole Melanoma Syndrome; HP, Hereditary Pancreatitits; PJS, Peutz-Jeghers Syndrome; FBOC, Familial Breast Ovarian Cancer Syndrome; PCMS, Pancreatic Melanoma Cancer Syndrome.

Several prediction models for pancreatic cancer have been developed in populations with new-onset diabetes or a family history of pancreatic cancer and the general population; however, these require further validation. Despite recent screening efforts, the quantity and quality of related studies remains unsatisfactory, especially regarding the definitions of high-risk groups and screening modality design. Apart from the populations of individuals with familial genetic risk and those at a high risk of sporadic pancreatic cancer, risk factors such as new-onset diabetes, obesity, and others may provide a new direction for the screening of at-risk populations.

Increased attention and investment in the field of pancreatic cancer epidemiology are needed to provide more high-quality evidence for its prevention and control. High-quality cohorts of high-risk populations and a global sharing data platform of pancreatic cancer may be helpful

in the development of this field.

CRediT authorship contribution statement

Jie Cai: Conceptualization, Writing – original draft. **Hongda Chen:** Conceptualization, Writing – review & editing. **Ming Lu:** Methodology. **Yuhan Zhang:** Visualization. **Bin Lu:** Visualization. **Lei You:** Conceptualization. **Taiping Zhang:** Supervision. **Min Dai:** Writing – review & editing, Supervision. **Yupei Zhao:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

GLOBOCAN	Global Cancer Observatory
ASR	age standardized rate
AAPC	average annual percent change
HDI	human development index
DALYs	disability adjusted of life years
SEER	Surveillance, Epidemiology, and End Results
CI	confidence interval
OR	odds ratio
Cag	acytotoxin-associated gene A
RR	relative risk
HPC	hereditary pancreatic cancer
PJS	Peutz-Jeghers syndrome
HP	hereditary pancreatitis
FAMMM	familial atypical mole and multiple melanoma
HBOC	hereditary breast and ovarian cancer syndrome
LS	Lynch syndrome
FAP	familial adenomatous polyposis
BRCA2	breast cancer gene 2
PALB2	partner and localizer of BRCA2
ATM	ataxia-telangiectasia-mutated
APC	adenomatous polyposis coli
MLH1	MutL homolog 1
MSH2	MutS homolog 2
PMS2	PMS1 homolog 2
PRSS1	serine protease 1
STK11	serine/threonine kinase 11
CTRC	chymotrypsin C
LFS	Li-Fraumeni syndrome
AT	ataxia telangiectasia
CF	Cystic fibrosis
HR	hazard ratio
BMI	body mass index
RCT	randomized controlled trial
PPC	pancreatic pseudocyst
PCN	pancreatic cystic neoplasms
IPMN	intraductal papillary mucinous neoplasms
MCN	mucinous cystic neoplasms
SCN	serous cystic neoplasms
PDAC	pancreatic ductal adenocarcinoma
SPN	solid pseudopapillary neoplasms
cNET	cystic neuroendocrine tumors
AUC	area under curve
NOD	new-onset diabetes
CT	computed tomography
MRI	magnetic resonance imaging
EUS	endoscopic ultrasonography
ERCP	endoscopic retrograde cholangiopancreatography
MRCP	magnetic resonance cholangiopancreatography
CA19-9	carbohydrate antigen 19-9
CEA	carcinoembryonic antigen
CA-125	carbohydrate antigen-125
LYVE1	lymphatic vessel endothelial hyaluronic acid receptor 1
REG1B	regenerating family member 1 beta
TFF1	trefoil factor 1
MUC1	mucin 1
CEMIP	cell migration-inducing hyaluronan binding protein
NLR	Neutrophil-to lymphocyte ratio
FPC	familial pancreatic cancer
QM-PDA	Quasi-mesenchymal
PRMT1	protein arginine methyltransferase 1
lncRNAs	long non-coding RNAs
MUC	Mucins
DM	diabetes mellitus

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