

Assessment of risk factors in the development of pancreatic cancer in Latvia

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Abstract

The aim of the study was to assess the possibility of identifying individuals at risk of pancreatic cancer (PC) on the basis of information from questionnaires filled in by patients and analyses of the DNA from peripheral blood of PC patients for mutations in *BRCA1*, *CDKN2A*, *INK4/ARF* and *STK11* genes. Questionnaires showed unknown risk factors in ethiology and pathogenesis of PC besides smoking and other known risk factors. Two carriers of frameshift mutations in the *BRCA1* gene of 68 PC patients tested were detected. Screening for two founder mutations in the *BRCA1* gene should be carried out in PC patients to identify at least a part of cancer-prone families in order to offer to mutation carriers comprehensive care, surveillance and preventive procedures. No deleterious mutations were detected in *CDKN2A*, *INK4/ARF* and *STK11* genes. We conclude that mutations in these genes do not contribute significantly to PC incidence in the population of Latvia. The role of missense mutations detected can not be estimated unambiguously on the basis of our data.

Key words: genes, mutations, pancreatic cancer, risk factors.

Introduction

Pancreatic cancer (PC) is one of the most aggressive and therapeutically resistant cancers of the gastrointestinal tract and is the fifth leading cause of cancer related death in both men and women. The annual mortality rate is almost equal the annual incidence rate, and the survival rate of PC patients is usually less than one year (mortality/incidence ratio is 98 %). Very few of the patients diagnosed with PC have been found to be operable at the time of diagnosis and even in these patients the postoperative five-year survival rate has remained low (< 5 %) because of a very high rate of recurrence (Jemal et al. 2002; Parkin et al. 2005). PC has been resistant to all conventional and modern therapies available, although some promising results were shown in the ESPAC-1 (European Study of Pancreatic Cancer) trial (Neoptolemos et al. 2004).

Increased mortality from PC has been recorded during the last years in Latvia. In total 375 new cases (16 per 100 000 persons) were diagnosed in 2004, but only 18 patients underwent radical operations. In 2002 and 2003 the incidence of PC was 14 cases per

100 000 persons, which is considerably higher than the overall incidence in Europe and USA. Overdiagnosis, especially in rural hospitals in Latvia, can not be excluded as one of the reasons for the higher incidence of PC found in our population.

Pancreatic adenocarcinoma represents about 90 % of all pancreatic tumours. The incidence of PC is increasing in developed Western countries and incidence and mortality rates are between seven to nine cases per 100 000 in males and five to six cases per 100 000 in females (Parkin et al. 2005). Mortality rates are lower in developing countries, which is rather due to diagnostic capacities than ethiology. Accordingly, the main problem remains early stage diagnosis and the availability of efficient screening procedures.

Much success have been achieved during the past years in understanding the mechanisms of the pancreatic carcinogenesis. Various habitual and environmental exposure factors have been reported to be associated with increased risk of PC, such as smoking, high fat diet and familial background of cancer (Ahlged 1996; Stolzenberg-Solomon et al. 2002; Michaud et al 2003). However, the most important risk factor of cancer is genetic predisposition associated with structural alterations in cancer-associated genes (Lal et al. 2000; Efthimiou et al. 2001; Tersmette et al. 2001).

The genetic basis for neoplasms of pancreas has been the subject of a number of investigations in recent years. While no specific gene(s) associated with PC development have been detected up to now, approximately 5 to 10 % of the PC cluster in families and can be considered as hereditary. Several hereditary cancer syndromes, such as breast/ovarian cancer syndrome, hereditary non-polyposis colorectal cancer, familial atypical mole-melanoma syndrome, ataxia telangiectasia, and Li-Fraumeni or Peutz-Jegher's syndrome, may be associated with significantly increased risk of developing pancreatic cancer (Lal et al. 2000; Efthimiou et al. 2001; Vimalachandran et al. 2004). Early age at onset of disease and multiple primary tumours in cancer patients may indicate genetic predisposition, even if there are no cancer cases known in the family (too small families or no information available in some cases). There are genes such as *BRCA1*, *BRCA2* or DNA mismatch repair genes highly penetrant and strongly associated with disease in mutation carriers. A number of other genes may each make a subtle contribution to a person's susceptibility to a disease. Genes may also affect how a person reacts to environmental factors. Therefore, the characterization of genetic alterations in cancer-associated genes of PC patients may help to understand better the pathogenesis of PC, as well as to contribute to identification of risk individuals and earlier diagnosis of cancer (de Vos tot Nederveen Cappel et al.2003).

To introduce this approach in clinical practice it is necessary to characterise genetic alterations prevalent in the population. In breast and ovarian cancer patients in Latvia, a high prevalence of a limited number of the *BRCA1* gene mutations was detected indicating a strong founder effect in this population (Csokay et al. 1999; Tikhomirova et al. 2005). This allows targeted testing of cancer patients and improvement of testing yields not only in cases of breast and ovarian cancer but even more in cases of different associated cancers, including pancreatic cancer. Targeted testing in mutation carrier families allows to identify persons at elevated risk of cancer and to apply available preventive procedures.

This population-based study was designed to assess the possibilities for identification of individuals at risk of pancreatic cancer using information available from questionnaires and the results of genetic analyses of the DNA from peripheral blood of PC patients.

Materials and methods

Patients with pancreatic adenocarcinoma were recruited in the Department of Gastroenterology of P. Stradiņš Clinical University hospital in the period between 2002 and 2005. Diagnosis was established using at least two of the following methods: ultrasound, computer tomography, magnetic resonance imaging, endoscopic ultrasound, positive cytology, histology, intraoperative finding and other additional diagnostic tools (oncomarkers CA 19-9, CEA, upper gastrointestinal endoscopy, etc.).

A specially designed questionnaire was created for this study, to provide information concerning family cancer history (in first and second degree relatives), history of allergic diseases and asthma, smoking habits, age, education etc. Patients, who were mentally fit to answer the questionnaire were included in the study.

Peripheral blood samples (5 ml) were collected in vacutainers from patients who agreed to participate in the study. Samples were kept in refrigerator until the isolation of DNA, but not more than week. DNA was isolated from 88 blood samples and 68 DNA samples were used further for genetic analyses.

Analysis of questionnaires was carried out to test the role of heredity in PC, the possible association of PC to other cancers in the family history, to investigate if asthma and other allergic diseases are the risk factors for PC and to assess the role of smoking habits as risk factor of PC in the population of Latvia.

Genetic analyses of DNA samples isolated from peripheral blood of PC patients included the screening of the *BRCA1* gene for prevalent mutations, determination of the entire coding sequence and adjacent intronic sequences of the *CDKN2A* gene encoding p16, determination of the alternative exon1 of *CDKN2A* gene encoding p14^{ARF}, and screening for mutations in the exon 3 of *STK11* gene.

Genomic DNA was isolated by conventional phenol/chloroform extraction procedure.

DNA analysis was carried out for the most prevalent *BRCA1* gene mutations (5382insC, 4154delA) and for 300T>G and 185delAG, found less frequently.

Oligonucleotide primer sequences have been described for *BRCA1* (Tikhomirova et al. 2005) and for exons 1 and 2 of the *CDKN2A* (Soto-Martinez et al. 2005 and Hussussian et al. 1994, respectively).

The forward primer for exon 3 of the *CDKN2A* was 5'-GATGTGCCACACATCTT-TGAC-3', reverse primer – 5'-TGTGGACCTTCGGTGACTG-3'. Primers for the *INK4/ARF* locus were obtained from Soufir et al. (2000).

The forward primer used for exon 3 of *STK11* was 5'-GGCCATCATCCTGACGTTG-3', the reverse primer was 5'-GCCAGTCTCCTTCAAGGAG-3'.

Fragments were amplified using a MJ Research PTC100 Programmable Thermal Controller and SSCP/HDA (single strand conformation polymorphism and heteroduplex analysis) was carried out as described earlier (Tikhomirova et al. 2005).

Variants detected were identified by direct DNA sequencing (ABI PRISM 3100).

The *BRCA1* gene was screened in 68 pancreatic cancer patients. The same DNA samples were analysed for mutations in the entire *CDKN2A* gene. DNA samples from 20 patients diagnosed before 56 years or with positive family cancer history were analysed for p14^{ARF} and 39 patients diagnosed before 65 years or with positive family cancer history were analysed for exon 3 of *STK11* gene.

An agreement to participate in the study including genetic analysis of cancer predisposing genes was obtained from all pancreatic cancer patients, and a written consent was received for the interview and blood specimen analysis. The required research permission was obtained from the Ethics Committee of Latvian Institute of Cardiology.

Results and discussion

Analysis of questionnaires

Individuals with pancreatic adenocarcinoma from Pauls Stradiņš Clinical University Hospital (138 patients) were included in this study from November 2002 until May 2005. Blood samples for further genetic analyses were collected from 60 women and 78 men: 90 (65 %) were city inhabitants, 48 (35 %) patients were from rural areas. Characteristics of patients are presented in the Table 1.

A positive family history of PC was reported only by three patients (one first degree relative in each case). A positive family history of other cancers was reported by 36 of 138 patients, slightly more cases were reported by women, probably because they are usually best informed about diseases of relatives. More than two family members with cancer were noted by 12 (33 %) of 138 patients. The overall proportion of patients with a significant cancer history in family was not high in our patient group, and it represents mainly consecutive patients from our hospital. In total 50 cases cancers other than PC were detected in family histories. Gastric cancer was found more often than all other cancers – in 12 cases, followed by gynaecologic cancers (seven cases), lung cancer (five cases), breast, kidney, urinary bladder (each one of three cases), melanoma and carcinoma of esophagus (each in two cases). Colon cancer, hepatocarcinoma, sarcoma, leukaemia, larynx and brain cancer were found in single cases. Overall cancer localisations reported in family members coincided with data found in the literature. More than one cancer location was reported by three patients: one women had breast cancer (radical mastectomy was performed), another woman had gastric cancer (radical gastrectomy was performed) and a third patient (man) had urinary bladder cancer and palliative therapy due to metastasis in liver (possibly from pancreatic cancer) was performed.

It is impossible to estimate the contribution of hereditary factors in PC reliably taking into account only the information provided by patient. One problem was that large families are not typical in the population of Latvia, and in small families it is less likely to find a family history of cancer. In addition, because of the specific historical situation in Latvia in the past century, information about cancer cases in relatives may be lost or

Table 1. Characteristics of pancreatic cancer (PC) patients included in the study

Characteristics of PC patients	PC patients included in the study		
	Total 138 (100 %)	Female 60 (43 %)	Male 78 (57 %)
Mean age (years)	65.7	68.0 (42 ÷ 87)	63.5 (37 ÷ 83)
Pancreatic cancer in family	3 (2.1 %)	2 (1.4 %)	1 (0.7 %)
Other cancers in family	36 (26.0 %)	20 (33.3 %)	16 (20.5 %)
Allergic diseases	22 (16.0 %)	15 (25.0 %)	7 (8.9 %)
Smoking	69 (50.0 %)	6 (10.0 %)	63 (80.0 %)

not available in many families. On the whole, the patients we included in our study had unremarkable family histories of cancer. It should be noted that we cannot confirm the family history data given by patients, and this information may not be reliable in some cases. Characterisation of genetic alterations in the genomic DNA of patients may help to estimate the role of heredity in the incidence of PC in Latvia.

Smoking is a well-known risk factor for lung cancer and was shown to be an important risk factor for PC as well (Ahlgedred 1996; Stolzenberg-Solomon et al. 2002). Our study confirms that 69 (50 %) of PC patients were smokers. Analysis of smoking as a risk factor for PC showed that 80 % (63 cases) of men with PC and 10 % (six cases) of women were smokers. Closer analysis of smoking duration showed that 63 % (mostly men) were heavy smokers, it means that they had smoked more than 20 pack years. A small percentage of smoking women has PC, but an almost equal sex incidence of PC indicates that there are many other known and unknown factors in the ethiology and pathogenesis of PC.

Age is one of the significant risk factors of PC. About 75 % of PC develop after 65 years of age and it is quite unusual in persons younger than 50 years, if there are no predisposing conditions such as familial genetic predisposition to cancer, hereditary pancreatitis or specific genetic abnormalities present (Löhr et al. 1999; Lowenfel et al. 1993). Overall in our study, 100 (72 %) of patients were older than 60 years, however we had a quite large subgroup of patients – 38 (28 %, 29 men and 9 women) who were younger than 61 years. Additional risk factors, such as significant cancer history in the family or hereditary pancreatitis were not found in these patients (positive, but not significant family cancer history was detected only in 28 % cases), except in two patients who had another cancer localization (breast cancer or urinary bladder cancer).

Regarding allergic diseases, the literature suggests that allergy is associated with reduced risk of PC, especially allergies related to atopy (Gandini et al. 2005). The analysis of questionnaires showed that 14 % of patients in our study had a history of allergic diseases (22 % of females and 9 % of males). Four patients had asthma, others had different types of allergies (atopic, food or drug allergy). We can conclude that a large population based on case-control studies can establish a relation between PC and allergic diseases.

BRCA1 gene mutations

Out of 68 pancreatic cancer patients tested only one woman reported a breast cancer in her family. Hence, according to common criteria, it did not seem that patients with breast/ovarian cancer syndrom in their families could be detected among patients included in this study. However, a strong founder effect detected earlier in the population of Latvia suggested that the same prevalent mutations in the *BRCA1* gene strongly associated with susceptibility to breast and ovarian cancer may have a considerable effect in the ethiology of other tumours. This indicates that targeted screening in mutation carrier families might facilitate the identification of risk individuals predisposed not only to breast or ovarian cancer, but to other oncological diseases as well. Well-timed preventive and diagnostic procedures may be especially useful in these individuals.

SSCP analysis was carried out for exon 5 and the 3'-end of exon 11, and heteroduplex analysis was carried out for exons 2 and 20. Positive controls were included in each experiment. No mutations were detected in exons 2 and 5, however one carrier of a deleterious mutation in exon 20 (5382insC) and one mutation in exon 11 (4154delA) was detected.

A patient carrying the mutation 5382insC was diagnosed at 55 years of age and he did not report cancer cases in his family members. The other mutation (4154delA) carrier was diagnosed at 70 and no cancer cases in the family were reported. This corresponds to our previous data (Tihomirova et al. 2005) as well as to data from International Hereditary Cancer Center, Pomeranian Medical University (Poland) concerning a less pronounced pathogenic effect of the frameshift mutation 4154delA as compared to the 5382insC mutation (Gorski et al. 2005), associated with earlier age at diagnosis. The absence of cancer history in family indicated in questionnaires may be associated with a limited number of family members or absence of information in proband.

No other genetic variants were detected in DNA fragments of the *BRCA1* gene analysed.

Two *BRCA1* mutation carriers among 68 PC patients tested amounted to 3 %, which is a rather high frequency of deleterious mutation prevalence. It was suggested that *BRCA2* gene mutations may be associated with risk of PC in some populations (Lal et al. 2000), however, the association of *BRCA1* gene mutations with PC has been established as well (Lynch et al. 2005). The analysis of family histories of breast and ovarian cancer patients showed that PC is a rather frequent associated cancer localization in breast/ovarian cancer syndrome (Thompson, Easton 2002) and the management of *BRCA1* gene mutation carriers should include comprehensive care, surveillance and preventive procedures.

CDKN2A gene mutations

It has been shown that mutations in the *CDKN2A* gene predispose individuals carrying these mutations to hereditary melanoma and mutations in *CDKN2A* can be detected very frequently in pancreatic tumours (Schneider, Schmid 2003). We assessed the role of mutations in this gene in inherited predisposition to PC by characterization of the prevalence of mutations in the *CDKN2A* gene in the genomic DNA of 68 patients diagnosed with PC. *CDKN2A* gene mutations are known as an important risk factor in the development of familial atypical mole melanoma (Hall, Peters 1996). Only two patients included in this genetic testing had melanoma in their families (each reported one first degree relative with melanoma).

The entire coding sequence of the *CDKN2A* gene and adjacent intronic sequences were analysed by SSCP/HDA, followed by direct sequencing of the variants detected. Results of the analyses are presented in Table 2.

No genetic alterations were detected in exon 1. Missense mutation A148T in exon 2 (alanine to threonine in codon 148) was detected only in two patients. It was suggested recently that this genetic variant may be associated with slightly increased risk of breast cancer (Debniak et al. 2005a). Our results do not suggest an increased risk of pancreatic cancer associated with this mutation. Low prevalence of this common variant do not indicate that it is an important factor affecting susceptibility to pancreatic cancer in the population of Latvia. More data will help to evaluate the role of this missense mutation. At present, it may be considered as one of the possible genetic factors which may modify the risk of cancer in the association with another genetic variants or epigenetic mechanisms and might therefore affect cancer susceptibility to some degree. Significantly increased frequency of the A148T variant among patients with melanoma (7 %) in comparison with the general population (3 %) was observed in Poland (Debniak et al. 2005b). However, the role of the A148T missense mutation in exon 2 of *CDKN2A* gene should be assessed

Table 2. Genetic variants detected in the genomic DNA of 68 pancreatic cancer (PC) patients. M, mother; F, father; B, brother; S, sister; gM, grandmother; ca, cancer

Patients Nr	Age	Cancer in family history	CDKN2A (68 patients)	STK11 (39 patients)	BRCA1 (68 patients)
1	66	unknown cancer in 2 nd degree relative (gM)		IVS3 +12 G>T	
3	71	-	500 C>G		
6	64	melanoma (B)	500 C>G		
9	55	-			5382insC
10	56	-		IVS3 +12 G>T	
14	67	-	500 C>G		
17	43	-	500 C>G		
20	68	-	500 C>G		
23	69	-	500 C>G		
31	45	two gastric ca (M, B)	500 C>G		
32	63	gastric ca (F), cervical ca (M)	500 C>G		
34	37	-	500 C>G and A148T	IVS3 +12 G>T	
35	80	lung (S), two gastric ca (M, F)		IVS3 +12 G>T	
39	51	-	500 C>G	IVS3 +12 G>T	
41	70	-			4154delA
43	50	-	500 C>G	IVS3 +12 G>T	
45	67	breast ca (S)	500 C>G	IVS3 +12 G>T	
47	62	-		IVS3 +12 G>T	
53	71	-	500 C>G		
58	76	larynx ca (B), unknown ca (S)		IVS3 +12 G>T	
63	65	bronchial ca (M)	500 C>G	IVS3 +12 G>T	
64	76	-	500 C>G		
67	69	esophag ca (M), leukosis (S)	500 C>G		
69	57	gynaecological ca (M)	500 C>G and A148T		

more carefully taking into account very early onset of disease (37 years) in one of patients and not late (57 years) diagnosis in another patient, both having in addition a 500C>G variant in the noncoding region of exon 3 and gynaecological cancer in the mother in one of them.

A frequent missense mutation 500C>G in 3'-non-coding region (29 nucleotides behind the stop codon) of the exon 3 of the *CDKN2A* gene was detected in 17 patients, in some patients it was found in the homozygotic state G/G, indicating that it is a rather frequent alteration in the population. The prevalence of the 500C>G variant was characterised in the Polish population. It was not found overrepresented in Polish cancer patients compared to control subjects (Debniak et al. 2005b) and therefore was considered as a nonsignificant risk factor.

The alternative exon 1 of CDKN2A gene encoding p14^{ARF}

DNA samples from 20 patients with pancreatic cancer diagnosed before the age of 56 years or reporting cancer history in their families were tested for genetic alterations in p14^{ARF}. No genetic alterations were detected in the DNA samples analysed.

Exon 3 of the STK11 gene

Pathogenic mutations in the serine/threonine kinase *STK11* (alias *LKB1*) causes Peutz-Jeghers syndrome (PJS) in most affected individuals. PJS is an autosomal dominantly inherited disease characterized by hamartomatous gastrointestinal polyps and mucocutaneous pigmentation, with an increased risk for various neoplasms, including gastrointestinal cancer. Recently, the PJS gene encoding serine/threonine kinase *STK11* was mapped to chromosome 19p13.3, and germline mutations were identified in PJS patients (Lim et al. 2004).

It was suggested previously (Lim et al. 2004) that genetic alterations in exon 3 of *STK11* gene may be associated with increased risk of pancreatic cancer. However, the data from different populations are controversial (Grutzmann et al. 2004). To characterise genetic alterations in the genome of pancreatic cancer patients in Latvia, along with other genes we analysed exon 3 of *STK11* gene. DNA samples from 39 patients with pancreatic cancer diagnosed before the age of 65 years or reporting cancer history in their families were tested.

No mutations in coding sequence were detected, however a frequently represented missense mutation in adjacent intron 3 (+12G>T) was detected in 10 of 38 DNA samples analysed, several of them in homozygotic state +12T/T, indicating that this variant probably may be prevalent in the population as well.

It should be noted that one patient (Nr 34) diagnosed at 37 years of age carried A148T missense mutation in exon 2 of the *CDKN2A* gene with possible pathogenic effect, along with two variants of unknown significance, namely, 500C>G in the noncoding region of exon 3 and +12G>T variant in intron 3 of the *STK11* gene. Its possible role in correct splicing can not be excluded, regardless of the high frequency of this alteration. We can suggest that two other genetic variants detected may enhance the pathogenic effect of the A148T mutation in this patient.

We can conclude that the role of genetic factors in PC incidence can not be assessed only on the basis of questionnaires concerning family history of cancer because of the small size of typical families in Latvia and the absence of information in many cases. Questions about family size and availability of information should be included in all cases as well as age at diagnosis of cancer in first degree relatives.

Taking into account the high prevalence of founder mutations in the *BRCA1* gene in the population of Latvia, screening for the two mutations would be useful for identification of at least a part of cancer-prone families.

No known or new deleterious mutations were detected in *CDKN2A*, *ARF* or *STK11* genes. The role of missense mutations detected can not be assessed in an unambiguous manner and more data must be accumulated concerning prevalence of these variants in the population of Latvia and association with cancer cases. These genes do not contribute significantly to incidence of PC in our population. Nevertheless it should be noted that PC patients included in this study had no significant cancer histories in their families, therefore we hardly could expect to find a deleterious mutations in these genes. However,

the significance of missense variants detected needs to be studied more carefully, by segregation studies in families and probably by the characterization of the prevalence in control samples.

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Riska faktori vēža slimniekiem

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Kopsavilkums

Mūsu pētījuma mērķis bija novērtēt riska personu identificēšanas iespējas, balstoties uz informāciju, kuru snieguši aizkuņģa dziedzera vēža slimnieki, aizpildot anketas, un gēnu (*BRCA1*, *GDKN2A*, *INK4/ARF* un *STK11*) analīzēm, izmantojot slimnieku perifērās asins DNS. Slimnieku aizpildīto anketu analīze norāda, ka, neskaitot smēķēšanu un citus zināmos riska faktorus, slimības etioloģija ir saistīta ar citiem, nezināmiem riska faktoriem. Analizējot 68 aizkuņģa dziedzera vēža slimnieku DNS, noteikti divi *BRCA1* gēna patogēnu mutāciju nesēji – tas nozīmē, ka veicot skrīningu tikai pēc divām visbiežāk izplatītajām *BRCA1* gēna mutācijām, iespējams identificēt vismaz daļu no riska ģimenēm un piedāvāt mutāciju nesējiem atbilstošus profilakses un aprūpes pasākumus. *CDKN2A*, *INK4/ARF* un *STK11* gēnu pilnas analīzes rezultātā mutācijas ar skaidri paredzamu patogēnu efektu netika atrastas, no kā mēs varam secināt, ka šo gēnu mutācijām nav būtiskas nozīmes saslimšanā ar aizkuņģa dziedzera vēzi Latvijas populācijā. Balstoties uz līdz šim iegūtajiem datiem noteikto ģenētisko variantu („missense” mutāciju) nozīmi slimības izpausmē nav iespējams raksturot viennozīmīgi.