Review paper

Genetic determination of pancreatic cancer

Determinacja genetyczna w raku trzustki

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Słowa kluczowe: rak trzustki, mutacje dziedziczne, gen *BRCA*, gen *PALB2*, gen *STK11*.

Abstract

In Poland, malignant pancreatic cancer constitutes approximately 2% of the total number of cancer cases. The prognoses are very unfavourable, compared to other serious cancerous diseases of the gastrointestinal tract. Pancreatic cancer is a disease about which little is known concerning the etiopathogenesis and risk factors. The presented study demonstrates the role of the best recognised genetic mutations in the development of pancreatic cancer. The objective of the review of literature is the analysis of selected genetic risk factors of pancreatic cancer: *BRCA1*, *BRCA2*, *PALB2*, and *STK11*. The role of genetic mutations in the development of pancreatic cancer remains unclear. To-date, no gene has been discovered the damage of which is specifically related with cancer of this organ. Multi-centre studies allowing analysis of a large group of patients are a chance for better recognition of the genetic relationships

Streszczenie

W Polsce nowotwory złośliwe trzustki stanowią ok. 2% ogólnej liczby zachorowań na raka. Prognozy są bardzo niekorzystne w porównaniu z innymi poważnymi chorobami nowotworowymi przewodu pokarmowego. Rak trzustki jest chorobą, w której niewiele wiadomo na temat etiopatogenezy i czynników ryzyka. Przedstawione badanie pokazuje rolę najlepiej poznanych mutacji genetycznych, które mogą mieć znaczenie w rozwoju raka trzustki. Celem przeglądu piśmiennictwa jest analiza wybranych genetycznych czynników ryzyka wystąpienia raka trzustki: *BRCA1*, *BRCA2*, *PALB2*, *STK11*. Rola mutacji genetycznych w rozwoju raka trzustki wciąż jest nieznana. Dotąd nie odkryto żadnego genu, którego uszkodzenie byłoby specyficznie związane z rakiem tego narządu. Szansą na lepsze poznanie genetycznych zależności są wieloośrodkowe badania, które pozwalą przeanalizować dużą grupę chorych.

Introduction

According to data from the International Agency for Research on Cancer, World Health Organisation, the estimated frequency of occurrence of pancreatic cancer worldwide is 337,872 cases, which constitutes 2.4% of total morbidity due to cancer [1]. The highest risk of contracting the disease is observed in highly developed countries: the USA, Argentina, Australia, and Central and Northern Europe. In Poland, malignant pancreatic cancer constitutes approximately 2% of the total number of cancer cases. In recent years, about 3,200 cases of pancreatic cancer have been registered annually, with a similar frequency among males and females [2]. The risk of contracting the disease increases at the age of over 50 years and is highest at the age of about 90 years [2].

The prognoses in pancreatic cancer are very unfavourable, compared to other serious cancerous diseases of the gastrointestinal tract, for which 1- and 5-year survival in the whole of Europe was 23% and 6%, respectively, during the period 2000–2012 [3]. In the years 2003–2005, in Poland, the annual survival was 22.7% [2]. The SUDCAN study conducted in six European countries using the EUROCARE-5 database, showed a slight decrease in the death rate from pancreatic cancer during the years 1992–2004; however, the survival is limited to just 18 months after diagnosis [4]. It is prognosticated that by 2030 pancreatic cancer will be the second cause of death due to cancer in the USA [5].

Identification of the group at high risk, and early detection of pancreatic cancer, is the precondition for decreasing the risk of death.

Among various causes of pancreatic cancer, environmental factors are indicated, such as: tobacco smoking, obesity, type 2 diabetes, non-alcoholic fatty liver disease, cirrhosis, chronic pancreatitis, and genetic factors [6–12].

Cigarette smoking increases mortality from pancreatic cancer by 71% in current smokers. The risk increases with the number of cigarettes smoked and duration of smoking. Five years after the discontinuation of smoking the risk is comparable to that in non-smokers [10].

Arslan *et al.* [13] confirmed that the relationship between BMI and pancreatic cancer is stronger among non-smokers than smokers. The risk of contracting the disease may be higher in young obese persons, compared to those who are older [8, 14]. There is a linear relationship between waist circumference and the risk of pancreatic cancer, which suggests a relationship with the distribution of the adipose tissue [13]. What is important is that moderate physical activity decreases the risk of pancreatic cancer, especially in overweight persons [15].

Many studies confirm the risk of progression of chronic pancreatitis to pancreatic cancer. The first episode of acute pancreatitis may precede the diagnosis of cancer, but the risk is nine-times higher in the group of patients who developed chronic pancreatitis [16]. The absolute risk of pancreatic cancer after acute pancreatitis during a 2-year observation was 0.68%, while after 5 years – 0.85% [17]. It is estimated that approximately 5% patients with chronic pancreatitis will develop pancreatic cancer within 20 years [9].

The risk of progression of chronic pancreatitis to pancreatic cancer is highest in patients who contracted the disease at a young age, especially those with hereditary pancreatitis [9, 18]. Thus, mutations in the genes *PRSS1*, *SPINK1*, and *CFTR*, described as genetic factors responsible for hereditary pancreatitis, indirectly increase the risk of pancreatic cancer, causing the progression of the inflammatory state to cancer. It is estimated that in the group of patients with hereditary pancreatitis, the risk of contracting pancreatic cancer is 53-times higher than in the group of healthy individuals, especially in tobacco smokers [19, 20]. The recommendations concerning oncologic surveillance in chronic pancreatitis recommend examinations for pancreatic adenocarcinoma in patients with hereditary pancreatitis and family history of pancreatic cancer (occurrence of cancer in at least two family members) starting from the age of 40 years. It is recommended that an annual EUS examination be performed and the concentration of CA 19-9 marker in serum be determined [21]. In the remaining group of patients with CP, the performance of routine examinations for pancreatic cancer is not recommended; however, in each case, when new, alarming symptoms occur, detailed diagnostics are recommended [21].

Hereditary and acquired genetic mutations may play an important role in the development of pancreatic cancer. Approximately 10–15% of cases of pancreatic cancer are of a family character [6]. Family pancreatic cancer is defined as the occurrence of cancer in at least two first-degree relatives, or two, or more relatives of any degree [6, 22]. The occurrence of families with three or more members ill from pancreatic cancer is rare, and in Japan it is 0.5% [23]. The risk of falling ill in the case of the occurrence of cancer in a family is 1.9- to 13-times higher, and is characterised by earlier onset, compared to sporadic cancer [23, 24].

A higher risk of pancreatic cancer occurs in Peutz-Jeghers syndrome (PJS), hereditary pancreatitis, familial atypical multiple mole melanoma (FAMMM), hereditary breast-ovarian cancer (HBOC), hereditary nonpolyposis colorectal cancer, Lynch syndrome (LS), familial adenomatous polyposis (FAP), and Werner syndrome. These syndromes are excluded from the definition of family pancreatic cancer in the narrow sense [23]. An increased risk of contracting the disease occurs also in patients with hereditary pancreatitis and cystic fibrosis.

To better understand the genetic relationships in a large group of patients, the PANcreatic Disease ReseArch (PANDORA) consortium was formed. The consortium brought together researchers from six European countries, including the Medical University of Lodz [25]. In 1994, a register of studies of pancreatic cancer was established: The National Familial Pancreas Tumour Registry (NFPTR) in the Johns Hopkins Hospital [26]. To-date, several genes have been recognised that are related with pancreatic cancer, including high-penetration genes such as *BRCA2* [27], *PALB2* [28], *STK11* [29], and low-penetration genes such as the blood group ABO locus [18].

The objective of the review of the literature is the analysis of selected genetic risk factors of pancreatic cancer.

BRCA1 and *BRCA2*

The BRCA1 and BRCA2 proteins are involved in the recognition and repair of the double-stranded DNA through homologous recombination [30]. The *BRCA* gene is inherited in an autosomal dominant manner that is high-penetrating and, therefore, causes an increase in the frequency of occurrence of familial breast and ovarian cancer, as well as pancreatic, prostate, and colorectal cancer [31].

Pancreatic cancer is a type of cancer in which an increased risk of contracting the disease has been ultimately confirmed in *BRCA* mutation carriers [32, 33]. Most often, attention is paid to the relation with *BRCA2* mutation, whereas more rarely with *BRCA1* mutation. The *BRCA1* and *BRCA2* mutations occur with a frequency from 3% to 21% of patients with pancreatic cancer in the western population [34], with the

highest risk of the disease in the case of *BRCA2* mutation [27] – occurring especially often in the group of Ashkenazi Jewish patients (10–14%) [27, 35]. In the study by Salo-Mullen *et al*. [35], *BRCA2* mutation constituted 54% of all pathogenic mutations identified in this group of patients. It is estimated that *BRCA1* increases the risk of contracting the disease at the age 70 years by two times, and *BRCA2* by 3.5 times [36, 37]. However, a 2008 study of Polish patients did not confirm a relationship between *BRCA1* mutation and falling ill with pancreatic cancer [38], similar to the Italian study [39]. The National Comprehensive Cancer Network (NCCN) recommends the performance of BRCA tests in patients with PDAC if they have one or more first-, second-, or third-degree relatives with ovarian or breast cancer aged 50 years or under, or two relatives with breast, prostate, or pancreatic cancer at any age, and in each patient with PDAC of AJ origin [40].

The carriers of *BRCA1* and *BRCA2* mutations with sporadic PDAC had lower survival outcomes after pancreatectomy, compared to patients with wild-type *BRCA* [30]. The presence of *BRCA* mutation may be an important predictive and prognostic factor in pancreatic cancer [41]. Early performed screening imaging tests using endoscopic ultrasound (EUS) or magnetic resonance cholangiopancreatography (MRCP) in the group of *BRCA* carriers may be the key test enabling the diagnosis at an early stage of the disease [31, 42]. However, overuse of CT in the group of *BRCA* carriers should be avoided [43].

PALB2

Protein encoded by the PALB2 interacts with the BRCA2 protein creating a complex stabilising DNA. It is responsible for the process of DNA repair, and the PALB2 mutation results in abnormal DNA copies. In 2006, it was confirmed that PALB2 interacting with BRCA2 is a breast cancer susceptibility gene [28]. Hereditary mutations in the *PALB2* gene have been shown to predispose to PDAC; however, frequencies of mutations vary among distinct geographical populations [44].

STK11

The STK11 is a tumour suppressor gene, it encodes serine/threonine kinase, which plays a crucial role in the regulation of cell growth and apoptosis. Mutations of this gene lead to inactivation of STK11, and finally cause various types of cancer [29]. The *STK11* mutations are most often related with Peutz-Jeghers syndrome, characterised by intestinal polyps, mucocutaneous pigmentation, and an increased predisposition to cancer concerning many organs, including the pancreas and bile ducts [45, 46]. Inactivation of *STK11* in the Peutz-Jeghers syndrome causes a 100-fold higher risk of pancreatic cancer. Nevertheless, no *STK11* mutation has been detected in patients with hereditary pancreatic cancer [47].

Last year, interesting results were published indicating a frequent occurrence of mutations considered as pathogenic in patients with pancreatic cancer without family history. The researchers suggest that examinations of newly diagnosed patients and their families should be biased towards seeking mutations only of selected genes: *BRCA2*, *ATM*, *PALB2*, *CDKN2A*, and *BRCA1*, as well as *PRSS1* and *STK11* in persons suspected of the occurrence of adequate clinical syndromes [48].

Summary

Many studies provide evidence that the majority of cancers develop on the background of genetic predispositions. Pancreatic cancer is a disease in which little is known concerning the aetiopathogenesis and risk factors. Although many reports have been published, the role of genetic mutations in the development of pancreatic cancer remains unclear. To-date, no gene has been discovered the damage of which would be specifically related with cancer of this organ. Multi-centre studies allowing analysis of a large group of patients are a chance for better recognition of the genetic relationships.

Conflict of interest

The authors declare no conflict of interest.

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