Environmental risk factors of pancreatic cancer: an update

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Abstract

Pancreatic cancer (PC) is one of the most aggressive diseases. Only 10% of all PC cases are thought to be due to genetic factors. Here, we analysed the most recently published case-control association studies, meta-analyses, and cohort studies with the aim to summarize the main environmental factors that could have a role in PC. Among the most dangerous agents involved in the initiation phase there are the inhalation of cigarette smoke, and the exposure to mutagenic nitrosamines, organ-chlorinated compounds, heavy metals and ionizing radiations. Moreover, pancreatitis, high doses of alcohol drinking, the body microbial infections, obesity, diabetes, gallstones and/or cholecystectomy, and the accumulation of asbestos fibres seem to play a crucial role in the progression of the disease. However, some of these agents act both as initiators and promoters in pancreatic acinar cells. Protective agents include dietary flavonoids, marine omega-3, vitamin D, fruit, vegetables and the habit of regular physical activity. The identification of the factors involved in PC initiation and progression could be of help in establishing novel therapeutic approaches by targeting the molecular signalling pathways responsive to these stimuli. Moreover, the identification of these factors could facilitate the development of strategies for an early diagnosis or measures of risk-reduction for high-risk people.

Keywords: environmental factors, pancreas, pancreatic cancer, protective factors, risk factors.

Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer deaths in the developed countries (Jemal et al. 2011). The vast majority (99%) occurs as a cancer of the exocrine gland and the ductal adenocarcinoma (arising from the acinar cells of the ductal epithelium) is by far the most common type. Most PC patients are diagnosed between 60 and 80 years old and have a 5-year survival rate of 7% (American Cancer Society 2014). The observation that the incidence is very different across geographical regions (Maisonneuve and Lowenfels, 2010) suggests that most of PC cases could be attributed to non-genetics factors. Indeed, ascertained genetics factors account for less than 10% of all PC cases (Landi 2009, Raimondi et al. 2009).

In this review, we will describe the main non-genetics factors suspected to be associated with increased risks of PC, whose perception could be helpful in prevention strategies for high-risk people. In particular, we will pay attention to environmental factors, where, as environment, we will mean both the external (e.g. the exposure to xenobiotics or polluted air) and internal (e.g. predisposing medical conditions) environment. We will focus on recent case-control association studies, meta-analyses, and cohort studies recovered through PubMed (http://www.ncbi.nlm.nih.gov/pubmed) using the key-words: "pancrea* [ti] AND (carcinoma OR cancer) AND risk [ti] AND factor* AND associat*".

1. Life-style and risk of pancreatic cancer

1.a Smoking habit

The most well documented risk factor associated with the onset of PC is the exposure to cigarette smoke (in particular the active smoking) and the most recent studies confirmed this knowledge. In a meta-analysis (Iodice et al. 2008), current smokers showed a relative risk (RR) of 1.74, with a 95% confidence interval (95% CI) of 1.61-1.87 (p=0.08), as compared to never-smokers, whereas former smokers had a global risk of 1.2 (95% CI, 1.11-1.29; p=0.90). The authors estimated also the RR for different indices of cigarette consumption and reported an increase of about 2% for every cigarette smoked daily, and an increased RR ranging between 37% and 62% for an average of 20 cigarettes smoked daily. For smoking duration, the risk increases by 1% for each year of smoking, and by 16% for each 10 years of smoking. In agreement with these data, a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan) showed that smokers have an odds ratio (OR) of 1.77 (95% CI, 1.38-2.26; $p=5x10^{-6}$) and the RR estimates were similar for retrospective (1.77) and prospective (OR=1.70; 95% CI, 1.53-1.90; $p<1x10^{-20}$) studies (Lynch et al. 2009). In a recent work on Early Onset Pancreatic Cancer (EOPC) (defined as aged ≤50 years at diagnosis; Piciucchi et al. 2015) the role of smoking habit as risk factor was evaluated in a group of 25 EOPC patients and in a group of 268 older subjects. While no differences were noticed for sex distribution, medical conditions, and alcohol intake, EOPC patients were more frequently current smokers (56% vs 28%; p=0.001) and started smoking at a significantly lower mean age (19.8 years; 95% CI, 16.7-22.9) than older patients (26.1 years; 95% CI, 24.2-28; p=0.001). Current smoking (OR=7.5; 95% CI, 1.8-30; p=0.004) and age at smoking initiation (OR=0.8 for every increasing year; 95% CI, 0.7-0.9; p=0.01) were significant and independent risk factors for diagnosis of EOPC (Piciucchi et al. 2015).

Also the habit of smoking cigars was associated with a risk of PC, while pipe-smoking was not. Bertuccio and co-workers (Bertuccio et al. 2011) carried out a pooled analysis (6,056 cases and 11,338 controls) of cigar and pipe smoking and smokeless tobacco use collecting data from 11 case-control studies within the International Pancreatic Cancer Case-Control Consortium (PanC4). Compared with never tobacco users, the OR for cigar-only smokers was 1.6

(95% CI, 1.2-2.3; $p=5x10^{-3}$), comparable to that of cigarette-only smokers (OR=1.5; 95% CI, 1.4-1.6; $p=1.14x10^{-32}$). The OR was 1.1 (95% CI, 0.69-1.6; p=0.65) for pipe-only smokers.

According to another study, passive smoking was not associated with the risk of PC. However, when considering the exposure since childhood, a positive association has been shown with maternal smoking (RR=1.56; 95% CI, 1.13-1.98; p=0.018) (not for paternal), suggesting that a prolonged exposure to passive smoke, especially *in utero* or early in life, could constitute a risk factor for PC (Ding et al. 2015). Smoking also increases the risk of PC onset 10–20 years earlier in smokers with familial predisposition or with hereditary pancreatitis than in non-smokers (Lowenfels et al. 2000; Rulyak et al. 2003). In summary, the most recent estimates suggest that tobacco smoking is the major external risk factor associated with PC, with an estimated population attributable fraction of 11-32% (Maisonneuve and Lowenfels, 2015). Quitting smoking both prevents the development of PC and chronic pancreatitis (Maisonneuve and Lowenfels, 2002) within 5–10 years (Larsson et al. 2005) with an initial reduction of risk of 50% within the first 2 years (Maisonneuve and Lowenfels, 2015).

Cigarette smoke consists of a mix of over 4000 compounds, and most of the identified substances are known carcinogens (Edderkaoui and Thrower, 2013). Of these constituents, nicotine and nicotine-derived nitrosamine ketone (NNK), and the combustion by-products such as polycyclic aromatic hydrocarbons (PAHs) or nitrosamines, are the most dangerous. In general, these compounds adduct to DNA and cause genetic mutations. The analysis of pancreatic tissues showed no association between smoking habit and levels of mutations in cancer-associated genes such as *KRAS* or *TP53* (Blackford et al. 2009; Porta et al. 2009). However, in the study carried out by Blackford (Blackford et al. 2009), PC tissues from smokers had an overall mutational load higher than PC tissues from non-smokers. NNK interacts with pancreatic cells through β-adrenergic receptors and nAChR (Momi et al. 2013) mediating the activation of cyclooxygenase 2 (Cox2), epidermal growth factor receptor, and extracellular signal–regulated kinase (ERK) within pancreatic cells (Weddle et al. 2001; Askari et al. 2005). Park et al. (2013) showed that NNK and other smoke extracts increase the proliferation and also inhibit apoptosis of normal pancreatic ductal cells through AKT and AMP kinase. An *in vitro* study showed that nicotine stimulates proliferation and invasion of the AsPC1 cell line. Recently, it has been demonstrated that nicotine stimulates growth, invasion, and resistance of PC cells to chemotherapy through Src and the inhibitor of differentiation-1 transcription factor pathways (Trevino et al. 2012). Furthermore, nicotine stimulates epithelial-to-mesenchymal transition (EMT) by down-regulating E-cadherin and β-catenin and by up-regulating vimentin and fibronectin (Dasgupta et al. 2009). Regulation of EMT/invasion/metastasis pathways and resistance to chemotherapeutic drugs is an important point to understand as these are the major contributors to the aggressiveness of PC. So, in the last years, many studies suggested that smoking compounds do not only contribute to the initiation but also to the promotion of pancreatic carcinogenesis. They can have a role also in the transformation of cancer cells into metastatic cells and in their resistance to chemotherapeutic compounds (Edderkaoui et al. 2013).

1.b Alcohol drinking

Although early investigations could not detect alcohol drinking as a clear risk factor for PC, more recent studies highlighted that heavy drinkers could undergo to increased risks. Various authors (Soler et al. 1998; Bagnardi et al. 2001; Rahman et al. 2015) studied the relationship between the habit of alcohol drinking and PC but none of them found a statistically significant association with the risk. In Rahman's study, the age-adjusted OR was 0.78 (95% CI, 0.58-1.05; p=0.1) for 1 - 3 drinks/week, 0.86 (95% CI, 0.63-1.17; p=0.34) for 4 - 20 drinks/week, and 1.35 (95% CI, 0.81-2.27; p=0.25) for≥21 drinks/week, recapitulating the "J-shape" curve already observed for alcohol drinking in relation with various other causes of mortality (Rehm et al. 1998). More studies actually seem to prove, in a statistically significant way, that heavy drinking is associated with increased risk of PC. Talamini and co-workers (Talamini et al.

2010) showed that heavy alcohol drinkers had ORs of 2.03 (95% CI, 1.10–3.74; p=0.02) and 3.42 (95% CI, 1.79–6.55; $p=2x10^{-3}$) for 21–34 and ≥35 drinks/week, respectively, and similar results were reported also by Gupta (OR=2.6; 95% CI, 1.3-5.1; p=0.01) (Gupta et al. 2010).

The exposure to high doses of alcohol (≥21 drinks/week) together with high doses of tobacco smoke (≥20 cigarettes/day) showed an additive effect with a significant increased risk of 4.3-fold in heavy smokers and heavy drinkers in comparison with never smokers who drunk <7 drinks/week (Talamini et al. 2010). In the study by Anderson et al. (2012) alcohol status and dose were independently associated with increased risk of early-onset PC in a multivariate analysis, with the greatest risk occurring in heavy drinkers with a hazard ratio (HR) of 1.62 (95% CI, 1.04–2.54; p=0.03).

According to a recent Italian case-control study, including 326 patients, 13% of PCs cases (95% CI, 2.7-23.2) were attributable to heavy alcohol drinking (Rosato et al. 2015). The most recent meta-analysis (Bagnardi et al. 2015), that includes a total of 572 studies, confirmed a significant association between heavy drinking and PC (RR=1.19; 95% CI, 1.11–1.28; $p=2x10^{-5}$). This result was confirmed by another work (Wang et al. 2016a) which includes 19 prospective studies reporting no effect of a low (0–12 g per day) to moderate (≥12-24 g per day) alcohol intake, while an increased risk of PC with high doses (≥24 g per day) (RR=1.15; 95 % CI, 1.06-1.25; $p=8x10^{-4}$).

Ethanol could promote pancreatic carcinogenesis through a direct effect exert by its main oxidized metabolite, the acetaldehyde, that is a known carcinogen able to form protein and DNA adducts (Tuma et al. 2003; Yu et al. 2010). However, within pancreas, ethanol is metabolized also by non-oxidative pathways. In fact, it is converted to fatty acid ethyl esters that, following *in organo* accumulation, could induce inflammatory processes and fibrosis hence triggering chronic pancreatitis, the major risk factor for the development of PC (McKay et al. 2008; Duell et al. 2012). Finally, it has been shown that ethanol could induce cell-damage in pancreatic ductal epithelial cells by changing the mitochondria membrane potential, thereby increasing the local production of reactive oxygen species (Shalbueva et al. 2013, Huang et al. 2014).

1.c Diet

1.c.1 Red meat intake

With the exception of one study carried out by Jansen (Jansen et al. 2013a), most of the reported works showed significant positive associations for intake of red and processed meat and risk of PC (Zheng et al. 2009; Paluszkiewicz et al. 2012; Bosetti et al. 2013). The meta-analysis made by Paluszkiewicz, which includes 11 case-control studies, revealed an increased PC risk by 48% (OR=1.48; 95% CI, 1.25-1.76; $p=7x10^{-5}$) associated with red meat intake. The increase appeared to be dose-dependent, although this assessment should be taken with caution because the evaluations were performed with self-administered questionnaires. In a recent large prospective study of NIH-AARP Diet and Health Study, Taunk et collaborators (Taunk et al. 2016) observed an increase of PC risk associated with the intake of total meat (top highest quintile of daily total meat intake vs the lowest quintile: HR=1.20; 95% CI, 1.02–1.42; p-trend= 0.03) and in particular of red meat (HR=1.22; 95% CI, 1.01–1.48, p-trend= 0.02). This study was the largest to evaluate which meat cooking technique could boost PC risk. The intake of pan-fried and microwaved meats was not associated with PC while high-temperature cooked meat and grilled/barbequed meat consumption showed a statistical significant association with HR of 1.21 (95% CI, 1.00–1.45; p-trend=0.02) and HR of 1.24 (95% CI, 1.03–1.50; p-trend=$7x10^{-3}$), respectively. Although not all the studies have yielded positive results (Malfatti et al. 2016), the risk from red meat could be ascribed to high levels of mutagens, such as heterocyclic amines and PAHs, formed during high-temperature cooking (Zheng et al. 2009; Anderson et al. 2012).

1.c.2 Fruits and vegetables

In a pooled analysis of 14 cohort studies (Koushik et al. 2012) and according to the results of the Ohsaki National Health Insurance Cohort Study (Shigihara et al. 2014) no statistically significant associations were found between risk of PC and the intake of fruit or vegetables. However, the literature is plenty of positive studies with reductions of PC risks ranging between 30% and 40% such as those e.g. by Bae (Bae et al. 2009), Jansen (Jansen et al. 2011), Paluszkiewicz (Paluszkiewicz et al. 2012), or Liu (Liu et al. 2014). A recent meta-analysis by Wu et al. (2016) summarized the results from 15 case-control studies, 8 prospective studies, and one pooled analysis and it further confirmed the reduced risk. The RR was 0.73 (95% CI, 0.63-0.84; $p=10^{-5}$) when the category of the highest fruit intake was compared to the lowest one, whereas it was 0.76 (95% CI, 0.69-0.83; $p=6x10^{-9}$) for vegetable intake.

According to the clinic-based case-control study made by Jansen et al. (2013b), there is a significant inverse association between PC and most of the nutrients contained in fruit and vegetables, like magnesium (OR=0.30; 95% CI, 0.19–0.46; p-trend<10^{-4}), potassium (OR=0.36; 95% CI, 0.23–0.55; p-trend<10^{-4}), selenium (OR=0.65; 95% CI, 0.45–0.95; p-trend=$5x10^{-3}$), alpha-carotene (OR=0.52; 95% CI 0.35–0.77; p-trend=$2x10^{-4}$), beta-carotene (OR=0.42; 95% CI, 0.28–0.63; p-trend<10^{-4}), beta-cryptoxanthin (OR=0.55; 95% CI, 0.37–0.82; p-trend=0.01), lutein and zeaxanthin (OR=0.46; 95% CI, 0.31–0.70; p-trend <10^{-4}), niacin (OR=0.52; 95% CI, 0.35–0.77; p-trend=$5x10^{-4}$), total alpha-tocopherol (OR=0.52; 95% CI, 0.34–0.79; p-trend=$4x10^{-3}$), total vitamin A activity (OR=0.55; 95% CI, 0.37–0.81; p-trend =0.03), vitamin B6 (OR=0.49; 95% CI, 0.33–0.72; p-trend=$5x10^{-4}$), and vitamin C (OR=0.51; 95% CI, 0.34–0.76; p-trend=10^{-4}). Also a recent Chinese study confirmed a statistically significant decreased risk comparing the lowest quartile with the highest quartile of vitamin B6 (HR=0.52; 95% CI, 0.36-0.74; p-trend=0.001) and choline (HR=0.67; 95% CI, 0.48-0.93; p-trend=0.04) intake (Huang et al. 2016).

Concerning folates, although some studies did not report positive findings (Bao et al. 2011; Huang et al. 2016), three meta-analyses showed consistent results regarding the reduction of PC risk associated with high folate dietary intake. In 2006 the meta-analysis carried out by Larsson (Larsson et al. 2006b) showed a 51% decreased risk among individuals with the highest folate intake (RR=0.49; 95% CI, 0.35-0.67; $p=1.6x10^{-5}$), compared to the lowest. The dose-response meta-analysis carried out by Lin confirmed a pooled RRs of 0.66 (95% CI, 0.49-0.88; $p=5x10^{-3}$) for the highest vs lowest level of folates, while it was not statistically significant (RR=1.08; 95% CI, 0.82-1.41; p=0.57) for folates taken as dietary supplements (Lin et al. 2013). Also, the meta-analysis performed by Tio (Tio et al. 2014) confirmed the association between a high dietary folate intake and a reduced risk of PC (OR=0.66; 95% CI, 0.49-0.89; p= 0.01).

1.c.3 Beverages

Green tea, tea, and soft drinks have been investigated as putative risk modulators of PC. Zatonski et al. (1993), Lin et al. (2008), Genkinger et al. (2012) and Zeng et al. (2014) reported that green tea intake is not associated with decreased PC risk. The most recent one is a meta-analysis comprising 2,317 incident cases and 288,209 subjects from China and Japan and the final OR is almost flat (high vs low green consumption OR=0.99; 95% CI, 0.78-1.25; p=0.93) (Zeng et al. 2014).

Conversely, several studies observed a reduced risk of PC associated with increased tea consumption. The population-based case-control study carried out in urban Shanghai, including 908 cases of PC and 1,067 healthy controls, reported a 32% reduction of PC risk (OR_{adj} = 0.68; 95% CI, 0.48-0.96; p=0.03) in regular green tea drinking women, compared to those who did not drink tea regularly (Wang et al. 2012b).

In 2014 Chen published a meta-analysis (Chen et al. 2014) showing a statistical decreased PC risk among Chinese having a high consumption of tea (RR=0.76, 95% CI, 0.59-0.98, p=0.036). Similar results were found in the subgroup of individuals >60 years old with a RR=0.76 (95% CI, 0.60-0.96; p=0.023) underlying the necessity of a more rigorous design of these studies to further confirm this relationship. Finally, in a more recent Chinese multicenter case-control

study, the habit of drinking any type of tea was associated with a 51% reduction in the risk of PC (OR_{adj} = 0.49; 95% CI, 0.25–0.84; p=0.02) (Zheng et al. 2016), confirming the inverse relationship (OR=0.49; 95% CI, 0.30-0.80; p=0.004) observed also by Liu et al. (2014).

Although the inconsistencies of the epidemiological studies, we should consider that tea contains biologically active compounds, such as catechins, which are considered to be potent inducer of apoptosis and cytotoxicity to cancer cells through a pro-oxidant effect (Hadi et al. 2000, 2007; Farhan et al. 2016). *In vitro* studies by Lambert (Lambert et al. 2005), McMillan (McMillan et al. 2007) and Shankar (Shankar et al. 2008) have shown the inhibitory ability of catechins on tumor growth. Moreover Appari (Appari et al. 2014) suggested that green tea-derived catechins promote the inhibition of PC progression through the induction of miR-let7-a and inhibition of Kras. These mixed findings reinforce the necessity of larger and more accurate studies, involving different population with different mean-intake of green tea, to better clarify this relationship.

Sugar-sweetened carbonated beverages (called soft drinks) and juices, that yield a high glycemic load, have been hypothesized as PC risk factors (Schernhammer et al. 2005; Larsson et al. 2006a).

The study by Larsson found that the multivariate hazard ratios for the highest compared with the lowest consumption categories were 1.69 (95% CI, 0.99-2.89; p-trend=0.06) for sugar, 1.93 (95% CI, 1.18-3.14; p-trend=0.02) for soft drinks, and 1.51 (95% CI, 0.97-2.36; p-trend=0.06) for sweetened fruit soups or stewed fruit (Larsson et al. 2006a). The association between soft drink and juice consumption with PC was also evaluated in 60,524 participants of the Singapore Chinese Health Study with up to 14 years of follow-up. The consumption ≥ 2 soft drinks per week significantly increased the risk (HR=1.87; 95% CI, 1.10-3.15; p-trend=0.02) while there was no statistically significant association between juice consumption and risk of PC (Mueller et al. 2010). However, in a meta-analysis and 14 cohort-studies, soft drink intake has been associated with a poorly increased risk (15–20%; multivariate RR=1.19; 95% CI, 0.98-1.46; p=0.087 comparing ≥250 to 0 g/d; 355g ≈ 12oz; Genkinger et al. 2012). Also the results of an Italian case-control study combined with results published before June 2010 did not found any statistical significant relationship: the pooled RRs for heavy consumers were 1.08 (95% CI, 0.73-1.60; p=0.7) for case-control, 1.21 (95% CI, 0.90-1.63; p=0.2) for cohort, and 1.16 (95% CI, 0.93-1.45; p=0.19) for all studies (Gallus et al. 2011).

The putative carcinogenic effect could be ascribed to the high content of sugar that, increasing the glucose and insulin levels, could promote the proliferation of cancer cells as well as obesity and diabetes status. The increase of insulin levels induce insulin-like growth factor (IGF) which in turn activate IGF receptor, leading to cancer cell proliferation (Le Roith 1997). However, soft drinks do not seem to constitute a significant risk factor for PC.

1.c.4 Other dietary constituents: marine omega-3, fatty acids, and vitamin D

The Japan Public Health Center-based Prospective Study, one of the most recent and largest on this topic, following-up 140,420 volunteers for at least 15 years, identified 449 PC patients who were analyzed in relation to food intake. The authors found an inverse association between PC risk and the consumption of marine omega-3 poly-unsaturated fatty acids (PUFAs) that include the eicosapentaenoic acid (EPA), the docosapentaenoic acid (DPA), and the docosahexaenoic acid (DHA). Compared with the lowest quartile of the intake, multivariate-adjusted HRs in the highest quartile were 0.70 (95% CI, 0.51-0.95; p-trend=0.07) and 0.69 (95% CI, 0.51-0.94; p-trend=0.03) for PUFA and DHA, respectively (Hidaka et al. 2015). These results were remarkably similar to those found in the American-based Mayo Clinic case-control study, where a significant inverse association with PUFA intake was reported on 384 cases and 983 controls (OR=0.64; 95% CI, 0.42-0.98; p=0.038). Interestingly, in the same study an increased risk was found for saturated FAs that include the butyric acid (OR=1.77; 95% CI, 1.19-2.64; $p=4x10^{-3}$), the caproic acid (OR=2.15; 95%

CI, 1.42-3.27; $p=3x10^{-4}$), the caprylic acid (OR=1.87; 95% CI, 1.27-2.76; $p=10^{-3}$), and the capric acid (OR=1.83; 95% CI, 1.23-2.74; $p=3x10^{-3}$) (Jansen et al. 2014).

Vitamin D was also studied in relation to PC. In a meta-analysis of 9 studies, including 1,206,011 participants, by Liu et al (2013), there was no association between dietary or circulating vitamin D and PC risk (pooled OR=1.14; 95% CI, 0.90-1.45; Z-score for the overall effect=1.06; p=0.288). On the other hand, according to a pooled analysis of nine case control studies from PanC4, the risk of PC increased with dietary intake of vitamin D. Per 100 daily international units (IU)/day the OR was 1.13 (95% CI, 1.07–1.19; $p=7.4\times10^{-6}$), whereas the risk of people with high intake (≥230) vs people with low intake (<110 IU/day) was OR=1.31 (95% CI, 1.10–1.55; $p=2.4\times10^{-3}$), with a stronger association in people with low retinol/vitamin A intake (Waterhouse et al. 2015). However, other epidemiological studies suggested a correlation between vitamin D deficiency and PC risk (Wolpin et al. 2012) and these results were corroborated also by *in vivo* experiments on mice xenograft models (Swami et al. 2012). In addition, incidence and/or mortality rates of about 15 cancers have been found inversely correlated with indices of UVB dose exposure, with the most likely reason being the production of vitamin D (Moukayed and Grant 2013). The anti-proliferative effect of vitamin D analogues, on PC cells, has been demonstrated *in vitro* (Zugmaier et al. 1996; Pettersson et al. 2000) and *in vivo* (Chiang et al. 2013, 2014). The most common mechanism involves the regulation of cyclin-dependent kinases p21 and p27 (Kawa et al. 1997; Schwartz et al. 2008). Vitamin D exerts also an inhibitory effect on invasion and migration of PC cells, via blocking EMT process (Chiang et al. 2014). Thus, while the epidemiological data are inconsistent, there are experimental evidences that vitamin D could play a role in both risk of and survival from PC. Further researches are needed to better ascertain the role of vitamin D in pancreas and the use of calcitriol (the hormonally active metabolite of vitamin D) analogues in PC prevention.

1.d Physical activity

Physical activity has been studied in relation to the risk of PC. Although in two studies, the occupational physical activity showed slightly decreased PC risks not statistically significant (Brenner et al. 2014; Kollarova et al. 2014), more studies suggested its protective role against PC onset. Indeed, the occupational physical activity was associated with significant protective effects for PC in several studies. Bao and Michaud (2008) reported that the occupational physical activity was associated with decreased risk of PC with a RR of 0.75 (95% CI, 0.58-0.96; p=0.025), the same results was reported in the analysis carried out by O'Rorke (RR=0.75; 95% CI, 0.59–0.95; p=0.023). Also the leisure physical activity was suggested to be a protective factor for PC. Kollarova (Kollarova et al. 2014) reported an OR of 0.63 (95% CI, 0.43-0.9; p=0.018) for people having regular physical activity and similar results were obtained also by Brenner (Brenner et al. 2014) in a study carried out in the central Europe population describing a 35% decreased risk (OR=0.65; 95% CI, 0.52-0.87; p<0.001) (Brenner et al. 2014). Other analyses with more detailed measurement of physical activity and control of potential confounders are needed to understand better the role of this factor in relation to PC risk.

2. Drugs use

Following preliminary observations, several works described the possible effect of the intake of non-steroidal anti-inflammatory drugs (NSAIDS), statins, and anti-diabetic drugs (including metformin, incretins, and insulin) on the risk of PC. NSAIDs constitute a class of drugs (such as aspirin and other analgesic and antipyretic agents) that were suggested to be associated with reduced risks of different types of cancer, as reported by different research groups (Abnet et al. 2009; Cole et al. 2009). Likely, the protection could be ascribed to the ability to inhibit cyclooxygenase isoforms, Cox1 and Cox2, activity which are connected to carcinogenesis and tumor growth (Van Rees and Ristimaki 2001). In 2014 Cui (Cui et al. 2014) carried out a study analyzing the use of aspirin. A total of 7,252 cases of PC and

more than 120,000 healthy control subjects were enrolled and the pooled analyses showed that high-dose aspirin intake was marginally associated with decreased risk of PC (OR=0.88; 95% CI, 0.76-1.01; p=0.069). The use of aspirin was evaluated also in an Italian multicentric hospital-based case-control study. Among 308 incident PC cases and 477 patients admitted for other diseases, twenty-two PC cases (7%) and 37 controls (8%) used regularly aspirin, with OR of 0.87 (95% CI, 0.47-1.61; p=0.65). No association was found also when the length of aspirin intake was considered: OR=0.53 (95% CI, 0.21-1.33; p=0.18) and OR=0.69 (95% CI, 0.25-1.93; p=0.48), for >5 and ≥10 years, respectively. The authors concluded that the regular intake of aspirin is not associated with PC risk (Bonifazi et al. 2010). Also the use of other NSAIDs was evaluated in relation to PC risk, with unclear results. In the Capurso's meta-analysis (Capurso et al. 2007), eight studies were evaluated, for a total of 6,301 patients and the pooled ORs were 0.99 (95% CI, 0.83–1.19; p=0.95), 1.11 (95% CI, 0.84–1.47; p=0.45) and 1.09 (95% CI, 0.67–1.75; p=0.74) in the low, intermediate and high exposure to aspirin/NSAIDs, respectively. A nested case-control study carried out in UK showed that there was not significant reduction in PC risk among NSAIDs users within five years before the index date (OR=0.96; 95% CI, 0.84–1.10; p=0.55). However, the use of NSAIDs for more than 2 years during the five years before the diagnosis, was associated with a reduction of PC risk with an OR 0.78 (95% CI, 0.62–0.97; p=0.03). The OR was 0.70 (95% CI, 0.49–0.99; p=0.05) when considering a low dose intake of NSAIDs over five years before the diagnosis (Bradley et al. 2010).
In a recent clinic based case-control study enrolling 904 PC patients and 1,224 healthy controls, Tan et al. (2011) demonstrated that there was not any relation between non-aspirin NSAID use and risk of PC for all analyzed parameters: the time of use (> 1 day monthly vs < 1 day monthly) (OR=1.01; 95% CI, 0.79-1.29; p=0.941), frequency of use (2-5 days weekly or >6 days weekly, using <1 day weekly as reference) (OR=0.75; 95% CI, 0.48-1.16 and OR=0.66; 95% CI, 0.41-1.04, respectively; p=0.106) and dosage (1-2 tables daily or >3 tables daily, using no intake as reference) (OR=0.96; 95% CI, 0.72-1.28 and OR=0.99; 95% CI, 0.69-1.45, respectively; p=0.943).
The use of statins was weakly associated with PC risk (Bosetti et al. 2012; Cui et al. 2012; Cui et al. 2014). In a meta-analysis (1,692,863 participants and 7,807 PC cases) carried out in 2012 by Cui (Cui et al. 2012), a possible correlation between PC risk and statins taken daily for preventing cardiovascular diseases was investigated (Cui et al. 2012) and the pooled results showed a non-significant decrease of PC risk among all statin users (RR=0.89; 95% CIs, 0.74-1.07; p=0.21). Negative results were obtained also in the subgroup of the long-term users (more than 4 years) (RR=0.94; 95% CIs, 0.81-1; p=0.25) and no association was found between lipophilic statin use and PC risk (RR=1.03; 95% CIs, 0.92-1.16; p=0.61).
Concerning other drugs, Singh and co-workers systematically reviewed and meta-analysed the effect of metformin, sulfonylureas (SUs), thiazolidinediones (TZDs), and insulin on the risk of PC in patients affected by diabetes mellitus. Meta-analysis of observational studies showed no significant association between the intake of metformin (OR=0.76; 95% CI, 0.57-1.03; p=0.073) or TZD (OR=1.02; 95% CI, 0.81-1.30; p=0.844) and risk of developing PC, whereas SU intake was associated with a 70% increase (OR=1.70; 95% CI, 1.27-2.28; p<0.001) (Singh et al. 2013). Recently, evidences have arisen that PC is an important potential side effect of the intake of incretin agents (Butler et al. 2013). These agents are administered as new drugs for type 2 diabetes mellitus (T2DM) patients. They include the glucagon-like peptide-1 receptor agonists, such as exenatide or liraglutide, or the dipeptidyl peptidase-4 (DPP-4) inhibitors, such as saxagliptin or sitagliptin (Knapen et al. 2016). These drugs have a sustained anti-hyper-glycemic effect, while promoting weight loss with a minimal risk of hypo-glycemia (Butler et al. 2013). According to various studies reviewed by Butler (Butler et al. 2013), the intake of exanatide, sitagliptin, liraglutide, and saxagliptin was associated with ORs of pancreatitis ranging from roughly 19 up to 56 with a high statistical significance (95% CI, 16.41-74.71; $p<2.2x10^{-16}$), whereas the OR of PC ranged between 1.8 and 6 (95% CI, 2.41-10.95; $p<2.2x10^{-16}$).

A modest risk of PC for these molecules was also described in a retrospective population based cohort study by Knapen with HR ranging between 1.5 and 2 and with a statistical significance depending on the employed adjustments (Knapen et al. 2016). On the other hand, no associations were found for the use of DPP-4 inhibitors by Gokhale (Gokhale et al. 2014). Thus, more studies are needed to better ascertain the role of these molecules in the context of PC risk.

In Bosetti's study, among diabetics, the use of oral antidiabetic drugs for long duration was associated with a decreased PC risk (OR=0.31; 95% CI, 0.14-0.69; p=0.004 for ≥15 years) (Bosetti et al. 2014). Another intriguing question is whether the intake of insulin or insulin glargine could be a risk factor for PC. In fact, in previous studies patients treated with insulin had a higher risk of developing PC than those receiving metformin as an antidiabetic drug (Li et al. 2009; Grouven et al. 2010). More recently, in a large meta-analysis, representing data for 1,332,120 people and 41,947 cancers, PC risk was found increased among new users of insulin (RR=3.18; 95% CI, 2.73-3.71; $p<10^{-6}$) and insulin glargine (RR=1.63; 95% CI, 1.05-2.51; p=0.03) (Colmers et al. 2012). A similar trend for the intake of insulin was reported also by Singh (Singh et al. 2013) (OR=1.59; 95% CI, 0.85-2.96), although the increase was not statistically significant (p=0.144). In another study on Taiwanese population by Tseng (2013), a total of 39,988 men and 46,909 women with T2DM were followed up and the smoking habit or the insulin use were associated with increased risks of PC (about + 50%), in a non-statistically significant way (smoking habits: HR=1.51; 95% CI, 0.99-2.29; p=0.0549 and insulin use: HR=1.46; 95% CI, 0.82-2.62; p=0.2007). However, smoking and insulin use jointly increased the risk with a HR_{adj} of 3.04 (95% CI, 1.37-6.73; $p=6.1x10^{-3}$) when compared to patients who did not smoke and did not use insulin.

The use of insulin is strongly related to the diabetic status. Given that diabetes is a strong predisposing factor for PC (see "Diabetes section") one could hypothesize that, actually, the association between insulin intake and PC risk could be driven by the diabetes. However, a pooled analysis from 15 case-control studies within the PanC4, including 8,305 cases and 13,987 controls, showed that diabetic patients taking insulin had an OR_{adj} of 2.66 (95% CI, 2.07-3.43; $p<1x10^{-12}$) as compared to diabetic patients who did not use insulin (Bosetti et al. 2014). The relation between the high levels of insulin and cancer risk is reported in several studies all confirming the activation of mitogenic signals on cells (McCarty, 2001; Belfiore et al. 2009; Malaguarnera and Belfiore, 2011). Some mechanisms have been proposed to understand the role of insulin in PC. In T2DM patients, an increase of ductal replication rate that precedes PC has been reported (Butler et al. 2010). Moreover, in human PC tissues and cell lines, an overexpression of docking peptides that permit the intracellular activation of insulin receptor (IR) and insulin receptor substrate IRS1 and IRS2 (leading to the activation of the PI3K signaling cascade) was observed (Bergmann et al. 1996; Kornmann et al. 1998; Asano et al. 2005). Rozengurt showed that IR cross-talks with G-protein-coupled receptors and then activates mTOR signaling and stimulates DNA synthesis and proliferation of PC cells (Rozengurt et al. 2010). Also, PC cancer cells kept in culture increased their percentage of proliferation when insulin was added into the medium (Fisher et al. 1996; Chan et al. 2014). In *in vitro* study, it has been showed that excessive insulin signaling may contribute to proliferation and survival in human immortalized pancreatic ductal cells (HPDE cells) and metastatic PC cells (PANC1 cells), but not in normal adult human pancreatic ductal cells. Moreover, Chan found that primary cells were more dependent on AKT signaling, while HPDE cells and PANC1 cells were more dependent on RAF/ERK signaling. According to these data, the authors hypothesized that signaling pathways involved in cell survival may be different during PC progression (Chan et al. 2014).

We would like to report here, literally, what discussed by Colmers (Colmers et al. 2012) about the apparent increased risk of PC among users of insulin. We agree with the hypothesis that, as they say, "the observed dramatic increase of PC risk could be due in part to reverse causality, where a subclinical pancreatic tumor disturbs insulin production and leads to unstable insulin signaling, which may lead to the diagnosis of diabetes or the prescription of more aggressive

glucose-lowering therapies. However, while the risk of pancreatic cancer does fall toward the null over time, it remains elevated, which might be due to accelerated growth of subclinical tumors when exposed to insulin or insulin glargine." In summary, there are clues that among diabetic patients the use of insulin or incretins could be an important risk factor for PC, to be better ascertained.

3. Occupational exposures

Ojajärvi carried out a meta-analysis of studies published between 1969 and May 1998 and concluded that about 12% of PC cases could be ascribed to the exposure to occupational risk factors (Ojajärvi et al. 2000). Positive associations were described in a review published in 2012 by Andreotti and Silverman where the exposure to chlorinated hydrocarbon compounds, pesticides, PAHs (due to diesel exhausts or aluminum production), metals, nitrosamines, ionizing radiations, or to various airborne particles was considered.

3.a Hydrocarbon compounds

PAHs compounds are widespread in the environment and they can be found in crude oils, mineral oils and tar, and are by-products of combustion (Andreotti and Silverman, 2012). Occupational exposure to PAHs can be found among coke oven workers, workers in steel or aluminum smelting plants, iron foundries or among people generally exposed to engine exhausts (in particular diesel engines) including mechanics working in inspection pits, electromechanics, mechanics-locksmith, forklift operators, or carbon-arc welding electrodes workers (Andreotti and Silverman 2012; Reul et al. 2016). In various studies (Ojajärvi et al. 2000; Andreotti and Silverman, 2012) a non-significant elevated risk of PC was found in relation to the exposure to PAHs. However, Kauppinen's reported a statistically significant increased mortality for PC among road paving workers (standardized mortality ratios, SMR=2.34; 95% CI, 1.34–3.08) on a Finnish cohort. No significant increased incidence or mortality for PC was found for bitumen workers (Kauppinen et al. 2003).

Concerning solvents, in a recent work, Reul found increased risks of PC in a cohort of female textile Chinese workers and a correlation with the time of exposure (0-10 years, HR=0.61; 95% CI, 0.35-1.07; 10-20 years, HR=0.99; 95% CI, 0.60-1.63; > 20 years, HR=1.40; 95% CI, 0.99-2.30; p-trend=$4x10^{-3}$) (Reul et al. 2016). No increased risks were noticed when other occupational risk factors (such as the exposure to endotoxins or metals) were considered (Reul et al. 2016). Three meta-analyses carried out in 20 populations on 32 specific agents showed that chlorinated hydrocarbon solvents and related compounds had a meta-risk ratio, MRR, of 1.4 (95% CI, 1.0–1.8) (Ojajärvi et al. 2001). In particular, a suggestive, but not statistically significant, excess risk was reported for trichloroethylene, polychlorinated biphenyl, methylene chloride, vinyl chloride, and tetrachloroethylene (Ojajärvi et al. 2001). The same authors reported also the highest risk of PC for occupational positions related to the highest exposure to chlorinated hydrocarbons such as it is for metal degreasers (MRR=2.0; 95% CI, 1.2–3.6) or dry cleaners (MRR =1.4; 95% CI, 1.1–2.4) (Ojajärvi et al. 2001). Also the duration of exposure was a relevant element for cases with PC. A significant positive trend in risk was observed with increasing duration of exposure (OR=4.11; 95% CI, 1.11–15.23; p-trend=0.04) (Santibanez et al. 2010). In conclusion, chlorinated hydrocarbon exposure was reported as one of the most ascertained occupational risk factors for PC.

3.b Pesticides

Weak evidences are available for the role of pesticides in relation to the risk to develop PC. The data reported by Lo indicated an OR of 2.6, not statistically significant (95% CI, 0.97-7.2; p=0.06), for PC among subjects exposed to pesticides (Lo et al. 2007). Ji found lower but statistically significant trends in PC risk: low and moderate/high exposure levels were associated with OR of 1.3 and 1.4, respectively (Ji et al. 2001). Moreover, increased risks were found among people with a past exposure to fungicides (OR=1.5) and herbicides (OR=1.6). In the Agricultural Health

prospective Study (that considered 89,000 participants including pesticide applicators and 82,503 cancer-free controls) 24 pesticides were considered in relation to the risk (adjusted for age, smoking, and diabetes) of developing PC. Among pesticide applicators, pendimethalin users had a 3.0-fold (95% CI, 1.3-7.2; p-trend=0.01) risk of PC compared with never users, whereas the handling of S-ethyl-dipropyl-thiocarbamate was associated with a risk of 2.56 (95% CI, 1.1-5.4; p-trend=0.01) (Andreotti et al. 2009). On the other hand in the population-based Queensland Pancreatic Cancer case–control Study, Fritschi could not detect any association with pesticides or N-nitrosamines exposure (Fritschi et al. 2015).

3.c Heavy metals

The exposure to different heavy metals and the PC risk was evaluated in different studies with discordant results. In 2012, Amaral carried out a study among smokers based on the hypothesis of dangerous effects of heavy metals (such as cadmium) found in tobacco smoke (Amaral et al. 2012). They analyzed the concentrations of cadmium, selenium, lead, nickel and arsenic in toenails. Statistically significant increased PC risks were found in patients with the highest concentrations of cadmium (OR=3.58; 95% CI, 1.86–6.88; p-trend=5×10^{-6}), arsenic (OR=2.02; 95% CI, 1.08–3.78; p-trend=0.009), and lead (OR=6.26; 95% CI, 2.71–14.47; p-trend=3×10^{-5}), while inverse associations were found for elevated concentrations of selenium (OR=0.05; 95% CI, 0.02–0.15; p-trend=8×10^{-11}) and nickel (OR=0.27; 95% CI, 0.12–0.59; p-trend=2×10^{-4}) (Amaral et al. 2012).

Concerning the occupational exposure to inorganic lead, a cohort study including printing workers was carried out in Moscow for a total of 1,423 men and 3,102 women. SMRs were calculated based on the total Russian mortality rate (Ilychova and Zaridze, 2012). In the overall cohort, mortality for PC increased up to 2-fold in the highest tertile of cumulative lead exposure with SMR=2.32 (95% CI, 1.46-3.68) (Ilychova and Zaridze, 2012) and the same results were found also after the adjustment for gender (Ilychova and Zaridze, 2012).

In a recent study by Antwi and co-authors (2015), both PC patients (1,892) and healthy subjects (2,316) completed the same risk factor questionnaires answering yes/no about the exposure to heavy metals, in particular chromium and nickel (Antwi et al. 2015). The association between PC risk and exposure to chromium and nickel was not statistically significant with ORs of 1.42 (95 % CI, 0.89–2.26; p=0.14) and 1.55 (95 % CI, 0.95–2.52; p=0.08), respectively (Antwi et al. 2015).

A particular attention must be given to cadmium, because it is also present in the diet, tobacco smoking, air, soil, and water as pollutant released from industries to the atmosphere (US Department of Health and Human Services 2011). Thus the effects of the exposure to cadmium were investigated in several studies, also in populations without occupational exposure history. In a meta-analysis, including 6 studies (Li et al. 2011b; Adams et al. 2012; Amaral et al. 2012; Luckett et al. 2012; Sawada et al. 2012; García-Esquinas et al. 2014) cadmium exposure was significantly associated with the increased risk of PC among individuals without occupational cadmium exposure (Chen et al. 2015). The summarized RR was 2.05 (95% CI, 1.58-2.66; p=$6.6\text{x}10^{-8}$), comparing the highest to the lowest category of cadmium exposure. The association was found only among men (RR=1.78; 95% CI, 1.04-3.05; p=0.035) but not in women (RR=1.02; 95% CI, 0.63-1.65; p=0.94).

In rodents, cobalt induced PC following inhalation exposure (Behl et al. 2015). The design of the inhalation study, conducted using 100 rats and 100 mice with equal proportion between female and male genders, proposed the exposure to cobalt sulfate with the inhalation of aqueous aerosols containing 0, 0.3, 1.0, or 3.0 mg/m^3 cobalt sulfate (corresponding to 0.114, 0.32 or 1.14 mg/m^3 cobalt) while for the exposition to cobalt metal, it has been proposed the inhalation of particulate aerosol at different concentrations (0, 1.25, 2.5, or 5 mg/m^3). In male rats, the incidences of PC were significantly higher when exposed to 2.5 and 5 mg/m^3 concentrations of cobalt metal while in the female groups

only at 5 mg/m^3 concentration (NTP, 2014). Following these studies, some concerns on the health effects of cobalt exposure have arisen for humans. Occupational exposure to soluble cobalt salts could occur in electroplating and electrochemical industries, and in the industry of inks and paints. The exposure to the insoluble form of cobalt occurs in the production of cemented tungsten cobalt (hard metal) and when used as an alloying element (Behl et al. 2015). Even though there is a correlation between cobalt exposure and cancer (in particular lung cancer, Wild et al. 2009), epidemiological studies are not published for PC. In a study carried out in 1987, the concentration of several metals including cobalt was measured in human pancreatic juice (Ishihara et al. 1987). No significant different metal concentrations were found between males and females or between healthy volunteers versus patients affected by pancreatic diseases (PC or chronic pancreatitis) (Ishihara et al. 1987).

3.d Organic and inorganic fine particles

The role of cotton dusts and endotoxins was investigated in a cohort of female cotton workers from Asia. A decreasing risk of PC with the increase of the exposure to these agents was observed in this study. HR calculated in workers with an annual cumulative exposure >143.4 mg/m^3 of cotton dusts and >3530.6 EU/m^3 of endotoxins were 0.6 (95% CI, 0.3-0.9; p-trend=0.006) and 0.5 (95% CI, 0.3-0.9; p-trend<0.001), respectively. It has been hypothesized that endotoxins may be the biologically active agent in cotton dust, and that the reduced risk could be associated to an enhanced immune response (Li et al. 2006). Concerning the exposure to other organic fine particles, a meta-analysis of the studies carried out before the year 2000 reported negative findings for wood powder and flour dusts (Ojajärvi et al. 2000). The exposure to inorganic particles has been analyzed in a higher number of studies, with a special concern for asbestos, and vitreous or silica fibers. Other potential risk factors (e.g. the exposure to PM2, PM10, and PM20 fine particles from polluted air) have never been approached. The meta-analysis by Ojajärvi reported a slightly increased risk for silica fibers, still non-statistically significant (MRR=1.4; 95% CI, 0.9–2.0; p=0.2) (Ojajärvi et al. 2000). However, more recent studies reported positive associations. Silica fibers were associated with a significantly increased PC mortality in a cohort of German porcelain and fine ceramic workers (SMR=1.71; 95% CI, 1.18–2.41) (Birk et al. 2009). Other significant associations with PC were reported among males for asbestos and for synthetic polymer dust exposure with OR of 7.54 (95% CI, 1.61–35.19; p-trend<0.001) and 5.40 (95% CI, 1.04–28.11; p=0.04), respectively (Santibanez et al. 2010). The same results were obtained by Antwi with an OR of 1.54 (95% CI, 1.23–1.92; p=0.0001) for people regularly exposed to asbestos (Antwi et al. 2015). Thus, the available evidences are still not conclusive but highly suggestive for a role of the exposure to asbestos and silica fibers.

3.e Ionizing radiations

Studies have shown that the exposure to moderate-to-high levels of ionizing radiations (IR) (within the range between 0.05 and 4 Sv) are associated with 5-10% increased risks of cancer in humans (Picano and Vano, 2011). Although a first review could not show an association between occupational exposure to IR and risk of developing PC (Committee BEIR 1990), successive case-control studies showed increased risks. In a nationwide case-control study, an elevated OR (OR=4.3; 95% CI, 1.6-11.4; p=0.003) was found for IR exposure among Finns (Kauppinen et al. 1995). In 2008, Zielinski analyzed the National Dose Registry (NDR) of Canada as unique resource for the direct estimation of potential health risks associated with the exposure to low doses of IR. A cohort of 200,000 workers exposed before 1984 was followed up through 1988 for cancer incidence. The analysis revealed a significant dose-response for the incidence of various cancers with an excess RR (ERR) for PC of 9.2 (90% CI, 0.1-36.8) per Sv (ERR/Sv) (Zielinski et al. 2008). Also Santibanez and co-workers (2010) were able to report higher risk of PC among males exposed to IR with OR of 16.73 (95% CI, 2.32–120; p=0.005).

4. Infective agents

4.a Helicobacter pylori

Helicobacter pylori (*H. pylori*) infection attracted increasing attention in the last 30 years (Wang and Li 2015) and it has been suspected to be an independent and preventable risk factor not only for gastric cancer but also for other cancers of the digestive tract, including pancreas. In 1998 a first case-control study reported a 2-fold increased risk of PC among patients infected with *H. pylori* (OR=2.1; 95% CI, 1.09–4.05; p=0.035) although on a limited number of subjects (92) (Raderer et al. 1998). In 2002, a study described the presence of *Helicobacter* species within tumor tissue specimens resected from PC patients (Nilsson et al. 2002). Another study, on 45 cases and 45 controls, evaluated *H. pylori, H. hepaticus, H. bilis* and *H. pullorum* and found increased PC risk in infected people (Wadstrom et al. 2004). These preliminary observations were further reinforced by The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) prospective Study. Males with *H. pylori* or CagA+ strains positivity had a statistically significant elevated PC risk than seronegative subjects (OR=1.87; 95% CI, 1.05-3.34; p=0.03 and OR=2.01; 95% CI, 1.09-3.70; p=0.02, respectively) (Stolzenberg-Solomon et al. 2001).

These results found a confirmation in a more recent meta-analysis. Trikudanathan and co-workers reanalyzed the results of six previous studies (Trikudanathan et al. 2011), for a total of 2,335 patients, showing a statistically significant association between the presence of *H. pylori* infection and PC with adjusted OR (OR_{adj}) of 1.38 (95% CI, 1.08-1.75; p=0.009). Furthermore, in a recent study *H.pylori* infection was associated with the development of colorectal (HR=1.73; 95% CI, 1.08–2.77; p=0.022), stomach (HR=5.21; 95% CI, 2.46–11.05; $p=1.6x10^{-5}$), and pancreatic (HR=2.77; 95% CI, 1.04–7.39; p=0.04) cancers. These findings further suggest that *H. pylori* infections could be an independent carcinogenic risk factor not only for stomach but also for other organs, including pancreas (Hsu et al. 2014). There seems to be also some evidences for the existence of strain-specific associations between *H. pylori* and PC (Schulte et al. 2015). However, not all the studies are concordant with these risk assessments. Several works could not find increased risks of PC in relation to *H. pylori* infections (de Martel et al. 2008; Lindkvist et al. 2008; Gawin et al. 2012). In 2013, Yu and co-workers (2013) used a multiplex serology assay to evaluate the serum status of antibodies against 15 *H. pylori*-specific antigens in 706 samples (353 PC and 353 healthy controls) and obtained a non-statistically significant OR of 0.85 (95% CI, 0.49-1.49; p=0.56). Moreover, Risch, empowering a previous study of 2010 (Risch et al. 2010 and 2014), evaluated the antibody seropositivity for *H. pylori* and its virulence protein CagA in 761 patients and 794 controls and found PC risk reduction for CagA seropositive subjects vs subjects seronegative for both *H. pylori* and CagA (OR=0.68; 95% CI, 0.54–0.84; p=0.0052). A statistically non-significant increased risk was reported in CagA-negative but *H. pylori* seropositive subjects (OR=1.28; 95% CI, 0.76–2.13; p=0.35). In summary, the epidemiological studies are inconclusive in determining the actual role of *H. pylori* infections. Theoretically, *H. pylori* could cause the reduction of the number of antral D-cells leading to suppress somatostatin release with a consequent increased secretion of secretin and pancreatic bicarbonate (Bulajic et al. 2014). Secretin acts positively on murine pancreatic growth as well as DNA synthesis in pancreatic ductal cells (Bulajic et al. 2014). Thus, it could be hypothesized that the induced ductal epithelial cell proliferation enhances the effects of known carcinogens, leading to the development of PC. Alternatively, *H. pylori* could induce atrophic gastritis leading to hypochlorhydria, bacteria overgrowth, and increased release of carcinogenic N-nitrosamines, transported to the pancreas via bloodstream (Kokkinakis et al. 1993; Houben and Stockbrugger, 1995).

4.b Periodontal diseases and infection by Porphyromonas gingivalis

Recently, some data suggested that periodontal diseases, including those related to infections by *Porphyromonas gingivalis* (*P. gingivalis*), could also play a role in pancreatic carcinogenesis (Hujoel et al. 2003; Stolzenberg-Solomon et al. 2003; Michaud et al. 2007; Ahn et al. 2012). In ATBC study cohort, it has been reported the increase in PC risk

(63%) for individuals who were edentulous at baseline compared with those with 0–10 teeth missing, after adjusting for smoking and other risk factors (HR=1.63; 95% CI, 1.09-2.46; p-trend=0.02) (Stolzenberg-Solomon et al. 2003). However, no specific data were collected on periodontal diseases of the volunteers. In the National Health and Nutrition Examination Survey (NHANES) I Epidemologic Follow-up Study, individuals with periodontitis at baseline showed a non-statistically increased risks of PC (RR=1.77; 95% CI, 0.85–1.85; p=0.004) compared to those with healthy periodontium. Edentulous individuals had a non-statistically significant elevation of PC risk (RR=1.90; 95% CI, 0.95–3.81; p=0.07) after the adjustment for age and gender (Hujoel et al. 2003). Recently, data obtained by NHANES III showed a 4-fold increase in risk of PC in individuals with severe periodontitis, although this was not statistically significant likely due to the small sample size (RR=4.56; 95% CI, 0.93–22.29; p=0.06) (Ahn et al. 2012). These results were corroborated by the prospective Health Professionals Follow-up Study (Michaud et al. 2007). Data about periodontal diseases were reported in 51,529 male volunteers that self-reported tooth loss and periodontal disease at baseline and were subsequently followed for 16 years. In that period, 216 cases of PC were newly diagnosed. Individuals with periodontal disease had a 64% higher risk of PC (RR=1.64; 95% CI, 1.19-2.26; p=0.002) compared with those reporting no periodontal disease (data adjusted for active smoking, age, diabetes, body mass index and dietary factors). The same increased risk was found also among never smokers (RR=2.09; 95% CI, 1.18–3.71; p=0.01) suggesting that periodontitis is an independent risk factor for PC. Among all the categories of physicians, the strongest association was among dentists (RR=1.91; 95% CI, 1.31–2.78; $p=7.48x10^{-4}$). The authors supposed that dentists provide more accurate answers to the self-administered questionnaires in reporting their own dental health status (Michaud et al. 2007). Implicitly, this information should reassure about the quality of the data collected and the validity of the analyses in that work. Later on, the same authors investigated the presence of antibodies towards periodontal pathogens in relation to the risk of PC in the European Prospective Investigation into Cancer cohort (Michaud et al. 2013). Using a nested case–control study design of 405 PC cases and 410 controls, a >2-fold increased PC risk was observed among those with high levels of antibodies for *P.gingivalis* (OR_{adj}=2.14; 95% CI, 1.05–4.36, comparing >200 ng/ml vs ≤200 ng/ml; p=0.03) (Michaud et al. 2013). In the same study, the authors showed that increased levels of antibodies against specific commensal oral bacteria (no pathogenic) can inhibit growth of pathogenic bacteria and could reduce the risk of PC.

A recent study published in 2016 by Chang et al, analyzed 139,805 Taiwanese patients and 75,085 healthy controls without periodontal diseases using the database of National Health Insurance Research. The authors showed a statistically positive association between periodontal diseases (including periodontitis, gingivitis, and others) and PC risk (HR=1.55; 95% CI, 1.02-2.33; p=0.037) independently from other factors such as diabetes, pancreatitis, and viral hepatitis. The positive association was stronger in patients over 65 years old (HR=2.17; 95% CI, 1.03-4.57; p=0.04), while it was not reported among patients under 65 years old (HR=0.83; 95% CI, 0.52-1.34; p=0.44) (Chang et al. 2016). The possible suggested mechanisms include the stimulation of the Toll-like receptor signaling pathways (in particular triggered by TLR4) (Zhang et al. 2010a; Ochi et al. 2012). In fact, in animal models, *P. gingivalis* was involved in the stimulation of TLR4. Further, the overexpression of TLR4 is present in several tumors such as lung cancer, ovarian cancer and PC cancer where there is also an increase of TRL4 protein than normal tissues (Zhang et al. 2010a). TLR4 activation facilitates the activation of MyD88 pathway in a dependent or in an independent manner and it leads to an (early or late) activation of NF-κB (Zhang et al. 2010a). Thus, it has been hypothesized a relation between the pancreatic tumorigenesis and bacterial stimulation. Alternatively, PC carcinogenesis could be stimulated by oral bacteria through the release of carcinogenic toxins, such as the N-nitrosamines (Risch, 2003; Michaud and Izard, 2014), as already showed in the mouth of patients affected by gum diseases (Shapiro et al. 1991; Nair et al. 1996).

4.c Hepatitis B (HBV) and C (HCV) virus infection

Approximately 350 million people worldwide are chronically infected by hepatitis B virus (HBV) and 180 million by hepatitis C virus (HCV) (Xing et al. 2013). In the last years, some epidemiological studies have been published about the possible role of both viruses as risk factors not only for liver, but also for pancreas (Fiorino et al. 2013b). Several studies (Hassan et al. 2008; Wang et al. 2012; Luo et al. 2013) have assessed various anti-HBV antibody patterns, such as HBcAb+/HBsAb–, HBcAb+/HBsAg+, and HBcAb+/HBsAb+, with inconclusive results. In 2013, Xing and co-workers meta-analyzed six previous studies (Hassan et al. 2008; Li and Lin, 2010; Hong et al. 2010; Zhu et al. 2011; Ben et al. 2012; Wang et al. 2012a) and found that the presence of HBsAb and HBeAb was associated with a statistically significant decrease in the PC risk (OR=0.40; 95% CI, 0.20-0.79; p=0.008 and OR=0.62; 95% CI, 0.39-0.99; p=0.04, respectively).

The presence of serum HBcAb and HBeAg did not correlate with the PC risk (OR=1.10; 95% CI, 0.77-1.57; p=0.59 and OR=1.75; 95% CI, 0.77-4.01; p=0.18, respectively). These authors analyzed also the combinations HBsAg–/HBcAb+/HBsAb– and HBsAg–/HBcAb+/HBsAb+ (considered as markers of a complete recovery from a HBV infections) and concluded that these viral antigen/antibody patterns are not associated with the risk of PC (Hassan et al. 2008; Ben et al. 2012; Wang et al. 2012a).

However, the presence of HBsAg (a marker for chronic or active HBV infection) was associated with a higher risk of pancreatic carcinoma. In 2013 several meta-analyses were published. In Luo's work (2013), seven of the reviewed studies could evaluate the HBsAg positive/negative status for a total of 2,817 cases and 4,740 controls in cross-sectional studies and 2,242 cases and 222,204 controls in cohort studies. Overall, they found increased risks for chronic and active HBV infections with OR=1.39 (95% CI, 1.22-1.59; $p<10^{-5}$) and OR=3.83 (95% CI, 1.76-8.36; $p=7x10^{-4}$), respectively. A weaker statistical significance was found for past infections (OR=1.41; 95% CI, 1.06-1.87; p=0.02). Fiorino and collaborators (2013a) reviewed four case-control studies and one cohort study and showed similar results: the presence of HBsAg was associated with PC risk (RR=1.18; 95% CI, 1.04-1.33; p=0.008), whereas the detection of HBeAg (RR=1.31; 95% CI, 0.85-2.0; p=0.21) or other anti-HB antibodies was not. Finally, in Li's meta-analysis (2013), eight studies were included (five case-control studies and three cohort studies) and the risk of PC in HBV infected people was 1.40 (OR) (95% CI, 1.149-1.73; p=0.001). Similar results were obtained also by Xu and collaborators (2013), by Majumder and co-workers (2014), and by Zhuang and co-workers (2014). In 2015, Andersen et al. carried out a study where 4,345 patients infected with HBV and 26,070 patients without a positive test for HBV were enrolled. All patients (infected and not infected) were linked to The Danish Cancer Registry to compare the risk of all-type cancer. The incidence rate ratio of PC among HBV-infected patients was 0.9 (95% CI, 0.3-2.5). The authors showed that the risk of PC was not higher in the HBV-infected cohort than to non-HBV infected (Andersen et al. 2015). A population-based cohort study carried out in Japan Public Health Center including 20,360 subjects, showed a value of the multivariate-adjusted HR 1.22 (95% CI, 0.81-1.84; p=0.34) for anti-HBc and no association between PC and HBsAg-status (Abe et al. 2016). In summary, not all the studies are in agreement with the hypothesis that HBV could be a risk factor for PC, clearly showing that more research is needed.

Also HCV infection could not elicit conclusive findings. Studies were reviewed recently (Fiorino et al. 2015; Abe et al. 2016) and four meta-analyses were performed. In two of these (Fiorino et al. 2013a, 2015), no statistically significant relationship between anti-HCV positivity and PC risk was reported, although a borderline value was detected in Fiorino et al's meta-analysis (2013a) with RR 1.16 (95% CI, 0.99-1.3; p=0.03). Increased PC risks in HCV-infected patients (compared to non-infected people) were also found in two Asian studies, with an OR of 1.21 (95% CI, 1.02-1.44; p=0.03 Xing et al. 2013) and 1.26 (95% CI, 1.03-1.5; p=0.01 Xu et al. 2013). Finally, Abe and co-workers reported

negative results (multivariate-adjusted HR=0.69; 95% CI, 0.28-1.69; p=0.4) in a large prospective cohort study on Asians presenting anti-HC antibodies (Abe et al. 2016).

Among Caucasians, a Swedish study suggested that HCV infection could be associated with an increased PC risk. Thirty-four PC cases were identified among a total of 340,819 person-years in the HCV cohort and the standardized incidence ratio (SIR) for HCV was 2.1 (95% CI, 1.4-2.9), whereas the HR for HCV infection was 1.6 (95% CI, 1.04-2.4; p=0.03) after adjustment for potential confounders (Huang et al. 2013).

5. Predisposing medical conditions related to PC

5.a Pancreatitis, hereditary pancreatitis, and other inherited conditions

It is an early observation that pancreatitis is a risk factor for PC. Following an observation period of over 20 years, about 5% of all patients with chronic pancreatitis will develop PC (Horner et al. 2009). Pancreatitis has been associated with PC in multiple independent epidemiological studies and it should be considered as a robust risk factor for PC. A meta-analysis published by Raimondi and co-workers in 2010 documented a statistically significant RR=13.3 (95% CI, 6.1-28.9; $p=7x10^{-11}$) in patients with chronic pancreatitis and RR=69.0 (95% CI, 56.4–84.4; $p<10^{-11}$) for hereditary pancreatitis (Raimondi et al. 2010) whereas Brodovicz (Brodovicz et al. 2012) showed 12-fold increased risk of PC in patients with both chronic pancreatitis and T2DM ($HR_{adj}=12.12$; 95% CI, 6.02–24.40; $p=2.78x10^{-12}$). In 2012 a pooled analysis of 10 case–control studies (for a total of 5,048 cases of PC and 10,947 controls) measured a 5.6-fold increased PC risk (OR=5.57; 95% CI, 4.39–7.07; p-trend <0.0001) in patients with a positive history of pancreatitis (Duell et al. 2012). A more recent systematic review, including 3 cohort and 14 case-control studies for a total of 17,587 pancreatitis cases, confirmed a strong association between chronic pancreatitis and PC risk (pooled OR=10.35; 95% CI, 9.13-11.75; $p<10^{-6}$). Also acute episodes of pancreatitis were associated, although to a lesser extent, with PC: pooled OR=2.12; 95% CI, 1.59-2.83; p=0.005 (Tong et al. 2014). In this study the risk of PC was also correlated with the duration of pancreatitis. The highest risk was found in pancreatitis cases diagnosed within 1 year (OR=23.30; 95% CI, 13.95-38.93; p=0.393), dropping as duration since diagnosis of pancreatitis increased: OR=3.03 (95% CI, 2.41-3.81; $p=2.3x10^{-21}$), 2.82 (95% CI, 2.12-3.76; $p=1.3x10^{-12}$), and 2.25 (95% CI, 1.59-3.19; $p=5x10^{-6}$), for 2, 5, and 10 years, respectively. It is conceivable that the very strong association in the 1-year group could be ascribed to a pre-existing undiagnosed PC whose symptoms were revealed as a pancreatitis. However, the high risk in the 5 and 10 years categories reveals, without room for doubts, that pancreatitis is a predisposing condition for PC development. Similar conclusions have been drawn also when the hereditary pancreatitis (HP) has been studied.

HP usually presents with acute attacks in childhood together with a positive family history of pancreatitis and it is frequently caused by mutations within the cationic trypsinogen gene (*PRSS1*) or the serine protease inhibitor gene (*SPINK1*) (Klein 2012). In an early study, Lowenfels and co-workers showed a SIR of PC of 53 (95% CI, 23–105) for people reporting a positive history of HP (Lowenfels et al. 1997). This result was confirmed further in the European registry of hereditary pancreatitis and pancreatic cancer (EUROPAC) study. Howes and co-workers (2004), analysing 418 individuals in 112 families from 14 countries, showed a SIR of 67 (95% CI, 50–82) for PC, after the correction for age, smoking habit, nationality, and surgical interventions (Howes et al. 2004). More recently, similar results were also found in a French study with a SIR of 142 (95% CI, 38–225) in females and 69 (95% CI, 25–150) among males (Rebours et al. 2012). In HP the risk for PC does not correlate with the severity of acute episodes, rather with the duration of the inflammation and the early-onset HP appears as the strongest predisposing factor for PC (Whitcomb et al. 1999).

It is known that inflammation is involved in cancer progression and in PC. The Hedgehog, Notch, and Cox2 inflammatory signalling pathways have been shown to be particularly important (Maitra et al. 2002; Avila and Kissil,

2013; Hamada et al. 2014). Inflammation is hypothesized to interact with toxic environmental factors and in PC this hypothesis is reinforced by the observation that among patients diagnosed for HP, smokers develop PC, on the average, 20 years earlier than non-smokers (50 years and 70 years old, respectively) (Lowenfels et al. 2001). Thus, the exposure to genotoxicants could trigger the initiation of the carcinogenesis, but the inflammation takes a decisive role in the promotion.

Other inherited predisposing conditions not limited to HP have been described for PC. Among them, it is known the Peutz-Jehgers syndrome (PJS), caused by a mutation in the *STK11/LKB1* gene, confers an increased risk for many different types of cancers including PC (Lim et al. 2004). Also individuals with mutations within *CDKN2A*/p16 locus, in particular the mutations known as "p16-Leiden", show increased risks of developing PC (RR=47.8; 95% CI, 28.4-78.7; $p=5x10^{-50}$), in a spectrum encompassing also other malignant conditions such as the familial atypical multiple mole melanoma (FAMMM) (de Snoo et al. 2008). Increased PC risks, although at lesser extent, can be found in the context of other familial syndromes, including the hereditary breast and ovarian cancer syndromes caused by mutations within *BRCA1* and *BRCA2*, with RRs ranging from 2.13 (95% CI, 0.36-7.03; p=0.31) to 6.6 (95% CI, 1.9-23; p=0.003) (Risch et al. 2006; Iqbal et al. 2012).

Also people affected by the hereditary non-polyposis colorectal cancer (Lynch syndrome), caused by mutations within *MLH1*, *MSH2*, *MSH6*, or *PMS2* loci, showed increased risks of PC (up to 10.9, 95% CI, 5.5-21.9; $p=1.2x10^{-11}$) with a cumulative age-specific risk of 3.68% (95% CI, 1.45%-5.88%) up to the age of 70 years (Kastrinos et al. 2009). Other genes such as *APC* (responsible for the familial adenomatous polyposis), *CFTR* (cystic fibrosis) (Giardiello et al. 1993; Cohn et al. 1998; Sharer et al. 1998), and *PALB2* (Jones et al. 2009) were also found responsible for a share of familial PC cases and further studies are needed to identify more significant risk factors. Overall, we could conclude that high risk of PC in the general population could derive from a combination of existing pathogenic cancer gene variants, inflammation, and the exposure to environmental carcinogens.

5.b Obesity

Several studies have associated obesity with an increased risk for different types of cancer (Wang et al. 2016b) and PC is one of them. In 2007 a meta-analysis of 21 prospective studies, including 3,495,981 individuals and 8,062 PC cases, reported similar increments of risk in men and women with increasing body mass index (BMI) (RR=1.16; 95% CI, 1.05-1.28; p=0.003 in men and RR=1.10; 95% CI, 1.02-1.19; p=0.015 in women every $5kg/m^2$ of BMI; Larsson et al. 2007). This result has been confirmed by three pooled analysis with statistically significant 20-30% elevated risk for those with the highest waist to hip ratios (Arslan et al. 2010; Jiao et al. 2010; Genkinger et al. 2011). In agreement with this, a study on 720,000 Jewish men showed that overweight adolescents had a higher risk to develop PC later on in the life (HR=2.09; 95% CI, 1.26-3.50; p=0.005) (Levi et al. 2012). In the NIH-AARP Diet and Health Study cohort has been observed that an excess body weight across a lifetime remains significantly associated with risk of PC at any age, in particular when comparing the category BMI (kg/m^2) ≥25 to that 18.5-22.5. The multivariate HRs were 1.25 at 18 years old (95% CI, 1.04-1.49; p-trend=0.02), 1.24 at 35 years old (95% CI, 1.08-1.43; p-trend=0.002), 1.15 at 50 (95% CI, 1.02-1.30; p-trend=0.02), and 1.12 over 50 years old (1.02-1.23; p-trend=0.01; Stolzenberg-Solomon et al. 2013).

In 2014 the systematic meta-analysis carried out by Alsamarrai and collaborators confirmed obesity as one of the most important risk factor for PC reporting the result of the analysis of 51 population-based studies with more than 3 million individuals and nearly 11,000 patients with pancreatic diseases (RR=1.48; 95% CI, 1.15-1.92; p=0.0027) (Alsamarrai et al. 2014). More recently also a case-control study carried out in China listed the obesity among the risk factors for PC with an OR_{adj} of 1.77 for BMI ≥24 (95% CI, 1.22-2.57; p=0.0027) (Zheng et al. 2016). Furthermore, increased BMI has

been significantly associated with PC incidence in both European-Australian (RR=1.18; 95% CI, 1.09–1.27; $p=2.18x10^{-5}$) and North-American groups (RR=1.07; 95% CI, 1.03–1.11; p=0.0004) (Wang et al. 2016b).

In several preclinical models it has been suggested that obesity status could initiate pancreatic carcinogenesis and promote growth and metastasis (Zyromski et al. 2009; White et al. 2010; Philip et al. 2013; Fukumura et al. 2016; Incio et al. 2016a,b). In particular, a high-fat diet can activate oncogenic Kras and Cox2 causing inflammation and fibrosis in pancreas with subsequent pancreatic intraephitelial neoplasia (PanINs) and PC onset (Philip et al. 2013). On the other hand, calorie restriction decreases pancreatic tumor cell growth, as observed in mice subjected to a restricted calorie diet. Moreover, diet restriction caused a 70% decrease in the expression of NF-κB-related and inflammation-related gene expression reducing the stimuli for cancer progression (Harvey et al. 2014). A recent study gave evidence that the number of PanIN was correlated with intravisceral fat (r=0.22; p=0.04) and the presence of PanIN was associated with intralobular fat (OR=17.86; 95% CI, 4.935-88.12; $p=8.8x10^{-5}$) (Rebours et al. 2015). In summary, a fat diet leading to pancreatic fatty infiltration could play an important role in PC.

5.c Diabetes mellitus

Several studies showed that, like for other types of tumors, PC occurs with increased frequency among individuals with diabetes (Li et al. 2011a; Sasazuki et al. 2013; Starup-Linde et al. 2013; Zheng et al. 2016). In the meta-analysis by Li, carried out collecting datasets from three American studies (for 2,192 PC patients and 5,113 controls), diabetic patients showed a 1.8-fold increased risk of PC (95% CI, 1.5-2.1; $p=7.5x10^{-12}$). Similar results have been observed in the Japanese population (HR=1.85; 95% CI, 1.46–2.34; $p=3.2x10^{-7}$; Sasazuki et al. 2013) and in a recent case-control study designed in China (OR_{adj}=2.96; 95% CI, 1.48-5.92; p=0.002; Zheng et al. 2016). Moreover, a systematic review and meta-analysis conducted by Starup-Linde, showed a RR of 2.2 for PC among diabetic patients (Starup-Linde et al. 2013). Bosetti et al. (2014) showed also that PC risk decreased with duration of diabetes: (i) ≤2 years, OR = 2.9; 95% CI, 2.1-3.9; (ii) 3-5 years, OR=1.9; 95% CI, 1.3-2.6; (iii) 6-10 years, OR=1.6; 95% CI, 1.2-2.3; (iv) 11-15 years, OR=1.3; 95% CI, 0.9-2.0; (v) > 15 years, OR=1.4; 95% CI, 1.0-2.0; p-trend < 0.0001. Interestingly, a 30% excess risk persisted for more than two decades after diabetes diagnosis (OR=1.30; 95% CI, 1.03–1.63; p=0.025). Song found similar results: (i) ≥2 years, RR=1.64 (95% CI, 1.52-1.78, $p=1.14x10^{-34}$); (ii) ≥5 years, RR=1.58 (95% CI, 1.42-1.75; $p=9.4x10^{-18}$); (iii) ≥10 years, RR=1.50 (95% CI, 1.28-1.75; $p=3.7x10^{-7}$) (Song et al. 2015). Moreover, seven meta-analyses and seven pooled analyses showed consistent results revealing that long-term diabetes is associated with a ≥50% increased risk of PC (Maisonneuve et al. 2015). In contrast, a pooled analysis (Elena et al. 2013) showed that the highest risk of PC in diabetics was among patients with a duration of 2-8 years (OR=1.79; 95% CI, 1.25-2.55; p=0.0001) while no significant association was observed among those with over 9 years of diabetes (OR=1.02; 95% CI, 0.68-1.52; p=0.9).

A recent pooled analysis of 8 case-control studies, including 1,954 patients and 3,278 age and sex matched controls, focused the attention on risk factors among PC patients younger than 60 years revealing that most of the established risk factors for PC, including diabetes, have been found also in EOPC: diabetes for over 3 years was associated with risk of EOPC (OR=1.55; 95% CI, 1.16-2.06; p=0.003) but not of VEOPC (Very Early Onset of Pancreatic Cancer; younger than 45 years) (OR= 0.85; 95% CI, 0.25-2.93; p=0.8) (McWilliams et al. 2016).

The possible mechanism for increased cancer risk in diabetics is hypothesized to be due to the cellular proliferative effects of hyperglycemia, hyperinsulinemia, and abnormalities in insulin/IGF receptor pathways (Cui and Andersen 2012). The stimulation of cancer cell proliferation has been observed in diabetic mice that developed pancreatic ductal adenocarcinomas with significantly increased tumor weight when compared to normoglycemic (Zechner et al. 2015).

5.d Allergies and asthma

In many studies, it is suggested that the overall cancer incidence is lower in allergic than in non-allergic subjects and this status could be explained by the increasing immune surveillance in allergic people. In 2005, it has published a meta-analysis, including 4 cohort and 10 case-control studies (3,040 PC patients in total) with the aim to clarify the possible relation between any kind of allergies and PC risk (Gandini et al. 2005). A general status of allergy was associated in a non-statistically significant way to the reduction of PC risk, with RR of 0.82 (95% CI, 0.68-0.99; p=0.07). The RR was 0.71 (95% CI, 0.64-0.80; p=0.12) for atopic allergies, 1.01 (95% CI, 0.77-1.31; p=0.22) for asthma, and 1.08 (95% CI, 0.74-1.58; p=0.08) for food and drugs.

More recently, a pooled analysis from the PanC4, for a total of 3,567 cases and 9,145 controls, reported statistically significant reduced risks. The OR for any type of allergy was 0.79 (95% CI, 0.62-1.00; p=0.05), for hay fever was 0.74 (95% CI, 0.56-0.96; p=0.028) and for animal allergy OR=0.62 (95% CI, 0.41-0.94; p=0.023). So, allergic subjects appeared to have a slightly reduced risk of PC, while there was no statistically significant association with asthma (Olson et al. 2013).

In Cotterchio et al's study, a reduction of PC risk was found in the group of volunteers with skin prick test positive for hay fever allergens (age-AOR_{adj}=0.43; 95% CI, 0.26–0.72; p=0.001) (Cotterchio et al. 2014). The most recent publication (2015) not only confirmed a reduction of PC risk in patients with nasal allergies (OR=0.66; 95% CI, 0.52-0.83; $p=5x10^{-4}$) but also in patients with asthma with OR=0.64 (95% CI, 0.47-0.88; $p=5x10^{-3}$), in particular long-standing asthma (>=17 years, OR=0.39; 95% CI, 0.24-0.65; $p=2x10^{-4}$) (Gomez-Rubio et al. 2015). In conclusion, a possible explanation of these results could be found in the hyperactive immune system of allergic individuals with an increase of protection and surveillance against the development of PC (Gandini et al. 2005).

5.e Cholecystectomy, appendectomy, and tonsillectomy

In a review of 17 published manuscripts, Olson (2012) identified several studies showing statistically significant elevated risks of PC in cholecystectomized patients, in particular for people undergone to surgery in more recent times. The statistical significance of the risk of PC in patients with cholecystectomy was borderline when the follow up was extended to a period of 5-20 years (Olson, 2012). In the same year, Lin et al. (2012) carried out a meta-analysis (10 case-control studies and 8 cohort studies) and confirmed a positive association between cholecystectomy and PC with an increased risk of 23% (SRR =1.23; 95% CI, 1.12-1.35; $p=6x10^{-3}$). Also the work by Zhang and co-workers (Zhang et al. 2014) reported a statistically significant association with an OR of 2.11 (95% CI, 1.32-3.35; $p=1.7x10^{-3}$). These data were further confirmed by Fan who has performed a meta-analysis of all currently published studies about PC risk and cholecystectomy and gallstones alone or in combination. Individuals with both gallstones and cholecystectomy had an increased PC risk with RR 1.39 (95% CI, 1.28-1.52; p<0.001), while gallstones and cholecystectomy alone were also associated with an elevated PC risk with RR 1.70 (95% CI, 1.30-2.21; p<0.001) and RR 1.31 (95% CI, 1.19-1.43; p<0.001), respectively (Fan et al. 2016). The population based-cohort study carried out in Taiwan (Lai et al. 2013), reported increased risk of PC for diabetic patients with gallstones, cholecystitis, or a cholecystectomy, with a HR 1.92 (95% CI, 1.18-3.11). The risk greatly increased for those with comorbidity of chronic pancreatitis (HR=22.9; 95% CI, 12.6–41.4; p<0.001). However, the PC risk did not increase in the non-diabetic patients with gallstones, cholecystitis, or cholecystectomy. It should be considered that several studies could not show any statistically significant association between cholecystectomy and PC, such as the combined analysis of the Nurses' Health Study and the Health Professional Follow-up Study (Schernhammer et al. 2002), or the study by Bosetti et al. (2003).

In summary, in spite of numerous evidences the etiological role played by gallstones and cholecystectomy is still open to discussion. A hypothesized mechanism was proposed based on the fact that cholecystectomized patients have

increased circulating levels of cholecystokinin, a peptide hormone well demonstrated to stimulate the growth of human PC cell lines (Matters et al. 2011).

In the review by Olson et al. (2013), reporting different medical conditions, it has been reviewed also a possible relationship between the surgical resection of appendix or tonsils and PC risk. The author examined ten studies reporting null results for appendectomy, whereas for tonsillectomy the published data were conflicting. In fact, 3 out of 8 studies showed a statistical reduction of PC risk in patients with tonsillectomy (Lin and Kessler, 1981; Gold et al. 1985; Farrow and Davis, 1990) while the other five showed null results. In a recent population-based case-control study carried out in Minnesota, Zhang and co-workers (2014) analyzed 215 PC patients with tonsillectomy and found an OR=0.67 (95% CI, 0.48-0.94; p=0.02) after adjustment for other confounders. More epidemiologic studies need to further investigate whether the medical interventions reported in this section are associated with PC risk in a causal way.

5.f Parity and reproductive factors

It has been observed that anti-estrogenic agents inhibited the growth of PC in both animal and human models and that the steroid hormone receptors were present not only in normal human pancreatic but also in neoplastic tissues. Thus, researchers hypothesized that the reproductive factors could be involved in the etiology of PC. In several studies, it has been investigated the role of reproductive factors (parity, age at first birth, age of menarche, age of menopause) obtaining unclear results (Lo et al. 2007; Stevens et al. 2009; Zhang et al. 2010b; Duell et al. 2013). The most studied covariate was the parity (Navarro Silvera et al. 2005; Teras et al. 2005; Chang et al. 2010).

In a recent and most complete meta-analysis, the authors collected ten cohort studies and ten case-control studies (8,205 cases) (Zhu et al. 2014). They found an inverse association between parity and PC with a RR of 0.91 (95% CI, 0.85-0.97; $p<0.01$; parous vs nulliparous). According to the number of parities (0, 1 and two parities), they observed an inverse association between giving birth to two children and PC risk, with RR of 0.86 (95% CI, 0.80-0.93; $p<0.01$). The authors suggested some mechanisms to explain their results. Parous women had high levels of circulating estrogens for longer periods and these data are supported by animal studies in which it has been reported the inhibitor effect on the growth of pre-neoplastic pancreatic lesions by estrogens (Sandberg et al. 1973), indicating that estrogens could have effect against PC. Moreover, other mechanisms were proposed such as a different increase of insulin resistance during the pregnancy (this is correlated with the PC risk in independent manner, Stanley et al. 1998; Wolpin et al. 2013) or the obesity following the pregnancy (obesity is a factor risk for PC) (Michaud et al. 2001). Thus, insulin released and the obesity could counteract the estrogen protective effects.

The hypothesized protective role of female steroid hormones for PC risk has been proposed in several studies. However, results from epidemiologic studies that examined hormone-related exposures have been inconsistent (Lee et al. 2013). In a study conducted in USA, it has been evaluated the PC risk in correlation with reproductive factors and exogenous hormone use (Lee et al. 2013). In 323 women (on 118,164 eligible study participants) current users of estrogen-only therapy at baseline had a lower risk of PC than did participants who had never used hormone therapy (HR=0.59; 95% CI, 0.42-0.84; p=0.003). Use of estrogen-plus-progestin therapy was not associated with the risk of PC. Thus, these findings suggested that increased estrogen exposure through estrogen-only therapy may reduce PC risk in women (Lee et al. 2013). However, in contrast, a longer use of oral contraceptive (≥10 years of use compared with never use) was associated with an increased risk of PC (HR=1.72; 95% CI, 1.19-2.49; p-trend=0.014) (Lee et al. 2013).

Other reproductive factors (e.g. menstrual cycle or hysterectomy) were analyzed in the PanC4 (Lujan-Barroso et al. 2016) that included 11 case-control studies with 2,838 PC case women and 4,748 controls. A reduced OR was observed in hysterectomized women (OR=0.78; 95% CI, 0.67-0.91; $p=1.5x10^{-3}$) and the same result was also obtained in the

oophorectomized+hysterectomized women (OR=0.79; 95% CI, 0.62-1; p=0.05). Oophorectomy alone was not associated with OR 0.91 (95% CI, 0.60-1.39; p=0.6). A mutually adjusted model with the joint effect for hormone replacement therapy and only hysterectomy showed statistically significant inverse associations with PC in hysterectomized women under hormone replacement therapy (OR=0.64; 95% CI, 0.48-0.84; $p=1.8x10^{-3}$) as well as for hysterectomized women without hormone replacement therapy (OR=0.70; 95% CI, 0.54-0.92; $p=8.7x10^{-3}$). No statistically significant results were found in the oophorectomized women. Summarized, the reported data suggested that hysterectomized women could have reduced PC risk but further studies, especially on the role of hormone replacement therapy+hysterectomy, will be needed (Lujan-Barroso et al. 2016).

6. Discussion

The data reported in this work were collected from published meta-analyses, and case-control and cohort studies with the aim to review the main PC etiological factors. This work showed that for PC the risk factors are various and interrelated, lacking a single main agent causative for the disease (**Fig. 1**). Among mutagenic factors for the initiation of PC, the most dangerous appear the inhalation of cigarette smoke, the exposure to mutagenic nitrosamines (e.g. released by *H. pylori* or via the ingestion of well-done red meat), and the exposure to organ-chlorinated compounds (e.g. pesticides or Cl-PAHs), heavy metals (especially cadmium), ionizing radiations, or asbestos fibers. Dietary flavonoids (in particular catechines), marine omega-3, vitamin D, fruit and vegetables appear to protect acinar cells reducing the risk of PC. However, the pancreas is not an organ directly hit by the exposure to carcinogens and, likely, this explains its uncommon incidence. On the other hand, it is known that following the initiation by carcinogens, cancer needs a promotion phase in order to progress as disease. Typically, the most important and acknowledged tumor promotion factor is the inflammation. Under this point of view, many are the factors triggering an inflammatory status of the pancreas. Thus, this should explain why pancreatitis, high doses of alcohol drinking, body microbial infections, obesity, diabetes, gallstones and/or cholecystectomy, and the accumulation of asbestos fibers are decisively associated with the risk of PC. In agreement with this hypothesis, aspirin and NSAIDs were found associated with reduced risk, likely because their anti-inflammatory activity. Moreover, insulin or other anti-diabetic drugs could promote pancreatic carcinogenesis not through inflammation, but through a direct stimulation of acinar cell proliferation or by altering the pancreatic homeostasis. Also the increase of the glycemic index associated with a continuous intake of soft drinks (sweet beverages) could act in a similar way. Physical activity could have a protective effect both by reducing the glycemic index and the obesity (**Fig. 1**).

After the acknowledgement of risk and protective factors, it could be hypothesized that targeting the interaction between them and the deregulated molecular signaling pathways within acinar cells could provide new strategies for the therapy of PC. Development of multiple drugs that target various aspects of this complex interaction will be paramount in halting disease initiation and progression. More in general, once important risk factors have been identified, strategies could be applied for high-risk people to prevent the onset of this aggressive disease.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Fig. 1 The protective and risk factors are classified in three categories defined “unclear”, “likely” and “ascertained” (as listed from left to right) in base of the results reported in the largest studies analysed in our review. We report the risk levels of each wider study by gauges, while the geometrical figures point out the “weight” of initiation (△) and promotion (☐) role in PC.

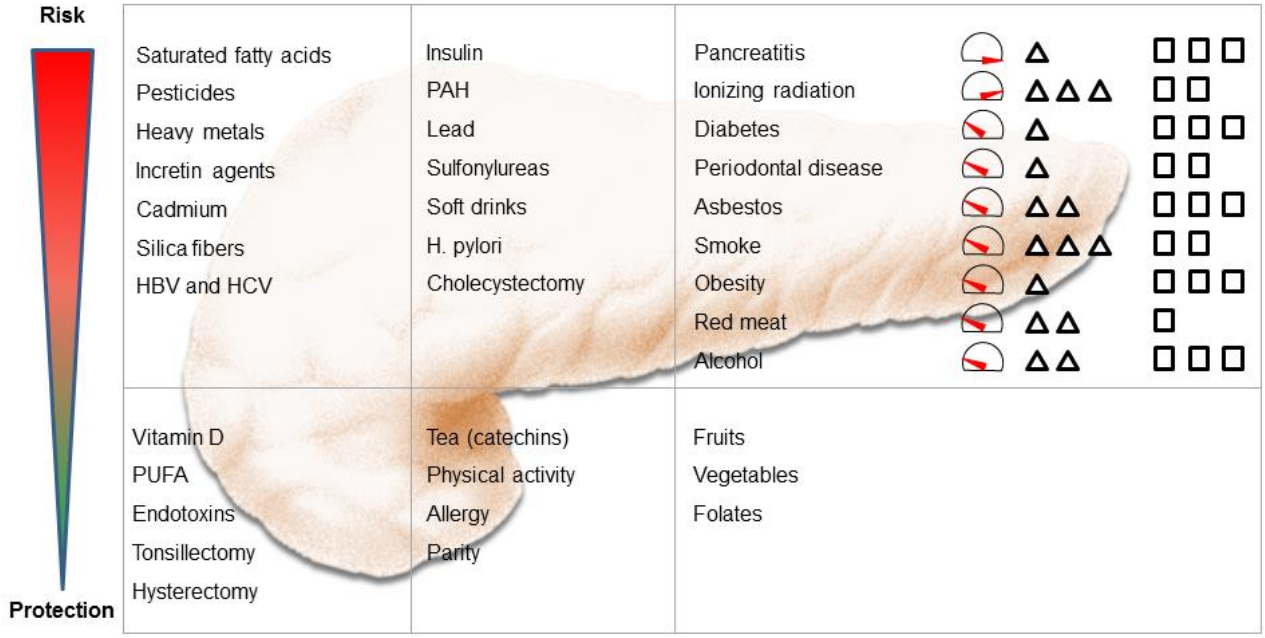

Fig. 1