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PREDICTIVE AND PROGNOSTIC SIGNIFICANCE OF LOSS OF HETEROZYGOSITY IN ABC TRANSPORTER GENES IN BREAST CANCER

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Abstract

ABC-transporter family genes have been well studied and their involvement in the development of drug resistance has been assessed. The presence of aberrant conditions in these genes can affect the treatment and prognosis of the disease. Loss of heterozygosity (LOH) is one of these conditions; it is a common event in cancer development. Therefore, **the aim of this study** was to investigate the relationship between LOH in ABC transporter genes in breast cancer and response to chemotherapy and disease prognosis. **Material and Methods.** A total of 130 breast cancer patients were included in the study. Microarray analysis was performed on Affymetrix CytoScan™ HD Array high-density DNA chips to assess LOH status. Chromosome Analysis Suite 4.1 software (Affymetrix, USA) was used to process microarray results. **Results.** Forty-nine ABC transporter genes were evaluated for LOH. The frequency of LOH ranged from 6.9 % to 90 %. An association analysis identified two genes: *ABCG5* and *ABCG8*, in which the presence of LOH was associated with a lack of objective response to neoadjuvant chemotherapy. The presence of LOH in the *ABCA5, ABCA6, ABCA8, ABCA9, ABCA10* and *ABCC3* genes was associated with high rates of metastasis-free survival (log-rank test, $p<0.04$). **Conclusion.** The presence of loss of heterozygosity in the ABC transporter genes was found to have no significant effect on the response to chemotherapy. However, a high prognostic potential of *ABCA* family genes was found.

Key words: breast cancer, loss of heterozygosity, efficacy of neoadjuvant chemotherapy, metastasis-free survival, prognosis.

ПРЕДИКТИВНАЯ И ПРОГНОСТИЧЕСКАЯ ЗНАЧИМОСТЬ ЯВЛЕНИЯ ПОТЕРИ ГЕТЕРОЗИГОТНОСТИ В ГЕНАХ ABC-ТРАНСПОРТЕРОВ В ОПУХОЛИ МОЛОЧНОЙ ЖЕЛЕЗЫ

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Аннотация

Гены семейства ABC-транспортеров хорошо изучены, оценено их влияние на формирование лекарственной устойчивости. Показано, что наличие аберрантных состояний в этих генах может влиять на лечение и прогноз заболевания. Одним из таких состояний является потеря гетерозиготности (LOH), которая часто встречается в опухолевых клетках. **Цель исследования** – изучение связи потери гетерозиготности в генах ABC-транспортеров в опухоли молочной железы с эффектом химиотерапии и прогнозом заболевания. **Материал и методы.** В исследование было включено 130 больных раком молочной железы. Для оценки статуса LOH был проведен микрочиповый анализ на ДНК-чипах высокой плотности Affymetrix CytoScan™ HD Array. Для обработки результатов микрочипов использовалось программное обеспечение Chromosome Analysis Suite 4.1 (Affymetrix, USA). **Результаты.** На предмет потери гетерозиготности было оценено 49 генов ABC-транспортеров. Частота LOH варьировала от 6,9 до 90 %. Ассоциативный анализ выявил два гена *ABCG5* и *ABCG8*, наличие потери гетерозиготности в которых было связано с отсутствием объективного ответа на неоадъювантную химиотерапию. Наличие LOH в генах *ABCA5, ABCA6, ABCA8, ABCA9, ABCA10* и *ABCC3* было связано с более высокими показателями безметастатической выживаемости (log-rank test, p<0,04). **Выводы.** Было установлено, что наличие потери гетерозиготности в генах ABC-транспортеров не оказывает значительного влияния на эффективность химиотерапии. Однако был показан высокий прогностический потенциал генов семейства ABCA.

Ключевые слова: рак молочной железы, явление потери гетерозиготности, эффективность неоадъювантной химиотерапии, безметастатическая выживаемость, прогноз.

Introduction

ABC transporter family genes are currently well studied, and their impact on chemotherapy response and disease prognosis in various types of cancer has been evaluated [1–3]. Our previous studies have shown that ectopic expression, as well as the presence of chromosomal aberrations in the chromosomal loci, where these genes are localized, affects the response to chemotherapy in breast cancer patients [1, 4, 5].

However, one of the most effective ways to study malignant tumors at the molecular genetic level is the analysis of genomic loci imbalance, a situation in which the normal ratio of alleles changes due to the loss or increase in copies of one of them [6]. The imbalance sites, first, contain candidate genes involved in the development of the disease and, second, may themselves be molecular markers [7]. A particular case of allelic imbalance is loss of heterozygote (LOH), in which there is a loss (structural or functional) of one of the alleles of a heterozygous genotype and a decrease in detectable frequencies of heterozygous genotypes compared to genomic DNA. Loss of heterozygosity at certain chromosomal sites is a structural aberration often found in tumor cells, which can be caused by deletion of certain chromosomal regions, aberrant mitotic recombination, etc. [8]. However, the effect of LOH on treatment outcomes is highly controversial. It was demonstrated that LOH on chromosome 18p11.32 containing *TYMS* in metastatic colorectal cancer cells changed the genotype of the tumor cells and resulted in a different response to 5-fluorouracil-based therapy [9]. In breast cancer (BC), the main focus of research is the study of allelic imbalance in biomarkers, such as *ERBB2 (HER2)* [10], *BRCA1* and *BRCA2* [11]. In a study on allelic imbalance and LOH in breast cancer, the authors examined genes, such as *EGFR, TERT, TP53, CASP8, PARP2, GATA3,* and *BRCA1* [12]. Studies on LOH of ABC transporter genes are virtually non-existent. There are only sporadic studies on this issue. The association between breast cancer risk and the frequency of the G allele 538G > A (Gly180Arg) and the *ABCC11* gene, was studied. It was found that the frequency of the G allele was higher in breast cancer patients than in healthy individuals in the control group. The odds ratio of developing breast cancer for the genotypes (G/G+G/A) was 1.63 (p=0.026), indicating that the G allele in *ABCC11* was associated with the risk of developing breast cancer [13]. A mediated effect of LOH on *ABCB1* expression was also found. The presence of sites of LOH in the *ABCB1* gene with amplification of this gene function is the main, if not the only, mechanism of *ABCB1* overexpression in *Candida albicans* strains [14]. We also found that regions with significant LOH frequency included 2p25.3, 2p21, 2p15~p16.1, 2q23.3, and 16q12.1.It is worth noting that ABC genes such as *ABCC11* and *ABCC12* are localized in the 16q12.1 region [15].

However, LOH in the ABC transporter genes has hardly been studied, and the effect of heterozygosity loss in these genes on the response to chemotherapy and disease prognosis has not been assessed. Thus, **the aim of this study** was to investigate the relationship between LOH of ABC transporter genes in breast cancer and the response to neoadjuvant chemotherapy and metastasis-free survival.

Material and Methods

The study involved 130 patients with stage IIA–IIIB breast cancer. The median age of the patients was 48 years (range, 27–68) (Table 1). The retrospective study included 90 patients. In accordance with «Consensus Conference on Neoadjuvant Chemotherapy in Carcinoma of the Breast, April 26–28, 2003, Philadelphia,

Table 1/Таблица 1

Clinical and pathological characteristics of breast cancer patients

Клинико-патологическая характеристика больных раком молочной железы

Clinical and pathological parameter/Клинико-патологический параметр		Number of patients/ Количество пациентов
Age, years/Возраст, лет	≤45	56 (43.1 %)
	> 45	74 (56.9 %)
Menstrual status/ Менструальный статус	Premenopause/Пременопауза	71 (54.6 %)
	Postmenopause/Постменопауза	59 (45.4 %)
Tumor size/ Размер опухоли	T1	17 (13.1 %)
	T2	97 (74.6 %)
	T3	7 (5.4 %)
	T4	9 (6.9 %)
Lymphogenous metastasis/ Лимфогенное метастазирование	N0	53 (40.8 %)
	N1	58 (44.6 %)
	N2	8 (6.2 %)
	N3	11 (8.5 %)
Molecular subtype/ Молекулярный подтип	Luminal B/Люминальный B	94 (72.3 %)
	Triple negative/Трипл-негативный	23 (17.7 %)
	HER2-positive/HER2-позитивный	13 (10.0 %)
Histological form/ Гистологическая форма	Unicentric/Моноцентричный	67 (51.5 %)
	Multicentric/Мультицентричный	63 (48.5 %)
NAC regimens/Схема НХТ	CAX	28 (21.5 %)
	AC	45 (34.6 %)
	Taxotere	26 (20.0 %)
	ACT/AT	16 (12.3 %)
	CP	15 (11.5 %)
NAC response/Эффект НХТ	Progression/Прогрессирование	9 (6.9 %)
	Stabilization/Стабилизация	32 (24.6 %)
	Partial regression/Частичная регрессия	76 (58.5 %)
	Complete regression/Полная регрессия	13 (10.0 %)

Table 2/Таблица 2

Correlation of the presence loss of heterozygosity sites in ABC transporter genes at the level of expressed tendency

Связь наличия участков потери гетерозиготности в генах ABC-транспортеров на уровне выраженной тенденции

Genes/Гены	Effect of NAC/Эффект НХТ				p-level
	Complete and partial regression/ Полная и частичная регрессия		Stabilization and progression/ Стабилизация и прогрессирование		
	LOH	n	LOH	n	
ABCA11P	28 (31.5 %)	61 (68.5 %)	7 (17.1 %)	34 (82.9 %)	0.09
ABCB1	25 (28.1 %)	64 (71.9 %)	3 (7.3 %)	38 (92.7 %)	0.07
ABCB4	25 (28.1 %)	64 (71.9 %)	3 (7.3 %)	38 (92.7 %)	0.07
ABCB8	14 (15.7 %)	75 (84.3 %)	2 (4.9 %)	39 (95.1 %)	0.09
ABCF2	14 (15.7 %)	75 (84.3 %)	2 (4.9 %)	39 (95.1 %)	0.09

Pennsylvania» [16] all patients received 2–8 courses of neoadjuvant chemotherapy: AC (doxorubicin (60 mg/m^2 intravenously on the 1st day), cyclophosphamide (600 mg/m^2 intravenously on the 1st day)), CAX (cyclophosphamide (100 mg/m^2 intravenously on the 1st-14th days), doxorubicin (30 mg/m^2 intravenously on the 1st and 8th days), xeloda (2000 mg/m^2 intravenously on the 1st–14th days, by mouth)), ACT/AT (doxorubicin (60 mg/m^2 intravenously on the 1st day), cyclophosphamide (600 mg/m^2 intravenously on the 1st day), (100 mg/m^2 hourly infusion per day)), CP (cyclophosphamide (600mg/m^2 1st day), cisplatin (100 mg/m^2 – 1st day)).

We analyzed biopsy tumor samples before treatment (~10 mm^3 volume) and 3–5 weeks after the last course of neoadjuvant chemotherapy (~60–70 mm^3 volume). Tumor samples were placed in an RNAlater solution (Ambion, USA) and stored at –80°C (after a 24-hour incubation at +4° C) for further DNA isolation.

DNA extraction. DNA was isolated from 130 samples of tumor tissue using the QIAamp DNA mini Kit (Qiagen, Germany). DNA concentration and purity of isolation were evaluated on a NanoDrop-2000 spectrophotometer (Thermo Scientific, USA) (from 50 to 190 ng/µl, A_{260}/A_{280}=2.05–2.20; A_{260}/A_{230}=1.95–2.20). DNA integrity was assessed by capillary electrophoresis on a TapeStation instrument (Agilent Technologies, USA); DNA fragments had a mass of more than 60 kbp.

Microarray analysis. Microarray analysis was performed on high density microarrays (DNA chips) of Affymetrix (USA) CytoScan™ HD Array to determine the loss of heterozygosity. Sample preparation, hybridization, and scanning procedures were performed according to the manufacturer's protocol on an Affymetrix GeneChip® Scanner 3000 7G system (Affymetrix, USA). To process the results of microchipping, we used the Chromosome Analysis Suite 4.0 program (Affymetrix, USA) for detection of loss of heterozygosity.

Statistical methods. Statistical analysis was performed using the Statistica 8.0 software package (StatSoft Inc., USA). .The survival probability was calculated using the Kaplan-Meier method. The log-rank test was used to compare the significance of differences between groups in terms of survival. Frequency comparisons were based on two-tailed Fisher's test and/or Chi-square test.

Results

The frequency of LOH in the ABC transporter genes was estimated (Fig. 1, Supplement 1 Table 1). It was found that the highest frequency of LOH (over 50 %) was observed in genes: *ABCC11* (90.0 %), *ABCC12* (90.0 %), *ABCB7* (69.2 %), *ABCD1* (67.7 %), and *ABCD2* (53.8 %), (Supplement 1, Table 1). The genes: *ABCC9* (9.2 %), *ABCD3* (9.2 %), *ABCB5* (8.5 %), *ABCA7* (7.7 %), *ABCG1* (7.7 %), and *ABCA13* (6.9 %) had the lowest frequency of LOH.

Analysis of the association of the presence of LOH in 49 ABC-transporter genes with the response to neoadjuvant chemotherapy showed that the frequency of LOH in *ABCG5* and *ABCG8* genes was significantly higher in patients with tumor stabilization and progression (26.8 %, 11/41 cases) compared to that in patients with objective response to treatment (5.6 %, 5/89 cases), p=0.001 (Fig. 2).

The presence of LOH in *ABCA11P, ABCB1, ABCB4, ABCB8,* and *ABCF2* genes demonstrated a tendency towards increase in the frequency of tumor response to neoadjuvant chemotherapy (Table 2).

The frequency of LOH in *ABCA11P, ABCB1, ABCB4, ABCB8,* and *ABCF2* genes was 3–4 times higher in patients with complete and partial regression.

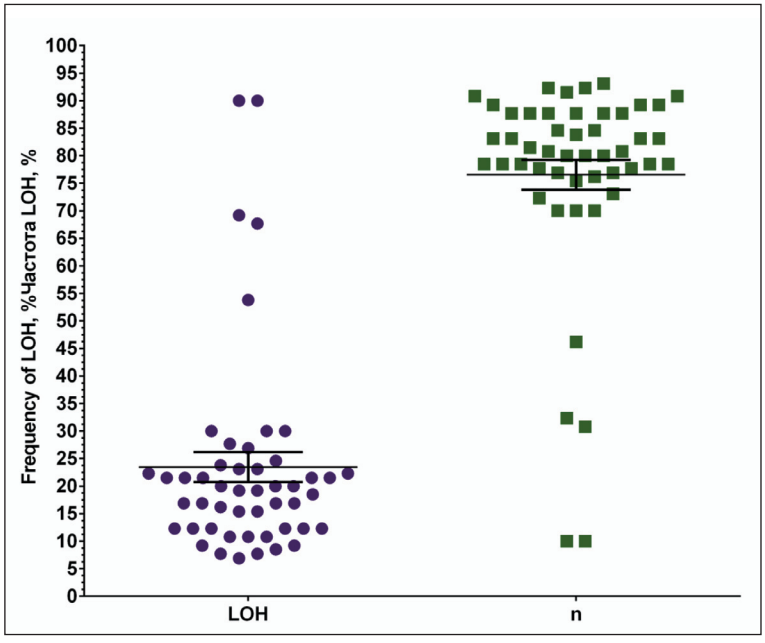

Fig. 1. Variation in the frequency of loss of heterozygosity sites in ABC transporter genes
Рис. 1. Разброс частоты встречаемости участков потери гетерозиготности в генах АВС-транспортеров

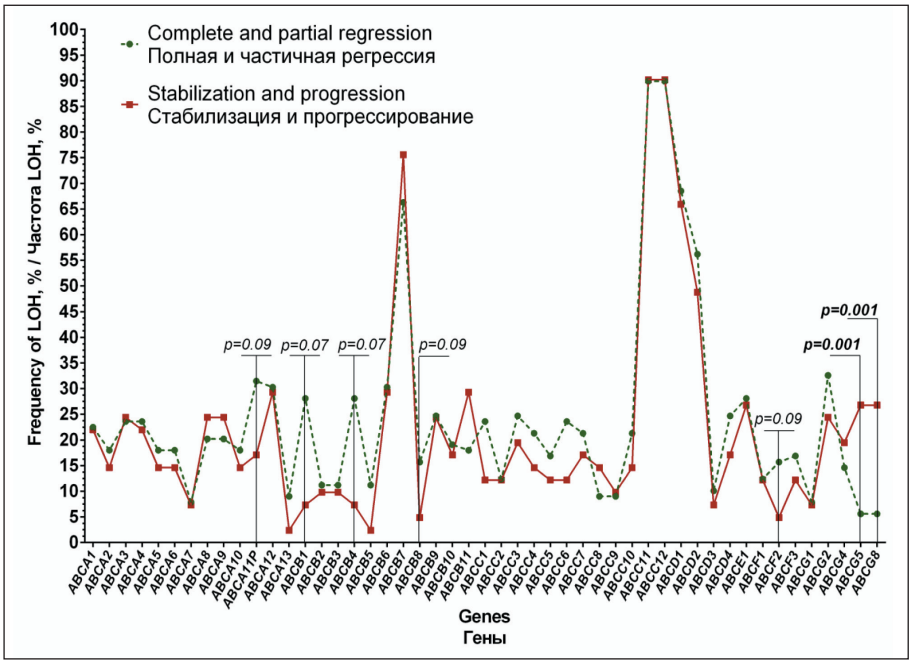

Fig. 2. Frequency of LOH in ABC-transporter genes with respect to the response to neoadjuvant chemotherapy
Рис. 2. Частота встречаемости участков потери гетерозиготности генов ABC-транспортеров в зависимости от эффекта неоадъювантной химиотерапии

Analysis of metastasis-free survival rates with respect to the presence of LOH is shown in Figure 3. In the total group of 130 patients examined, distant metastases developed in 37 (29 %) patients within 4-130 days after diagnosis.

The 5-year MFS rate in patients with the presence of LOH in the *ABCA5, ABCA6,* and *ABCA10* genes was 95 % versus 67.5 % in the group of patients without the presence of LOH (log-rank test p=0.007). For the *ABCA8* and *ABCA9* genes, this rate was 96 % versus 66 % (log-rank test p=0.008). For the *ABCC3* gene, we also showed statistically significant differences in survival rates between patients with and without LOH (log-rank test p=0.04).

No statistically significant association with treatment efficacy and disease prognosis was found for the remaining ABC-transporter genes.

Discussion

The phenomenon of LOH occurs when a tumor cell initially heterozygous for a certain locus loses one of its two alleles at that locus, either by simple deletion of one allele or by deletion of one allele accompanied by duplication of the remaining allele [17].

There are no available data on the effect of LOH in ABC-transporter genes on the functional component, as well as on the response to chemotherapy and disease prognosis. Nevertheless, it has been shown that the presence of polymorphisms in the ABCG2 gene correlates with severe myelosuppression induced by the irinotecan, while the presence of polymorphisms in the *ABCG1* and *ABCC5* genes correlate with gastrointestinal toxicity [18].

In our study, we observed the highest frequency of LOH in genes, such as: *ABCC11, ABCC12, ABCB7, ABCD1,* and *ABCD2*. However, the presence of LOH in the *ABCG5* and *ABCG8* genes is associated with the effect of LOH. According to the literature data, genes *ABCG5* and *ABCG8* function as semitransporters and form a heterodimeric complex, which is reflected in the functioning of these genes [19].

ABCB1 is the most extensively investigated gene in terms of mutations. The missense variant (rs2032582) and synonymous substitution (rs1045642) have been shown to be associated with the risk of adverse reactions during fluoropyrimidine therapy [20], as well as the high toxicity of taxanes [21] and anthracyclines [22]. The results of the meta-analysis indicate associations between the *ABCB1* G2677T/A polymorphism and the risk of breast cancer and the effect on treatment, with an overall comparison across four genetic models (heterozygous model: OR=1. 01, 95 % CI=0.92–1.09, p=0.90; homozygous model: OR=1.01, 95 % CI=0.65–1.55, p=0.97; recessive model: OR=1.06, 95 % CI=0.75–1.50, p=0.76; dominant model: OR=0.98, 95 % CI=0.77–1.24, p=0.85) [23]. The *ABCB1* G1199 T/A (rs2229109) polymorphism was found to have no effect on overall and recurrence-free survival in breast cancer patients [24]. Despite the fact that the effect of LOH in the *ABCF2* gene on the response to NAC is shown only at the level of a marked trend, the authors report that ABCF2 plays a role in mediating drug resistance induced by cisplatin [25]. In addition, Seborova K. et al. showed that the best effectiveness of chemotherapy and high rates of progression free survival occurred in patients with ovarian cancer with loss of function of *ABCF1, ABCF2* and *ABCF3* genes [26].

According to our data, the presence of LOH predominantly in the *ABCA* family is associated with metastasis-free survival rates. This is consistent with the literature data: the presence of a deletion

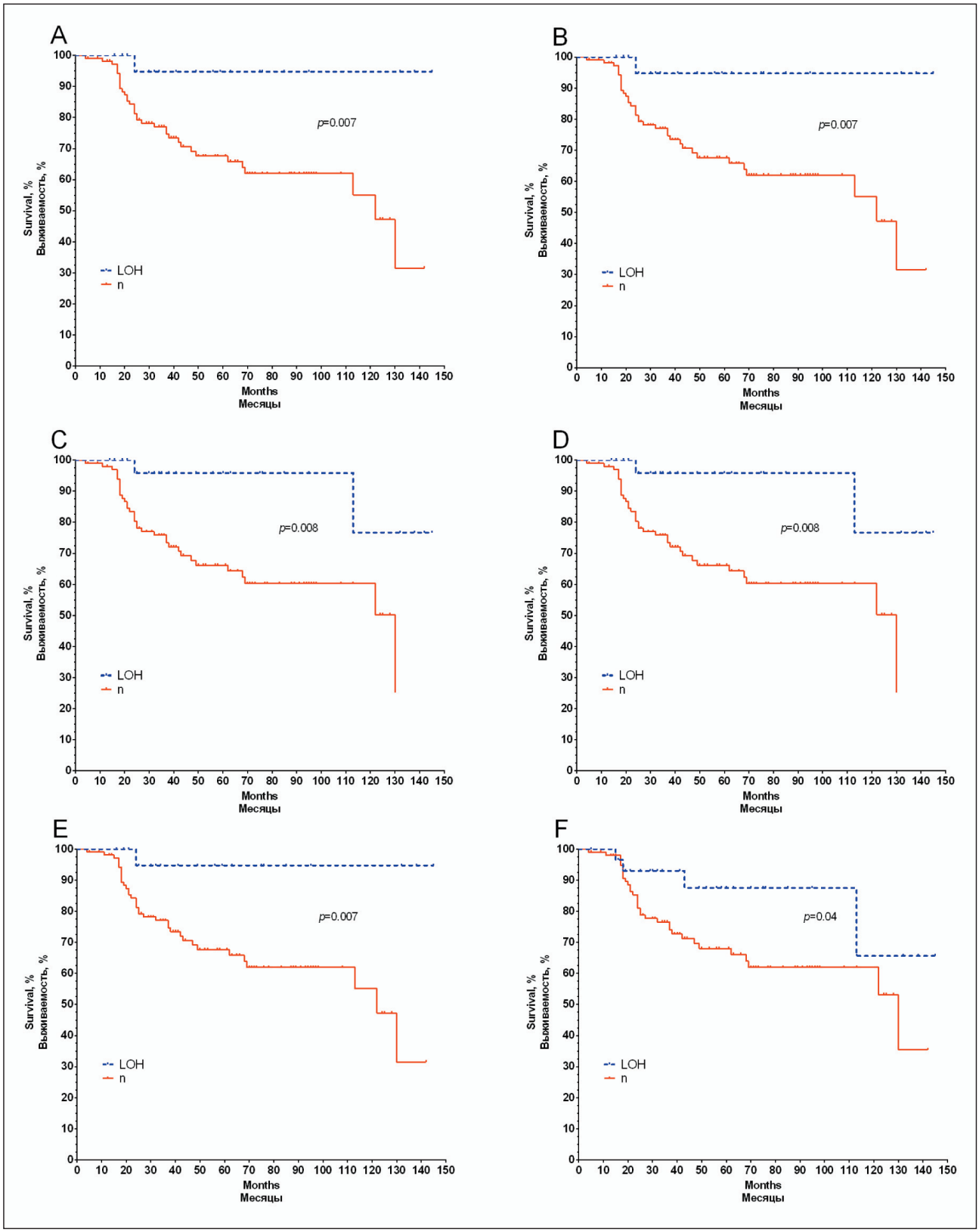

Fig. 3. Metastatic-free survival curves of breast cancer patients as a function of the presence of loss of heterozygosity sites in the *ABCA5* (A), *ABCA6* (B), *ABCA8* (C), *ABCA9* (D), *ABCA10* (E), *ABCC3* (F) genes

Рис. 3. Показатели безметастатической выживаемости больных раком молочной железы в зависимости от наличия участков потери гетерозиготности в генах *ABCA5* (A), *ABCA6* (B), *ABCA8* (C), *ABCA9* (D), *ABCA10* (E), *ABCC3* (F)

Supplement 1. Table 1/Таблица 1

Frequency of loss of heterozygosity in ABC transporter genes in breast tumors

Частота потери гетерозиготности в генах транспортера ABC в опухолях молочной железы

Genes/ Гены	Chromosome locus/ Хромосомный локус	Frequency of loss of heterozygosity/ Частота потери гетерозиготности	
		LOH	n
ABCA1	9q31.1	29 (22.3 %)	101 (77.7 %)
ABCA2	9q34.3	22 (16.9 %)	108 (83.1 %)
ABCA3	16p13.3	31 (23.8 %)	99 (76.2 %)
ABCA4	1p22.1	30 (23.1 %)	100 (76.9 %)
ABCA5	17q24.3	22 (16.9 %)	108 (83.1 %)
ABCA6	17q24.2	22 (16.9 %)	108 (83.1 %)
ABCA7	19p13.3	10 (7.7 %)	120 (92.3 %)
ABCA8	17q24.2	28 (21.5 %)	102 (78.5 %)
ABCA9	17q24.2	28 (21.5 %)	102 (78.5 %)
ABCA10	17q24.3	22 (16.9 %)	108 (83.1 %)
ABCA11P	4p16.3	35 (26.9 %)	95 (73.1 %)
ABCA12	2q35	39 (30.0 %)	91 (70.0 %)
ABCA13	7p12.3	9 (6.9 %)	121 (93.1 %)
ABCB1	7q21.12	28 (21.5 %)	102 (78.5 %)
ABCB2	6p21.32	14 (10.8 %)	116 (89.2 %)
ABCB3	6p21.32	14 (10.8 %)	116 (89.2 %)
ABCB4	7q21.12	28 (21.5 %)	102 (78.5 %)
ABCB5	7p21.1	11 (8.5 %)	119 (91.5 %)
ABCB6	2q35	39 (30.0 %)	91 (70.0 %)
ABCB7	Xq13.3	90 (69.2 %)	40 (30.8 %)
ABCB8	7q36.1	16 (12.3 %)	114 (87.7 %)
ABCB9	12q24.31	32 (24.6 %)	98 (75.4 %)
ABCB10	1q42.13	24 (18.5 %)	106 (81.5 %)
ABCB11	2q31.1	28 (21.5 %)	102 (78.5 %)
ABCC1	16p13.11	26 (20.0 %)	104 (80.0 %)
ABCC2	10q24.2	16 (12.3 %)	114 (87.7 %)
ABCC3	17q21.33	30 (23.1 %)	100 (76.9 %)
ABCC4	13q32.1	25 (19.2 %)	105 (80.8 %)
ABCC5	3q27.1	20 (15.4 %)	110 (84.6 %)
ABCC6	16p13.11	26 (20.0 %)	104 (80.0 %)
ABCC7	7q31.2	26 (20.0 %)	104 (80.0 %)
ABCC8	11p15.1	14 (10.8 %)	116 (89.2 %)
ABCC9	12p12.1	12 (9.2 %)	118 (90.8 %)
ABCC10	6p21.1	25 (19.2 %)	105 (80.8 %)
ABCC11	16q12.1	117 (90.0 %)	13 (10.0 %)
ABCC12	16q12.1	117 (90.0 %)	13 (10.0 %)
ABCD1	Xq28	88 (67.7 %)	42 (32.3 %)
ABCD2	12q12	70 (53.8 %)	60 (46.2 %)
ABCD3	1p21.3	12 (9.2 %)	118 (90.8 %)
ABCD4	14q24.3	29 (22.3 %)	101 (77.7 %)
ABCE1	4q31.21	36 (27.7 %)	94 (72.3 %)
ABCF1	6p21.33	16 (12.3 %)	114 (87.7 %)
ABCF2	7q36.1	16 (12.3 %)	114 (87.7 %)
ABCF3	3q27.1	20 (15.4 %)	110 (84.6 %)
ABCG1	21q22.3	10 (7.7 %)	120 (92.3 %)
ABCG2	4q22.1	39 (30.0 %)	91 (70.0 %)
ABCG4	11q23.3	21 (16.2 %)	109 (83.8 %)
ABCG5	2p21	16 (12.3 %)	114 (87.7 %)
ABCG8	2p21	16 (12.3 %)	114 (87.7 %)

in the *ABCA7* gene (rs9282562) has been found to be associated with lower recurrence-free survival in patients with breast cancer [27]. This may be due to the fact that the loss of functional activity of *ABCA7* inhibits migration, cell proliferation and invasion of tumor cells [28].

Thus, it has been shown that the presence of loss of heterozygosity sites of some ABC transporter genes are predictors of the efficacy of therapeutic treatment and potential prognostic markers of metastasis-free survival in breast cancer patients.

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Evgeny A. Usynin: critical revision of the manuscript for important intellectual content.
Nikolay V. Litviakov: critical revision of the manuscript for important intellectual content.

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The authors declare that they have no conflict of interest.
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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
Informed consent
Informed consent was obtained from all individual participants included in the study. The experiments comply with the current laws of the country.

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От лиц, участвующих в исследовании, получено информированное согласие. Эксперименты соответствуют действующим законам страны.