INTRODUCTION
Pancreatic cancer belongs to carcinomas associated with poor prognosis and low survival rate. It has been highlighted that the cancer risk is linked to both environmental and genetic factors. Available studies allow to estimate that genetic factors play a role in 5–10% of patients with pancreatic cancer. Beside other carcinomas, pancreatic cancer occurs in hereditary neoplastic syndromes associated with gene mutations, including CDKN2A, CHEK2, BRCA2. It has also been suggested that BRCA1 mutation is involved given the fact that BRCA1 mutation carriers are at increased risk for pancreatic cancer. However, a role of this mutation is not fully understood.

OBJECTIVES
The purpose of the study was to assess the relationship between BRCA1 gene mutation and pancreatic cancer in Polish population.

PATIENTS AND METHODS
88 pancreatic cancer patients (56 males and 35 females) and 3784 carriers of BRCA1 mutation from 1637 families were enrolled in the study. Almost 65% of pancreatic cancer patients were cigarette smokers. Genotyping for constitutive BRCA1 gene mutation was performed in all patients with pancreatic cancer. ASA-PCR and PCR-RFLP methods were used to detect BRCA1 (5382insC, C61G, 4153delA) mutations. The frequency of pancreatic cancer in families of BRCA1 mutation carriers was evaluated.

RESULTS
No carriers of BRCA1 mutation were identified in patients with pancreatic cancer. Only in 11 families (0.7%) with BRCA1 mutation carriers, pancreatic cancer was diagnosed.

CONCLUSIONS
Our results suggest that there is no relationship between BRCA1 mutation and pancreatic cancer development in Polish population.

KEY WORDS
BRCA1 gene mutation, pancreatic cancer

ABSTRACT
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INTRODUCTION
Pancreatic cancer is associated with extremely poor prognosis. Despite the progress in medicine with implementation of new diagnostic imaging techniques, this cancer is the fourth leading cause of cancer death in the USA, and in Poland it is the seventh among men and eighth among women.1,2 Every year 4000 people die of pancreatic cancer in Poland. The 5-year overall survival rate of pancreatic cancer patients is 5% or less.3

As causes of pancreatic cancer, environmental factors, including cigarette smoking, and genetic factors have been postulated. The genetic factors of particular importance include the BRCA2 gene, one of the genes regulating the DNA repair, the mutation of which increases the risk for breast and ovarian cancer development, and the suppressor CDKN2A gene, with its mutation being responsible for about 25% cases of family melanoma occurrence.4,5 Other rare genetic syndromes predisposing to pancreatic cancer have also been reported. Some, for example hereditary pancreatitis, are specific to this organ. Other, like ataxia telangiectasia and the Peutz-Jeghers syndrome, are related to cancer development in various organs, including the pancreas.5,6 In other genetic syndromes, e.g. hereditary non-polyposis colorectal cancer, pancreatic cancer occurs much less frequently than the cancer typical of this syndrome (i.e. colon cancer).6 A role of the BRCA1 gene in the pancreatic cancer development is not yet fully understood.

Available data have shown the relation between the BRCA1 gene mutation and breast, ovarian and
Thus, there is a need for follow-up studies which Thompson et al. estimated that the risk for pancreatic cancer development increases in individuals whose close family relatives had pancreatic cancer.\(^7\) According to database of the International Hereditary Cancer Center in Szczecin, it may be assumed that there are about 200,000 BRCA1 gene mutation carriers in Poland, who, in the case of a confirmed increased risk for pancreatic cancer development, should require a special oncologic care system.

Previous studies that estimated the BRCA1 mutation frequency in the Polish population concerned only families with a history of breast or ovarian cancer. In one of their studies, Górski et al. reported that the BRCA1 gene mutations (5382insC, C61G, 4153delA) occurred in 82% of Polish families with a strong aggregation of breast or ovarian cancer.\(^8\) There are few studies regarding associations between pancreatic cancer development, the BRCA1 gene mutation and family predisposition to this cancer worldwide, and such studies in the Polish population are lacking. Thus, there is a need for follow-up studies which may increase our understanding of the cancer and lead to its early detection and effective patient treatment.

**Patients and Methods**

We studied 88 pancreatic cancer patients, 53 (60%) men and 35 (40%) women, diagnosed or treated with palliative endoscopy in the Department of Gastroenterology and Internal Medicine Pomeranian Medical Academy in the years 2002–2007. Pancreatic cancer was documented in histological examination in 63 individuals. Adenocarcinoma was detected in 61 patients, anaplastic carcinoma in one individual, and undifferentiated carcinoma in one patient. In the remaining patients the diagnosis was established based on clinical symptoms, laboratory abnormalities, including abnormal CA19-9 values, on imaging results (computer tomography, endoscopic retrograde cholangiopancreatography, echoendoscopy, ultrasound examination) and the history of patients. The average patient age at the time of the diagnosis was 64 (standard deviation [SD]: 5.6) years. There were 11 patients aged 40–50, and 22 patients aged 51–60. The 61–70 aged group was largest and consisted of 29 individuals. The 71–80 aged group consisted of 24 patients, and in the oldest, the >80 aged group, there were 2 individuals.

Each patient had been previously informed about the aim and methods of the study and had given his written consent to genetic analyses. Samples of 10 ml fresh whole blood were obtained to EtylenoDiaminoTetraAcetic test tubes, and subsequently stored in a deep freezer, at a temperature of \(-27^\circ{\text{C}}\). A questionnaire with complete clinical data was filled out for each patient, including the symptom duration, a family history of cancer, data on diagnosis and treatment, and histopathological examination results. The DNA test, based on the multiplex PCR, which with practically a 100% specificity detects BRCA1 mutations (5382insC, C61G, 4153delA) located on exons 20, 5 and 11, respectively, was developed at the International Hereditary Cancer Center in Szczecin. The DNA was isolated from peripheral blood leukocytes, and subsequently amplified using starters specific to the gene sequence. The 20 and 11 exon mutations were detected using the ASA-PCR method, and the exon 5 mutation using the PCR-RFLP method. The result was read on agarose gel.\(^9\)

To determine pancreatic cancer prevalence in the families of the BRCA1 gene mutation carriers was also planned. A database comprising 3784 BRCA1 mutation carriers, originating from 1637 families whose lineages had been analyzed, was prepared in the International Hereditary Cancer Center.

**Results**

In the examined group of 88 pancreatic cancer patients no carrier of the BRCA1 gene mutation was detected. The average clinical symptoms duration (abdominal pain, jaundice, body mass loss) in patients before the diagnosis of pancreatic cancer was 3.8 months (SD: 5.6). The longest duration of symptoms was 48 months and concerned a patient, who attributed the epigastric pain, at first discreet later more intense, to the previously diagnosed cholelithiasis. Because of its advanced stage at the time of diagnosis, the pancreatic lesion did not qualify for surgery. Due to the local progression of the disease in 68 patients at diagnosis, the cancer was inoperable. In 16 individuals the lesion was generalized with distant metastases, and 4 individuals underwent surgery. The most frequent localization was the pancreatic head: 56 (63.6%) patients, in 14 (16%) the lesion was located in the body of the pancreas, in 11 (12.5%) in both the body and the tail, in 5 (5.6%) in the head and the body, whereas in 2 (2.3%) the whole pancreas was affected. A detailed patient’s history regarding family cancer occurrence was reported in 86 patients. The occurrence
of cancer among first- and second-degree relatives was confirmed in 41 (47.7%) patients, while the remaining patients denied family history of cancer. Among the first- and second-degree relatives, the most common was lung cancer (21%), colon cancer (15.8%), gastric cancer (13%) and female reproductive organ cancer (13%). Pancreatic cancer occurred in the family of every tenth patient with family history of cancer.

In the whole pancreatic cancer patient group, 57 (64.8%) individuals had smoked cigarettes for 10 years or longer, however 31 (35.2%) patients had never smoked.

A different aspect of the study was to determine the pancreatic cancer prevalence in the families of the BRCA1 gene mutation carriers. A database comprising 3784 BRCA1 mutation carriers originating from 1637 families, which lineages had been analyzed, was prepared in the International Hereditary Cancer Center. Pancreatic cancer occurred only in 11 (0.7%) families, in which there was at least one carrier of the studied mutation.

**DISCUSSION** Few studies concerning the issue of pancreatic cancer and the BRCA1 gene mutation focus on the increased risk for pancreatic cancer development in carriers of the mutated BRCA1 gene (relative risk = 2.26–4.06). Among available data there is only one performed in the Canada study which authors investigated a potential relation between the BRCA1 mutation and pancreatic cancer. Lal et al. assessed the BRCA1 mutation carrier state in 102 patients with diagnosed and histopathologically confirmed pancreatic cancer. In 27 (26%) patients the criteria for various hereditary cancer syndromes, including family pancreatic cancer were met. The BRCA1 (5382insC) mutation carrier state was reported in one patient and the BRCA2 mutation carrier state in three patients, all of them with a family history of hereditary breast-ovarian cancer occurrence. The results of the present study, which did not demonstrate BRCA1 gene mutation carriership in any of pancreatic cancer patients, are comparable with another study, in which in 102 individuals only one mutation was reported. Data on the number of men and women in the analyzed group are also similar. As in the present study, there were almost twice as many men, as there were women in this study. The occurrence of pancreatic cancer that is lower in women results from the protective effect of estrogen, as it has demonstrated that the exocrine pancreas has estrogen receptors.

The available data regarding the issue of pancreatic cancer and BRCA1 gene mutation focus mainly on the risk for pancreatic cancer development in relatives of patients with a diagnosed cancer of this organ. Fernandez et al. demonstrated that this risk is significantly increased (odds ratio [OR]: 3.0). The risk for pancreatic cancer development rises among members of families, in which two or more cases of pancreatic cancer have been reported (OR: 3.5). Based on the analysis of their own material, the authors of the present study demonstrated that pancreatic cancer occurred in families of four study patients, and pulmonary cancer was most frequently reported. This can be most probably related to the fact that this cancer represents one of the leading causes of cancer morbidity rate in Poland.

Studies on pancreatic cancer and the role of environmental factors definitely confirm there being a relation between cigarette smoking and the risk for pancreatic cancer. It has been suggested that the risk increases with the number of cigarettes smoked daily. Almost 65% of individuals from the patient group in the current study were cigarette smokers, which provides indirect evidence for the influence of cigarette smoking on pancreatic cancer development.

In conclusion, there were no BRCA1 gene mutation carriers in the group of 88 pancreatic cancer patients. This leads to the statement that pancreatic cancer development in the Polish population is not related to the BRCA1 gene mutation, and search for this gene mutation does not contribute to identity individuals at risk for pancreatic cancer development. Given the small size of the study group, this issue requires further investigation.

In this study, over half of the pancreatic cancer patients were long-term cigarette smokers; this may constitute further evidence for the relationship between pancreatic cancer and cigarette smoking.

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