ORIGINAL ARTICLE

Is there any relationship between *BRCA1* gene mutation and pancreatic cancer development?

Małgorzata Ławniczak[1], Alicja Gawin[1], Andrzej Białek[1], Jan Lubiński[2], Teresa Starzyńska[1]

1 Department of Gastroenterology and Internal Diseases, Pomeranian Medical University, Szczecin, Poland
2 Department of Genetics and Patomorfology, Pomeranian Medical University, Szczecin, Poland

KEY WORDS

BRCA1 gene mutation, pancreatic cancer

ABSTRACT

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.

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 teleangiektasia and the Peutz-Jeghers syndrome, are related to cancer development in various organs, including the pancreas.[6,7] 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).[8] 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

Correspondence to:
Małgorzata Ławniczak, MD, PhD, Klinika Gastroenetrologii i Chorób Wewnętrznych, Pomorska Akademia Medyczna, ul. Unii Lubelskiej 1, 71-252 Szczecin, Poland, phone/fax: +48-91-425-32-11, e-mail: gosiaml7@wp.pl
Received: February 24, 2008.
Accepted: June 3, 2008.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2008; 118 (11): 645-649

prostate cancer development and there have also been suggestions based on the observations in animal models demonstrating a potential role of this gene in glioma development.[9-11]

The *BRCA1* gene, located on the 17 (17q21) chromosome, is approximately 80,000 base pairs long. It is involved in the DNA repair through the regulation of other genes expression. This gene inactivation leads to cell cycle disturbances, and in consequence to neoplastic disease. Mutations in this gene are responsible for the autosomal, dominant inherited breast and ovarian cancer predisposition. In constitutional *BRCA1* gene mutation carriers, the risk for breast cancer development is about 72–85%, and 40–60% for ovarian cancer development.[5,12] British authors have recently reported that there is a relation between pancreatic cancer and the *BRCA1* gene mutation. Thompson et al. estimated that the risk for pancreatic cancer development in individuals with the confirmed *BRCA1* gene mutation is about twice as high, both in men and women.[13] It has been pointed out at the same time that the risk for pancreatic cancer development increases in individuals whose close family relatives had pancreatic cancer.[14] 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.[9] 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°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.[15]

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).[5,13] 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.[16] 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 been demonstrated that the exocrine pancreas has estrogen receptors.[17]

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).[18] 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).[19,20] 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.[21] 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.

ACKNOWLEDGEMENTS This study was supported by the State Committee for Scientific Research as a research project No PBZ-KBN-090/P05/2003.

REFERENCES

1 Jemal A, Siegel R, Ward E, et al. Cancer Statistic, 2007. CA Cancer J Clin. 2007; 57: 43-66.

2 Wojciechowska U, Didkowska J, Tarkowski W, Zatoński W. [Cancer in Poland in 2004]. Centrum Onkologii – Instytut im. Marii Skłodowskiej-Curie. Warszawa, 2006. Polish.

3 Sant M, Aareleid T, Berrino F, et al. Eurocare-3: survival of cancer patients diagnosed 1990-1994 results and comentary. Ann Oncol. 2003; 14 (Suppl 5): S61-S118.

4 Goldstein AM, Fraser MC, Struewing JP, et al. Increased risk of pancreatic cancer in melanoma-prone kindreds with p16INK4 mutations. N Engl J Med. 1995; 333: 970-974.

5 Brose MS, Rebbeck TR, Calzone KA, et al. Cancer risk estimates for *BRCA1* mutation carriers identified in a risk evaluation program. J Natl Cancer Inst. 2002; 94: 1365-1372.

6 Swift M, Chase CL, Morell D. Cancer praedysposition of ataxia–teleangiectasia heterozygotes. Cancer Genet Cytogenet. 1990; 46: 21-27.

7 Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology. 2000; 119: 1447-1453.

8 Park JG, Park YJ, Wijnen JT, Vasen HF. Gene-environment interaction in hereditary nonpolyposis colorectal cancer with implications for diagnosis and genetic testing. Int J Cancer. 1999; 82: 516-519.

9 Górski B, Byrski T, Huzarski T, et al. Founder mutation in *BRCA1* gene in Polish families with breast-ovarian cancer. Am J Genet. 2000; 66: 1963-1968.

10 Cybulski C, Górski B, Gronwald J, et al. *BRCA1* mutation and prostate cancer in Poland. Eur J Cancer Prev. 2008; 17: 62-66.

11 Benckova Z, Pauron L, Devic C, et. al. Molecular and cellular response of the most extensively used rodent glioma models to radiation and/or cisplatin. J Neurooncol. 2007; 83: 2-7.

12 Easton DF, Ford D, Bishop DT. Breast and ovarian cancer incidence in *BRCA1*-mutation carries. Breast Cancer Linkage Consortium. Am J Hum Genet. 1995; 56: 265-271.

13 Thompson D, Easton DF, Cancer incidence in *BRCA1* mutation Carries. J Natl Cancer Inst. 2002: 94: 1358-1365.

14 Klein AP, Hruban RH, Brune KA, et al. Familial pancreatic cancer. Cancer J. 2001; 7: 266-273.

15 Górski B, Cybulski C, Huzarski T, et al. Breast cancer predysposing alleles in Poland. Breast Cancer and Treatment. 2005; 92: 19-24.

16 Lal G, Liu G, Schmocker B, et al. Inherited predisposition to pancreatic adenocarcinoma: role of family history and germ-line p16, *BRCA1*, and *BRCA2* mutations. Cancer Res. 2000; 60: 409-416.

17 Greer JB, Whitcomb DC. Role of *BRCA1* and *BRCA2* mutations in pancreatic cancer. Gut. 2007; 56: 601-605.

18 Fernandez E, La Vecchia C, D'Avanzo B, et al. Family history and the risk of liver, gallbladder, and pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 1994; 3: 209-212.

19 Silverman DT, Schiffman M, Everhart J, et. al. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. Br J Cancer. 1999; 80:1830-1837.

20 Hruban RH, Petersen GM, Goggins M, et al. Familial pancreatic cancer. Ann Oncol. 1999; 10 (Suppl 4): S69-S73.

21 Silverman DT, Dunn JA, Hoover RN, et al. Cigarette smoking and pancreas cancer: a case-control study based on direct interviews. J Natl Cancer Inst. 1994; 86: 1510-1516.