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The exposome and pancreatic cancer, lifestyle and environmental risk factors for PDAC

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Abstract

Pancreatic cancer (PC), particularly pancreatic ductal adenocarcinoma (PDAC), is a significant global health issue with high mortality rates. PDAC, though only 3% of cancer diagnoses, causes 7% of cancer deaths due to its severity and asymptomatic early stages. Risk factors include lifestyle choices, environmental exposures, and genetic predispositions. Conditions like new-onset type 2 diabetes and chronic pancreatitis also contribute significantly. Modifiable risk factors include smoking, alcohol consumption, non-alcoholic fatty pancreatic disease (NAFPD), and obesity. Smoking and heavy alcohol consumption increase PC risk, while NAFPD and obesity, particularly central adiposity, contribute through chronic inflammation and insulin resistance. Refined sugar and sugar-sweetened beverages (SSBs) are also linked to increased PC risk, especially among younger individuals. Hormonal treatments and medications like statins, aspirin, and metformin have mixed results on PC risk, with some showing protective effects. The gut microbiome influences PC through the gut-pancreas axis, with disruptions leading to inflammation and carcinogenesis. Exposure to toxic substances, including heavy metals and chemicals, is associated with increased PC risk. Glycome changes, such as abnormal glycosylation patterns, are significant in PDAC development and offer potential for early diagnosis. Interactions between environmental and genetic factors are crucial in PDAC susceptibility. Genome-wide association studies (GWAS) have identified several single nucleotide polymorphisms (SNPs) linked to PDAC, but gene-environment interactions remain largely unexplored. Future research should focus on polygenic risk scores (PRS) and large-scale studies to better understand these interactions and their impact on PDAC risk.

Keywords: Exposome, Pancreatic Cancer, Risk factors

1. Introduction

Pancreatic cancer (PC), particularly pancreatic ductal adenocarcinoma (PDAC), has emerged as a significant global health challenge, marked by rising incidence and persistently high mortality rates. Over recent decades, the global burden of PC has escalated, with PDAC now recognized as one of the most lethal malignancies due to its severity and asymptomatic presentation in the early stages [1]. Although it accounts for only 3% of all cancer diagnoses, PDAC is responsible for 7% of cancer-related deaths, underscoring its disproportionate lethality. Furthermore, according to the World Health Organization (WHO), the incidence and mortality rates are nearly identical (8.0 per 100,000 vs. 7.3 per 100,000, respectively), emphasizing its serious incidence-to-mortality ratio [2].

PC is a complex disease, whose development has been linked to several lifestyle (*e.g.*, smoking and obesity), environmental, and genetic risk factors[3, 4]. Additionally, conditions such as new-onset type 2 diabetes mellitus (NOD) and chronic pancreatitis have been shown to significantly contribute to its development [3]. The identification of additional risk factors, whether external or endogenous, will be pivotal in enhancing our comprehension of the disease and, in the long term, in the establishment of preventive and screening programs designed to identify individuals at high risk.

This review presents the current state of knowledge regarding the exposome and its relationship with PC risk (**Figure 1**). It begins by outlining the lifestyle and environmental risk factors that contribute to this disease and then examines the interaction between these factors and an individual's genetic background.

2. Non-modifiable risk factors

Non-modifiable risk factors are defined as those which cannot be altered during a lifetime. These include age, sex, the presence of diabetes, allergies, blood group, genetic background, metabolic syndrome, cholelithiasis and dyslipidemia. These are described in detail below, while **Table 1** summarizes the characteristics, mechanism and epidemiological findings.

2.1. Age, sex, blood group and allergies

PDAC incidence is increasing over time across all ethnicities and both sexes in the U.S. and Europe [4, 5]. Although a recent study has shown a sharper rise in incidence among women under 55 years, with the highest incidence observed in those aged 15 to 34 years [4], larger European studies

consistently report a higher incidence of PDAC in males compared to females across all age groups. In addition, worldwide, the incidence rate for PDAC is slightly higher for males (5.5/100,000 new cases every year in males, compared to 4.0/100,000 new cases every year in females)[2]. These gender differences are partially attributed to modifiable factors such as tobacco smoking and alcohol consumption, which are higher in males than in females [6, 7].

Additionally, older individuals have a higher incidence of PDAC, highlighting the need for early prevention and control programs. Interestingly, a recent study has reported that age at diagnosis is a significant and negative prognostic factor for PDAC [8]. Nonetheless, a retrospective study also showed that outcomes of patients aged 70 years or older undergoing surgical resection are not inferior to those of younger patients[9].

Non-O blood groups have been associated with increased risk of PDAC. Individuals with A, B, or AB blood groups have a higher risk compared to those with blood group O[10]. Although the biological mechanisms underlying these differences are not fully understood, studies have suggested that changes in blood-type antigens might interfere with cell signaling, adhesion, and the immune system's ability to kill preneoplastic cells[10]. It has been demonstrated that ABO antigens can influence disease outcomes by modulating tumor onset and behavior [11]. However, additional studies are needed, as no direct evidence has proven that blood-type antigens interfere with host immunity.

Allergies and asthma represent other medical conditions that may impact PDAC risk[12-15]. Large studies and meta-analyses consistently indicated that allergies reduce PDAC risk[15, 16]. Although the protective effect of allergies is consistent, it is stronger for specific allergies and less for others. For instance, atopic allergies have a clear protective effect on PDAC onset [12, 17]. In contrast the association with asthma remains controversial, with studies reporting a potentially protective effect[13] or no effect on disease risk [16]. These findings suggest a role for immune surveillance, leading to increased detection and elimination of pre-tumoral cells. This hypothesis is supported by evidence indicating that the inverse association with PDAC risk is stronger for more aggressive allergies of longer duration[13].

The primary epidemiological data can be found in **Table1**.

2.2. Diabetes

Type 2 diabetes mellitus (T2D) has been demonstrated to be both a risk factor for pancreatic cancer and a consequence of PC. Indeed, both long-standing and newly diagnosed cases have been associated with an elevated risk of developing the disease. It has been reported that up to 85% of PDAC patients present with either NOD or impaired glucose tolerance at the time of diagnosis [11], underscoring the crucial role of T2D in PDAC.

Approximately 15% of cases of T2D in patients with PDAC are long-standing (with a duration of T2D of more than three years[18]. This condition is associated with a range from 1.5 to 2.4-fold increased risk of PDAC[3]. Two studies have reported that individuals diagnosed with diabetes for 15-20 years may not have an increased risk of PC[19, 20]. In contrast, other studies suggest that individuals with diabetes for more than 20 years continue to have a higher risk of PC[21].

Patients with NOD represents a high-risk group for PC, as NOD is associated with a significantly higher risk of developing PC, with estimates ranging from 3.81 to 5.2-fold[22, 23]. Furthermore, individuals with NOD who are over 50 years of age have a 6–8-fold higher risk of PDAC in comparison to the general population[18, 22, 24]. This condition presents specific risk factors including gallstones, pancreatitis, weight loss, and high or rapidly increasing glycemia or insulin use[25]. Despite the undeniable link between NOD and PDAC, the exact underlying biological mechanisms remain unidentified. Nonetheless, efforts to establish early and close follow-up programs, particularly for individuals with early-onset T2DM, along with improved glucose control, may be effective strategies for enhancing the detection and treatment outcomes of pancreatic cancer [26].

2.3. Genetic background

Genetic variants associated with PDAC risk are usually classified in two groups: rare high penetrance mutations and common low penetrance mutations, the majority of which are single nucleotide polymorphisms (SNPs). Increased risk of PDAC is associated with the presence of inherited pathogenic mutations in 12 genes (*BRCA2, PALB2, BRCA1, ATM, STK11, CDKN2A, PRSS1, MLH1, MSH2, MSH6, PMS2, APC*)[3]. In addition, several common germline variants increase the risk of developing PDAC. The two most widely used approaches to identify new susceptibility loci are: candidate gene studies and genome wide association studies (GWAS). In the past decade, a substantial number of studies have been conducted on polymorphisms of candidate genes/pathways[27-34]. The first GWAS on PDAC was conducted in 2009 by Amundadottir in the context of Pancreatic Cancer Cohort Consortium (PanScan) in European population[35]. To expand the knowledge on PDAC susceptibility, in the following years additional GWAS and meta-analysis

were also conducted in samples of European descent by PanScan and the Pancreatic Cancer Case Control Consortium (PanC4) and the PANcreatic Disease ReseArch (PANDoRA) consortium [36-40]. Also, three GWASs and a meta-analysis were performed in Chinese[41]and Japanese[42-44] populations.

The main epidemiological information has been reported in **Table 1**.

2.4. Metabolic syndrome, Cholelithiasis and dyslipidemia

Metabolic syndrome

Metabolic syndrome (MetS) and PC are both complex conditions that share intriguing connections, though the direct link between them is still being explored. Metabolic syndrome is characterized by high blood pressure, insulin resistance, obesity, excess body fat around the waist, and abnormal lipid levels. These conditions can contribute to chronic inflammation and oxidative stress, promoting tumor growth and progression, and potentially increasing the risk of PC. Several epidemiological studies have observed an increased risk of PC in individuals with MetS [45-48]. A recent population-based cohort study reported a 31% increased risk of PC in participants with MetS compared to those without MetS [49]. Furthermore, a recent meta-analysis of nine studies found a strong correlation between PC and MetS (relative risk (RR) of 1.34, 95% CI: 1.23–1.46), with females having an increased risk compared to males (male: RR 1.26, 95% confidence interval (CI):1.03–1.54; female: RR 1.64, 95% CI: 1.41–1.90)[50]. Another population-based cohort study reported that recovering from MetS was associated with a reduced risk of PC, suggesting that restoration of metabolic heath may help avoid PC development [51]. Therefore, managing metabolic syndrome through lifestyle improvements such as a healthy diet, regular physical activity, and maintaining a healthy weight may help reduce the risk of PC.

Cholelithiasis

People with gallstones have a slightly increased risk of developing PC compared to those without gallstones [52]. However, the exact mechanism underlying the association between cholelithiasis and PC is not fully understood. It likely involves chronic inflammation caused by gallstones [53], biliary obstructive diseases [54], or high cholecystokinin levels in cholecystectomized patients [55].

Despite this, most PCs occur in individuals without a history of gallstones, indicating the need for additional research to fully understand the underlying mechanisms.

Dyslipidemia

The relationship between abnormal lipid levels and PC is complex, involving the interplay between several mechanisms such as metabolic syndrome, insulin resistance, chronic inflammation, lipid metabolism, and the secretion of various adipokines and cytokines that can influence cancer growth[56]. Animal studies have shown that manipulating lipid levels can influence PC development [57]. Several epidemiological studies have found an association between dyslipidemia and a higher risk of PC [58-61]. In a large sample of 1 million subjects, dyslipidemia was associated with 40% higher PC risk[62]. Recent meta-analyses evaluated the effect of dietary cholesterol and serum total cholesterol on the risk of PC, concluding that dietary cholesterol may be associated with an increased risk of PC in worldwide populations, except for Europeans [63]. This evidence highlights the need to develop effective regional strategies for screening, early detection, and lifestyle intervention in individuals with dyslipidemia to reduce the risk of PC.

The key epidemiological information regarding metabolic syndrome, cholelithiasis and dyslipidemia has been reported in **Table 1**.

3. Modifiable risk factors

Modifiable risk factors are those that can be changed through lifestyle modifications. This category includes smoking habit, alcohol consumption, non-alcoholic fatty pancreatic disease, body mass index (BMI), diet, intake of refined sugar and sodas, physical activity, exposure to local environment, sleep quality, stress, hormonal treatments, prescription medications, infectious agents and the influence of the microbiota, exposure to toxic substances and heavy metals, and glycome changes. These are described in detail below, while **Table 2, Table 3** and **Table 4** summarize the characteristics**,** mechanism and epidemiological findings.

3.1. Smoking habit

Tobacco smoking has been attributed to approximately 11-32% of PC cases worldwide [64]A recent meta-analysis including 45,527 PC cases from 38 case-control and 40 cohort studies reported a RR of 1.80 (95% CI:1.70-1.90) for current vs. never-smokers and 1.20 (95% CI:1.10-1.20) for former vs. never-smokers [65]. This meta-analysis included different genetic ancestries and observed significant heterogeneity in the results. A PanC4 analysis on 6,507 cases and 12,890 controls from 12 case-control studies reported a 20% (95% CI:1.00-1.30) and more than two-fold increased risk (95% CI:1.70-2.80) for former and current smokers, respectively, compared to never-smokers [66]. Similarly, a pooled analysis from eight nested case-control studies from the PanScan (1,481 cases and 1,539 controls) reported an odds ratio (OR) of 1.77 (95% CI:1.38-2.26) when comparing current with never-smokers [67]. These risk estimates are similar to those of other smoking-related cancers like esophageal, colorectal, kidney, and urinary bladder cancers [68].

The risk increases with the duration and intensity of exposure, with long-time smokers having a higher risk than short-time smokers. Zou and colleagues conducted a meta-analysis of 42 studies comprising different genetic ancestry populations and found a non-linear relationship between the number of cigarettes per day and risk[69]. Park and colleagues suggested a linear trend in a nationwide study on over 7 million Korean subjects, including 22,543 PC cases[70]. A recent Australian study based on seven prospective cohorts including 365,084 individuals reported an increased risk only if smoking more than 10 cigarettes/day [71]. However, the study included only 604 subjects with incident PC.

Lynch and colleagues reported a relationship between the intensity and duration of exposure, suggesting that, given the same total smoking exposure (total pack years), longer smoking duration at lower intensity was associated with higher PC risk compared to shorter smoking duration at

higher intensity [67]. It has been estimated that PC risk decreases after at least ten years since smoking cessation, reaching a risk comparable to non-smokers [66, 67, 72].

The relationship between smoking and early-onset (EO) PDAC (and very EO-PDAC) has been investigated to a lesser extent [73]. A retrospective study comprising 1,789 individuals, including 156 EO cases, suggested an association between smoking and EOPDAC risk, reporting a lower age at diagnosis in smokers compared to non-smokers [74]. However, a pooled analysis of 5,232 individuals (1,954 EO cases) from eight case-control studies in the PanC4 consortium[75], a retrospective analysis of 36,145 individuals (526 EO cases) from the Japanese Cancer Registry[76], and other smaller studies [77, 78] did not find evidence for such an age difference between smokers and non-smokers in EO PDAC. Moreover, smoking was recognized as a key risk factor for EO PDAC risk in some studies[75, 79], but not in others[78]. Possible explanations may reside in the slightly different thresholds used for defining EO PDAC (ranging from 40 to 60 years of age) and the limited number of cases analyzed. Data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study (465,910 participants and 524 PC cases) suggested that passive smoking may also increase PC risk (Hazards ratio (HR) 1.54, 95% CI:1.00-2.39)[80]. However, other studies did not find a statistically significant association [81-84], leaving the question without a definitive answer.

The key epidemiological data can be found in **Table 2**.

3.2. Alcohol consumption

Alcohol consumption is a well-known risk factor for pancreatitis[85], which in turn is a recognized risk factor for PC [3]. However, the direct relationship between alcohol consumption and PC risk has been long debated. A meta-analysis of 21 case-control and 11 cohort studies from the U.S., Europe, and Asia estimated a pooled RR of 1.22 (95% CI:1.12–1.34) for heavy drinkers (≥ 3 drinks/day) compared to non-drinkers or occasional drinkers [86]. Data from the PanC4 consortium, which included 5,585 cases and 11,827 controls, suggested an OR of 1.6 (95% CI:1.20–2.20) for heavy drinkers (≥ 9 drinks/day) compared with non-drinkers or occasional drinkers (≤ 1 drink/day) [87]. A prospective study of over 500,000 Chinese individuals, including 688 incident cases, reported an increased risk in weekly drinkers compared to non-drinkers (HR 1.33, 95% CI:1.11–1.58), with heavy drinkers having a higher risk (HR 1.60, 95% CI:1.12–2.30) [88]. Wang and colleagues performed a pooled analysis of data from 4,211,129 individuals of mixed ethnicities, including 11,846 incident cases, and suggested a higher risk in heavy drinkers compared to non-drinkers (RR 1.15, 95% CI:1.06–1.25)[6]. Another pooled analysis of cohort studies comprising 862,664 individuals,

including 2,187 incident cases, reported an association between high alcohol intake (≥ 30 grams/day) and PC risk compared to non-drinkers (RR 1.22, 95% CI:1.03-1.45)[89].

No strong association has been identified between low-to-moderate alcohol drinking and PC risk[6, 87, 88, 90]. Notably, a PanScan study on 1,530 cases and 1,530 controls did not report a statistically significant association between alcohol consumption and PC risk at all [91]. The relationship between alcohol consumption and PC risk may be partly confounded by tobacco smoking[90, 92, 93]. Mendelian randomization studies, which minimize confounding, did not support a causal effect of alcohol drinking on PC risk [94, 95]. In summary, growing evidence supports the association between heavy alcohol drinking and an increased risk of PC, but there is no strong evidence linking low-to-moderate alcohol consumption with PC risk.

The key epidemiological data can be found in **Table 2**.

3.3. Non-alcoholic fatty pancreatic disease

Non-alcoholic fatty pancreatic disease (NAFPD) is characterized by fat accumulation in pancreatic tissue and is considered an emerging clinical entity [96] that might affect PDAC risk [51, 97-99]. Although NAFPD is not explicitly classified as a modifiable risk factor for PDAC, it is associated with several conditions that are known risk factors for PDAC, such as age, obesity, metabolic syndrome, and T2D[100]. However, its effect on PDAC risk occurs in both obese and non-obese subjects, suggesting it might act independently of obesity [51]. Several pathways may link NAFPD to PDAC, including insulin resistance, cellular damage due to the direct interaction of fatty tissue with pancreatic cells, chronic oxidative stress, and local secretion of inflammatory markers. Additionally, pathological activation of lipid-glucose metabolism and imbalance of hormone homeostasis may play a role [96]. Furthermore, NAFPD is associated with inflammatory cell infiltration in the pancreatic tissue and the release of pro-inflammatory cytokines and adipocytokines, which may increase the risk of PDAC in patients with T2D[98, 100], a condition often comorbid with NAFPD.

Although the exact mechanisms involved require further investigation, evidence suggests that pro-inflammatory cytokines and adipocytokines released in NAFPD could drive sustained inflammation, fibrosis, and insulin resistance, thereby increasing the risk of PDAC. The key epidemiological data can be found in **Table 2**.

3.4. Body mass index

Obesity, defined as BMI > 30 kg/m², is a pathological condition that impacts a wide range of physiological processes and is one of the main risk factors for PDAC development and mortality [101]. A large study pooling data from 846,340 individuals in 14 cohorts, mostly comprising Caucasian individuals, reported a 47% increased risk of PDAC in obese subjects [102]. Similarly, a large meta-analysis of 19 studies estimated RRs of 1.36 for men and 1.34 for women [103]. A national-level Israeli study on over 1.7 million individuals reported that overweight and obesity conditions in adolescence are associated with higher PC risk in adulthood, with HRs of 1.68 (95% CI:1.27-2.21) and 3.89 (95% CI:2.76-5.50), respectively [104].

A study based on PanScan data, including 2,170 cases and 2,209 controls, reported a statistically significant trend between decreasing median age at diagnosis and higher BMI, categorized into normal, overweight, and obese conditions [105]. The study by Pang and colleagues, consisting of a case-control analysis of 841 cases and 754 controls, additionally reported a stronger association between young adulthood (30-39 years) obesity and PDAC risk, with an OR of 3.03 (95% CI:1.88-4.90). This result was replicated in a population of 512,891 Chinese individuals from the China Kadoorie Biobank, comprising 595 incident cases: HR of 1.36 (95% CI:1.16-1.61) for young adulthood BMI and HR of 1.11 (95% CI: 0.97-1.27) for later adulthood BMI [106].

It has been proposed that measures of obesity like waist-to-hip ratio (WHR), waist circumference (WC), and hip circumference (HC) may indicate distinct functional consequences of location-dependent fat accumulation on cancer risk [107-110]. A pooled analysis of 846,340 individuals reported a BMI-independent association between WHR and PC risk (HR 1.35, 95% CI:1.03-1.78), but not with WC and HC [102]. An EPIC cohort study, which included 324 incident PC cases and 438,081 controls, reported statistically significant associations between WC (RR 1.13, 95% CI:1.01-1.26) and WHR (RR of 1.24, 95% CI: 1.04-1.48) and PC risk[111]. A U.S. study on more than 200,000 individuals, including 290 incident PDAC cases with data on different central adiposity measures, reported a BMI-independent association between WC and PC risk in females (HR 2.53, 95% CI:1.13-5.65), but not in males[112].

Despite the high heterogeneity, probably due to the limited number of cases included in the studies, these results clearly indicate an association between overweight and obesity and PC risk. Supporting observational associations, Mendelian randomization analyses provided further evidence for a causal role of BMI on PC risk, indicating causal ORs of 1.34 (95% CI:1.09-1.65) [113] and 1.96 (95% CI:1.10-3.48) [114]].

The key epidemiological data can be found in **Table 2**.

3.5 Diet

The effect of diet on PC risk is still a matter of debate, with conflicting evidence emerging from different studies. An umbrella review analyzing 23 meta-analyses that included data from case-control studies, cohort studies, or a combination of the two types, suggested an association between adherence to healthy/prudent or plant-based dietary patterns and reduced risk of PC [115]. Healthy/prudent patterns were associated with reduced risk of PC in two of the four meta-analyses evaluating this aspect. One meta-analysis, conducted on seven case-control and six cohort studies (3,197 cases and 655,223 controls), estimated a OR of 0.84 (95% CI:0.75–0.95) [115].

Another meta-analysis on three case-control studies (4,932 cases and 23,107 controls) reported a random RR of 0.67 (95% CI: 0.50–0.91) [116]. The association between adherence to a plant-based dietary pattern and reduced risk of PC was supported by two different meta-analyses. The first one, conducted on three case-control studies (1,586 cases and 46,634 controls), found a random OR of 0.66 (95% CI: 0.55–0.78) [117]. While the other was conducted on two cohort studies (3,150 cases and 587,502 controls) and reported a RR of 0.72 (95% CI:0.60–0.86) [117].

Diets characterized by a high "dietary inflammatory index" (DII) or adherence to unhealthy or Western dietary patterns were associated with an increased risk of PC. A meta-analysis conducted on four case-control and two cohort studies (5,889 cases and 644,717 controls), compared the highest vs. lowest DII categories and estimated a RR of 1.45 (95% CI:1.11-1.90)[118]. A smaller meta-analysis included two case-control studies and evaluated the effect of a 1-unit increment of the DII (1,143 cases and 2,408 controls), reporting a RR of 1.16 (95% CI:1.05-1.28)[119].

An umbrella review including only meta-analyses of prospective cohort studies or randomized control trials was also conducted by Qin and colleagues, which did not find an association between DII and PC in a total of 3,152 cases and 450,000 controls [120]. An association between unhealthy diet and increased PC risk was described in case-control studies (1,443 cases and 8,575 controls; RR of 1.38, 95% CI: 1.11–1.70)[115, 116], but not in cohort studies (622 cases and 82,135 controls) [115, 116].

A meta-analysis including one case-control and one cohort study found no association between adherence to the "Mediterranean diet" and reduced PC risk, but a limited number of case subjects was evaluated (735 cases and 79,355 controls) [121], while data from four cohort studies showed a weak association [120, 122]. Aside from dietary patterns, the association between various foods

and specific food components and PC has been evaluated. Two meta-analyses based on three (2,332 cases and 372,692 controls) and four (2,386 cases and 604,266 controls) cohort samples reported that nut intake was negatively associated with PC with a RR of 0.83 (95% CI: 0.72-0.97) and 0.89 (95% CI: 0.81-0.98), respectively[123, 124]. Contrasting results were obtained when analyzing the intake of total fruit, citrus fruit, total vegetables, and cruciferous vegetables[115, 120]. An association between red meat consumption and increased PC risk was reported in two meta-analyses, with a RR of 1.27 (95% CI: 1.10-1.47) in 3,511 cases and 1,036,747 controls [125] and a male-specific RR of 1.21 (95% CI:1.07-1.37) in 6,819 cases and 2,504,431 controls [126]. Another meta-analysis conducted on 11 cohort studies (8,427 cases and 2,307,787 controls) found a similar trend (RR 1.16, 95% CI: 0.96–1.39)[127]. Lastly, suggestive evidence exists of an association between fructose intake and increased PC risk in a meta-analysis of six cohort studies (2,430 cases and 1,031,605 controls; RR=1.22, 95% CI: 1.09–1.55)[128].

In conclusion, adherence to plant-based or, in general, healthy/prudent dietary patterns results in a slightly reduced risk of developing PC, while a diet characterized by a high inflammatory index conferred an increased risk. Red meat consumption seems to significantly affect PC risk, although not all studies reported a statistically significant association. Overall, the link between dietary habits and PC risk seems weak and not easily reproducible across different studies, suggesting that while diet may slightly affect the risk, other predominant etiological factors are probably determinants in the onset of PC. The key epidemiological data can be found in **Table 2**.

3.6. Refined sugar and sodas

In addition to well-established modifiable risk factors, studies have linked sugar-sweetened beverages (SSBs) and refined sugar consumption to increased risks of developing PDAC[129]. A large Chinese study showed that individuals who drank two or more soft drinks per week had an estimated 87% higher risk of developing PDAC compared to never-drinkers [130]. Similarly, a large cohort study found that consuming two or more servings of SSBs per day was associated with a 50% increase in PDAC mortality[129]. The effect of SSBs on PDAC risk showed a dose-response relationship, with risk increasing progressively based on SSB intake [129, 131].

Considering that people under 40 years have a higher prevalence and frequency of SSB consumption compared to older subjects, it was suggested that consuming two or more SSBs daily tripled the risk of PDAC in this group. Additionally, people who added sugar to drinks such as coffee or milk (at least

five times a day) had a 70% greater risk of PDAC compared to those who did not[130]. Similar results were found for those adding sugar to their diets in other ways [130], suggesting that sugar intake, insulin production, insulin resistance, and inflammation could be key factors in determining disease onset [132].

However, some studies have failed to find an association between SSB consumption and PDAC risk[133], indicating that additional research is needed. Moreover, it remains unclear whether the observed effect of sugar or sodas is influenced by other PDAC risk factors, such as tobacco smoking and alcohol consumption, age, sex, and diabetes, which could potentially explain the observed tumor-promoting effects and the contradictory findings among studies. Some studies have reported a sex-specific effect of soft drinks on PDAC risk that may depend on factors like BMI or physical activity [134]. On the other hand, it is important to rule out the idea of an effect of specific food intake and diet regimens rather than SSBs on PDAC risk and whether this affects disease progression [133, 135-137], indicating that additional research is needed. The key epidemiological data can be found in **Table 2**.

3.7. Other lifestyle habits (i.e. stress, work-related factors, income, exercise, leisure social activities)

Physical activity

In addition to the well-established risk factors for PDAC, numerous other potential exposures have been investigated. These include physical activity, local environmental factors, stress, work factors, sleep quality and duration, and occupational status.

Among these, physical activity is the most extensively studied variable in relation to PDAC susceptibility [114, 138-143]. These studies examine various aspects of physical activity, including intensity and type. Regarding intensity, only the study by Brenner and colleagues found a statistically significant association between light and moderate physical activity and a reduced risk of developing PDAC (OR 0.43, 95% CI: 0.25–0.75, and OR 0.57, 95% CI: 0.37–0.88, respectively) [133]. In contrast, other studies did not identify a significant correlation between different intensities of physical activity and PDAC susceptibility [138, 141, 143].

Another extensively investigated aspect is the categorization of physical activity into occupational and leisure domains. The findings across various studies are highly inconsistent. Notably, Brenner and colleagues demonstrated a statistically significant correlation between leisure physical activity

and a reduced risk of PDAC (OR 0.65, 95% CI: 0.52–0.87)[139]. In contrast, research by Bao and colleagues and O'Rorke and colleagues identified a significant association between occupational physical activity and decreased susceptibility to PDAC (OR 0.75, 95% CI: 0.58-0.96 and OR 0.75, 95% CI: 0.59-0.96, respectively)[138, 141].

In addition to examining the role of physical activity, the study conducted by Peduzzi and colleagues also considered variables indicative of a sedentary lifestyle, including the use of computers, telephones, television viewing, and time spent driving. The findings indicated that prolonged telephone use, as well as higher intensity, increased the risk of developing PDAC (OR1.88, 95% CI: 1.53-2.31, and OR 4.70, 95% CI: 2.71-7.64, respectively)[143]. It is unlikely that mobile phone use per se is the causal factor in this association; however, it may serve as an excellent proxy for a low level of physical activity. Gentiluomo et al. recently conducted a Mendelian randomization analysis to elucidate the causality of physical activity and sedentary behaviours on PDAC risk. They reported that the amount of time spent watching television increased PDAC risk with an OR of 1.52 (95% CI:1.17-1.98) and found that more than half of the observed effect was mediated by BMI[114]. The principal epidemiological data are presented in **Table 3**.

Local Environment

Since the International Agency for Research on Cancer (IARC) classified outdoor air pollution and airborne particulate matter as human carcinogens (Group 1) for lung cancer[144], a growing number of studies have investigated whether these exposures could increase the risk of other cancers, including PC. Although several studies have examined the association between particulate matter (PM2.5 and PM10) and PC[145-151], few statistically significant associations have been reported, and results are often heterogeneous.

Wang et al. and Bogumil et al. indicated an association between PM2.5 and an elevated risk of developing PC (HR1.16, 95% CI: 1.13-1.20, and HR1.61, 95% CI: 1.09-2.37, respectively)[146, 151]. Conversely, Craver and colleagues suggested a negative association between PM2.5 and the risk of developing PC (OR 0.65, 95% CI: 0.52–0.80)[148]. Additionally, Ancona and colleagues identified a link between PM10 exposure and increased risk of PC in both sexes (HR1.40, 95% CI: 1.03-1.90 in males and HR1.47, 95% CI: 1.12-1.93 in females)[145]. Nevertheless, these associations remain unconfirmed in the Turner, Coleman, and Felici studies[147, 149, 150]. In addition to particulate matter, other environmental variables were examined, including nitrogen oxides (NO_x), nitrogen dioxide (NO_2), hydrogen sulfide (H_2S), sulfur oxides (SO_X), ozone (O_3), noise pollution, urban traffic,

distance from the coast, percentage of green space, natural environment, water, and domestic gardens within 1000 meters from residential coordinates. Notably, only two variables, O_3 [150] and SO_X [145] have been associated with increased risk of developing PC.

Based on the data available to date, there is no conclusive evidence that the local environment significantly affects PC susceptibility. The principal epidemiological data are presented in **Table 3**.

Sleep Quality

Over the past decade, there has been a notable increase in research aimed at elucidating the extent to which altered sleep patterns, including habitual short sleep, exposure to light at night, or shift work, are associated with various adverse health outcomes, such as PC. Three studies and a meta-analysis investigated the relationship between sleep duration and susceptibility to PC[143, 152-154]. However, the results have been inconclusive, not providing evidence to support an association between sleep duration and the risk of PC.

Xiao and colleagues investigated the effects of light at night (LAN) and suggested that higher exposure to LAN is associated with increased PDAC risk (HR1.24, 95% CI: 1.03-1.49)[155]. Despite these findings supporting the hypothesis that LAN and circadian disruption may be risk factors for PDAC, further research is needed to replicate these results.

The potential role of circadian disruption in PC susceptibility has also been explored in the context of shift work, but the results have been inconclusive to date. Specifically, Parent et al. identified an elevated risk of developing PC among individuals engaged in shift work (OR 2.31, 95% CI: 1.48-3.61) [156], but three other studies did not confirm this association [143, 152, 157]. In summary, definitive evidence is still lacking for the association between sleep quality and PC. The principal epidemiological data are presented in **Table 3**.

Stress

The potential role of psychological stress in susceptibility to PC has rarely been the subject of investigation in epidemiological studies. The few studies conducted to date have investigated stress in various forms, such as psychological stress or stress caused by traumatic events like the loss of a child, divorce, or income-related issues.

Li Peng and colleagues examined the potential role of pre-existing anxiety and depression at the onset of PC as risk factors. The findings suggest that a pre-existing state of anxiety may be associated

with an increased risk of PC (OR 1.13, 95% CI: 1.04-1.22) [158]. A few studies, including those conducted by Huang, Nilsen, and Peduzzi, have examined the role of stress in the context of traumatic events such as the loss of a child or divorce. Huang and colleagues demonstrated that the loss of a child increases the risk of developing PC (OR1.09, 95% CI: 1.02-1.17) [159]. Meanwhile, Nilsen and Peduzzi reported an association between divorce and increased PC risk (RR 3.1, 95% CI: 1.3-7.2 and OR 2.90, 95% CI: 1.62-4.80, respectively)[143, 160]. These results indicate that traumatic events leading to stressful conditions can increase the risk of developing PC.

It is evident that stress represents a particularly challenging variable to investigate, given that it can be induced by a multitude of causes. Nevertheless, the limited number of studies conducted have consistently demonstrated that stress is a factor that affects susceptibility to PC. The principal epidemiological data are presented in **Table 3**.

3.8. Hormonal treatments & prescription medications (statin, aspirin, metformin)

Hormonal treatments

The acknowledged disparity in exposure to established risk factors, such as smoking habits and alcohol consumption, only partially accounts for the differences in incidence rates of PDAC between males and females. Consequently, it has been hypothesized that hormones associated with pregnancy, menstrual cycle, oral contraception (OC), and hormone replacement therapy (HRT) may be responsible for this observed imbalance.

Several exposure variables were analysed to ascertain whether female hormones exert an influence on the susceptibility of PDAC. For the sake of convenience, this paragraph will focus on the most studied variables, including OC and HRT use, age at menarche, menopause, and number of births.

Twenty-five studies focused on OC use and the length, expressed in years, of OC use[161-185]. However, only three of them reported a statistically significant association between OC use and decreased PDAC risk[163, 164, 173]. Furthermore, a meta-analysis conducted in 2021 by Ilic and colleagues, encompassing 21 studies, found that OC use is associated with decreased PDAC risk (RR 0.85, 95%CI: 0.73-0.98) [186]. These results suggest a protective effect of OC use in the development of PDAC.

The use of HRT has also been extensively studied[161-163, 168-170, 172-176, 179-181, 184, 185, 187, 188]. While several investigations have not identified a statistically significant association between HRT use and PDAC, five studies have demonstrated an association between HRT and

reduced risk of developing the disease [163, 174, 176, 186, 188]. Nevertheless, a recent meta-analysis did not identify a significant association between HRT use and PDAC risk (RR 0.92, 95%CI: 0.83-1.02)[7] (). Therefore, these results still demonstrate a degree of doubt regarding the potential association between HRT usage and PDAC.

Numerous studies have investigated the potential association between ages at menarche or menopause and PDAC susceptibility. Regarding the age at menarche, only three studies identified a statistically significant association with increased PDAC risk[165, 176, 186] in women with an early age at menarche , which was not supported by other studies [161, 163, 164, 168-175, 177, 179-181, 183-185]. The latest meta-analysis, suggesting the lack of association between early age at menarche and PDAC risk (RR 0.94, 95% CI: 0.83-1.07), was conducted in 2015 and, therefore, does not encompass more recent studies[183]. Regarding the age at menopause, few studies observed significant results, and the findings are often contradictory. Specifically, two studies indicated that older age at menopause is inversely associated with PDAC risk [163, 180], while only one study suggested a positive association[168]. The remaining studies did not indicate any impact on PDAC development [162, 169-175, 177, 181, 183, 184, 185. Again, the most recent meta-analysis was conducted by Tang in 2015 and did not confirm the association between late age at menopause and PDAC risk (RR 0.98, 95%CI: 0.85-1.13){Tang, 2015 #177, 189-192].

Several studies have demonstrated that women with at least one child have a significantly reduced risk of developing PDAC in comparison to nulliparous women [163, 172, 173, 175, 181, 184, 189, 190]. However, other studies did not confirm this association[161, 162, 164, 168-170, 174, 179, 180, 183, 185, 191, 192]. The most recent meta-analysis identified a statistically significant association between having children and reduced risk of PDAC, with a RR 0.91 (95% CI: 0.85-0.97)[193].

In addition to exposure variables, common genetic variability related to signalling and biosynthesis of sex hormones was also investigated in two studies[170, 194]. Duell and colleagues investigated common genetic variability within the *CYP17A1* gene, which plays an essential role in the biosynthesis of glucocorticoids and sex steroids. No significant association was observed between the studied SNPs, either individually or in haplotype combinations with the risk of developing PC[170]. Peduzzi and colleagues evaluated the role of common SNPs in 208 genes involved in pregnenolone biosynthesis, oestrogen biosynthesis and oestrogen receptor-mediated signalling in the development of PDAC, but no associations were reported[194]. Therefore, despite differences in incidence between males and females, common genetic variability in genes related to the signalling and biosynthesis of sex hormones does not appear to play a role in PDAC susceptibility.

The hormone hypothesis has been subjected to extensive investigation in numerous case-control and cohort studies. However, the results of these studies are discordant, and the role of hormones in the onset of PDAC remains a topic of considerable debate. The relevant epidemiological data are provided in **Table 4**.

Aspirin

Aspirin has long been recognized as an important chemopreventive agent, particularly for colon cancer, where it is even prescribed solely for prevention [195]. Its effect appears to be linked to its ability to modulate cyclo-oxygenase-2, thereby influencing prostaglandin E2, which increases cellular proliferation, promotes angiogenesis, and reduces apoptosis. Its roles in NFκB signaling, Wnt signaling, DNA repair, and polyamine metabolism have also been demonstrated[196-198]. Regarding PDAC risk, the most recent meta-analysis by Bosetti C et al.[199] included fifteen studies with a total of 12,193 cases, reporting a RR of 0.78 (95%CI: 0.68-0.89), with a favorable effect increasing with longer duration of use. While a previous meta-analysis also showed a risk reduction[200], an earlier one did not observe significant protection[201] . Newer studies, such as the retrospective cohort study by Florensa et al. with over 118,000 individuals, identified a protective effect with an HR of 0.5 [202]. Additionally, the Women's Health Initiative reported a 39% risk reduction among more than 117,000 women [203, 204]. Other studies found a protective effect for specific subgroups, such as a population-based study from the U.S. including over 30 million individuals, which observed a risk reduction associated with aspirin use in patients with chronic pancreatitis (CP) and those older than 65; a subgroup analysis found this significant only for white males [204]. However, two recent studies, one from the Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Cancer Screening Trial cohort with about 140,000 participants[205] and another case-control study on 470 PDAC patients[206]), showed no association between aspirin use and disease risk.

Aspirin use might also be beneficial in reducing the risk of disease recurrence after PDAC surgical resection, with recent studies describing an association with disease-free survival (HR 0.62)[207]. The relevant epidemiological data are provided in **Table 4**.

Metformin

Metformin is well-known for its ability to control glucose metabolism in diabetes[208]. Its role in inhibiting tumor development and growth seems related to both the reduction of glucose and insulin levels in the blood, thereby suppressing the mTOR pathway and inhibiting cancer cell proliferation

[209, 210]. It has been suggested that metformin might reduce the risk of PDAC onset, with multiple meta-analyses on the topic. Several meta-analyses reported statistically significant risk reduction in PDAC onset, with a RR or OR ranging between 0.56 and 0.63[211-215]. Zhang et al. in 2021 also reported a significant risk reduction with an OR of 0.62[216]. More recently, a meta-analysis by Chen et al. on biguanides in general (which include metformin and other diabetes drugs) showed no association with the risk of developing PC, although a reduced risk was observed in case-control studies [217]. Zhao et al. also reported no association in their meta-analysis of 9 observational studies [218]. However, the most recent and comprehensive meta-analysis by Hu et al., including 29 studies on more than 2 million patients, reported a risk reduction compared to no metformin use (OR 0.82, 95% CI: 0.69-0.98) [212]. This effect could be enhanced when metformin is used in combination with simvastatin, as shown in mouse models[219]. Furthermore, a few studies have investigated its use in prolonging the prognosis of patients already diagnosed with PDAC, with meta-analyses showing a HR on overall survival ranging between 0.77 and 0.88, despite the majority being of low quality and having several biases related to the retrospective nature of the included studies [220]. The relevant epidemiological data are provided in **Table 4**.

Statins

Statins are cholesterol-lowering drugs commonly prescribed for primary and secondary cardiovascular prevention, acting as inhibitors of the 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG CoA) reductase [221]. Beyond their well-known action, the mevalonate pathway impacts numerous intra- and intercellular cascades, with pleiotropic effects including carcinogenesis and tumor progression [222]. Both in vitro and in vivo studies have demonstrated that statins inhibit the cell cycle and DNA synthesis [223], exert direct cytotoxic effects in human cancer cells via pro-apoptotic activity [224], and reduce angiogenesis [225]. Consistent evidence highlights the role of statins in reducing the risk of developing PDAC. Karbowska et al. [226] meta-analyzed 26 interventional studies (retrospective and prospective trials), showing a significant difference in PDAC occurrence between the statin and non-statin groups (0.4% vs 0.6%, OR 0.83, 95% CI: 0.72-0.96), although a sub-analysis showed similar PDAC occurrence in randomized controlled trials (RCTs). Another recent meta-analysis by Bagheri et al.[227] included 32 studies (observational and interventional) with a sample size of almost 6 million patients, showing that individuals who received statins had a reduced risk of developing PDAC compared to those who did not (risk ratio for statin recipients 0.75, 95% CI: 0.66-0.86), indicating a 25% decrease in risk. However, it remains unclear whether statins benefit

patients with diagnosed PDAC. Tamburrino et al. [228] analyzed 14 studies showing that statin use is associated with reduced mortality risk, especially in patients with resectable disease who underwent surgery (HR 0.87; 95% CI: 0.82-0.93), as did Anbari et al. [229] in a pooled cohort of 100,888 patients (HR 0.86, 95% CI: 0.80-0.92). Conversely, in a large retrospective cohort of upfront resected patients, statin treatment did not influence survival [230]. Considering specific statin subtypes, rosuvastatin is significantly associated with reduced mortality in resected patients (HR 0.88, 95% CI: 0.81-0.96)[228], while simvastatin and atorvastatin have the highest chemoprophylactic effect [231, 232]. Unfortunately, the protective effect of statins has not been demonstrated in advanced stages, even when combined with chemotherapy [231]. Recent studies suggest that statins may enhance epithelial-to-mesenchymal transition (EMT) through TGFβ signaling, leading to chemoresistance and poorer outcomes [233]. The relevant epidemiological data are provided in **Table 4**.

3.9. Infectious agents and the influence of the microbiota

Emerging evidence indicates that the gut microbiome can influence pancreatic disease via the gut-pancreas axis[234]. This axis involves complex interactions where gut microbiota and their toxic products can reach the pancreas, affecting its function and contributing to inflammation and carcinogenesis. Disruptions of the microbiota homeostasis due to imbalances in microbial abundances, changes in their activity or function, or a shift in their spatial niche can cause a state transition from eubiosis to a potentially pathogenic dysbiosis, which has been associated with multiple gastrointestinal cancers [235]. Metagenomic studies have consistently shown differences in bacterial abundances in the fecal microbiomes of PDAC patients and controls, as reviewed by Pandya and colleagues [236]. Although there are large variations between populations and individuals, increases in *Fusobacterium*, *Veillonella*, and *Streptococcus* and decreases in *Bifidobacterium*, *Faecalibacterium*, and *Eubacterium* species have repeatedly been observed in the feces of PDAC patients [237-241]. The mycobiome, particularly *Malassezia* species, has also been observed to be significantly altered in PDAC, suggesting a potential role in tumorigenesis[242]. Most existing evidence remains correlative, with thus possible issues of reverse causality. Mendelian randomization studies significantly contributed to this field, suggesting causal associations between the abundance of *Romboutsia* genus and circulating metabolites related to the gut microbiome with PDAC risk [243]. Metagenomic analyses performed on PDAC tumor tissue samples showed that

increased abundances of *Acinetobacter*, *Pseudomonas*, and *Sphingopyxis* were associated with a more aggressive tumor phenotype. RNA-seq analyses also revealed that abundances of these genera were positively associated with the expression of genes involved in cancer-associated processes, including DNA replication, *EMT*, and *KRAS* and *MAPK* signaling, suggesting a potential pro-oncogenic mechanism [244].

However, the mechanisms underlying how the gut microbiome may promote PDAC development are currently the subject of emerging investigation. The relevant epidemiological data are provided in **Table 4**.

Microbial Translocation

Increased intestinal permeability and disruption of the mucosal barrier may allow bacterial translocation, a process by which low levels of viable bacteria, their genetic material, and metabolic products, such as mRNA, lipopolysaccharide (LPS), flagellin, and colibactin, escape the intestinal lumen and migrate to other organs [245].

Porphyromonas gingivalis (*P. gingivalis*) is an established periodontal pathogen that has been increasingly linked with PDAC. A higher level of antibodies against *P. gingivalis* (and crucially before disease onset in this large, European prospective study) and studies showing higher levels of this bacterium in the oral microbiome have observed associations with an increased risk of PC [246-248]. Mechanistically, intracellular *P. gingivalis* can promote proliferation as seen in PDAC cells[249], while infection induces a pro-inflammatory tumor microenvironment (TME) with an elevation of neutrophil elastase, which ultimately promotes PDAC progression as observed in murine models[250]. Results from qPCR performed on DNA extracted from PDAC tumor tissue samples found that *Fusobacterium* species were positively associated with markedly worse prognosis [251]. Mechanistically, this may be explained by increased secretion of GM-CSF, CXCL1, IL8, and MIP3α, which in turn promotes proliferation, migration, and invasion as evidenced by inoculation of PDAC cells with *Fusobacterium nucleatum* [252]. The relevant epidemiological data are provided in **Table 4**.

Microbial Metabolites

Short-chain fatty acids (SCFAs) are products of bacterial fermentation and play roles in energy synthesis, regulating inflammation, immunomodulation, and supporting intestinal health [253]. Peripheral blood mononuclear cells taken from PDAC patients and treated with SCFA butyrate

showed decreased levels of MDSCs and enhanced functioning of CD8+ T cells [254]. Additionally, metagenomic sequencing and gas chromatography performed on fecal samples from PDAC cases and controls have shown significant reductions in butyrate-producing bacteria such as *Eubacterium rectale*, *Faecalibacterium prausnitzii*, and *Roseburia intestinalis*, as well as reduced fecal butyrate content in cases relative to controls [241].

Indoles are products of dietary tryptophan metabolism by commensal bacteria and play roles in gut barrier homeostasis [255]. The expression of the aryl hydrocarbon receptor (AhR), a sensor of indoles, is associated with an immunosuppressive tumor-associated macrophage (TAM) phenotype as well as rapid progression and mortality in PDAC patients [256].

In conclusion, the gut-pancreas axis appears to significantly influence pancreatic carcinogenesis through microbial translocation, production of circulating metabolites, and immunomodulation. While notable progress has been made, there remains a rudimentary understanding of the microbiome's role in PDAC. For example, *Helicobacter pylori* (*H. pylori*) infection has a potential association with PC. Several studies have found no association [257-259], while others have found a weak but significant association in some populations [155, 260, 261]. As such, the link between *H. pylori* infection and PDAC remains equivocal. This illustrates the need for robustly designed longitudinal studies on microbial translocation and gut microbiome composition, including non-bacterial components, specific species, and community interactions. Additionally, clinical studies on the interactions between the microbiome and cancer drugs, along with better mechanistic insights into the multifaceted roles of bacterial metabolites, are essential to further elucidate the complex role of the gut microbiome in PDAC development and progression. The relevant epidemiological data are provided in **Table 4**.

3.10 Exposure to toxic substances and heavy metals

Hundreds of everyday products, including food wrappers, non-stick cookware, and pan coatings, are made with highly toxic fluorinated chemicals such as perfluorooctanoic acid (PFO), also known as "Forever chemicals" [262, 263]. Exposure to toxic substances varies depending on factors such as location (urban versus rural areas) and dietary and cooking habits. Given the objective of this review, the focus will be on some of the more common toxic substances that circulate in the food chain, which could increase the risk of developing PC.

Heavy Metals

Elements such as lead (Pb), nickel (Ni), iron (Fe), cadmium (Cd), chromium (Cr), manganese (Mn), and zinc (Zn) are often classified as heavy metals and can accumulate in the body over time, potentially leading to various health issues, including PC [264]. While some of these metals are essential micronutrients at low concentrations, human activities have significantly increased their levels, raising concerns about their potential toxicity. Heavy metals disrupt various biological functions, including cell proliferation, differentiation, damage repair, and apoptosis. Comparing their mechanisms of action reveals that these metals often induce toxicity through common processes, such as the generation of reactive oxygen species (ROS), weakening of antioxidant defenses, enzyme inactivation, and the promotion of oxidative stress [265]. In nature, these metals typically exist at low levels [266]. Fish and seafood are likely the most exposed to these heavy metals through various pathways: consuming contaminated food, absorbing metals that enter aquatic environments and their sediments from fertilizers used in intensive farming, as well as from industrial effluents, tannery waste, etc. [267]. There are some epidemiological studies evaluating the relationship between dietary mineral intake and PC [268]. While some studies show a potential association between certain minerals like Ca and Mg and a reduced risk of PC, the evidence remains inconsistent. A recent retrospective cohort study in 2024 found decreased serum levels of Mg, K, Ca, Fe, Zn, Se, As, and Hg, along with increased levels of Mo, were associated with an increased PDAC risk[268, 269]. Additionally, lower serum levels of selenium, iron, and calcium, and higher levels of manganese were significantly associated with poorer overall survival in PDAC patients [270]. An increase in serum molybdenum was observed in stage II or III/IV patients but not in stage I when compared with healthy controls [270]. Focusing on heavy metals, a significant increase was observed in the adjacent normal pancreas of PDAC patients compared to the control group with intraductal papillary mucinous neoplasm (IPMN) patients. Therefore, it could be hypothesized that As, Pb, and Hg are involved in PDAC development, suggesting that higher heavy metals-contaminated food intake should be avoided to prevent PDAC [270].

On the other hand, despite the limitation of assessing heavy metals exposure through questionnaires, a clinic-based case-control study from 2000 to 2014 at the Mayo Clinic observed no association between regular exposure to chromium and nickel and PC [271]. The relevant epidemiological data are provided in **Table 4**.

Cadmium

Cd and Cd-containing compounds have been classified as carcinogenic by IARC [272, 273]. Several studies have shown an association between Cd exposure and an elevated risk of PC [264, 274-276]. At the molecular level, Cd exposure modulates ROS, causing DNA damage, lipid peroxidation, and protein modifications that contribute to cellular transformation and tumor progression [277]. It was reported that Cd activates NF-κB and AP-1 signaling pathways, which promote cell proliferation and inhibit apoptosis [278]. Lower doses of Cd exposure led to tumor cell characteristics and changes in apoptotic pathways and microRNA expression [279-281]. These data point towards Cd exposure as a significant risk factor for PDAC development. The relevant epidemiological data are provided in **Table 4**.

Nickel

IARC has classified Ni compounds as a 'group 1' human carcinogen [282, 283]. It was reported that Ni-induced carcinogenesis involves hypoxia-inducible factor pathways and the generation of oxidative stress, which further leads to DNA damage and the targeting of DNA repair pathways [284, 285]. Moreover, recent studies indicated a link between Ni content, pancreatic dysfunctions, and PDAC [286, 287]. Ojajärvi found that occupational exposure to Ni compounds significantly raised the risk of PC among workers in the Ni refining industry (meta-risk ratio (MRR) 1.90, 95% CI: 1.20-3.20); however, a later review of this analysis suggested that more studies are needed [288, 289]. Moreover, Ni has been shown to inhibit DNA repair mechanisms, compounding its genotoxic effects and promoting malignant transformation [290]. In addition to its direct genotoxic effects, Ni disrupts cellular signaling pathways in cell growth and impacts microRNA expression signatures in vitro [291]. Overall, the evidence indicates that Ni exposure plays a significant role in PC development through mechanisms involving oxidative stress, DNA damage, non-coding RNA expression, and disruption of critical signaling pathways. The relevant epidemiological data are provided in **Table 4**.

Arsenic

Arsenic is a poisonous heavy metal abundantly found in the earth's crust. Previously, it was reported that exposure to contaminated drinking water wells may be associated with an increased risk of PC [292]. As exposure induces oxidative stress, generating ROS that causes DNA damage and genomic instability. Studies have shown that Arsenic can induce DNA methylation changes, thereby altering

the expression of oncogenes and tumor suppressor genes [293]. Reichard et al.[294], demonstrated that exposure resulted in hypermethylation of the tumor suppressor gene p16, thus contributing to the dysregulation of cell cycle control in pancreatic cells. The relevant epidemiological data are provided in **Table 4**.

Acrylamide

In 1994, acrylamide was classified as a probable human carcinogen by IARC. However, the PanC4 case-control studies conducted in North America, Europe, and Australia found no association between dietary acrylamide and PC risk [295]. Similarly, no association was found in the EPIC cohort [296], an Italian case-control study [297], or among Japanese individuals [298]. Therefore, current data support the absence of a significant association between dietary acrylamide and PC. The relevant epidemiological data are provided in **Table 4**.

Heterocyclic Aromatic Amines and Polycyclic Aromatic Hydrocarbons

Heterocyclic Aromatic Amines (HCAs) and Polycyclic Aromatic Hydrocarbons (PAHs) are mutagens and carcinogens commonly found in food, formed during cooking processes such as boiling, frying, barbecuing, and grilling of meat and fish [299, 300]. In general, the estimated daily intake of HCAs varies significantly between countries, with the USA having the highest consumption and Japan and Singapore the lowest [301, 302]

In a North American case-control study, it was observed that HCAs and benzo(alpha)pyrene (representative of PAHs) derived from well-done barbecued and pan-fried meats may be associated to an elevated risk of PC (OR 2.20, 95% CI: 1.20-4.00)[303].

In the study by Anderson and colleagues, conducted in the PLCO Cancer Screening Trial, it was found that meat cooked at high temperatures is associated with an increased risk of PC (Proportional Hazard Estimates (PHE) 1.63, 95% CI: 1.13-2.34) [304]. Moreover, the NIH-American Association of Retired Persons (NIH-AARP) Diet and Health Study cohort included 537,302 individuals. Over 5 years of follow-up, 836 cases of PC were identified (281 females and 555 males). This study revealed that high total meat intake was linked to a 26% increased risk of PC in both men and women [305]. Furthermore, another study using data from the same cohort with a longer follow-up period of 9.2 years also found significant associations between PC risk and total meat intake (HR 1.20, 95% CI: 1.02–1.42,), red meat intake (HR 1.22, 95% CI: 1.01–1.48), and exposure to high cooking

temperatures (HR 1.21, 95% CI: 1.00–1.45) [306]. The relevant epidemiological data are provided in **Table 4**.

3.11 Glycome changes in the PDAC development

Minimally invasive serum biomarkers are highly attractive for their low risk to patients and ease of access. In PC [307], the most used biomarkers for PDAC include carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA). The CA 19-9 epitope is a Lewis antigen (sLeA) carried by mucin-1 (MUC1), mucin-5AC (MUC5AC), and mucin-16 (MUC16) proteins. Although these biomarkers are used clinically, their limitations highlight the continued need for more reliable diagnostic tools for detecting and diagnosing PDAC. Both biomarkers lack sufficient specificity and sensitivity for early PDAC screening, as elevated levels of CA 19-9 or CEA may indicate not only PDAC but also CP or benign pancreatic diseases [308, 309].

A key hallmark of PDAC is its complex TME, characterized by an extracellular matrix containing stromal cells, tumor cells, and immune cells. Abnormal glycosylation patterns, including sialylation, are a universal feature of malignant transformation in various cancers, including PDAC [307, 310]. In humans, there are twenty different sialyltransferases identified to date. These enzymes are responsible for adding sialic acid to glycolipids or to the sugar chains (N- or O-linked) of glycoproteins [307].

The emergence of glycomics, alongside transcriptomic and genomic methodologies, has significantly enhanced our understanding of the molecular mechanisms and glycoprofiling changes that occur during PDAC development. Over the past decade, various N-glycan biomarker signatures have been identified and validated for PDAC. These novel biomarkers hold promise for enhancing surveillance in individuals at risk of PDAC, potentially enabling early detection and improving patient outcomes. Experiments conducted in different cell lines have demonstrated that the activation of several cell surface receptors, such as TGF-β, can induce aberrations in the N-glycome. Common changes observed include elevated levels of sugar branching, core fucosylation, and sialylation [311].

Furthermore, transcriptomic analysis of tissue samples from PDAC patients, as well as studies involving organoids and cell lines, identified two distinct glycan profiles associated with PDAC [312]. In detail, two glyco-clusters were defined. Cluster A (the fucosylated subtype) is characterized by increased expression of genes involved in fucosylation and O-glycosylation and is associated with the classical PDAC subtype. Cluster B presented a higher expression of genes encoding galectin-1

and the mucins MUC4 and MUC16 and it is more linked to the PDAC basal subtype[312]. MUC4 is a glycosylated protein aberrantly expressed in PDAC, promoting tumorigenesis[313]. Additionally, aberrant expression of MUC16 has been associated with PDAC progression and metastasis. MUC16 activates the AKT and GSK3Beta oncogenic signaling pathways through its interaction with ErbB [314]. In addition, the two glycan profiles have been found to correlate with EMT status which is recognized as a critical mechanism driving metastasis in PDAC[312].

Manfred Wuhrer and collaborators identified glycome biomarkers that distinguish PDAC patients from healthy individuals, highlighting three key N-glycosylation differences through cross-sectional and longitudinal analysis in two Dutch surveillance cohorts [315, 316]. A classification model built with these three glycosylation traits was used for discovery (area under the curve, AUC 0.88) and independent validation (AUC 0.81), with sensitivity and specificity values of 0.85 and 0.71 for the discovery set, and 0.75 and 0.72 for the validation set.

In the longitudinal study by Levink and colleagues that built upon the cross-sectional findings, significant advancements were made in understanding glycosylation changes preceding PDAC. The research revealed that a majority of PDAC cases exhibited alterations in 13 glycosylation traits evaluated from 3 to 50 months before PDAC development. Among these traits, the N-glycan trait A3F, which denotes fucosylation of triantennary glycans, showed the most notable increase compared to controls during the 3-50 months period prior to PDAC development [315].

Furthermore, Wagatsuma et al. (2020) and Kurz et al. (2021) also detected increased levels of α-2,6-sialic acid (sialoglycans) and identified the overexpression of a specific sialyltransferase, ST6 beta-galactoside alpha-2,6-sialic acid (ST6GAL1) in PDAC. These studies highlighted that elevated expression of ST6GAL1 confers protection against DNA damage induced by gemcitabine, which is a frontline treatment for PC. The ability of ST6GAL1 to withstand cytotoxic stimuli may be through fostering cancer stem cells that are resistant to apoptosis [310].

Finally, a recently published case-control study of Chinese PDAC patients highlighted two promising glycan markers that showed potential for distinguishing between early (stage I and II) and advanced (stage III and IV) PDAC. These glycan markers are NGA2FB (agalacto core α-1,6 fucosylated bisecting biantennary glycan) and NA2FB (bigalacto core α-1,6 fucosylated bisecting biantennary glycan)[317].

Considering these studies and recent clinical research, they highlight the substantial potential of glycans to serve as valuable biomarkers for PDAC, offering significant benefits for disease surveillance. The relevant epidemiological data are provided in **Table 4**.

4. Links with pancreatic diseases (pancreatitis & mucinous cystic neoplasms) and co-morbidities

Chronic Pancreatitis

CP is a known risk factor for PDAC onset. However, careful interpretation of study results is necessary, as PDAC is often initially misdiagnosed as CP. PDAC can cause Wirsung duct stenosis with upstream dilation and parenchymal atrophy, which could be misdiagnosed as CP [318]. A history of CP has been associated with a HR for PDAC of 6.9 (95% CI: 5.6-8.6) in a Danish nationwide study [319], and in Korean populations with an HR of 3.9 (95% CI: 2.7-5.5) [320] and an incidence ratio of 18.1 (95% CI: 10.4-29.5) [321]. A recent meta-analysis by Gandhi et al. reported an even higher risk, with a standardized incidence ratio ranging from 13.3 (95% CI: 6.1-28.9) to 22.61 (95% CI: 14.42-35.44) [322]. Regarding the risk of bias, some papers focused specifically on the lag time between the diagnoses of PDAC and CP. Kirkegard et al. [323] reported that the risk of PDAC in CP patients is highest at 2 years (pooled effect estimate 16) from diagnosis, decreasing with longer follow-up (7.9 at five years and 3.5 at nine years). Conversely, Munigala et al. described a PDAC risk increasing in CP patients after two years of follow-up, with the risk being consistent and sustained beyond 5 and 10 years of follow-up [324]. The risk of PDAC onset also varies based on CP etiology. Genetic causes have different risks based on the affected gene, with *PRSS1* mutations conferring the highest risk (44% risk at 70 years from symptom onset, a standardized incidence ratio of 67 (95% CI: 50-82) [325, 326] .Other affected genes also carry an increased risk, with *SPINK1*-mutated patients bearing a 12-fold RR [325] and *CFTR* mutations bearing a 1.41-fold RR [327]. Even when no mutation is found, a family history of autosomal dominant pancreatitis increases the risk of PDAC onset [328]. Furthermore, the risk increases in cases of acute pancreatitis developing on CP, especially with a higher number of acute pancreatitis episodes [329]. The risk of PDAC in CP with toxic etiologies is more complex to evaluate, as heavy alcohol use and smoking are already independent known risk factors for PDAC, even in patients without a diagnosis of CP, though data on the topic are scant [3, 330]. Autoimmune pancreatitis (AIP) has also been linked to an increased risk of PDAC, especially type 1 AIP, typically metachronous, developing 2 years after the diagnosis of AIP and in the same part of the pancreas affected by AIP [331]. The reason behind CP being a risk factor for PDAC seems to be the ongoing inflammatory process during CP, which can lead to a range of molecular alterations promoting tumor development [331]. Oxidative stress and the generation of reactive oxygen species and reactive nitrogen species are known to cause acinar cell necrosis and fibrosis. Furthermore, as with sporadic cancers, there is an initial activation of the oncogene *KRAS*, followed

by the epigenetic or genetic inactivation of tumor suppressor genes such as *CDKN2A*, *TP53*, and *DPC4*, with a well-known progression from pancreatic intraepithelial neoplasia (PanIN) to cancer [332]. In animal models, an additional step of this process has been observed with acinar-to-ductal metaplasia development. Other pathways also seem to be involved, with Cox2, NF-κB, and STAT3 generating secondary oxidative injury, promoting inflammatory infiltration and acinar cell damage, and promoting de-differentiation of the acinar component, making them susceptible to KRAS-initiated and promoted transformation [333].

IPMN

IPMN is a recognized risk factor for developing PDAC. The risk is related to the potential adenoma-carcinoma progression from low-grade dysplasia (LGD) to high-grade dysplasia (HGD)/invasive carcinoma (IC) [333], driven not only by specific mutations (*KRAS, TP53, CDKN2A, SMAD4, GNAS*) [334], but also by exposure factors such as smoking [335]. Studies from Japan have shown a higher possibility of developing concomitant PDAC, 3 to 5-fold compared to the general population[336], and recent studies from other countries have demonstrated similar risk [337]. Predictive factors of HGD/IC are the so-called high-risk stigmata (HRS) and worrisome features (WF), primarily defined in 2012 [338]. HRS are the strongest predictors of malignancy, with a risk ranging from an OR of 1.09 (95% CI: 104-1.14) for a main pancreatic duct (MPD) ≥10 mm [339], to an OR of 2.93 (95% CI: 1.77-4.84) for smaller nodules (between 5 mm and 10 mm), reaching the highest OR of 7.9 (95% CI: 4.66-13.40) for larger mural nodules (>1 cm) [339]. On the other hand, WF alone are not strong predictors of malignancy, with a risk ranging from an OR of 1.27 (95% CI: 1.01-1.59) in the case of new-onset diabetes [340] to an OR of 3.51 (95% CI: -) with a septal thickness ≥2.5 mm [339]. The presence of multiple WF increases the risk exponentially, reaching 100% in the presence of 4 or more [341]. Therapeutic management of patients is usually discussed in a multidisciplinary setting, considering not only the presence of HRS/WF but also general conditions, age, comorbidities, and personal choices [338]. In most patients not undergoing surgery, follow-up remains a debated issue, considering the economic burden linked to the high prevalence of IPMN in the general population. It is still unclear, considering the low long-term risk of malignancy, whether follow-up discontinuation after 5 years, especially in older patients with small and stable cysts, might be suitable. Growing evidence in recent years supports this possibility. In a long-term retrospective study on 1,036 BD-IPMN without WF/HRS at diagnosis, only 4.2% developed WF or HRS, and 1.1% developed PDAC after a median of 62 months [342]. In a multicenter international cohort of 3,844

patients with BD-IPMN without WF/HRS at diagnosis, 1.8% developed HRS, and the incidence of PC in patients with stable cysts for at least 5 years and who were at least 75 years old was not significantly higher than that of the general population [337].

MCN

Unlike IPMN, mucinous cystic neoplasms (MCN) of the pancreas are mucin-secreting cystic tumors that do not communicate with the ductal system [343]. MCNs can progress to invasive cancer, with a reported risk ranging from 10% to 39% [344]. A recent meta-analysis found a low global risk of progression (16%) in more than 3,000 resected MCNs, questioning the current liberal policies regarding surgical indications [345]. The risk of malignancy in MCNs depends on specific features. Several large series of resected MCNs have reported no incidence of cancer in small (<3 cm) lesions without solid nodules. Conversely, a tumor size ≥4 cm has been identified as a strong predictor of malignancy (OR 16.9 95% CI: 2.04-140) [346, 347]. Mural nodules have also been reported as predictors of malignancy in many studies [348, 349], with a pooled OR of 4.34 (95% CI: 3.00-6.29) [345]. Therefore, current guidelines recommend surgical resection for MCNs ≥4 cm, when patients are symptomatic, or have risk factors (e.g., mural nodules), regardless of their size [350]. Despite these aggressive indications, risk factors for developing malignant MCNs are still not well characterized, with a lack of defined high-risk features compared to their intraductal counterparts. Consequently, despite being two different entities, MCNs usually follow the same management flowchart and malignancy risk estimation as IPMN[345].

A summary of all information regarding characteristics, mechanisms and epidemiological findings of this chapter is included in **Table 5**.

5. Interactions between environmental and genetic factors in differential susceptibility to PDAC development

In addition to the effect of the exposome, several SNPs have been identified through genome-wide association studies (GWAS) or secondary analysis of GWAS data done in large consortia {Amundadottir, 2009 #30;Childs, 2015 #33;Klein, 2018 #35;Petersen, 2010 #31;Wolpin, 2014 #32;Zhang, 2016 #34;
Corradi, 2021 #350;Corradi, 2023 #351;Galeotti, 2021 #353;Gentiluomo, 2022 #349;Pistoni, 2021 #352}. The identification of interactions between lifestyle, environmental exposure, and genetic

variability in cancer has been a long-sought goal of many scientists. For common cancers, such as breast and prostate, many studies carried out using very large populations reported promising, although heterogeneous, results.

Several researchers have tried to characterize the possible gene-environment (GxE) interactions in PDAC. The earlier attempts were based on simple logistic regression fitting SNPs, environmental factors (E), and an interaction (SNP x E) term into the model comparing cases and controls [351]. These studies had many limitations: they were all carried out before GWAS data availability and therefore focused on candidate genes. Furthermore, they used inadequate sample sizes, hampering their statistical power, and a method that is prone to false positives[351]. A detailed list of these studies has been reviewed elsewhere [351]. After these first approaches, later studies took advantage of GWAS data and used different methodologies. However, it was clear from studies carried out in other cancers that rarely, if ever, have the GWAS hits shown interaction with common risk factors for a specific tumor. For example, there were no clear indications of the interaction between breast cancer susceptibility loci and common etiologic risk factors [352-354]. Therefore, the most common way to explore GxE was the genome-wide gene interaction study (GWIS) strategy. The idea is to extend the interaction analysis (using various methods, including simple logistic regression) to all SNPs genotyped in a specific study and test the possible interaction of all the variants with one or more environmental factors.

Tang and coworkers tested the interaction of 870,000 SNPs with diabetes and obesity. The large sample size comprised 8,255 PDAC cases and 11,900 controls of European ancestry from the PanScan I-III and the PanC4 studies. In addition to single SNPs, a gene-level analysis was also performed. The authors did not observe any genome-wide significant interactions with the individual SNPs, whereas the gene-level analysis showed an association of the family with sequence similarity 63 member A (*FAM63A*) gene and diabetes [140]. This gene plays a role in genome stability, but there is no direct link with either PDAC or diabetes. Mocci and colleagues conducted a genome-wide smoking interaction analysis using genotyping data of 7,937 PDAC cases and 11,774 controls from PanC4 and PanScan I-III studies. The authors identified a locus on 2q21.3 that significantly modified PDAC risk by smoking status [355]. A recent GWIS study by Ni and colleagues of heavy alcohol consumption (defined by the authors as more than 3 drinks per day) identified a promising interaction on 10p11.22 [356].

Although these three studies show promising results, GWIS suffers from inherent difficulties in data interpretation. Many tests are performed, and usually, the link between the genetic variant and the

environmental factor remains unclear. Additionally, the small effect of the SNPs decreases the statistical power. An alternative approach is the use of the cumulative effect of a polygenic risk score (PRS) instead of the individual SNPs [361]. This approach, which was successfully employed in breast cancer [362], has been attempted only using a limited number of PDAC cases from the UK Biobank cohort and did not show any statistically significant interactions [143, 149].

In conclusion, GxE interactions in PC are largely unexplored, and studies that use the most promising approach, PRSs by environment, need to be conducted in large studies such as PanScanI-III or PANDoRA.

6. Conclusions and future research

PC, particularly PDAC, remains a formidable global health challenge due to its rising incidence and high mortality rates. Despite accounting for only 3% of all cancer diagnoses, PDAC is responsible for 7% of cancer-related deaths, underscoring its disproportionate lethality. The asymptomatic nature of early-stage PDAC further complicates timely diagnosis and treatment, emphasizing the need for improved screening and preventive measures.

Understanding the multifaceted risk factors for PDAC, including lifestyle choices, environmental exposures, and genetic predispositions, is crucial for developing effective prevention and early detection strategies. Modifiable risk factors such as smoking, heavy alcohol consumption, non-alcoholic fatty pancreatic disease (NAFPD), and obesity highlight the importance of lifestyle interventions in reducing PC risk. Additionally, the role of refined sugar and sugar-sweetened beverages (SSBs) in increasing PC risk, particularly among younger individuals, warrants further investigation and public health initiatives to reduce consumption.

Emerging evidence on the influence of the gut microbiome and exposure to toxic substances, including heavy metals and chemicals, on PC development opens new avenues for research. The gut-pancreas axis and microbial translocation, along with microbial metabolites, present potential targets for therapeutic intervention. Furthermore, advancements in glycomics have identified distinct glycan profiles and potential biomarkers for early PDAC detection, offering promise for improved diagnostic tools.

The interplay between environmental and genetic factors in PDAC susceptibility remains an area of active research. Genome-wide association studies (GWAS) have identified several single nucleotide polymorphisms (SNPs) linked to PDAC, but gene-environment (GxE) interactions are still largely

unexplored. Future research should focus on polygenic risk scores (PRS) and large-scale studies to better understand these interactions and their impact on PDAC risk.

In conclusion, addressing the complex etiology of PDAC requires a multidisciplinary approach, integrating insights from epidemiology, genetics, microbiology, and glycomics. Continued research into the mechanisms underlying PDAC development and progression, along with the identification of novel biomarkers and therapeutic targets, will be essential for improving patient outcomes. Public health initiatives aimed at reducing modifiable risk factors and enhancing early detection efforts will also play a critical role in combating this deadly disease.

CRediT authorship contribution statement

Conceptualization: GP, CR; Funding acquisition: DC, CR; Methodology: GP, CR; Supervision: GP, LA, RF, RPLP, LV, PV, BK, JSP, DBC, ND, RS, PO, SL, JDL, AC, DC, DJH, CR; Writing -original draft: GP, LA, RF, RPLP, LV, PV, BK, JSP, DBC, ND, RS, PO, SL, JDL, AC, DC, DJH, CR; Writing -review & editing: GP, LA, RF, RPLP, LV, PV, BK, JSP, DBC, ND, RS, PO, SL, JDL, AC, DC, DJH, CR.

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.

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References

[1] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries, CA Cancer J Clin 71(3) (2021) 209-249.

[2] F. Bray, M. Laversanne, H. Sung, J. Ferlay, R.L. Siegel, I. Soerjomataram, A. Jemal, Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J Clin 74(3) (2024) 229-263.
[3] A.P. Klein, Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors, Nat Rev Gastroenterol Hepatol 18(7) (2021) 493-502.
[4] S. Gaddam, Y. Abboud, J. Oh, J.S. Samaan, N.N. Nissen, S.C. Lu, S.K. Lo, Incidence of Pancreatic Cancer by Age and Sex in the US, 2000-2018, JAMA 326(20) (2021) 2075-2077.
[5] V. Beral, R. Peto, UK cancer survival statistics, BMJ 341 (2010) c4112.
[6] Y.T. Wang, Y.W. Gou, W.W. Jin, M. Xiao, H.Y. Fang, Association between alcohol intake and the risk of pancreatic cancer: a dose-response meta-analysis of cohort studies, BMC Cancer 16 (2016) 212.
[7] W. Jiang, C. Xiang, Y. Du, X. Li, W. Zhou, The Global, Regional and National Burden of Pancreatic Cancer Attributable to Smoking, 1990 to 2019: A Systematic Analysis from the Global Burden of Disease Study 2019, Int J Environ Res Public Health 20(2) (2023).
[8] H. Wang, J. Liu, G. Xia, S. Lei, X. Huang, X. Huang, Survival of pancreatic cancer patients is negatively correlated with age at diagnosis: a population-based retrospective study, Sci Rep 10(1) (2020) 7048.
[9] T.J. Hayman, T. Strom, G.M. Springett, L. Balducci, S.E. Hoffe, K.L. Meredith, P. Hodul, M. Malafa, R. Shridhar, Outcomes of resected pancreatic cancer in patients age >/=70, J Gastrointest Oncol 6(5) (2015) 498-504.
[10] J. Kim, C. Yuan, L.T. Amundadottir, B.M. Wolpin, C. Pancreatic Cancer Cohort, A.P. Klein, C. Pancreatic Cancer Case-Control, H.A. Risch, P. Kraft, Relationship between ABO Blood Group Alleles and Pancreatic Cancer Is Modulated by Secretor (FUT2) Genotype, but Not Lewis Antigen (FUT3) Genotype, Cancer Epidemiol Biomarkers Prev 32(9) (2023) 1242-1248.
[11] Y. Tanaka, T. Kumagi, T. Terao, T. Kuroda, T. Yokota, N. Azemoto, Y. Imamura, K. Uesugi, Y. Kisaka, N. Shibata, M. Koizumi, Y. Ohno, K. Kanemitsu, A. Yukimoto, K. Tange, M. Nishiyama, T. Miyake, H. Miyata, H. Ishii, M. Abe, Y. Hiasa, G. Ehime Pancreato-Cholangiology Study, ABO Blood Type and the Long-term Outcomes of Pancreatic Cancer, Intern Med 59(6) (2020) 761-768.
[12] M. Cotterchio, E. Lowcock, T.J. Hudson, C. Greenwood, S. Gallinger, Association between allergies and risk of pancreatic cancer, Cancer Epidemiol Biomarkers Prev 23(3) (2014) 469-80.
[13] P. Gomez-Rubio, J.P. Zock, M. Rava, M. Marquez, L. Sharp, M. Hidalgo, A. Carrato, L. Ilzarbe, C. Michalski, X. Molero, A. Farre, J. Perea, W. Greenhalf, M. O'Rorke, A. Tardon, T. Gress, V. Barbera, T. Crnogorac-Jurcevic, E. Dominguez-Munoz, L. Munoz-Bellvis, C. Alvarez-Urturi, J. Balcells, L. Barneo, E. Costello, C. Guillen-Ponce, J. Kleeff, B. Kong, R. Lawlor, M. Lohr, J. Mora, L. Murray, D. O'Driscoll, P. Pelaez, I. Poves, A. Scarpa, F.X. Real, N. Malats, E.U.S.I. PanGen, Reduced risk of pancreatic cancer associated with asthma and nasal allergies, Gut 66(2) (2017) 314-322.
[14] B.Z. Huang, L. Le Marchand, C.A. Haiman, K.R. Monroe, L.R. Wilkens, Z.F. Zhang, V.W. Setiawan, Atopic allergic conditions and pancreatic cancer risk: Results from the Multiethnic Cohort Study, Int J Cancer 142(10) (2018) 2019-2027.
[15] S.H. Olson, M. Hsu, J.M. Satagopan, P. Maisonneuve, D.T. Silverman, E. Lucenteforte, K.E. Anderson, A. Borgida, P.M. Bracci, H.B. Bueno-de-Mesquita, M. Cotterchio, Q. Dai, E.J. Duell, E.H. Fontham, S. Gallinger, E.A. Holly, B.T. Ji, R.C. Kurtz, C. La Vecchia, A.B. Lowenfels, B. Luckett, E. Ludwig, G.M. Petersen, J. Polesel, D. Seminara, L. Strayer, R. Talamini, C. Pancreatic Cancer Case-Control, Allergies and risk of pancreatic cancer: a pooled analysis from the Pancreatic Cancer Case-Control Consortium, Am J Epidemiol 178(5) (2013) 691-700.
[16] S. Gandini, A.B. Lowenfels, E.M. Jaffee, T.D. Armstrong, P. Maisonneuve, Allergies and the risk of pancreatic cancer: a meta-analysis with review of epidemiology and biological mechanisms, Cancer Epidemiol Biomarkers Prev 14(8) (2005) 1908-16.

[17] E.A. Holly, C.A. Eberle, P.M. Bracci, Prior history of allergies and pancreatic cancer in the San Francisco Bay area, Am J Epidemiol 158(5) (2003) 432-41.
[18] K. Murray, L. Oldfield, I. Stefanova, M. Gentiluomo, P. Aretini, R. O'Sullivan, W. Greenhalf, S. Paiella, M.N. Aoki, A. Pastore, J. Birch-Ford, B.H. Rao, P. Uysal-Onganer, C.M. Walsh, G.B. Hanna, J. Narang, P. Sharma, D. Campa, C. Rizzato, A. Turtoi, E.A. Sever, A. Felici, C. Sucularli, G. Peduzzi, E. Oz, O.U. Sezerman, R. Van der Meer, N. Thompson, E. Costello, Biomarkers, omics and artificial intelligence for early detection of pancreatic cancer, Semin Cancer Biol 111 (2025) 76-88.
[19] J.W. Elena, E. Steplowski, K. Yu, P. Hartge, G.S. Tobias, M.J. Brotzman, S.J. Chanock, R.Z. Stolzenberg-Solomon, A.A. Arslan, H.B. Bueno-de-Mesquita, K. Helzlsouer, E.J. Jacobs, A. LaCroix, G. Petersen, W. Zheng, D. Albanes, N.E. Allen, L. Amundadottir, Y. Bao, H. Boeing, M.C. Boutron-Ruault, J.E. Buring, J.M. Gaziano, E.L. Giovannucci, E.J. Duell, G. Hallmans, B.V. Howard, D.J. Hunter, A. Hutchinson, K.B. Jacobs, C. Kooperberg, P. Kraft, J.B. Mendelsohn, D.S. Michaud, D. Palli, L.S. Phillips, K. Overvad, A.V. Patel, L. Sansbury, X.O. Shu, M.S. Simon, N. Slimani, D. Trichopoulos, K. Visvanathan, J. Virtamo, B.M. Wolpin, A. Zeleniuch-Jacquotte, C.S. Fuchs, R.N. Hoover, M. Gross, Diabetes and risk of pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium, Cancer Causes Control 24(1) (2013) 13-25.
[20] D. Li, H. Tang, M.M. Hassan, E.A. Holly, P.M. Bracci, D.T. Silverman, Diabetes and risk of pancreatic cancer: a pooled analysis of three large case-control studies, Cancer Causes Control 22(2) (2011) 189-97.
[21] C. Bosetti, V. Rosato, D. Li, D. Silverman, G.M. Petersen, P.M. Bracci, R.E. Neale, J. Muscat, K. Anderson, S. Gallinger, S.H. Olson, A.B. Miller, H. Bas Bueno-de-Mesquita, G. Scelo, V. Janout, I. Holcatova, P. Lagiou, D. Serraino, E. Lucenteforte, E. Fabianova, P.A. Baghurst, W. Zatonski, L. Foretova, E. Fontham, W.R. Bamlet, E.A. Holly, E. Negri, M. Hassan, A. Prizment, M. Cotterchio, S. Cleary, R.C. Kurtz, P. Maisonneuve, D. Trichopoulos, J. Polesel, E.J. Duell, P. Boffetta, C. La Vecchia, P. Ghadirian, Diabetes, antidiabetic medications, and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case-Control Consortium, Ann Oncol 25(10) (2014) 2065-2072.
[22] H.S. Lee, W. Chae, M.J. Sung, J. Keum, J.H. Jo, M.J. Chung, J.Y. Park, S.W. Park, S.Y. Song, E.C. Park, C.M. Nam, S.I. Jang, S. Bang, Difference of Risk of Pancreatic Cancer in New-Onset Diabetes and Long-standing Diabetes: A Population-based Cohort Study, J Clin Endocrinol Metab 108(6) (2023) 1338-1347.
[23] Q. Zhao, Y. Wang, T. Huo, F. Li, L. Zhou, Y. Feng, Z. Wei, Exploration of Risk Factors for Pancreatic Cancer and Development of a Clinical High-Risk Group Rating Scale, J Clin Med 12(1) (2023).
[24] D. McDonnell, A.W.E. Cheang, S. Wilding, S.H. Wild, A.E. Frampton, C.D. Byrne, Z.Z. Hamady, Elevated Glycated Haemoglobin (HbA1c) Is Associated with an Increased Risk of Pancreatic Ductal Adenocarcinoma: A UK Biobank Cohort Study, Cancers (Basel) 15(16) (2023).
[25] C. Mellenthin, V.D. Balaban, A. Dugic, S. Cullati, Risk Factors for Pancreatic Cancer in Patients with New-Onset Diabetes: A Systematic Review and Meta-Analysis, Cancers (Basel) 14(19) (2022).
[26] B. Shen, Y. Li, C.S. Sheng, L. Liu, T. Hou, N. Xia, S. Sun, Y. Miao, Y. Pang, K. Gu, X. Lu, C. Wen, Y. Cheng, Y. Yang, D. Wang, Y. Zhu, M. Cheng, K. Harris, Z.T. Bloomgarden, J. Tian, J. Chalmers, Y. Shi, Association between age at diabetes onset or diabetes duration and subsequent risk of pancreatic cancer: Results from a longitudinal cohort and mendelian randomization study, Lancet Reg Health West Pac 30 (2023) 100596.
[27] Y. Lin, K. Yagyu, N. Egawa, M. Ueno, M. Mori, H. Nakao, H. Ishii, K. Nakamura, K. Wakai, S. Hosono, A. Tamakoshi, S. Kikuchi, An overview of genetic polymorphisms and pancreatic cancer risk in molecular epidemiologic studies, J Epidemiol 21(1) (2011) 2-12.

[28] H. Tang, X. Dong, M. Hassan, J.L. Abbruzzese, D. Li, Body mass index and obesity- and diabetes-associated genotypes and risk for pancreatic cancer, Cancer Epidemiol Biomarkers Prev 20(5) (2011) 779-92.
[29] X. Dong, Y. Li, K.R. Hess, J.L. Abbruzzese, D. Li, DNA mismatch repair gene polymorphisms affect survival in pancreatic cancer, Oncologist 16(1) (2011) 61-70.
[30] X. Dong, Y. Li, P. Chang, K.R. Hess, J.L. Abbruzzese, D. Li, DNA mismatch repair network gene polymorphism as a susceptibility factor for pancreatic cancer, Mol Carcinog 51(6) (2012) 491-9.
[31] D. Campa, C. Rizzato, R. Stolzenberg-Solomon, P. Pacetti, P. Vodicka, S.P. Cleary, G. Capurso, H.B. Bueno-de-Mesquita, J. Werner, M. Gazouli, K. Butterbach, A. Ivanauskas, N. Giese, G.M. Petersen, P. Fogar, Z. Wang, C. Bassi, M. Ryska, G.E. Theodoropoulos, C. Kooperberg, D. Li, W. Greenhalf, C. Pasquali, T. Hackert, C.S. Fuchs, B. Mohelnikova-Duchonova, C. Sperti, N. Funel, A.K. Dieffenbach, N.J. Wareham, J. Buring, I. Holcatova, E. Costello, C.F. Zambon, J. Kupcinskas, H.A. Risch, P. Kraft, P.M. Bracci, R. Pezzilli, S.H. Olson, H.D. Sesso, P. Hartge, O. Strobel, E. Malecka-Panas, K. Visvanathan, A.A. Arslan, S. Pedrazzoli, P. Soucek, D. Gioffreda, T.J. Key, R. Talar-Wojnarowska, A. Scarpa, A. Mambrini, E.J. Jacobs, K. Jamroziak, A. Klein, F. Tavano, F. Bambi, S. Landi, M.A. Austin, L. Vodickova, H. Brenner, S.J. Chanock, G. Delle Fave, A. Piepoli, M. Cantore, W. Zheng, B.M. Wolpin, L.T. Amundadottir, F. Canzian, TERT gene harbors multiple variants associated with pancreatic cancer susceptibility, Int J Cancer 137(9) (2015) 2175-83.
[32] D. Campa, G. Capurso, M. Pastore, R. Talar-Wojnarowska, A.C. Milanetto, L. Landoni, E. Maiello, R.T. Lawlor, E. Malecka-Panas, N. Funel, M. Gazouli, A. De Bonis, H. Kluter, M. Rinzivillo, G. Delle Fave, T. Hackert, S. Landi, P. Bugert, F. Bambi, L. Archibugi, A. Scarpa, V. Katzke, C. Dervenis, V. Lico, S. Furlanello, O. Strobel, F. Tavano, D. Basso, R. Kaaks, C. Pasquali, M. Gentiluomo, C. Rizzato, F. Canzian, Common germline variants within the CDKN2A/2B region affect risk of pancreatic neuroendocrine tumors, Sci Rep 6 (2016) 39565.
[33] M. Gentiluomo, G. Peduzzi, Y. Lu, D. Campa, F. Canzian, Genetic polymorphisms in inflammatory genes and pancreatic cancer risk: a two-phase study on more than 14 000 individuals, Mutagenesis 34(5-6) (2019) 395-401.
[34] G. Peduzzi, M. Gentiluomo, F. Tavano, P.G. Arcidiacono, S. Ermini, P. Vodicka, U. Boggi, G.M. Cavestro, G. Capurso, L. Morelli, A.C. Milanetto, R. Pezzilli, R.T. Lawlor, S. Carrara, M. Lovecek, P. Soucek, F. Guo, T. Hackert, F.G. Uzunoglu, M. Gazouli, A. Parniczky, J. Kupcinskas, M.F. Bijlsma, B. Bueno-de-Mesquita, R. Vermeulen, C.H.J. van Eijck, K. Jamroziak, R. Talar-Wojnarowska, W. Greenhalf, D. Gioffreda, M.C. Petrone, S. Landi, L. Archibugi, M. Puzzono, N. Funel, C. Sperti, M.L. Piredda, B. Mohelnikova-Duchonova, Y. Lu, V. Hlavac, X. Gao, M. Schneider, J.R. Izbicki, G. Theodoropoulos, S. Bunduc, E. Kreivenaite, O.R. Busch, E. Malecka-Panas, E. Costello, F. Perri, S.G.G. Testoni, G. Vanella, C. Pasquali, M. Oliverius, H. Brenner, M. Loos, M. Gotz, K. Georgiou, B. Eross, E. Maiello, A. Szentesi, F. Bazzocchi, D. Basso, J.P. Neoptolemos, P. Hegyi, V. Kiudelis, F. Canzian, D. Campa, Genetic Polymorphisms Involved in Mitochondrial Metabolism and Pancreatic Cancer Risk, Cancer Epidemiol Biomarkers Prev 30(12) (2021) 2342-2345.
[35] L. Amundadottir, P. Kraft, R.Z. Stolzenberg-Solomon, C.S. Fuchs, G.M. Petersen, A.A. Arslan, H.B. Bueno-de-Mesquita, M. Gross, K. Helzlsouer, E.J. Jacobs, A. LaCroix, W. Zheng, D. Albanes, W. Bamlet, C.D. Berg, F. Berrino, S. Bingham, J.E. Buring, P.M. Bracci, F. Canzian, F. Clavel-Chapelon, S. Clipp, M. Cotterchio, M. de Andrade, E.J. Duell, J.W. Fox, Jr., S. Gallinger, J.M. Gaziano, E.L. Giovannucci, M. Goggins, C.A. Gonzalez, G. Hallmans, S.E. Hankinson, M. Hassan, E.A. Holly, D.J. Hunter, A. Hutchinson, R. Jackson, K.B. Jacobs, M. Jenab, R. Kaaks, A.P. Klein, C. Kooperberg, R.C. Kurtz, D. Li, S.M. Lynch, M. Mandelson, R.R. McWilliams, J.B. Mendelsohn, D.S. Michaud, S.H. Olson, K. Overvad, A.V. Patel, P.H. Peeters, A. Rajkovic, E. Riboli, H.A. Risch, X.O. Shu, G. Thomas, G.S. Tobias, D. Trichopoulos, S.K. Van Den Eeden, J. Virtamo, J. Wactawski-Wende, B.M. Wolpin, H. Yu, K. Yu, A. Zeleniuch-Jacquotte, S.J. Chanock, P. Hartge, R.N. Hoover, Genome-wide association

study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer, Nat Genet 41(9) (2009) 986-90.
[36] G.M. Petersen, L. Amundadottir, C.S. Fuchs, P. Kraft, R.Z. Stolzenberg-Solomon, K.B. Jacobs, A.A. Arslan, H.B. Bueno-de-Mesquita, S. Gallinger, M. Gross, K. Helzlsouer, E.A. Holly, E.J. Jacobs, A.P. Klein, A. LaCroix, D. Li, M.T. Mandelson, S.H. Olson, H.A. Risch, W. Zheng, D. Albanes, W.R. Bamlet, C.D. Berg, M.C. Boutron-Ruault, J.E. Buring, P.M. Bracci, F. Canzian, S. Clipp, M. Cotterchio, M. de Andrade, E.J. Duell, J.M. Gaziano, E.L. Giovannucci, M. Goggins, G. Hallmans, S.E. Hankinson, M. Hassan, B. Howard, D.J. Hunter, A. Hutchinson, M. Jenab, R. Kaaks, C. Kooperberg, V. Krogh, R.C. Kurtz, S.M. Lynch, R.R. McWilliams, J.B. Mendelsohn, D.S. Michaud, H. Parikh, A.V. Patel, P.H. Peeters, A. Rajkovic, E. Riboli, L. Rodriguez, D. Seminara, X.O. Shu, G. Thomas, A. Tjonneland, G.S. Tobias, D. Trichopoulos, S.K. Van Den Eeden, J. Virtamo, J. Wactawski-Wende, Z. Wang, B.M. Wolpin, H. Yu, K. Yu, A. Zeleniuch-Jacquotte, J.F. Fraumeni, Jr., R.N. Hoover, P. Hartge, S.J. Chanock, A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33, Nat Genet 42(3) (2010) 224-8.
[37] B.M. Wolpin, C. Rizzato, P. Kraft, C. Kooperberg, G.M. Petersen, Z. Wang, A.A. Arslan, L. Beane-Freeman, P.M. Bracci, J. Buring, F. Canzian, E.J. Duell, S. Gallinger, G.G. Giles, G.E. Goodman, P.J. Goodman, E.J. Jacobs, A. Kamineni, A.P. Klein, L.N. Kolonel, M.H. Kulke, D. Li, N. Malats, S.H. Olson, H.A. Risch, H.D. Sesso, K. Visvanathan, E. White, W. Zheng, C.C. Abnet, D. Albanes, G. Andreotti, M.A. Austin, R. Barfield, D. Basso, S.I. Berndt, M.C. Boutron-Ruault, M. Brotzman, M.W. Buchler, H.B. Bueno-de-Mesquita, P. Bugert, L. Burdette, D. Campa, N.E. Caporaso, G. Capurso, C. Chung, M. Cotterchio, E. Costello, J. Elena, N. Funel, J.M. Gaziano, N.A. Giese, E.L. Giovannucci, M. Goggins, M.J. Gorman, M. Gross, C.A. Haiman, M. Hassan, K.J. Helzlsouer, B.E. Henderson, E.A. Holly, N. Hu, D.J. Hunter, F. Innocenti, M. Jenab, R. Kaaks, T.J. Key, K.T. Khaw, E.A. Klein, M. Kogevinas, V. Krogh, J. Kupcinskas, R.C. Kurtz, A. LaCroix, M.T. Landi, S. Landi, L. Le Marchand, A. Mambrini, S. Mannisto, R.L. Milne, Y. Nakamura, A.L. Oberg, K. Owzar, A.V. Patel, P.H. Peeters, U. Peters, R. Pezzilli, A. Piepoli, M. Porta, F.X. Real, E. Riboli, N. Rothman, A. Scarpa, X.O. Shu, D.T. Silverman, P. Soucek, M. Sund, R. Talar-Wojnarowska, P.R. Taylor, G.E. Theodoropoulos, M. Thornquist, A. Tjonneland, G.S. Tobias, D. Trichopoulos, P. Vodicka, J. Wactawski-Wende, N. Wentzensen, C. Wu, H. Yu, K. Yu, A. Zeleniuch-Jacquotte, R. Hoover, P. Hartge, C. Fuchs, S.J. Chanock, R.S. Stolzenberg-Solomon, L.T. Amundadottir, Genome-wide association study identifies multiple susceptibility loci for pancreatic cancer, Nat Genet 46(9) (2014) 994-1000.
[38] E.J. Childs, E. Mocci, D. Campa, P.M. Bracci, S. Gallinger, M. Goggins, D. Li, R.E. Neale, S.H. Olson, G. Scelo, L.T. Amundadottir, W.R. Bamlet, M.F. Bijlsma, A. Blackford, M. Borges, P. Brennan, H. Brenner, H.B. Bueno-de-Mesquita, F. Canzian, G. Capurso, G.M. Cavestro, K.G. Chaffee, S.J. Chanock, S.P. Cleary, M. Cotterchio, L. Foretova, C. Fuchs, N. Funel, M. Gazouli, M. Hassan, J.M. Herman, I. Holcatova, E.A. Holly, R.N. Hoover, R.J. Hung, V. Janout, T.J. Key, J. Kupcinskas, R.C. Kurtz, S. Landi, L. Lu, E. Malecka-Panas, A. Mambrini, B. Mohelnikova-Duchonova, J.P. Neoptolemos, A.L. Oberg, I. Orlow, C. Pasquali, R. Pezzilli, C. Rizzato, A. Saldia, A. Scarpa, R.Z. Stolzenberg-Solomon, O. Strobel, F. Tavano, Y.K. Vashist, P. Vodicka, B.M. Wolpin, H. Yu, G.M. Petersen, H.A. Risch, A.P. Klein, Common variation at 2p13.3, 3q29, 7p13 and 17q25.1 associated with susceptibility to pancreatic cancer, Nat Genet 47(8) (2015) 911-6.
[39] M. Zhang, Z. Wang, O. Obazee, J. Jia, E.J. Childs, J. Hoskins, G. Figlioli, E. Mocci, I. Collins, C.C. Chung, C. Hautman, A.A. Arslan, L. Beane-Freeman, P.M. Bracci, J. Buring, E.J. Duell, S. Gallinger, G.G. Giles, G.E. Goodman, P.J. Goodman, A. Kamineni, L.N. Kolonel, M.H. Kulke, N. Malats, S.H. Olson, H.D. Sesso, K. Visvanathan, E. White, W. Zheng, C.C. Abnet, D. Albanes, G. Andreotti, L. Brais, H.B. Bueno-de-Mesquita, D. Basso, S.I. Berndt, M.C. Boutron-Ruault, M.F. Bijlsma, H. Brenner, L. Burdette, D. Campa, N.E. Caporaso, G. Capurso, G.M. Cavestro, M. Cotterchio, E.

Costello, J. Elena, U. Boggi, J.M. Gaziano, M. Gazouli, E.L. Giovannucci, M. Goggins, M. Gross, C.A. Haiman, M. Hassan, K.J. Helzlsouer, N. Hu, D.J. Hunter, E. Iskierka-Jazdzewska, M. Jenab, R. Kaaks, T.J. Key, K.T. Khaw, E.A. Klein, M. Kogevinas, V. Krogh, J. Kupcinskas, R.C. Kurtz, M.T. Landi, S. Landi, L. Le Marchand, A. Mambrini, S. Mannisto, R.L. Milne, R.E. Neale, A.L. Oberg, S. Panico, A.V. Patel, P.H. Peeters, U. Peters, R. Pezzilli, M. Porta, M. Purdue, J.R. Quiros, E. Riboli, N. Rothman, A. Scarpa, G. Scelo, X.O. Shu, D.T. Silverman, P. Soucek, O. Strobel, M. Sund, E. Malecka-Panas, P.R. Taylor, F. Tavano, R.C. Travis, M. Thornquist, A. Tjonneland, G.S. Tobias, D. Trichopoulos, Y. Vashist, P. Vodicka, J. Wactawski-Wende, N. Wentzensen, H. Yu, K. Yu, A. Zeleniuch-Jacquotte, C. Kooperberg, H.A. Risch, E.J. Jacobs, D. Li, C. Fuchs, R. Hoover, P. Hartge, S.J. Chanock, G.M. Petersen, R.S. Stolzenberg-Solomon, B.M. Wolpin, P. Kraft, A.P. Klein, F. Canzian, L.T. Amundadottir, Three new pancreatic cancer susceptibility signals identified on chromosomes 1q32.1, 5p15.33 and 8q24.21, Oncotarget 7(41) (2016) 66328-66343.

[40] A.P. Klein, B.M. Wolpin, H.A. Risch, R.Z. Stolzenberg-Solomon, E. Mocci, M. Zhang, F. Canzian, E.J. Childs, J.W. Hoskins, A. Jermusyk, J. Zhong, F. Chen, D. Albanes, G. Andreotti, A.A. Arslan, A. Babic, W.R. Bamlet, L. Beane-Freeman, S.I. Berndt, A. Blackford, M. Borges, A. Borgida, P.M. Bracci, L. Brais, P. Brennan, H. Brenner, B. Bueno-de-Mesquita, J. Buring, D. Campa, G. Capurso, G.M. Cavestro, K.G. Chaffee, C.C. Chung, S. Cleary, M. Cotterchio, F. Dijk, E.J. Duell, L. Foretova, C. Fuchs, N. Funel, S. Gallinger, M.G. JM, M. Gazouli, G.G. Giles, E. Giovannucci, M. Goggins, G.E. Goodman, P.J. Goodman, T. Hackert, C. Haiman, P. Hartge, M. Hasan, P. Hegyi, K.J. Helzlsouer, J. Herman, I. Holcatova, E.A. Holly, R. Hoover, R.J. Hung, E.J. Jacobs, K. Jamroziak, V. Janout, R. Kaaks, K.T. Khaw, E.A. Klein, M. Kogevinas, C. Kooperberg, M.H. Kulke, J. Kupcinskas, R.J. Kurtz, D. Laheru, S. Landi, R.T. Lawlor, I.M. Lee, L. LeMarchand, L. Lu, N. Malats, A. Mambrini, S. Mannisto, R.L. Milne, B. Mohelnikova-Duchonova, R.E. Neale, J.P. Neoptolemos, A.L. Oberg, S.H. Olson, I. Orlow, C. Pasquali, A.V. Patel, U. Peters, R. Pezzilli, M. Porta, F.X. Real, N. Rothman, G. Scelo, H.D. Sesso, G. Severi, X.O. Shu, D. Silverman, J.P. Smith, P. Soucek, M. Sund, R. Talar-Wojnarowska, F. Tavano, M.D. Thornquist, G.S. Tobias, S.K. Van Den Eeden, Y. Vashist, K. Visvanathan, P. Vodicka, J. Wactawski-Wende, Z. Wang, N. Wentzensen, E. White, H. Yu, K. Yu, A. Zeleniuch-Jacquotte, W. Zheng, P. Kraft, D. Li, S. Chanock, O. Obazee, G.M. Petersen, L.T. Amundadottir, Genome-wide meta-analysis identifies five new susceptibility loci for pancreatic cancer, Nat Commun 9(1) (2018) 556.

[41] C. Wu, P. Kraft, R. Stolzenberg-Solomon, E. Steplowski, M. Brotzman, M. Xu, P. Mudgal, L. Amundadottir, A.A. Arslan, H.B. Bueno-de-Mesquita, M. Gross, K. Helzlsouer, E.J. Jacobs, C. Kooperberg, G.M. Petersen, W. Zheng, D. Albanes, M.C. Boutron-Ruault, J.E. Buring, F. Canzian, G. Cao, E.J. Duell, J.W. Elena, J.M. Gaziano, E.L. Giovannucci, G. Hallmans, A. Hutchinson, D.J. Hunter, M. Jenab, G. Jiang, K.T. Khaw, A. LaCroix, Z. Li, J.B. Mendelsohn, S. Panico, A.V. Patel, Z.R. Qian, E. Riboli, H. Sesso, H. Shen, X.O. Shu, A. Tjonneland, G.S. Tobias, D. Trichopoulos, J. Virtamo, K. Visvanathan, J. Wactawski-Wende, C. Wang, K. Yu, A. Zeleniuch-Jacquotte, S. Chanock, R. Hoover, P. Hartge, C.S. Fuchs, D. Lin, B.M. Wolpin, Genome-wide association study of survival in patients with pancreatic adenocarcinoma, Gut 63(1) (2014) 152-60.

[42] Y. Lin, M. Nakatochi, Y. Hosono, H. Ito, Y. Kamatani, A. Inoko, H. Sakamoto, F. Kinoshita, Y. Kobayashi, H. Ishii, M. Ozaka, T. Sasaki, M. Matsuyama, N. Sasahira, M. Morimoto, S. Kobayashi, T. Fukushima, M. Ueno, S. Ohkawa, N. Egawa, S. Kuruma, M. Mori, H. Nakao, Y. Adachi, M. Okuda, T. Osaki, S. Kamiya, C. Wang, K. Hara, Y. Shimizu, T. Miyamoto, Y. Hayashi, H. Ebi, T. Kohmoto, I. Imoto, Y. Kasugai, Y. Murakami, M. Akiyama, K. Ishigaki, K. Matsuda, M. Hirata, K. Shimada, T. Okusaka, T. Kawaguchi, M. Takahashi, Y. Watanabe, K. Kuriki, A. Kadota, R. Okada, H. Mikami, T. Takezaki, S. Suzuki, T. Yamaji, M. Iwasaki, N. Sawada, A. Goto, K. Kinoshita, N. Fuse, F. Katsuoka, A. Shimizu, S.S. Nishizuka, K. Tanno, K. Suzuki, Y. Okada, M. Horikoshi, T. Yamauchi, T. Kadowaki, H. Yu, J. Zhong, L.T. Amundadottir, Y. Doki, H. Ishii, H. Eguchi, D. Bogumil, C.A. Haiman, L. Le

Marchand, M. Mori, H. Risch, V.W. Setiawan, S. Tsugane, K. Wakai, T. Yoshida, F. Matsuda, M. Kubo, S. Kikuchi, K. Matsuo, Genome-wide association meta-analysis identifies GP2 gene risk variants for pancreatic cancer, Nat Commun 11(1) (2020) 3175.
[43] M. Nakatochi, Y. Lin, H. Ito, K. Hara, F. Kinoshita, Y. Kobayashi, H. Ishii, M. Ozaka, T. Sasaki, N. Sasahira, M. Morimoto, S. Kobayashi, M. Ueno, S. Ohkawa, N. Egawa, S. Kuruma, M. Mori, H. Nakao, C. Wang, T. Nishiyama, T. Kawaguchi, M. Takahashi, F. Matsuda, S. Kikuchi, K. Matsuo, Prediction model for pancreatic cancer risk in the general Japanese population, PLoS One 13(9) (2018) e0203386.
[44] S.K. Low, A. Kuchiba, H. Zembutsu, A. Saito, A. Takahashi, M. Kubo, Y. Daigo, N. Kamatani, S. Chiku, H. Totsuka, S. Ohnami, H. Hirose, K. Shimada, T. Okusaka, T. Yoshida, Y. Nakamura, H. Sakamoto, Genome-wide association study of pancreatic cancer in Japanese population, PLoS One 5(7) (2010) e11824.
[45] M. Inoue, M. Noda, N. Kurahashi, M. Iwasaki, S. Sasazuki, H. Iso, S. Tsugane, f.t.J.P.H.C.-b.P.S. Group, Impact of metabolic factors on subsequent cancer risk: results from a large-scale population-based cohort study in Japan, European Journal of Cancer Prevention 18(3) (2009) 240.
[46] Y. Miyashita, T. Hitsumoto, H. Fukuda, J. Kim, S. Ito, N. Kimoto, K. Asakura, Y. Yata, M. Yabumoto, T. Washio, M. Kitakaze, Metabolic syndrome is linked to the incidence of pancreatic cancer, EClinicalMedicine 67 (2024) 102353.
[47] V. Rosato, A. Tavani, C. Bosetti, C. Pelucchi, R. Talamini, J. Polesel, D. Serraino, E. Negri, C. La Vecchia, Metabolic syndrome and pancreatic cancer risk: a case-control study in Italy and meta-analysis, Metabolism 60(10) (2011) 1372-1378.
[48] S.K. Park, C.-M. Oh, M.-H. Kim, E. Ha, Y.-S. Choi, J.-H. Ryoo, Metabolic syndrome, metabolic components, and their relation to the risk of pancreatic cancer, Cancer 126(9) (2020) 1979-1986.
[49] B. Xia, Q. He, Y. Pan, F. Gao, A. Liu, Y. Tang, C. Chong, A.Y.B. Teoh, F. Li, Y. He, C. Zhang, J. Yuan, Metabolic syndrome and risk of pancreatic cancer: A population-based prospective cohort study, International Journal of Cancer 147(12) (2020) 3384-3393.
[50] L. Zhong, J. Liu, S. Liu, G. Tan, Correlation between pancreatic cancer and metabolic syndrome: A systematic review and meta-analysis, Front. Endocrinol. 14 (2023).
[51] J.H. Park, J.Y. Hong, K. Han, W. Kang, J.K. Park, Increased risk of pancreatic cancer in individuals with non-alcoholic fatty liver disease, Sci Rep 12(1) (2022) 10681.
[52] S. Naudin, V. Viallon, D. Hashim, H. Freisling, M. Jenab, E. Weiderpass, F. Perrier, F. McKenzie, H.B. Bueno-de-Mesquita, A. Olsen, A. Tjønneland, C.C. Dahm, K. Overvad, F.R. Mancini, V. Rebours, M.-C. Boutron-Ruault, V. Katzke, R. Kaaks, M. Bergmann, H. Boeing, E. Peppa, A. Karakatsani, A. Trichopoulou, V. Pala, G. Masala, S. Panico, R. Tumino, C. Sacerdote, A.M. May, C.H. van Gils, C. Rylander, K.B. Borch, M.D. Chirlaque López, M.-J. Sánchez, E. Ardanaz, J.R. Quirós, P. Amiano Exezarreta, M. Sund, I. Drake, S. Regnér, R.C. Travis, N. Wareham, D. Aune, E. Riboli, M.J. Gunter, E.J. Duell, P. Brennan, P. Ferrari, Healthy lifestyle and the risk of pancreatic cancer in the EPIC study, Eur J Epidemiol 35(10) (2020) 975-986.
[53] Y. Fan, J. Hu, B. Feng, W. Wang, G. Yao, J. Zhai, X. Li, Increased Risk of Pancreatic Cancer Related to Gallstones and Cholecystectomy: A Systematic Review and Meta-Analysis, Pancreas 45(4) (2016) 503-509.
[54] M. Capasso, M. Franceschi, K.I. Rodriguez-Castro, P. Crafa, G. Cambiè, C. Miraglia, A. Barchi, A. Nouvenne, G. Leandro, T. Meschi, G.L. De' Angelis, F. Di Mario, Epidemiology and risk factors of pancreatic cancer, Acta Biomed 89(9-S) (2018) 141-146.
[55] G. Lin, Z. Zeng, X. Wang, Z. Wu, J. Wang, C. Wang, Q. Sun, Y. Chen, H. Quan, Cholecystectomy and risk of pancreatic cancer: a meta-analysis of observational studies, Cancer Causes Control 23(1) (2012) 59-67.

[56] L. Gabitova, A. Gorin, I. Astsaturov, Molecular pathways: sterols and receptor signaling in cancer, Clin Cancer Res 20(1) (2014) 28-34.
[57] M. Takahashi, M. Hori, M. Mutoh, K. Wakabayashi, H. Nakagama, Experimental animal models of pancreatic carcinogenesis for prevention studies and their relevance to human disease, Cancers 3(1) (2011) 582-602.
[58] Y. Wang, M. Haque, S. Young, M. Cotterchio, R. Truscott, Association between Cancer Risk and Behaviors Adherent to Cancer Prevention Recommendations in Ontario, Canada, J Registry Manag 48(3) (2021) 92-103.
[59] Y. Huang, L. Zhou, X. Meng, B. Yu, H. Wang, Y. Yang, Y. Wu, X. Tan, IRS-1 regulates proliferation, invasion and metastasis of pancreatic cancer cells through MAPK and PI3K signaling pathways, Int J Clin Exp Pathol 11(11) (2018) 5185-5193.
[60] G. La Torre, A. Sferrazza, M.R. Gualano, C. de Waure, G. Clemente, A.M. De Rose, N. Nicolotti, G. Nuzzo, R. Siliquini, A. Boccia, W. Ricciardi, Investigating the synergistic interaction of diabetes, tobacco smoking, alcohol consumption, and hypercholesterolemia on the risk of pancreatic cancer: a case-control study in Italy, Biomed Res Int 2014 (2014) 481019.
[61] S. Bian, H. Dong, L. Zhao, Z. Li, J. Chen, X. Zhu, N. Qiu, X. Jia, W. Song, Z. Li, S. Zheng, H. Wang, P. Song, Antihypertension Nanoblockers Increase Intratumoral Perfusion of Sequential Cytotoxic Nanoparticles to Enhance Chemotherapy Efficacy against Pancreatic Cancer, Adv Sci (Weinh) 9(29) (2022) e2201931.
[62] C.H. Tseng, New-onset diabetes with a history of dyslipidemia predicts pancreatic cancer, Pancreas 42(1) (2013) 42-8.
[63] J. Wang, W.-J. Wang, L. Zhai, D.-F. Zhang, Association of cholesterol with risk of pancreatic cancer: a meta-analysis, World J Gastroenterol 21(12) (2015) 3711-3719.
[64] P. Maisonneuve, A.B. Lowenfels, Risk factors for pancreatic cancer: a summary review of meta-analytical studies, Int J Epidemiol 44(1) (2015) 186-98.
[65] A. Lugo, G. Peveri, C. Bosetti, V. Bagnardi, A. Crippa, N. Orsini, M. Rota, S. Gallus, Strong excess risk of pancreatic cancer for low frequency and duration of cigarette smoking: A comprehensive review and meta-analysis, Eur J Cancer 104 (2018) 117-126.
[66] C. Bosetti, E. Lucenteforte, D.T. Silverman, G. Petersen, P.M. Bracci, B.T. Ji, E. Negri, D. Li, H.A. Risch, S.H. Olson, S. Gallinger, A.B. Miller, H.B. Bueno-de-Mesquita, R. Talamini, J. Polesel, P. Ghadirian, P.A. Baghurst, W. Zatonski, E. Fontham, W.R. Bamlet, E.A. Holly, P. Bertuccio, Y.T. Gao, M. Hassan, H. Yu, R.C. Kurtz, M. Cotterchio, J. Su, P. Maisonneuve, E.J. Duell, P. Boffetta, C. La Vecchia, Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4), Ann Oncol 23(7) (2012) 1880-1888.
[67] S.M. Lynch, A. Vrieling, J.H. Lubin, P. Kraft, J.B. Mendelsohn, P. Hartge, F. Canzian, E. Steplowski, A.A. Arslan, M. Gross, K. Helzlsouer, E.J. Jacobs, A. LaCroix, G. Petersen, W. Zheng, D. Albanes, L. Amundadottir, S.A. Bingham, P. Boffetta, M.C. Boutron-Ruault, S.J. Chanock, S. Clipp, R.N. Hoover, K. Jacobs, K.C. Johnson, C. Kooperberg, J. Luo, C. Messina, D. Palli, A.V. Patel, E. Riboli, X.O. Shu, L. Rodriguez Suarez, G. Thomas, A. Tjonneland, G.S. Tobias, E. Tong, D. Trichopoulos, J. Virtamo, W. Ye, K. Yu, A. Zeleniuch-Jacquette, H.B. Bueno-de-Mesquita, R.Z. Stolzenberg-Solomon, Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium, Am J Epidemiol 170(4) (2009) 403-13.
[68] S.L. Stewart, C.J. Cardinez, L.C. Richardson, L. Norman, R. Kaufmann, T.F. Pechacek, T.D. Thompson, H.K. Weir, S.A. Sabatino, C. Centers for Disease, Prevention, Surveillance for cancers associated with tobacco use--United States, 1999-2004, MMWR Surveill Summ 57(8) (2008) 1-33.
[69] L. Zou, R. Zhong, N. Shen, W. Chen, B. Zhu, J. Ke, X. Lu, T. Zhang, J. Lou, Z. Wang, L. Liu, L. Qi, X. Miao, Non-linear dose-response relationship between cigarette smoking and pancreatic cancer risk: evidence from a meta-analysis of 42 observational studies, Eur J Cancer 50(1) (2014) 193-203.

[70] B.K. Park, J.H. Seo, J.B. Chung, J.K. Choi, Lifestyle, body mass index, diabetes, and the risk of pancreatic cancer in a nationwide population-based cohort study with 7.4 million Korean subjects, Br J Cancer 127(3) (2022) 549-557.
[71] M.E. Arriaga, C.M. Vajdic, R.J. MacInnis, K. Canfell, D.J. Magliano, J.E. Shaw, J.E. Byles, G.G. Giles, A.W. Taylor, T.K. Gill, V. Hirani, R.G. Cumming, R.P. Mitchell, E. Banks, J. Marker, B.-A. Adelstein, M.A. Laaksonen, The burden of pancreatic cancer in Australia attributable to smoking, Med J Aust 210(5) (2019) 213-220.
[72] S. Iodice, S. Gandini, P. Maisonneuve, A.B. Lowenfels, Tobacco and the risk of pancreatic cancer: a review and meta-analysis, Langenbecks Arch Surg 393(4) (2008) 535-545.
[73] S.R. Chandana, L.M. Woods, F. Maxwell, R. Gandolfo, T. Bekaii-Saab, Risk factors for early-onset pancreatic ductal adenocarcinoma: A systematic literature review, Eur J Cancer 198 (2024) 113471.
[74] J. Qing-Long, Z. Shui-Sheng, Z. Shui-Sheng, Z. Jian-Wei, W. Cheng-Feng, Risk factors for early-onset pancreatic cancer patients, and survival analysis, 10(6) (2017) 9416-9423.
[75] R.R. McWilliams, P. Maisonneuve, W.R. Bamlet, G.M. Petersen, D. Li, H.A. Risch, H. Yu, E.T.H. Fontham, B. Luckett, C. Bosetti, E. Negri, C. La Vecchia, R. Talamini, H.B. Bueno de Mesquita, P. Bracci, S. Gallinger, R.E. Neale, A.B. Lowenfels, Risk Factors for Early-Onset and Very-Early-Onset Pancreatic Adenocarcinoma: A Pancreatic Cancer Case-Control Consortium (PanC4) Analysis, Pancreas 45(2) (2016) 311-316.
[76] H. Eguchi, H. Yamaue, M. Unno, M. Mizuma, S. Hamada, H. Igarashi, T. Kuroki, S. Satoi, Y. Shimizu, M. Tani, S. Tanno, Y. Hirooka, T. Fujii, A. Masamune, K. Mizumoto, T. Itoi, S. Egawa, Y. Kodama, M. Tanaka, T. Shimosegawa, J.P.S. Committee of Clinical Research, Clinicopathological Characteristics of Young Patients With Pancreatic Cancer: An Analysis of Data From Pancreatic Cancer Registry of Japan Pancreas Society, Pancreas 45(10) (2016) 1411-1417.
[77] A. Ohmoto, S. Yachida, E. Kubo, E. Takai, M. Suzuki, K. Shimada, T. Okusaka, C. Morizane, Clinicopathologic Features and Germline Sequence Variants in Young Patients (≤40 Years Old) With Pancreatic Ductal Adenocarcinoma, Pancreas 45(7) (2016) 1056-1061.
[78] Ș. Bunduc, R. Iacob, R. Costache, B. Stoica, C. Radu, C. Gheorghe, Very Early Onset Pancreatic Adenocarcinoma - Clinical Presentation, Risk Factors and Therapeutic Options, Chirurgia (Bucur) 113(3) (2018) 405-411.
[79] S. Raimondi, P. Maisonneuve, J.M. Löhr, A.B. Lowenfels, Early onset pancreatic cancer: evidence of a major role for smoking and genetic factors, Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology 16(9) (2007) 1894-1897.
[80] A. Vrieling, H.B. Bueno-de-Mesquita, H.C. Boshuizen, D.S. Michaud, M.T. Severinsen, K. Overvad, A. Olsen, A. Tjønneland, F. Clavel-Chapelon, M.-C. Boutron-Ruault, R. Kaaks, S. Rohrmann, H. Boeing, U. Nöthlings, A. Trichopoulou, E. Moutsiou, V. Dilis, D. Palli, V. Krogh, S. Panico, R. Tumino, P. Vineis, C.H. van Gils, P.H.M. Peeters, E. Lund, I.T. Gram, L. Rodríguez, A. Agudo, N. Larrañaga, M.-J. Sánchez, C. Navarro, A. Barricarte, J. Manjer, B. Lindkvist, M. Sund, W. Ye, S. Bingham, K.-T. Khaw, A. Roddam, T. Key, P. Boffetta, E.J. Duell, M. Jenab, V. Gallo, E. Riboli, Cigarette smoking, environmental tobacco smoke exposure and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition, International Journal of Cancer 126(10) (2010) 2394-2403.
[81] G.J. Tranah, E.A. Holly, F. Wang, P.M. Bracci, Cigarette, cigar and pipe smoking, passive smoke exposure, and risk of pancreatic cancer: a population-based study in the San Francisco Bay Area, BMC cancer 11 (2011) 138.

[82] P.J. Villeneuve, K.C. Johnson, Y. Mao, A.J. Hanley, G. Canadian Cancer Registries Research, Environmental tobacco smoke and the risk of pancreatic cancer: findings from a Canadian population-based case-control study, Can J Public Health 95(1) (2004) 32-37.
[83] M.M. Heinen, B.A.J. Verhage, R.A. Goldbohm, P.A. van den Brandt, Active and passive smoking and the risk of pancreatic cancer in the Netherlands Cohort Study, Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology 19(6) (2010) 1612-1622.
[84] L. Gallicchio, A. Kouzis, J.M. Genkinger, A.E. Burke, S.C. Hoffman, M. Diener-West, K.J. Helzlsouer, G.W. Comstock, A.J. Alberg, Active cigarette smoking, household passive smoke exposure, and the risk of developing pancreatic cancer, Prev Med 42(3) (2006) 200-205.
[85] D. Yadav, A.B. Lowenfels, The epidemiology of pancreatitis and pancreatic cancer, Gastroenterology 144(6) (2013) 1252-1261.
[86] I. Tramacere, L. Scotti, M. Jenab, V. Bagnardi, R. Bellocco, M. Rota, G. Corrao, F. Bravi, P. Boffetta, C. La Vecchia, Alcohol drinking and pancreatic cancer risk: a meta-analysis of the dose-risk relation, International Journal of Cancer 126(6) (2010) 1474-1486.
[87] E. Lucenteforte, C. La Vecchia, D. Silverman, G.M. Petersen, P.M. Bracci, B.T. Ji, C. Bosetti, D. Li, S. Gallinger, A.B. Miller, H.B. Bueno-de-Mesquita, R. Talamini, J. Polesel, P. Ghadirian, P.A. Baghurst, W. Zatonski, E. Fontham, W.R. Bamlet, E.A. Holly, Y.T. Gao, E. Negri, M. Hassan, M. Cotterchio, J. Su, P. Maisonneuve, P. Boffetta, E.J. Duell, Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4), Ann Oncol 23(2) (2012) 374-382.
[88] Y. Pang, M.V. Holmes, Y. Guo, L. Yang, Z. Bian, Y. Chen, A. Iona, I.Y. Millwood, F. Bragg, J. Chen, L. Li, C. Kartsonaki, Z. Chen, Smoking, alcohol, and diet in relation to risk of pancreatic cancer in China: a prospective study of 0.5 million people, Cancer Med 7(1) (2018) 229-239.
[89] J.M. Genkinger, D. Spiegelman, K.E. Anderson, L. Bergkvist, L. Bernstein, P.A. van den Brandt, D.R. English, J.L. Freudenheim, C.S. Fuchs, G.G. Giles, E. Giovannucci, S.E. Hankinson, P.L. Horn-Ross, M. Leitzmann, S. Männistö, J.R. Marshall, M.L. McCullough, A.B. Miller, D.J. Reding, K. Robien, T.E. Rohan, A. Schatzkin, V.L. Stevens, R.Z. Stolzenberg-Solomon, B.A.J. Verhage, A. Wolk, R.G. Ziegler, S.A. Smith-Warner, Alcohol intake and pancreatic cancer risk: a pooled analysis of fourteen cohort studies, Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology 18(3) (2009) 765-776.
[90] F. Rahman, M. Cotterchio, S.P. Cleary, S. Gallinger, Association between alcohol consumption and pancreatic cancer risk: a case-control study, PLoS One 10(4) (2015) e0124489.
[91] D.S. Michaud, A. Vrieling, L. Jiao, J.B. Mendelsohn, E. Steplowski, S.M. Lynch, J. Wactawski-Wende, A.A. Arslan, H. Bas Bueno-de-Mesquita, C.S. Fuchs, M. Gross, K. Helzlsouer, E.J. Jacobs, A. Lacroix, G. Petersen, W. Zheng, N. Allen, L. Ammundadottir, M.M. Bergmann, P. Boffetta, J.E. Buring, F. Canzian, S.J. Chanock, F. Clavel-Chapelon, S. Clipp, M.S. Freiberg, J. Michael Gaziano, E.L. Giovannucci, S. Hankinson, P. Hartge, R.N. Hoover, F. Allan Hubbell, D.J. Hunter, A. Hutchinson, K. Jacobs, C. Kooperberg, P. Kraft, J. Manjer, C. Navarro, P.H.M. Peeters, X.-O. Shu, V. Stevens, G. Thomas, A. Tjønneland, G.S. Tobias, D. Trichopoulos, R. Tumino, P. Vineis, J. Virtamo, R. Wallace, B.M. Wolpin, K. Yu, A. Zeleniuch-Jacquotte, R.Z. Stolzenberg-Solomon, Alcohol intake and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium (PanScan), Cancer Causes Control 21(8) (2010) 1213-1225.
[92] E.J. Duell, Epidemiology and potential mechanisms of tobacco smoking and heavy alcohol consumption in pancreatic cancer, Molecular Carcinogenesis 51(1) (2012) 40-52.
[93] W. Ye, J. Lagergren, E. Weiderpass, O. Nyrén, H.O. Adami, A. Ekbom, Alcohol abuse and the risk of pancreatic cancer, Gut 51(2) (2002) 236-239.

[94] Y. Lu, M. Gentiluomo, J. Lorenzo-Bermejo, L. Morelli, O. Obazee, D. Campa, F. Canzian, Mendelian randomisation study of the effects of known and putative risk factors on pancreatic cancer, 57(12) (2020) 820-828.
[95] S. Yuan, J. Chen, X. Ruan, Y. Sun, K. Zhang, X. Wang, X. Li, D. Gill, S. Burgess, E. Giovannucci, S.C. Larsson, Smoking, alcohol consumption, and 24 gastrointestinal diseases: Mendelian randomization analysis, Elife 12 (2023) e84051.
[96] A. Pagkali, A. Makris, K. Brofidi, A.P. Agouridis, T.D. Filippatos, Pathophysiological Mechanisms and Clinical Associations of Non-Alcoholic Fatty Pancreas Disease, Diabetes Metab Syndr Obes 17 (2024) 283-294.
[97] A.Q.M. Rezende, M.A. Gestic, M.P. Utrini, F.D.M. Chaim, H.P.A. Saito, E.A. Chaim, F. Callejas-Neto, E. Cazzo, Is there a link between non-alcoholic fatty liver disease aspects and pancreatic cancer? Results of a case-matched study, Rev Col Bras Cir 48 (2021) e20202913.
[98] T. Sakaue, H. Terabe, H. Takedatsu, T. Kawaguchi, Association between nonalcholic fatty liver disease and pancreatic cancer: Epidemiology, mechanisms, and antidiabetic medication, Hepatol Res 54(8) (2024) 729-735.
[99] M. Takahashi, M. Hori, R. Ishigamori, M. Mutoh, T. Imai, H. Nakagama, Fatty pancreas: A possible risk factor for pancreatic cancer in animals and humans, Cancer Sci 109(10) (2018) 3013-3023.
[100] X. Duan, W. Wang, Q. Pan, L. Guo, Type 2 Diabetes Mellitus Intersects With Pancreatic Cancer Diagnosis and Development, Front Oncol 11 (2021) 730038.
[101] E.E. Calle, C. Rodriguez, K. Walker-Thurmond, M.J. Thun, Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults, N Engl J Med 348(17) (2003) 1625-1638.
[102] J.M. Genkinger, D. Spiegelman, K.E. Anderson, L. Bernstein, P.A. van den Brandt, E.E. Calle, D.R. English, A.R. Folsom, J.L. Freudenheim, C.S. Fuchs, G.G. Giles, E. Giovannucci, P.L. Horn-Ross, S.C. Larsson, M. Leitzmann, S. Männistö, J.R. Marshall, A.B. Miller, A.V. Patel, T.E. Rohan, R.Z. Stolzenberg-Solomon, B.A.J. Verhage, J. Virtamo, B.J. Willcox, A. Wolk, R.G. Ziegler, S.A. Smith-Warner, A pooled analysis of 14 cohort studies of anthropometric factors and pancreatic cancer risk, International Journal of Cancer 129(7) (2011) 1708-1717.
[103] M. Dobbins, K. Decorby, B.C.K. Choi, The Association between Obesity and Cancer Risk: A Meta-Analysis of Observational Studies from 1985 to 2011, ISRN Prev Med 2013 (2013) 680536.
[104] L. Zohar, Y. Rottenberg, G. Twig, L. Katz, A. Leiba, E. Derazne, D. Tzur, S. Eizenstein, L. Keinan-Boker, A. Afek, J.D. Kark, Adolescent overweight and obesity and the risk for pancreatic cancer among men and women: a nationwide study of 1.79 million Israeli adolescents, Cancer 125(1) (2019) 118-126.
[105] D. Li, J.S. Morris, J. Liu, M.M. Hassan, R.S. Day, M.L. Bondy, J.L. Abbruzzese, Body mass index and risk, age of onset, and survival in patients with pancreatic cancer, JAMA 301(24) (2009) 2553-2562.
[106] Y. Pang, M.V. Holmes, C. Kartsonaki, Y. Guo, L. Yang, Z. Bian, Y. Chen, F. Bragg, A. Iona, I.Y. Millwood, J. Chen, L. Li, Z. Chen, Young adulthood and adulthood adiposity in relation to incidence of pancreatic cancer: a prospective study of 0.5 million Chinese adults and a meta-analysis, J Epidemiol Community Health 71(11) (2017) 1059-1067.
[107] G. Fagherazzi, N. Chabbert-Buffet, A. Fabre, G. Guillas, M.C. Boutron-Ruault, S. Mesrine, F. Clavel-Chapelon, Hip circumference is associated with the risk of premenopausal ER-/PR- breast cancer, Int J Obes (Lond) 36(3) (2012) 431-439.
[108] H. Freisling, M. Arnold, I. Soerjomataram, M.G. O'Doherty, J.M. Ordóñez-Mena, C. Bamia, E. Kampman, M. Leitzmann, I. Romieu, F. Kee, K. Tsilidis, A. Tjønneland, A. Trichopoulou, P. Boffetta, V. Benetou, H.B.A. Bueno-de-Mesquita, J.M. Huerta, H. Brenner, T. Wilsgaard, M. Jenab,

Comparison of general obesity and measures of body fat distribution in older adults in relation to cancer risk: meta-analysis of individual participant data of seven prospective cohorts in Europe, British Journal of Cancer 116(11) (2017) 1486-1497.
[109] L. Lissner, C. Björkelund, B.L. Heitmann, J.C. Seidell, C. Bengtsson, Larger hip circumference independently predicts health and longevity in a Swedish female cohort, Obes Res 9(10) (2001) 644-646.
[110] S. Shyam, D. Greenwood, C.-W. Mai, S.S. Tan, B.N. Mohd Yusof, F.M. Moy, J. Cade, Traditional and Novel Adiposity Indicators and Pancreatic Cancer Risk: Findings from the UK Women's Cohort Study, Cancers 13(5) (2021) 1036.
[111] A. Berrington de González, E.A. Spencer, H.B. Bueno-de-Mesquita, A. Roddam, R. Stolzenberg-Solomon, J. Halkjaer, A. Tjønneland, K. Overvad, F. Clavel-Chapelon, M.-C. Boutron-Ruault, H. Boeing, T. Pischon, J. Linseisen, S. Rohrmann, A. Trichopoulou, V. Benetou, A. Papadimitriou, V. Pala, D. Palli, S. Panico, R. Tumino, P. Vineis, H.C. Boshuizen, M.C. Ocke, P.H. Peeters, E. Lund, C.A. Gonzalez, N. Larrañaga, C. Martinez-Garcia, M. Mendez, C. Navarro, J.R. Quirós, M.-J. Tormo, G. Hallmans, W. Ye, S.A. Bingham, K.-T. Khaw, N. Allen, T.J. Key, M. Jenab, T. Norat, P. Ferrari, E. Riboli, Anthropometry, physical activity, and the risk of pancreatic cancer in the European prospective investigation into cancer and nutrition, Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology 15(5) (2006) 879-885.
[112] R.Z. Stolzenberg-Solomon, K. Adams, M. Leitzmann, C. Schairer, D.S. Michaud, A. Hollenbeck, A. Schatzkin, D.T. Silverman, Adiposity, physical activity, and pancreatic cancer in the National Institutes of Health-AARP Diet and Health Cohort, American Journal of Epidemiology 167(5) (2008) 586-597.
[113] R. Carreras-Torres, M. Johansson, V. Gaborieau, P.C. Haycock, K.H. Wade, C.L. Relton, R.M. Martin, G. Davey Smith, P. Brennan, The Role of Obesity, Type 2 Diabetes, and Metabolic Factors in Pancreatic Cancer: A Mendelian Randomization Study, J Natl Cancer Inst 109(9) (2017).
[114] M. Gentiluomo, S.C. Dixon-Suen, R. Farinella, G. Peduzzi, F. Canzian, R.L. Milne, B.M. Lynch, D. Campa, Physical Activity, Sedentary Behavior, and Pancreatic Cancer Risk: A Mendelian Randomization Study, J Endocr Soc 8(4) (2024) bvae017.
[115] V. Gianfredi, P. Ferrara, M. Dinu, M. Nardi, D. Nucci, Diets, Dietary Patterns, Single Foods and Pancreatic Cancer Risk: An Umbrella Review of Meta-Analyses, International Journal of Environmental Research and Public Health 19(22) (2022) 14787.
[116] G. Grosso, F. Bella, J. Godos, S. Sciacca, D. Del Rio, S. Ray, F. Galvano, E.L. Giovannucci, Possible role of diet in cancer: systematic review and multiple meta-analyses of dietary patterns, lifestyle factors, and cancer risk, Nutr Rev 75(6) (2017) 405-419.
[117] Y. Zhao, J. Zhan, Y. Wang, D. Wang, The Relationship Between Plant-Based Diet and Risk of Digestive System Cancers: A Meta-Analysis Based on 3,059,009 Subjects, Front Public Health 10 (2022) 892153.
[118] Z. Guo, Y. Hong, Y. Cheng, Dietary inflammatory index and pancreatic cancer risk: a systematic review and dose-response meta-analysis, Public Health Nutr 24(18) (2021) 6427-6435.
[119] A. Jayedi, A. Emadi, S. Shab-Bidar, Dietary Inflammatory Index and Site-Specific Cancer Risk: A Systematic Review and Dose-Response Meta-Analysis, Adv Nutr 9(4) (2018) 388-403.
[120] X. Qin, J. Chen, G. Jia, Z. Yang, Dietary Factors and Pancreatic Cancer Risk: An Umbrella Review of Meta-Analyses of Prospective Observational Studies, Advances in Nutrition (Bethesda, Md.) 14(3) (2023) 451-464.
[121] L. Schwingshackl, G. Hoffmann, Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis of observational studies, Cancer Med 4(12) (2015) 1933-47.

[122] J. Zheng, M.A. Guinter, A.T. Merchant, M.D. Wirth, J. Zhang, R.Z. Stolzenberg-Solomon, S.E. Steck, Dietary patterns and risk of pancreatic cancer: a systematic review, Nutr Rev 75(11) (2017) 883-908.
[123] S. Naghshi, M. Sadeghian, M. Nasiri, S. Mobarak, M. Asadi, O.A.-O. Sadeghi, Association of Total Nut, Tree Nut, Peanut, and Peanut Butter Consumption with Cancer Incidence and Mortality: A Comprehensive Systematic Review and Dose-Response Meta-Analysis of Observational Studies, (2156-5376 (Electronic)).
[124] D. Zhang, C. Dai, L. Zhou, Y. Li, K. Liu, Y.-J. Deng, N. Li, Y. Zheng, Q. Hao, S. Yang, D. Song, Y. Wu, Z. Zhai, S. Cao, Z. Dai, Meta-analysis of the association between nut consumption and the risks of cancer incidence and cancer-specific mortality, Aging (Albany NY) 12(11) (2020) 10772-10794.
[125] P. Paluszkiewicz, K. Smolińska, I. Dębińska, W.A. Turski, Main dietary compounds and pancreatic cancer risk. The quantitative analysis of case–control and cohort studies, Cancer Epidemiology 36(1) (2012) 60-67.
[126] Z. Zhao, Z. Yin, Z. Pu, Q. Zhao, Association Between Consumption of Red and Processed Meat and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis, Clin Gastroenterol Hepatol 15(4) (2017) 486-493.e10.
[127] S.C. Larsson, A. Wolk, Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies, British Journal of Cancer 106(3) (2012) 603-607.
[128] D. Aune, D.S.M. Chan, A.R. Vieira, D.A. Navarro Rosenblatt, R. Vieira, D.C. Greenwood, J.E. Cade, V.J. Burley, T. Norat, Dietary fructose, carbohydrates, glycemic indices and pancreatic cancer risk: a systematic review and meta-analysis of cohort studies, Ann Oncol 23(10) (2012) 2536-2546.
[129] C.H. Chen, M.K. Tsai, J.H. Lee, R.T. Lin, C.Y. Hsu, C. Wen, X. Wu, T.W. Chu, C.P. Wen, "Sugar-Sweetened Beverages" Is an Independent Risk From Pancreatic Cancer: Based on Half a Million Asian Cohort Followed for 25 Years, Front Oncol 12 (2022) 835901.
[130] S.C. Larsson, L. Bergkvist, A. Wolk, Consumption of sugar and sugar-sweetened foods and the risk of pancreatic cancer in a prospective study, Am J Clin Nutr 84(5) (2006) 1171-6.
[131] E.W. Davis, S.E. McCann, J.M. Joseph, K.H.K. Yeary, C. Fountzilas, K.B. Moysich, Sugar Sweetened and Artificially Sweetened Beverage Consumption and Pancreatic Cancer: A Retrospective Study, Nutrients 15(2) (2023).
[132] K.E. Diaz, A.L. Lucas, Familial Pancreatic Ductal Adenocarcinoma, Am J Pathol 189(1) (2019) 36-43.
[133] E.M. Navarrete-Munoz, P.A. Wark, D. Romaguera, N. Bhoo-Pathy, D. Michaud, E. Molina-Montes, A. Tjonneland, A. Olsen, K. Overvad, M.C. Boutron-Ruault, F. Clavel-Chapelon, G. Fagherazzi, V.A. Katzke, T. Kuhn, A. Steffen, A. Trichopoulou, E. Klinaki, E.M. Papatesta, G. Masala, V. Krogh, R. Tumino, A. Naccarati, A. Mattiello, P.H. Peeters, C. Rylander, C.L. Parr, G. Skeie, E. Weiderpass, J.R. Quiros, E.J. Duell, M. Dorronsoro, J.M. Huerta, E. Ardanaz, N. Wareham, K.T. Khaw, R.C. Travis, T. Key, M. Stepien, H. Freisling, E. Riboli, H.B. Bueno-de-Mesquita, Sweet-beverage consumption and risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC), Am J Clin Nutr 104(3) (2016) 760-8.
[134] E.S. Schernhammer, F.B. Hu, E. Giovannucci, D.S. Michaud, G.A. Colditz, M.J. Stampfer, C.S. Fuchs, Sugar-sweetened soft drink consumption and risk of pancreatic cancer in two prospective cohorts, Cancer Epidemiol Biomarkers Prev 14(9) (2005) 2098-105.
[135] Y. Li, V.L. Go, F.H. Sarkar, The Role of Nutraceuticals in Pancreatic Cancer Prevention and Therapy: Targeting Cellular Signaling, MicroRNAs, and Epigenome, Pancreas 44(1) (2015) 1-10.
[136] R. Noe, A. Carrer, Diet predisposes to pancreatic cancer through cellular nutrient sensing pathways, FEBS Lett 598(20) (2024) 2470-2481.
[137] D. Nucci, M. Nardi, A. Cinnirella, E. Campagnoli, M. Maffeo, P.M. Perrone, V. Shishmintseva, F.M. Grosso, A. Castrofino, S. Castaldi, L. Romano, V. Gianfredi, Adherence to Mediterranean Diet

and Risk of Pancreatic Cancer: Systematic Review and Meta-Analysis, Int J Environ Res Public Health 20(3) (2023).
[138] Y. Bao, D.S. Michaud, Physical activity and pancreatic cancer risk: a systematic review, Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology 17(10) (2008) 2671-2682.
[139] D.R. Brenner, M.B. Wozniak, C. Feyt, I. Holcatova, V. Janout, L. Foretova, E. Fabianova, O. Shonova, A. Martinek, M. Ryska, Z. Adamcakova, E. Flaska, A. Moskal, P. Brennan, G. Scelo, Physical activity and risk of pancreatic cancer in a central European multicenter case-control study, Cancer Causes Control 25(6) (2014) 669-681.
[140] H. Cui, Y. Qu, L. Zhang, W. Zhang, P. Yan, C. Yang, M. Zhang, Y. Bai, M. Tang, Y. Wang, L. Chen, C. Xiao, Y. Zou, Y. Liu, L. Zhang, Y. Yang, Y. Yao, J. Li, Z. Liu, C. Yang, X. Jiang, B. Zhang, Epidemiological and genetic evidence for the relationship between ABO blood group and human cancer, International Journal of Cancer 153(2) (2023) 320-330.
[141] M.A. O'Rorke, M.M. Cantwell, C.R. Cardwell, H.G. Mulholland, L.J. Murray, Can physical activity modulate pancreatic cancer risk? a systematic review and meta-analysis, International Journal of Cancer 126(12) (2010) 2957-2968.
[142] A.V. Patel, C.M. Friedenreich, S.C. Moore, S.C. Hayes, J.K. Silver, K.L. Campbell, K. Winters-Stone, L.H. Gerber, S.M. George, J.E. Fulton, C. Denlinger, G.S. Morris, T. Hue, K.H. Schmitz, C.E. Matthews, American College of Sports Medicine Roundtable Report on Physical Activity, Sedentary Behavior, and Cancer Prevention and Control, Med Sci Sports Exerc 51(11) (2019) 2391-2402.
[143] G. Peduzzi, A. Felici, R. Pellungrini, F. Giorgolo, R. Farinella, M. Gentiluomo, A. Spinelli, G. Capurso, A. Monreale, F. Canzian, M. Calderisi, D. Campa, Analysis of exposome and genetic variability suggests stress as a major contributor for development of pancreatic ductal adenocarcinoma, Digestive and Liver Disease (2023).
[144] I.W.G.o.t.E.o.C.R.t. Humans, Outdoor Air Pollution, IARC Monogr Eval Carcinog Risks Hum 109 (2016) 9-444.
[145] C. Ancona, C. Badaloni, F. Mataloni, A. Bolignano, S. Bucci, G. Cesaroni, R. Sozzi, M. Davoli, F. Forastiere, Mortality and morbidity in a population exposed to multiple sources of air pollution: A retrospective cohort study using air dispersion models, Environ Res 137 (2015) 467-474.
[146] D. Bogumil, A.H. Wu, D. Stram, J. Yang, C.-C. Tseng, L. Le Marchand, J. Wu, I. Cheng, V.W. Setiawan, The association between ambient air pollutants and pancreatic cancer in the Multiethnic Cohort Study, Environ Res 202 (2021) 111608.
[147] N.C. Coleman, R.T. Burnett, J.D. Higbee, J.S. Lefler, R.M. Merrill, M. Ezzati, J.D. Marshall, S.-Y. Kim, M. Bechle, A.L. Robinson, C.A. Pope, Cancer mortality risk, fine particulate air pollution, and smoking in a large, representative cohort of US adults, Cancer Causes Control 31(8) (2020) 767-776.
[148] A. Craver, J. Luo, M.G. Kibriya, N. Randorf, K. Bahl, E. Connellan, J. Powell, P. Zakin, R.R. Jones, M. Argos, J. Ho, K. Kim, M.L. Daviglus, P. Greenland, H. Ahsan, B. Aschebrook-Kilfoy, Air quality and cancer risk in the All of Us Research Program, Cancer Causes Control 35(5) (2024) 749-760.
[149] A. Felici, G. Peduzzi, F. Giorgolo, A. Spinelli, M. Calderisi, A. Monreale, R. Farinella, R. Pellungrini, F. Canzian, D. Campa, The local environment and germline genetic variation predict cancer risk in the UK Biobank prospective cohort, Environ Res 241 (2024) 117562.
[150] M.C. Turner, D. Krewski, W.R. Diver, C.A. Pope, R.T. Burnett, M. Jerrett, J.D. Marshall, S.M. Gapstur, Ambient Air Pollution and Cancer Mortality in the Cancer Prevention Study II, Environ Health Perspect 125(8) (2017) 087013.

[151] Y. Wang, M. Li, X. Wan, Y. Sun, K. Cheng, X. Zhao, Y. Zheng, G. Yang, L. Wang, Spatiotemporal analysis of PM2.5 and pancreatic cancer mortality in China, Environ Res 164 (2018) 132-139.
[152] J.R. Freeman, P.F. Saint-Maurice, T. Zhang, C.E. Matthews, R.Z. Stolzenberg-Solomon, Sleep and Risk of Pancreatic Cancer in the UK Biobank, Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology 33(4) (2024) 624-627.
[153] C.R. Stone, T.R. Haig, K.M. Fiest, J. McNeil, D.R. Brenner, C.M. Friedenreich, The association between sleep duration and cancer-specific mortality: a systematic review and meta-analysis, Cancer Causes Control 30(5) (2019) 501-525.
[154] O.E. Titova, K. Michaëlsson, M. Vithayathil, A.M. Mason, S. Kar, S. Burgess, S.C. Larsson, Sleep duration and risk of overall and 22 site-specific cancers: A Mendelian randomization study, International Journal of Cancer 148(4) (2021) 914-920.
[155] M. Xiao, Y. Wang, Y. Gao, Association between Helicobacter pylori infection and pancreatic cancer development: a meta-analysis, PLoS One 8(9) (2013) e75559.
[156] M.-É. Parent, M. El-Zein, M.-C. Rousseau, J. Pintos, J. Siemiatycki, Night work and the risk of cancer among men, American Journal of Epidemiology 176(9) (2012) 751-759.
[157] Y. Lin, J. Ueda, K. Yagyu, M. Kurosawa, A. Tamakoshi, S. Kikuchi, A prospective cohort study of shift work and the risk of death from pancreatic cancer in Japanese men, Cancer Causes Control 24(7) (2013) 1357-1361.
[158] P. Li, Y. Hu, G. Scelo, M. Myrskyla, P. Martikainen, Pre-existing psychological disorders, diabetes, and pancreatic cancer: A population-based study of 38,952 Finns, Cancer Epidemiol 82 (2023) 102307.
[159] J. Huang, U. Valdimarsdóttir, K. Fall, W. Ye, F. Fang, Pancreatic cancer risk after loss of a child: a register-based study in Sweden during 1991-2009, American Journal of Epidemiology 178(4) (2013) 582-589.
[160] T.I. Nilsen, L.J. Vatten, A prospective study of lifestyle factors and the risk of pancreatic cancer in Nord-Trondelag, Norway, Cancer Causes Control 11(7) (2000) 645-52.
[161] A. Alvarez, K. Benjaminsen Borch, C. Rylander, Reproductive Factors, Use of Exogenous Hormones, and Pancreatic Cancer Incidence: The Norwegian Women and Cancer Study, Clin Epidemiol 13 (2021) 67-80.
[162] G. Andersson, S. Borgquist, K. Jirstrom, Hormonal factors and pancreatic cancer risk in women: The Malmo Diet and Cancer Study, Int J Cancer 143(1) (2018) 52-62.
[163] L. Archibugi, B. Graglia, R. Valente, S. Stigliano, M. Roberto, C. Capalbo, P. Marchetti, G. Nigri, G. Capurso, Gynecological and reproductive factors and the risk of pancreatic cancer: A case-control study, Pancreatology 20(6) (2020) 1149-1154.
[164] K. Azeem, D. Horakova, H. Tomaskova, J. Sevcikova, J. Vlckova, D. Pastucha, V. Prochazka, O. Shonova, A. Martinek, V. Janout, V. Zidkova, H. Kollarova, [A multifactor epidemiological analysis of risk factors for pancreatic cancer in women], Epidemiol Mikrobiol Imunol 64(1) (2015) 34-40.
[165] H.B. Bueno de Mesquita, P. Maisonneuve, C.J. Moerman, A.M. Walker, Anthropometric and reproductive variables and exocrine carcinoma of the pancreas: a population-based case-control study in The Netherlands, Int J Cancer 52(1) (1992) 24-9.
[166] S.A. Butt, O. Lidegaardi, C. Skovlund, P.C. Hannaford, L. Iversen, S. Fielding, L.S. Morch, Hormonal contraceptive use and risk of pancreatic cancer-A cohort study among premenopausal women, PLoS One 13(10) (2018) e0206358.
[167] T. Dorjgochoo, X.O. Shu, H.L. Li, H.Z. Qian, G. Yang, H. Cai, Y.T. Gao, W. Zheng, Use of oral contraceptives, intrauterine devices and tubal sterilization and cancer risk in a large prospective study, from 1996 to 2006, Int J Cancer 124(10) (2009) 2442-9.

[168] E.J. Duell, E.A. Holly, Reproductive and menstrual risk factors for pancreatic cancer: a population-based study of San Francisco Bay Area women, Am J Epidemiol 161(8) (2005) 741-7.
[169] E.J. Duell, P. Maisonneuve, P.A. Baghurst, H.B. Bueno-de-Mesquita, P. Ghadirian, A.B. Miller, W. Zatonski, A. Vrieling, P. Boffetta, P. Boyle, Menstrual and reproductive factors and pancreatic cancer in the SEARCH program of the IARC, Cancer Causes Control 20(9) (2009) 1757-62.
[170] E.J. Duell, N. Travier, L. Lujan-Barroso, L. Dossus, M.C. Boutron-Ruault, F. Clavel-Chapelon, R. Tumino, G. Masala, V. Krogh, S. Panico, F. Ricceri, M.L. Redondo, M. Dorronsoro, E. Molina-Montes, J.M. Huerta, A. Barricarte, K.T. Khaw, N.J. Wareham, N.E. Allen, R. Travis, P.D. Siersema, P.H. Peeters, A. Trichopoulou, E. Fragogeorgi, E. Oikonomou, H. Boeing, M. Schuetze, F. Canzian, A. Lukanova, A. Tjonneland, N. Roswall, K. Overvad, E. Weiderpass, I.T. Gram, E. Lund, B. Lindkvist, D. Johansen, W. Ye, M. Sund, V. Fedirko, M. Jenab, D.S. Michaud, E. Riboli, H.B. Bueno-de-Mesquita, Menstrual and reproductive factors in women, genetic variation in CYP17A1, and pancreatic cancer risk in the European prospective investigation into cancer and nutrition (EPIC) cohort, Int J Cancer 132(9) (2013) 2164-75.
[171] B.T. Ji, M.C. Hatch, W.H. Chow, J.K. McLaughlin, Q. Dai, G.R. Howe, Y.T. Gao, J.F. Fraumeni, Jr., Anthropometric and reproductive factors and the risk of pancreatic cancer: a case-control study in Shanghai, China, Int J Cancer 66(4) (1996) 432-7.
[172] G.C. Kabat, V. Kamensky, T.E. Rohan, Reproductive factors, exogenous hormone use, and risk of pancreatic cancer in postmenopausal women, Cancer Epidemiol 49 (2017) 1-7.
[173] N. Kreiger, J. Lacroix, M. Sloan, Hormonal factors and pancreatic cancer in women, Ann Epidemiol 11(8) (2001) 563-7.
[174] E. Lee, P.L. Horn-Ross, R.P. Rull, S.L. Neuhausen, H. Anton-Culver, G. Ursin, K.D. Henderson, L. Bernstein, Reproductive factors, exogenous hormones, and pancreatic cancer risk in the CTS, Am J Epidemiol 178(9) (2013) 1403-13.
[175] E. Lucenteforte, A. Zucchetto, C. Bosetti, R. Talamini, E. Negri, D. Serraino, S. Franceschi, L. Lipworth, C. La Vecchia, Reproductive and hormonal factors and pancreatic cancer risk in women, Pancreas 40(3) (2011) 460-3.
[176] L. Lujan-Barroso, W. Zhang, S.H. Olson, Y.T. Gao, H. Yu, P.A. Baghurst, P.M. Bracci, H.B. Bueno-de-Mesquita, L. Foretova, S. Gallinger, I. Holcatova, V. Janout, B.T. Ji, R.C. Kurtz, C. La Vecchia, P. Lagiou, D. Li, A.B. Miller, D. Serraino, W. Zatonski, H.A. Risch, E.J. Duell, Menstrual and Reproductive Factors, Hormone Use, and Risk of Pancreatic Cancer: Analysis From the International Pancreatic Cancer Case-Control Consortium (PanC4), Pancreas 45(10) (2016) 1401-1410.
[177] S. Masoudi, Z. Momayez Sanat, A. Mahmud Saleh, N. Nozari, N. Ghamarzad, A. Pourshams, Menstrual and Reproductive Factors and Risk of Pancreatic Cancer in Women, Middle East J Dig Dis 9(3) (2017) 146-149.
[178] K.A. Michels, L.A. Brinton, R.M. Pfeiffer, B. Trabert, Oral Contraceptive Use and Risks of Cancer in the NIH-AARP Diet and Health Study, Am J Epidemiol 187(8) (2018) 1630-1641.
[179] S.A. Navarro Silvera, A.B. Miller, T.E. Rohan, Hormonal and reproductive factors and pancreatic cancer risk: a prospective cohort study, Pancreas 30(4) (2005) 369-74.
[180] A.E. Prizment, K.E. Anderson, C.P. Hong, A.R. Folsom, Pancreatic cancer incidence in relation to female reproductive factors: Iowa Women's Health Study, JOP 8(1) (2007) 16-27.
[181] H.G. Skinner, D.S. Michaud, G.A. Colditz, E.L. Giovannucci, M.J. Stampfer, W.C. Willett, C.S. Fuchs, Parity, reproductive factors, and the risk of pancreatic cancer in women, Cancer Epidemiol Biomarkers Prev 12(5) (2003) 433-8.
[182] B. Tang, J. Lv, Y. Li, S. Yuan, Z. Wang, S. He, Relationship between female hormonal and menstrual factors and pancreatic cancer: a meta-analysis of observational studies, Medicine (Baltimore) 94(7) (2015) e177.

[183] Y. Teng, E. Saito, S.K. Abe, N. Sawada, M. Iwasaki, T. Yamaji, T. Shimazu, S. Sasazuki, M. Inoue, S. Tsugane, J.S. Group, Female reproductive factors, exogenous hormone use, and pancreatic cancer risk: the Japan Public Health Center-based prospective study, Eur J Cancer Prev 26(5) (2017) 378-384.
[184] L.R. Teras, A.V. Patel, C. Rodriguez, M.J. Thun, E.E. Calle, Parity, other reproductive factors, and risk of pancreatic cancer mortality in a large cohort of U.S. women (United States), Cancer Causes Control 16(9) (2005) 1035-40.
[185] Y. Zhang, P.F. Coogan, J.R. Palmer, B.L. Strom, L. Rosenberg, A case-control study of reproductive factors, female hormone use, and risk of pancreatic cancer, Cancer Causes Control 21(3) (2010) 473-8.
[186] M. Ilic, B. Milicic, I. Ilic, Association between oral contraceptive use and pancreatic cancer risk: A systematic review and meta-analysis, World J Gastroenterol 27(20) (2021) 2643-2656.
[187] J.H. Nam, S.I. Jang, H.S. Park, J.H. Kim, J.K. Lee, Y.J. Lim, M.S. Koh, J.H. Lee, S. Park, C.M. Nam, E.C. Park, The effect of menopausal hormone therapy on gastrointestinal cancer risk and mortality in South Korea: a population-based cohort study, BMC Gastroenterol 21(1) (2021) 440.
[188] B.A. Watkins, Influences of biotin deficiency and dietary trans-fatty acids on tissue lipids in chickens, Br J Nutr 61(1) (1989) 99-111.
[189] E. Fernandez, C. La Vecchia, B. D'Avanzo, E. Negri, Menstrual and reproductive factors and pancreatic cancer risk in women, Int J Cancer 62(1) (1995) 11-4.
[190] V. Kalapothaki, A. Tzonou, C.C. Hsieh, N. Toupadaki, A. Karakatsani, D. Trichopoulos, Tobacco, ethanol, coffee, pancreatitis, diabetes mellitus, and cholelithiasis as risk factors for pancreatic carcinoma, Cancer Causes Control 4(4) (1993) 375-82.
[191] Y. Lin, S. Kikuchi, A. Tamakoshi, T. Kawamura, Y. Inaba, M. Kurosawa, Y. Motohashi, K. Yagyu, Y. Obata, T. Ishibashi, J.S. Group, Association of menstrual and reproductive factors with pancreatic cancer risk in women: findings of the Japan Collaborative Cohort Study for Evaluation of Cancer Risk, J Gastroenterol 41(9) (2006) 878-83.
[192] R.J. Stevens, A.W. Roddam, J. Green, K. Pirie, D. Bull, G.K. Reeves, V. Beral, C. Million Women Study, Reproductive history and pancreatic cancer incidence and mortality in a cohort of postmenopausal women, Cancer Epidemiol Biomarkers Prev 18(5) (2009) 1457-60.
[193] B. Zhu, L. Zou, J. Han, W. Chen, N. Shen, R. Zhong, J. Li, X. Chen, C. Liu, Y. Shi, X. Miao, Parity and pancreatic cancer risk: evidence from a meta-analysis of twenty epidemiologic studies, Scientific Reports 4 (2014) 5313.
[194] G. Peduzzi, L. Archibugi, V. Katzke, M. Gentiluomo, G. Capurso, A.C. Milanetto, M. Gazouli, M. Goetz, H. Brenner, R.C.H. Vermeulen, R. Talar-Wojnarowska, G. Vanella, F. Tavano, M. Lucchesi, B. Mohelnikova-Duchonova, X. Chen, V. Kiudelis, P. Hegyi, M. Oliverius, H. Stocker, C. Stornello, L. Vodickova, P. Souček, J.P. Neoptolemos, S.G.G. Testoni, L. Morelli, R.T. Lawlor, D. Basso, J.R. Izbicki, S. Ermini, J. Kupcinskas, R. Pezzilli, U. Boggi, H.W.M. van Laarhoven, A. Szentesi, B. Erőss, G. Capretti, B. Schöttker, J. Skieceviciene, M.N. Aoki, C.H.J. van Eijck, G.M. Cavestro, F. Canzian, D. Campa, Common variability in oestrogen-related genes and pancreatic ductal adenocarcinoma risk in women, Scientific Reports 12(1) (2022) 18100.
[195] K. Bibbins-Domingo, U.S.P.S.T. Force, Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement, Ann Intern Med 164(12) (2016) 836-845.
[196] Y. Cao, R. Nishihara, K.N. Wu, M.L. Wang, S. Ogino, W.C. Willett, D. Spiegelman, C.S. Fuchs, E.L. Giovannucci, A.T. Chan, Population-wide Impact of Long-term Use of Aspirin and the Risk for Cancer, Jama Oncol 2(6) (2016) 762-769.

[197] A. Kokawa, H. Kondo, T. Gotoda, H. Ono, D. Saito, S. Nakadaira, T. Kosuge, S. Yoshida, Increased expression of cyclooxygenase-2 in human pancreatic neoplasms and potential for chemoprevention by cyclooxygenase inhibitors, Cancer 91(2) (2001) 333-338.
[198] R.A. Perugini, T.P. McDade, F.J. Vittimberga, Jr., A.J. Duffy, M.P. Callery, Sodium salicylate inhibits proliferation and induces G1 cell cycle arrest in human pancreatic cancer cell lines, J Gastrointest Surg 4(1) (2000) 24-32, discussion 32-3.
[199] C. Bosetti, C. Santucci, S. Gallus, M. Martinetti, C. La Vecchia, Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis through 2019, Ann Oncol 31(5) (2020) 558-568.
[200] C. Bosetti, V. Rosato, S. Gallus, J. Cuzick, C. La Vecchia, Aspirin and cancer risk: a quantitative review to 2011, Ann Oncol 23(6) (2012) 1403-15.
[201] Y. Qiao, T. Yang, Y. Gan, W. Li, C. Wang, Y. Gong, Z. Lu, Associations between aspirin use and the risk of cancers: a meta-analysis of observational studies, BMC Cancer 18(1) (2018) 288.
[202] D. Florensa, J. Mateo, F. Solsona, L. Galván, M. Mesas, R. Piñol, L. Espinosa-Leal, P. Godoy, Low-dose acetylsalicylic acid for cancer prevention considering risk factors: a retrospective cohort study, Annals of Epidemiology 84 (2023) 60-66.
[203] T.M. Brasky, L.R. Jager, A.M. Newton, X. Li, H.A. Loomans-Kropp, J.L. Hays, K.L. Margolis, J. Luo, Use of Nonsteroidal Anti-Inflammatory Drugs and Pancreatic Cancer Risk in the Women's Health Initiative, Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology 33(9) (2024) 1203-1210.
[204] G. Khoudari, M. Alkhayyat, M. Abou Saleh, E. Mansoor, M.T. Sarmini, F. Baidoun, K.J. Vega, M.R. Sanaka, The Epidemiology of Pancreatic Cancer and the Association With Acetylsalicylic Acid in the United States: A Population-Based Study, Pancreas 49(9) (2020) 1207-1212.
[205] H.A. Loomans-Kropp, P. Pinsky, A. Umar, Evaluation of Aspirin Use With Cancer Incidence and Survival Among Older Adults in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, JAMA Netw Open 4(1) (2021) e2032072.
[206] Z. Momayez Sanat, S. Masoudi, S.P. Tabaeian, M. Jameh Shorani, M. Soruri, A. Pourshams, Aspirin Use and Risk of Pancreatic Ductal Adenocarcinoma: A Large Case-Control Study, Arch Iran Med 26(4) (2023) 181-185.
[207] D. Tamburrino, G. Guarneri, M. Pagnanelli, S. Crippa, S. Partelli, G. Belfiori, G. Capurso, M. Falconi, Chemopreventive Agents After Pancreatic Resection for Ductal Adenocarcinoma: Legend or Scientific Evidence?, Ann Surg Oncol 28(4) (2021) 2312-2322.
[208] I. Pernicova, M. Korbonits, Metformin--mode of action and clinical implications for diabetes and cancer, Nat Rev Endocrinol 10(3) (2014) 143-56.
[209] T. Laeeq, M. Ahmed, H. Sattar, M.H. Zeeshan, M.B. Ali, Role of SGLT2 Inhibitors, DPP-4 Inhibitors, and Metformin in Pancreatic Cancer Prevention, Cancers 16(7) (2024) 1325.
[210] M. Pollak, The insulin and insulin-like growth factor receptor family in neoplasia: an update, Nat Rev Cancer 12(3) (2012) 159-69.
[211] M. Franciosi, G. Lucisano, E. Lapice, G.F. Strippoli, F. Pellegrini, A. Nicolucci, Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review, PLoS One 8(8) (2013) e71583.
[212] J. Hu, H.D. Fan, J.P. Gong, Q.S. Mao, The relationship between the use of metformin and the risk of pancreatic cancer in patients with diabetes: a systematic review and meta-analysis, BMC Gastroenterol 23(1) (2023) 50.
[213] H. Noto, A. Goto, T. Tsujimoto, M. Noda, Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis, PLoS One 7(3) (2012) e33411.

[214] S. Singh, P.P. Singh, A.G. Singh, M.H. Murad, R.R. McWilliams, S.T. Chari, Anti-diabetic medications and risk of pancreatic cancer in patients with diabetes mellitus: a systematic review and meta-analysis, Am J Gastroenterol 108(4) (2013) 510-9; quiz 520.
[215] Z. Wang, S.T. Lai, L. Xie, J.D. Zhao, N.Y. Ma, J. Zhu, Z.G. Ren, G.L. Jiang, Metformin is associated with reduced risk of pancreatic cancer in patients with type 2 diabetes mellitus: a systematic review and meta-analysis, Diabetes Res Clin Pract 106(1) (2014) 19-26.
[216] K. Zhang, P. Bai, H. Dai, Z. Deng, Metformin and risk of cancer among patients with type 2 diabetes mellitus: A systematic review and meta-analysis, Prim Care Diabetes 15(1) (2021) 52-58.
[217] Y. Chen, F. Mushashi, S. Son, P. Bhatti, T. Dummer, R.A. Murphy, Diabetes medications and cancer risk associations: a systematic review and meta-analysis of evidence over the past 10 years, Scientific Reports 13(1) (2023) 11844.
[218] Z. Zhao, X. He, Y. Sun, Hypoglycemic agents and incidence of pancreatic cancer in diabetic patients: a meta-analysis, Front Pharmacol 14 (2023) 1193610.
[219] Y. Teper, L. Ye, R.T. Waldron, A. Lugea, X. Sun, J. Sinnett-Smith, O.J. Hines, S.J. Pandol, E. Rozengurt, G. Eibl, Low dosage combination treatment with metformin and simvastatin inhibits obesity-promoted pancreatic cancer development in male KrasG12D mice, Scientific Reports 13(1) (2023) 16144.
[220] Z. Nowicka, A. Matyjek, K. Płoszka, M. Łaszczych, W. Fendler, Metanalyses on metformin's role in pancreatic cancer suffer from severe bias and low data quality - An umbrella review, Pancreatology: official journal of the International Association of Pancreatology (IAP) ... [et al.] 23(2) (2023) 192-200.
[221] P.E. Miller, S.S. Martin, Approach to Statin Use in 2016: an Update, Curr Atheroscler Rep 18(5) (2016) 20.
[222] R.E. Duncan, A. El-Sohemy, M.C. Archer, Statins and Cancer Development, Cancer Epidemiology, Biomarkers & Prevention 14(8) (2005) 1897-1898.
[223] H. Ura, T. Obara, N. Nishino, S. Tanno, K. Okamura, M. Namiki, Cytotoxicity of Simvastatin to Pancreatic Adenocarcinoma Cells Containing Mutant ras Gene, Japanese Journal of Cancer Research 85(6) (1994) 633-638.
[224] R. Kamiński, K. Kozar, M. Kopeć, G. Basak, J.S. Skierski, M. Koronkiewicz, M. Jakóbisiak, J. GołĄb, Discussion on 3-hydroxy-3-methylglutaryl-coenzyme a reductase inhibitors reduce human pancreatic cancer cell invasion and metastasis, Gastroenterology 123(5) (2002) 1747.
[225] J. Dulak, A. Jozkowicz, Anti-Angiogenic and Anti-Inflammatory Effects of Statins: Relevance to Anti-Cancer Therapy, CCDT 5(8) (2005) 579-594.
[226] E. Karbowska, D. Swieczkowski, A. Gasecka, M. Pruc, K. Safiejko, J.R. Ladny, T. Kopiec, M.J. Jaguszewski, K.J. Filipiak, Z. Rafique, L. Szarpak, Statins and the risk of pancreatic cancer: A systematic review and meta-analysis of 2,797,186 patients, Cardiol J. 31(2) (2024) 243-250.
[227] H. Bagheri, O.-A. Adeli, S. Heidari-Soureshjani, Z. Azadegan-Dehkordi, C. Mt Sherwin, The Relationship between Statin Intake and Risk of Pancreatic Cancer: A Systematic Review and Meta-Analysis, CDRR 16 (2024).
[228] D. Tamburrino, S. Crippa, S. Partelli, L. Archibugi, P.G. Arcidiacono, M. Falconi, G. Capurso, Statin use improves survival in patients with pancreatic ductal adenocarcinoma: A meta-analysis, Digestive and Liver Disease 52(4) (2020) 392-399.
[229] K. Anbari, M.M. Amiri, S. Heidari-Soureshjani, C.M. Sherwin, K. Kasiri, A Systematic Review and Meta-analysis on the Role of Statins in the Prevention ofMortality Following Pancreatic Cancer, ACAMC 23(19) (2023) 2073-2082.
[230] G.-R. Joliat, S. Gaspar-Figueiredo, I. Labgaa, D. Vrochides, J. Perinel, M. Adham, N. Demartines, M. Schäfer, Impact of preoperative statin medication on long-term outcomes after

pancreatoduodenectomy for ductal adenocarcinoma: an international multicentric cross-sectional study, J Cancer Res Clin Oncol 149(19) (2023) 17007-17014.
[231] L. Archibugi, P.G. Arcidiacono, G. Capurso, Statin use is associated to a reduced risk of pancreatic cancer: A meta-analysis, Digestive and Liver Disease 51(1) (2019) 28-37.
[232] L. Archibugi, M. Piciucchi, S. Stigliano, R. Valente, G. Zerboni, V. Barucca, M. Milella, P. Maisonneuve, G. Delle Fave, G. Capurso, Exclusive and Combined Use of Statins and Aspirin and the Risk of Pancreatic Cancer: a Case-Control Study, Scientific Reports 7(1) (2017) 13024.
[233] L. Gabitova-Cornell, A. Surumbayeva, S. Peri, J. Franco-Barraza, D. Restifo, N. Weitz, C. Ogier, A.R. Goldman, T.R. Hartman, R. Francescone, Y. Tan, E. Nicolas, N. Shah, E.A. Handorf, K.Q. Cai, A.M. O'Reilly, I. Sloma, R. Chiaverelli, R.A. Moffitt, V. Khazak, C.Y. Fang, E.A. Golemis, E. Cukierman, I. Astsaturov, Cholesterol Pathway Inhibition Induces TGF-β Signaling to Promote Basal Differentiation in Pancreatic Cancer, Cancer Cell 38(4) (2020) 567-583.e11.
[234] Z. Zhang, I. Tanaka, Z. Pan, P.B. Ernst, H. Kiyono, Y. Kurashima, Intestinal homeostasis and inflammation: Gut microbiota at the crossroads of pancreas–intestinal barrier axis, European Journal of Immunology 52(7) (2022) 1035-1046.
[235] K. Mima, K. Kosumi, Y. Baba, T. Hamada, H. Baba, S. Ogino, The microbiome, genetics, and gastrointestinal neoplasms: the evolving field of molecular pathological epidemiology to analyze the tumor-immune-microbiome interaction, Human genetics 140(5) (2021) 725-746.
[236] G. Pandya, A. Kirtonia, A. Singh, A. Goel, C.D. Mohan, K.S. Rangappa, A.K. Pandey, S. Kapoor, S. Tandon, G. Sethi, M. Garg, A comprehensive review of the multifaceted role of the microbiota in human pancreatic carcinoma, Seminars in Cancer Biology 86 (2022) 682-692.
[237] S. Hashimoto, T. Tochio, K. Funasaka, K. Funahashi, T. Hartanto, Y. Togashi, M. Saito, Y. Nishimoto, M. Yoshinori, K. Nakaoka, A. Watanabe, M. Nagasaka, Y. Nakagawa, R. Miyahara, T. Shibata, Y. Hirooka, Changes in intestinal bacteria and imbalances of metabolites induced in the intestines of pancreatic ductal adenocarcinoma patients in a Japanese population: a preliminary result, Scandinavian Journal of Gastroenterology 58(2) (2023) 193-198.
[238] E. Kartal, T.S.B. Schmidt, E. Molina-Montes, S. Rodríguez-Perales, J. Wirbel, O.M. Maistrenko, W.A. Akanni, B. Alashkar Alhamwe, R.J. Alves, A. Carrato, H.-P. Erasmus, L. Estudillo, F. Finkelmeier, A. Fullam, A.M. Glazek, P. Gómez-Rubio, R. Hercog, F. Jung, S. Kandels, S. Kersting, M. Langheinrich, M. Márquez, X. Molero, A. Orakov, T. Van Rossum, R. Torres-Ruiz, A. Telzerow, K. Zych, V. Benes, G. Zeller, J. Trebicka, F.X. Real, N. Malats, P. Bork, A faecal microbiota signature with high specificity for pancreatic cancer, Gut 71(7) (2022) 1359-1372.
[239] N. Nagata, S. Nishijima, Y. Kojima, Y. Hisada, K. Imbe, T. Miyoshi-Akiyama, W. Suda, M. Kimura, R. Aoki, K. Sekine, M. Ohsugi, K. Miki, T. Osawa, K. Ueki, S. Oka, M. Mizokami, E. Kartal, T.S.B. Schmidt, E. Molina-Montes, L. Estudillo, N. Malats, J. Trebicka, S. Kersting, M. Langheinrich, P. Bork, N. Uemura, T. Itoi, T. Kawai, Metagenomic Identification of Microbial Signatures Predicting Pancreatic Cancer From a Multinational Study, Gastroenterology 163(1) (2022) 222-238.
[240] Z. Ren, J. Jiang, H. Xie, A. Li, H. Lu, S. Xu, L. Zhou, H. Zhang, G. Cui, X. Chen, Y. Liu, L. Wu, N. Qin, R. Sun, W. Wang, L. Li, W. Wang, S. Zheng, Gut microbial profile analysis by MiSeq sequencing of pancreatic carcinoma patients in China, Oncotarget 8(56) (2017) 95176-95191.
[241] W. Zhou, D. Zhang, Z. Li, H. Jiang, J. Li, R. Ren, X. Gao, J. Li, X. Wang, W. Wang, Y. Yang, The fecal microbiota of patients with pancreatic ductal adenocarcinoma and autoimmune pancreatitis characterized by metagenomic sequencing, Journal of Translational Medicine 19(1) (2021) 215.
[242] R. Bellotti, C. Speth, T.E. Adolph, C. Lass-Flörl, M. Effenberger, D. Öfner, M. Maglione, Micro- and Mycobiota Dysbiosis in Pancreatic Ductal Adenocarcinoma Development, Cancers (Basel) 13(14) (2021).
[243] N. Daniel, R. Farinella, A.C. Chatziioannou, M. Jenab, A.L. Mayen, C. Rizzato, F. Belluomini, F. Canzian, A. Tavanti, P. Keski-Rahkonen, D.J. Hughes, D. Campa, Genetically predicted gut bacteria,

circulating bacteria-associated metabolites and pancreatic ductal adenocarcinoma: a Mendelian randomisation study, Sci Rep 14(1) (2024) 25144.
[244] W. Guo, Y. Zhang, S. Guo, Z. Mei, H. Liao, H. Dong, K. Wu, H. Ye, Y. Zhang, Y. Zhu, J. Lang, L. Hu, G. Jin, X. Kong, Tumor microbiome contributes to an aggressive phenotype in the basal-like subtype of pancreatic cancer, Communications Biology 4(1) (2021) 1019.
[245] R.D. Berg, A.W. Garlington, Translocation of certain indigenous bacteria from the gastrointestinal tract to the mesenteric lymph nodes and other organs in a gnotobiotic mouse model, Infection and immunity 23(2) (1979) 403-11.
[246] D.S. Michaud, J. Izard, C.S. Wilhelm-Benartzi, D.H. You, V.A. Grote, A. Tjønneland, C.C. Dahm, K. Overvad, M. Jenab, V. Fedirko, M.C. Boutron-Ruault, F. Clavel-Chapelon, A. Racine, R. Kaaks, H. Boeing, J. Foerster, A. Trichopoulou, P. Lagiou, D. Trichopoulos, C. Sacerdote, S. Sieri, D. Palli, R. Tumino, S. Panico, P.D. Siersema, P.H. Peeters, E. Lund, A. Barricarte, J.M. Huerta, E. Molina-Montes, M. Dorronsoro, J.R. Quirós, E.J. Duell, W. Ye, M. Sund, B. Lindkvist, D. Johansen, K.T. Khaw, N. Wareham, R.C. Travis, P. Vineis, H.B. Bueno-de-Mesquita, E. Riboli, Plasma antibodies to oral bacteria and risk of pancreatic cancer in a large European prospective cohort study, Gut 62(12) (2013) 1764-70.
[247] I. Olsen, Oral microbial dysbiosis precedes development of pancreatic cancer, Journal of oral microbiology 9(1) (2017) 1374148.
[248] I. Olsen, Ö. Yilmaz, Possible role of Porphyromonas gingivalis in orodigestive cancers, Journal of oral microbiology 11(1) (2019) 1563410.
[249] J. Gnanasekaran, A. Binder Gallimidi, E. Saba, K. Pandi, L. Eli Berchoer, E. Hermano, S. Angabo, H.A. Makkawi, A. Khashan, A. Daoud, M. Elkin, G. Nussbaum, Intracellular Porphyromonas gingivalis Promotes the Tumorigenic Behavior of Pancreatic Carcinoma Cells, Cancers (Basel) 12(8) (2020).
[250] Q. Tan, X. Ma, B. Yang, Y. Liu, Y. Xie, X. Wang, W. Yuan, J. Ma, Periodontitis pathogen Porphyromonas gingivalis promotes pancreatic tumorigenesis via neutrophil elastase from tumor-associated neutrophils, Gut microbes 14(1) (2022) 2073785.
[251] K. Mitsuhashi, K. Nosho, Y. Sukawa, Y. Matsunaga, M. Ito, H. Kurihara, S. Kanno, H. Igarashi, T. Naito, Y. Adachi, M. Tachibana, T. Tanuma, H. Maguchi, T. Shinohara, T. Hasegawa, M. Imamura, Y. Kimura, K. Hirata, R. Maruyama, H. Suzuki, K. Imai, H. Yamamoto, Y. Shinomura, Association of Fusobacterium species in pancreatic cancer tissues with molecular features and prognosis, Oncotarget 6(9) (2015) 7209-20.
[252] B. Udayasuryan, R.N. Ahmad, T.T.D. Nguyen, A. Umaña, L. Monét Roberts, P. Sobol, S.D. Jones, J.M. Munson, D.J. Slade, S.S. Verbridge, Fusobacterium nucleatum induces proliferation and migration in pancreatic cancer cells through host autocrine and paracrine signaling, Science signaling 15(756) (2022) eabn4948.
[253] C.H. Kim, Complex regulatory effects of gut microbial short-chain fatty acids on immune tolerance and autoimmunity, Cellular & Molecular Immunology 20(4) (2023) 341-350.
[254] P. Pan, Z. Zhu, K. Oshima, M. Aldakkak, S. Tsai, Y.W. Huang, W. Dong, J. Zhang, C.W. Lin, Y. Wang, M. Yearsley, J. Yu, L.S. Wang, Black raspberries suppress pancreatic cancer through modulation of NKp46(+), CD8(+), and CD11b(+) immune cells, Food frontiers 1(1) (2020) 70-82.
[255] Y. Shimada, M. Kinoshita, K. Harada, M. Mizutani, K. Masahata, H. Kayama, K. Takeda, Commensal bacteria-dependent indole production enhances epithelial barrier function in the colon, PLoS One 8(11) (2013) e80604.
[256] K. Hezaveh, R.S. Shinde, A. Klötgen, M.J. Halaby, S. Lamorte, M.T. Ciudad, R. Quevedo, L. Neufeld, Z.Q. Liu, R. Jin, B.T. Grünwald, E.G. Foerster, D. Chaharlangi, M. Guo, P. Makhijani, X. Zhang, T.J. Pugh, D.M. Pinto, I.L. Co, A.P. McGuigan, G.H. Jang, R. Khokha, P.S. Ohashi, G.M. O'Kane, S. Gallinger, W.W. Navarre, H. Maughan, D.J. Philpott, D.G. Brooks, T.L. McGaha,

Tryptophan-derived microbial metabolites activate the aryl hydrocarbon receptor in tumor-associated macrophages to suppress anti-tumor immunity, Immunity 55(2) (2022) 324-340.e8.
[257] M. Hirabayashi, M. Inoue, N. Sawada, E. Saito, S.K. Abe, A. Hidaka, M. Iwasaki, T. Yamaji, T. Shimazu, S. Tsugane, Helicobacter pylori infection, atrophic gastritis, and risk of pancreatic cancer: A population-based cohort study in a large Japanese population: the JPHC Study, Sci Rep 9(1) (2019) 6099.
[258] A.A. Lee, Q.L. Wang, J. Kim, A. Babic, X. Zhang, K. Perez, K. Ng, J. Nowak, N. Rifai, H.D. Sesso, J.E. Buring, G.L. Anderson, J. Wactawski-Wende, R. Wallace, J.E. Manson, E.L. Giovannucci, M.J. Stampfer, P. Kraft, C.S. Fuchs, C. Yuan, B.M. Wolpin, Helicobacter pylori Seropositivity, ABO Blood Type, and Pancreatic Cancer Risk From 5 Prospective Cohorts, Clin Transl Gastroenterol 14(5) (2023) e00573.
[259] B.-G. Zhou, Y.-Z. Mei, J.-S. Wang, J.-L. Xia, X. Jiang, S.-Y. Ju, Y.-B. Ding, Is Helicobacter pylori infection associated with pancreatic cancer? A systematic review and meta-analysis of observational studies, Therapeutic Advances in Chronic Disease 14 (2023) 20406223231155119.
[260] V. Panthangi, A.R. Cyril Kurupp, A. Raju, G. Luthra, M. Shahbaz, H. Almatooq, P. Foucambert, F.D. Esbrand, S. Zafar, S. Khan, Association Between Helicobacter pylori Infection and the Risk of Pancreatic Cancer: A Systematic Review Based on Observational Studies, Cureus 14(8) (2022) e28543.
[261] G. Trikudanathan, A. Philip, C.A. Dasanu, W.L. Baker, Association between Helicobacter pylori infection and pancreatic cancer. A cumulative meta-analysis, Jop 12(1) (2011) 26-31.
[262] P. Saravanan, V. Saravanan, R. Rajeshkannan, G. Arnica, M. Rajasimman, G. Baskar, A. Pugazhendhi, Comprehensive review on toxic heavy metals in the aquatic system: sources, identification, treatment strategies, and health risk assessment, Environ Res 258 (2024) 119440.
[263] A.C.E. Silva, G.D. Loizou, K. McNally, O. Osborne, C. Potter, D. Gott, J.K. Colbourne, M.R. Viant, A novel method to derive a human safety limit for PFOA by gene expression profiling and modelling, Front Toxicol 6 (2024) 1368320.
[264] G. Forte, A. Pisano, B. Bocca, G. Fenu, C. Farace, F. Etzi, T. Perra, A. Sabalic, A. Porcu, R. Madeddu, Toxic Metal and Essential Element Concentrations in the Blood and Tissues of Pancreatic Ductal Adenocarcinoma Patients, Toxics 12(1) (2024).
[265] L. Parida, T.N. Patel, Systemic impact of heavy metals and their role in cancer development: a review, Environ Monit Assess 195(6) (2023) 766.
[266] Y. Zhakypbek, B.D. Kossalbayev, A.M. Belkozhayev, T. Murat, S. Tursbekov, E. Abdalimov, P. Pashkovskiy, V. Kreslavski, V. Kuznetsov, S.I. Allakhverdiev, Reducing Heavy Metal Contamination in Soil and Water Using Phytoremediation, Plants (Basel) 13(11) (2024).
[267] P. Dey, J.W. Osborne, K.B. Lincy, An insight on the plausible biological and non-biological detoxification of heavy metals in tannery waste: A comprehensive review, Environ Res 258 (2024) 119451.
[268] M. Hoyt, Y. Song, S. Gao, J. O'Palka, J. Zhang, Intake of Calcium, Magnesium, and Phosphorus and Risk of Pancreatic Cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, J Am Nutr Assoc 41(8) (2022) 747-757.
[269] H. Fan, Y. Yu, H. Nan, M. Hoyt, M.K. Reger, A. Prizment, K.E. Anderson, J. Zhang, Associations between intake of calcium, magnesium and phosphorus and risk of pancreatic cancer: a population-based, case-control study in Minnesota, Br J Nutr 126(10) (2021) 1549-1557.
[270] S. Byeon, T. du Toit-Thompson, L. Hipperson, S. Maloney, R. Wenzel, A.J. Gill, J.S. Samra, A. Mittal, S. Sahni, Serum and tissue metallome of pancreatic ductal adenocarcinoma, Cancer Sci 115(5) (2024) 1446-1458.

[271] S.O. Antwi, A.L. Oberg, N. Shivappa, W.R. Bamlet, K.G. Chaffee, S.E. Steck, J.R. Hebert, G.M. Petersen, Pancreatic cancer: associations of inflammatory potential of diet, cigarette smoking and long-standing diabetes, Carcinogenesis 37(5) (2016) 481-90.
[272] I.W.G.o.t.E.o.C.R.t. Humans, Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry, International Agency for Research on Cancer1993.
[273] Iarc, Personal Habits and Indoor Combustions, 2012.
[274] A.F. Amaral, M. Porta, D.T. Silverman, R.L. Milne, M. Kogevinas, N. Rothman, K.P. Cantor, B.P. Jackson, J.A. Pumarega, T. Lopez, A. Carrato, L. Guarner, F.X. Real, N. Malats, Pancreatic cancer risk and levels of trace elements, Gut 61(11) (2012) 1583-8.
[275] L. Manić, D. Wallace, P.U. Onganer, Y.M. Taalab, A.A. Farooqi, B. Antonijević, A. Buha Djordjevic, Epigenetic mechanisms in metal carcinogenesis, Toxicol Rep 9 (2022) 778-787.
[276] G.G. Schwartz, I.M. Reis, Is cadmium a cause of human pancreatic cancer?, Cancer Epidemiol Biomarkers Prev 9(2) (2000) 139-45.
[277] P. Joseph, T.K. Muchnok, M.L. Klishis, J.R. Roberts, J.M. Antonini, W.Z. Whong, T. Ong, Cadmium-induced cell transformation and tumorigenesis are associated with transcriptional activation of c-fos, c-jun, and c-myc proto-oncogenes: role of cellular calcium and reactive oxygen species, Toxicol Sci 61(2) (2001) 295-303.
[278] M. Waisberg, P. Joseph, B. Hale, D. Beyersmann, Molecular and cellular mechanisms of cadmium carcinogenesis, Toxicology 192(2-3) (2003) 95-117.
[279] V.R. Djordjevic, D.R. Wallace, A. Schweitzer, N. Boricic, D. Knezevic, S. Matic, N. Grubor, M. Kerkez, D. Radenkovic, Z. Bulat, B. Antonijevic, V. Matovic, A. Buha, Environmental cadmium exposure and pancreatic cancer: Evidence from case control, animal and in vitro studies, Environ Int 128 (2019) 353-361.
[280] M. Mortoglou, A. Buha Djordjevic, V. Djordjevic, H. Collins, L. York, K. Mani, E. Valle, D. Wallace, P. Uysal-Onganer, Role of microRNAs in response to cadmium chloride in pancreatic ductal adenocarcinoma, Arch Toxicol 96(2) (2022) 467-485.
[281] W. Qu, E.J. Tokar, A.J. Kim, M.W. Bell, M.P. Waalkes, Chronic cadmium exposure in vitro causes acquisition of multiple tumor cell characteristics in human pancreatic epithelial cells, Environ Health Perspect 120(9) (2012) 1265-1271.
[282] Iarc, Nickel and Nickel Compounds, 2018.
[283] A.R. Oller, M. Costa, G. Oberdörster, Carcinogenicity assessment of selected nickel compounds, Toxicol Appl Pharmacol 143(1) (1997) 152-166.
[284] Y. Zhu, Q.Y. Chen, A.H. Li, M. Costa, The Role of Non-Coding RNAs Involved in Nickel-Induced Lung Carcinogenic Mechanisms, Inorganics 7(7) (2019) 81.
[285] K.S. Cameron, V. Buchner, P.B. Tchounwou, Exploring the molecular mechanisms of nickel-induced genotoxicity and carcinogenicity: a literature review, Rev Environ Health 26(2) (2011) 81-92.
[286] Á. Gómez-Tomás, J. Pumarega, J. Alguacil, A.F.S. Amaral, N. Malats, N. Pallarès, M. Gasull, M. Porta, P.I.S. Group, Concentrations of trace elements and KRAS mutations in pancreatic ductal adenocarcinoma, Environ Mol Mutagen 60(8) (2019) 693-703.
[287] D. Wallace, A.B. Djordjević, A. Benton, Toxicity of Organic and Inorganic Nickel in Pancreatic Cell Cultures: Comparison to Cadmium, 1 70(Notebook 6) (2020) 344-359.
[288] I.A. Ojajärvi, T.J. Partanen, A. Ahlbom, P. Boffetta, T. Hakulinen, N. Jourenkova, T.P. Kauppinen, M. Kogevinas, M. Porta, H.U. Vainio, E. Weiderpass, C.H. Wesseling, Occupational exposures and pancreatic cancer: a meta-analysis, Occup Environ Med 57(5) (2000) 316-324.
[289] S.K. Seilkop, Occupational exposures and pancreatic cancer: a meta-analysis, Occup Environ Med 58(1) (2001) 63-64.

[290] E. Denkhaus, K. Salnikow, Nickel essentiality, toxicity, and carcinogenicity, Crit Rev Oncol Hematol 42(1) (2002) 35-56.
[291] M. Mortoglou, L. Manić, A. Buha Djordjevic, Z. Bulat, V. Đorđević, K. Manis, E. Valle, L. York, D. Wallace, P. Uysal-Onganer, Nickel's Role in Pancreatic Ductal Adenocarcinoma: Potential Involvement of microRNAs, Toxics 10(3) (2022) 148.
[292] W. Liu-Mares, J.A. Mackinnon, R. Sherman, L.E. Fleming, C. Rocha-Lima, J.J. Hu, D.J. Lee, Pancreatic cancer clusters and arsenic-contaminated drinking water wells in Florida, BMC cancer 13 (2013) 111.
[293] C.V. Rao, S. Pal, A. Mohammed, M. Farooqui, M.P. Doescher, A.S. Asch, H.Y. Yamada, Biological effects and epidemiological consequences of arsenic exposure, and reagents that can ameliorate arsenic damage in vivo, Oncotarget 8(34) (2017) 57605-57621.
[294] J.F. Reichard, M. Schnekenburger, A. Puga, Long term low-dose arsenic exposure induces loss of DNA methylation, Biochem Biophys Res Commun 352(1) (2007) 188-192.
[295] C. Pelucchi, V. Rosato, P.M. Bracci, D. Li, R.E. Neale, E. Lucenteforte, D. Serraino, K.E. Anderson, E. Fontham, E.A. Holly, M.M. Hassan, J. Polesel, C. Bosetti, L. Strayer, J. Su, P. Boffetta, E.J. Duell, C. La Vecchia, Dietary acrylamide and the risk of pancreatic cancer in the International Pancreatic Cancer Case-Control Consortium (PanC4), Ann Oncol 28(2) (2017) 408-414.
[296] M. Obon-Santacana, N. Slimani, L. Lujan-Barroso, N. Travier, G. Hallmans, H. Freisling, P. Ferrari, M.C. Boutron-Ruault, A. Racine, F. Clavel, C. Saieva, V. Pala, R. Tumino, A. Mattiello, P. Vineis, M. Arguelles, E. Ardanaz, P. Amiano, C. Navarro, M.J. Sanchez, E. Molina Montes, T. Key, K.T. Khaw, N. Wareham, P.H. Peeters, A. Trichopoulou, C. Bamia, D. Trichopoulos, H. Boeing, R. Kaaks, V. Katzke, W. Ye, M. Sund, U. Ericson, E. Wirfalt, K. Overvad, A. Tjonneland, A. Olsen, G. Skeie, L.A. Asli, E. Weiderpass, E. Riboli, H.B. Bueno-de-Mesquita, E.J. Duell, Dietary intake of acrylamide and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, Ann Oncol 24(10) (2013) 2645-2651.
[297] C. Pelucchi, C. Galeone, R. Talamini, E. Negri, J. Polesel, D. Serraino, C. La Vecchia, Dietary acrylamide and pancreatic cancer risk in an Italian case--control study, Ann Oncol 22(8) (2011) 1910-5.
[298] K. Kito, J. Ishihara, A. Kotemori, L. Zha, R. Liu, N. Sawada, M. Iwasaki, T. Sobue, S. Tsugane, Dietary Acrylamide Intake and the Risk of Pancreatic Cancer: The Japan Public Health Center-Based Prospective Study, Nutrients 12(11) (2020).
[299] E.N. Hamidi, P. Hajeb, J. Selamat, A.F. Abdull Razis, Polycyclic Aromatic Hydrocarbons (PAHs) and their Bioaccessibility in Meat: a Tool for Assessing Human Cancer Risk, Asian Pac J Cancer Prev 17(1) (2016) 15-23.
[300] M. Iwasaki, S. Tsugane, Dietary heterocyclic aromatic amine intake and cancer risk: epidemiological evidence from Japanese studies, Genes Environ 43(1) (2021) 33.
[301] I.A. Khan, A. Khan, Y. Zou, Z. Zongshuai, W. Xu, D. Wang, M. Huang, Heterocyclic amines in cooked meat products, shortcomings during evaluation, factors influencing formation, risk assessment and mitigation strategies, Meat Sci 184 (2022) 108693.
[302] X. Zhao, J. Gao, L. Zhai, X. Yu, Y. Xiao, Recent Evidence on Polycyclic Aromatic Hydrocarbon Exposure, Healthcare (Basel) 11(13) (2023).
[303] K.E. Anderson, F.F. Kadlubar, M. Kulldorff, L. Harnack, M. Gross, N.P. Lang, C. Barber, N. Rothman, R. Sinha, Dietary intake of heterocyclic amines and benzo(a)pyrene: associations with pancreatic cancer, Cancer Epidemiol Biomarkers Prev 14(9) (2005) 2261-5.
[304] K.E. Anderson, S.J. Mongin, R. Sinha, R. Stolzenberg-Solomon, M.D. Gross, R.G. Ziegler, J.E. Mabie, A. Risch, S.S. Kazin, T.R. Church, Pancreatic cancer risk: associations with meat-derived carcinogen intake in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) cohort, Mol Carcinog 51(1) (2012) 128-37.

[305] R.Z. Stolzenberg-Solomon, A.J. Cross, D.T. Silverman, C. Schairer, F.E. Thompson, V. Kipnis, A.F. Subar, A. Hollenbeck, A. Schatzkin, R. Sinha, Meat and meat-mutagen intake and pancreatic cancer risk in the NIH-AARP cohort, Cancer Epidemiol Biomarkers Prev 16(12) (2007) 2664-75.
[306] P. Taunk, E. Hecht, R. Stolzenberg-Solomon, Are meat and heme iron intake associated with pancreatic cancer? Results from the NIH-AARP diet and health cohort, Int J Cancer 138(9) (2016) 2172-89.
[307] M.P. Marciel, B. Haldar, J. Hwang, N. Bhalerao, S.L. Bellis, Role of tumor cell sialylation in pancreatic cancer progression, Adv Cancer Res 157 (2023) 123-155.
[308] R.G. Hanna-Sawires, J.H. Schiphuis, M. Wuhrer, H.F.A. Vasen, M.E. van Leerdam, B.A. Bonsing, W.E. Mesker, Y.E.M. van der Burgt, R. Tollenaar, Clinical Perspective on Proteomic and Glycomic Biomarkers for Diagnosis, Prognosis, and Prediction of Pancreatic Cancer, Int J Mol Sci 22(5) (2021).
[309] Y. Xu, Y. Wang, N. Hoti, D.J. Clark, S.Y. Chen, H. Zhang, The next "sweet" spot for pancreatic ductal adenocarcinoma: Glycoprotein for early detection, Mass Spectrom Rev 42(2) (2023) 822-843.
[310] T. Wagatsuma, C. Nagai-Okatani, A. Matsuda, Y. Masugi, M. Imaoka, K. Yamazaki, M. Sakamoto, A. Kuno, Discovery of Pancreatic Ductal Adenocarcinoma-Related Aberrant Glycosylations: A Multilateral Approach of Lectin Microarray-Based Tissue Glycomic Profiling With Public Transcriptomic Datasets, Front Oncol 10 (2020) 338.
[311] J. Zhang, Z. Zhang, S. Holst, C. Blochl, K. Madunic, M. Wuhrer, P. Ten Dijke, T. Zhang, Transforming growth factor-beta challenge alters the N-, O-, and glycosphingolipid glycomes in PaTu-S pancreatic adenocarcinoma cells, J Biol Chem 298(3) (2022) 101717.
[312] E. Rodriguez, K. Boelaars, K. Brown, K. Madunic, T. van Ee, F. Dijk, J. Verheij, R.J.E. Li, S.T.T. Schetters, L.L. Meijer, T.Y.S. Le Large, E. Driehuis, H. Clevers, S.C.M. Bruijns, T. O'Toole, S.J. van Vliet, M.F. Bijlsma, M. Wuhrer, G. Kazemier, E. Giovannetti, J.J. Garcia-Vallejo, Y. van Kooyk, Analysis of the glyco-code in pancreatic ductal adenocarcinoma identifies glycan-mediated immune regulatory circuits, Commun Biol 5(1) (2022) 41.
[313] S. Sagar, P.D. Leiphrakpam, D. Thomas, K.L. McAndrews, T.C. Caffrey, B.J. Swanson, H. Clausen, H.H. Wandall, M.A. Hollingsworth, P. Radhakrishnan, MUC4 enhances gemcitabine resistance and malignant behaviour in pancreatic cancer cells expressing cancer-associated short O-glycans, Cancer Lett 503 (2021) 91-102.
[314] D. Thomas, S. Sagar, X. Liu, H.R. Lee, J.A. Grunkemeyer, P.M. Grandgenett, T. Caffrey, K.A. O'Connell, B. Swanson, L. Marcos-Silva, C. Steentoft, H.H. Wandall, H.C. Maurer, X.L. Peng, J.J. Yeh, F. Qiu, F. Yu, R. Madiyalakan, K.P. Olive, U. Mandel, H. Clausen, M.A. Hollingsworth, P. Radhakrishnan, Isoforms of MUC16 activate oncogenic signaling through EGF receptors to enhance the progression of pancreatic cancer, Mol Ther 29(4) (2021) 1557-1571.
[315] I.J.M. Levink, D.C.F. Klatte, R.G. Hanna-Sawires, G.C.M. Vreeker, I.S. Ibrahim, Y.E.M. van der Burgt, K.A. Overbeek, B.D.M. Koopmann, D.L. Cahen, G.M. Fuhler, M. Wuhrer, B.A. Bonsing, R. Tollenaar, F.P. Vleggaar, H.F.A. Vasen, M.E. van Leerdam, M.J. Bruno, W.E. Mesker, Longitudinal changes of serum protein N-Glycan levels for earlier detection of pancreatic cancer in high-risk individuals, Pancreatology 22(4) (2022) 497-506.
[316] G.C.M. Vreeker, R.G. Hanna-Sawires, Y. Mohammed, M.R. Bladergroen, S. Nicolardi, V. Dotz, J. Nouta, B.A. Bonsing, W.E. Mesker, Y.E.M. van der Burgt, M. Wuhrer, R. Tollenaar, Serum N-Glycome analysis reveals pancreatic cancer disease signatures, Cancer Med 9(22) (2020) 8519-8529.
[317] Y.R. Wen, X.W. Lin, Y.W. Zhou, L. Xu, J.L. Zhang, C.Y. Chen, J. He, N-glycan biosignatures as a potential diagnostic biomarker for early-stage pancreatic cancer, World J Gastrointest Oncol 16(3) (2024) 659-669.

[318] W. Chen, Q. Chen, R.A. Parker, Y. Zhou, E. Lustigova, B.U. Wu, Risk Prediction of Pancreatic Cancer in Patients With Abnormal Morphologic Findings Related to Chronic Pancreatitis: A Machine Learning Approach, Gastro Hep Adv 1(6) (2022) 1014-1026.
[319] U.C. Bang, T. Benfield, L. Hyldstrup, F. Bendtsen, J.E. Beck Jensen, Mortality, cancer, and comorbidities associated with chronic pancreatitis: a Danish nationwide matched-cohort study, Gastroenterology 146(4) (2014) 989-94.
[320] M. Han, T.P.T. Tran, J.K. Oh, Chronic pancreatitis and cancer risk in a matched cohort study using national claims data in South Korea, Sci Rep 12(1) (2022) 5545.
[321] H.S. Kim, T.G. Gweon, S.H. Park, T.H. Kim, C.W. Kim, J.H. Chang, Incidence and risk of pancreatic cancer in patients with chronic pancreatitis: defining the optimal subgroup for surveillance, Sci Rep 13(1) (2023) 106.
[322] S. Gandhi, J. de la Fuente, M.H. Murad, S. Majumder, Chronic Pancreatitis Is a Risk Factor for Pancreatic Cancer, and Incidence Increases With Duration of Disease: A Systematic Review and Meta-analysis, Clin Transl Gastroenterol 13(3) (2022) e00463.
[323] J. Kirkegard, F.V. Mortensen, D. Cronin-Fenton, Chronic Pancreatitis and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis, Am J Gastroenterol 112(9) (2017) 1366-1372.
[324] S. Munigala, D.S. Subramaniam, D.P. Subramaniam, T.E. Burroughs, D.L. Conwell, S.G. Sheth, Incidence and Risk of Pancreatic Cancer in Patients with a New Diagnosis of Chronic Pancreatitis, Dig Dis Sci 67(2) (2022) 708-715.
[325] W. Greenhalf, P. Levy, T. Gress, V. Rebours, R.E. Brand, S. Pandol, S. Chari, M.T. Jorgensen, J. Mayerle, M.M. Lerch, P. Hegyi, J. Kleeff, C.F. Castillo, S. Isaji, T. Shimosegawa, A. Sheel, C.M. Halloran, P. Garg, K. Takaori, M.G. Besselink, C.E. Forsmark, C.M. Wilcox, P. Maisonneuve, D. Yadav, D. Whitcomb, J. Neoptolemos, P. Working group for the International Consensus Guidelines for Chronic, International consensus guidelines on surveillance for pancreatic cancer in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club, Pancreatology 20(5) (2020) 910-918.
[326] N. Howes, M.M. Lerch, W. Greenhalf, D.D. Stocken, I. Ellis, P. Simon, K. Truninger, R. Ammann, G. Cavallini, R.M. Charnley, G. Uomo, M. Delhaye, J. Spicak, B. Drumm, J. Jansen, R. Mountford, D.C. Whitcomb, J.P. Neoptolemos, P. European Registry of Hereditary, C. Pancreatic, Clinical and genetic characteristics of hereditary pancreatitis in Europe, Clin Gastroenterol Hepatol 2(3) (2004) 252-61.
[327] I.M. Cazacu, N. Farkas, A. Garami, M. Balasko, B. Mosdosi, H. Alizadeh, Z. Gyongyi, Z. Rakonczay, Jr., E. Vigh, T. Habon, L. Czopf, M.A. Lazarescu, B. Eross, M. Sahin-Toth, P. Hegyi, Pancreatitis-Associated Genes and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis, Pancreas 47(9) (2018) 1078-1086.
[328] C.J. Grocock, V. Rebours, M.N. Delhaye, A. Andren-Sandberg, F.U. Weiss, R. Mountford, M.J. Harcus, E. Niemczyck, L.J. Vitone, S. Dodd, M.T. Jorgensen, R.W. Ammann, O. Schaffalitzky de Muckadell, J.V. Butler, P. Burgess, B. Kerr, R. Charnley, R. Sutton, M.G. Raraty, J. Deviere, D.C. Whitcomb, J.P. Neoptolemos, P. Levy, M.M. Lerch, W. Greenhalf, P. European Registry of Hereditary, C. Pancreatic, The variable phenotype of the p.A16V mutation of cationic trypsinogen (PRSS1) in pancreatitis families, Gut 59(3) (2010) 357-63.
[329] S. Munigala, S. Almaskeen, D.S. Subramaniam, S. Bandi, B. Bowe, H. Xian, S.G. Sheth, T.E. Burroughs, B. Agarwal, Acute Pancreatitis Recurrences Augment Long-Term Pancreatic Cancer Risk, Am J Gastroenterol 118(4) (2023) 727-737.
[330] G. Capurso, M. Tacelli, G. Vanella, R. Ponz de Leon Pisani, G. Dell'Anna, M. Abati, R. Mele, G. Lauri, A. Panaitescu, R. Nunziata, P. Zaccari, L. Archibugi, P.G. Arcidiacono, Managing complications

of chronic pancreatitis: a guide for the gastroenterologist, Expert Rev Gastroenterol Hepatol 17(12) (2023) 1267-1283.
[331] P. Macinga, L. Bajer, M. Del Chiaro, S.T. Chari, P. Dite, L. Frulloni, T. Ikeura, T. Kamisawa, K. Kubota, I. Naitoh, K. Okazaki, R. Pezzilli, M. Vujasinovic, J. Spicak, T. Hucl, M. Löhr, Pancreatic cancer in patients with autoimmune pancreatitis: A scoping review, Pancreatology 21(5) (2021) 928-937.
[332] L. Buscail, B. Bournet, P. Cordelier, Role of oncogenic KRAS in the diagnosis, prognosis and treatment of pancreatic cancer, Nat Rev Gastroenterol Hepatol 17(3) (2020) 153-168.
[333] Y. Saiki, C. Jiang, M. Ohmuraya, T. Furukawa, Genetic Mutations of Pancreatic Cancer and Genetically Engineered Mouse Models, Cancers (Basel) 14(1) (2021).
[334] K. Fujikura, W. Hosoda, M. Felsenstein, Q. Song, J.G. Reiter, L. Zheng, V. Beleva Guthrie, N. Rincon, M. Dal Molin, J. Dudley, J.D. Cohen, P. Wang, C.G. Fischer, A.M. Braxton, M. Noë, M. Jongepier, C. Fernández-del Castillo, M. Mino-Kenudson, C.M. Schmidt, M.T. Yip-Schneider, R.T. Lawlor, R. Salvia, N.J. Roberts, E.D. Thompson, R. Karchin, A.M. Lennon, Y. Jiao, L.D. Wood, Multiregion whole-exome sequencing of intraductal papillary mucinous neoplasms reveals frequent somatic KLF4 mutations predominantly in low-grade regions, Gut 70(5) (2021) 928-939.
[335] G. Lauri, L. Apadula, L. Archibugi, P. Lazzano, R. Ponz De Leon Pisani, M. Cobreros, M. Tacelli, G. Marchegiani, S. Crippa, M. Falconi, P.G. Arcidiacono, G. Capurso, Association of Smoking with progression from low-risk to high-risk intraductal papillary mucinous neoplasms and pancreatic cancer, Digestive and Liver Disease (2024) S1590865824007758.
[336] H. Oyama, M. Tada, K. Takagi, K. Tateishi, T. Hamada, Y. Nakai, R. Hakuta, H. Ijichi, K. Ishigaki, S. Kanai, H. Kogure, S. Mizuno, K. Saito, T. Saito, T. Sato, T. Suzuki, N. Takahara, Y. Morishita, J. Arita, K. Hasegawa, M. Tanaka, M. Fukayama, K. Koike, Long-term Risk of Malignancy in Branch-Duct Intraductal Papillary Mucinous Neoplasms, Gastroenterology 158(1) (2020) 226-237.e5.
[337] G. Marchegiani, T. Pollini, A. Burelli, Y. Han, H.-S. Jung, W. Kwon, D.M. Rocha Castellanos, S. Crippa, G. Belfiori, P.G. Arcidiacono, G. Capurso, L. Apadula, P. Zaccari, J.L. Noia, M. Gorris, O. Busch, A. Ponweera, K. Mann, I.E. Demir, V. Phillip, N. Ahmad, T. Hackert, M. Heckler, A.M. Lennon, E. Afghani, D. Vallicella, T. Dall'Olio, A. Nepi, C.M. Vollmer, H. Friess, P. Ghaneh, M. Besselink, M. Falconi, C. Bassi, B.K.-P. Goh, J.-Y. Jang, C. Fernández-Del Castillo, R. Salvia, Surveillance for Presumed BD-IPMN of the Pancreas: Stability, Size, and Age Identify Targets for Discontinuation, Gastroenterology 165(4) (2023) 1016-1024.e5.
[338] T. Ohtsuka, C. Fernandez-del Castillo, T. Furukawa, S. Hijioka, J.-Y. Jang, A.M. Lennon, Y. Miyasaka, E. Ohno, R. Salvia, C.L. Wolfgang, L.D. Wood, International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas, Pancreatology 24(2) (2024) 255-270.
[339] Y. Shimizu, S. Hijioka, S. Hirono, T. Kin, T. Ohtsuka, A. Kanno, S. Koshita, K. Hanada, M. Kitano, H. Inoue, T. Itoi, T. Ueki, K. Matsuo, A. Yanagisawa, H. Yamaue, M. Sugiyama, K. Okazaki, New Model for Predicting Malignancy in Patients With Intraductal Papillary Mucinous Neoplasm, Annals of Surgery 272(1) (2020) 155-162.
[340] I. Pergolini, S. Schorn, C. Jäger, R. Göß, A. Novotny, H. Friess, G.O. Ceyhan, I.E. Demir, Diabetes mellitus in intraductal papillary mucinous neoplasms: A systematic review and meta-analysis, Surgery 169(2) (2021) 411-418.
[341] P. Zelga, Y.G. Hernandez-Barco, M. Qadan, C.R. Ferrone, A. Kambadakone, N. Horick, A. Jah, A.L. Warshaw, K.D. Lillemoe, A. Balakrishnan, C. Fernández-del Castillo, Number of Worrisome Features and Risk of Malignancy in Intraductal Papillary Mucinous Neoplasm, Journal of the American College of Surgeons 234(6) (2022) 1021-1030.

[342] G. Marchegiani, S. Andrianello, T. Pollini, A. Caravati, M. Biancotto, E. Secchettin, D. Bonamini, G. Malleo, C. Bassi, R. Salvia, "Trivial" Cysts Redefine the Risk of Cancer in Presumed Branch-Duct Intraductal Papillary Mucinous Neoplasms of the Pancreas: A Potential Target for Follow-Up Discontinuation?, American Journal of Gastroenterology 114(10) (2019) 1678-1684.
[343] J.J. Farrell, Prevalence, Diagnosis and Management of Pancreatic Cystic Neoplasms: Current Status and Future Directions, Gut Liver 9(5) (2015).
[344] J.W. Park, J.-Y. Jang, M.J. Kang, W. Kwon, Y.R. Chang, S.-W. Kim, Mucinous cystic neoplasm of the pancreas: Is surgical resection recommended for all surgically fit patients?, Pancreatology 14(2) (2014) 131-136.
[345] T. Pollini, G. Marchegiani, A. Facciorusso, A. Balduzzi, M. Biancotto, C. Bassi, A.V. Maker, R. Salvia, It is not necessary to resect all mucinous cystic neoplasms of the pancreas: current guidelines do not reflect the actual risk of malignancy, HPB (Oxford) 25(7) (2023) 747-757.
[346] G. Marchegiani, S. Andrianello, S. Crippa, T. Pollini, G. Belfiori, L. Gozzini, F. Cassalia, A. Caravati, C. Luchini, C. Doglioni, C. Bassi, M. Falconi, R. Salvia, Actual malignancy risk of either operated or non-operated presumed mucinous cystic neoplasms of the pancreas under surveillance, British Journal of Surgery 108(9) (2021) 1097-1104.
[347] M. Servin-Rojas, Z.V. Fong, C. Fernandez-Del Castillo, C.R. Ferrone, D.M. Rocha-Castellanos, J. Roldan, P.J. Zelga, A.L. Warshaw, K.D. Lillemoe, M. Qadan, Identification of high-risk features in mucinous cystic neoplasms of the pancreas, Surgery 173(5) (2023) 1270-1274.
[348] G.H. Kim, K. Choi, N. Paik, K.T. Lee, J.K. Lee, K.H. Lee, I.W. Han, S.H. Kang, J.S. Heo, J.K. Park, Diagnostic Concordance and Preoperative Risk Factors for Malignancy in Pancreatic Mucinous Cystic Neoplasms, Gut Liver 16(4) (2022) 637-644.
[349] T. Ohtsuka, M. Nakamura, S. Hijioka, Y. Shimizu, M. Unno, M. Tanabe, Y. Nagakawa, K. Takaori, S. Hirono, N. Gotohda, W. Kimura, K. Ito, A. Katanuma, T. Sano, T. Urata, E. Kita, K. Hanada, M. Tada, T. Aoki, M. Serikawa, K. Okamoto, H. Isayama, Y. Gotoh, K. Ishigami, H. Yamaguchi, K. Yamao, M. Sugiyama, K. Okazaki, Prediction of the Probability of Malignancy in Mucinous Cystic Neoplasm of the Pancreas With Ovarian-Type Stroma: A Nationwide Multicenter Study in Japan, Pancreas 49(2) (2020) 181-186.
[350] P. The European Study Group on Cystic Tumours of the, European evidence-based guidelines on pancreatic cystic neoplasms, Gut 67(5) (2018) 789-804.
[351] R.J. Jansen, X.L. Tan, G.M. Petersen, Gene-by-Environment Interactions in Pancreatic Cancer: Implications for Prevention, Yale J Biol Med 88(2) (2015) 115-26.
[352] M. Barrdahl, F. Canzian, A.D. Joshi, R.C. Travis, J. Chang-Claude, P.L. Auer, S.M. Gapstur, M. Gaudet, W.R. Diver, B.E. Henderson, C.A. Haiman, F.R. Schumacher, L. Le Marchand, C.D. Berg, S.J. Chanock, R.N. Hoover, A. Rudolph, R.G. Ziegler, G.G. Giles, L. Baglietto, G. Severi, S.E. Hankinson, S. Lindstrom, W. Willet, D.J. Hunter, J.E. Buring, I.M. Lee, S. Zhang, L. Dossus, D.G. Cox, K.T. Khaw, E. Lund, A. Naccarati, P.H. Peeters, J.R. Quiros, E. Riboli, M. Sund, D. Trichopoulos, R.L. Prentice, P. Kraft, R. Kaaks, D. Campa, Post-GWAS gene-environment interplay in breast cancer: results from the Breast and Prostate Cancer Cohort Consortium and a meta-analysis on 79,000 women, Hum Mol Genet 23(19) (2014) 5260-70.
[353] D. Campa, R. Kaaks, L. Le Marchand, C.A. Haiman, R.C. Travis, C.D. Berg, J.E. Buring, S.J. Chanock, W. Ryan Diver, L. Dostal, A. Fournier, S.E. Hankinson, B.E. Henderson, R.N. Hoover, C. Isaacs, M. Johansson, L.N. Kolonel, P. Kraft, I.M. Lee, C.A. McCarty, O. Kim, S. Panico, P.H.M. Peeters, E. Riboli, M.J. Sanchez, F.R. Schumacher, G. Skeie, D.O. Stram, M.J. Thun, D. Trichopoulos, S. Zhang, R.G. Ziegler, D.J. Hunter, S. Lindström, F. Canzian, Interactions between genetic variants and breast cancer risk factors in the breast and prostate cancer cohort consortium, 103(16) (2011) 1252-1263.

[354] A.D. Joshi, S. Lindström, A. Hüsing, M. Barrdahl, T.J. Van Der Weele, D. Campa, F. Canzian, M.M. Gaudet, J.D. Figueroa, L. Baglietto, C.D. Berg, J.E. Buring, S.J. Chanock, M.D. Chirlaque, W. Ryan Diver, L. Dossus, G.G. Giles, C.A. Haiman, S.E. Hankinson, B.E. Henderson, R.N. Hoover, D.J. Hunter, C. Isaacs, R. Kaaks, L.N. Kolonel, V. Krogh, L.L. Marchand, I.M. Lee, E. Lund, C.A. McCarty, K. Overvad, P.H. Peeters, E. Riboli, F. Schumacher, G. Severi, D.O. Stram, M. Sund, M.J. Thun, R.C. Travis, D. Trichopoulos, W.C. Willett, S. Zhang, R.G. Ziegler, P. Kraft, Additive interactions between susceptibility single-nucleotide polymorphisms identified in genome-wide association studies and breast cancer risk factors in the breast and prostate cancer cohort consortium, 180(10) (2014) 1018-1027.
[355] E. Mocci, P. Kundu, W. Wheeler, A.A. Arslan, L.E. Beane-Freeman, P.M. Bracci, P. Brennan, F. Canzian, M. Du, S. Gallinger, G.G. Giles, P.J. Goodman, C. Kooperberg, L. Le Marchand, R.E. Neale, X.O. Shu, K. Visvanathan, E. White, W. Zheng, D. Albanes, G. Andreotti, A. Babic, W.R. Bamlet, S.I. Berndt, A.L. Blackford, B. Bueno-De-Mesquita, J.E. Buring, D. Campa, S.J. Chanock, E.J. Childs, E.J. Duell, C.S. Fuchs, J.M. Gaziano, E.L. Giovannucci, M.G. Goggins, P. Hartge, M.M. Hassan, E.A. Holly, R.N. Hoover, R.J. Hung, R.C. Kurtz, I.M. Lee, N. Malats, R.L. Milne, K. Ng, A.L. Oberg, S. Panico, U. Peters, M. Porta, K.G. Rabe, E. Riboli, N. Rothman, G. Scelo, H.D. Sesso, D.T. Silverman, V.L. Stevens, O. Strobel, J.I.M. Thompson, A. Tjonneland, A. Trichopoulou, S.K. van Den Eeden, J. Wactawski-Wende, N. Wentzensen, L.R. Wilkens, H. Yu, F. Yuan, A. Zeleniuch-Jacquotte, L.T. Amundadottir, D. Li, E.J. Jacobs, G.M. Petersen, B.M. Wolpin, H.A. Risch, P. Kraft, N. Chatterjee, A.P. Klein, R. Stolzenberg-Solomon, Smoking modifies pancreatic cancer risk loci on 2q21.3, 81(11) (2021) 3134-3143.
[356] Z. Ni, P. Kundu, D.F. McKean, W. Wheeler, D. Albanes, G. Andreotti, S.O. Antwi, A.A. Arslan, W.R. Bamlet, L.E. Beane Freeman, S.I. Berndt, P.M. Bracci, P. Brennan, J.E. Buring, S.J. Chanock, S. Gallinger, J.M. Gaziano, G.G. Giles, E.L. Giovannucci, M.G. Goggins, P.J. Goodman, C.A. Haiman, M.M. Hassan, E.A. Holly, R.J. Hung, V. Katzke, C. Kooperberg, P. Kraft, L. Le Marchand, D. Li, M.L. McCullough, R.L. Milne, S.C. Moore, R.E. Neale, A.L. Oberg, A.V. Patel, U. Peters, K.G. Rabe, H.A. Risch, X.-O. Shu, K. Smith Byrne, K. Visvanathan, J. Wactawski-Wende, E. White, B.M. Wolpin, H. Yu, A. Zeleniuch-Jacquotte, W. Zheng, J. Zhong, L.T. Amundadottir, R.Z. Stolzenberg-Solomon, A.P. Klein, Genome-wide analysis to assess if heavy alcohol consumption modifies the association between SNPs and pancreatic cancer risk, Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology (2024).

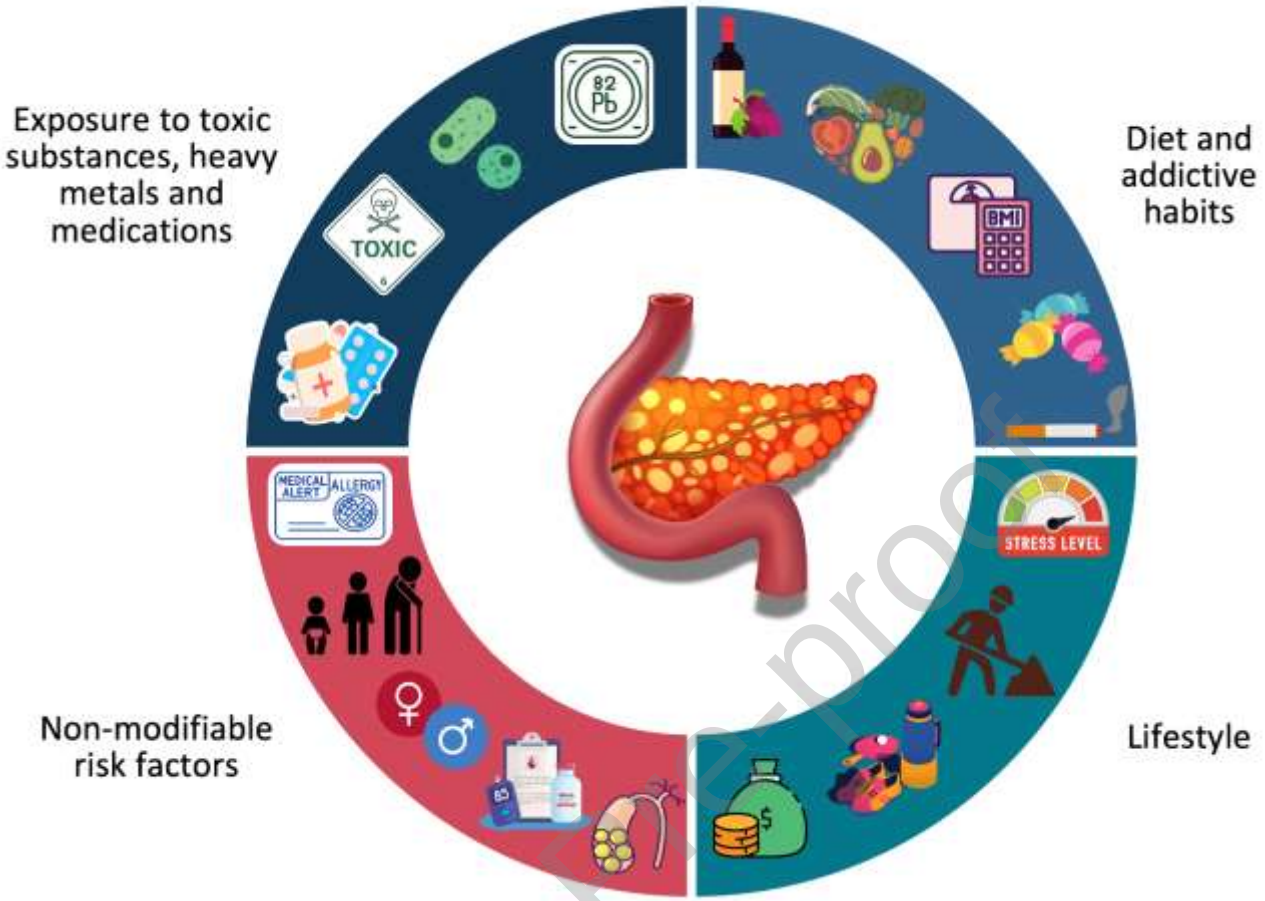

Figure 1. Modifiable and non-modifiable risk factor for pancreatic cancer

Table 1. Key facts of non-modifiable risk factors

Condition	Characteristics	Mechanisms	Epidemiological Findings
Age	Increase in age	not defined	PDAC incidence is increasing over time across all ethnicities and both sexes in the U.S. and Europe (Gaddam et al. 2021; Beral and Peto 2010). Older individuals have a higher incidence of PDAC and a worse prognosis. Since patients diagnosed at an early stage have the best survival rates, this emphasizes the need for early prevention and control programs (Wang et al. 2020).
Sex	Female or male sex	Different exposure between sex and different hormonal level	Larger European studies consistently show that pancreatic ductal adenocarcinoma (PDAC) occurs more frequently in males than in females across all age groups. Globally, the incidence rate is also slightly higher in males, with 5.5 new cases per 100,000 each year compared to 4.0 per 100,000 in females (Bao et al., 2008). This gender disparity is partly explained by modifiable risk factors—such as tobacco use and alcohol consumption—which tend to be more common among males (Wang et al., 2016a; Jiang et al., 2023)
Type 2 diabetes	Chronic metabolic	Hyperinsulinemi	Both long-standing and newly diagnosed cases associated with elevated risk of PDAC [11].

	condition characterized by insuline resistence	a, insuline resistence, chronic inflammation, hyperglycaemia	Up to 85% of PDAC patients present with either new-onset T2D (NOD) or impaired glucose tolerance at the time of diagnosis (De Souza et al. 2016); NOD patients have a 3.81 to 5.2-fold higher risk of PC [22, 23], and those over 50 years old face a 6-8-fold higher risk [18, 22, 24]. 15% of T2D cases in PDAC patients are long-standing, with a 1.5 to 2.4-fold increased risk of PDAC [3, 18].
			Gallstones, pancreatitis, weight loss, and high or rapidly increasing glycemia or insulin use are specific risk factors for NOD (Mellenthin et al. 2022).
Allergies	Presence of allergies	Immune surveillance	Allergies and asthma represent other medical conditions that may impact PDAC risk (Cotterchio et al. 2014; Gomez-Rubio et al. 2017; Huang et al. 2018; Olson et al. 2013).
			Large studies and meta-analyses consistently indicated that allergies reduce PDAC risk (Gandini et al. 2005; Olson et al. 2013).
			Although the protective effect of allergies is consistent, it is stronger for specific allergies and less for others. Atopic allergies have a clear protective effect on PDAC onset (Cotterchio et al. 2014; Holly, Eberle, and Bracci 2003).
Blood group	A, B, AB or O blood group	Changes in blood-type antigens might interfere with cell signaling, adhesion, and the immune system's ability to kill preneoplastic cells	Individuals with A, B, or AB blood groups have a higher risk compared to those with blood group O (Kim, Yuan, et al. 2023). Changes in blood-type antigens might interfere with cell signaling, adhesion, and the immune system's ability to kill preneoplastic cells (Kim, Yuan, et al. 2023).
Genetic background	Presence of germline high or low pentrance mutation	Mechanisms could vary depending on the genetic variation, many are still	Genetic variants associated to PDAC risk are categorized as rare high-penetrance mutations or common low-penetrance muation (the majority of which are single nucleotide polymorphisms (SNPs)).
			Increased risk of PDAC is associated with the presence of inherited pathogenic mutations in 12 genes (*BRCA2, PALB2, BRCA1, ATM, STK11, CDKN2A, PRSS1, MLH1, MSH2, MSH6, PMS2, APC*) (Klein, 2021).
			The two most widely used approaches to identify new susceptibility loci are: candidate gene studies and genome wide association studies (GWAS).

		not defined	Five GWAS and one meta-analysis was conducted in the context of Pancreatic Cancer Cohort Consortium (PanScan), Pancreatic Cancer Case Control Consortium (PanC4) and the PANcreatic Disease ReseArch (PANDoRA) in European population (Amundadottir et al., 2009; Petersen et al., 2010; Wolpin et al., 2014; Childs et al., 2015; Zhang et al., 2016; Klein et al., 2018).
			Three GWASs and a meta-analysis were performed in Chineseand Japanese populations (Wu et al., 2014; Lin et al., 2020; Nakatochi et al., 2018).
Metabolic Syndrome	High blood pressure, insulin resistance, obesity, excess body fat around the waist, abnormal lipid levels	Chronic inflammation and oxidative stress promoting tumor growth and progression	Metabolic syndrome (MetS) Increases risk of pancreatic cancer through mechanisms like chronic inflammation and oxidative stress (Inoue et al. 2009; Miyashita et al. 2024; Park et al. 2020; Rosato et al. 2011)
			One cohort study reporting a 31% increased risk (Xia et al. 2020)
			A meta-analysis of nine studies confirmed a strong association (RR 1.34, 95% CI 1.23–1.46, P < 0.001) especially in females (women: RR 1.64, 95% CI 1.41–1.90, P < 0.001 versus RR 1.26, 95% CI 1.03–1.54, P = 0.022 in males) (Zhong et al. 2023)
			Importantly, recovery from MetS has been linked to a lower risk of PC, suggesting that improving metabolic health through lifestyle changes may reduce PC risk (Park, Hong, et al. 2022)
Cholelithiasis	Presence of gallstones	Chronic inflammation caused by gallstones, biliary obstructive diseases, high cholecystokinin levels	Individuals with gallstones (cholelithiasis) have slightly increased risk of pancreatic cancer (Naudin et al. 2020). It likely involves chronic inflammation caused by gallstones [53], biliary obstructive diseases [54], or high cholecystokinin levels in cholecystectomized patients [55].
			Most pancreatic cancers occur in individuals without a history of gallstones
Dyslipidemia	Abnormal lipid levels	Interplay between metabolic syndrome, insulin resistance, chronic inflammation, lipid	Abnormal lipid levels have been associated with higher risk of pancreatic cancer (Wang et al. 2021; Huang et al. 2022; La Torre et al. 2014; Bian et al. 2022) In a large study of 1 million subjects, the risk of pancreatic cancer was estimated to be 40% higher in those with dyslipidemia (Tseng 2013)
			Dietary cholesterol may be associated with increased risk except for Europeans (Wang et al. 2015)

		metabolism, secretion of adipokines and cytokines	

Table 2. Key facts of diet and addictive habits

Condition	Characteristics	Mechanisms	Epidemiological Findings
Tobacco Smoking	Smoking tobacco	Chronic inflammation, oxidative stress, genetic mutations	Contributes to approximately 11-32% of pancreatic cancer cases worldwide (Maisonneuve and Lowenfels 2015b)
			A large meta-analysis reported: RRs of 1.8 (95% CI 1.7-1.9) for current vs. never-smokers and 1.2 (95% CI 1.1-1.2) for former vs. never-smokers (Lugo et al. 2018)
			PanC4 analysis reported: 20% (OR 1.2, 95% CI 1.0-1.3) and more than two-fold increased risk (OR 2.2, 95% CI 1.7-2.8) for former and current smokers, respectively (Bosetti et al. 2012)
			PanScan study reported: OR of 1.77 (95% CI 1.38-2.26) for current vs. never-smokers (Lynch et al. 2009)
			Risk increases with duration and intensity of exposure
			Meta-analysis of 42 studies: RR estimates of 1.5 (95% CI 1.4-1.6) for 10 cigarettes/day, 1.9 (95% CI 1.8-2.0) for 20 cigarettes/day, 2.0 (95% CI 1.9-2.1) for 30 cigarettes/day, and 2.1 (95% CI 1.9-2.3) for 40 cigarettes/day (Zou et al. 2014)
			Nationwide study: HRs of 1.33 for <10 cigarettes/day, 1.45 for 10-19 cigarettes/day, and 1.55 for >20 cigarettes/day (Park, Seo, et al. 2022)
			An Australian study based on seven prospective cohorts reported an increased risk only if smoking more than 10 cigarettes/day (Arriaga et al. 2019)
			Risk decreases after at least ten years since smoking cessation
			Relationship between smoking and early-onset PDAC is less clear, possibly because of different thresholds used for defining early-onset PDAC (ranging from 40 to 60 years of age) and the limited number of cases analyzed.
			EPIC study suggested that also passive smoking may increase pancreatic cancer risk (HR of 1.54, 95% CI 1.00-2.39) (Vrieling et al. 2010)
Alcohol Consumption	Heavy drinking (≥ 3 drinks/day)	Chronic inflammation and pancreatitis	Meta-analysis of 21 case-control and 11 cohort studies from the U.S., Europe, and Asiareported a pooled RR of 1.22 (95% CI 1.12–1.34) for heavy drinkers compared to non-drinkers or occasional drinkers (Tramacere et al. 2010)

			PanC4 consortium: OR of 1.6 (95% CI 1.2–2.2) for heavy drinkers compared with non-drinkers or occasional drinkers (Lucenteforte et al. 2012)
			Prospective study of Chinese individuals: HR of 1.33 for weekly drinkers compared to non-drinkers; HR of 1.60 for heavy drinkers compared to non-drinkers (Pang et al.,2018)
			Pooled analysis from 4,211,129 individuals of mixed ethnicities: RR of 1.15 for heavy drinkers compared to non-drinkers (Wang et al.,2016)
			Pooled analysis of 14 prospective cohort studies: RR of 1.22 for high alcohol intake (≥ 30 grams/day) compared to non-drinkers (Genkinger et al.,2009)
			No strong association between low-to-moderate alcohol drinking and pancreatic cancer risk in several studies (Lucenteforte, La Vecchia et al. 2012, Rahman, Cotterchio et al. 2015, Wang, Gou et al. 2016, Pang, Holmes et al. 2018).
			PanScan study: No statistically significant association between alcohol consumption and pancreatic cancer risk (Michaud et al.,2010)
			Relationship may be confounded by tobacco smoking (Ye, Lagergren et al. 2002, Duell 2012, Rahman, Cotterchio et al. 2015)
			Mendelian randomization studies did not support a causal effect of alcohol drinking on pancreatic cancer risk (Lu, Gentiluomo et al. 2020, Yuan, Chen et al. 2023).
Non-alcoholic fatty pancreatic disease (NAFPD)	Fat accumulation in pancreatic tissue	Insulin resistance, cellular damage, chronic oxidative stress, local secretion of inflammatory markers, pathological activation of lipid-glucose metabolism and imbalance of hormone homeostasis.	NAFPD is not explicitly classified as a modifiable risk factor for PDAC, but it is associated with age, obesity, metabolic syndrome, and T2D that are known risk factor for PDAC (Duan et al., 2021).
			Effect of NAFPD on PDAC risk occurs in both obese and non-obese subjects (Park et al., 2022)
Body Mass Index (BMI)	Obesity (BMI > 30 kg/m²)	Location-dependent fat accumulation, chronic inflammation	A large study pooling data from 14 cohorts reported 47% increased risk of PDAC in obese subjects (Genkinger et al. 2011)
			A large meta-analysis of 19 studies estimated RRs of 1.36 for men and 1.34 for women (Dobbins, Decorby, and Choi 2013)
			A higher pancreatic cancer risk in adulthood for overweight and obesity conditions in adolescence (Zohar et al. 2019) was reporte in a national-level Israeli study ; a

			case control study (Li, Morris et al. 2009) and a study on Chinese incident case (Pang, Holmes et al. 2017)
			BMI-independent association between waist-to-hip ratio (WHR)and hip circumference (HC)and pancreatic cancer risk may reflect site-specific fat effect (Genkinger et al. 2011; Berrington de Gonzalez et al. 2006; Stolzenberg-Solomon et al. 2008)
			Mendelian randomization analyses provided further evidence for a causal role of BMI on pancreatic cancer risk (Carreras-Torres, et al., 2017; (Gentiluomo, et al., 2024)
Specific Foods and Components	Intake of total nut, tree nut, peanut, peanut butter, total fruit, citrus fruit, total vegetables, cruciferous vegetables, red meat, fructose	Varied associations with pancreatic cancer risk	Total nut consumption associated with reduced PC risk in two meta-analyses (D. Zhang et al., 2020; (Naghshi, Sadeghian et al., 2020).
			Contrasting results for total fruit, citrus fruit, total vegetables, and cruciferous vegetables (Gianfredi et al., 2022; Qin et al., 2023)
			Red meat consumption associated with increased PC risk in two meta-analyses (Paluszkiewicz et al., 2012; Z. Zhao et al., 2017). Similar trend,but not statistically significant, found in another meta-analysis (S. C. Larsson & Wolk, 2012)
			Fructose intake associated with increased PC risk in one meta-analysis (Aune et al., 2012)
Dietary Inflammatory Index (DII)	High DII, adherence to unhealthy or Western dietary patterns	Increased risk of pancreatic cancer	High DII associated with increased risk of PC in two meta-analyses (Z. Guo, Hong, & Cheng, 2021; Jayedi, Emadi, & Shab-Bidar, 2018), but no association was found in cohort studies (Qin et al., 2023)
			Unhealthy diet associated with increased PC risk in case-control studies (Grosso et al., 2017); but no association was found in cohort studies(Grosso, et al., 2017; Gianfredi, et al., 2022).
Dietary Patterns	Adherence to healthy	Reduced risk of pancreatic cancer	Healthy/prudent patterns associated with reduced risk of PC in two meta-analyses (Gianfredi et al., 2022; Grosso et al., 2017)

	/prudent or plant-based dietary patterns		Plant-based dietary pattern associated with reduced risk of PC in two meta-analyses of case- control or cohort studies (Y. Zhao et al., 2022)
Mediterranean Diet	Adherence to Mediterranean diet	Weak association with reduced risk of pancreatic cancer	No association found in one meta-analysis (Schwingshackl & Hoffmann, 2015)
			Weak association with reduced PC risk in four cohort studies (Jiali Zheng et al., 2017)
Sugar-Sweetened Beverages (SSBs) and Refined Sugar Consumption	Consumption of SSBs and refined sugar	Sugar intake, insulin production, insulin resistance, inflammation	Increased risk of PDAC with SSB consumption (Chen et al. 2022; Larsson, Bergkvist, and Wolk 2006)
			Dose-response relationship with risk increasing progressively from as little as one serving (Chen et al. 2022; Davis et al. 2023) A higher prevalence of PDAC has been associated with increased frequency of SSB consumption among individuals under 40 years of age. Estimating, in this age group, a threefold increase in PDAC risk in individuals consuming two or more SSBs per day (Larsson, Bergkvist, and Wolk 2006).
			70% greater risk of PDAC in people adding sugar to drinks at least five times a day (Larsson, Bergkvist, and Wolk 2006)
			Some studies failed to find a correlation between SSB consumption and PDAC risk (Navarrete-Munoz et al. 2016), Confounders possibly affecting results are tobacco, alcohol, diabetes, BMI, age, sex, physical activity, and overall dietary patterns (Schernhammer, Hu et al. 2005; Li, Go et al. 2015; Nucci, Nardi et al. 2023).
			Sex or age specific effect of soft drinks on PDAC risk may depend on BMI or physical activity (Schernhammer et al. 2005)

Table 3. Key facts of life-style

Condition	**Characteristics**	**Mechanisms**	**Epidemiological Findings**
Physical Activity	Intensity and type of physical activity, occupational and leisure domains, sedentar	Reduced risk with light and moderate physical activity; Prolonged sedenta	Statistically significant association between light, moderate, leisure and occupational ivity physical activity and reduced risk of PDAC ((Bao and Michaud 2008; O'Rorke et al. 2010; Brenner et al. 2014)
			Inconsistent findings across studies for different intensities of physical activity
			Prolonged telephone use and higher intensity (Peduzzi et al. 2023), as well as, time spent watching television(Gentiluomo et al. 2024) increased risk of developing PDAC

	y lifestyle	ry behavior increases risk	
Local Environment	Exposure to outdoor air pollution, particulate matter (PM2.5 and PM10), nitrogen oxides (NOx), nitrogen dioxide (NO2), hydrogen sulfide (H2S), sulfur oxides (SOX), ozone (O3), noise pollution, urban traffic, distance from the coast, percentage of green space, natural environment, water, and domestic gardens within 1000	Potential carcinogenic effects of air pollution and particulate matter	Several studies have investigated the association between particulate matter (PM2.5 and PM10) and PC, with mixed and often inconclusive results Association between PM2.5 and elevated risk of developing pancreatic cancer (HR of 1.16, 95% CI 1.13-1.20) (Wang et al. 2018); (HR of 1.61, 95% CI 1.09-2.37) (Bogumil et al. 2021) and between PM10 exposure and increased risk of pancreatic cancer (Ancona et al. 2015) Negative association between PM2.5 and risk of developing pancreatic cancer (OR of 0.65, 95% CI 0.52–0.80) (Craver et al. 2024) No significant associations were observed in studies by Turner et al. (2017), Coleman et al. (2020), and Felici et al. (2024). Additional environmental exposures were examined, but only O3 (Turner et al. 2017), and SOX (Ancona et al. 2015) were associated with a higher risk of PC.

	meters from residential coordinates		
Sleep Quality	Altered sleep patterns, habitual short sleep, exposure to light at night, shift work	Circadian disruption, exposure to light at night	Inconclusive results on the association between sleep duration and PDAC risk (Freeman et al. 2024; Stone et al. 2019; Titova et al. 2021; Peduzzi et al. 2023)
			Higher exposure to light at night associated with increased PDAC risk (HR of 1.24, 95% CI 1.03-1.49) (Xiao, Wang, and Gao 2013)
			Elevated risk of developing PDAC among individuals engaged in shift work (OR of 2.31, 95% CI 1.48-3.61) (Parent et al. 2012)
			Other studies did not confirm the association between shift work and PDAC risk (Peduzzi et al. 2023; Freeman et al. 2024; Lin et al. 2013)
Stress	Psychological stress, stress caused by traumatic events like loss of a child, divorce, income-related issues	Psychological stress, anxiety, depression	Pre-existing anxiety associated with increased risk of PDAC (OR of 1.13, 95% CI 1.04-1.22) (Li et al. 2023)
			Loss of a child increases risk of developing PDAC (OR of 1.09, 95% CI 1.02-1.17) (Huang et al. 2013)
			Association between traumatic events and increased PDAC risk (RR of 3.1, 95% CI 1.3-7.2 and OR of 2.90, 95% CI 1.62-4.80) (Nielsen and Peduzzi)

Table 4. Key facts of exposure to toxic substances, heavy metals and prescription medications

Condition	Characteristics	Mechanisms	Epidemiological Findings
Hormonal Treatments & Prescription Medications	OC use, HRT use, age at menarche, menopause, number of births	Hormones associated with pregnancy, menstrual cycle, oral contraception (OC), hormone	25 studies investigated **OC use**; of which 3 studies((Krieger et al. 2001; Azeem et al. 2015; Archibugi et al. 2020) and a 2021 meta-analysis(Ilic et al. 2021) found OC use linked to reduced PDAC risk.
			5 studies showed a reduced PDAC risk with **HRT use** (Watkins 1989; Lee et al. 2013; Lujan-Barroso et al. 2016; Archibugi et al. 2020; Ilic et al. 2021), while a meta-analysis (Jang et al. 2023)found no significant association

	replacement therapy (HRT)	**Age at menarche** associated with increased PDAC risk (Ilic, Milicic, e Ilic 2021; Lujan-Barroso et al. 2016; Bueno de Mesquita et al. 1992) while many other studies (Alvarez, Benjaminsen Borch, e Rylander 2021; Teng et al. 2017; Masoudi et al. 2017; E. Lee et al. 2013; Duell et al. 2013; Ersilia Lucenteforte et al. 2011; Duell et al. 2009; Prizment et al. 2007; Navarro Silvera, Miller, e Rohan 2005; Duell e Holly 2005; Kreiger, Lacroix, e Sloan 2001; Archibugi et al. 2020; Y. Zhang et al. 2010; Kalapothaki et al. 1993; Ji et al. 1996; Hanley et al. 2001; Skinner et al. 2003; Teras et al. 2005; Y. Lin et al. 2006; Stevens et al. 2009; Azeem et al. 2015; Kabat, Kamensky, e Rohan 2017)and a meta-analysis (Teng et al. 2017) found no association .
		Findings in studies on association between **age at menopause** and PDAC risk are inconsistent: Two studies suggest late menopause is protective (Prizment et al. 2007; Archibugi et al. 2020). One study suggests increased risk with late menopause (Duell and Holly 2005). Others studiest (Kalapothaki, Tzonou et al. 1993, Fernandez, La Vecchia et al. 1995, Ji, Hatch et al. 1996, Kreiger, Lacroix et al. 2001, Skinner, Michaud et al. 2003, Teras, Patel et al. 2005, Lin, Kikuchi et al. 2006, Duell, Maisonneuve et al. 2009, Stevens, Roddam et al. 2009, Zhang, Coogan et al. 2010) and meta-analysis (Tang et al. 2015) found no impact.
		Findings in studies on association between **parity** and PDAC risk are inconsistent: Several studies women (Kreiger, Lacroix, e Sloan 2001; Archibugi et al. 2020; Ersilia Lucenteforte et al. 2011; Kalapothaki et al. 1993; Skinner et al. 2003; Teras et al. 2005; Kabat, Kamensky, e Rohan 2017; Fernandez et al. 1995)and a Meta-analysis (Zhu et al. 2014): found that having ≥1 child is linked to reduced PDAC risk However, many other studies reported no association (Azeem et al. 2015; E. Lee et al. 2013; Alvarez, Benjaminsen Borch, e Rylander 2021; Teng et al. 2017; Duell et al. 2013; Duell et al. 2009; Prizment et al. 2007; Navarro Silvera, Miller, e Rohan 2005; Duell e Holly 2005; Y. Zhang et al. 2010; Y. Lin et al. 2006; Stevens et al. 2009; Andersson, Borgquist, e Jirström 2018)
		Common genetic variability related to signalling and biosynthesis of sex hormones not associated with PDAC susceptibility (Duell et al. 2013; Peduzzi et al. 2022)

			Some studies reported an association between asprin use and reduced PDAC risk (Risch et al. 1993; Langman et al. 2004; Baine et al. 2010).Others show no association (Bao et al. 2010; Anderson et al. 2002). also metanalysi findings are mixed: Risch et al. 2017and Bosetti et al. 2012: indicating protective effect. Sun et al. 2021 reported no significant effect. Kim et al. 2017: Showed a dose-response relationship, but results were not always statistically significant.
Aspirin, metformin, and statins	**Aspirin, metformin, and statins** have all been studied for their potential **chemopreventive and survival-improving effects** in **pancreatic ductal adenocarcinoma (PDAC)**.	Aspirin, Metformin and Statins may interfere with proliferation, angiogenesis, and inflammation.	Multiple meta-analyses reported significant risk reduction in pancreatic ductal adenocarcinoma (PDAC) with metformin use.(Noto, Goto et al., 2012; Franciosi, Lucisano et al., 2013; Singh, Singh et al., 2013; Wang, Lai et al., 2014; Hu, Fan et al., 2023;Zhang, Bai et al., 2021; Hu et al. (2023):). Other metanalysis reported confliting results: Chen et al. (2023): Found no overall association between biguanides (incl. metformin) and PDAC risk, but observed reduced risk in case-control studies Zhao et al. (2023): No association in a meta-analysis of 9 observational studies
			Meta-analyses suggest improved overall survival for metformin users with PDAC, with HRs ranging from 0.77 to 0.88.(Nowicka, Matyjek et al., 2023).
			Two large meta-analysis showed lower PDAC incidence in statin users vs. non-users: Karbowska et al. (2024) Bagheri et al. (2024): two studies Tamburrino et al. (2020) and Anbari et al. (2023): reported an improved survival for statin users with resectable PDAC. Another study Joliat et al. (2023): Found no survival benefit in a retrospective cohort of upfront resected patients studies on use of different sub types of statin reported: Use of Rosuvastatin was linked to reduced mortality in resected PDAC (HR 0.88, 95% CI: 0.81–0.96) (Tamburrino, Crippa et al., 2020). While Simvastatin & Atorvastatin showed strongest preventive effects (Archibugi, Piciucchi et al., 2017; Archibugi, Arcidiacono et al., 2019). No demonstrated protective effect in advanced PDAC, even when combined with chemotherapy (Archibugi, Arcidiacono et al., 2019).
Infectious Agents and the Influence of the Microbiota	Gut microbiome, microbial translocation, immune modulation	Gut-pancreas axis, disruptions in microbiota homeostasis, bacterial translocatio	Differences in bacterial abundances in fecal microbiomes of PDAC patients and controls (Pandya et al., 2022)
			Increases in Fusobacterium, Veillonella, and Streptococcus and decreases in Bifidobacterium, Faecalibacterium, and Eubacterium species in PDAC patients (Kartal et al., 2022; Nagata et al., 2022; Ren et al., 2017; Hashimoto et al., 2023; W. Zhou et al., 2021)
			Altered mycobiome, particularly Malassezia species, in PDAC (Bellotti et al., 2021)

		n, immune modulation	Increased abundances of Acinetobacter, Pseudomonas, and Sphingopyxis associated with more aggressive tumor phenotype (W. Guo et al., 2021)
			High levels of P. gingivalis antibodies or presence in oral microbiome associated with higher risk of developing pancreatic cancer (Olsen, 2017; Olsen & Yilmaz, 2019; D. S. Michaud et al., 2013)
			Fusobacterium species positively associated with worse prognosis (Mitsuhashi et al., 2015)
			Ablation of microbiome via oral antibiotics caused increase in intra-tumoral T cells and reduction of MDSCs (Pushalkar et al., 2018)
			Increased IL-1β following activation of TLR4 signaling by LPS promoted immunosuppressive milieu (Das et al., 2020)
			LPS promoted tumor T cell infiltration but also T cell exhaustion (Yin et al., 2021)
			Bacteroides, Lactobacillus, and Peptoniphilus associated with decrease in tumor-infiltrating CD4, CD8, and CD45RO positive T cells and reduced survival times (Abe et al., 2024)
Microbial Metabolites	Production or alteration of metabolites by the microbiome	Microbiome-mediated metabolism of primary bile acids to secondary derivatives, production of short-chain fatty acids (SCFAs), indoles, polyamines	Secondary bile acid deoxycholic acid increases EGFR, MAPK, and STAT3 signaling in PDAC cells (Nagathihalli et al., 2014); ; ; ; ;
			Secondary bile acid lithocholic acid inhibits proliferation and induces mesenchymal-to-epithelial transition in PDAC cells (Schwarcz et al., 2024)
			Reduced levels of butyrate-producing bacteria and fecal butyrate content in PDAC cases (W. Zhou et al., 2021)
			Expression of aryl hydrocarbon receptor (AhR) associated with immunosuppressive tumor-associated macrophage (TAM) phenotype and rapid progression in PDAC patients (Hezaveh et al., 2022)
			Elevated serum polyamine levels in murine PDAC models and patients (Mendez et al., 2020; Löser et al., 1990)
			Potential association between Helicobacter pylori infection and pancreatic cancer remains equivocal (B.-G. Zhou et al., 2023; Hirabayashi et al., 2019; A. A. Lee et al., 2023; M. Xiao, Wang, & Gao, 2013; Panthangi et al., 2022; Trikudanathan et al., 2011)
Heavy Metals	Exposure to heavy metals like lead (Pb), nickel (Ni), iron (Fe), cadmium (Cd), chromium (Cr),	Accumulation in the body, oxidative stress, DNA damage, disruption of cellular	Increased PDAC risk associated with decreased serum levels of magnesium, potassium, calcium, iron, zinc, selenium, arsenic, and mercury, and increased levels of molybdenum (Byeon et al., 2024)
			Significant increase in heavy metals in adjacent normal pancreas of PDAC patients (Byeon et al., 2024)
			No statistically significant association between regular exposure to chromium and nickel and pancreatic cancer (Antwi et al., 2015)

	manganese (Mn), zinc (Zn), arsenic (As)	signaling pathways	Correlation between cadmium exposure and elevated risk of pancreatic cancer (Schwartz & Reis, 2000; Amaral et al., 2012; Manić et al., 2022; Forte et al., 2024); Nickel exposure linked to pancreatic dysfunctions and PDAC (Gómez-Tomás et al., 2019; Wallace, Djordjević, & Benton, 2020)
			Occupational exposure to nickel compounds significantly raised the risk of pancreatic cancer among workers in the Ni refining industry (Ojajärvi et al., 2000)
			Arsenic exposure associated with increased risk of pancreatic cancer (Liu-Mares et al., 2013)
Acrylamide	Exposure to acrylamide in food	Probable human carcinogen	No association between dietary acrylamide and pancreatic cancer risk (Pelucchi et al., 2017; Obón-Santacana et al., 2013; Pelucchi et al., 2011; Kito et al., 2020)
Heterocyclic Aromatic Amines (HCAs) and Polycyclic Aromatic Hydrocarbons (PAHs)	Exposure to HCAs and PAHs formed during cooking processes such as boiling, frying, barbecuing, and grilling of meat and fish	Mutagens and carcinogens	HCAs and benzo(alpha)pyrene from well-done barbecued and pan-fried meats linked to elevated risk of pancreatic cancer (Anderson et al., 2005)
			Higher meat consumption positively associated with increased risk of pancreatic cancer, particularly in individuals over 60 years old (Beaney et al., 2017)
			Meat cooked at high temperatures associated with increased risk of pancreatic cancer (Anderson et al., 2012)
			High total meat intake linked to 26% increased risk of pancreatic cancer in both men and women (Stolzenberg-Solomon et al., 2007; Taunk, Hecht, & Stolzenberg-Solomon, 2016)
Glycome Changes in PDAC Development	Non-invasive serum biomarkers, abnormal glycosylation patterns, glycan profiles	Changes in glycosylation patterns, sialylation, fucosylation, O-glycosylation , EMT	CA 19-9 and CEA used as biomarkers for PDAC but have limitations lack sensitivity and specificity, especially for early detection. Elevated levels can also occur in CP or benign diseases (Hanna-Sawires et al., 2021; Xu et al., 2023)
			Characterized by stromal, tumor, and immune cells; abnormal glycosylation, especially sialylation, is a hallmark of PDAC and other malignancies (Marciel et al., 2023; Wagatsuma et al., 2020)
			Integration with transcriptomic/genomic tools has revealed diagnostic N-glycan signatures for PDAC. Common changes: increased branching, core fucosylation, and sialylation (Zhang, Zhang et al. 2022). PDAC Glycan Subtypes (Rodriguez, Boelaars et al. 2022): Cluster A (fucosylated/classical): ↑ fucosylation/O-glycosylation gene expression. Cluster B (basal): ↑ MUC4, MUC16, galectin-1; associated with EMT and metastasis.
			MUC4 and MUC16 aberrantly expressed in PDAC and promote tumorigenesis (Sagar et al., 2021; Thomas et al., 2021)

			Glycome biomarkers distinguish PDAC patients from healthy individuals (Vreeker et al., 2020; Levink et al., 2022)
			Increased levels of α-2,6-sialic acid and overexpression of ST6GAL1 in PDAC (Wagatsuma et al., 2020; Kurz et al., 2021)
			Two promising glycan markers (NGA2FB and NA2FB) for distinguishing early and advanced PDAC (Wen et al., 2024)

Table 5. Key facts on links with pancreatic diseases and co-morbidities

Condition	**Characteristics**	**Mechanisms**	**Epidemiological Findings**
Chronic pancreatitis	Long-term, progressive inflammatory of the pancreas	Inflammation	CP is a known risk factor for PDAC onset.
			A history of CP has been associated with a HR for PDAC of 6.9 (95% CI: 5.6-8.6) in a Danish nationwide study, and in Korean populations with an HR of 3.9 (95% CI: 2.7-5.5) and an incidence ratio of 18.1 (95% CI: 10.4-29.5) (bang et al., 2014; Han et al., 2022; Kim et al., 2023).
			A recent meta-analysis reported a standardized incidence ratio ranging from 13.3 (95% CI: 6.1-28.9) to 22.61 (95% CI: 14.42-35.44) (Gandhi et al., 2022).
			The risk of PDAC in CP patients is highest at 2 years from diagnosis, decreasing with longer follow-up (Kirkegard et al., 2017).
Intraductal Papillary Mucinous Neoplasm (IPMN)	Mass-forming cystic lesions	Progression to high-grade displasia or invasive carcinoma	IPMN is a recognized risk factor for developing PDAC, related to the potential adenoma-carcinoma progression from low-grade dysplasia (LGD) to high-grade dysplasia (HGD)/invasive carcinoma (IC) (Saiki et al., 2021).
			Studies have shown a higher possibility of developing concomitant PDAC, 3 to 5-fold compared to the general population (Oyama et al., 2020).
			Predictive factors of HGD/IC include high-risk stigmata (HRS) and worrisome features (WF) (Ohtsuka et al., 2024).
Mucinous Cystic Neoplasms (MCN)	Mucin-secreting cystic tumors that do not communicate with the ductal system	Progression to invasive carcinoma	MCNs are mucin-secreting cystic tumors that do not communicate with the ductal system and can progress to invasive cancer, with a reported risk ranging from 10% to 39% (Park et al., 2014).
			A recent meta-analysis found a low global risk of progression (16%) in more than 3,000 resected MCNs (Pollini et al., 2023).
			The risk of malignancy depends on specific features such as tumor size and presence of mural nodules (Pollini et al., 2023; Marchegiani et al., 2021; Servin-Rojas et al., 2023; Ohtsuka et al, 2020; Kim et al., 2022).

Declaration of Competing Interest

There are no conflicts of interest regarding this manuscript.