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PREVALENCE OF *BRCA1* AND *BRCA2* GENES PROMOTER HYPERMETHYLATION IN BREAST CANCER TISSUE

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***Background*: Recent advances in the treatment of breast cancer (BC) have been related to the personalization of therapy. The methylation status of the promoter regions of tumor suppressor genes such as *BRCA1* and *BRCA2* is supposed to be useful as a prognostic factor in BC patients. *Aim:* To investigate the frequency of hypermethylation in the promoter regions of *BRCA1* and *BRCA2* genes in tumor tissue of BC patients, and the relation of hypermethylation to the clinical course of the disease. *Materials and Methods:* Molecular genetic studies were performed on 50 BC tissue samples in order to determine the methylation status of the promoter regions of the *BRCA1* and *BRCA2* genes. *Results:* Hypermethylation of the *BRCA1* promoter region was detected in 34% of BC cases, hypermethylation of the *BRCA2* promoter region — in 50% of cases, and hypermethylation of the promoter region of both genes — in 20% of cases. A significant increase in the incidence of hypermethylation of the *BRCA2* promoter region was found in the group of patients older than 56 years, mainly in patients with triple-negative breast cancer and without family history of BC. *Conclusions:* The high frequency of hypermethylation in the promoter regions of *BRCA1* and *BRCA2* genes, as well as their co-methylation in tumor tissue of BC patients has been detected.**

***Key Words*: breast cancer, promoter, hypermethylation, *BRCA1*, *BRCA2*.**

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DNA methylation is a significant cancer risk marker, including breast, ovary, liver and colon cancer [1]. Aberrant methylation, including gene-specific DNA hypermethylation and global genomic hypomethylation, can lead to genomic instability, altered gene transcription, and increased mutation rates, which can affect normal cell growth and increase the likelihood of tumor growth [2, 3]. All types of environmental factors, from pesticides and pollutants to diet, exercise, smoking and alcohol, can change the status of DNA methylation [4]. It can cause long-lasting consequences that will persist for decades and exacerbate genetic instability. Some long-term changes in methylation status can be inherited [5]. Gene expression is reduced or absent in a case of DNA hypermethylation and may not be restored even with therapeutic measures [6].

In some diagnostic studies, only triple-negative breast cancer (TNBC) cases or cases of ovarian cancer (OC) after BRCA1 and BRCA2 mutation testing were selected for the analysis of methylation. In such setting, promoter hypermethylation of *BRCA1* gene in OC patients was found with frequency from 10% to 53% [7, 8].

Determining the methylation status of promoter sites of tumor suppressor genes, such as *BRCA1* and *BRCA2*, is currently used to select treatment strategies in patients with OC and breast cancer (BC) [9–17].

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Abbreviations used: BC – breast cancer; bp – base pair; ER – estrogen receptors; LBC – luminal breast cancer; OC – ovarian cancer; OS – overall survival; PR –progesterone receptors; TNBC – triple-negative breast cancer.

Taking into account that targeted treatment strategies are currently being used in BC patients with hypermethylated promoter of *BRCA1* and *BRCA2* genes [10, 13, 16], it is important to conduct the methylation study in combination with other standard tests. In addition, the determination of the methylation status of the *BRCA1* and *BRCA2* promoter regions could be used as a prognostic marker of the response to cancer therapy.

The aim of our study was to investigate the frequency of hypermethylation of the promoter regions of the *BRCA1* and *BRCA2* genes in tumor tissue in women with BC and the relation of such hypermethylation to the clinical course of the disease.

MATERIALS AND METHODS

A prospective study design was used. The study included 50 female patients (mean age 54.2 ± 13.2 years) with BC, who were treated at the clinical base of the Oncology Department of Bogomolets National Medical University in Kyiv City Clinical Oncology Center. The clinical data, i.e. age, family history of cancer, stage of the disease, histological tumor type, status of regional lymph nodes, tumor grade, and immunohistochemical features of tumor (expression of estrogen and progesterone receptors (ER and PR) and proliferative marker Ki-67) as well as radiological imaging were assessed. Treatment options correspond to the National and International Standards [18–20]. Chemotherapy (taxane/anthracycline or platinum based), targeted therapy (trastuzumab), hormonal therapy were performed depending on the tumor pathology and immunohistochemical phenotype. The study was authorized by the Commission on Bioethical

Expertise and Research Ethics of Bogomolets National Medical University (0120U100871).

Hypermethylation in the promoter regions of the *BRCA1* (chromosome 17, NC_000017.11) and *BRCA2* (chromosome 13, NC_000013.11) genes was analyzed using the molecular genetic method. For *BRCA1* gene: the sense primer of the unmethylated reaction began at 1536 base pairs (bp), and the sense primer of the methylated reaction — at 1543 bp from GenBank sequence U37574; for *BRCA2* gene: the sense primer of the unmethylated reaction began at 54589 bp, and the sense primer of the methylated reaction — at 54665 bp from GenBank sequence Z74739.

The material for the study was tumor tissue collected during surgical treatment of the BC patients and stored using the DNA/RNA Shield (Zymo Research, USA). DNA isolation from tumor tissue was performed with the Quick-DNA Miniprep Plus Kit (Zymo Research, USA). A commercial EZ DNA Methylation-Gold Kit (Zymo Research, USA) was used for the bisulfide conversion of the isolated DNA.

Allele-specific PCR was performed using ZymoTaq PreMix (Zymo Research, USA) and specific primers (Metabion, Germany) in a FlexCycler BU amplifier (Analytik Jena GmbH, Germany) [12, 21]. The products were analyzed by agarose gel electrophoresis (agarose CSL-AG500, Cleaver Scientific Ltd, United Kingdom) according to the presence or absence of amplification of fragments of methylated DNA (Met) and unmethylated DNA (UnMet). Electrophoregrams of *BRCA1* gene amplification products (Fig. 1) and *BRCA2* (Fig. 2) were visualized in the Micro DOC System with UV Transilluminator Clear View (Cleaver Scientific Ltd, United Kingdom).

The amplification products of each sample with methylated and unmethylated primers were added to individual wells of agarose gel and, depending on the presence or absence of amplicon, the state of the allele was determined. In Figures and onwards in the text UnMet DNA is indicated for convenience U, and Met DNA — M. Hypermethylation in the promoter region of the *BRCA1* and *BRCA2* genes was detected in the examined tumor tissues in a heterozygous state — one allele of the studied gene was hypermethylated in samples 3, 5, 6, 7, 9 (see Fig. 1) and in samples 2, 3, 4, 6, 9 (see Fig. 2).

Statistical processing was performed using standard packages of Microsoft Excel 2010. Significance of differences was determined using χ^2 criterion with Yates correction and Irwin-Fisher test (significance level of $p < 0.05$).

RESULTS AND DISCUSSION

Hypermethylation of the promoter region of *BRCA1* gene in the heterozygous state (Met/UnMet *BRCA1* gene) was detected in 17 (34%) tumor tissue samples, and in the promoter region of *BRCA2* gene (Met/UnMet *BRCA2* gene) — in 25 (50%) samples of tumor tissues. The frequency of the co-methylation detection in the sample Met/UnMet *BRCA1* gene and Met/UnMet *BRCA2* gene was 20% (Table 1). Hypermethylation of *BRCA1* and *BRCA2* genes was not detected in 18 (36%) samples.

The results of our study coincided with the results obtained by Joosse *et al*. [22] who reported 34% frequency of methylation of the *BRCA1* promoter region in samples of basal-like BC. In contrary, Tabano *et al*. [23] found low level of methylation of the *BRCA1* promoter (4.3%) in the peripheral blood of women with BC and/or OC suggesting that such assay in peripheral blood samples seems to be less effective than directly in samples of tumor tissue.

We evaluated the relationship of the hypermethylation of *BRCA1* and *BRCA2* genes in tumor tissues with the main clinical features of the examined BC patients (Table 2).

The mean age of patients with Met/UnMet *BRCA1* gene (53.9 ± 13.2) was lower than that of pa-

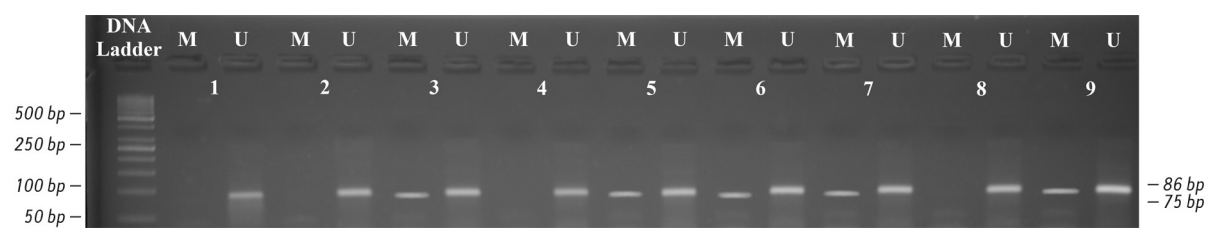

Fig. 1. Electrophoregram of Met and UnMet DNA amplification products in the promoter region of the *BRCA1* gene. Samples № 1, 2, 4, 8 — UnMet/UnMet, samples № 3, 5, 6, 7, 9 — Met/UnMet. Marker — molecular weight marker GeneRuler 50bp DNA Ladder (Thermo Scientific, USA)

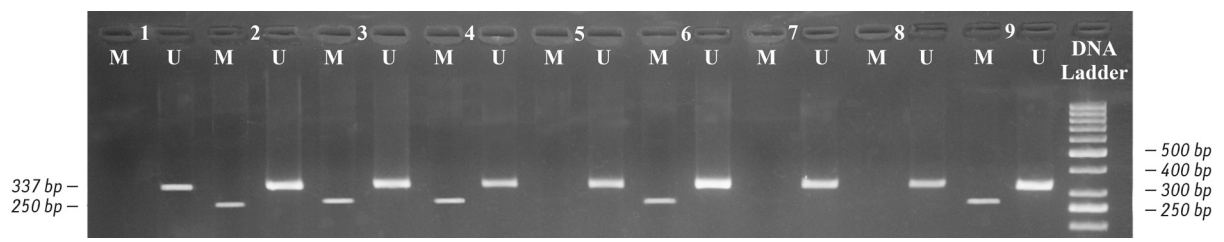

Fig. 2. Electrophoregram of Met and UnMet DNA amplification products in the promoter region of the *BRCA2* gene. Samples № 1, 5, 7, 8 — UnMet/UnMet, samples № 2, 3, 4, 6, 9 — Met/UnMet. Marker — molecular weight marker GeneRuler 50bp DNA Ladder (Thermo Scientific, USA)

Table 1. Frequency of co-metylation of the promoter region of *BRCA1* and *BRCA2* genes in BC patients

Co-methylation/genes	*BRCA2* MU	*BRCA2* UU
BRCA1 MU	10 (20%)	7 (14%)
BRCA1 UU	15 (30%)	18 (36%)

tients with Met/UnMet *BRCA2* gene (57.1 ± 11.8). In the age group over 56 years old, there was an increase in the proportion of people with Met/UnMet *BRCA1* gene compared to younger patients, and the number of patients with Met/UnMet *BRCA2* gene was significantly increased in BC patients in the age group over 56 years old compared with age group < 55 years ($p < 0.05$). French researchers also found an increase in the incidence of hypermethylation in elderly patients [24], we found the same feature for the *RUNX3* gene in BC patients [25].

It is known that the status of gene methylation changes with age, and the frequency of hypermethylation increases [26]. Such increased hypermethylation was found in both *BRCA1* and *BRCA2* genes in older BC patients compared to the younger age group (significant for *BRCA2* gene but insignificant for *BRCA1*).

The highest incidence of BC is observed at the age of 40–45 and 50–55 years, and in Ukraine the BC incidence and related mortality increases in 50–55 year old women [27]. Therefore, the study of hypermethylation of the *BRCA2* promoter in Ukrainian BC patients can be considered important from the point of search for potential therapeutic targets.

The incidence of Met/UnMet *BRCA2* gene in BC patients not treated with neoadjuvant therapy was slightly higher compared with BC patients who received neoadjuvant therapy, while the frequency of Met/UnMet *BRCA1* in the former group was insignificantly lower than in the latter. Met/UnMet *BRCA1* and *BRCA2* genes were recorded in patients treated with taxanes as well as in patients treated with platinum based neoadjuvant therapy. Re-assessment of the methylation status in BC patients could be useful to establish the effectiveness of neoadjuvant therapy.

We have analyzed the relation between family history of cancer in relatives of the I–II order and the methylation status of *BRCA1* and *BRCA2* genes in BC tissue. Our data showed that in patients with family history of BC, the promoter region of the *BRCA2* gene had higher frequency of methylation (47.8% cases) compared to the *BRCA1* gene (26.1% cases). Bosviel *et al*. [24, 28] showed, in contrary, a tendency for higher hypermethylation of the *BRCA1* promoter (47.1%) and lower — of *BRCA2* promoter (16.9%) in the blood of patients with sporadic BC. In our study, Met/UnMet *BRCA1* gene and Met/UnMet *BRCA2* gene was detected in 47.1% and 51.9% patients with sporadic BC. The frequency of Met/UnMet *BRCA2* gene was almost the same in patients with sporadic or hereditary BC.

The study included patients in both the early stage of the disease (T1–2N0M0) and the advanced stage (T1–3N1–3M0–1). We have revealed a higher methylation status of the promoter region of the *BRCA2* gene compared to the *BRCA1* gene in patients in the early stages of the disease. Hypermethylation of the promoter regions of the *BRCA1* and *BRCA2* genes was not associated with the levels of ER, PR and Ki-67 expression in contrast to the study by Vos *et al*. [29] where methylation of the *BRCA1* and *BRCA2* promoters with a high frequency was found in high grade, ER- and

Table 2. Basic clinical features of patients with breast cancer depending on the methylation status of the *BRCA1* and *BRCA2* genes

	BRCA1 Methylation				BRCA2 Methylation			
	MU		UU		MU		UU	
	n	%	n	%	n	%	n	%
Number of samples	17	34	33	66	25	50	25	50
Age (years)								
Median	53.9 ± 13.2		54.4 ± 13.4		**57.1 ± 11.8***		**51.4 ± 14.1**	
up to 55	7	29.2	17	70.8	**8**	33.3	16	66.7
over 56	10	38.5	16	61.5	**17***	65.4	9	34.6
Grade								
T1–2N0M0	9	34.6	17	65.4	14	53.8	12	46.2
T1–3N1–3M0–1	8	33.3	16	66.7	11	45.8	13	54.2
Tumor type								
Ductal	14	34.1	27	65.9	22	53.7	19	46.3
Other	4	44.4	5	55.6	3	33.3	6	66.7
ER								
Positive	13	76.5	23	74.2	17	70.8	20	83.3
Negative	4	23.5	8	25.8	7	29.2	4	16.7
PR								
Positive	11	64.7	21	67.7	14	58.33	18	75
Negative	6	35.3	10	32.3	10	41.66	6	25
HER2/neu								
Positive	4	23.5	5	16.1	6	25	3	12.5
Negative	13	76.5	26	83.9	18	75	21	87.5
Hereditary								
Burdened	6	26.1	17	73.9	11	47.8	12	52.2
Not burdened	11	40.7	16	59.3	14	51.9	13	48.1
Group								
TNBC	4	36.4	7	63.6	7	63.6	4	36.4
LBC	13	33.3	26	66.7	18	46.2	21	53.8
Neoadjuvant therapy								
With NAT	6	37.5	10	62.5	5	31.3	11	68.8
Without NAT	11	32.4	23	67.6	20	58.8	14	41.2
Taxane/anthracycline based NAT	5	41.7	7	58.3	4	33.3	8	66.7
Platinum based NAT	1	25	3	75	1	25	3	75

Note: *The difference is significant between MU and UU ($p < 0.05$); between age groups < 55 and > 56 ($p < 0.05$).

PR-negative tumors. In our study, the methylation status of the promoter regions of the *BRCA1* and *BRCA2* genes was determined in patients with different receptor status. This approach is more informative because in this case hypermethylation is detected in the case of positive receptor status as in the work of Tabano *et al*. [23].

According to Staaf *et al*. [15], in 67% of TNBC cases germinal and somatic mutations in the *BRCA1* and *BRCA2* genes as well as hypermethylation of the *BRCA1* promoter. In our study, the proportion of TNBC was 22%, which corresponded to the average TNBC frequency (10–20%) [21]. Analysis of the methylation status depending on the molecular type of tumor (TNBC or luminal breast cancer — LBC) in the main age groups (Fig. 3) showed an increased frequency of hypermethylated *BRCA1* promoter in patients with TNBC from the age group < 55 years, and patients with LBC > 56 years. The increased frequency of hypermethylated *BRCA2* promoter was registered in both TNBC and LBC patients from the age group over 56 years.

TNBC is more often detected among the cases of hereditary BC, so accounting for the family history of cancer can indirectly assess the transfer of the hypermethylation status of the studied genes. The incidence of hypermethylation of the *BRCA1* promoter in patients with TNBC with family cancer history was insignificantly higher compared with patients with sporadic tumors (Fig. 4). The opposite trend was found in patients with LBC. Hypermethylation of the *BRCA2* promoter was the highest in patients with TNBC and without family history of cancer.

The results indicated an absence of association of *BRCA1* hypermethylation with TNBC, which confirms the data of Watanabe *et al*. [30]. However, we found an increasing frequency of *BRCA2* promoter hypermethylation in patients older than 56 years with sporadic TNBC.

No significant difference in disease free survival and overall survival (OS) (96 *vs* 92%; 98 *vs* 100%) could be demonstrated between groups with hypermethylation of *BRCA1* and hypermethylation of *BRCA2* under follow-up 25 months. Locally advanced forms

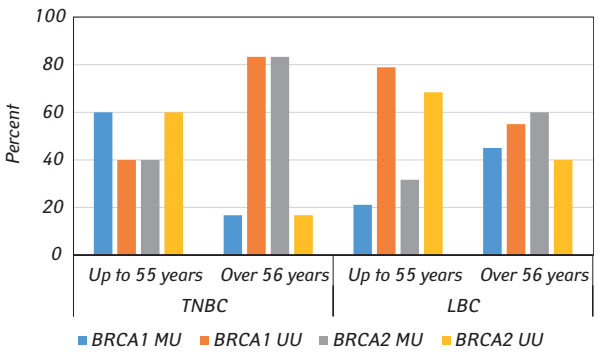

Fig. 3. Distribution of hypermethylation of *BRCA1* and *BRCA2* gene promoters in patients with TNBC and LBC cancer by age: MU — hypermethylation of the promoter region of gene in the heterozygous state, UU — unmethylated status of the promoter region of gene

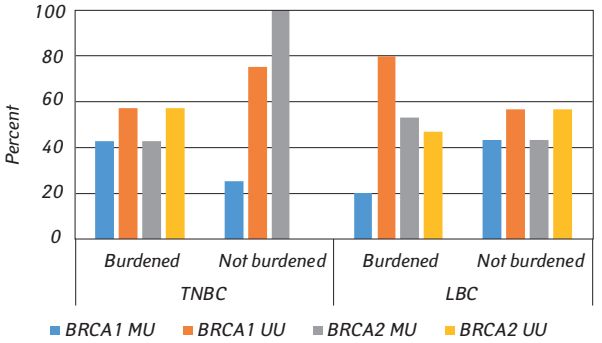

Fig. 4. Distribution of hypermethylation of *BRCA1* and *BRCA2* gene promoters in patients with TNBC and LBC depending on family history: MU — hypermethylation of the promoter region of gene in the heterozygous state, UU — unmethylated status of the promoter region of gene

of BC were found in most patients with disease progression, and only one patient with disease progression during the first year after treatment was with early stage BC and hypermethylation of both *BRCA1* and *BRCA2* genes. TNBC was detected in 50% patients with disease progression. We found a tendency for increased progression of the disease dependent on hypermethylation of the promoter region of *BRCA2*. Other researchers have established this earlier [31].

In conclusion, we detected no significant association of hypermethylation of the *BRCA1* and *BRCA2* promoter regions with the family history of cancer, expression levels of Ki-67, ER or PR. We determined hypermethylation of the *BRCA1* promoter region in 34%, hypermethylation of the *BRCA2* promoter region in 50%, and hypermethylation of the promoter region of both genes in 20% of BC cases. We found out a significant increase in the incidence of hypermethylation of the *BRCA2* promoter region in the age group over 56 years old, mainly in patients with TNBC and sporadic tumors. The high prevalence of hypermethylation of *BRCA1* and *BRCA2* and co-methylation in tumor tissue indicates the need for further analysis to assess the diagnostic and prognostic value of these genetic markers for patients with BC.

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ПОШИРЕНІСТЬ ГІПЕРМЕТИЛУВАННЯ ПРОМОТОРНОЇ ДІЛЯНКИ ГЕНІВ *BRCA1* ТА *BRCA2* В ТКАНИНІ РАКУ МОЛОЧНОЇ ЗАЛОЗИ

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Стан питання: Останні досягнення в лікуванні раку молочної залози (РМЗ) пов'язані з персоналізацією терапії. Вважають, що статус метилування промоторних ділянок генів-супресорів пухлин, таких як *BRCA1* та *BRCA2*, може бути інформативним як прогностичний фактор у хворих на РМЗ. ***Мета:*** Оцінити частоту гіперметилування промоторних ділянок генів *BRCA1* та *BRCA2* в пухлинній тканині хворих на РМЗ, а також зв'язок гіперметилування з клінічним перебігом захворювання. ***Матеріали та методи:*** У 50 зразках пухлинної тканини молочної залози провели молекулярно-генетичні дослідження з метою визначення статусу метилування промоторних ділянок генів *BRCA1* та *BRCA2*. ***Результати:*** Гіперметилування промоторної ділянки гена *BRCA1* було виявлено в 34% випадків РМЗ, гіперметилування промоторної ділянки гена *BRCA2* — у 50% випадків, а гіперметилування промоторних ділянок обох генів — у 20% випадків. Значне підвищення частоти гіперметилування промоторної ділянки гена *BRCA2* було виявлено в групі хворих віком старше 56 років, в основному у хворих з тричі негативним РМЗ та без обтяженого сімейного анамнезу РМЗ. ***Висновки:*** Виявлено високу частоту гіперметилування промоторних ділянок генів *BRCA1* та *BRCA2*, а також їх кометилування в пухлинній тканині хворих на РМЗ.

Ключові слова: рак молочної залози, промотор, гіперметилування, *BRCA1, BRCA2.*

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