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ORIGINAL ARTICLE

CTRC gene polymorphism may increase pancreatic cancer risk – preliminary study

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

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ABSTRACT:

Pancreatic cancer is often fatal due to delayed diagnosis and treatment difficulties.

Objective: To analyze selected *SPINK1*, *CTRC*, *CFTR*, and *PRSS1* gene mutations in cancer tissue and blood samples of patients with pancreatic tumors.

Materials and method: We enrolled 16 consecutive patients diagnosed with pancreatic tumors. We collected cancer tissue, normal pancreatic tissue, and blood samples for genetic tests. The control group consisted of 419 healthy individuals. Peripheral blood samples were collected from all study participants in EDTA-coated tubes.

Results: Out of 16 patients with pancreatic tumors, 12 had pancreatic cancer on microscopic examination (mean age, 60.2 years). The *CTRC* polymorphism Hetero p.G60=(c.180C>T) was found in 5 patients with pancreatic cancer (41.7% vs. 18.6% in the control group). One patient with pancreatic cancer and a positive family history had the *SPINK1* (p.N34S) mutation [8.3% vs. 2.9% (12/419) in the control group]. One patient with pancreatic cancer had the *CTRC* (p.R254W) mutation [8.3% vs. 1% (4/419) in the control group].

Conclusions: Our preliminary results show that the CTRC polymorphism p.G60= (c.180C>T) is frequent in patients with pancreatic cancer. However, further research is needed to verify our findings.

KEYWORDS: pancreatic cancer; *CTRC* polymorphism; etiology

BACKGROUND

Pancreatic cancer is often fatal due to delayed diagnosis and treatment difficulties (1). In 2014, 337,872 cases of pancreatic cancer were diagnosed worldwide, and 330,391 patients died due to pancreatic cancer (2). In 2010, 3,254 pancreatic cancer cases were registered in the Polish National Cancer Registry, with high morbidity among patients in the ninth decade of life (3). Although current guideline do not require (2) histological diagnosis before surgical treatment for pancreatic cancer, neoadjuvant or palliative chemotherapy require prior cytological/histological confirmation; thus, endoscopic ultrasound-guided fine needle aspiration biopsy (EUS-FNA) is recommended. Surgery outcomes are best in patients with tumors smaller than 2 cm that do not spread beyond the pancreatic capsule and into the lymph nodes (early disease stage, i.e., stages I and II A). After tumor resection, the 5-year survival ranges from 18-24% (2).

Studies on carcinogenesis, tumor progression, early detection techniques, new surgical methods, and new drugs for patients with pancreatic cancer did not lead to reduced mortality, which still remains high (2), and the causes of pancreatic cancer are not fully elucidated. Pancreatic cancer risk factors include tobacco smoking, diabetes, pancreatitis, obesity, and genetic factors (4). A hereditary component can be observed in 5-10% of patients with pancreatic cancer; however, the genetic basis for familial pancreatic cancer has not been identified (5). An increased risk of pancreatic cancer is observed in the following genetic syndromes: Peutz-Jeghers syndrome – caused *STK11/LKB1* (*serine/threonine kinase 11*) gene mutations ; HBOC (*Hereditary Breast and Ovarian Cancer*) – caused *BRCA1 and BRCA*2 gene abnormalities; FAMMM *(Familial Atypical Multiple Mole Melanoma Syndrome*) – caused *CDKN2A* tumor-suppressor gene mutations; and Lynch syndrome – caused *HNPCC - MLH1, MSH2, MSH6* gene mutations (5-12). Familial pancreatic cancer (FPC) is diagnosed when pancreatic cancer occurs in at least two first-degree relatives in the absence of other hereditary syndromes or when pancreatic cancer occurs in at least 3 relatives regardless of kinship degree (13). Compared to the general population, people with 1, 2, or 3 first-degree relatives diagnosed with pancreatic cancer have a relative risk of pancreatic cancer of 2, 6, and 30, respectively (1). In pancreatic ductal adenocarcinoma (PDAC), *KRAS* mutations are frequently observed (>90%). Desmoplastic reaction of the pancreas leads to decreased blood supply and hypoxia, which changes cell metabolism and favors cancer development (1). Pre-cancerous changes, i.e., pancreatic intraepithelial neoplasia (PIN), develop in the pancreatic ducts due accumulation of genetic changes. *CDKN2A*, *p53*, and *SMAD4* mutations are often detected in advanced PIN, i.e., PIN 2 and PIN 3 (1). Based on recent research, loss-of-function mutations in the SWI/SNF nucleosome component are detected in approximately 10-15% of PDAC cases. Mutations responsible for the development of hereditary pancreatitis and cystic fibrosis may also be pancreatic cancer risk factors (13, 14). Cationic trypsinogen gene (*PRSS1)* and secretory trypsin inhibitor gene (*SPINK1)* mutations may increase the risk of hereditary pancreatitis by up to 50 times (1). It is thought that *PRSS1* and *SPINK1* mutations increase pancreatic cancer risk indirectly by increasing the frequency of pancreatic inflammatory changes (15).

Genetic pancreatic cancer risk factors are of interest to both scientists and clinicians. We performed a preliminary analysis of ge-

netic changes in cancer tissue, healthy tissue, and blood of patients with pancreatic tumors.

OBJECTIVE

The objective of this pilot study was to analyze *SPINK1,* chymotrypsinogen gene (*CTRC),* cystic fibrosis transmembrane conductance regulator gene (*CFTR),* and *PRSS1* gene mutations in cancer tissue and blood of patients with pancreatic tumors.

MATERIALS AND METHODS

We enrolled 16 consecutive patients with pancreatic tumors. We collected cancer tissue, healthy pancreatic tissue, and blood for genetic tests. Pancreatic cancer was diagnosed based on medical history, physical examination, imaging (USG, CT, MR), and endoscopic examinations, i.e., retrograde cholangiopancreatography and gastroscopy. The endoscopic examinations enabled collection of material for microscopy, i.e., specimens from the ampulla of Vater, duodenal wall infiltration, and fine-needle aspiration biopsy (FNAB). In some patients, the material for histological examinations was collected with EUS. In all patients, final diagnosis was based on the pathological assessment of tissue samples after laparotomy or laparoscopy. In the study, we used the clinical and pathological TNM evaluation system according to the 7th edition of TNM classification. In total, we enrolled 12 patients with confirmed pancreatic cancer and 4 patients with non-cancer pancreatic tumors.

Analysis included age at diagnosis, sex, occupation (potential carcinogenic factors in the work environment), lifestyle-associated risk factors (cigarette smoking, alcohol consumption), medical history (diseases of the pancreas, the bile ducts, the gallbladder, and the liver), and family history of pancreatic diseases (inflammation, cancer).

The control group consisted of 419 adult healthy volunteers selected by random sampling. The controls did not have diseases that could affect the structure and expression of the genes tested in the study. The study was approved by the Committee on Bioethics, Faculty of Medicine and Health Sciences, Jan Kochanowski University in Kielce. Each patient and member of the control group gave informed consent for performance of genetic testing.

DNA isolation

Peripheral blood samples were collected from all study participants in EDTA-coated tubes. DNA was isolated using the Micro AX Blood Gravity Kit (A&A Biotechnology, Gdańsk, Poland). DNA from tumor tissue was isolated with the Maxwell 16 (Promega, USA) instrument for automated nucleic acid purification. Quality and concentration of the isolated DNA was measured with the Nano Drop 2000 equipment (Thermo Scientific, TK Biotech, Poland).

Detection of CFTR mutations

The p.F508del (delF508_CTT) mutation was detected in a solution containing 10 µl ASA-PCR mixture, 5 µl of the Sybr Green Kit (Qiagen, Syngen-Biotech, Wrocław, Poland), 1 µl water, 1 µl of each primer, and 1 µl of DNA template. PCR was performed in the Veriti 96 Well Thermal Cycler (Applied Biosystems, USA). The cycling profile was set at 95°C initial denaturation for 1 min, followed by 35 cycles of 15s at 95°C, 15s at 60°C, 30s at 72°C, and a final extension at 72°C for 7 min. ASA-PCR product detection and visualization were performed using a microchip electrophoresis system (MCE-202 Multi NA, Shimadzu, Shim-pol, Warsaw, Poland).

Tab. I. Sequences of primers used

GENE		PRIMERS	PCR PRODUCT
CFTR ek10 (ex11)	F	GCAAGTGAATCCTGAGCGTG	307 bp
	R	TGGGTAGTGTGAAGGGTTCAT	
	M	GCACCATTAAAGAAAATATCATTGG	142 bp
SPINK ex3	F	TTGCTATGAACTCAAGAATGGAGA	168 bp
	R	CCGATTTTCAAAACATAACACG	
PRSS1 ex3	F	GGTCCTGGGTCTCAT	555 bp
	R	GTAATGGGCACTCGAAATGT	
PRSS1 ex2	F	TCCCTTCCCATCTCCACTCC	214 bp
	R	GGGAGCTTTGCAGTCGGG	
CTRC ex7	F	CTTATGCCCTCCCGGTCTGG	203 bp
	R	GGACAGCTGTGGAGGCAG	
CTRC ex3	F	CTGACACACAGCCCTCCC	162 bp
	R	ATGGCCAGGTCTCAGGGTAT	

Detection of SPINK1, PRSS1 and CTRC mutations

Mutation detection was performed with capillary sequencing and primers (Tab. 1) that flanked the genetic regions containing the following mutations: *SPINK1* - exon 3 (p.N34S and p.P55S), *PRSS1* - exon 2 (p.A16V, p.N29I) and exon 3 (p.R116C, p.R122C, p.R122H), and *CTRC* - exon 3 and exon 7(p.I259V, p.V235I, p.K247_R254del, and p.E225A).

PCR products were enzymatically purified with the Exo SAP reagent containing phosphatase and exonuclease. The purified PCR product was sequenced with the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems). The reaction conditions were 25 cycles at 96°C for 10s, 55°C for 5s, and 60°C for 105s. The reaction products were purified after sequencing with the Big Dye X Terminator Kit (Applied Biosystems). Sequencing was carried with the 3130 Genetic Analyzer (Applied Biosystems). The resulting chromatograms were analyzed manually and compared using the BLAST software from the NCBI site.

RESULTS

Among 16 patients with pancreatic tumors, pancreatic cancer was confirmed microscopically in 12 patients [4 females and 8 males; mean age 60.2 years (females – 58.8 years; males – 61 years)]. Table 2 presents the characteristics of the enrolled participants.

In 5 patients with pancreatic cancer, *CTRC* gene polymorphism was observed in the blood, healthy pancreatic tissue, and cancer tissue [CTRC - polymorphism Hetero p.G60= (c.180C>T)]

Tab. II. Characteristics of patients with pancreatic cancer.

NO.	GENDER	AGE	SURGERY TYPE	HISTOPATHOLOGIC EXAMINATION	LOCALIZATION	FOLLOW-UP	ALCOHOL	TOBACCO SMOKING	BMI	FAMILY HISTORY
1.	m	55	Total pancreatectomy, splenectomy	Adenocarcinoma (pT2)	head of pancreas	Alive, hepatic metastasis	+	+	24,8	-
2.	f	56	Total pancreatectomy splenectomy	Adenocarcinoma G2. Lymph node 4/6. pT3N1M1L1	head of pancreas	Death after 8 months	+	+	26,1	-
3.	f	72	Laparoscopic palliative surgery, ductal-duodenal, gastrointestinal anastomosis	Adenocarcinoma	head of pancreas	Death after 6 months	-	-	24,1	-
4.	f	44	Total pancreatectomy, splenectomy	Adenocarcinoma, L. node 0/24 pT3N0MxL0Pn1	head of pancreas	Death after 10 months	-	+	24,1	-
5.	m	72	Total pancreatectomy, splenectomy	Adenocarcinoma G2. L. node 0/9 pT3N0MxPn1	head of pancreas	3 years, no local recurrence and metastasis	+	+	20,8	-
6.	f	63	Pancreaticoduodenectomy	Neuroendocrine cancer Lymph node 3/10	head of pancreas	No local recurrence and metastasis	-	-	20,5	+
7.	m	47	Pancreaticoduodenectomy	Adenocarcinoma	head of pancreas	3 years, no local recurrence and metastasis	-	+	25,7	-
8.	m	60	Unresectable	Adenocarcinoma	head of pancreas	Death after 4 months	+	+	22,3	-
9.	m	68	Pancreaticoduodenectomy	Adenocarcinoma G3	head of pancreas, ampulla of Vater	4 years, no local recurrence and metastasis	+	+	22,2	-
10.	m	63	Resection of the body and tail of the pancreas	Adenocarcinoma	body and tail of the pancreas	1 year, liver metastasis	+	+	29,5	Colorectal cancer
11.	m	56	Pancreaticoduodenectomy	Adenocarcinoma	head of pancreas	6 months, no local recurrence and metastasis	+	+	20,5	+
12.	m	66	Laparotomy, collecting liver specimen	Neuroendocrine cancer G3 (NEC G3) hepatic metastasis, CgA (+), synaptophysin (===), Ki-67>90%	head of pancreas, ampulla of Vater	Death after 7 months	+	+	25,9	-

- 41.7% of the patients examined vs. 18.6% in the control group. In 3 out of those 5 patients, family history of pancreatic cancer was confirmed. Four patients with pancreatic cancer and the p.G60=(c.180C>T) polymorphism smoked cigarettes and consumed high-volume alcohol. No occupational risk factors of pancreatic cancer were noted.

As regards the remaining patients with pancreatic cancer, one patient had a positive family history and the *SPINK1* (p.N34S) mutation - 8.3% vs. 2.9% (12/419) in the control group; one patient had the *CTRC* (p.R254W) mutation in the blood and cancer tissue - 8.3% vs. 1% (4/419) in the control group. Both patients with PDAC were tobacco smokers and frequently consumed high-volume alcohol. No patients with pancreatic cancer had *CFTR* or *PRSS1* mutations; in the control group: 13/419 (3.1%) and 0/419, respectively (Tables. 3 and 4).

In total, genetic changes were observed in 7 out of 12 patients with pancreatic cancer [*CTRC* - polymorphism p.G60= (c.180C>T), *SPINK1* (p.N34S), and *CTRC* (p.R254W) mutations].

None of 4 patients with non-cancer pancreatic tumors had the *CTRC* Hetero p.G60= polymorphism or mutations in the *SPINK1* (p.N34S), *CTRC* (p.R254W), *CFTR,* or *PRSS1* genes in tumor tissue or blood samples.

DISCUSSION

In recent years, knowledge of the molecular mechanisms responsible for pancreatic cancer development has considerably increased, with a large number of genes potentially implicated in this process. However, an early diagnosis of pancreatic cancer is still rare, and treatment outcomes are unsatisfactory regardless of surgery type.

KRAS gene mutations are found most frequently in patients with pancreatic cancer (1). A number of studies showed that *KRAS* mutations are associated with an unfavorable prognosis in patients with resectable or unresectable pancreatic cancer (16). In the study by Kinugas et al. (17), *KRAS* mutations were found in serum (circulating tumor DNA) of 62.5% patients with advanced pancreatic cancer. The same researchers found *KRAS* mutations in cancer tissue samples of 93% patients (n=40) with pancreatic cancer (48% in plasma and serum) (18). They concluded that plasma and serum were appropriate for detection of cancer-specific DNA and that *KRAS* mutations detected in blood-isolated DNA may be a prognostic marker in pancreatic cancer. EGFR, nuclear factor (KB), BCL-Xl, and protein kinases may be implicated in PDAC development as co-mediators of *KRAS* (19). *KRAS* may potentially re-program metabolism through an alternative expression of enzymes involved in glucose utilization. *KRAS* negatively influences the oxidoreductive metabolic state by inducing nuclear

Tab. III. Distribution of the *CTRC* - polymorphisms Hetero p.G60= and *SPINK1*, *CFTR*, *PRSS*, and *CTRC* mutation in patients with pancreatic cancer and healthy controls.

	CTRC - POLYMORPHISM HETERO P.G60=(C.180C>T)		P VALUE	SPINK1 EXON 3 P.N34S C.101A>G		P VALUE	CTRC EXON 3 EXON 7		P VALUE	CFTR EXON 11 (DELF508_CTT) (C.1521_1523 DELCTT)		PRSS1 EXON 2 (P.A16V, P.N29I) EXON 3 (P.R116C, P.R122C, P.R122H)	
	PDAC N=12	Control N=419	PDAC N=12	PDAC N=12	Control N=419	PDAC N=12	PDAC N=12	Control N=419	PDAC N=12	PDAC N=12	Control N=419	PDAC N=12	Control N=419
Females	2	50	-	-	9	-	-	2	-	-	6	-	-
Males	3	28	-	1	3	-	1	2	-	-	7	-	-
Total	5	78	0,04	1	12	0,27	1	4	0,02	-	13	-	-

CTRC- chymotrypsinogen C; *SPINK 1* - secretory trypsin inhibitor gene; *CFTR* - cystic fibrosis transmembrane conductance regulator gene; *PRSS1*- cationic trypsinogen gene; PDAC - pancreatic ductal adenocarcinoma.

Tab. IV. Contingency table for the relationship between sex and *SPINK1*, *CFTR*, *PRSS*, and *CTRC* mutations in patients with pancreatic cancer.

	GENDER	AGE	TISSUE RESULTS SPINK EXON 3 pN34S (C.101A>G)	CFTR EXON 11 (delF508_CTT) C.1521_1523 delCTT	PRSS1 EXON 2 (pA16V, pN29I) EXON 3 (P.R116C, pR122C, pR122H)	CTRC EXON 3	CTRC EX. 7	BLOOD RESULTS
1	K	56	-	-	-	p.G60=(c.180C>T)	-	CTRC p.G60=(c.180C>T)
2	M	72	-	-	-	p.G60=(c.180C>T)	-	CTRC p.G60=(c.180C>T)
3	K	63	-	-	-	p.G60=(c.180C>T)	-	CTRC p.G60=(c.180C>T)
4	M	47	-	-	-	p.G60=(c.180C>T)	-	CTRC p.G60=(c.180C>T)
5	M	63	-	-	-	p.G60=(c.180C>T)	-	CTRC p.G60=(c.180C>T)
6	M	56	p.N34S	-	-	-	-	SPINK p.N34S ;
7	M	66	-	-	-	-	CTRC p.R254W	CTRC p.R254W

SPINK1- secretory trypsin inhibitor gene; *CFTR* - cystic fibrosis transmembrane conductance regulator gene; *CTRC* - chymotrypsinogen C

factor erytroid-2-related factor 2 (Nrf2) transcription as a regulator of antioxidant genes (20).

To date, research on the changes in suppressor genes and oncogenes has not led to new therapeutic interventions in pancreatic cancer (21, 22).

Therefore, we studied whether the genetic mutations responsible for pancreatitis may be associated with PDAC. Recently, we found a relationship between the *CTRC* polymorphism (p.G60= (c.180C>T) and acute pancreatitis risk (23). The *CTRC* gene encodes chymotrypsin C, which is produced by the pancreatic acinar cells, and regulates trypsin activity (24). Tissue and blood samples of patients with histologically confirmed PDAC were used for DNA sequencing. Our present findings show a frequent occurrence of the *CTRC* Hetero p G60=. (41.7%) polymorphism in patients with pancreatic cancer. Compared to controls, we observed the CTRC polymorphism significantly more often in patients with pancreatic cancer, both in tissue and blood samples. In previous research, compared to healthy controls, a significantly more frequent occurrence of the *CTRC* p.G60= (c.180C>T) polymorphism was found in patients with acute pancreatitis (29.1% vs. 18.5%; p=0.015) (23). If the *CTRC* p.G60= (c.180C>T) polymorphism in the blood signifies an increased risk of pancreatic cancer, should early screening tests be included in the diagnostic workup? Certainly, this would require verification of our results in a larger group of patients.

In patients suspected for pancreatic cancer, endoscopic ultrasonography (EUS) with potential biopsy of suspected focal pancreatic changes and computed tomography or magnetic resonance imaging of the abdominal cavity should be performed. In special situations, positron emission tomography (PET) or even somatostatin receptor scintigraphy, in the case of suspected neuroendocrine changes, should be considered (25-27). Currently, one does not need to look for genetic mutations in patients without family history of pancreatic diseases (28). It is unclear at what age screening tests should be started (29).

Mutation of the *PRSS1* gene, which encodes cationic trypsinogen, is a well-recognized risk factor of pancreatitis (30). Compared to healthy controls, patients with hereditary pancreatitis are at least 35-times more likely to have pancreatic cancer by the age of 70-75 years (31). In the examined group of 12 patients with pancreatic cancer, no *PRRS1* mutations were observed. In a German study, cationic trypsinogen gene (*PRSS1*), pancreatic secretory trypsin inhibitor gene (*SPINK1*), cystic fibrosis transmembrane conductance regulator gene (*CFTR*), and chymotrypsinogen gene (*CTRC*) mutations did not significantly increase the risk of pancreatic adenocarcinoma (25). In the small group examined in the presented study, mutations in the *SPINK1* or the *CTRC genes* were noted in only single cases.

CONCLUSIONS

Our preliminary results show that the *CTRC* polymorphism p.G60= (c.180C>T) is frequent in patients with pancreatic cancer. However, further research is needed to verify our findings.

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