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Risk Factors in Pancreatic Cancer

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1. Introduction

Pancreatic cancer is one of the most lethal malignant diseases with the worst prognosis. It is ranked as the fourth leading cause of cancer-related deaths in the United States. An unknown but important proportion of cancers develop in people who carry mutation in a cancer-predisposing gene. Identification of cancer-predisposing genetic mutations in susceptible individuals affords the opportunity to practise preventive medicine. Pancreatic cancer is an aetiologically complex disease whose development is contingent on the independent and joint effects of genes and environment. (Greer &Whitcomb, 2007). Recent analysis of human pancreas genomes showed that 12 common signaling pathways involved in cellular repair mechanisms, metabolism, cell-cycle regulation, genomic repair, and metastasis are affected in over two thirds of the pancreatic cancer genome, including mainly point mutations(Jones et al., 2008).

Many risk factors have been associated with PC such as genetic factors and premalignant lesions, predisposing diseases and exogen factors. Genetic susceptibility, observed in 10% of cases includes inherited pancreatic cancer syndromes and familial cancers. However, the rest of 90% of pancreatic cancer recognise as risk factors a mix between genetic factors and environmental factors, too, but the exact etiopathogenesis remains unknown.

2. Hereditary pancreatic cancer syndromes

2.1 Hereditary breast ovarian cancer syndrome

Hereditary breast ovarian cancer syndrome is associated with germ line mutation in the BRCA 2 and BRCA 1 gene and it is associated with a 7% lifetime risk in pancreatic cancer at 70 years old. BRCA1 and 2 are tumour suppressor genes that are inherited in an autosomal dominant fashion with incomplete penetrance. They controls cell growth and differentiation and their loss drives tumorigenesis by involving in transcriptional regulation of gene expression and reairing of damaged DNA. The 6174delT mutation of BRCA2, occur ten times more frequently in Ashkenazi Jewish population and it is responsible for breast and ovarian familial cancer. BRCA2 mutations are found in as many as 12 to 17 percent of

patients with familial pancreatic cancer. Single nucleotide polymorphism of BRCA 1 and 2 does not influence the risk for pancreatic cancer in sporadic pancreatic adenocarcinoma (McWilliams et al., 2009). For BRCA1 carriers, this relative risk is estimated to be 2-fold higher (Thomson et al., 2002) and for BRCA2 carriers, this relative risk is approximately 3-to 4-fold higher (The Breast Cancer Linkage Consortium, 1999). Within 24/219 BRCA1 and 17/156 BRCA2 families (representing 11% of overall individuals included in the study) there was at least 1 individual with pancreatic cancer. The onset of cancer was earlier than in general population : 59 in males and 69 in females in BRCA1families and 67 in males and 59 in females in BRCA2 families (Kim et al., 2009). Compared to SEER data which showed a 0.96:1 male:female ratio occurence of pancreatic cancer in general population, in BRCA1 families, showed a 2:1 male: female ratio, possible linked to the competing mortality for breast and ovarian cancer in their female relatives (Kim et al., 2009). For these reasons, males under 65 years old in families with a strong history of breast, ovarian, and pancreatic cancer be considered for BRCA1/2 testing along with their female relatives. Cigarette smoking and exposure to oestrogen influences pancreatic cancer risk, but in a direction opposite to that of breast cancer risk in BRCA1/2 mutation carriers (Greer & Whitcomb, 2007).

2.2 The Peutz-Jeghers syndrome

The Peutz-Jeghers syndrome is an autosomally dominant hereditary disease with characteristic of hamartoma polyps of the gastrointestinal tract, and mucocutaneous melanin pigmentation. Almost half of these patients are carriers of a germinal serine-treonine kinase 11*STK11/LKB1* gene mutation (Giardiello et al., 2000). Wild-type *STK11/LKB1* activates adenine monophosphate–activated protein kinase, which is a regulator of cellular energy metabolism. Activation of adenine monophosphate–activated protein kinase leads to inhibition of the mammalian target of rapamycin 1 (mTOR1), a serine/threonine kinase with a key position in the regulation of cell growth. The risk of PC is 132 times higher than for the general population (lifetime risk for cancer is 11-36%).

2.3 Familial atypical multiple mole melanoma syndrome (FAMMM)

Familial atypical multiple mole melanoma syndrome (FAMMM) is an autosomal dominant syndrome caused by a germline mutation in CDKN2A (or p16) gene on chromosome 9p21 or in a minority of cases in the CDK4 gene on chromosome 12 (Goldstein et al., 2000; Wheelan et al., 1995). This syndrome is characterized by multiple nevi, multiple atypical nevi, and an increased risk of melanoma. The relative risk of developing pancreatic cancer is 20 to 47 and the lifetime risk for pancreatic cancer is 16%(Vasen et al., 2000, De Snoo et al., 2008). Among cases who reported having a first-degree relative with pancreatic cancer or melanoma, the carrier proportions were 3.3 and 5.3%, respectively. Penetrance for mutation carriers by age 80 was calculated to be 58% for pancreatic cancer and the risk of pancreatic cancer in smokers was 25 compared to non-carriers (McWilliams et al., 2011). The onset of pancreatis cancer in a historical cohort of 36 patients from 26 families with FAMM was 65 years old. In a follow-up study group of 77 carriers of p16 mutation, 7 individuals developed a pancreatic cancer within 4 years and only 5 had curative resection, confirming rapidly growing tumor that could originate from small PanIN lesions in p16 mutation carriers(Vasen et al., 2010).

2.4 Lynch syndrome

Lynch syndrome is an autosomal dominant condition caused by defects in mismatch repair genes (MLH1, MSH2, MSH6 or PMS2). It has recently been shown that in addition to colorectal and endometrial cancers these individuals have a 9-fold increased risk of developing pancreatic cancer compared with general population(Kastrinos et al., 2009).

2.5 Hereditary pancreatitis

Hereditary pancreatitis is a rare autosomal dominant disorder, in more than two-thirds of cases caused by a mutation in the SPINK1 and PRSS1 genes, with a high risk of pancreatic cancer. For this population, the cumulative risks of pancreatic cancer at the age of 50 and 75 years are 11% and 49% for men and 8% and 55% for women, respectively(Rebours et al., 2008). The risk was higher for smokers and for those with diabetes mellitus.

2.6 Ataxia-teleangiectasia

Ataxia-teleangiectasia with mutation of ATM gene on chromosome 17p is associated with pancreatic cancer , but the relative risk is unknown yet.

3. Familial pancreatic cancer

It may be considered in families with at least two first-degree relatives suffering from the disease, thus suggesting an autosomal dominant penetrance (Greenhalf et al., 2009). Families with only one relative with pancreatic cancer or with multiple pancreatic cancers in more distant relatives are considered as sporadic PC. The lifetime risk increases with the number of relatives involved. Individuals with two first-degree relatives with pancreatic cancer have a 6-fold increased risk of developing pancreatic cancer, and individuals with three or more first-degree relatives with pancreatic cancer have a 14 to 32-fold increased risk (Klein et al., 2004) . The risk of pancreatic cancer was similar in familial PC kindred compared to sporadic pancreatic cancer kindred members. Analysing more than 9000 subjects, the presence of a young-onset pancreatic cancer patient, under 50 years old did not influence the risk of having pancreatic cancer inside familial PC kindred, but it added risk compared to sporadic pancreatic cancer (Brune et al., 2010). Smoking is a strong risk factor in familial pancreatic cancer kindred, particularly in males and people younger than 50 years of age, as it increases the risk of pancreatic cancer by 2 to 3.7 times over the inherited predisposition and lowers the age of onset by 10 years (Rulyak et al., 2003).

The genetic basis is not known, the BRCA2, palladin gene and PALB2 could play some role (Murphy et al., 2002; Couch et al., 2007; Pogue-Geile et al.,2006; Jones et al.,2009). The *PALB2* gene codes for a protein that binds to the BRCA2 protein and helps to localize BRCA2. (Tischkowitz et al.,2009, Jones et al.,2009). Palladin is a cytoskeleton-associated scaffold protein, with role in the formation of a desmoplastic tumor microenvironment (Giocoechea et al., 2010), but recent studies denied its involvement in carcinogenesis (Klein et al.,2009, Slater et al.,2007)

There has been developed and validated a risk prediction model PancPRO based on age, pancreatic cancer status, age of onset, and relationship for all biological relatives (Wang et al., 2007).

Even genetic testing may be of benefit to many families, more than 80% of the clustering of pancreatic cancer in families remains unknown or the known mutation are not found. Mutations in the *BRCA2*gene account about 11% of families, *PALB2* 1–3% and the remaining genes account for <1% of familial pancreatic cancer. Genetic susceptibility for developing pancreatic cancer has been recently atributed to a single nucleotide polymorphism of gene located on 13q22.1 chromosome, considered as specific for pancreatic cancer, or of a gene located on 1p32.1 chromosome, which interact with betacatenin pathway(Petersen et al., 2010).

3.1 Genetic predisposition: ABO blood group

Compared with blood group O, individuals with non-O blood group (type A, AB, or B) were significantly more likely to develop pancreatic cancer (adjusted hazard ratio for incident pancreatic cancer 1.32, 1.51. and 1.72, respectively)(Wolpin et al., 2009, Risch et al., 2010), probably based on genetic variants in ABO locus 9q34 (Amundadottir et al, 2009). Another extended study identified susceptibility loci on 3 chromosomes- 13q22.1, 1q32.1 and 5q15.33, the most specific being considered 13q22.1(Petersen et al., 2010). The incidence rates for pancreatic cancer (cases per 100,000 persons at risk) among White participants with blood types O, A, AB, and B were 28.9, 39.9, 41.8, and 44.5, respectively. In combination with smoking, overweight or diabetes, the non-O blood type was associated with ORs of 2.68, 1.66, and 2.29, respectively, compared to subjects who had O blood type and lacked the exposure(Wolpin et al., 2010). The mechanism of influence of blood group antigens on risk for pancreatic cancer might be the alteration of the systemic inflammatory state (Wolpin et al., 2010).

4. Premalignant lesions

There are three known precursor lesions to pancreatic cancer: intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasia (MCN) and pancreatic intra-epithelial neoplasia (PanIN). PanIN is by far the most common lesion and three grades of PanIN have been described as cellular atypia progresses from low grade dysplasia (PanIN 1) to high grade dysplasia (PanIN3), similar to colorectal cancer carcinogenesis. The 5-year-risk of PC is about 50% for MCN, 50% for main ductal IPMN while only 15% for branch IPMN.

5. Predisposing diseases

5.1 Chronic pancreatitis

The risk of developing pancreatic cancer is about 5%(Raimondi et al., 2010), probably due to PanIN lesions or chronic inflammation. In a large multicentric study, the total risk reached 1.8 percent at 10 years and 4 percent at 20 years, independently of the type of pancreatitis(Lowenfels et al., 1993; Howes et al., 2004). There is no need for systematic screening in patients with chronic pancreatitis, but acute onset of pain after long free-pain interval, a non-equilibrated diabetes without explanation, the onset of jaundice or weight loss require looking for pancreatic cancer. The risk is higher for non-alcoholic pancreatitis, as hereditary pancreatitis linked to PRSS1 mutations (40% at 70 years old) or tropical pancreatitis, form of hereditary pancreatitis linked to SPINK1 mutation (a 100 times higher risk than for the general population)(Lowenfels et al., 1993).

5.2 Diabetes mellitus

Diabetes is associated with pancreatic cancer in about 40 to 60% of patients at the onset of symptoms, being a consequence or the cause of the disease. A meta-analysis of 20 studies (predominantly of patients with type 2 diabetes) estimated that the pooled relative risk for pancreatic compared to patients without diabetes was 2.1, especially among patients with long-standing diabetes(Everhart&Wright, 1995; Huxley et al., 2005).Diabetes associated with pancreatic cancer is often new-onset (<2-year duration), it resolves following cancer resection and appears to be associated with conventional risk factors for diabetes such as age, obesity and familial history (Pannala et al., 2008; Gupta et al., 2006). Even in the absence of frank diabetes mellitus, abnormal glucose metabolism and insulin resistance have been associated with pancreatic cancer(Stolzenberg-Solomon et al., 2005; Gapstur et al.,2000), and the insulin-growth factor(IGF) involvement might be the pathway in the pathogenesis. Although not all studies found an association between the risk of pancreatic cancer and the level of IGF, it seems that the polymorphism of IGF is associated with lower susceptibility to pancreatic cancer(Lin et al., 2004; Wolpin et al., 2007; Suzuki et al., 2008).The risk is higher in insulin ever users compared with nonusers (OR = 2.2, 95% CI = 1.6-3.7) and was restricted to insulin use of ≤3 years (OR = 2.4), but decreases after ten years of insulin use(Li et al., 2011). The explanation might be that the two diseases could share genetic risk factors in common. The CT screening is recommended for older patients with new-onset diabetes, especially those with family history or symptoms, as shown in a recent description of French families.

5.3 Postgastrectomy or postcolecystectomy status

Postgastrectomy or postcolecystectomy status were associated with an increased risk of pancreatic cancer, probably due to high level of circulating colecystokinin(Smith et al., 1990).

5.4 Helicobacter pylori and hepatitis B

Helicobacter pylori and hepatitis B have been found as associated factors to pancreatic cancer. The pathway may be represented by the polymorphism of genes involved in the inflammatory response, but further studies are needed for confirmation.

6. Environmental factors

6.1 Smoking

The risk for pancreatic cancer is 1.5-2.5, higher with the numbers of cigarettes and in glutathione-S-transferase deficient persons and decreases 10 years after the smoking cessation. (Iodice et al, 2008). It increases the risk in hereditary chronic pancreatitis. Mutations in carcinogen-metabolizing genes, such as glutathione-S-transferase, N-acetyl-transferase, cytochrome P450 and DNA-repair genes in oxidative metabolism(XRCC1, OGG1) with multiple sequence variants may be genetic modifiers for smoking-related pancreatic cancer (Duell et al., 2002; Li et al., 2006). In a recent case-control publication, the risk more than 15 years after smoking cessation was similar to that for never smokers. Also, there was a more significant risk for total exposure delivered at lower intensity for longer duration than for higher intensityfor shorter duration. These findings and the decline in risk after smoking cessation suggested that smoking has a latestage role in carcinogenesis. (Lynch et al., 2009). There is a synergistic interaction with diabetes mellitus and family

history of pancreatic cancer (Hassan et al.,2007). Smoking can be reponsible for familial agregation of pancreatic cancer individuals with lung and larynx cancer (Hiripi et al., 2009).

6.2 Obesity

A body mass index of at least 30 kg/m2 was associated with a significantly increased risk of pancreatic cancer compared with a BMI of less than 23 kg/m2 (relative risk 1.72), but an inverse relationship was observed for moderate physical activity when comparing the highest versus the lowest categories (relative risk 0.45) (Michaud et al., 2001). Centralized fat distribution may increase pancreatic cancer risk,especially in women, (Arslan et al., 2010).

There have recently been discovered genetic factors which can reduce the risk of PC (PPARγ P12A GG genotype, NR5A2 variants) or which can enhance th risk in overweight patients (FTO, ADIPOQ) (Tang et al., 2011). Others have suggested that overweight and obese individuals develop pancreatic cancer at a younger age than do patients with a normal weight, and that they also have lower rates and duration of survival once pancreatic cancer is diagnosed (Li et al., 2009). Obesity in early adulthood was a risk factor for pancreatic cancer (Genkinger et al., 2010).

6.3 The diet

The diet based on fat and meat has been linked to the development of pancreatic cancer in many (Nothlings et al., 2005; Thiebaut et al., 2009), but not all studies (Michaud et al,2003, 2005). The consumption of fresh fruits and vegetables were not associated with pancreatic cancer risk (Coughlin et al.,2000). Lower serum levels of lycopene and selenium have been found in subjects who subsequently developed pancreatic cancer (Burney et al.,1989). Although the majority of prospective cohort studies found no significant increase in the risk of pancreatic cancer with moderate to high levels of alcohol intake in a general population., a recent study has shown that a certain polymorphism of genes involved in the production and/or oxidation of acetaldehyde is associated with an increasing risk in developping pancreatic cancer (Michaud, 2004;Kanda et al., 2008). Folate deficiency, involved in DNA mutations and DNA methylation, may increase the risk of cancer. Although at least two variants of genes involved in folate metabolism were found to be associated to pancreatic cancer and smoking, these findings were not confirmed in all studies. Because the sample size was considered to be insufficient and the criteria for control selection of patients were different,these evidence were considered inadequately powered for drawing a conclusion. (Wang et al., 2005; Matsubayashi et al., 2005; Suzuki et al., 2008; Ohnami et al., 2008). No epidemiologic study has provided evidence to support the hypothesis that high glycemic index or glycemic load increases the risk of pancreatic cancer (Jiao L et al., 2009).

Also, the role of TGF-beta pathway, proved to be linked to pancreatic cancer, and its genetic variants, but it still remains unclear.

6.4 Exposure to sunlight

Exposure to sunlight with increase of *vitamin D* synthesis might decrease the cancer risk and polymorphic variants in genes encoding the for synthesis enzyme is an important task for future research, as the role of melatonin receptor and genetic variants in clock genes. Based on different sun exposure in different geographic latitude, several studies sustained the

protective role of vitamin D against pancreatic cancer, in association with other factors as age and obesity (Grant, 2002, Guyton et al., 2003). The quantification of Vitamin D concentration must consider also the race (Afro-Americans has a higher risk for PC), the season of blood drawn and presence of supplemental in diet (Stolzenberg-Solomon, 2009).

6.5 Alcohol consumption

A recent study showed a moderate risk to heavy alcohol drinkers (about 40 g alcohol daily) and liquor users (relative risk 1.45-1.62) , probably due to their nitrosamine content (Jiao et al., 2009), sustained by other studies only in men (Hassan et al., 2007).

6.6 Demographic factors

Advanced age, between 60 and 80 is associated with 80% of pancreatic cancers. Other demographic factors that are associated with a modest (about 2-fold) increased risk include male gender, Jewish descent and black ethnicity(Lillemoe et al., 2000).

Gene function	Gene symbol	Gene full name	Gene location	Concentration tumor vs normal
Transcription	ZNF	zinc finger protein	19q13.31	3.38
	MIXL1	Mix1 homeobox-like 1	1q42.12	6.24
	SEPT1	Septin 1	16p11.1	3.42
Intracellular signaling	FLJ 42953	breakpoint cluster region pseudogene 2	22q11.21	3.02
	AGRP	agouti related protein homolog	16q22	6.51
Intracellular transport	CCDC 88	coiled-coil domain containing 88B	11q12.3	4.61
	UTP14 A	U3 small nucleolar ribonucleoprotein	Xq26.1	3.44
	VPS11	vacuolar protein sorting 11 homolog	17p11.2	3.33
	LLRC 21	leucine-rich repeat, immunoglobulin-like and transmembrane domains	10q23	3.33
	CHRM3	cholinergic receptor, muscarinic 3	1q43	3.01

Table 1. Genes with significant different expression (overexpressed or underexpressed) in pancreatic cancer compared to normal pancreatic tissue.

Our research on 16 tissue samples of T3 pancreatic cancer comparing to normal tissue in the same patients analysed by microarray showed that there were 41 overexpressed genes and 402 underexpressed genes. From those with tumor concentration three times modified compared to normal tissue we noticed genes involved in transcription, intracellular signaling and intracellular transport (Table I), which need further validation on larger sample groups (data unpublished). This showed that genomic tissue microarray analysis represents a powerful strategy for identification of potential biomarkers in pancreatic cancer.

7. Conclusions

Pancreatic cancer is a pathological status with clear inheritance in only 10% of cases, the others seems to be linked to premalignant situations, other diseases or environmental factors in which genetic implications need further investigations. The gene-gene and gene-environment interactions have to be more extensively studied, especially because there are not only single-nuclear polymorphisms, but also DNA copy number variations and variable-number tandem repeats which can be linked to the risk of pancreatic cancer.

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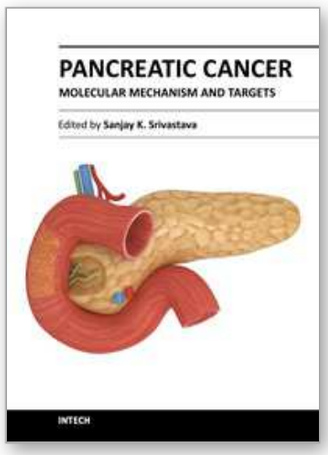

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This book provides the reader with an overall understanding of the biology of pancreatic cancer, hereditary, complex signaling pathways and alternative therapies. The book explains nutrigenomics and epigenetics mechanisms such as DNA methylation, which may explain the etiology or progression of pancreatic cancer. Book also summarizes the molecular control of oncogenic pathways such as K-Ras and KLF4. Since pancreatic cancer metastasizes to vital organs resulting in poor prognosis, special emphasis is given to the mechanism of tumor cell invasion and metastasis. Role of nitric oxide and Syk kinase in tumor metastasis is discussed in detail. Prevention strategies for pancreatic cancer are also described. The molecular mechanisms of the anti-cancer effects of curcumin, benzyl isothiocyante and vitamin D are discussed in detail. Furthermore, this book covers the basic mechanisms of resistance of pancreatic cancer to chemotherapy drugs such as gemcitabine and 5-flourouracil.

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