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Environmental Risk Factors for Chronic Pancreatitis and Pancreatic Cancer

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Abstract
Chronic pancreatitis has long been thought to be mainly associated with immoderate alcohol consumption. The observation that only ~10% of heavy drinkers develop chronic pancreatitis not only suggests that other environmental factors, such as tobacco smoke, are potent additional risk factors, but also that the genetic component of pancreatitis is more common than previously presumed. Either disease-causing or protective traits have been indentified for mutations in different trypsinogen genes, the gene for the trypsin inhibitor SPINK1, chymotrypsinogen C, and the cystic fibrosis transmembane conductance regulator (CFTR). Other factors that have been proposed to contribute to pancreatitis are obesity, diets high in animal protein and fat, as well as antioxidant deficiencies. For the development of pancreatic cancer, preexisting chronic pancreatitis, more prominently hereditary pancreatitis, is a risk factor. The data on environmental risk factors for pancreatic cancer are, with the notable exception of tobacco smoke, either sparse, unconfirmed or controversial. Obesity appears to increase the risk of pancreatic cancer in the West but not in Japan. Diets high in processed or red meat, diets low in fruits and vegetables, phytochemicals such as lycopene and flavonols, have been proposed and refuted as risk or protective factors in different trials. The best established and single most important risk factor for cancer as well as pancreatitis and the one to clearly avoid is tobacco smoke.

Chronic Pancreatitis

The only established risk factor for the development of chronic pancreatitis was, for a long time, the immoderate use of alcohol, frequently in combination with a poor socioeconomic status, because several epidemiologic studies had identified alcohol consumption to be associated with chronic pancreatitis. Since less than 10% of heavy drinkers develop chronic pancreatitis and, on the other hand, teetotalers also develop pancreatitis, other risk factors have to exist. While risk factors only imply a statistical association they may also point towards an underlying mechanism of the disease. In the last two decades much progress has been made in understanding the biol-

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ogy of acute and chronic pancreatitis. We have learned that the serine protease trypsin plays a central role in pancreatitis [1, 2] and that pancreatic fibrosis, not unlike liver cirrhosis, represents an impaired balance between connective tissue synthesis and degradation with a pathological shift towards the former [3]. Exogenous factors that regulate these processes are manifold and discussed below.

Nutritional Factors

Obesity has been shown in several studies to be associated with a higher mortality and greater complication rate in patients with acute pancreatitis [4–7]. In a prospective study investigating additional risk factors for alcohol-induced chronic pancreatitis, 54% of patients were overweight (15.0% obese) before the onset of the disease but only 37.7% (3.1% obese) in controls. This suggests that obesity and being overweight are additional risk factors for developing alcohol-induced chronic pancreatitis [8]. Older studies, however, showed conflicting results about the impact of obesity and being overweight on the progression of alcohol-induced chronic pancreatitis, but few, if any of the older studies investigated whether differences in weight existed before the disease onset [8–10]. Diets high in fat and protein appeared to facilitate the progression of chronic pancreatitis, but evidence that overnutrition is an initiating factor for the disease is less convincing.

Especially for tropical pancreatitis, malnutrition was long believed to be a risk factor. In a prospective case-control trial by Midha et al. [11], malnutrition was investigated in the context of chronic pancreatitis in India. The authors focused on patients with idiopathic pancreatitis (i.e. those who do not consume alcohol) and found that malnutrition is the result of chronic pancreatitis and its progression, rather than a risk factor for the disease onset. Similar findings were made by earlier but smaller studies. Uscanga et al. [12] found no relationship between malnutrition and idiopathic or alcohol-induced chronic pancreatitis at the time of disease manifestation. On the other hand, all studies showed a significant increase in malnutrition after the onset of the disease, indicating that malnutrition is either the result of maldigestion due to reduced pancreatic enzymes synthesis or the result of insufficient dietary intake due to pain or other disease complications in patients with chronic pancreatitis. Neither of these studies provided evidence that malnutrition can actually induce chronic pancreatitis.

No report has conclusively shown a direct association between distinct diets and a risk for developing chronic pancreatitis, although the consumption of cassava has been implicated in the onset of tropical pancreatitis before its association with mutations in the SPINK1 gene were known and cassava as a risk factor was ruled out in case-control studies. Much more is presently known about genetic risk factors. The most important ones are mutations in the cationic trypsinogen gene [2, 13–15] which were the first identified cause of hereditary pancreatitis. In contrast to mutations in the cationic trypsin gene, a G191R mutation in the anionic trypsin gene (PRSS2) was shown to have a protective effect [16]. Other genetic changes that predispose to pancreatitis were found in the trypsin inhibitor gene SPINK1 [16–18] as well as in the cystic fibrosis transmembrane regulator CFTR (cystic fibrosis transmembane conductance regulator) gene [19–25]. Because lysosomal cathepsins are a known activator of the digestive protease cascade in the pancreas [26] it has been proposed that cathepsin B mutations may represent a genetic risk factor for pancreatitis [27]. In Caucasian patients such an association has, however, yet to be confirmed [28].

Environmental Toxins

The best-established risk factor for chronic pancreatitis is alcohol. Excessive alcohol consumption has long been known to be associated with chronic pancreatitis and this fact has been confirmed in various epidemiologic studies [29–33]. However, since only less than 10% of chronic alcoholics develop chronic pancreatitis, additional risk factors are likely to exist. One of these is tobacco smoke as a well-established independent risk factor for chronic pancreatitis as well as for pancreatic cancer [34–36]. Since many high alcohol consumers also smoke it has long been difficult to distinguish between the two toxic exposures. Only recent studies have made that distinction and have determined that the impact of tobacco smoke on the onset of chronic pancreatitis is at least as great, if not greater, than that of immoderate alcohol consumption [35]. No single genetic alteration has been identified that would determine whether a smoker or drinker develops pancreatitis. However, the factors associated with idiopathic and tropical pancreatitis such as SPINK1 mutations, seem to somewhat contribute also to alcohol-induced pancreatitis [37].

Protective Factors

In several studies antioxidants have been proposed to have a protective role in pancreatitis. Various antioxidants have been used to treat acute pancreatitis without much success and were also discussed as a preventive

measure for chronic pancreatitis. Several controlled trials investigating the effect of antioxidants on the course of chronic pancreatitis have been reported. They showed a significant reduction in pain in the antioxidant-treated cohort [38–40]. However, these trials cannot convincingly show a protective role of antioxidants in the development of chronic pancreatitis but indicate that treatment with antioxidants can reduce the number of pancreatitis episodes and pain in individuals already suffering from chronic pancreatitis.

A recent systematic review of the 22 available placebo-controlled studies, including those using allopurinol and N-acetylcysteine, could not demonstrate a general benefit of antioxidant treatment on the course of acute pancreatitis, post-ERCP pancreatitis or chronic pancreatitis [41].

In an Italian case-control study published in 2005 that serum selenium levels were lower in patients with chronic pancreatitis, especially in patients with pancreatic insufficiency. While this correlation indicates selenium deficiency in chronic pancreatitis patients, it should not be regarded as proof that low selenium was the cause of the disease [32, 42–44].

In clinical trials using antioxidants for treatment of chronic pancreatitis, most formulations also contained vitamin E. A study investigating the progression of fibrosis in a rat model of chronic pancreatitis could demonstrate that vitamin E reduces oxidative stress and collagen deposition [45]. Human clinical trials or epidemiologic studies on the effect of vitamin E in the development or progression of chronic pancreatitis are currently not available.

Many different fruits and vegetables including grape seeds are rich in phytochemicals with antioxidant properties. In in vitro studies as well as in one clinical trial, grape seed proanthocyanidin extract was found to improve chronic pancreatitis [46]. A confirmatory would still be needed before grape seed extracts could become a therapeutic option for chronic pancreatitis. A similarly low level of evidence exists for green tea and green tea extracts. Animal models show a protective effect of green tea polyphenols and aqueous extracts from green and black tea [47, 48], but no convincing clinical trial or epidemiologic data supporting this effect in humans are currently available.

Pancreatic Cancer

Pancreatic cancer is often diagnosed at an advanced stage and even when diagnosed early it has a worse prognosis than almost any other cancer. This is mainly because of the poor response of pancreatic ductal adenocarcinoma to chemotherapy and radiation. Pancreatic cancer prevention may therefore become a more promising strategy. As for many other cancer types, advanced age is a risk factor for pancreatic cancer and the disease is virtually unknown in children and young adults. Many risk factors have been proposed to be associated with pancreatic cancer, but only for very few does reliable evidence exist that they indeed contribute to an enhanced cancer risk.

Chronic Pancreatitis

Chronic pancreatitis is generally regarded as a risk factor for developing pancreatic cancer and estimates range from between 2 and 16% in case-control studies regarding the increase in pancreatic cancer risk in patients with chronic pancreatitis. Population-based studies generally indicate a much lower (<1%) risk of pancreatic cancer in chronic pancreatitis patients than case-control studies. The greatest risk for pancreatic cancer is found among patients with hereditary pancreatitis (40–70% lifetime risk) rather than sporadic pancreatitis, particularly when affected patients smoke [34]. While alcohol is a risk factor for chronic pancreatitis and chronic pancreatitis, it is in turn also a risk factor for pancreatic cancer which does not translate into a direct association between alcohol and pancreatic cancer [33, 49].

Overweight and Obesity

Being overweight in Western countries seems to be a risk factor for pancreatic cancer development [50–53], but no association between obesity and pancreatic cancer could be demonstrated in Japan [54]. New onset diabetes is a suggested risk factor of pancreatic cancer, or is at least associated with pancreatic cancer. However, it is not clear whether diabetes predisposes to pancreatic cancer or represents an early manifestation of pancreatic cancer [55].

Other evidence that glucose tolerance and insulin resistance might be a risk factor for pancreatic cancer comes from an Italian cohort study. In this study an increased use of table sugar was associated with an increased risk for pancreatic cancer. The authors suggest that this increased risk is mediated through insulin resistance [56]. Also the intake of more than two soft drinks (sweetened soda) per week is associated with a 2-fold increase in pancreatic cancer risk [57]. On the other hand, other studies have shown an inverse correlation between sugar consumption and pancreatic cancer [58]. It needs to be considered that the latter study did not discriminate between table sugar and sweet fresh fruit or other sources of sugar.

Thus the protective effect might be due to protective compounds in fruit other than fructose and does not need to be directly linked to the sugar consumption.

Three independent studies from 1998 to 2003 showed a small but significant increase in pancreatic cancer risk in *Helicobacter pylori*-positive individuals [59–61]. More recent studies from Sweden and the USA could not confirm this correlation [62, 63]. Thus a possible effect of *H. pylori* infection on the risk to develop pancreatic cancer is still unclear.

Tooth loss and periodontal diseases have been associated with a variety of cancers. For pancreatic cancer a 1.5- to 1.7-fold increased risk was seen in individuals with a history of periodontal disease or tooth loss of between 1 and 10 teeth [64–66]. The underlying mechanisms have not been investigated yet. The authors suggest that periodontal disease and tooth loss might be a marker for a susceptible immune system.

Environmental Toxins

Only few risk factors for pancreatic cancer have been well established. The one with the best evidence is tobacco smoke. Current smokers have a 2- to 3-fold increased risk of developing pancreatic cancer compared to nonsmokers [67, 68]. The risk of pancreatic cancer seems to increase according to the duration and the amount of smoking.

A study investigating two US cohorts with nearly 2 million participants could not find any correlation between coffee consumption or alcohol intake and pancreatic cancer [69]. Also a recent meta-analysis could not find a correlation between moderate alcohol drinking and pancreatic cancer [33].

Nutritional Risk Factors

Dietary factors have been discussed for years as risk or protective factors for pancreatic cancer. Several recent epidemiologic studies found a correlation between dietary habits and pancreatic cancer.

A case-control study from Italy reported a positive association between high animal protein intake and pancreatic cancer but a negative correlation for diets high in sugar (mainly from fruits) [58]. A similar Canadian case-control study showed a 49% risk reduction for males consuming high amounts of fruits and vegetables. However, no association was seen in this study between pancreatic cancer and alcohol or a Western diet (high in fat, processed meat, sweets and desserts) [70]. A multiethnic cohort study has investigated this dietary pattern more closely. They found a 50% increased risk for high intake of red meat, and a 70% increased risk for high consumption of processed meat, but no association for fat and saturated fat [71].

Mainly case-control studies reported a reduced cancer risk associated with diets high in fruits and vegetables. However, cohort studies could often not reproduce these findings.

In an Italian cohort study, frequent meat consumption doubled the risk for pancreatic cancer [56]. A cohort study from the Netherlands, on the other hand, could not show any correlation between the intake of fresh meat, other types of meat, fish, eggs, total fat intake or different types of fat and risk of pancreatic cancer [72]. Another European prospective cohort study including 520,000 individuals and 555 pancreatic cancer cases [73] also found no association between nutritional habits and pancreatic cancer. A cohort study investigated the effect of diets with high glycemic index, a high glycemic load or the total carbohydrate intake. Also in this study involving 482,362 participants and 1,151 pancreatic cancer cases, no convincing association between diet and pancreatic cancer was found. The authors postulated a possible association between pancreatic cancer and a high intake of free fructose [74]. A similar association was found by a group who identified a 2-fold increased risk of pancreatic cancer in persons consuming more than two soft drinks (sweetened soda) per week [57]. However, these data were, again, not confirmed by other groups, and a meta-analysis of four available studies showed no contribution of soft drinks to pancreatic cancer development [75]. Taken together, the available data do not allow to make definite dietary recommendations regarding a reduction in pancreatic cancer risk.

Protective Factors

Green tea polyphenols have been shown to inhibit tumor growth in animal models and in in vitro studies. Lin et al. [76] examined the relationship between green tea consumption and the risk of death from pancreatic cancer in humans and found no significant risk reduction in mortality with increasing intake of green tea.

These data were confirmed by another population-based cohort study from Japan which followed 101,137 subjects for 11 years and found no correlation between pancreatic cancer and green tea consumption [77]. Therefore the protective effect of green tea postulated in cell culture models could not be confirmed in epidemiologic human studies.

Citrus Fruits. In 1986 a case-control study suggested a reduced risk of pancreatic cancer for individuals with a

high intake of citrus fruits (daily consumption) [78]. Studies investigating compounds from Mexican lime recently showed that flavonoids and limoids extracted from lime can inhibit pancreatic cancer cell proliferation [79]. A systematic review published in 2009 summarized the available studies. The authors found an inverse association between intake of citrus fruits and the risk of pancreatic cancer, but there was a large variation across studies and only the case-control studies showed significant effects [80].

Phytochemicals. Since many claims were made that fruits and vegetables might protect against pancreatic cancer, studies were conducted to investigate some more well-defined phytocemicals. One candidate was lycopene, a carotenoid with high concentrations in tomatoes. A Canadian study found a significant (31%) decrease in pancreatic cancer risk for individuals with high intake of lycopene, and a lower but still significant risk reduction for β-carotene and total carotenoids [81] was reported. Flavonols have also been shown to have anticancer effects in pancreatic cancer models [82, 83], but the epidemiologic data have shown only a weak association. A US-based as well as a Finnish study found no significant association between flavonol intake and pancreatic cancer in an overall analysis, but both studies could show a significant risk reduction for the subpopulation of male smokers. In the Finnish study, individuals consuming supplemental α-tocopherol and/or β-carotene had been excluded [84–86].

Vitamins. Vitamins have often been claimed to decrease the risk for various cancers. A review of three large cohort studies from Harvard Medical School showed that higher vitamin D intake was associated with a lower pancreatic cancer risk in men and women [87]. In contrast to this, a second case-control study found no association between low vitamin D levels and pancreatic cancer, but a 2-fold increased risk in individuals with high 25-hydroxyvitamin D [88]. While investigating the effect of genetic variations in antioxidant genes, Tang et al. [89] found a significant reduction of pancreatic cancer risk for high vitamin E intake and an increased risk for low vitamin E intake in individuals with the superoxide dismutase-2 1221G>A AA genotype, indicating that defined genetic predispositions can interact with environmental factors in determining an individual's pancreatic cancer risk. Folate intake has also been claimed to reduce cancer risk. A Swedish cohort study found a tendency towards risk reduction for high folate intake from food sources but not for folic acid supplementation [90]. A second cohort study could not confirm a reduced risk for either total dietary folate or supplemental folic acid vitamers [91].

The existing data about a correlation between specific diets or their components and the risk of pancreatic cancer remains rather inconclusive and conflicting. Even if certain diets were to increase or decrease the risk of developing pancreatic cancer, their impact is marginal at best and well-founded recommendations cannot be made at this point. Advice beyond: don't be overweight, eat a well-balanced diet, drink alcohol only with moderation and do not smoke – ever – would be premature as far as either chronic pancreatitis or pancreatic cancer is concerned.

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