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***BRCA1*-associated breast and ovarian cancer risks in Poland: no association with commonly studied polymorphisms**

Anna Jakubowska · Jacek Gronwald · Janusz Menkiszak · Bohdan Górski · Tomasz Huzarski · Tomasz Byrski · Aleksandra Tołoczko-Grabarek · Michael Gilbert · Lutz Edler · Marc Zapatka · Roland Eils · Jan Lubiński · Rodney J. Scott · Ute Hamann

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Abstract Polymorphisms in genes involved in DNA repair, steroid hormone biosynthesis/metabolism/signaling, folate metabolism as well as cell growth are prime candidates for possible associations with breast and ovarian cancer risk in women with an inherited predisposition. We investigated 29 polymorphisms in 20 genes encoding key proteins of the above four biological pathways for their breast and ovarian cancer risk modifying effect in Polish women harboring *BRCA1* founder mutations. Of the analyzed genes, *ERCC2*, *XRCC1*, *XRCC2*, *XRCC3* and *Lig4* participate in DNA repair, *TP53* in cell cycle check point control, *AIB1*, *AR*, *COMT*, *CYP11A1*, *CYP17A1*, *CYP19A1*, *HSD17* and *PGR* in steroid hormone biosynthesis/metabolism/signaling, *TYMS* in folate metabolism and *HER2*, *IL6*, *LRP1*, *TGFB* and *TGFBR1* affect cell growth. Using validated methods, we genotyped 319 breast cancer cases, 146 ovarian cancer cases and 290 unaffected controls, all of whom harbored one of three causative mutations in *BRCA1*.

Our results revealed no association of any of the investigated polymorphisms with *BRCA1*-associated breast or ovarian cancer risk. Thus, it appears that these polymorphisms do not influence disease risk in Polish women carrying one of the three common *BRCA1* founder mutations.

Keywords *BRCA1* · Breast cancer · Ovarian cancer · Polymorphism · Modifying gene

Introduction

Breast and ovarian cancers are a leading cause of morbidity and mortality in women worldwide. The major inherited susceptibilities to these cancers are germline mutations in either *BRCA1* or *BRCA2* [1]. It has been estimated that *BRCA1* mutation carriers have high average lifetime risks of developing breast and ovarian cancers [2]. Notwithstanding, there are substantial differences in the penetrance

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of disease both within and between families that is best explained by genetic and/or shared environmental factors affecting the risk of breast and ovarian cancers [3].

Both, breast and ovarian cancers are hormonally influenced diseases that point to the importance of mechanisms underlying steroid biosynthesis, metabolism and signaling as well as cell growth. A number of reports have suggested that polymorphisms in steroid receptors and some of their downstream effectors may be associated with an altered risk of disease [4–13]. However, these reports are controversial, since conflicting results have also been published [14–21]. The relationship between aberrant estrogen metabolism and increased levels of DNA damage implicate the various DNA repair pathways that are invoked as a result of an increased level of free-radicals in the target tissue. Excessive levels of estrogen are associated with increased cell division, which requires a large pool of purines and pyrimidines for rapid DNA synthesis. The supply of methionine is crucial for pyrimidine synthesis, as decreased levels are associated with base mis-incorporation, which ultimately results in an increased likelihood of not only genetic errors, but also invocation of DNA repair enzymes.

While a large number of previous studies have reported associations of various polymorphic variants in genes involved in DNA repair, steroid hormone biosynthesis/metabolism/signaling, folate metabolism and cell growth with sporadic breast or ovarian cancer risk [4–33], little data on the potential role of these genetic factors as modifiers of hereditary disease risks have been published [34–42]. Therefore, we investigated whether variants in genes of these four regulatory pathways may act as modifiers of breast and ovarian cancer risk in Polish women carrying one of the three common *BRCA1* founder mutations (4153delA, 5328insC and C61G) [43, 44]. Genotyping analysis was performed in 319 breast cancer cases, 145 ovarian cancer cases and 290 controls.

Materials and methods

Study participants

The Pomeranian cancer registry contained clinical and epidemiological data from 1,940 individuals carrying one of the three common Polish *BRCA1* founder mutations, 5382insC, 300 T>G and 4153delA. Mutation carriers were selected from families with at least one breast cancer diagnosed before 50 years of age or ovarian cancer at any age or with strong history of breast and/or ovarian cancer. All clinical data have been verified from medical records and were collected from 1997 to 2002. A self-administered

questionnaire was used to collect information on potential epidemiological risk factors.

From the registered *BRCA1* carriers, 755 female *BRCA1* mutation carriers for whom DNA samples were available—319 breast cancer cases, 146 ovarian cancer cases and 290 unaffected controls—were included in this study. All study participants were of Polish origin and resided in Poland. They were considered as breast cancer cases, if they were diagnosed with an invasive primary breast cancer and had not undergone prophylactic mastectomy or adnexectomy prior to the age of breast cancer diagnosis and as ovarian cancer cases, if they were diagnosed with invasive primary ovarian cancer (excluding borderline ovarian carcinoma) and had not undergone prophylactic mastectomy, adnexectomy or tubal ligation prior to the age of ovarian cancer diagnosis. They were considered as controls for breast cancer cases, if they were unaffected by breast cancer, in situ breast carcinoma or any other type of cancer and had not undergone prophylactic mastectomy or adnexectomy and as controls for ovarian cancer cases if they were unaffected by ovarian cancer or any other type of cancer and had not undergone prophylactic mastectomy, adnexectomy or tubal ligation.

The number of subjects in the various subgroups, the median ages of breast and ovarian cancer cases at the time of diagnosis and the median ages of controls at the time of interview are shown in Table 1. The research was approved by the Ethics Committee of Pomeranian Medical University in Szczecin, Poland and all participants gave informed consent prior to enrolling in the study. All women received genetic counseling prior to and at the provision of their test results.

Genetic analyses

Twenty-nine polymorphisms in 20 genes involved in DNA repair, steroid hormone biosynthesis/metabolism/signaling, folate metabolism and cell growth were genotyped. The genes, variants under investigation and genotyping methods are given in Supplementary Tables 1 and 2.

Genomic DNA was isolated from peripheral blood leukocytes according to Lahiri and Schnabel [45]. Seventeen restriction fragment lengths polymorphisms (RFLPs), six insertion/deletion polymorphisms and six repeat polymorphisms were genotyped by PCR-based fragment analyses using the CEQTM 8000 Genetic DNA Analysis System (Beckman Coulter, Krefeld, Germany) and/or ethidium bromide-stained agarose gels (Sigma–Aldrich, Steinheim, Germany), which were scored by UV visualization. Primer sequences, PCR and genotyping conditions are presented in Supplementary Table 2. *CYP17A1* -34T>C, *CYP19A1* 15210(TTTA)_n, *CYP19A1* 15262delCTT and *COMT* 1222G>A were genotyped as described earlier [46].

Table 1 Study groups, median ages of cases at diagnosis of breast and ovarian cancers and of controls at the time of interview

	No. of cases and controls ^a	Risk factor data available	Median age of cases at cancer diagnosis in years (range)	Median age of controls at the time of interview in years (range)
<i>Breast cancer cases/controls</i>				
	319/290 (total)		41 (22–74)	44 (18–85)
	232/225	Yes	41 (24–74)	44 (18–85)
	87/65	No	39 (22–56)	48 (34–75)
<i>Ovarian cancer cases/controls</i>				
	146/280 (total)		47 (25–75)	44 (18–85)
	85/215	Yes	46 (25–71)	44 (18–85)
	61/65	No	48 (27–75)	48 (34–75)

^a Two-hundred and eighty of the controls were used as controls for both breast and ovarian cancers

Genotyping was performed by laboratory personnel blinded to the case–control status. The reproducibility of the genotyping data was assessed by repeated analysis of 5% of randomly selected DNA samples. Genotyping accuracy was assessed by sequencing of several samples with detected polymorphic variants. Call rates for individual polymorphisms were greater than 96% and concordance of duplicates was 100%.

Statistical analysis

Risk estimates were calculated as odds ratios (OR) with 95% confidence intervals (CI) using both univariate and multivariate unconditional logistic regression. Crude ORs (OR_{crude}) were calculated for 319 breast cancer cases and 290 controls and 146 ovarian cancer cases and 280 controls. For 232 breast cancer cases and 225 controls and 85 ovarian cancer cases and 215 controls, we adjusted for potential breast/ovarian cancer risk factors, referred to as adjusted ORs (OR_{adj}), by including age at first live birth (0, ≤24, >24 years), parity, lifetime cumulative months of breastfeeding (≤12, >12 months), age at menarche, oral contraceptive (OC) use (<5, ≥5 years), smoking (0, <4, ≥4 pack-years), body mass index (BMI) (at age of breast cancer diagnosis for cases and at time of interview for controls), year of birth and *BRCA1* mutation in the multivariate logistic regression model.

The statistical analyses were performed using the SAS/STAT(r) software (Version 9.1 of the SAS System for Windows, Cary, NC, USA, SAS Institute Inc. 2003), with the procedure LOGISTIC.

Repeat polymorphisms were treated as a two- or three-level categorized variable defined by a certain cutpoint. The cutpoints used were described earlier and provided the categories <28/<28+<28/≥28 and ≥28/≥28 for *AIB1* 28824 (CAG/CAA)*n* [34–37], ≥29/≥29+≥29/<29 and <29/<29 for *AR* 171(CAG)*n* [38, 39], <10/<10, <10/≥10 and ≥10/≥10 for *CYP19A1* 15210(TTTA)*n* [9], 3/3, 2/2 and 2/3+2/4 for *TYMS* -97(28)*n* [11] and 6/6+6/9 and 9/9+9/10 for *TGFBR1* 52(GCG)*n* [32]. For *XRCC3* 204(GT)*n*, cutpoint

14 was selected using maximal selected rank statistics [47], yielding the categories ≤14/≤14, ≤14/>14 and >14/>14. For *CYP11A1* (AAAAT)*n*, the categories were 4/4, 4/6, 6/6, 8/any and others [26]. Allele frequencies of repeat polymorphisms between cases and controls were compared using Pearson's chi square test. For each SNP, statistical modeling was performed using unconditional logistic regression to assess the predicted power of the study. Bonferroni correction was used to account for multiple testing and a two-tailed *P* value < 0.0017 was considered statistically significant.

Results

The distribution of selected cancer risk factors including year of birth, age at menarche, age at first live birth, parity, duration of breastfeeding, smoking, BMI and *BRCA1* mutation was similar between breast and ovarian cancer cases and their corresponding controls (Table 2).

In total, 755 study participants were genotyped at 29 polymorphisms in 20 genes, which included eleven variants in five DNA repair genes (*ERCC2*, *XRCC1*, *XRCC2*, *XRCC3* and *Lig4*) and the cell cycle check point control gene (*TP53*), five variants in five growth factor and receptor genes (*HER2*, *IL6*, *LRP1*, *TGFBI* and *TGFBR1*), two variants in the thymidylate synthetase gene (*TYMS*) and eleven variants in eight genes associated with steroid hormone biosynthesis, metabolism and signaling (*AIB1*, *AR*, *COMT*, *CYP11A1*, *CYP17A1*, *CYP19A1*, *HSD17B1* and *PGR*).

The distribution of the genotype frequencies among breast and ovarian cancer cases and their respective controls is shown in Table 3. Three polymorphisms, *XRCC3* 204(GT)*n*, *COMT* 1222G>A and *CYP11A1* (AAAAT)*n* appeared to be related to disease expression in ovarian cancer (OR_{crude} 2.24, 95% CI 1.02–4.92 OR_{crude} 1.85, 95% CI 1.01–3.48 and OR_{crude} 0.54, 95% CI 0.31–0.95, respectively). Two other polymorphisms, *TP53* 441G>C and *TGFBI* -1349C>T, were associated with an increased breast cancer risk after adjustment for potential risk factors (OR_{adj}

Table 2 Characteristics of breast and ovarian cancer cases and their corresponding controls

Characteristics	Breast cancer cases (<i>n</i> = 232)	Controls for breast cancer cases (<i>n</i> = 225)	Ovarian cancer cases (<i>n</i> = 85)	Controls for ovarian cancer cases (<i>n</i> = 215)
Median year of birth (range)	1955 (1926–1974)	1958 (1917–1985)	1952 (1930–1971)	1958 (1917–1985)
Median age of first live birth (range)	23 (17–37)	23 (16–36)	23 (16–38)	23 (16–36)
Median age at menarche (range)	13 (10–18)	14 (9–18)	14 (10–17)	14 (9–18)
Median BMI (range)	24 (12–42)	24 (16–42)	25 (18–38)	24 (16–44)
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Parity				
0	17 (7)	26 (12)	7 (8)	23 (11)
1	46 (20)	42 (19)	14 (16)	40 (19)
2	110 (47)	96 (43)	43 (51)	96 (45)
3	41 (18)	45 (20)	14 (16)	42 (19)
4	10 (4)	11 (5)	6 (7)	9 (4)
>4	8 (3)	5 (2)	1 (1)	5 (2)
Breastfeeding ^a				
≤12 months	81 (38)	61 (31)	23 (29)	58 (30)
>12 months	134 (62)	138 (69)	55 (71)	134 (70)
OC use				
<5 years	221 (95)	207 (92)	84 (99)	197 (92)
≥5 years	11 (5)	18 (8)	1 (1)	18 (8)
Smoking				
<4 pack-years	138 (59)	143 (64)	58 (68)	136 (63)
≥4 pack-years	94 (41)	82 (36)	27 (32)	79 (37)
<i>BRCA1</i> mutation				
5382insC	165 (71)	156 (69)	63 (74)	149 (69)
C61G	53 (23)	52 (23)	16 (19)	49 (23)
4153delA	14 (6)	17 (8)	6 (7)	17 (8)

BMI body mass index, OC oral contraceptive

^a Nulliparous women were excluded

1.56, 95% CI 1.04–2.34 and OR_{adj} 1.91, 95% CI 1.01–3.60, respectively). However, upon correction for multiple testing the significance of these effects vanished.

There were no significant differences in the allele frequencies of the *AIB1* 28824(CAG/CAA)*n*, *AR* 171(CAG)*n*, *CYP11A1* (AAAAT)*n*, *CYP19A1* 15210(TTTA)*n*, *TYMS* -97(28)*n*, *TGFBR1* 52(GCG)*n* and *XRCC3* 204(GT)*n* repeat polymorphisms between breast and ovarian cancer cases and their corresponding controls (Supplementary Table 3).

Discussion

We performed association studies at 29 polymorphic loci in 20 genes encoding proteins involved in DNA repair, folate metabolism, steroid hormone biosynthesis/metabolism/

signaling and cell growth to identify genetic variants that may modify *BRCA1*-associated breast and ovarian cancer risk. Numerous studies investigated polymorphisms in sporadic breast and ovarian cancer populations often yielding controversial results [4–31]; however, little is known about the effects of these polymorphisms on disease risk in women with an inherited predisposition.

A few of the polymorphisms investigated in this study have been previously analyzed for their potential risk modifying effect in *BRCA1/2* mutation carriers. An association of long *AIB1* 28824(CAG/CAA)*n* alleles (≥28 and ≥29 repeats) with an increased breast cancer risk was reported in two studies among *BRCA1/2* mutation carriers [34, 35], which, however, was not confirmed in two other studies [36, 37] or in the present study. Similarly, conflicting results were published for *AR* 171(CAG)*n*. One study reported an

Table 3 Genotype frequencies in the breast and ovarian cancer cases and their corresponding controls

Genotype	Breast cancer				Ovarian cancer							
	Cases n (%)	Controls n (%)	OR _{crude} (95% CI)	P	OR _{adj} ^a (95% CI)	P	Cases n (%)	Controls n (%)	OR _{crude} (95% CI)	P	OR _{adj} ^a (95% CI)	P
<i>DNA repair</i>												
<i>ERCC2 6540G>A</i>												
G/G	118 (38)	106 (37)	1.00 (reference)		1.00 (reference)		59 (36)	102 (36)	1.00 (reference)		1.00 (reference)	
G/A	152 (48)	135 (46)	1.01 (0.71–1.43)	0.95	1.19 (0.78–1.81)	0.42	59 (41)	129 (46)	0.79 (0.51–1.23)	0.30	0.83 (0.45–1.53)	0.54
A/A	44 (14)	49 (17)	0.81 (0.50–1.31)	0.38	0.97 (0.54–1.73)	0.91	26 (18)	49 (18)	0.92 (0.52–1.63)	0.77	1.09 (0.49–2.40)	0.83
<i>ERCC2 18880A>C</i>												
A/A	107 (34)	105 (36)	1.00 (reference)		1.00 (reference)		58 (40)	100 (36)	1.00 (reference)		1.00 (reference)	
A/C	154 (49)	128 (44)	1.18 (0.83–1.69)	0.36	1.22 (0.79–1.87)	0.36	65 (45)	123 (44)	0.91 (0.59–1.42)	0.68	1.09 (0.59–2.00)	0.79
C/C	54 (17)	57 (20)	0.93 (0.59–1.47)	0.76	1.08 (0.63–1.86)	0.78	22 (15)	57 (20)	0.66 (0.36–1.20)	0.17	0.79 (0.35–1.74)	0.55
<i>LIG4 1704C>T</i>												
T/T	207 (65)	196 (68)	1.00 (reference)		1.00 (reference)		91 (63)	188 (67)	1.00 (reference)		1.00 (reference)	
T/C+C/C	112 (35)	94 (32)	1.13 (0.81–1.58)	0.48	1.01 (0.67–1.51)	0.97	54 (37)	92 (33)	1.21 (0.80–1.84)	0.37	1.50 (0.85–2.65)	0.16
<i>TP53 237ins16</i>												
del/del	208 (67)	195 (68)	1.00 (reference)		1.00 (reference)		99 (69)	189 (68)	1.00 (reference)		1.00 (reference)	
del/ins+ins/ins	103 (33)	92 (32)	1.05 (0.74–1.48)	0.78	1.21 (0.81–1.83)	0.35	45 (31)	88 (32)	0.98 (0.63–1.51)	0.91	1.05 (0.58–1.93)	0.86
<i>TP53 441G>C</i>												
G/G	152 (48)	144 (50)	1.00 (reference)		1.00 (reference)		68 (47)	141 (50)	1.00 (reference)		1.00 (reference)	
G/C	142 (45)	113 (39)	1.19 (0.85–1.67)	0.31	1.56 (1.04–2.34)	0.03	63 (44)	108 (39)	1.21 (0.79–1.85)	0.38	1.35 (0.75–2.45)	0.32
C/C	24 (7)	33 (11)	0.69 (0.39–1.22)	0.20	0.67 (0.34–1.35)	0.27	13 (9)	31 (11)	0.87 (0.43–1.77)	0.70	0.92 (0.37–1.31)	0.86
<i>TP53 1798G>A</i>												
G/G	230 (72)	208 (72)	1.00 (reference)		1.00 (reference)		107 (74)	201 (72)	1.00 (reference)		1.00 (reference)	
G/A	82 (26)	76 (26)	0.97 (0.68–1.40)	0.89	1.08 (0.69–1.67)	0.74	34 (23)	73 (26)	0.87 (0.55–1.40)	0.58	1.12 (0.59–2.12)	0.73
A/A	7 (2)	6 (2)	1.06 (0.35–3.19)	0.92	3.64 (0.68–19.35)	0.13	4 (3)	6 (2)	1.25 (0.35–4.53)	0.73	4.35 (0.53–35.50)	0.17
<i>XRCC1 23885G>A</i>												
G/G	131 (41)	105 (36)	1.00 (reference)		1.00 (reference)		52 (36)	100 (36)	1.00 (reference)		1.00 (reference)	
G/A	150 (47)	142 (49)	0.85 (0.60–1.19)	0.34	0.73 (0.48–1.10)	0.13	68 (48)	138 (49)	0.95 (0.61–1.48)	0.81	0.70 (0.38–1.3)	0.26
A/A	36 (11)	43 (15)	0.67 (0.40–1.12)	0.13	0.67 (0.36–1.25)	0.20	23 (16)	42 (15)	1.05 (0.57–1.94)	0.87	0.91 (0.38–2.19)	0.83
<i>XRCC2 27158G>A</i>												
G/G	272 (87)	254 (88)	1.00 (reference)		1.00 (reference)		128 (89)	246 (88)	1.00 (reference)		1.00 (reference)	
G/A+A/A	42 (13)	36 (12)	1.09 (0.68–1.75)	0.72	1.22 (0.67–2.23)	0.52	16 (11)	34 (12)	0.90 (0.48–1.70)	0.76	0.62 (0.22–1.72)	0.36
<i>XRCC3 204(GT)n</i>												
≤ 14/≤ 14	42 (13)	38 (13)	1.00 (reference)		1.00 (reference)		9 (6)	36 (13)	1.00 (reference)		1.00 (reference)	
≤ 14/>14	144 (46)	121 (42)	1.08 (0.65–1.78)	0.77	1.21 (0.66–2.04)	0.53	65 (45)	117 (42)	2.22 (1.01–4.90)	0.05	2.12 (0.72–6.28)	0.17
>14/>14	127 (41)	129 (45)	0.89 (0.54–1.47)	0.65	1.11 (0.61–2.04)	0.73	70 (49)	125 (45)	2.24 (1.02–4.92)	0.04	2.15 (0.73–6.37)	0.17

Table 3 continued

Genotype	Breast cancer				Ovarian cancer					
	Cases n (%)	Controls n (%)	OR _{crude} (95% CI)	OR _{adj} ^a (95% CI)	P	Cases n (%)	Controls n (%)	OR _{crude} (95% CI)	OR _{adj} ^a (95% CI)	P
<i>XRCC3</i> 11498A>G										
A/A	131 (41)	106 (37)	1.00 (reference)	1.00 (reference)		46 (32)	101 (36)	1.00 (reference)	1.00 (reference)	
A/G	142 (44)	151 (52)	0.76 (0.54–1.07)	0.12 0.73 (0.48–1.1)	0.13	82 (57)	146 (52)	1.23 (0.79–1.92)	1.39 (0.74–2.60)	0.31
G/G	46 (8)	33 (11)	1.128 (0.67–1.89)	0.65 0.16 (0.62–2.17)	0.64	16 (11)	33 (12)	1.06 (0.53–2.12)	1.56 (0.62–3.97)	0.35
<i>XRCC3</i> 11672C>T										
C/C	135 (43)	131 (45)	1.00 (reference)	1.00 (reference)		67 (47)	127 (45)	1.00 (reference)	1.00 (reference)	
C/T	141 (44)	118 (41)	1.16 (0.82–1.63)	0.39 1.10 (0.72–1.67)	0.65	66 (46)	114 (41)	1.1 (0.72–1.68)	1.08 (0.60–1.95)	0.80
T/T	41 (13)	41 (14)	0.97 (0.59–1.59)	0.90 0.78 (0.43–1.42)	0.42	10 (7)	39 (14)	0.49 (0.23–1.03)	0.58 (0.22–1.52)	0.27
<i>Growth factors and receptors</i>										
<i>HER2</i> 23097A>G										
A/A	184 (58)	177 (61)	1.00 (reference)	1.00 (reference)		93 (64)	170 (61)	1.00 (reference)	1.00 (reference)	
A/G+G/G	135 (42)	113 (39)	1.15 (0.83–1.59)	0.40 1.07 (0.72–1.59)	0.73	52 (36)	110 (39)	0.86 (0.57–1.31)	0.49 0.73 (0.41–1.31)	0.29
<i>IL6</i> -237G>C										
G/G	93 (29)	73 (25)	1.00 (reference)	1.00 (reference)		42 (29)	72 (26)	1.00 (reference)	1.00 (reference)	
G/C	159 (50)	144 (50)	0.87 (0.59–1.27)	0.46 0.88 (0.56–1.40)	0.60	68 (47)	139 (50)	0.52–1.35)	0.47 0.97 (0.50–1.87)	0.92
C/C	67 (21)	73 (25)	0.72 (0.46–1.13)	0.15 0.82 (0.48–1.43)	0.49	35 (24)	69 (24)	0.87 (0.50–1.52)	1.12 (0.52–2.44)	0.77
<i>LRP1</i> 12519C>T										
C/C	233 (73)	204 (70)	1.00 (reference)	1.00 (reference)		113 (78)	198 (71)	1.00 (reference)	1.00 (reference)	
C/T+T/T	86 (27)	86 (30)	0.87 (0.61–1.25)	0.46 0.85 (0.55–1.31)	0.45	32 (22)	82 (29)	0.68 (0.43–1.09)	0.11 0.69 (0.35–1.33)	0.27
<i>TGFB1</i> -1349C>T										
C/C	127 (40)	115 (40)	1.00 (reference)	1.00 (reference)		56 (39)	108 (39)	1.00 (reference)	1.00 (reference)	
C/T	144 (45)	145 (50)	0.90 (0.64–1.27)	0.54 0.89 (0.59–1.34)	0.58	74 (51)	143 (51)	1.0 (0.65–1.53)	1/23 (0.68–2.24)	0.49
T/T	48 (15)	30 (10)	1.45 (0.86–2.44)	0.16 1.91 (1.01–3.60)	0.046	14 (10)	29 (10)	0.93 (0.46–1.9)	1.37 (0.48–3.88)	0.55
<i>TGFBR1</i> 52(GCG)n										
9A/9A+9A/10A	282 (88)	252 (87)	1.00 (reference)	1.00 (reference)		122 (85)	244 (87)	1.00 (reference)	1.00 (reference)	
6A/6A+6A/9A	37 (12)	38 (13)	0.87 (0.54–1.41)	0.57 0.85 (0.49–1.50)	0.58	22 (15)	35 (13)	1.26 (0.71–2.24)	0.44 0.75 (0.33–1.74)	0.50
<i>Folate metabolism</i>										
<i>TYMS</i> -97(28)n										
3/3	90 (29)	87 (30)	1.00 (reference)	1.00 (reference)		47 (33)	81 (29)	1.00 (reference)	1.00 (reference)	
2/2	66 (21)	63 (22)	1.01 (0.64–1.59)	0.95 1.04 (0.58–1.85)	0.89	33 (23)	63 (22)	0.90 (0.52–1.57)	0.72 0.58 (0.30–1.09)	0.79
2/3+2/4	158 (50)	140 (48)	1.09 (0.75–1.58)	0.64 1.13 (0.72–1.77)	0.61	64 (44)	136 (49)	0.81 (0.51–1.29)	1.55 (0.42–5.72)	0.09
<i>TYMS</i> 15699del6										
wt/wt	166 (54)	134 (46)	1.00 (reference)	1.00 (reference)		66 (46)	130 (46)	1.00 (reference)	1.00 (reference)	
wt/del+del/del	144 (46)	156 (54)	0.74 (0.54–1.03)	0.07 0.79 (0.54–1.17)	0.24	78 (54)	150 (54)	1.02 (0.68–1.53)	0.91 0.88 (0.51–1.54)	0.65

Table 3 continued

Genotype	Breast cancer				Ovarian cancer							
	Cases n (%)	Controls n (%)	OR _{crude} (95% CI)	P	OR _{adj} ^a (95% CI)	P	Cases n (%)	Controls n (%)	OR _{crude} (95% CI)	P	OR _{adj} ^a (95% CI)	P
<i>Steroid hormone biosynthesis, metabolism and signaling</i>												
<i>ATBI 28824(CAG/CAA)n</i>												
<28/<28+<28/≥28	73 (24)	66 (23)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	33 (23)	64 (24)	1.00 (reference)	1.00 (reference)	1.00 (reference)	0.71
≥28/≥28	234 (76)	215 (77)	0.98 (0.67–1.44)	0.93 (0.54–1.41)	0.58	0.58	110 (77)	207 (76)	1.03 (0.64–1.66)	0.90	1.14 (0.57–2.27)	0.71
<i>AR 171(CAG)n</i>												
<29/<29	296 (95)	276 (96)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	6 (4)	12 (4)	1.00 (reference)	1.00 (reference)	1.00 (reference)	0.47
≥29/≥29+≥29/<29	14 (5)	10 (4)	1.08 (0.49–2.41)	0.85 (0.60–4.28)	0.34	0.34	138 (96)	264 (96)	0.96 (0.35–2.60)	0.93	1.64 (0.42–6.39)	0.47
<i>COMT 1222G>A</i>												
G/G	71 (22)	68 (23)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	27 (19)	67 (24)	1.00 (reference)	1.00 (reference)	1.00 (reference)	0.09
G/A	164 (52)	168 (58)	0.93 (0.63–1.39)	0.74 (0.46–1.21)	0.23	0.23	82 (56)	164 (59)	1.85 (1.01–3.48)	0.05	2.18 (0.87–5.43)	0.09
A/A	84 (26)	54 (19)	1.49 (0.92–2.40)	0.10 (0.73–2.34)	0.36	0.36	37 (25)	49 (17)	1.24 (0.74–2.09)	0.42	1.62 (0.76–3.45)	0.21
<i>CYP11A1 (AAAAT)n</i>												
4/4	105 (34)	103 (36)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	59 (41)	100 (36)	1.00 (reference)	1.00 (reference)	1.00 (reference)	0.08
4/6	92 (29)	77 (27)	1.17 (0.78–1.76)	0.44 (0.69–1.83)	0.63	0.63	24 (17)	75 (27)	0.54 (0.31–0.95)	0.03	0.51 (0.24–1.08)	0.08
6/6	20 (6)	11 (4)	1.78 (0.81–3.91)	0.15 (0.42–2.64)	0.92	0.92	7 (5)	11 (4)	1.08 (0.40–2.93)	0.88	0.48 (0.11–2.16)	0.34
8/any	51 (16)	62 (21)	0.81 (0.51–1.28)	0.36 (0.49–1.51)	0.60	0.60	30 (21)	60 (21)	0.85 (0.49–1.46)	0.55	0.72 (0.34–1.55)	0.41
Others	45 (14)	37 (13)	1.19 (0.71–1.99)	0.50 (0.68–2.34)	0.46	0.46	24 (17)	34 (12)	1.20 (0.65–2.21)	0.57	1.13 (0.47–2.72)	0.78
<i>CYP17A1 -34T>C</i>												
T/T	108 (34)	100 (34)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	48 (33)	97 (35)	1.00 (reference)	1.00 (reference)	1.00 (reference)	0.50
T/C	166 (52)	136 (47)	1.13 (0.79–1.61)	0.50 (0.70–4.18)	0.72	0.72	77 (53)	130 (46)	1.20 (0.77–1.87)	0.43	1.24 (0.66–2.31)	0.50
C/C	45 (14)	54 (19)	0.77 (0.48–1.25)	0.29 (0.83 (0.46–1.49)	0.53	0.53	21 (14)	53 (19)	0.80 (0.43–1.48)	0.48	1.03 (0.44–2.40)	0.94
<i>CYP19A1 15162delCTT</i>												
ins/ins	164 (53)	152 (53)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	71 (49)	148 (53)	1.00 (reference)	1.00 (reference)	1.00 (reference)	0.47
ins/del	117 (37)	113 (39)	0.96 (0.68–1.35)	0.81 (0.82–1.86)	0.32	0.32	59 (41)	108 (39)	1.14 (0.74–1.74)	0.55	1.25 (0.68–2.28)	0.47
del/del	31 (10)	24 (8)	1.20 (0.67–2.13)	0.54 (0.62–2.63)	0.50	0.50	14 (10)	23 (8)	1.27 (0.62–2.61)	0.52	1.14 (0.43–3.02)	0.80
<i>CYP19A1 15210(TTTA)</i>												
<10/<10	102 (33)	89 (31)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	52 (36)	86 (31)	1.00 (reference)	1.00 (reference)	1.00 (reference)	0.67
<10/≥10	151 (48)	141 (49)	0.93 (0.65–1.35)	0.71 (0.57–1.37)	0.58	0.58	67 (47)	136 (49)	0.81 (0.52–1.28)	0.37	0.87 (0.47–1.63)	0.67
≥10/≥10	59 (19)	59 (20)	0.87 (0.55–1.38)	0.56 (0.36–1.13)	0.12	0.12	25 (17)	57 (20)	0.72 (0.41–1.30)	0.28	0.79 (0.35–1.82)	0.58
<i>HSD17B1 -7163del12</i>												
ins/ins	216 (68)	185 (64)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	96 (67)	177 (63)	1.00 (reference)	1.00 (reference)	1.00 (reference)	0.26
ins/del	98 (31)	99 (34)	0.71 (0.21–2.38)	0.34 (0.54–1.23)	0.33	0.33	48 (33)	103 (37)	0.86 (0.56–1.31)	0.48	0.71 (0.4–1.29)	0.26
del/del	5 (1)	6 (2)	0.85 (0.60–1.19)	0.58 (0.71 (0.18–2.74)	0.61	0.61	–	–	–	–	–	–
<i>HSD17B1 1955A>G</i>												

Table 3 continued

Genotype	Breast cancer				Ovarian cancer				
	Cases n (%)	Controls n (%)	OR _{crude} (95% CI)	OR _{adj} ^a (95% CI)	P	P	OR _{crude} (95% CI)	OR _{adj} ^a (95% CI)	P
A/A	48 (15)	48 (17)	1.00 (reference)	1.00 (reference)	1.00 (reference)	18 (13)	46 (17)	1.00 (reference)	1.00 (reference)
A/G	163 (51)	159 (55)	1.02 (0.65–1.62)	0.91 (0.74–2.54)	0.32	77 (54)	155 (55)	1.27 (0.69–2.33)	0.44 (0.40–2.36)
G/G	107 (34)	83 (29)	1.29 (0.79–2.11)	0.31 (0.76–3.09)	0.24	48 (33)	79 (28)	1.55 (0.81–2.98)	0.18 (0.52–3.95)
<i>PGR</i> -413 (+331)G>A									
G/G	267 (86)	248 (86)	1.00 (reference)	1.00 (reference)	1.00 (reference)	130 (90)	239 (86)	1.00 (reference)	1.00 (reference)
G/A+A/A	44 (14)	41 (14)	1.0 (0.63–1.58)	0.99 (1.1 (0.61–1.98)	0.74	14 (10)	40 (14)	0.64 (0.34–1.23)	0.18 (0.36–2.11)
<i>PGR</i> 88022ins306									
del/del	226 (71)	217 (75)	1.00 (reference)	1.00 (reference)	1.00 (reference)	103 (72)	211 (75)	1.00 (reference)	1.00 (reference)
del/ins+ins/ins	93 (29)	73 (25)	1.22 (0.86–1.75)	0.27 (1.2 (0.77–1.85)	0.41	41 (28)	69 (25)	1.22 (0.77–1.91)	0.39 (0.42–1.63)

Significant results are given in bold

OR_{crude} crude odds ratio^a Odds ratio adjusted for age at first live birth, parity, lifetime cumulative months of breastfeeding, age at menarche, oral contraceptive use, smoking, body mass index (at age of breast cancer diagnosis for cases and at time of interview for controls), year of birth and *BRCA1* mutation

association of long *AR* alleles (≥ 28 , ≥ 29 and ≥ 30 repeats) with an increased breast cancer risk among *BRCA1/2* mutation carriers [38], whereas in three other studies, including the present study, this observation was not confirmed [39, 40]. The inconsistent results may be explained by differences between these studies including size, inclusion of *BRCA1*, *BRCA2* or both *BRCA1* and *BRCA2* carriers, type of *BRCA1/2* mutations or ethnicity. The latter explanation is supported by data from Kadouri et al. of significantly shorter allele lengths, on average, in 256 *BRCA1/2* mutation carriers of Ashkenazi origin compared with 55 British non-Ashkenazi carriers ($P_{\text{trend}} 0.0007$) [35]. Similar findings were observed for *AR* 171 (CAG)*n*, where median CAG repeat length was significantly longer in the Ashkenazi carriers compared with non-Ashkenazi carriers (23 and 21, respectively, two-sided $P = 0.01$) and at least one allele with repeat length ≥ 28 was found in 17/154 (11%) of the Ashkenazi carriers, but in none of the 30 non-Ashkenazi carriers [39]. These observations suggest that differences between studied populations are an important factor in association studies on modifiers of *BRCA1/2*-associated breast or ovarian cancer risk.

In this study, *TP53* 441G>C and *TGFBI* -1349C>T were associated with an increased breast cancer risk in analyses adjusted for potential risk factors. However, these effects were not stable and vanished upon correction for multiple testing. We also found no association of the *HER2* 23097A>G polymorphism with *BRCA1*-associated breast cancer risk. This contrasts with findings from another study among Ashkenazi carriers of the three common *BRCA1/2* founder mutations, which reported an association of this SNP with an increased breast cancer risk. This study however was based on a small number of 120 *BRCA1/2* carriers [41].

Three polymorphisms, *XRCC3* 204(GT)*n*, *COMT* 1222G>A and *CYP11A1* (AAAAT)*n*, were associated with ovarian cancer risk in the present study. These results however were also not stable and vanished once corrected for multiple testing. We also observed no association of the *TP53* 237ins16 and 1798G>A polymorphisms with disease risk. The findings of the *TP53* 237ins16 are in line with those reported in a previous study [42].

In this study, patients affected by breast or ovarian cancer as well as healthy individuals were of Polish origin and all carried one of the three Polish *BRCA1* founder mutations. Because of the strong founder effect and the Polish population being relatively stable and ethnically homogeneous, it is ideal for association studies of risk modifying genes not influenced by *BRCA1* allelic or ethnic variation.

Based on statistical modeling, our study on 319 breast cancer cases, 146 ovarian cancer cases and 290 unaffected controls was sufficiently large to identify any potential association. For the breast cancer population, all

comparisons of the reference genotype with the two genotypes had a power of at least 90% to detect an OR of at least 2.0 at the significance level of 5%, except for *TGFBR1* 52(GCG)*n* and *AR* 171(CAG)*n*. Those had a power larger than 80 and 60%, respectively, when compared with the heterozygous genotype, and larger than 80% when compared with the homozygous variant genotype, but then only for an OR of 2.5. For the ovarian cancer population, all comparisons of the reference genotype with the two genotypes had a power of at least 80% to detect an OR of at least 2 (in about half of the polymorphisms larger than 90%) at the significance level of 5%, except for *AR* 171(CAG)*n*, *HSD17B1* 1995A>G, *XRCC2* 27158G>A, *AIB1* 28824(CAG/CAA)*n*, *TGFBR1* 52(GCG)*n* and *PGR* -413G>A (power of 20, 65, 66, 74, 78 and 78%, respectively) when comparing with the heterozygous genotype, and except for *TP53* 1798G>A, *CYP11A1* (AAAAT)*n*, *TP53* 441G>C and *CYP19A1* 15162delCTT (power of 44, 66, 78 and 78%, respectively) when comparing with the homozygous variant genotype.

Our study has some limitations. A general selection bias may have occurred due to the use of study participants from a registry. Furthermore, due to the inclusion of incident and prevalent cases in the Polish registry, the presence of prevalent cases among our study participants may have led to a survival-bias, which is a general limitation of this type of retrospective study. However, because the frequency of *BRCA1* mutation carriers is low, in the Polish population nearly 0.5% [48], it makes a recruitment of study participants from the population unrealistic. Therefore, the use of registry participants seems to be the only acceptable approach to perform this kind of study.

In summary, no association of the 29 polymorphisms in genes involved in DNA repair, folate metabolism, steroid hormone biosynthesis/metabolism/signaling and cell growth with *BRCA1*-associated breast and ovarian cancer risks was observed. These findings indicate that these genetic variants are likely to play no or a minor role as modifiers of breast and ovarian cancer risks in Polish women carrying one of the three common *BRCA1* founder mutations.

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