ORIGINAL ARTICLE

# Possible association of the *BRCA2* gene C5972T variant with gastric cancer: a study on Polish population

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**KEY WORDS**

*BRCA2,* gastric cancer, polymorphism

**ABSTRACT**

**INTRODUCTION** Gastric cancer (GC) belongs to a group of cancers linked to *BRCA2* gene mutations and observed in patients with a family history of breast and ovarian cancers. A common variant allele (C5972T) observed in the *BRCA2* gene in the Polish population is associated with an increased risk of breast cancer.

**OBJECTIVES** The objective of the study was to assess a relationship between the *BRCA2* C5972T variant and GC.

**PATIENTS AND METHODS** A total of 380 patients with GC (234 men and 146 women; mean age, 59.0 ±12.8 years) and 380 sex- and age-matched healthy individuals (234 men and 146 women; mean age, 59.0 ±12.9 years) were included in this retrospective study. Polymerase chain reaction–restriction fragments length polymorphism (PCR-RFLP) was used to detect the *BRCA2* C5972T variant. We compared the frequency of *BRCA2* allele carriers among patients and controls. We also compared selected clinical and pathological features between allele carriers and noncarriers among patients with GC.

**RESULTS** The *BRCA2* C5972T variant was observed in 28 patients with GC (7.4%) and in 18 controls (4.7%) ($P = 0.17$). The odds ratio [OR] for GC in allele carriers was 1.59 (95% confidence interval [CI], 0.87–2.94). A comparison of selected clinical and pathological features between carriers and noncarriers did not show any significant differences. The analysis of a family history showed a trend for an increased risk of breast or ovarian cancer in the families of patients with GC carrying the C5972T allele (OR, 2.51; 95% CI, 0.80–7.88, $P = 0.11$).

**CONCLUSIONS** Our study showed that the C5972T allele is a low-penetrant variant of the *BRCA2* gene, which tended to increase the risk of GC. Further research is needed to fully elucidate the role of *BRCA2* polymorphisms in GC.

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**INTRODUCTION** Gastric cancer (GC) ranks as the second most common cancer-related cause of death in the world. On a global scale, there are almost 1 million new incidents of GC and more than 700 000 deaths each year.[1] In Poland, GC is the fourth and seventh leading cancer-related cause of death in men and women, respectively.[2] Stomach carcinogenesis is a complex process, and environmental causes, *Helicobacter pylori* infection, and genetic factors have all been implicated in its etiology. In 1998, Guilford et al.[3] described a hereditary diffuse gastric cancer (HDGC) syndrome, caused by germline mutations in the *CDH1* (E-cadherin) gene. Successive authors have focused on genetic causes in cancer development, particularly those that impede the repair of DNA damage. Not only germline but also missense mutations may play causative roles in carcinogenesis.

Numerous studies have examined the association between selected DNA repair gene polymorphisms and cancer susceptibility. Goode et al.,[4] analyzed 30 studies focusing on polymorphisms in DNA repair genes and their role in cancer development and showed that variants of selected

genes including *OGG1* (8-oxoguanine DNA glycosylase), *XRCC1* (X-ray repair cross-complementing protein 1), and *BRCA2* (breast cancer 2) may increase or reduce the risk of cancer at various sites. Dong et al.[5] reviewed the results of meta-analyses and pooled analyses examining the role of candidate gene polymorphisms in genetic susceptibility to cancer. A positive relationship was evident between genetic variants and cancer risk including an association between *MTHFR* (methylenetetrahydrofolate reductase) C677T variants and GC. Moreover, authors from Spain and Turkey confirmed the role of selected gene variants in gastric carcinogenesis in their countries.[6,7] Particularly in Asian populations, an increased risk of GC development has been attributed to the genetic variants of just 2 repair genes, *XRCC1* and *XRCC3*.[8-11] However, other studies performed in Brazilian, Chinese, Italian, and Polish populations have failed to find such an association.[12-15] Therefore, the relationship between the most commonly studied repair gene variants and GC is not entirely clear.

Less attention has been paid to the *BRCA2* gene mutation and its variants in gastric carcinogenesis even though indirect family-based studies have reported an increased risk for GC in families carrying *BRCA2* mutations.[16,17] Jakubowska et al.[18] confirmed that the *BRCA2* gene mutation is associated with familial aggregations of both breast cancer and GC in the Polish population. Similarly, our previous report on families with ovarian cancer and GC suggested that GC is part of the spectrum of cancers linked to BRCA2 gene mutations.[19] Still, a role of *BRCA2* variants in gastric carcinogenesis has not been fully clarified despite the evidence that common *BRCA2* human polymorphisms confer an increased risk of breast and ovarian cancers.[20-22]

The *BRCA2* gene is located on the long (q) arm of chromosome 13 at position 12.3 and encodes a tumor suppressor protein which helps repair damaged DNA and ensures stability of cellular genetic material. Even a single amino acid substitution resulting from a polymorphism might be pathogenic to genome integrity. Given the proven link between *BRCA2* germline mutations and GC risk in families with a history of breast and ovarian cancers as well as considering the role of *BRCA2* polymorphisms in breast and ovarian cancer development, it would be valuable to establish whether *BRCA2* nonsense mutations are also related to gastric carcinogenesis. This is a reasonable supposition because more than one-sixth of the patients in our GC group with a positive family history of cancer reported breast or ovarian cancers in close family relatives.

The purpose of this study was to examine a correlation between the *BRCA2* C5972T common polymorphism, recognized as being associated with an increased risk of early-onset breast cancer in Poland and GC, by examining the prevalence of the *BRCA2* variant in GC patients compared with controls.[23] We also searched for any unique clinical and pathological features in GC patients carrying the *BRCA2* polymorphism and examined a relationship between the polymorphism and risk of selected cancers in close family relatives of GC patients.

## PATIENTS AND METHODS

All enrolled participants were informed about the aim and methods of the study and signed an informed consent statement reviewed by our Institutional Ethics Committee. DNA from each patient was isolated from peripheral blood leukocytes and amplified using start sites specific to the gene sequence.

### Subjects

A total of 380 patients, diagnosed between January 1999 and December 2007 at the Department of Gastroenterology, Pomeranian Medical University, Szczecin, Poland, with histopathologically-confirmed GC, were included in this retrospective case control study. The mean age of all 380 patients (234 men and 146 women) was 59.0 ±12.8 years (range, 15–89 years). The following clinical and pathological data were collected: sex and age of the patients, family history of cancer, duration of symptoms, tumor site, stage, histology, *H. pylori* status, and blood group.

### Control group

The control group included 380 healthy individuals (234 men and 146 women; mean age 59.0 ±12.9 years) with a negative family history of cancer and residing in the region of Szczecin, Poland. These subjects were part of a population-based study of 1.3 million inhabitants of the West Pomerania province. The study was designed to identify familial aggregations of cancer and was performed by the International Hereditary Cancer Center, Department of Genetics and Pathology, Szczecin, Poland. Controls were matched to cases by age and sex.

### Tumor classification

The stage and histological type of GC were assessed by a routine histopathological examination. Histological types were classified according to the Lauren classification system.[24] The UICC TNM classification for malignant tumors was used for GC staging. Early GC was defined as invasive cancer that invaded no deeper than the submucosa, irrespective of lymph node metastasis. Tumor stage was defined as advanced in patients who had not undergone surgery or who presented with distal metastases or tumor infiltration confirmed by diagnostic procedures. Tumor location was classified as proximal (cardiac region) or other (truncus, antrum). Cases with complete stomach involvement were classified as having undetermined primary localization.

### *BRCA2* C5972T variant analysis

A *BRCA2* polymorphism analysis was performed at the International Hereditary Cancer Center, Department of Genetics and Pathology, Szczecin, Poland. The common *BRCA2* variant (Thr1915Met) was analyzed in 380 patients with GC and 380 controls by the polymerase chain reaction–restriction fragments

length polymorphism (PCR-RFLP) assay using primers b5972F (5'-CTC TCT AGA TAA TGA TGA ATG ATG CA) and b5972R (5'-CCA AAC TAA CAT CAC AAG GTG). The forward primer introduces an artificial restriction site for the Mph1103I enzyme (Fermentas, St. Leon-Rot, Germany).

***Helicobacter pylori* test** *Helicobacter pylori (H. pylori)* status was tested using the rapid urease test (GOLD Hpdry, Grupo Bios, Chile). The *H. pylori* test was regarded as reliable only in patients who were not treated with antimicrobial agents or antisecretory drugs or 2 weeks after stopping such treatment.

Four patients after a previous successful eradication therapy, which had been administered no longer than for 2 to 3 months before the diagnosis of GC, were included into the H. pylori-positive group. The eradication treatment was applied because of the endoscopic view suggesting uncomplicated peptic ulcer disease.

**Statistical analysis** For statistical analysis, we used the $\chi^2$ or Fisher exact test for categorical variables, and *t* test and Mann–Whitney test for continuous variables. A *P* value of less than 0.05 was considered statistically significant. All statistical analyses were performed with the statistical software package STATISTICA 10. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from 2-by-2 tables.

GC patients were compared to the control group according to the frequency of the tested polymorphism. GC patients with the *BRCA2* C5972T common variant were compared with GC patients–noncarriers with respect to selected clinical and pathological data. The family history of *BRCA2* C5972T allele carriers was investigated more thoroughly to estimate the risk of gastric, breast, and ovarian cancers in the first- and second-degree relatives of those patients.

## RESULTS

The baseline characteristics of GC patients are shown in TABLE 1. The median duration of symptoms was 6 months (range, 0–480 months). A surgery was performed in 244 patients, and the remainder underwent an exploratory surgery or were treated nonsurgically because of advanced GC or general contraindications. In 22.9% of all 353 cases with a well-defined site of cancer, a tumor was located in the proximal stomach. In the remaining 77.1% of the cases, the tumor site was classified as "other". In 27 cases, the entire stomach was involved or the tumor was located in the anastomosis from previous operations to treat ulcers; therefore, primary localization was not clear and could not be defined as either proximal or other. The primary histological type of the observed GC was diffuse (45.6%), followed by intestinal (44.9%) and mixed (9.5%). The most common stage of disease, according to the TNM classification, was stage IV (35.3%), followed by stage III (27.0%), stage II (20.7%), and stage I (17.0%). Fifty-nine patients with GC (18%) and a known stage (early vs advanced) of disease (n = 327) had early GC. The most common blood group in GC cases was group A (35.6%), followed by group O (34.9%), group B (19.0%), and group AB (10.5%). Of 169 cases with a known status of *H. pylori* infection, 76.9% were positive.

**Family history of cancers** A family history of GC patients is shown in TABLE 1 with more details presented in TABLE 2. Of 346 patients with a known family history, 180 (52%) had first- or second-degree relatives with cancer. Among those 180 cases, 72 (40%) reported GC and 33 (18.3%)—breast (n = 28) or ovarian (n = 5) cancer in first- or second-degree relatives. There were 11 GC cases with both GC and breast or ovary cancers in the family. Three of the 380 patients were afflicted with metachronous breast cancer and 1 with metachronous ovarian and skin cancers instead of GC. Three of those GC cases without a positive family history of breast or ovarian cancer were included into a risk analysis as first-degree relatives. In addition, 13.9% of the patients reported lung cancer; 11.1%, colon cancer; 6.7%, uterus cancer; and 14.4%, various other cancers (eg, leukemia, brain, skin, laryngeal, pancreatic, esophageal, thyroid) in close family members (there were families affected with 2 or more various cancers).

***BRCA2* C5972T variant** The *BRCA2* C5972T variant was observed in 28 patients with GC (7.4%) and in 18 controls (4.7%) (OR, 1.59; 95% CI, 0.87–2.94; *P* = 0.17; TABLE 2). The following characteristics were not different between cases with and without the *BRCA2* polymorphism: sex, age, duration of symptoms, family history of cancers (positive vs negative), disease stage, site of GC (proximal vs other), histology, *H. pylori* status, and blood group (TABLE 1). Two of four women with GC and metachronous breast or ovarian cancer were positive for the *BRCA2* variant allele.

Four cases with the *BRCA2* C5972T variant and early GC were further evaluated by colonoscopy, gynecological ultrasound, and mammography. Two of those cases presented other neoplasms or potentially preneoplastic lesions. In 1 case, a tumor in the periuterum region was diagnosed. The second case was diagnosed with multiple colon polyps.

TABLE 2 shows overall ORs between carriers and noncarriers of the *BRCA2* variant for gastric, breast, and ovarian cancers depending on family penetrance and the type of cancer. We observed a trend for an increased risk for breast and ovarian cancers in families testing positive for the polymorphism (OR, 2.51; 95% CI, 0.80–7.88; *P* = 0.11) but there was no risk of increase in GC (OR, 0.28; 95% CI, 0.04–2.16; *P* = 0.33).

## DISCUSSION

The current study suggests a possible link between the *BRCA2* C5972T common variant and GC development in the Polish population as well as a role of this variant in breast and ovarian carcinogenesis. The *BRCA2* C5972T

**TABLE 1** Comparison of the clinicopathological features of GC patients *BRCA2* variant carriers vs noncarriers

| Characteristics | | All patients, n | *BRCA2* carriers, n (%) | *BRCA2* noncarriers, n (%) | *P* value |
|---|---|---|---|---|---|
| sex | male | 234 | 13 (46.4) | 221 (62.8) | 0.09 |
| | female | 146 | 15 (53.6) | 131 (37.2) | |
| | total | 380 | – | – | |
| age, y, mean ± SD | | 59.0 ±12.8 | 57.0 ±12.6 | 59.2 ±12.9 | 0.39 |
| age, y | ≤50 | 104 | 7 (25.0) | 97 (27.6) | 0.77 |
| | >50 | 276 | 21 (75.0) | 255 (72.4) | |
| duration of symptoms, mo, median (range) | | 6 (0–480) | 5 (1–192) | 6 (0–480) | 0.74 |
| FHC | negative | 166 | 16 (61.5) | 150 (46.9) | |
| | positive | 180 | 10 (38.5) | 170 (53.1) | |
| | not available | 34 | | | |
| localization[a] | proximal | 81 | 5 (17.9) | 76 (23.4) | 0.72 |
| | other location | 272 | 23 (82.1) | 249 (76.6) | |
| | not determined | 27 | | | |
| histology | intestinal | 132 | 10 (41.7) | 122 (45.2) | |
| | diffuse | 134 | 12 (50.0) | 122 (45.2) | |
| | mixed | 28 | 2 (8.3) | 26 (9.6) | |
| | not available | 86 | | | |
| stage[b] | I | 55 | 5 (20.8) | 50 (16.7) | 0.49 |
| | II | 67 | 3 (12.5) | 64 (21.4) | |
| | III | 87 | 9 (37.5) | 78 (26.1) | |
| | IV | 114 | 7 (29.2) | 107 (35.8) | |
| | not available | 57 | | | |
| stage | early | 59 | 5 (20.8) | 54 (17.8) | 0.71 |
| | advanced | 268 | 19 (79.2) | 249 (82.2) | |
| | not available | 53 | | | |
| blood group | A | 105 | 13 (52.0) | 92 (34.1) | 0.18 |
| | B | 56 | 5 (20.0) | 51 (18.9) | |
| | 0 | 103 | 4 (16.0) | 99 (36.6) | |
| | AB | 31 | 3 (12.0) | 28 (10.4) | |
| | not available | 85 | | | |
| *Helicobacter pylori* | positive | 130 | 9 (69.2) | 121 (77.6) | 0.49 |
| | negative | 39 | 4 (30.8) | 35 (22.4) | |
| | not available | 211 | | | |

**a** tumor location in the stomach
**b** UICC TNM classification

Abbreviations: FHC, family history of cancer; SD, standard deviation

polymorphism was observed in 28 patients with GC (7.4%) and in 18 controls (4.7%) ($P = 0.17$). Although the difference was not significant, the percentage of *BRCA2* allele carriers in the GC group was almost twice higher that in controls and may indicate an increased risk for GC in *BRCA2* polymorphism carriers.

To the best of our knowledge, there are no direct data linking any *BRCA2* polymorphism with GC. A single study from Israel[25] examined 35 GC patients and found 2 patients (5.7%) carrying the 6174delT *BRCA2* mutation. The authors concluded that *BRCA2* germline mutations may contribute to GC genetic susceptibility in Jewish individuals. Berman et al.[26] analyzed DNA from 83 patients diagnosed with breast cancer and 93 diagnosed with ovarian cancer, with 42 of those patients reporting a family history of cancer. They identified 8 individuals carrying a common mutation (6174delT ) of the *BRCA2* gene and 3 of them (37%) had stomach cancer. The authors suggested that the *BRCA2* 6174delT mutation predisposed patients to various cancers, among others, to GC. These findings were supported by other reports suggesting that *BRCA2* mutations are likely to be the molecular basis for stomach cancer, but a direct relationship between *BRCA2* silent allele variants and GC development has not been examined.[16-19] Such an association is feasible on the basis of reports documenting the relationship between *BRCA2* polymorphisms and breast and ovarian cancers as well as considering the

**TABLE 2** Cancer risk in relation to *BRCA2* C5972T variant and family history of cancer

| Group | | No. of carriers, % | No. of noncarriers, % | OR (95% CI) | *P* value |
|---|---|---|---|---|---|
| controls | | 18 (4.7) | 362 (95.3) | reference | |
| cases | | 28 (7.4) | 352 (92.6) | 1.59 (0.87–2.94) | 0.17 |
| FHC | first-degree | 9 (5.8) | 145 (94.2) | 1.25 (0.55–2.84) | 0.66 |
| | second-degree | 1 (3.8) | 25 (96.2) | 0.80 (0.10–6.23) | 1.00 |
| FHC | GC only | 1 (1.4) | 71 (98.6) | 0.28 (0.04 | 0.33 |
| | BC/OC[a] | 4 (11.1) | 32 (88.9) | 2.51 (0.80 | 0.11 |
| | GC and BC/OC[b] | 0 (0) | 11 (100) | – | – |
| | other[c] | 5 (5.6) | 84 (94.4) | 1.18 (0.43 | 0.78 |
| BC only[a] | | 3 (10) | 27 (90) | 2.23 (0.62–8.07) | 0.19 |
| OC only[a] | | 1 (16.7) | 5 (83.3) | 4.02 (0.45–36.27) | 0.26 |

**a** 3 cases affected with metachronous breast or ovarian cancer without a positive family history of those 2 neoplasms were included into risk analysis as first-degree relatives
**b** including probands with both GC and BC/OC
**c** including probands with other than GC and BC/OC

Abbreviations: BC, breast cancer; CI, confidence interval; OC, ovarian cancer; OR, odds ratio; others, see **TABLE 1**

relationship between an increased risk of GC and polymorphisms in other DNA repair genes.[6-11,20-23]

Our study suggests that the *BRCA2* C5972T variant is possibly involved in breast and ovarian carcinogenesis. We observed a trend towards an increased risk for breast and ovarian cancers in GC patient families carrying the variant allele. Similarly, a trend for an increased risk for developing either cancer was also observed in those families when the incidence of each cancer was analyzed separately (**TABLE 2**): breast cancer (OR, 2.23; 95% CI, 0.62–8.07; $P = 0.19$) and ovarian cancer (OR, 4.02; 95% CI, 0.45–36.27; $P = 0.26$). A trend for an increased risk in variant carriers is confirmed by the finding that 2 GC patients positive for the *BRCA2* common variant were diagnosed with other metachronous cancers (in the first patient, ovarian and skin cancers, and in the second, breast cancer). These observations are in accordance with previous data from Górski et al.,[23] who studied 3241 Polish breast cancer patients and controls and showed an association between the *BRCA2* C5972T silent mutation and breast cancer, particularly in women younger than 40 years (OR, 1.4; 95% CI, 1.0–1.9; $P = 0.04$). If the relationship between an increased incidence of breast and ovarian cancers in families of GC patients carrying the *BRCA2* variant was verified, it would be useful in genetic screening for both cancers in the families of GC patients. However, our results showed no evidence of an increased risk for GC in families carrying the variant allele.

Although we only found a trend for an increased risk for GC in *BRCA2* C5972T allele carriers, 2 observations are noteworthy. First, the youngest GC patient among the 28 *BRCA2* variant carriers was a 15-year-old woman without a positive family history of cancer. Taking into account her young age at diagnosis and the time required for cancer growth, it may be assumed that this case was not likely the result of environmental agents but was rather caused by genetic factors, perhaps including the variant *BRCA2* allele. Secondly, although there were no statistical differences between GC patient C5972T carriers and noncarriers in terms of histology, 50% of the carriers were diagnosed with diffuse GC. This was a surprising finding because none of the *BRCA2* variant carriers in our study with diffuse GC had a positive family history of GC. Future studies will require larger populations with a family history of cancer to fully examine the incidence of diffuse GC. It has been suggested that HDGC is caused by a germline mutation in the *CDH1* gene.[3,27,28] However, a study has documented that the *CDH1* gene mutation is not present in Polish families that meet HDGC criteria.[29] Thus, other genetic factors may play a more important role in the development of HDGC in Polish families.

The limitation of our study is its retrospective design, which resulted in the lack of selected data. Although the *H. pylori* status was not significantly different between individual cases with and without the *BRCA2* polymorphism, it should be underlined that the *H. pylori* status was known only in 44.5% of the patients. What is more, according to the current recommendations, *H. pylori* tests should be performed at least 4 weeks after antibiotic therapy was completed. The time of 2 weeks before the *H. pylori* test adopted in our study could have affected the results of the infection status in our patients.

Considering these data, the relationship between the infection of *H. pylori* and genetic factors cannot be clearly assessed. It is possible that DNA alterations may be involved in the early stages of environmental carcinogenesis.

In conclusion, our study conducted on the Polish population suggests that GC may arise from a genetic background related to the *BRCA2* C5972T common polymorphism and indicates a possible role of the variant allele in the development of breast and ovarian cancers. These observations will require further research to fully

elucidate the role of *BRCA2* polymorphisms in gastric carcinogenesis.

**Contribution statement** MŁ and AJ conceived the idea for the study. MŁ, AJ, and TS contributed to the design of the research. All authors were involved in data collection. All authors edited and approved the final version of the manuscript. MŁ wrote the paper.

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# Możliwy związek pomiędzy polimorfizmem C5972T genu *BRCA2* i rakiem żołądka: badanie w polskiej populacji

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*BRCA2*, polimorfizm, rak żołądka

**STRESZCZENIE**

**WPROWADZENIE** Rak żołądka należy do grupy nowotworów związanych z mutacją genu *BRCA2* występujących u pacjentów, u których w wywiadzie rodzinnym stwierdza się obecność raka sutka i jajnika. Powszechny wariant C5972T genu *BRCA2* stwierdzany w populacji polskiej wiąże się z większym ryzykiem raka sutka.

**CELE** Celem badania było zbadanie związku pomiędzy wariantem C5972T genu *BRCA2* a rakiem żołądka.

**PACJENCI I METODY** Do badania o charakterze retrospektywnym włączono 380 pacjentów z rakiem żołądka (234 mężczyzn i 146 kobiet; średni wiek 59,0 ±12,8 roku) oraz 380 zdrowych osób dobranych pod względem płci i wieku (234 mężczyzn i 146 kobiet; średni wiek 59,0 ±12,9 roku). Wykorzystując metodę analizy polimorfizmów długości fragmentów restrykcyjnych (PCR-RFLP), dokonano identyfikacji polimorfizmu C5972T w genie *BRCA2*. Częstość występowania nosicielstwa polimorfizmu porównano w grupie chorych oraz w grupie kontrolnej. Porównano również pod względem wybranych cech klinicznych i histopatologicznych grupę chorych nosicieli badanego wariantu z grupą chorych bez polimorfizmu.

**WYNIKI** Wariant C5972T genu *BRCA2* stwierdzono u 28 chorych (7,4%) oraz u 18 osób w grupie kontrolnej (4,7%, p = 0,17). Iloraz szans wystąpienia (*odds ratio*, OR) raka żołądka u nosicieli badanego wariantu wynosił 1,59 (95% CI 0,87–2,94). Porównanie wybranych cech klinicznych i histopatologicznych w grupie chorych nosicieli badanego wariantu i chorych bez nosicielstwa polimorfizmu nie wykazało istotnych różnic. Analiza wywiadu rodzinnego wykazała tendencję do wzrostu ryzyka występowania raka sutka lub jajnika w rodzinach pacjentów z rakiem żołądka, którzy są nosicielami polimorfizmu *BRCA2* (OR 2,51; 95% CI 0,80–7,88, p = 0,11).

**WNIOSKI** Badanie wykazało, że C5972T jest wariantem genu *BRCA2* o niskiej penetracji, wykazującym tendencję do zwiększania ryzyka raka żołądka. Konieczne są dalsze badania, które definitywnie wyjaśnią rolę polimorfizmów genu *BRCA2* u chorych z rakiem żołądka.

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