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Risk Factors of Pancreatic Cancer: A Literature Review

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Abstract

Objective: To identify and compare current modifiable and non-modifiable risk factors for pancreatic cancer (PaCa) that may have potential application in PaCa risk stratification, prevention, and early detection.

Material: All articles in this literature review were identified through systematic searches of PubMed, Medline, and Embase databases. All articles were published in the English language, between January 2000 to December 2021 and with an abstract. In this review study, we judge the evidence level of different PaCa risk factors through the criteria of grading evidence for cancer prevention.

Results: The modifiable risk factors identified included cigarette smoking, heavy alcohol consumption, increased Body Mass Index (BMI) and abdominal obesity, chronic pancreatitis, diabetes, hepatitis B virus (HBV) infection, periodontal disease, cholecystectomy and chemicals and asbestos exposure. The non-modifiable risk factors included age, gender, ethnicity, blood type, family history, inherited syndromes, germline mutation, and single nucleotide polymorphisms (SNPs). However, there are still some ambiguous risk factors for which the current evidence is inconclusive such as low physical activity, increased consumption of red/processed meat and dairy products, vitamin D insufficiency, and some medical-related conditions including gut microbiota such as Helicobacter Pylori infection, long-term usage of Proton-pump inhibitors (PPI), and Systemic Lupus Erythematosus (SLE) history.

Conclusions: This literature review summarizes the modifiable and non-modifiable risk factors of PaCa with strong evidence, which could be used to further establish PaCa predictive model as an application of PaCa risk stratification, raise public awareness and educate the public as a prevention program. Further studies are needed to investigate other potential risk factors.

Introduction

Globally, pancreatic cancer (PaCa) is the 12th most common cancer [1] and the 7th leading cause [1,2] of cancer death. Unlike the improving survival rates for common cancers such as breast and prostate cancer [3], less progress in terms of survival rate has been made [4] for PaCa. The 1-year survival rate of PaCa is approximately 28%, and the 5-year survival rate is about 6% [5]. This is partly because most PaCa patients are diagnosed at locally advanced or metastatic stages [6], which are usually unresectable.

According to 2020 Global Cancer Statistics [2], the PaCa incidence and mortality in high/very high human development index(HDI) countries are 4-5 fold higher than in low/medium HDI countries among males and females (Incidence: 7.2 versus 1.6 per 100,000 male, 5.0 versus 1.0 per 100,000 female; Mortality: 6.7 versus 1.5 per 100,000 male, 4.6 versus 1.0 per 100,000 female). The elevated incidence in high HDI countries could be due to high rates of obesity and type 2 diabetes, the common problem of smoking and drinking, and entering the aging society in these countries.

Due to the high incidence with a poor survival rate for PaCa patients, it is important to address newly discovered and established risk factors for potential prevention. Many risk factors have been documented; nevertheless, many studies have still shown inconsistent

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results. Moreover, genetic predisposition based single nucleotide polymorphisms (SNPs) are rarely discussed with other established risk factors. In this review, we aimed to explore potential risk factors of PaCa, which may provide a reference for clinicians and researchers for application in pancreatic cancer-related risk stratification, prevention, and early detection studies.

Methodology

A literature search was performed utilizing major search queries on PubMed, Medline, and Embase databases. The 'medical subject heading' (MeSH) terms combining Boolean logic operators 'AND' and 'OR' were applied to obtain relevant articles. The period of our search was from January 2000 through to December 2021. All articles were subsequently filtered as being those only published in the English language and with an abstract. Further to using the above search databases, the research articles were also manually selected from the reference lists of relevant review articles. In this review study, we have applied the judging the evidence criteria from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) [7] for grading evidence for cancer prevention to provide the evidence level of PaCa risk factors. The evidence grade levels are categorized into convincing (strong evidence), probable (strong evidence), limited (suggestive), limited (no conclusion), and substantial effect on risk unlikely.

Table 1. Modifiable, non-modifiable, and other potential risk factors of pancreatic cancer

Modifiable risk factors		**Non-Modifiable risk factors**		**Other potential risk factors**
Risk factors	**Characteristics**	**Risk factors**	**Characteristics**	**Risk factors**
Cigarette smoking **1. Current smokers** **2. Former smokers** **3. Exposure to environmental tobacco smoke(ETS)**	1. HR=2.69[8];OR=2.2[9] 2. OR=1.2[9] 3. HR=1.54[10]	**Age**	47% of new PaCa cases were diagnosed on ≥ 75 years old [48,50]	**Low physical activity**
Heavy alcohol consumption **1. High(≥24 g/day)** **2. Heavy(>39 g/day)** **3. Heavy (>45 g/day)**	1. RR=1.15[14] 2. HR=1.62[8] 3. RR=1.43[14]	**Gender**	The age-standardized incident rate of PaCa was 5.5 per 100,000 men and 4.0 per 100,000 women[1].	**Increased consumption of red/ processed meat and dairy products**
Increased body mass index(BMI)and abdominal obesity **1. Overweight** **2. Obesity** **3. Waist-to-hip ratio**	1. OR=1.67[16] 2. OR=2.58[16] 3. RR=1.19[18](per 0.1-unit increase)	**Ethnicity**	African Americans have a higher age-adjusted incidence (14.6/100,000) compared to Caucasians[52].	**Vitamin D insufficiency**
Chronic pancreatitis **1. ≦ 2 years** **2. >2 years**	1. OR=13.56[21] 2. OR=2.71[21]	**Blood Group** **1. AO** **2. AA** **3. AB** **4. BO** **5. BB**	1. OR=1.33[57] 2. OR=1.61[57] 3. OR=1.47[57] 4. OR=1.45[57] 5. OR=2.42[57]	**Helicobacter Pylori infection**
Diabetes mellitus (DM) **1. Prediabetic, per 0.56 mmol/L increase** **2. New-onset DM** **3. Long-term DM** **(1) ≥ 2 years** **(2) ≥ 5 years** **(3) ≥ 8 years**	1. RR=1.14[25] 2. RR=2.2[26] 3. OR=1.79[29] (1) RR=1.64[30] (2) RR= 1.58[30] (3) RR=1.50[30]	**Family history** **1. One first-degree relative** **2. Two first-degree relatives** **3. Three first-degree relatives**	1. SIR=4.6[59] 2. SIR=6.4[59] 3. SIR=32[59]	**Long-term usage of Proton-pump inhibitor(PPI)**
Hepatitis B virus infection **1. HBsAg or HBV DNA positive**	1. OR=1.50[37]; RR=1.39[38]	**Inherited syndromes** **1. Peutz-Jeghers syndrome** **2. Hereditary pancreatitis** **3. Familial malignant melanoma** **4. Lynch syndrome** **5. Hereditary breast-ovarian cancer**	1. HR=76.2[60]; RR=132[61,62] 2. SIR=67[65]; SIR=87[66] 3. 13-22 fold[68] increased 4. 7-10 fold[71,72] 5. *BRCA*1 carriers: 2-5 fold[72-74]; *BRCA*2 carriers: 2-6 fold[72,73,75,76]	**Systemic Lupus Erythematosus(SLE)**
Periodontal disease	RR=1.74 [41]	**Germline Mutations** **1. *CDKN2A*** **2. *TP53*** **3. *ATM*** **4. *BRCA2*** **5. *MSH2*** **6. *MSH6*** **7. *PALB2*** **8. *BRCA1*** **9. *MLH1***	1. OR=35.97[78] ;OR=12.33[77] 2. OR=7.15[78]; OR=6.70[77] 3. OR=8.96[78] ; OR=5.71[77] 4. OR=9.07[78] ; OR=6.20[77] 5. OR=7.10[78] 6. OR=7.79[78] 7. OR=14.82[78] 8. OR=2.95[78]; OR=2.58[77] 9. OR=6.66[77]	**Antidiabetic medications usage**
Chemicals and heavy metals exposure **1. Pesticides** **2. Asbestos** **3. Benzene** **4. Chlorinated hydrocarbons**	1. OR=1.21[44] 2. OR=1.54[44] 3. OR=1.70[44] 4. OR=1.63[44]	**Single nucleotide polymorphisms(SNPs)** **1. Higher PRS vs Lower PRS**	1. OR=2.70[91];OR=2.25[90]	
Cholecystectomy	RR=1.23[46]			

Literature review

All the risk factors were categorized into modifiable and non-modifiable risk factors as supported by current evidence and other potential risk factors. Modifiable factors were identified as those that occurred before PaCa diagnosis and could be prevented or modified based on convincing or probable evidence. Non-modifiable factors were identified as those that occur before the PaCa diagnosis but that could not be prevented or modified based on convincing or probable evidence. Other potential risk factors were defined as those still under suggestive or inconclusive/limited evidence.

Modifiable risk factors

Cigarette smoking

Many studies [8-10] have demonstrated a tenable relationship between tobacco smoking and PaCa risk. Smoking causes direct damage to pancreatic tissue. Hazardous substances from tobacco degradation products have been involved in stimulating the signal of angiogenesis, tumor cell growth, and tumor metastasis [11,12].

A prospective cohort study [8] revealed that current smokers significantly increased risk for PaCa with a hazard ratio (HR)=2.69 (95%CI: 1.97-3.68) compared to never smokers. A pooled analysis [9] has reported the dose-response relationship between PaCa and cigarette smoking. Their results showed that current smokers (cigarette smoking for ≥35 cigarettes per day) increased PaCa risk with an odds ratio (OR)=3.4, 95%CI: 2.4-4.9, p<0.0001. In addition, elevated PaCa risk in current smokers (OR=2.43, 95%CI: 1.91-3.09) has also been found with a longer duration of cigarette smoking for up to 40 years. Both current smokers and former smokers had increased PaCa risks (OR=2.2, 95%CI: 1.7-2.8; OR=1.2, 95%CI: 1.0-1.3) compared with never-smokers. Moreover, a prospective cohort study [10] explored the association between exposure to environmental tobacco smoke (ETS) and the PaCa risk. The result implied an increasing trend for PaCa risk with HR=1.54 (95%CI: 1.00-2.39) among never smokers who were exposed to ETS at home and/or work compared to never-smokers not exposed to ETS. In the same study, the researchers also found that former smokers who had quit smoking at least five years did not increase the risk of PaCa.

In sum, an elevated PaCa risk is associated with current cigarette smokers, former smokers, and exposure to ETS, and the grading evidence is convincing (strong evidence). However, quitting smoking for at least five years may not elevate the PaCa risk.

Heavy alcohol consumption

Alcohol and its metabolism products have been generally accepted to play a role in altering metabolic pathways and stimulating inflammation [13], which have taken part in pancreatic carcinogenesis.

The prospective cohort study [8] suggested that heavy alcohol consumption (>39 g/day) increased PaCa risk by 62% (HR=1.62, 95%CI: 1.04-2.54, p=0.035) compared to mild to moderate (≤39 g/day) alcohol consumption. Furthermore, the study also found that people who quit alcohol drinking for more than ten years compared to those who were never alcohol drinkers were not at increased PaCa risk (HR=0.95, 95%CI: 0.54-1.68). A meta-analysis [14] reported the dose-response relationship between alcohol intake and the PaCa risk. Compared with never alcohol consumption people, light (0-12 g/day) to moderate (≥12-24 g/day) alcohol consumption people barely had effects on PaCa risk, whereas high (≥24 g/day) alcohol consumption people were correlated with increased risks of PaCa (Relative risk (RR)=1.15, 95%CI: 1.06-1.25, P=0.001) and heavy (>45 g/day) consumption of liquor people had the highest risk with RR=1.43 (95%CI: 1.17-1.74).

In conclusion, an increased PaCa risk is related to high and heavy alcohol consumption, and the grading evidence is convincing (strong evidence). Nevertheless, quitting alcohol drinking for at least ten years may help prevent PaCa.

Increased BMI and abdominal obesity

Obesity is involved in metabolic syndrome and also plays a vital role [15] in the process of carcinogenic and inflammation by releasing the potential pro-carcinogenic mediators.

A case-control study [16] concluded that early adulthood (14-39 ages) overweight (BMI: 25-29.9 kg/m^2) had a higher risk for PaCa with an odds ratio of 1.67 (95%CI: 1.20-2.34) compared to normal-weight individuals. Furthermore, early adulthood (20-49 ages) obesity (BMI: ≥30 kg/m^2) had the highest risk for PaCa with an odds ratio of 2.58 (95%CI: 1.70-3.90). A meta-analysis study [17] showed that individuals with increasing BMI per 5 kg/m^2 had a higher PaCa risk (RR=1.12; 95%CI: 1.06-1.17).

Table 2. The grading evidence level of risk factors from the criteria for grading evidence for cancer prevention

Convincing (strong evidence)	Probable (strong evidence)	Limited (no conclusion)
Cigarette smoking (current smokers, former smokers, and exposure to environmental tobacco smoke (ETS))	Hepatitis B virus infection	Low physical activity
Heavy alcohol consumption	Periodontal disease	Increased consumption of red/processed meat and dairy products
Increased Body Mass Index (BMI), waist circumference and waist-to-hip ratio (WHR)	Cholecystectomy	Vitamin D insufficiency
Chronic pancreatitis	Chemicals exposure (Chlorinated hydrocarbons, polycyclic aromatic hydrocarbons (PAHs), organochlorine insecticides, and asbestos)	H.pylori infection
Diabetes Mellitus (DM) (prediabetic, new-onset DM, and long-term DM)	Aging	Long-term use of Proton-pump inhibitors (PPI)
	Male gender	Systemic Lupus Erythematosus (SLE)
	Ethnicity (African American/Black population)	Antidiabetic medications usage
	Non-O blood group	
	Germline mutation (kindred PaCa history, Peutz-Jeghers syndrome (PJS), Hereditary pancreatitis (HP), Familial malignant melanoma (FMM) syndrome, Lynch syndrome, and Hereditary breast-ovarian cancer (HBOC) syndrome, and germline mutations in *CDKN2A, TP53, ATM, BRCA2, MSH2, MSH6, PALB2, and BRCA1*)	
	Higher polygenic risk score (PRS)	

In addition, in recent years, abdominal obesity (measured by waist circumference or waist-to-hip ratio (WHR)) has also emerged as another risk factor for PaCa. A systematic review [18] suggested that per 10-cm increase in an individual's waist circumference, a higher PaCa risk with RR of 1.11 (95%CI: 1.05-1.18) and per 0.1-unit increase in individual's WHR, a higher risk of PaCa (RR=1.19, 95%CI: 1.09-1.31). Despite the difficulty in distinguishing whether the association between abdominal obesity and PaCa risk was independent, a pooled analysis [19] concluded that abdominal obesity is an independent risk factor of PaCa after controlling for BMI.

In sum, overweight, obesity, and abdominal obesity are all independent PaCa risk factors, and the evidence grading is convincing (strong evidence).

Chronic pancreatitis

Either acute or chronic pancreatitis is an inflammatory disease. The persistent inflammatory process is thought to stimulate cytokines [20], which participate in the progression of tumor carcinogenesis.

A pooled analysis [21] concluded that pancreatitis patients had a considerably higher risk (OR=13.56, 95%CI: 8.72-21.90) of PaCa within two years after diagnosis of chronic pancreatitis and still had an OR with 2.71 (95%CI: 1.96-3.74) beyond two years after diagnosis of chronic pancreatitis. A systemic review [22] showed that pooled effect estimates (EEs) of PaCa risk was 16.16 (95% CI: 12.59-20.73) in chronic pancreatitis patients diagnosed with PaCa at intervals of 2 years between diagnoses. The EEs of PaCa risk were also reduced in chronic pancreatitis patients diagnosed with PaCa at the interval of 5 years and 9 years between diagnoses (EE=7.90, 95%CI: 4.26-14.66; EE=3.53, 95%CI: 1.69-7.38, respectively).

In sum, medical history of chronic pancreatitis is associated with elevated PaCa risk, and the evidence grading is convincing (strong evidence). In addition, the shorter intervals between pancreatitis diagnosis and PaCa diagnosis had been observed with a stronger relationship. Therefore, recent pancreatitis may potentially indicate a mask of potential symptoms of PaCa.

Diabetes mellitus (DM)

The association between Diabetes mellitus (DM) and PaCa risk is multi-aspects. DM is thought to be both cause and consequence of PaCa.

Prediabetic status is related to the higher risk of PaCa [23]. A retrospective cohort study [24] revealed that the 5-year cumulative incidence rates of PaCa increased continuously with elevating fasting glucose levels (P<0.0001) from prediabetic level I (100 to 109 mg/dL), level II (110 to 125 mg/dL) to diabetes group (>126 mg/dL). A systematic review [25] reported a solid linear dose-response relationship between the fasting blood glucose concentration and the PaCa risk. In this study, per 0.56 mmol/L (10 mg/dL) increase in fasting blood glucose, there was a higher pooled RR with 1.14 (95%CI: 1.06 -1.2, P<0.001) within the prediabetes and diabetes individuals.

Several studies have revealed the incremental risk of PaCa in new-onset non-insulin-dependent diabetes papulation. A retrospective cohort study [26] suggested that patients with new-onset DM had higher PaCa risk (RR=2.2, 95%CI: 1.84-2.56) than in the non-DM population. Moreover, new-onset diabetes patients had the highest PaCa risk in the first two years after a diabetes diagnosis. Nevertheless, new-onset DM may also be a symptom of PaCa [27]. Like type 3c diabetes (T3cDM), which has been defined as diabetes secondary to pancreatic exocrine disease such as PaCa [27,28].

In addition, long-term diabetes is also correlated to elevating PaCa risk. A pooled analysis [29] discovered that PaCa risk was higher among patients with DM of 2 to 8 years (OR=1.79, 95%CI: 1.25-2.55). The other meta-analysis concluded that the pooled RRs of PaCa for DM patients with duration ≥ 2 years, ≥ 5 years, and ≥ 10 years were 1.64 (95%CI: 1.52-1.78), 1.58 (95% CI: 1.42-1.75), and 1.50 (95% CI: 1.28-1.75), respectively [30].

Whether taking antidiabetic medications is linked to the PaCa risk has been debatable for a long time. Some studies supported that taking insulin and sulfonylureas (SU) may increase PaCa risk [31,32]. In contrast, metformin has been thought to have a protective effect on PaCa risk [33,34]. A systematic review [35] showed no relationship between using metformin (OR=0.76, 95% CI: 0.57-1.03), insulin (OR=1.59, 95%CI: 0.85-2.96) and thiazolidinediones (TZDs) (OR=1.02, 95% CI: 0.81-1.30) and risk of developing PaCa. On the other hand, patients using sulfonylureas (SUs) had a higher OR with 1.70 (95 %CI: 1.27-2.28). In contrast, a meta-analysis study [33] did not find a significant relationship between using SU and PaCa risk. Interpretation of these results needs to consider reverse causality and protopathic bias [36].

In summary, prediabetic status, new-onset DM, and long-term DM are all related to higher PaCa risk; the evidence grading is convincing (strong evidence). As for the role of anti-diabetic medication usage, the grading of evidence is limited (no conclusion). Therefore, it still needs more prospective observational studies to evaluate the impact on PaCa risk.

Hepatitis B virus infection

Several studies have advocated that hepatitis B virus (HBV) infection individuals increased PaCa risk, although the mechanisms have not been confirmed. A meta-analysis [37] demonstrated that HBsAg-positive individuals are correlated to PaCa (OR=1.50, 95%CI: 1.21-1.87). Another meta-analysis study [38] concluded that Hepatitis B surface antigen (HBsAg) or HBV DNA positive individuals had higher PaCa risk with RR=1.39 (95%CI: 1.19-1.63). The current study revealed that HBsAg positivity or HBV DNA positive are associated with PaCa risk, and evidence grading is probable (strong evidence).

Periodontal disease

Periodontal disease (PD) is usually caused by the oral microbiome alteration, which has been liked to oral cavity and head and neck cancer [39]. Studies have also advocated that periodontal disease may involve in the development of PaCa [40]. A meta-analysis [41] suggested that patients with periodontal disease had a higher PaCa risk with RR of 1.74 (95%CI: 1.41-2.15) after controlling for other risk factors. Although the mechanisms are unclear, some published studies [40] bolstered that it may be related to the alterations of the oral microbiome. The evidence grading between periodontal disease and PaCa risk is probable (strong evidence).

Chemicals and asbestos

Evidence of chemicals and asbestos mechanism and risk of PaCa is still ambiguous. Workplace exposure such as specific chemicals and asbestos have been proposed to increase PaCa risk [42]. A review article [43] concluded that chlorinated hydrocarbons (meta-risk ratio (MRR)=1.4, 95%CI: 1.0-1.8) and polycyclic aromatic hydrocarbons (PAHs) (MRR=1.5, 95%CI: 0.9-2.5) had the most robust relationship between occupational exposures and PaCa risk. In addition, the early meta-analysis [42] also suggested that organochlorine insecticides (MRR=1.5, 95%CI: 0.6-3.7) and asbestos (MRR=1.1, 95%CI: 0.9-1.5) were associated with PaCa risk.

On the other hand, a non-occupational environment may also pose a similar problem of exposure to chemicals and asbestos. A case-control study [44] discovered that regular exposure 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) were related to higher PaCa risk.

In sum, there are many ethical concerns to conducting the population-based chemicals and asbestos exposure cohort studies in recent years. According to previous evidence, either occupational or non-occupational exposure to chlorinated hydrocarbons, PAH (benzene), organochlorine insecticides (pesticides), and asbestos indeed increased PaCa risk, and the grading of evidence is probable (strong evidence).

Cholecystectomy

Cholecystectomy is a common surgery that is a standard treatment for recurrent or intolerant pain in patients with gallstones or cholecystitis. Chronic inflammation and increased pressure in the biliary tract and nearby organs may be the sequences after cholecystectomy [45]. Therefore, some studies have investigated whether the medical history of cholecystectomy increased the risk for PaCa.

A meta-analysis [46] revealed that patients with cholecystectomy history had a higher summary relative risk (SRR) with 1.23 (95%CI: 1.12-1.35). The other meta-analysis [47] also discovered an elevated RR with 1.31 (95%CI: 1.19-1.43) in people with cholecystectomy history among the different populations, compared with patients without cholecystectomy history. According to the published studies, cholecystectomy may play a role in developing PaCa, and evidence grading is probable (strong evidence). However, further studies are needed to validate the underly reasons for the elevated PaCa risk.

Non-Modifiable risk factors

Age

Like many cancers, the incident rate of pancreatic cancer has also been observed to rise with age. According to Cancer Research UK (CRUK) statistics [4,48], nearly 47% of new PaCa cases were diagnosed on ≥ 75 years old. The most frequent incident rate of PaCa is around 85-89 years old females (98.1 per 100,000) and ≥ 90 years old males (125.2 per 100,000). In addition, the PaCa incident rates emerge to increase approximately on 35-39 years old individuals and dominantly elevate on around 60-65 years old individuals. According to USA National Institutes of Health (NIH) statistics [49], the median age at diagnosis of PaCa is around 70 years old, and the highest incident rate is in the group aged 65-74. The evidence grading between aging and PaCa risk is probable (strong evidence).

Gender

PaCa incident rate is more common in men than in women. According to CRUK statistics [48,50], males account for 52% of PaCa patients, and females account for 48% of PaCa patients in the UK. In the USA [49], the age-adjusted incidence rate of PaCa was 15 per 100,000 men and 11.8 per 100,000 women. According to global cancer statistics [1] in 2018, the age-standardized incident rate of PaCa was 5.5 per 100,000 men and 4.0 per 100,000 women. The grading of evidence for higher PaCa incidence in men is probable (strong evidence), which may be attributed to some lifestyle-related risk factors. Other environmental and occupational risk factors, as well as unveiled hormone and genetic factors, may also play a role in the difference in PaCa incidence between men and women.

Ethnicity

Previously statistics have shown the incident difference between different races. A statistic from Georgia study [51] showed that the age-adjusted incident rate was 14.6 per 100,000 in Africa America, which is higher than10.8 per 100,000 in Caucasians. In addition, according to Surveillance, Epidemiology, and End Results (SEER) statistics data [52], black males and females had higher incidence rate ratios (IRR) (IRR=1.24 and 1.37, respectively) compared with the white non-Hispanic population. In comparison to the white non-Hispanic population, Asian/pacific islander residents males and females (IRR=0.78 and 0.85, respectively), white Hispanic males (IRR=0.88), and American Indian/Alaskan Native males (IRR=0.79) had lower IRR.

Generally, African American/Black population may have a higher PaCa risk than other populations; the evidence grading is probable (strong evidence). However, the reasons underlying the disparities of PaCa incidence within different races still need further investigations (modifiable risk factors and other genetic-related risk factors) [53-55].

Blood Group

The previous studies [56,57] have revealed that ABO blood types were associated with PaCa risk. Two independent prospective cohort studies [56] discovered that blood type A, AB, or B individuals had higher adjusted hazard ratios (HR=1.32, 95%CI: 1.02-1.72; HR= 1.51, 95%CI:1.02-2.23; HR=1.72, 95%CI: 1.25-2.38, respectively) for PaCa risk, compared to blood type O individuals. A nest case-control study [57] concluded that genotype AO, AA, AB BO and BB individuals had higher PaCa risk (OR=1.33, 95%CI: 1.13-1.58; OR=1.61, 95%CI: 1.22-2.18; OR=1.47, 95%CI: 1.07-2.02; OR=1.45, 95%CI: 1.14-1.85; OR=2.42, 95%CI: 1.28-4.57, respectively) compared with the genotype OO individuals.

In general, an increased risk of PaCa was noted in blood type A, AB, or B individuals, and the evidence grading is probable (strong evidence). Furthermore, the addition of each non-O allele genotype was also addressed to be associated with higher PaCa risk compared to each O allele genotype.

Genetic predisposition

i. Germline Mutations

Approximately 10% of PaCa patients are associated with a familial component [58].

A prospective study [59] reported that individuals with only one PaCa among first-degree relatives were at increased risk by 4.6 fold (95%CI: 0.5-16.4). Moreover those with two and three PaCa histories in their first-degree relatives, PaCa risk was raised to 6.4 fold (95%CI: 1.8-16.4) and 32 fold (95%CI: 10.2-74.7), respectively. In addition, PaCa are also related to some inherited syndromes.

Peutz-Jeghers syndrome (PJS), is an autosomal dominant inherited disorder related to germline mutations in the *STK11* tumor suppressor gene [60]. A cohort study [60] demonstrated that PJS patients had higher PaCa risk (HR=76.2, 95%CI: 36.3-160.0) compared to the general population. Moreover, a meta-analysis [61] also concluded that PJS patients had a higher risk (RR= 132.0, 95%CI=44.0-261.0). A similar conclusion was reported by other systematic review [62], which also found PJS patients had a higher PaCa risk (RR=132).

Hereditary pancreatitis (HP), also known as familial pancreatitis, is associated with germline mutations including *PRSS1, CFTR, SPINK1, and CTRC* [63,64]. HP patients had a higher PaCa risk than the general population. The calculated standardized incidence ratio (SIR) of PaCa

in HP patients was 67 (95%CI: 50-82) in the the European Registry of Hereditary Pancreatitis and Pancreatic Cancer (EUROPAC) [65] cohort trial and was 87 (95%CI=42-113) in the French [66] cohort trial.

Familial malignant melanoma (FMM) syndrome, also known as melanoma-pancreatic cancer syndrome or familial atypical multiple mole melanoma (FAMMM) syndrome, is commonly related to *CDKN2A* gene mutation [67]. FMM syndrome patients were associated with 13-22 fold [68] increased PaCa risk.

Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is usually caused by germline mutations in DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*) [69,70]. Previous studies reported Lynch syndrome patients had approximately 7-10 fold [71,72] increased PaCa risk compared to the general population.

Hereditary breast-ovarian cancer (HBOC) syndrome is well-known to be associated with a germline mutation in either *BRCA1 or BRCA2*. Numerous studies demonstrated that *BRCA1* carriers had about 2-5 fold [72-74] increased PaCa risk, and *BRCA2* carriers had around 2-6 fold [72,73,75,76] higher PaCa risk, compared to the general population.

A case-control studies [77] explored the association between PaCa risk and inherited germline mutations. They discovered that 6 germline mutations including *CDKN2A* (OR=12.33, 95%CI: 5.43-25.61), *TP53* (OR=6.70, 95%CI: 2.52-14.95), *MLH1* (OR=6.66; 95%CI: 1.94-17.53), *BRCA2* (OR=6.20, 95%CI: 4.62-8.17), *ATM* (OR=5.71, 95%CI: 4.38-7.33) and *BRCA1* (OR=2.58, 95%CI: 1.54-4.05) had significant higher PaCa risk. Another case control study [78] found that germline mutations in *CDKN2A* (OR=35.97, 95%CI: 14.68-85.39), *TP53* (OR=7.15, 95%CI: 2.78-18.13), *ATM* (OR=8.96, 95%CI: 6.12-12.98), *BRCA2* (OR=9.07, 95%CI: 6.33-12.98), *MSH2* (OR=7.10, 95%CI: 1.04-37.16), *MSH6* (OR=7.79, 95%CI: 3.85-15.16), *PALB2* (OR=14.82, 95%CI: 8.12-26.22), *BRCA1* (OR=2.95, 95%CI: 1.49-5.60) were correlated to higher PaCa risk.

In sum, PaCa is more prevalent in individuals with kindred PaCa history, several familiar syndromes, including PJS, HP, FMM syndrome, Lynch syndrome, and HBOC syndrome, and germline mutations in *CDKN2A*, *TP53*, *MLH1, ATM*, *BRCA2,MSH2*, *MSH6*, *PALB2*, and *BRCA1*. The grading of evidence is probable (strong evidence).

ii. Single nucleotide polymorphisms (SNPs)

SNPs are one of the common types of individuals' genetic variants [79], which have been used to predict the risk of developing coronary heart disease [80], diabetes [81], and cancers [82-84]. Various susceptible loci for pancreatic cancer have been identified from the genome-wide association study (GWAS) [85-102]. Currently, there are 142 variants and risk alleles associated with pancreatic cancer listed in GWAS Catalogue [103]. Of these, most PaCa risk loci are found in European [85-96], and 35 PaCa risk loci were discovered in Japan [97,98], Jew [99] and China [100-102] populations.

The previous studies [104,105] have combined pancreatic cancer-associated SNPs obtained from GWAS into a polygenic risk score (PRS) to develop the risk prediction model. A case-control study [105] revealed that the highest quintile of the weighted PRS was related to increased PaCa risk (OR=2.70, 95%CI: 1.99-3.68) compared to the lowest quintile of the weighted PRS. The other case-control study [104] showed that the top quintile of the PRS was associated with higher PaCa risk (OR=2.25, 95%CI: 1.73-2.92), compared with the middle quintile of the PRS. In conclusion, a higher PRS can be used to identify the higher risk of PaCa-associated SNPs.

Other potential risk factors

Low physical activity

High physical activity has been proposed as a cancer preventive measure. However, whether low physical activity is associated with PaCa risk is still ambiguous. A case-control study [106] found no trajectories of physical activity significantly increased PaCa risk. In addition, a meta-analysis [107] showed no strong relationship between low physical activity and PaCa risk. Nevertheless, individuals with high physical activity indeed have a lower PaCa risk [107] (Cohort studies: RR=0.93, 95%CI: 0.88-0.98; Case-control studies: 0.78, 95%CI: 0.66–0.94), compared with individuals with low physical activity. The other meta-analysis [108] also revealed a similar inverse relationship between high physical activity and PaCa risk (RR =0.85, 95%CI: 0.78-0.93). Therefore, high physical activity is a robust protective factor against PaCa. However, there is limited grading evidence (no conclusion) of the relationship between low physical activity and PaCa risk.

Increased consumption of red/processed meat and dairy products

The association between increased consumption of red meat/processed meat and dairy products and PaCa risk is still controversial. A meta-analysis [109] revealed no significant association between red meat consumption and PaCa risk (RR=1.13; 95%CI=0.93-1.39). In a stratified analysis, men with higher red meat consumption had a significantly higher PaCa risk (RR=1.29; 95%CI: 1.08-1.53); however, a positive association was not found in women. Regardless of processed meat, this study also found an increased 50g of processed meat consumption per day had a higher RR of 1.19 (95%CI: 1.04-1.36).

Results from a prospective cohort [110] study indicated that increasing dairy product consumption was related to higher PaCa risk (HR=1.19, 95%CI: 1.01-1.42). Nevertheless, a pooled analysis concluded that there was no significant association between dietary consumption (HR=0.96, 95%CI: 0.77-1.19) and PaCa risk [111]. The relationship between increased consumption of red/processed meat and dairy products is still inconclusive, and evidence grading is limited (no conclusion).

Vitamin D insufficiency

Previously laboratory studies [112,113] supported that vitamin D and its analogues took roles in inhibiting pancreatic cancer cell growth. However, the evidence of vitamin D insufficiency and PaCa risk is still inconclusive.

A pooled analysis [114] showed that both individuals with relative insufficiency of 25(OH)D (50 to <75 nmol/L) and sufficient 25(OH)D levels (≥75 nmol/L) had lower PaCa risk (OR=0.75, 95%CI: 0.58-0.98; OR=0.71, 95%CI: 0.52-0.97, respectively), compared with individuals with insufficient 25(OH)D levels (<50 nmol/L). In contrast, the other pooled analysis [115] suggested a 13% higher PaCa risk (OR=1.13, 95%CI: 1.07-1.19; P< .001) in increasing dietary vitamin D intake by 100 IU/day in individuals. On the other hand, a meta-analysis [116] concluded that there was no significant association between vitamin D intake and PaCa risk (RR=1.11, 95%CI: 0.67-1.86). There is limited grading evidence (no conclusion) of the relationship between vitamin D insufficiency and PaCa risk.

Helicobacter Pylori (H. pylori) infection

In 1994, The World Health Organization (WHO) defined H. pylori as a group I carcinogen for gastric cancer. Several studies have then evaluated the correlation between H. pylori infection and PaCa risk.

A meta-analysis suggested that H. pylori infection individuals had a higher summary OR with 1.47 (95%CI: 1.22-1.77) for PaCa risk [117]. Besides, the relationship is more obvious in Europe and East Asia than in North America. On the other hand, the other meta-analysis [118] demonstrated that H.pylori infection (OR=1.09, 95% CI: 0.81-1.47) was not associated with PaCa risk. Nevertheless, the subgroup analysis found that cytotoxin-associated gene A (CagA)-negative strains of H.pylori infection might pose a higher risk of PaCa (OR= 1.3, 95% CI: 1.05-1.62). Similar findings were also supported by the other two meta-analysis [119,120], CagA-negative H.pylori had higher PaCa risk (OR=1.23, 95 % CI: 0.83-1.82; OR=1.47, 95%CI: 1.11-1.96, respectively).

In sum, the inconsistent conclusion of the association between overall H.pylori infection and PaCa risk, the grading of evidence is limited (no conclusion). However, CagA-negative strains of H.pylori infection are associated with an increased PaCa risk. Therefore, the association between H.pylori infection and PaCa must be validated in future studies.

Long-term usage of Proton-pump inhibitors (PPIs)

PPIs long-term usage has been advocated for an increased risk for carcinogenic such as gastric cancer in two meta-analysis studies [121,122]. For pancreatic cancer, a Swedish cohort study [123] revealed an increased risk (SIR=2.22, 95%CI: 2.12-2.32) for PaCa in long-term PPI users. However, this study did not consider some confounding factors such as smoking, obesity, and diabetes, which are commonly related to the usage of PPIs. The other Danish case-control study [124] showed no significant association between PPI users and PaCa risk. Therefore, whether PPI usage is linked to higher PaCa risk is still controversial, and evidence grading is limited (no conclusion).

Systemic Lupus Erythematosus (SLE)

Systemic Lupus Erythematosus (SLE) patients may increase the incidence of some cancers [125] such as non-Hodgkin's lymphoma and kidney cancer. However, evidence of SLE patients in relation to PaCa risk is still inconsistent. A recent meta-analysis [126] concluded that SLE patients had an increased risk for developing PaCa (HR=1.42, 95%CI: 1.32-1.53). Nevertheless, the other systematic review [127] suggested no significant association between SLE patients and PaCa incidence. It is limited grading evidence (no conclusion) of the relationship between SLE and PaCa risk.

Conclusion

This article describes pancreatic cancer risk factors. Established risk factors can be categorized into modifiable and non-modifiable risk factors. Modifiable risk factors include cigarette smoking, heavy alcohol consumption, increased BMI and abdominal obesity, chronic pancreatitis, DM, hepatitis B virus infection, periodontal disease, cholecystectomy, chemicals, and asbestos exposure. In addition, these modifiable risk factors all possess strong grading levels. The association between low physical activity and PaCa risk still needs further study to elucidate the full “dose-response” relationships, albeit high physical activity robustly mitigates the risk of PaCa. Regarding the association between microbiota and pancreatic cancer, Helicobacter pylori remains controversial. Further studies are required to establish the relationship of potential microbiota-related risk factors.

Globally, with the continued rising incidence and the poor survival rate of PaCa, there is an imperative need to prevent pancreatic cancer. The evidence presented in this report can be used to define a more complex risk prediction model. Once validated, the model can be used by healthcare professionals, clinicians, and policymakers to increase awareness of PaCa and identification of populations at risk. For the latter, appropriate strategies for risk reduction are important to reduce PaCa in the future.

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