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Do *BRCA1* modifiers also affect the risk of breast cancer in non-carriers?

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ABSTRACT

We studied whether or not single nucleotide polymorphisms (SNPs), which have been shown to modify the risk of breast cancer in women with a *BRCA1* mutation, are associated with cancer risk in unselected (non-hereditary) breast cancer patients. We genotyped seven SNPs in six distinct genes (*PHB*, *RAD51*, *ITGB3*, *TGFB1*, *VEGF*, *MTHFR*) in 1100 unselected Polish breast cancer patients and 1100 controls. The frequencies of genotypes were similar in cases and controls. In a subgroup analysis, we found a positive association between the homozygous genotype *PHB* 1630C/T and medullary breast cancer (odds ratio (OR) = 4.0, 95% confidence interval (CI) 1.1–14.0). *PHB* 1630C/T was also associated with tumours negative for oestrogen receptor (OR = 2.2, 95% CI 1.13–4.4) or progesterone receptor (OR = 2.8, 95% CI 1.4–5.8). Our results show that, in general, the single nucleotide polymorphisms which modify the risk of hereditary breast cancer in Poland do not modify the risk of sporadic breast cancer. The *PHB* 1630 C/T single nucleotide polymorphism was associated with breast cancers with clinical features typical for *BRCA1*-positive tumours and is deserving of further study.

1. Introduction

Breast cancer is the most common malignancy among Polish women with a lifetime risk of approximately 6%. This malignancy is diagnosed in 12,000 new cases and causes 5000 deaths every year. It is estimated that in Poland 50–60,000 women are currently affected by breast cancer. The three common founder mutations in *BRCA1* gene (4153delA, 5328insC, and C61G) account for the majority (~90%) of *BRCA1* mutations in Polish breast–ovarian cancer families. However, mutations in the *BRCA1* gene are responsible for only about 3% of all breast cancers and for the majority of patients, the genetic contribution remains unknown.[1–3]

Numerous studies have examined low-penetrance susceptibility single nucleotide polymorphisms (SNPs) in candidate genes for breast cancer. There are at least two categories of SNPs of interest: (1) SNPs which are believed to modify the risk of cancer in women from the general population and (2) SNPs which are believed to modify the risk of cancer in women who are already at an elevated risk (e.g. because of a mutation in *BRCA1*, *BRCA2* or *CHEK2*). It is of interest to know whether or not these two groups of SNPs are over-lapping, i.e.

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whether or not the SNPs which are relevant in the high-risk group are also relevant to women at average risk.

Recently, we have identified several SNPs which were associated with breast or ovarian cancer risk in Polish *BRCA1* mutation carriers.[4–8] The SNPs were localised within genes which are important in cancer development and progression, including: regulation of cell growth (*PHB*, *ITGB3*, *TGFB1*, *VEGF*), DNA repair (*RAD51*) or folate metabolism, which is essential in DNA biosynthesis and methylation (*MTHFR*). Only SNPs known to have functional activity were included. We conducted univariate and multivariate analyses; in the latter, the odds ratios (OR) were adjusted for other risk factors, including age at first live birth, parity, breastfeeding, age at menarche, oral contraceptive use, smoking, and body mass index.

In the current study, we sought to determine whether or not the SNPs which modified the risk of breast cancer in women with a *BRCA1* mutation are also associated with cancer risk in unselected breast cancer patients, or if the observed associations are restricted to mutation carriers. We analysed seven single nucleotide polymorphisms in six genes in a group of 1100 unselected Polish breast cancer cases and 1100 controls.

2. Materials and methods

2.1. Study participants

The study was performed on a series of 1100 prospectively-ascertained cases of invasive breast cancer patients (participation rates above 95%) who were diagnosed at the Regional Oncology Hospital (Szczecin) in the years 2002, 2003, 2006 and 2007 or the University Hospital from 2002 to 2007 in Szczecin, West-Pomerania, Poland. Patients with pure intraductal or intralobular cancer were excluded (DCIS or LCIS) but patients with DCIS with micro-invasion were included. Twenty-nine women carried one of the three Polish founder *BRCA1* mutations (4153delA, 5328insC, and C61G) and were excluded from the present analyses.

The control group was comprised of 1100 healthy adult females with a negative family history of cancer residing the region of Szczecin. These controls were part of a population-based study of the 1.3 million inhabitants of West Pomerania performed in 2003 and 2004 which was designed to identify familial aggregations of cancer by our centre. Cancer-free control women with a negative cancer family history were identified by a review of the records of the population based study and invited for an interview. The participation rate was 55%. These individuals were chosen for this study to be sex-, age- and geographically matched with the breast cancer cases (year of birth was matched within 2 years). Women affected with any malignancy or with any cancers diagnosed in a first- and second-degree relative were excluded from this control group.

All patients and controls were invited for an interview. During the interview the goals of the study were explained, informed consent was obtained, genetic counselling was given and a blood sample was taken for DNA analysis. A central pathology review was conducted in Szczecin by two pathologists associated with the study. Each case was reviewed with regard to histology (medullary, ductal, lobular, tubulo-lobular, DCIS with microinvasion, other). Information was recorded on age at diagnosis, stage, grade and lymph node status, oestrogen receptor, progesterone receptor status and bilaterality.

Table 1 – Primers, probes and annealing temperatures for SimpleProbe analysis.

PHB 1630 C/T (rs 6917)		
Forward	5′ CGTGAGAAGGGCAGTCTCTGA 3′	53 °C
Reverse	5′ TGCATCCTGCTGGGGCTGAA 3′	
Probe	FAM 5′ CTGCCAAAGACGTGTCCGACC 3′Phos	
RAD51 135 G/C (rs1801320)		
Forward	CTGGGGCAAGCGAGTAGAGA	56 °C
Reverse	TCCGACTTCACCCCGCGG	
Probe	FAM 5′ CCCAACGCCCCTGGCTTACGCTCCA 3′ Phos	
ITGB3 L59P (rs5918)		
Forward	5′ TGGGCTCCTGTCTTACAGG 3′	52 °C
Reverse	5′ GGCACAGTTATCCTTCAGCAG 3′	
Probe	FAM 5′CTGCCTCCGGGCTCACCTCGCTG 3′ Phos	
TGFB1 –509 C/T (rs1800469)		
Forward	5′ GGAGGGTGTCAGTGGGAGGA 3′	58 °C
Reverse	5′ TTCTTACAGGTGTCTGCCTCCTGA 3′	
Probe	FAM 5′ CTTCCATCCCTCAGGTGTCCTGTT 3′ Phos	
VEGF 936 C/T (rs3025039)		
Forward	5′ ACTCCGGCGGAAGCATTCCC 3′	56 °C
Reverse	5′ GGGCTCGGTGATTTAGCAGCAAGA 3′	
Probe	5′ CCAAGAGGGACCGTGCTGGGTCAC 3′ FAM	
MTHFR A222V (rs1801133)		
Forward	5′ GAAGAATGTGTCAGCCTCAAAG 3′	52 °C
Reverse	5′ CCTGAAGCACTTGAAGGAG 3′	
Probe	5′ TGAAATCGACTCCCGCAGACAC 3′ FAM	
MTHFR E429A (rs1801131)		
Forward	5′ GGTTCTCCCGAGAGGTAAAG 3′	53 °C
Reverse	5′ AGCTGCTGAAGATGTGGG 3′	
Probe	FAM 5′ CAGTGAAGCAAGTGTCTTTGAAG 3′Phos	

The study was approved by the Ethics Committee of the Pomeranian Medical University in Szczecin, Poland.

2.2. Genotyping analyses

Seven single nucleotide polymorphisms in six genes were genotyped: *PHB* 1630 C/T, *RAD51* 135G/C, *ITGB3* Leu59Pro, *TGFB1* -509 C/T, *VEGF* 677 C/T, *MTHFR* Ala222Val and *MTHFR* Glu429Ala. To determine genotype frequencies we performed SimpleProbe analysis, a melting-curve genotyping with fluorescence-labelled probes based on the LightCycler 480 System (Roche Applied Science). Primers and probes for genotyping of particular SNPs were designed according to the instructions included in LightCycler Probe

Table 2 – Genotype distributions of PHB 1630 C/T, RAD51 135 C/G, ITGB3 Leu59Pro, VEGF 677C/T, TGFB1 –509 C/T MTHFR Glu429Ala and MTHFR Ala222Val in breast cancer patients and controls.

Group	Number	Hetero-zygosity	% Hetero-zygosity	Odds ratio	95% CI	*p*-Value	Minor homo-zygote	% Minor homo-zygote	Odds ratio	95% CI	*p*-Value	HWE *p*-Value
PHB 1630 C/T												
Controls												
	1070	300	28.0	Reference			26	2.4	Reference			0.8
Unselected cases[a]												
	1012	290	29.0	1.0	0.8–1.2	0.8	35	3.4	1.4	0.9–2.4	0.2	0.8
<50	318	96	30.2	1.1	0.8–1.5	0.5	10	3.1	1.3	0.6–2.7	0.6	
>50	694	194	28.0	1.0	0.8–1.2	1.0	25	3.6	1.5	0.9–2.6	0.2	
RAD51 135 C/G												
Controls												
	1069	232	21.7	Reference			15	1.4	Reference			1.0
Unselected cases[a]												
	1007	207	20.5	0.9	0.7–1.1	0.6	15	1.5	1.1	0.5–2.1	0.9	0.9
<50	317	60	18.9	0.8	0.6–1.2	0.3	6	1.9	1.4	0.5–3.5	0.7	
>50	690	147	21.3	1.0	0.8–1.2	0.9	9	1.3	0.9	0.4–2.1	0.9	
ITGB3 Leu59Pro												
Controls												
	1073	296	27.6	Reference			32	3.0	Reference			0.9
Unselected cases[a]												
	1015	275	27.1	1.0	0.8–1.2	0.8	23	2.3	0.7	0.4–1.3	0.4	0.8
<50	319	79	24.8	0.9	0.6–1.1	0.3	4	1.2	0.4	0.1–1.2	0.1	
>50	696	196	28.2	1.0	0.8–1.3	0.8	19	2.7	0.9	0.5–1.6	0.9	
VEGF 677C/T												
Controls												
	1073	293	27.3	Reference			30	2.8	Reference			1.0
Unselected cases[a]												
	1015	252	24.8	0.9	0.7–1.1	0.2	32	3.1	1.1	0.7–1.9	0.7	0.2
<50	319	76	23.8	0.8	0.6–1.1	0.2	13	4.1	1.5	0.8–2.9	0.3	
>50	696	176	25.3	0.9	0.7–1.1	0.4	19	2.7	1.0	0.5–1.7	0.9	
TGFB1 -509 C/T												
Controls												
	1068	476	44.6	Reference			127	11.9	Reference			0.9
Unselected cases[a]												
	1011	451	44.6	1.0	0.8–1.2	1.0	106	10.5	0.9	0.7–1.1	0.3	0.9
<50	319	142	44.5	1.0	0.8–1.3	1.0	29	9.1	0.7	0.5–1.1	0.2	
>50	692	309	44.6	1.0	0.8–1.2	1.0	77	11.2	0.9	0.7–1.2	0.7	
MTHFR Glu429Ala												
Controls												
	1062	474	44.6	Reference			108	10.2	Reference			0.8
Unselected cases[a]												
	1015	433	42.7	0.9	0.8–1.1	0.4	102	10.0	1.0	0.7–1.3	1.0	1.0
<50	319	136	42.6	0.9	0.7–1.2	0.6	37	11.6	1.2	0.8–1.7	0.5	
>50	696	297	42.7	0.9	0.8–1.1	0.4	65	9.3	0.9	0.7–1.3	0.6	
MTHFR Ala222Val												
Controls												
	1071	467	43.6	Reference			91	8.5	Reference			0.6
Unselected cases[a]												
	1015	449	44.2	1.0	0.9–1.2	0.8	95	9.3	1.1	0.8–1.5	0.5	0.7
<50	319	152	47.6	1.2	0.9–1.5	0.2	21	6.6	0.8	0.5–1.2	0.3	
>50	696	297	42.7	1.0	0.8–1.2	0.7	74	10.6	1.3	0.9–1.8	0.1	

HWE, Hardy–Weinberg equilibrium.

a 29 patients with detected *BRCA1* mutation were excluded.

Design Software v2.0 (Roche Applied Science). The sequences and annealing temperatures for each genotyped SNP are listed in Table 1. Asymmetric PCR reaction was carried out in 5 μl including 25 ng of genomic DNA, 0.25 μl of 5× LightCycler 480 Genotyping Master (Roche Applied Science), 3 nmol/L $MgCl_2$, 1 μmol/L or 100 nmol/L each primer and 100 nmol/L of fluorescently labelled probe. The amplification conditions consisted of one denaturation cycle of 10 min at 95 °C and 55 cycles of three-temperature amplification. Each cycle consisted of 95 °C for 5 s, primer annealing temperature for 10 s, and 72 °C for 10 s with a single fluorescent acquisition step at the annealing temperature. This was followed by a melting curve analysis of 95 °C for 60 s, 40 °C for 60 s, and 80 °C with continuous fluorescent acquisition. Genotyping of each SNP has been performed on 384-well plates in the presence of positive and non-template (water blank) controls. The reproducibility of the genotyping data was assessed by repeated analysis of 100 randomly selected DNA samples for each tested SNP. Genotyping accuracy has been assessed by a second independent method of restriction fragment analysis (PCR-RFLP) of several samples, as described previously.[4–9]

2.3. *Statistical analysis*

The prevalence of the different genotypes in all seven SNPs was compared in cases and controls. ORs were generated from two-by-two tables and statistical significance was assessed using the Chi-square test with 1 degree of freedom (df = 1). Because of the low frequency (<5%) of minor allele in four of six tested SNPs we used Yate's continuity correction for all calculations. ORs with 95% confidence intervals (CI) were used as estimates of relative risk. For each analysed SNP, statistical modelling has been performed to estimate the predicted power of the present study. The Hardy–Weinberg equilibrium (HWE) assumption was assessed for case and control groups by comparing the observed numbers of different genotypes with those expected under HWE for the estimated allele frequency.

3. Results

We obtained genotypes for *PHB* 1630 C/T, *RAD51* 135G/C, *ITGB3* Leu59Pro, *TGFB1* -509 C/T, *VEGF* 677 C/T, *MTHFR* Ala222Val and *MTHFR* Glu429Ala in 95% or greater of cases

Table 3 – Frequency of PHB 1630 TT genotype in different subgroups of breast cancer patients.

Group	Number	Minor homozygote	Minor homozygote%	Odds Ratio	95% CI	*p*-Value
Controls	1070	26	2.4	Reference		
Family history						
positive	204	8	3.9	1.6	0.7–3.7	0.3
I°	126	5	4.0	1.7	0.6–4.4	0.5
Negative	791	26	3.3	1.4	0.8–2.4	0.3
Histopathology						
G1 + G2	404	12	3.0	1.2	0.6–2.5	0.7
G3	189	7	3.7	1.5	0.7–3.6	0.4
Medullary	33	3	9.1	4.0	1.1–14.0	0.1
Lobular	135	2	1.5	0.6	0.1–2.6	0.7
Tub-lob	17	0	–	–		
DCIS with microinvasion	42	0	–	–		
Bilateral BrC						
Yes	42	1	2.4	1.0	0.1–7.4	1.0
No	859	29	3.4	1.4	0.8–2.4	0.3
Tumour size[a]						
<1 cm	91	5	5.5	2.3	0.9–6.2	0.2
1–1.9	219	5	2.3	0.9	0.4–2.5	0.9
2–4.9	191	7	3.7	1.5	0.6–3.6	0.5
>5	10	1	10	4.5	0.5–36.5	0.6
Metastases[a]						
Yes	160	7	4.4	1.8	0.8–4.3	0.2
No	319	10	3.1	1.3	0.6–2.7	0.6
ER						
+	633	19	3.0	1.2	0.7–2.3	0.6
–	247	13	5.3	2.2	1.1–4.4	0.03
PGR						
+	87	2	2.3	0.9	0.2–4.0	0.9
–	168	11	6.5	2.8	1.4–5.8	0.01

DCIS, ductal carcinoma *in situ*.

a Patients with neo-adjuvant or missing data were excluded.

and controls enrolled to this study. Concordance for the quality control samples used for reproducibility and accuracy assessment was 100%. Statistical modelling of each tested SNP on 1100 breast cancer cases and 1100 controls revealed the predicted 88–100% power to detect an OR of 1.5–2.5. For each SNP, the genotype frequencies of cases and controls were consistent with the expected frequencies under the assumption of Hardy–Weinberg equilibrium (Table 2).

For each of the seven SNPs, the distribution of genotypes was similar in cases and controls (Table 2). We then performed subgroup analyses by family history, histologic subtype, tumour size and grade, lymph node status, laterality (unilateral versus bilateral), oestrogen and progesterone receptor status. For one SNP, *PHB* 1630 C/T, we found a positive association between the rare homozygote genotype and the risk of medullary breast cancer (OR = 4.0, 95% CI 1.1–14.0). In addition, the *PHB* 1630 TT genotype was also associated with oestrogen receptor-negative breast cancers (OR = 2.2, 95% CI 1.1–4.4) and with progesterone receptor negative breast cancers (OR = 2.8, 95% CI 1.4–5.8) (Table 3). We also saw an association between the TT genotype and advanced stage disease (OR = 1.8, 95% CI 0.8–4.3) and among patients with a positive family history (OR = 1.6, 95% CI 0.7–3.7) but neither of these associations were statistically significant.

4. Discussion

In this study, we investigated the effects of seven single nucleotide polymorphisms on the risk of breast cancer in a group of 1100 unselected Polish breast cancer patients and 1100 controls. Six of the seven SNPs have been previously reported to be associated with breast cancer and/or ovarian cancer risks in Polish carriers of *BRCA1* mutations and one was associated with ovarian cancer alone (*ITGB3* Leu59-Pro).[4–9]

In general, we did not find that these SNPs modify the risk of breast cancer in the non-carrier population. Based on statistical modelling, our study of 1100 cases and 1100 controls was sufficiently large that we were unlikely to have missed any effect – we had 88–100% power to detect ORs of 1.5–2.5, i.e. associations of the magnitude as those which we identified in *BRCA1* carriers.[4–9] It also cannot be ruled out that we were not able to detect those risks because the modifying effect of tested SNPs is weaker (OR < 1.5) in unselected breast cancers than in *BRCA1* carriers and thus our study size was too small. However, the most likely explanation why in this study no association is observed between most of the tested SNPs and breast cancer risk is their limitation in modifying effect to *BRCA1* carriers only.

Marginally significant associations with cancer risk were seen for *PHB* 1630 C/T in several subgroups. The association between *PHB* 1630 C/T polymorphism and breast cancer risk has been investigated in a few earlier studies; however, the results are conflicting.[10–12] In our previous study conducted on *BRCA1*-carriers[1] we detected an OR of 2.1 (95% CI 1.2–3.7) for T allele carriers indicating that *PHB* 1630 C/T polymorphism modifies *BRCA1*-positive breast cancer risk. In the present study we found an elevated risk for minor homozygote carriers and medullary breast cancer (OR = 4.0, 95% CI 1.1–14.0). We also observed a positive association for tumours with negative oestrogen receptor status (2.2, 95%CI 1.1–4.4) and for tumours with negative progesterone receptor status (2.8, 95%CI 1.4–5.8). These results suggest that the *PHB* 1630 C/T might be associated with patients with tumour characteristics similar to those *BRCA1* carriers: i.e. medullary histotype, negative for oestrogen and progesterone receptors status.[13,14] This observation can most probably be explained by the similarity of BRCA1 and PHB function in negative regulation of ERα transcriptional activity.

PHB is a tumour suppressor gene and is localised in the chromosome region which frequently undergoes loss of heterozygosity in familial and sporadic breast tumours.[15,16] Recently, it has been reported that in addition to its interaction with E2F-1[17], Rb[18], p53[19], Brg1/Brm[20], androgen receptor[21], and Akt[22], PHB functions as a transcriptional corepressor for ERα.[23] Similar function has been reported for *BRCA1* gene which was also shown to inhibit ERα-mediated transcriptional pathways related to cell proliferation.[24] *PHB* 1630 C/T polymorphism which was investigated in our study has been shown to affect protein function causing a lack of anti-proliferative activity.[16]

In conclusion, our results show that in general, the single nucleotide polymorphisms which modify the risk of hereditary breast cancer in Poland appear not to modify the risk of sporadic breast cancer. One exception, the *PHB* 1630 C/T SNP, appears to predispose to breast cancers with clinical features typical for *BRCA1*-positive tumours. This last observation may provide potential clinical implications in the detection, treatment and prophylaxis of unselected (non-hereditary) breast cancers patients and deserves further study.

Conflict of interest statement

None declared.

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