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A review of lifestyle and environment risk factors for pancreatic cancer

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Highlights

- Smoking, high alcohol and red meat intake increase PaCa risk.
- Obesity and diabetes stimulate insulin production and predispose to onset of PaCa
- Lifestyle and behaviour are linked with PaCa by plausible biological processes
- Inflammation a potential common mechanism to lifestyle environment, diseases & PaCa

Abstract

Pancreatic cancer (PaCa) is one of the most deadly cancers known and its incidence is increasing in developed countries. Because of the lack of biomarkers that allow early detection and the tendency of the disease to be asymptomatic, the diagnosis comes often too late for effective surgical or chemotherapy intervention.

Lifestyle factors, that may cause common genetic modifications occurring in the disease, interfere with pancreatic physiology or function, and play a role in PaCa development, have been of concern recently, since a strategy to prevent this severe cancer is needed.

This review identifies the latest evidences related to increased risk of developing PaCa due to dietary habits such as high alcohol, fructose and red or processed meat intake, and pathological conditions such as diabetes, obesity and infections in addition to stress and smoking behavior.

It aims to highlight the importance of intervening on modifiable risk factors: the action on these factors could prevent a considerable number of new cases of PaCa.

Keywords*:* Pancreatic cancer, life style factors, tobacco smoking, alcohol intake, sugar and fructose intake, red and processed meat, environmental and synthetic toxins, obesity, type 2 diabetes, metabolic syndrome, infectious diseases, psychological stress**.**

INTRODUCTION

Pancreatic Cancer (PaCa) is one of the most lethal diseases with a 5-year survival rate of about 8% and a survival rate after the first year of diagnosis of 20% [1]. According to last statistics, overall cancer incidence and mortality rates have both declined when considering the total American population [1] and, in the United Kingdom (UK), the number of deaths due to cancer is decreased by about 9% in the last ten years [2]. Despite this tendency, pancreatic carcinoma, along with liver, soft tissues and uterus cancer, represents an exception showing an increase, rather than a decrease, in both incidence and mortality rate of 0.3% for men and 0.4% for women per year in the United States [3]. During the last decade, PaCa mortality rates in the UK population have increased by 6%, whereas the incidence rate increased by 9% and 11% in men and women respectively. In 2015, this cancer represented 3% of all new cases with no heterogeneity between male and female [2]. Incidence increases with age: PaCa is rare in people under 25 years of age, still relatively uncommon for those under 40, while 80% of the cases are diagnosed in people between 60 and 80 [4]. Only after 80 years of age, a decrease in incidence in both sexes can be observed [1]. Epidemiological studies show that people of African American and Jewish descent have a higher incidence rate of PaCa than Caucasians; the incidence of PaCa is higher among men compared with women and positive clinical outcome is lower in people with a low socioeconomic status [5-9]. Ninety-five percentage of PaCa arises from ductal epithelial cells through a well-defined sequence of events from pancreatic intraepithelial neoplasia (PanIN) to invasiveness carcinoma and metastasis or pre-malignant lesions of the pancreas as intraductal papillary mucinous neoplasm (IPMNs) and mucinous cystic neoplasm (MCNs) [8]. Some of the most characterised genes whose mutations have been recognized in the pathogenesis of PaCa are the tumour suppressor genes CDKN2A (cyclin-dependent kinase inhibitor 2A), SMAD4, TP53 (Tumor Protein P53) and the KRAS oncogene [10].

To date acting on preventable risks is a way that should be pursued considering the lack of screening programs and effective therapeutic options [11, 12]. It has been estimated that about 37%

of new cases could be preventable [2]. The report on PaCa that was built together in 2012 under the Continuous Update project by the World Cancer Research Fund International (WCRF) [13] and the American Institute for Cancer Research listed several factors connected with lifestyle that could play a promoting or protective activity on the risk to develop PaCa [13]. Established risk factors, such as cigarette smoking, alcohol intake, consumption of red and processed meat and high fructose drinks have been the subject of consideration since long but other predisposing factors such as obesity and sedentary life are powerfully emerging. It has been predicted that obesity will overtake smoking as the biggest environmental risk factor for PaCa. World health organisation (WHO) data predict an increasing incidence to nearly 12,000 cases per annum by 2030: current incidence being 8,880, an increase of 35% in 14 years [14]. Therefore, the present review summarises the evidence of a relationship between lifestyle, environmental factors and diseases, and increased risk to develop PaCa focusing mainly on the underlying biological/molecular mechanisms.

Lifestyle and Environmental Risk Factors

Tobacco smoking

Tobacco smoking represents the first investigated modifiable risk factor for PaCa development, and, contrary to other environmental factors, the literature agrees worldwide that a significant elevated risk has been identified in current smokers compared with never smokers (odds ratio (OR) 1/4 1.77, 95% CI: 1.38, 2.26) [15], and the liability of smoking to PaCa development has been estimated to be about 15-20% [15, 16]. A large meta-analysis, including 254 studies, showed that current smokers, in addition to have a remarkably higher risk of developing respiratory tract cancers (lung relative risk (RR) =8.96; 95% confidence interval (CI): 6.73–12.11; laryngeal RR= 6.98; 95% CI: 3.14–15.52; pharyngeal RR= 6.76; 95% CI: 2.86–15.98), also have high RR for PaCa (RR=1.70; 95% CI: 1.51-1.91) [17]. These findings have been supported by a more recent meta-analysis that estimated an increase of 48% RR of PaCa development in ever smokers compared to never-smokers and an excess of risk of 82% and 17% in current and former smokers, respectively [18]. According

to a large cohort study, the population attributable risk (PAR) for smoking (calculated on current smokers and smoking cessation for <10 years) in PaCa was of 14%, compared with other 4 risk factors (alcohol use 3%, dietary quality 3%, body mass index (BMI) 8% and physical activity 3%) [19].

Smoking behaviors also influence the survival of diagnosed patients: habitual smokers have a higher risk to develop multiple primary malignancies compared to non-smokers; patients that continue to smoke, develop new malignancies earlier than patients that stopped smoking after the first diagnoses of cancer (6.11 vs 11.5 years, respectively) [20]; and smokers have a 7% increase of risk for each cigarette smoked per day as estimated from dose response analysis [17]. The duration and intensity of smoking were found to be related as well: the first is responsible for an increased risk of 1% for each year of smoking and of 16% for a total duration of smoking of 10 years, whereas an increase of 2% in risk was observed for every cigarette per day [16, 21]. A meta-analysis conducted on 42 observational studies (30 retrospective and 12 prospective) pointed out the existence of a non-linear dose-response association between cigarette smoking and PaCa risk: it markedly increased for moderate consumption (17% for 5-25 cigarettes per day) until it stabilized for a high intensity of consume (6% for 30-40 cigarettes/day) [22]. Similarly the duration of smoking was found to be related in a non-linear manner with increase of PaCa risk, in fact, after 10 years of smoking RR was 1.3 (95% CI: 1.3e 1.4), while RR of 1.7 (95% CI: 1.5e1.8) was observed after 20 years and 1.8 (95% CI: 1.6e2.0) after 30 years of smoking. Interestingly, the risk of PaCa development decreased consistently with the increase of the years since stopping smoking. The same risk of non-smokers (0.6 RR: 0.6; 95% CI: 0.5e0.6 for never vs. current smokers) was reached after 20 years of stopping [18]. Dose-response relationship between duration and intensity of smoking, and increased death for PaCa was observed in a meta-analysis comprising 20 studies and 2,517,623 participants. PaCa total mortality risk was found to increase by 56% in current smokers and by 15% in former smokers [23]. Furthermore, a link between cigarette smoking and decrease of survival rate was observed among PaCa patients (P trend = 0.008), with hazard ratio (HR) for death

of 1.49 (95% CI, 1.05 to 2.10) for > 60 pack-years when comparing smokers versus never smokers [24]. Differently from active smoking, passive exposure, referred as environmental tobacco smoke (ETS), is not indisputably linked to increased PaCa risk. In fact, Zhou *et al* in a meta-analysis including 10 studies did not found any significant association between PaCa incidence in non-smokers and ETS exposure [25].

Although cigarette smoking has been considered as one unique risk factor, smokers are exposed to a mixture of different carcinogenic and toxic compounds, both organic and inorganic, such as polycyclic aromatic hydrocarbons, heterocyclic aromatic amines, metals, and even radioactive gas. For this reason, cigarette smoking could act through several different mechanisms in PaCa development [21]. N-nitrosamines such as N0-nitrosonornicotine (NNN), 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanone (NNK) are widely studied. The latter and its metabolite 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol (NNAL) are considered the most important carcinogens in tobacco as they have been shown to cause PaCa in animal models [26]. They lead to KRAS mutation, the most common mutation that occurs in PaCa progression [27]. In mice, nicotine promotes carcinogenesis-inducing dedifferentiation of acinar cells through downregulation of GATA6 (GATA-binding factor 6) and subsequent hyperactivation of K-Ras [28]. Furthermore, NNK can exert an epigenetic effect on pancreatic cells, binding β-adrenergic receptors and causing the release of arachidonic acid (AA). AA metabolites exert a mitogenic effect activating cell proliferation and PaCa development in cancers that do not harbour KRAS mutations [27].

Alcohol intake

A large meta-analysis on 11 cohort studies and 21 case-control studies showed a strong association between PaCa development and heavy alcohol intake (>3 drinks/day or ≥40g/d for dose/risk analysis) with an increase of 20% in PaCa risk, but no association was observed among non- or occasional drinkers (<3 drinks/day). This positive association has been identified to be stronger in cohort studies compared to case-control studies [29]. In the context of the European Prospective

Investigation into Cancer and Nutrition (EPIC) study, considering 1,238 incident cases, alcohol intake was positively found associated with PaCa risk in men, especially in heavy drinkers (>60 g/day). Moreover, the intake of beer and liquor showed a stronger risk than wine consumption, whereas smoking status seemed not to affect the alcohol contribution in cancer [30]. Accordingly, Wang *et al*. confirmed the correlation between high alcohol intake (in particular liquor consumption) and PaCa incidence at a lower dose (15g/d) while Rosato *et al.* attributed 13% of PaCa cases in North Italy to heavy alcohol intake [31, 32]. This non-linear relation could be due to bias linked with the method of analysis, such as limited number of reported cases, the contemporary exposure to different risk factors and the difficulty in adjusting for them such as tobacco smoking. Alcohol, indeed, might amplify the negative effects of tobacco smoking and other risk factors involved in PaCa development [21].

A possible suggested mechanism that could link alcohol intake and PaCa development has been identified into the metabolites of ethanol such as acetaldehyde that are released into the bloodstream. Acetaldehyde is able to bind DNA repair proteins, give rise to DNA damage and cause the formation of DNA adducts promoting tumorigenesis [33]. In addition, the metabolites of ethanol produced by the non-oxidative pathway (fatty acid ethyl esters) cause a sustained elevation of calcium released from intracellular stores [34]. The marked increase of calcium mediates toxicity in pancreatic acinar cells initiating the process of pancreatic auto-digestion, caused by premature trypsinogen activation [35]. Recurrent injuries to pancreatic acinar cells impair autophagy, which is a process aimed at limiting the extension of inflammation and damage to healthy cells that prevent neoplastic transformation [36].

Sugar intake and fructose rich drinks

In order to understand the role of sugar intake on PaCa incidence, several studies have been conducted. The attention has been focused on added sugar present in beverages such as corn derived high fructose syrups, not only because its consumption has increased in the last fifty years [37], but

176 also because fructose from beverages is rapidly metabolized compared to the one present in solid
177 foods [38].
178 A prospective analysis on 131 cases of PaCa showed a greater risk among big consumers of soft
179 drink (> 2/day) and sweetened fruit soups compared with sporadic consumers [39]. Similarly, in
180 two additional cohort studies, an increased risk of PaCa was found among women (overweight and
181 not) with high consumption of sugar-sweetened soft drinks, but not in men [40]. An association was
182 also found when considering the intake of high free glucose and free fructose from fruit and fruit
183 juice [41]: a meta-analysis conducted in 2012 showed that the fructose intake of 25 g/day was
184 positively associated with a higher risk RR = 1.22 (95% CI: 1.08–1.37, I2 = 0%) while no
185 association was found between PaCa risk and respectively glycemic index, sucrose and high
186 carbohydrates consumption [42]. These results could be explained by the important differences in
187 sugars' type and their peculiarities in absorption. Despite fructose and glucose being chemically
188 very similar, they are metabolized differently [43]: while glucose uses Na-dependent transporter,
189 fructose is absorbed by glucose transporter type 5 (GLUT5) at the level of the small intestine and
190 metabolized principally in the liver. Pancreatic β-cells produce insulin in response to high level of
191 glucose in bloodstream causing the increase in transporters such as glucose transporter type 4
192 (GLUT4), used by glucose, and the store of this as glycogen, whereas GLUT5 is not responsive to
193 this hormone and the uptake of fructose remain unregulated [43]. This behavior specific to fructose
194 promotes pyruvate decarboxylation causing Acetyl-CoA synthesis, involved in *de novo* lipogenesis,
195 and the consequent diacylglycerol **(**DAGs) accumulation can cause protein kinase-C (PKC)
196 activation interfering with insulin signaling pathway leading to insulin resistance [44].
197 Furthermore, it has been demonstrated that fructose is preferentially used by PaCa cells compared
198 with glucose in the non-oxidative Pentose Phosphate Pathway (PPP) that leads the 5-carbon pentose
199 production from 6-carbon glucose, giving new substrates for RNA synthesis. Fructose is able to
200 induces higher transketolase (TK) expression causing a faster use of both, fructose and glucose, *via*

PPP [45]. The greater contribution of fructose to nucleic acid synthesis leads to the increase in uric acid production, resulting to purine metabolism [42].

Hsieh *et al*. carried out a study, using *in vitro* and *in vivo* models, to clarify the effective role of fructose in PaCa development. High levels of this sugar have been shown to promote aggressive cancer development in mice and specific KRAS mutations when compared with normal diet fed mice, characterized by a higher grade of panIN lesions, and development of neoplastic lesions with higher level of GLUT5, ATP-binding cassette transporter ABCG2, β-galactoside α2,6-sialyltransferase 1 (ST6gal1) and with a higher metastatic power. In i*n vitro* model*,* the substitution of glucose with fructose promoted the selectively outgrowth of invasive and drug resistant subpopulation of ABCG2-positive cells, and increased 2, 6 sialylation caused by upregulation of ST6gal1 involved in increased cancer cells metastatic potency [45].

Processed and red meat intake

Different studies have shown that a high intake of meat positively correlates with the risk of developing PaCa. A meta-analysis conducted in 2012 on 11 prospective cohort studies showed a positive association between red and processed meat consumption and PaCa risk [46]. In the multi-ethnic large prospective cohort study conducted in Hawaii and Los Angeles, 215,000 men and women aged 45-75, belonging to the main cultural groups residing there (African-American, Latino, Japanese-American, Native Hawaiian and Caucasian), were enrolled between 1993 and 1996 and the associations with risk of PaCa development, based on different dietary habits, were investigated. After 7-years follow up, data on 190,545 patients were finally available. Four hundred and eighty two incidental PaCa cases were reported. The analysis showed that the intake of processed meat and red meat was strongly linked to an increased risk in developing PaCa (68% increased risk for the subjects in fifth quintile of meat daily intake (18g/1000kcal) compared with those in the lowest quintile (2g/1000kcal); RR = 1.68, 95% CI = 1.35 to 2.07; p trend<0.01) and a positive trend with nitrosamine intake, derived by cooking on a grill, was observed (p=ns) [47]. In

2013, the associations between PaCa and meat and fish consumption were investigated in the EPIC study. No significant correlation was found between the consumption of red and processed meat and an increase risk to develop PaCa [48].

There are several biological mechanisms that could connect PaCa development and the intake of red or processed meat. Cooking meat, especially at high temperatures, is responsible for the release of polycyclic aromatic hydrocarbons (PHAs) and heterocyclic amines (HCAs) that cause DNA-damage. N-nitroso compounds (NOC), formed in the preserving process, can cause the formation of DNA-adducts, although tobacco smoking is known to expose to higher concentration of these compounds [49]. Recently also the presence of heme iron in red meat has been hypothesized to play a causal role being a promoting agent of oxidative stress [50]. Taking altogether the association between red and processed meat consumption and PaCa development appears weak and in need of further studies but it cannot be excluded.

Environmental and synthetic toxins

Among exogenous environmental factors, Bis[2-ethylhexyl]phthalate (DEHP) has been linked with an elevated risk of PaCa [51]. DEHP is widely used as plasticizers for PVC (polyvinyl chloride) and, as a consequence, is present in many products such as floor and wall coverings, car interiors, toys and child care articles [52]. DEHP is an endocrine-disrupting chemical (EDC) and the gestational exposure of pregnant rats has been linked with pancreatic beta-cells dysfunction in F1 offspring [53]. *In vitro* experiments on several human tumour cell-lines and tissues exposed to DEPH showed an increased cell proliferation, DNA damage, reversal of apoptosis and alteration in nuclear receptors expression [54].

Exposure to cadmium has also been linked with an increased risk of PaCa. Cadmium is a toxic metal generated by the smelting of zinc, lead or copper ores. It is commonly used in battery production and is present in phosphate fertilizers and sewage sludge. It is mostly found in food (e.g. leafy vegetables, farinaceous products, shellfish), which represents the main source of exposure in

253 the non-smoking population [55]. Interestingly, in south Louisiana, where a high rate of PaCa is
254 registered, dust specimens collected from 315 indoor and outdoor samples revealed that 64 of them
255 exceeded the Environmental Protection Agency's guidelines for cadmium, likely due to the
256 industrial activity that contaminated much of the wetlands in Louisiana [56, 57]. An increase in
257 urinary cadmium concentrations was found to be significantly associated with an increased risk of
258 PaCa (2^{nd} quartile OR=3.34, 3^{rd} = 5.58, 4^{th} =7.70; test for trend $p< 0.0001$) [58]. Because of the
259 mechanism of molecular mimicry, cadmium interferes with zinc-mediated processes binding to
260 metallothioneins, especially in the liver and kidney [55]. Accordingly, a study conducted in 2016
261 showed that chronic exposure to low levels of cadmium lead to the expression of special AT-rich
262 sequence-binding protein 2 (SATB2), a transcription factor, physiologically not expressed in
263 normal human pancreatic cells but expressed in cancer stem cells and pancreatic cancer cell lines.
264 The induction of SATB2 expression may represent one of the mechanisms involved in cell
265 transformation [59].
266 Further evidences are provided by a study focused on 12 trace elements found in toenail samples.
267 The research confirmed the link between PaCa and the exposure to arsenic and cadmium and
268 reported a novel association with lead [60]. Another toenail sample-based study investigated the
269 relation between the amount of trace elements and occupational history. Exposure to organic
270 solvents, pesticide and volatile sulphur compounds showed a higher concentration of different
271 metals. In particular, in presence of a pesticide exposure, cadmium levels were 0.056 μg/g (95% CI
272 0.029–0.108), whereas, for unexposed cases, was only 0.023 μg/g (95% CI 0.017–0.031) [61]. In
273 2013, a large epidemiological study including 3,932 people confirmed a correlation between arsenic
274 exposure and PaCa with a hazard ratio of 2.46 (1.09-5.58) [62]. In addition, an ecological cancer
275 mortality study on 7,917 Spanish towns highlighted an association between arsenic topsoil
276 concentration and PaCa mortality [63]. On the other hand, an inversely association between PaCa
277 risk and high selenium and nickel concentrations was found even if the inversely association with
278 nickel remains highly controversial in the literature. Selenium can exert a protective effect against

oxidative stress induced by other elements or boost the activity of proteins involved in DNA repairing or apoptosis [60].

A clinic-based case–control study showed an increased risk of PaCa caused by the regular exposure also to other chemicals such as benzene, asbestos and chlorinated hydrocarbons whereas chromium and nickel were not significantly associated [64]. A moderate increment in *K-Ras* activation has been observed analyzing the samples of pancreatic tumors collected by patient subjected to occupational exposure to metals such as lead, nickel and chromium and to different chemicals such as polycyclic aromatic hydrocarbons (PAHs), gasoline and benzo[a]pyrene [65].

Multifactorial Risk Factors

Obesity

Obesity, defined as a BMI equal or higher than 30 kg/m^2, has long been recognized as a risk factor for a variety of pathological conditions such as diabetes mellitus, hypertension, dyslipidaemia, ischemic heart disease and some types of cancer such as breast, endometrium, oesophagus, colon, kidney and pancreas [66, 67]. Central adiposity, measured as waist to hip ratio (WHR), is more strongly related to insulin resistance and diabetes, two recognized PaCa risk factors [68]. In 2007, WCRF reported that there are increasing and convincing evidences that obesity is linked with a higher risk of developing PaCa [13].

A case control study, involving 841 pancreatic adenocarcinoma patients and 754 controls, highlighted the relationship between overweight (BMI 25-29.9 kg/m^2 at 14-39 years), obesity (BMI >30 kg/m^2 at 20-49 years) in early adulthood and an increased risk of PaCa (OR, 1.67; 95% CI, 1.20-2.34 and OR, 2.58; 95% CI, 1.70-3.90, respectively) [69]. Moreover, a pooled analysis on 14 cohort studies was conducted to evaluate the association between obesity and anthropometric factors (BMI at younger ages, waist circumference, hip circumference or WHR), and PaCa risk distinguishing between men and women because of the different hormonal status and lifestyle factors that could affect the study [70]. A positive association between obese people and PaCa risk was found (increased by 47%, 95% CI= 23-75%) with the female and male groups showing similar

risk. PaCa risk was higher (54%, 95% CI=24–93%) for those who were overweight in early adulthood and obese at baseline, and 40% higher for those who gained weight (BMI ≥10 kg/m^2 between baseline time and younger ages compared to individuals who remained stable). Considering WHR and comparing the highest versus lowest quartile, a 35% greater risk was observed (p=ns) [70]. An analysis conducted on pooling data from nested case-control studies from the NCI PaCa Cohort Consortium (PanScan), which included 2,170 cases and 2,209 controls, showed a positive association between increasing BMI and risk of PaCa for all subjects (adjusted OR for the highest vs. lowest BMI quartile = 1.33, 95% CI = 1.12-1.58, $p_{trend} < 0.001$) [71]. A pooled analysis of nine Japanese cohort studies, reveled an increased risk of PaCa among obese men (≥30 kg/m^2 compared with 23 to <25 kg/m^2, adjusted HR 1.71; 95% CI, 1.03–2.86), whereas the risk among women was not clear [72]. However, recent studies have demonstrated that a loss of weight reduced the risk of PaCa development in overweight or obese postmenopausal women [73]. In the EPIC study, Kliemann *et al*. predicted and associated basal metabolic rate (BMR) to risk for different cancer types. Interestingly, BMR was found positively associated with PaCa risk ($HR_{1\text{-}sd}$: 1.37; 95%CI 1.13 - 1.66) also in normal-weight persons (BMI<25kg/m^2) [74].

Type 2 Diabetes

Obesity is a recognized cause of type 2 diabetes (T2D), one of the major established causes of PaCa itself: about 80% of T2D patients are overweight or obese. Both T2D and obesity are characterized by a pro-inflammatory state, having insulin resistance as common results. The adipose tissue is able to secrete several molecules known as adipokines, including hormones regulating energy homeostasis, cytokines with anti- and pro-inflammatory action and peptides involved in glucose homeostasis [75]. In addition, oxidative stress induced by high intake of glucose and macronutrients intake and the consequent increase in the production of pro-inflammatory cytokines, such as tumour necrosis factor alpha (TNF-α)-and interleukine-6 (IL-6), can interfere with the signal transduction of insulin, leading to insulin resistance [76]. Concerning the NIH-AARP Diet and Health Study

(AARP), Zheng *et al*. used a dietary inflammatory index (DII®) score to evaluate pancreatic cancer risk. They examined also the effect that modification by inflammation-related lifestyle factors would induce: no significant association was, however, detected in relation to PaCa risk [77]. Increasing and strong evidences related to the association between T2D and PaCa development are available. In a meta-analysis on 35 cohort studies, patients with diabetes showed a doubled risk to developing PaCa and Huxley's meta-analysis pointed out that individuals with long-standing diabetes have still a 50% RR more than individuals without diabetes even if a negative relationship was found with duration of diabetes [78, 79]. On the other hand, Magruder *et al.* reported that a 4-7-fold risk of PaCa is present also in recent onset diabetes [80], and positive relationship has been found between fasting glucose level and cancer risk in a cohort analysis of 1,298,385 Korean people [81]. It is, however, important to underline that studies on long standing diabetes are more likely to have biases due to self-reported illness.

The recent PanGenEU study has explored the different associations between PaCa risk and T2D subtypes evaluating also the interplay of obesity. Individuals with T2D compared with non-T2D showed an increased PaCa risk, and among diabetics, the ones with new-onset T2D had a higher risk. However, data suggest that, in the latter group, emerging diabetes may result as a consequence of cancer cell growth, whereas, in long-standing T2D, diabetes may represent a mediator within the pathway that leads from obesity to cancer [82]. Butler *et al*. found that replication of pancreatic cells duct was increased 10 folds in patients with T2D compared with lean nondiabetics: patients with both PaCa and T2D had enlarged ducts and hypertension and increased tumour size [83]. PaCa patients diagnosed with diabetes lasting five or more years showed a positive association with KRAS codon 12 mutations [84]. Recently, a study meant to investigate the role of diabetes in influencing pancreatic tumour immune microenvironment, highlighted the higher inflammatory status, due to high level of macrophage and lymphocyte infiltration, phenomenon associated with a poorer survival [85].

Interestingly, cancer risk associated with diabetes can also be influenced by antidiabetic therapy. A retrospective cohort study based on the population resident in the Saskatchewan province (around 1 million) found that, in a cohort of 10,309 people that used antidiabetic drugs for more than 1 year, people had a greater cancer-related mortality if exposed to sulfonylureas or exogenous insulin, compared with patients on metformin treatment (adjusted HR 1.3, 95% CI 1.1-1.6; p=0.012 and adjusted HR of 1.9 (95% CI 1.5-2.4; p<0.0001, respectively) [86]. This observation was also confirmed in other studies when considering in particular PaCa [87, 88]: metformin, contrarily to sulfonylureas or exogenous insulin, does not increase insulin levels and insulin itself is known to promote the growth of PaCa cells [89]. Metformin has also been shown, in a cell line study, to enhance the effect of different chemotherapeutic drug for PaCa treatment when used in combination [90]. Insulin resistance and compensatory hyperinsulinemia due to T2D is considered as a favourable condition for tumour growth [91]. Hyperinsulinemia causes the decrease of insulin like growth factor binding proteins (IGFBP-1 and 2) that results in a high level of circulating insulin-like growth factor-1 (IGF-1) in bloodstream. This growth factor may play a crucial role in cell proliferation and can interfere with sex hormones causing the typical differences of gender observed in PaCa risk [91].

Metabolic Syndrome

In the wider framework represented by the metabolic syndrome (MetS), biological processes occurring in diabetes and obesity, in addition to dyslipidaemia and hypertension, are strictly linked to each other and act synergistically enhancing the risk of developing several diseases. The combination of a different numbers of conditions, characterizing MetS, may act proportionally in enhancing the risk of PaCa, and among these, diabetes is the strongest risk factor [92].

The presence of comorbidities places attention on the need to conceive studies not oriented only on individual conditions but on their interaction. In a European case-control study, two multimorbidity patterns, related to MetS and gastric illness, were found positively associated with PaCa even

383 considering time and common background environmental and genetic aspects. In particular, T2D
384 and gastric morbidity pattern showed together a greater PaCa risk regardless of diagnosis time (OR,
385 7.89; 95% CI 3.9-16.1 and OR, 1.86; 95% CI 1.29-2.67 in recent and long-term diagnosed,
386 respectively) [93]. UK Biobank data had shown higher PaCa risk in individuals with MetS (HR =
387 1.31, 95% CI, 1.09-1.56), central obesity (HR = 1.24, 95% CI, 1.02-1.50) and hyperglycemia (HR =
388 1.60, 95% CI, 1.31-1.97). These two last MetS components seem to show an independent
389 association, whereas, the presence of MetS and elevated levels of C reactive protein (CRP) seems to
390 increase PaCa risk [94].
391 In a recent study, the role of advanced glycation end products' (AGEs) accumulation, occurring also
392 in aging and increased by obesity, diabetes, and smoking and western diet, has been underlined. Nε-
393 carboxymethyllysine (CML), the most common AGE *in vivo,* showed a strong capacity to enhance
394 tumor cells growth in a time and concentration-dependent manner promoting the expression of
395 AGE-receptors. These receptors can bind different ligands activating several inflammatory
396 pathways such as nuclear factor (NF)-κB directly involved in the up-regulation of AGE-receptors.
397 In addition, AGEs act at an early stage of tumor development accelerating the progression of PaCa
398 from PanIN lesions [95].
399

400 ***Infectious diseases***

401 Infectious diseases are known risk factors for three of the most common tumours (*Hepatitis B and C*
402 and liver cancer, *papillomavirus* and cervical cancer, H*elicobacter pylori* and gastric cancer).
403 However, the relation between PaCa and infectious disease is still unknown. A possible link has
404 been proposed for *Helicobacter pylori (H. pylori).* A meta-analysis on 6 observational studies
405 published until 2010 pointed out the existence of a significant association between *H. pylori*
406 seropositivity and development of PaCa (adjusted OR 1.38, 95% CI 1.08-1.75; p=0.009) [96].
407 Moreover, a review of 117 meta-analytical or pooled reports identified *H. pylori* infection, along
408 with tobacco smoking, as the major risk factors for PaCa with associated population attributable

fractions of 4-25% [97] although another subsequent meta-analysis did not confirm the results [98]. It has been calculated that with an estimated prevalence varying from 25% to 50% in Western countries, *H. pylori* infection could be responsible for 4-25% of cases of PaCa in that area [97]. *H. pylori* 16S ribosomal DNA was detected in 75% of paraffin-embedded PaCa tissues while none resulted positive in the control group, thus supporting the hypothesis of a causal role played by *H. pylori* infection in the development of PaCa [99]. The carcinogenic mechanism of *H. pylori* infection is still not clear. A possible indirect action of *H. pylori* in PaCa development is linked with an increase of gastric acidity and high pancreatic stimulation by secretin. This phenomenon is strictly related to bacterial strain features since the cytotoxin-associated gene A (CagA) negative strain can induce hyperacidity and is associated to an increased risk whereas the CagA positive strain may have a protective action inducing gastric hypoacidity [100].

An additional study focusing on the effect of *H. pylori* on human pancreatic cancer cells, identified that infection induces interleukin-8 (IL-8) and vascular endothelial growth factor (VEGF) secretion, in addition to promote the activation of the transcription factors NF-kB, the increase of the activator protein-1 (AP-1) and serum response element (SRE), which can all promote the malignant potential of PaCa cells [101].

Though epidemiological studies continue to investigate the involvement of *H. pylori* on PaCa development, literature is still discordant: a population-based prospective cohort study (ESTHER) published in 2016 with a 10-year follow up and the EPIC nested case-control cohort study published in 2017 did not find any association [102, 103] .

Recently, several studies focused on the composition of oral microbiome and the correlation with PaCa incidence. Interestingly, independent studies identified a potential correlation between PaCa and *P. gingivalis*, one of the main etiologic agents of periodontal disease [104, 105], also involved in rheumatoid arthritis [106]. The EPIC prospective cohort study pointed out the existence of a twofold increase of PaCa risk in individuals with high levels of antibody against *P. gingivalis* in bloodstream. On the other hand, the increased levels of antibodies against commensal (non-

pathogenic) oral bacteria are associated with a reduced risk of pancreatic cancer. This could be linked with the inhibition of pathogen bacterial growth [107]. Several mechanisms of *P. gingivalis* involvement in PaCa development have been proposed. A first mechanism may consist in the activation of carcinogens compound contained in cigarettes, such as nitrosamine, or the ability to convert ethanol into acetaldehyde. Secondly, *P. gingivalis* may activate the toll-like receptor (TLR) signaling pathways in dendritic cells. In particular, TLR4 overexpression has been found in PaCa cells and it may promote human PaCa [108, 109]. Furthermore *P. gingivalis*, may induce an inflammatory response in distant sites, suggesting that an abnormal immune function and the exposure to chronic inflammation could predispose to cancer, especially in adults.

Psychological stress

Psychological stress is a possible consequence of the complex relationship between human behavior and environmental context in coping with adverse life events. Although the individual's stress management is linked to specific gene variants, epigenetic effects or altered physiological mechanisms; it is still matter of debate how specific episodes can trigger significant behavioral problems with effects on the general health status [110]. Several studies have shown a link between severe and repeated psychological stress and cardiovascular diseases, immune diseases, tumors, as well as in tumor growth and the onset of metastases [111].

In a nationwide cohort study conducted in Sweden on 4,219,697 people, a severe emotional stress like the loss of a parent was linked with an increased risk of early-onset PaCa (<40 years) regardless of age at loss and PaCa showed the strongest association with parental death among all the type of cancers considered [112] although the increased risk could be related to smoking, which is a well-known lifestyle change after bereavement [113]. Similarly, the incidence of PaCa after the loss of a child showed comparable results [114]. A nested case-control study conducted in Sweden on 16,522 cases and 82,107 controls showed a slightly increased risk of PaCa after this traumatic event (OR=1.09, 95% CI: 1.02,1.17) that became significant when considering the first 5 years after child

loss, when the loss was due to a suicide and when considering persons with a history of psychiatric illnesses [114].

Animal studies had proven that, after a psychological stress, the released neurotransmitters (e.g. noradrenalin, adrenalin, cortisol) negatively impact the clinical outcome of PaCa promoting the growth of the mouse xenografts [115]. The mechanism is mediated by the multiple activation of cyclic adenosine 3', 5'-monophosphate (cAMP) and the concomitant inhibition of the γ-aminobutiric acid (GABA) response. In fact the overall reduction of cAMP induced by GABA treatment causes a decreased tumour growth and consequently the downregulation of the β-adrenergic signalling pathway, that is strictly involved in the stress response [115].

Two independent studies in 2017 showed how the use of non-selective β-blockers, antiarrhythmic drugs used also in chronic stress and depression, leads to a reduction of PaCa progression in patients without metastasis [116, 117]. These findings have been confirmed by a study on animal models. They were subjected to immobilization for 2h/day for a month and the changes in pancreatic tumour growth rate caused by stress were observed. The samples analysed showed an increased tumour growth and invasion of distant organs, compared to control, which is caused by the overexpression of β-adrenergic signalling pathways since the blocking of these receptor with propranolol contrasts tumour cells progression. Furthermore, the modulation of the receptor with the β-adrenergic agonist isoprenaline, caused the overexpression of metalloproteinase 2 and 9, involved in tumour cell invasion [118]. The β-adrenergic receptors also mediate the stimulatory effect of norepinephrine, a stress associated hormone, on pancreatic duct epithelial cells through the activation of the beta-adrenergic dependent p38/mitogen-activated protein kinases (MAPK) pathway [119, 120]. Both sympathetic and parasympathetic system innerves the pancreas, and the nerve density is higher in pancreatic tumor tissues. Through overexpression of β-adrenergic signaling (adrb2 up regulation), the psychological stress causes an increase in neurotrophins such as nerve growth factor and brain derived neurotrophic factor (BDNF) contributing to the nerve-tumor interaction by axogenesis [121]. The increased nerve growth factor (NGF) level is associated with a

higher aggressiveness and worst prognosis in case of high expression of tropomyosin receptor kinase A (TrkA) compared to the expression of the low-affinity nerve growth factor receptor p75NGFR from tumor cells [122]. In addition, as demonstrated by a recent study in a mouse model, stress subjection can act on PaCa progression compromising the immune system activity through the reduction of cytokines production, interferon gamma (IFN-γ) and interleukins [7, 8, 10-12] along with reduction in T lymphocytes (CD4 cells) population and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) protein expression from these. Moreover, the increase of transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF) in chronically stressed mice is involved in PaCa growth and diffusion [123].

DISCUSSION

PaCa is a multifactorial disease related to genetic alterations and associated with known risk factors. Nutrition and life style are involved in PaCa both as a pathogenic and as preventative factor [124]. From the National Institutes of Health (NIH)-AARP Diet and Health study, it emerged that 27% of cases of PaCa may have been prevented with a healthy lifestyle, which included the absence of smoke, limited alcohol intake, Mediterranean diet, normal weight and regular physical activity. Several causes have been proposed to be associated with an increasing risk of PaCa including a high-fat diet and the intake of fried food as well as red and processed meat [46]. On the other hand, foods which have been identified to be inversely related to the risk of developing PaCa include fresh fruit and vegetables [125, 126]. The WCRF guidelines on cancer prevention suggest to limit the consumption of fat, added sugar rich food, red and processed meat and to have 5 portions per day of vegetables and fruit and fibre rich food such as whole grains and pulses [127]. Within the EPIC study a Healthy Lifestyle Index (HLI) was used to give a score to the effect of combined smoking, alcohol intake, dietary exposure, physical activity and central adiposity using BMI or WHR, respectively. Observed scores confirmed that a healthy lifestyle was found inversely related to PaCa risk [128].

Obesity plays a key role as PaCa risk factor and represents one of the biggest problems in the United States with a forecast of people involved by 2030 of at least 44% in all 50 states of US and 400,000 new obesity-related cancer cases in the next 2 decades with an increasing costs of healthcare between $48 billion and $66 billion [129]. A possible explanation of the link between obesity and PaCa resides in tumour-promoting inflammation and hormonal effects associated with the accumulation of adipose tissue [68]. Body fatness stimulates insulin production in response to increased levels of free-fatty acids released from adipose tissue promoting a state of insulin-resistance as a compensatory mechanism [130]. It predisposes to the onset of T2D which is itself a risk factor for PaCa suggested by the fact that 80% of patients with PaCa are affected by glucose intolerance or frank diabetes [131]. As a consequence, pancreas secretes more insulin triggering mitotic activity. Hyperinsulinemia has been demonstrated to increase local blood flow, the growth of the exocrine part of the pancreas and a number of studies have confirmed the ability of insulin to stimulate the growth of PaCa cell lines [89, 132]. Another proposed mechanism that links obesity and PaCa resides in the formation of DNA adducts related to the formation of reactive oxygen species (ROS) and lipid peroxidation [133].

The relationship between T2D and PaCa has been widely investigated. However, the topic is still a matter of debate, also because the development of T2D is strongly associated with obesity, both conditions being in continuous increasing trend [134]. T2D as obesity is characterised by a condition of hyperglycaemia and hyperinsulinemia due to insulin resistance as part of MetS. Hyperglycaemia accompanies both long-standing and new outbreak diabetes. In the first case, diabetes is supposed to be the cause of PaCa and in the second one an expression of the tumour [80, 135]. There is several evidence to support that cancer is also the cause of T2D. From the literature, it emerges that 25-50% of PaCa cases have been diagnosed with T2D 1-3 years before the diagnosis of cancer [78, 136]. Unfortunately, T2D alone is not a sufficient indicator to justify an invasive intervention of screening given that only 1/50-100 new-onset diabetes cases observed will develop PaCa [80, 136].

539 Multiple gene polymorphisms have been investigated in the association between cancer and T2D:
540 the single nucleotide polymorphism -23HphI (A/T) located in the promoter region of the insulin
541 gene may play a role in the pathogenesis of PaCa and could contribute to tumour staging [137]. In
542 the hexokinase 2 gene, that is related to glucose metabolism, the genotype R844K GA/AA was
543 found to increase the risk of PaCa in diabetic patients (OR = 3.69; 95% CI, 2.34–5.82) and to
544 decrease it among the non-diabetic people (OR = 0.68; 95% CI, 0.56–0.83) [138].
545 In addition to obesity, there are other few established causes; one of the strongest is tobacco
546 smoking. It is linked with the risk of developing PaCa in dose and time-dependent manner. The
547 exposure to tobacco smoking products such as NNN, NNK and NNAL can cause PaCa in animal
548 models as they can cause DNA mutations like the ones involving KRAS gene, the most common to
549 be found in this disease [26, 27]. Tobacco effect seems to be emphasized by alcohol consumption
550 that is related as well to PaCa development when the intake is high.
551 Alcohol consumption causes the production of the oncogenic compound acetaldehyde, which is in
552 turn an established risk factor for pancreatitis. From a meta-analysis by Duell *et al*. it emerges that
553 who had a history of pancreatitis have a 6 fold increased risk to develop PaCa compared with
554 controls [139]. Alcohol consumption is classified by the International Agency for Research on
555 Cancer (IARC) as possible causes of PaCa. However, WCRF/AICR makes no judgment on the
556 association between PaCa risk and alcohol consumption, due to limited evidence.
557 Epigenetic alterations such as DNA methylations has been studied in regards to nutrients (e.g.
558 folate, vitamin B_{12}, vitamin B_6) [140] and a deficient diet in these nutrients may lead to DNA
559 hypomethylation that could determine chromosome instability, frequently found in tumours [141].
560 The methods of cooking also influence the carcinogenic potential of other foods and a positive
561 association has been reported for fried, grilled and barbequed foods in general [4]. The cooking of
562 meat at high temperatures determines the production of HCAs and PAHs [141], mutagenic
563 compounds that induce multiple tumours in animal models [142].

564 Life style, environmental and multifactorial factors affect therefore the risk of PaCa in different
565 ways and levels. Table 1 summarises, in more details, some of the RR, OR and HR obtained from
566 the most recent meta-analyses and some of the correlations identified between cancer risk and
567 specific risk factors related to lifestyle, environment and disease in cohort or case-control studies.
568 *Pre-neoplastic lesion as additional factors*
569 Some of the factors affecting the development of PaCa, and considered in this review, also play an
570 important role in the development of IPMNs and MCNs lesions that can lead to PaC. Even if
571 PanINs are the most important non-invasive precursor lesions linked to PaCa onset, they are more
572 often found in PaCa patients with family history and linked to genetic mutations [143, 144]. A
573 study carried out in a population of 390 IPMN patients, showed that history of chronic pancreatitis
574 (OR: 10.10, CI 95 % : 1.30 – 78.32), family history of PaCa (R: 2.94, CI 95 % : 1.17 –7.39) and
575 history of diabetes (OR, 1.79; 95% CI, 1.08–2.98; P = 0.025) were independent risk factors for
576 IPMN and that diabetics patients using insulin had a higher risk to develop IPMN (OR: 6.03, CI 95
577 % : 1.74 – 20.84), suggesting an overlap between certain risk factors for IPMN and PaCa [145].
578 Moreover, in IPMN patients, T2D was associated with more frequent main-duct involvement and
579 worse progression of IPMN into high-grade dysplasia and 2.7-fold higher risk to develop invasive
580 PaCa [146].
581 *Inflammation as common mechanism to investigated risk factors*
582 This review has highlighted inflammation as potential mechanism common to the considered
583 lifestyle and environmental factors, and diseases, and increased risk to develop PaCa. To this extent
584 and to support such hypothesis, few studies have highlighted the inverse association between use of
585 drugs such as aspirin and statins and cancer development. A meta-analysis carried out by Bosetti *et*
586 *al*. [147] showed a correlation between regular aspirin use and reduction of the risk to develop
587 pancreatic cancer (RR= 0.78, 95% CI: 0.68e0.89) and an inverse duration-risk relations with aspirin
588 use. Similar findings were observed in a previous meta-analysis which focused specifically on PaCa
589 and highlighted aspirin use to led to decreased PaCa incidence but not to reduction of mortality (OR

590 = 0.94; 95% CI = 0.73 to 1.22), whereas non-aspirin NSAIDs (non steroidal anti-inflammatory
591 drugs) were not significantly related with PaCa risk decrease [148]. Furthermore, the use of large
592 dose of aspirin was found to be preventive when continued for at least 5 years [149].
593 Statins use was also investigated as possible preventive factor for PaCa. Recent meta-analyses
594 found that statin use was inversely correlated with PaCa development, with an overall PaCa risk
595 reduction among statin users of 30% (OR 0.70;95% CI 0.60–0.82; $p < 0.0001$), in respect to non-
596 users [150, 151]. Furthermore, the use of statin has been linked to a survival improvement and
597 mortality reduction in PaCA patients (meta-HR = 0.75; 95% CI: 0.59, 0.90; $P < 0.001$) and
598 proposed as possible therapy for this disease [152, 153]. The mechanism, by which these two drugs
599 may affect cancer development and progression, is not fully known. It is hypothesized that aspirin
600 proposed cancer preventive mechanisms may be mediated by platelets inactivation, similar to its
601 cardioprotective effect: differently from others NSAIDs, aspirin inhibits cyclooxygenase (COX)
602 pathways through acetylation of COX isoforms' serine residues (Ser 516 and Ser529) blocking
603 them in an irreversible way and forcing cells to synthetize *de novo* the enzyme. In relation to statins,
604 there are different plausible mechanisms through which this drug may influence PaCa development
605 [154]: statin blocks conversion of the3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) into
606 mevalonate which is the precursor of different molecules such as isoprenoids involved in activation
607 of different signalling cascades involved in tumorigenesis and cancer progression such as RAS,
608 RAF/MEK/ERK, mTOR and Bcl-2 [154, 155]. Interestingly, statins showed also
609 immunomodulatory, antiproliferative and antiangiogenic effect and can inhibit matrix
610 metalloproteinases also involved in cancer invasion and metastasis. Taken together these properties
611 may explain the possible protective effect from PaCa [150].
612 *Limitations and future directives*
613 Although the present review has shown evidence of several life style or behavioural condition that
614 are linked with PaCa by plausible biological processes, the study and the assessment of the different
615 risk factors still represent a challenge for several reasons.

First, there are many risks factors that combined together predispose to the onset of PaCa and studies matching those together are still missing. A full risk factor assessment should be completed, and results should be adjusted by the weight of each potential risk factor. Therefore, we should always keep in mind that epidemiological studies are simplified and that reality is far more complex than a scientific model, indispensable in any case to conduct scientific research.

Secondly, when the scientific community move to epidemiological studies (prospective cohort studies and retrospective case-control studies) and clinical trials, the results are often conflicting and inconclusive. There could be many explanations for this, including, for example, the type of epidemiological studies conducted. Prospective cohort studies are ideal for studies that assess the relation between dietary factors and diseases such as cancer [156]. A large number of people could be involved and the questionnaires about food habits and life-style factors are less affected by bias. However problems reside in the fact that follow-up needs to be conducted for several years and often the number of cases observed is too small to draw conclusive results [157]. On the other hand, a far greater number of retrospective case-control studies have been lead. They require shorter time to be carried out and a larger number of cases could be included. However, the biggest limitation is represented by the fact that questionnaires are filled retrospectively placing the study at risk of recall bias.

For all of these reasons, the recognized environmental risk factors involved in PaCa are still few and not overall recognized as directly involved in tumour occurrence. Despite PaCa is rarer than other cancer types, it is one of the most aggressive and deadly with one of the lowest survival rate. By 2030, it is projected to become the second cause of cancer death [75]. Based on the presented findings, which are schematically summarised in Figure 1, a chemoprevention strategy is warranted and the intake of food and the behavioural attitudes known to be related to cancer onset should be limited.

Authors' contributions

SZ, PB, FG and GB conceptualized the study, SR and ARL identified relevant literature. SR, ARL, SZ, FG and GB wrote the manuscript, and all the authors reviewed manuscript.

Conflict of interest statement

None declared.

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1099 **Table 1: Risk Factors for PaCa**

Factors	Number patients	Effect size	CI 95%	P value	Type of study	Reference
Lifestyle and environmental factors						
Smoking						
Current smokers Former smokers	2,517,623	HR 1.56[a] HR 1.15[a]	1.34-1.83 1.06-1.26		Meta-analysis	Ben et al [23]
≥30 cigarettes/day >30 years smoking >20 years quitting		RR 2.2[a] RR 1.8[a] RR 0.6 [b]	1.9-2.4 1.6-2.0 0.6-0.7		Meta-analysis	Lugo et al. [18]
10 cigarettes/day 10 cigarettes/day 20 cigarettes/day 30 cigarettes/day 40 cigarettes/day	18,006	RR 1.5[a] RR 1.9[a] RR 2.0[a] RR 2.1[a] RR 2.1[a]	1.4-1.6 1.8-2.0 1.9-2.1 1.9-2.3 1.9-2.3	< 0.05	Meta-analysis	Zou *et al*. [22]
Alcohol, Smoking, BMI, Physical activity, Dietary quality	1,057	RR 0.42[c]	0.26–0.66	< 0.001	Cohort	Jiao *et al*. [19]
Alcohol						

Ever alcohol use Heavy alcohol use	827	OR 1.09 OR 2.72	0.64–1.85 1.25– 5.91	0.75 0.01	Meta-analysis	Haugvik *et al*. [158]
High alcohol intake (≥24 g / day) Liquor intake	11,846	RR 1.15[d] RR 1.43[d]	1.06-1.25 1.17-1.74	0.001/	Meta-analysis	Wang *et al*. [31]
<3 drink/day >3 drink/day		RR 0.92[e] RR 1.22[e]	0.86-0.97 1.12-1.34	0.06 0.266	Meta-analysis	Tramacere *et al*. [29]
<7 drinks/week 7-13 drinks/week 14-20 drinks/week 21-34 drinks/week >35 drinks/week	326	OR 1.04 OR 1.47 OR 1.50 OR 2.03 OR 3.42	0.60-1.80 0.83-2.62 0.86-2,62 1.10-3.74 1.79-6.55	<0.01	Case- Control	Talamini *et al.* [160]
>45 grams of alcohol from liqueur /day versus none (Men) >30 grams of alcohol from liqueur /day versus none (Women)	288	OR 2.23 OR 1.35	1.02–4.87 0.63-2.87	0.012 ns	Cohort	Michaud *et al.* [107]
Heavy drinkers Men (> 60 g/day) Heavy drinkers Women (> 30 g/day)	1,283	HR 1.77[f] HR 0.93[f]	1.06-2.95 0.47-1.85	0.03 ns	Prospective	Naudin *et al.[*30]
Foods						

Processed meat consumption		RR 1.18[g] (men) RR 0.99[g] (women)	1.06-1.31 0.84-1.16	0.003 0.88	Meta-analysis	Zhao *et al.* [159]
Red meat consumption		RR 1.21[g] (men) RR 1.06[g] (women)	1.07-1.37 0.85-1.31	0.002 0.61	Meta-analysis	Zhao *et al.* [159]
Red and processed meat	1,156	HR 1.32 (men)[h] HR 0.72 (women) [h]	0.90 – 1.95 0.47– 1.10	0.01	Prospective cohort	McCullough *et al*. [161]
Poultry consumption	1,156	HR 1.27[i]	1.04 – 1.55	0.01	Prospective cohort	McCullough *et al*. [161]
Barbecued Meat	193	OR 2.19	1.4– 3.4		Case-control	Anderson *et al*. [142]
Salt Smoked meat Dehydrated food Fried food Refined sugar Cooking with firewood	179	RR 4.28[j] RR 4.68[j] RR 3.10[j] RR 3.84[j] RR 2.81[j] RR 4.63[j]	2.20– 8.36 2.05– 10.69 1.55– 6.22 1.74– 8.48 0.94– 8.45 1.15– 16.52	< 0.01	Case-control	Ghadirian *et al*. [162]
Toxins						
Cadmium	1,769	*166	98–280	0.059	Meta-analysis	Schwartz *et al*. [55]

Cadmium 0.5 to <1 µg/g creatinine 1 to <1.5 µg/g creatinine 1.5+ µg/g creatinine	69	 OR 3.34 OR 5.58 OR 7.70	 1.38–8.07 2.03–15.34 3.06–19.34	≤ 0.0001	Case-control	Luckett *et al.* [58]
Synthetic resins	28	RR 7.15[k]	1.28-40.1		Case-control	Selenskas *et al.* [163]
Multifactorial factors						
Obesity BMI >30 kg/m^2 Overweigh in early adulthood and obese at baseline	 2,135 1,598	 RR 1.47[l] RR 1.54[l]	 1.23–1.75 1.24–1.93	 <0.001 <0.001	Meta-analysis	Genkinger *et al.* [70]
Obesity 5-unit increment in BMI 10cm increment in waist circumference 0.1unit increment in waist-to-hip ratio	 9,504 949 1,047	 RR 1.10[m] RR 1.11[m] RR 1.19[m]	 1.07–1.14 1.05–1.18 1.09–1.31	 0.005 0.28 0.29	Meta-analysis	Aune *et al.* [42]
Diabetes	827	OR 2.74	1.63–4.62	< 0.01	Meta-analysis	Haugvik *et al*. [158]
Diabetes	20,566	HR 1.91 (men)	1.52-2.41	0.009	Cohort	Jee *et al*. [81]

Highest fasting serum glucose (≥140 mg/dL) vs lowest level (<90 mg/dL)	5,907	HR 2.05 (women)	1.43-2.93	0.01		
Diabetes Presence of HK2 R844K GA/AA genotype in diabetic patients	1,654	OR 3.69	2.34–5.82	<0.001	Case-control	Dong *et al.* [138]
Diabetes in patients positive for K-ras codon 12 mutations	245	AOR[#] 3.4	1.3–8.8		Cohort	Fryzek *et al.* [84]
Infections *(H. pylori)*	2,049	OR 1.06	0.74-1.37	<0.001	Meta-analysis	Wang *et al*. [98]
Oral pathogens *Porphyromonas gingivalis* *Aggregatibacter actinomycetemcomitans*	361	OR 1.60 OR 2.20	1.15- 2.22 1.16- 4.18	0.0047	Case control	Fan *et al*. [164]
Periodontal disease	139,805	HR 1.55[n]	1.02–2.33	<0.001	Case control	Chang *et al*. [165]

AOR: adjusted odds ratio; BMI: body mass index; HR: hazard risk; ns: non-significant; OR: odds ratio; RR: relative risk.
Reference category; [a] never smokers; [b] current smokers; [c] lowest combined score; [d] lowest alcohol intake level or no alcohol intake; [e] non- or occasional drinkers; [f] 0.1-4.9 g/day; [g] lowest consumption; [h] lowest quartile of consumption; [i] lowest quintile of consumption; [j] never consumed; [k] no exposure; [l] baseline BMI between 21–22.9kg/m^2; [m] no increment; n no disease.
* Standardized mortality ratio
# adjusted for cigarette smoking, BMI and diabetes

Figure 1: Risk factors and potential mechanisms in PaCa development. Summary of lifestyle factors (e.g. high alcohol, fructose and red or processed meat intake), pathological conditions (e.g. obesity, type 2 diabetes, metabolic syndrome and infections), stress and smoking behaviour that may cause DNA damage, interfere with pancreatic physiology or function, induce inflammation and play a role in PaCa development.
NGF: increased nerve growth factor; PPP: pentose phosphate pathway; ROS: reactive oxygen species; VEGF: vascular endothelial growth factor