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ORIGINAL ARTICLE

Clinical and morphological features of breast tumors with *PIK3CA* mutations in Russian patients: Observational study

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Abstract

Background. By 2020, breast cancer (BC) has become the most frequent malignancy in the world. The most common type of BC is HR+/HER2-negative cancer, 25–40% of which harbors *PIK3CA* mutations that affect the catalytic subunit of the PI3K protein. *PIK3CA* alterations are actionable, as such neoplasms can be treated with a combination of fulvestrant and the PI3K inhibitor alpelisib. As *PIK3CA* mutations have an extremely versatile effect on the characteristics of a tumor cell, numerous associations of *PIK3CA* mutations and various clinico-pathological characteristics of BC can be traced.

Aim. Our aim was to clarify the information on the frequency and spectrum of *PIK3CA* mutations in Russian patients with HR+/HER2- advanced BC, and to study the association of *PIK3CA* mutations with clinical and pathological parameters of BC.

Materials and methods. Tissue samples from 694 patients with HR+/HER2- advanced BC (mixed population of primary metastatic and relapsed tumors) who received any line of anti-cancer treatment in Dec 2020 to June 2021 in Russian Federation were analyzed by high-resolution melting, allele-specific PCR, digital droplet PCR and Sanger sequencing (exons 7, 9, and 20 of the *PIK3CA* gene). Mutation rates in different BC subgroups were compared using the Fisher's exact test. The age at diagnosis in patients with different *PIK3CA* status was compared using the Mann–Whitney U-test. The relationship between the *PIK3CA* status and the degree of tumor differentiation was compared using the Cochrane–Armitage test for trends. Luminal A and B BC expression subtypes were distinguished with surrogate IHC markers according to St.-Gallen recommendations (2013).

Results. Mutations were identified in 220/694 (32%) BC patients. The three most frequent missense substitutions in the *PIK3CA* gene (p.E542K, p.E545K, and p.H1047R) accounted for 190/220 (86%) mutations. Associations of *PIK3CA* mutations with luminal A subtype of BC, low proliferation index, small size of the primary tumor, and absence of signs of hereditary cancer were revealed. Associations of mutations in the kinase domain of *PIK3CA* (p.H1047R) with late recurrence of locally advanced BC and with non-Slavic ethnic origin of patients were found.

Conclusion. *PIK3CA* mutation rate of 32% confirms high prevalence of mutation in Russian population, with some differences reflecting the ethnic origin of patients.

Keywords: breast cancer, HR+/HER2- breast cancer, breast cancer subtypes, PI3K, *PIK3CA*, screening, alpelisib, clinical and morphological parameters of the tumor

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Клинико-морфологические особенности опухолей молочной железы с мутациями *PIK3CA* у российских больных: наблюдательное исследование

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Аннотация

Обоснование. В 2020 г. рак молочной железы (РМЖ) вышел на первое место в структуре онкологической заболеваемости в мире. Наиболее частой разновидностью РМЖ являются положительные по гормональным рецепторам HER2-отрицательные (HR+ HER2-) опухоли, в 25–40% которых обнаруживаются мутации в онкогене *PIK3CA*, кодирующем каталитическую субъединицу белка PI3K. Такие новообразования поддаются лечению комбинацией фулвестранта и ингибитора PI3K алпелисиба. Известно, что мутации *PIK3CA* оказывают влияние на множество характеристик опухолевой клетки и демонстрируют ассоциации с разными клинико-биологическими параметрами РМЖ.

Цель. Дать характеристику частоты и спектра мутаций *PIK3CA* у российских пациенток с HR+/HER2- распространенным РМЖ, а также изучить ассоциации мутаций *PIK3CA* с клинико-морфологическими параметрами опухоли.

Материалы и методы. В образцах опухолевой ткани 694 пациенток с HR+ HER2- первично метастатическим или рецидивирующим РМЖ, получавших любую линию противоопухолевой терапии в период с декабря 2020 по июнь 2021 г. в лечебно-профилактических учреждениях Российской Федерации, были проанализированы экзоны 7, 9 и 20 гена *PIK3CA*. Для поиска мутаций использовали высокоточный анализ кинетики плавления ПЦР-амплификата, аллель-специфическую ПЦР, секвенирование по методу Сэнгера и цифровую капельную ПЦР. Сравнение частоты мутаций в разных подгруппах РМЖ было выполнено с помощью точного критерия Фишера. U-критерий Манна–Уитни применяли для сравнения возраста на момент постановки диагноза у пациенток с различным статусом *PIK3CA*. Для анализа связи статуса *PIK3CA* и степени дифференцировки опухоли применяли тест Кохрана–Армитажа для линейных трендов. Разграничение на люминальный A и люминальный B экспрессионный подтип выполняли при помощи суррогатных иммуногистохимических маркеров согласно рекомендациям St.-Gallen (2013).

Результаты. Мутации выявлены в 220/694 (32%) случаях HR+/HER2- распространенного РМЖ. На три наиболее частые миссенс-замены в гене *PIK3CA* (p.E542K, p.E545K и p.H1047R) пришлось 190/220 (86%) мутаций. Обнаружены ассоциации мутаций *PIK3CA* с люминальным A подтипом РМЖ, низким индексом пролиферации, малым размером первичной опухоли, отсутствием признаков наследственного рака. Обнаружена ассоциация мутаций киназного домена *PIK3CA* (p.H1047R) с необычно поздними рецидивами местно-распространенных РМЖ и с неславянским этническим происхождением пациенток.

Заключение. Частота и спектр мутаций *PIK3CA* в российской популяции в целом совпадают с данными крупных мировых исследований. Особенности распределения повреждений *PIK3CA* в неславянских этнических группах нуждаются в дальнейшем изучении.

Ключевые слова: рак молочной железы, HR+/HER2- рак молочной железы, подтипы рака молочной железы, PI3K, *PIK3CA*, скрининг, алпелисиб, клинико-морфологические параметры опухоли

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Background

Mutations in the *PIK3CA* gene encoding the PI3K kinase p110alpha catalytic subunit are one of the most common driver events in human tumors [1, 2]. The development of products targeting the inhibition of PI3K/Akt/mTOR signaling pathway has been underway for many years; however, the researchers have only recently achieved acceptable levels of clinical efficacy and safety profile of these products [3, 4]. The approval of a combination of alpelisib, a p110 alpha isoform-selective PI3K inhibitor and degrader, and standard hormone therapy for the treatment of metastatic *PIK3CA* mutated HR+/HER2 breast cancer (BC) has become a significant success in this area. It is noteworthy that this regimen has also demonstrated a clinical effect in patients after progression on CDK4/6 inhibitor [5–7]. The incidence of *PIK3CA* mutations in this type of BC may exceed 40% [8]. Although the PI3K inhibitor monotherapy of HR+ HER2- BC was shown to be ineffective, it can be expected to be beneficial as part of rationally selected combinations in other BCs or in other types of tumors; e.g. in combination with antiandrogens in luminal AR+ triple-negative BC; with trastuzumab in HER2-positive BC; with PARP inhibitors in ovarian cancer, etc. [9–11].

PIK3CA mutations affect a variety of biological parameters of tumor cells, including fats, carbohydrates, and amino acids metabolism, secreted immunocytokines, cell cycle stimulation, the formation of tolerance to polyploidy and chromosomal instability, etc. [12–14]. *PIK3CA* disease-promoting damages have both predictive and prognostic significance in BC; however, their significance varies in different clinical situations. While these mutations are associated with a favorable prognosis in the early stages of BC, they are associated with refractoriness to therapy and an unfavorable prognosis in metastatic HR+ and/or HER2+ carcinomas. The prognosis for patients with metastatic *PIK3CA* mutated triple-negative BC is also relatively favorable [15–19].

Mutations in different fragments of the gene affect the properties of the mutant *PIK3CA* protein in different ways. Amino acid substitutions in the helical domain (exon 9) allow signal transmission through the RAS-MAPK molecular cascade independently of the p85 regulatory subunit of PI3K. Unlike this, proteins mutated in the kinase domain (exon 20) need interaction with p85 and do not depend on RAS [20]. The most frequent *PIK3CA* damages, which account for more than 60% of all mutations, are the p.E542K, p.E545K (helical domain), and p.H1047R (kinase domain) missense substitutions. These mutations can complement each other; two disease-promoting mutations in the helical and kinase domain in cis have been reported, and tumors with double mutations seem to respond better to anti-PI3K therapy [8, 21]. The association of p.H1047R mutations (but not helical domain damage) with a low proportion of complete responses to anthracycline and taxane therapy in triple-negative BC has been reported, as well as HER2-positive tumor refractoriness to anti-HER2 therapy [22, 23]. Damaged helical domain demonstrates an association with well-differentiated luminal A HR+ BC and with a lobular molecular subtype [15, 24, 25]. Despite all functional differences, the predictive value of these two mutation categories in relation to alpelisib is apparently the same [5]. Unlike mutations in the *PIK3CA* spiral and kinase regions, damage to the PI3K C2 domain (exon 7) is less common. The clinical and biological significance of atypical helical and kinase domain mutations and of less frequent *PIK3CA* exon 7 mutations have not yet been fully described [8, 26, 27].

According to some studies, the frequency and structure of *PIK3CA* mutations in BC may have ethnic differences [28–30].

The purpose of this paper was to analyze the frequency, spectrum, and clinical and morphological associations of *PIK3CA* damage in Russian HR+ HER2- aBC patients.

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Table 1. Clinical and pathological characteristics of the studied BC samples

Characteristics	*PIK3CA* WT (n=474)	*PIK3CA* MUT (n=220)	*p*-value (*PIK3CA* WT vs MUT)§	*PIK3CA* MUT (exon 9, n=88)	*PIK3CA* MUT (exon 20, n=123)	*p*-value (exon 9 vs exon 20 mutations)§*
Age (median, range)	55 (27–83)	56 (31–92)		55 (31–89)	57 (31–92)	
Histologic type						
Ductal cancer (n=261)	175 (67%)	86 (33%)	0.7345 (ductal vs lobular)	33 (41%)	48 (59%)	0.3928 (ductal vs lobular)
Lobular cancer (n=45)	29 (64%)	16 (36%)		4 (27%)	11 (73%)	
Other (n=32)	27 (84%)	5 (16%)		3 (75%)	1 (25%)	
ND (n=356)	243 (68%)	113 (32%)		48 (35%)	63 (65%)	
Primary tumor size (T)**						
T1 (n=127)	75 (59%)	52 (41%)	**0.0177** (T1–T2 vs T3–T4)	22 (43%)	29 (57%)	1 (T1–T2 vs T3–T4)
T2 (n=283)	188 (66%)	95 (34%)		37 (42%)	51 (58%)	
T3 (n=43)	37 (86%)	6 (14%)		2 (33%)	4 (67%)	
T4 (n=139)	98 (71%)	41 (29%)		17 (43%)	23 (57%)	
ND (n=102)	76 (75%)	26 (25%)		10 (38%)	16 (62%)	
Lymph nodes involvement (N)**						
N0 (n=141)	92 (65%)	49 (35%)	0.4707 (N0 vs N1–N3)	19 (38%)	30 (62%)	0.7361 (N0 vs N1–N3)
N1 (n=208)	142 (68%)	66 (32%)		29 (46%)	34 (54%)	
N2 (n=120)	83 (69%)	37 (31%)		14 (30%)	19 (70%)	
N3 (n=110)	75 (68%)	35 (32%)		11 (29%)	22 (71%)	
ND (n=115)	82 (71%)	33 (29%)		15 (29%)	18 (71%)	
Stage**						
I (n=48)	31 (65%)	17 (35%)	0.1365 (I–II vs III–IV)	4 (24%)	13 (76%)	0.7689 (I–II vs III–IV)
II (n=208)	132 (63%)	76 (33%)		35 (48%)	38 (52%)	
III (n=267)	185 (69%)	82 (31%)		31 (41%)	45 (59%)	
IV (n=83)	59 (71%)	24 (29%)		9 (38%)	15 (62%)	
ND (n=88)	67 (76%)	21 (24%)		9 (43%)	12 (57%)	
Clinical situation at the time of the analysis						
Relapse (n=543)	366 (67%)	177 (33%)	0.3342 (recurrent vs primary metastatic and progressive) 1 (DFI < or >5 years)	71 (42%)	97 (58%)	1 (recurrent vs primary metastatic and progressive) 1.000 (DFI < or >5 years)
DFI<1 year (n=78)	50 (64%)	28 (36%)		13 (46%)	14 (54%)	
DFI 1–3 years (n=131)	92 (70%)	39 (30%)		17 (46%)	20 (54%)	
DFI 3–5 years (n=60)	41 (68%)	19 (32%)		7 (41%)	10 (59%)	
DFI>5 years (n=99)	67 (68%)	32 (32%)		14 (44%)	18 (67%)	
ND (n=175)	116 (66%)	59 (34%)		20 (36%)	35 (64%)	
Primary metastatic cancer (n=83)	59 (71%)	24 (29%)		9 (38%)	15 (62%)	
ND (n=6)	4 (67%)	2 (33%)		0 (25%)	2 (100%)	
Endocrine resistance status***						
Primary resistance	83 (61%)	52 (39%)	0.7637	22 (44%)	28 (56%)	0.7679
Secondary resistance	46 (67%)	23 (33%)		7 (35%)	13 (65%)	
Sensitivity	32 (64%)	18 (36%)		8 (44%)	10 (56%)	
Unusual relapse patterns****						
Indolent (n=28)	20 (71%)	8 (29%)	0.6404 (indolent vs aggressive)	1 (13%)	7 (87%)	0.0425 (indolent vs aggressive)
Agressive (n=74)	48 (65%)	26 (35%)		15 (58%)	11 (42%)	
Tumor differentiation grade						
G1 (n=19)	10 (53%)	9 (47%)	0.08 (G1 vs G2 vs G3)	3 (33%)	6 (67%)	0.2 (G1 vs G2 vs G3)
G2 (n=160)	105 (66%)	55 (34%)		25 (48%)	27 (52%)	
G3 (n=44)	33 (75%)	11 (25%)		7 (64%)	4 (46%)	
ND (n=471)	326 (71%)	145 (29%)		53 (38%)	86 (62%)	
Ki67						
Low (<20%; n=171)	105 (61%)	66 (39%)	***p*=0.0362** (low vs high)	32 (48%)	35 (52%)	0.4933 (low vs high)
High (≥20%; n=266)	190 (71%)	76 (29%)		29 (41%)	42 (59%)	
ND (n=257)	179 (70%)	78 (30%)		27 (37%)	46 (63%)	
Surrogate molecular subtype^						
Luminal A (n=130)	79 (61%)	51 (39%)	**0.0283** (A vs B)	21 (54%)	28 (46%)	0.8627 (A vs B)
Luminal B (n=366)	261 (71%)	105 (29%)		45 (45%)	56 (55%)	
ND (n=198)	134 (70%)	64 (30%)		22 (36%)	39 (64%)	
Menopausal status at diagnosis						
Premenopause (n=162)	113 (70%)	49 (30%)	0.8427 (pre- vs postmenopause)	20 (43%)	26 (57%)	1 (pre- vs postmenopause)
Peri- and postmenopause (n=438)	300 (68%)	138 (32%)		57 (43%)	77 (57%)	
ND (n=94)	61 (65%)	33 (35%)		11 (35%)	20 (65%)	

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Table 1. Clinical and pathological features of BC samples. The ending

Characteristics	*PIK3CA* WT (n=474)	*PIK3CA* MUT (n=220)	*p*-value (*PIK3CA* WT vs MUT)[§]	*PIK3CA* MUT (exon 9, n=88)	*PIK3CA* MUT (exon 20, n=123)	*p*-value (exon 9 vs exon 20 mutations)[§*]
Metastasis sites (n=260)						
Bones only (n=58)	34 (59%)	24 (41%)		9 (39%)	14 (61%)	
Lungs only (n=28)	15 (54%)	13 (46%)		4 (31%)	9 (69%)	
Soft tissues only (n=8)	7 (87%)	1 (13%)		0 (0%)	1 (100%)	
Distant lymph nodes only (n=37)	27 (73%)	10 (27%)	0.2067	6 (67%)	3 (33%)	0.3657
Liver only (n=22)	17 (77%)	5 (23%)		3 (75%)	1 (25%)	
Other (n=5)	3 (60%)	2 (40%)		1 (50%)	1 (50%)	
Multiple sites (n=89)	62 (70%)	27 (30%)		10 (40%)	15 (60%)	
Metastasis sites number						
1–3 (n=231)	152 (66%)	79 (34%)	1 (>3 vs 1–3)	34 (43%)	45 (67%)	1 (>3 vs 1–3)
>3 (n=7)	5 (71%)	2 (29%)		1 (50%)	1 (50%)	
Predictors of hereditary cancer (young age <45, multiple tumors. family history)						
Yes (n=215)	160 (74%)	55 (26%)	**0.0218**	26 (48%)	28 (52%)	0.2687
No or ND (n=479)	314 (66%)	165 (34%)		62 (39%)	95 (61%)	
Ethnicity						
Patients from the territories of the Russian Federation with Slavic population predominating (n=590)	400 (68%)	190 (32%)		79 (44%)	102 (56%)	
Patients from the territories of the Russian Federation with non-Slavic population predominating[#] (n=71)	55 (77%)	16 (23%)	0.1048	2 (12%)	14 (88%)	0.0165
A) North Caucasian Republics (n=24)	20 (83%)	4 (17%)		0 (0%)	4 (100%)	
B) Bashkortostan. Tatarstan (n=47)	35 (74%)	12 (26%)		2 (17%)	10 (83%)	
ND (n=33)	19 (58%)	14 (42%)		7 (50%)	7 (50%)	

Note. DFI – disease-free interval, ND – no data, WT – tumors without mutations, MUT – tumors with mutations; [§]the table shows the family-wise *p*-values, *nine cases of atypical and double *PIK3CA* mutations were excluded from the analysis, **in the case of bilateral BC, the source of the sample for genotyping was indicated where possible; the greater of the two degrees T, N, the stage was indicated where impossible, ***primary resistance: relapse while on the first 2 years of adjuvant ET; secondary resistance – relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET; endocrine sensitivity – relapse at least 12 months after the completion of adjuvant endocrine therapy, ****the indolent pattern of relapse is a situation when a stage III tumor recurs after 5 years; the aggressive pattern is an early (<3 years) relapse of stage I–II tumors, ^distinction between expression subtypes of receptor-positive HER2-negative BC, luminal A, and B was performed with surrogate IHC markers according to St.-Gallen 2013 [37]: luminal B: Ki-67>/=20 and/or low expression of PgR, high expression of ER, [#]the study included patients from the following territories of the Russian Federation where the non-Slavic population predominates (according to the All-Russian Census of 2010)[1]: Bashkortostan (n=40), Ingushetia (n=8), Tatarstan (n=7), Chechen Republic (n=6), North Ossetia-Alania (n=5), Kabardino-Balkaria (n=4).

[1]Federal State Statistics Service. Available at: https://rosstat.gov.ru/vpn_popul/ Accessed: 25.03.2022.

Materials and methods

The study included 694 cases of HR+ HER2- aBC treated in more than 50 cities of Russia. We described some of the cases mentioned (n=206) previously [31]. Clinical and morphological characteristics of the patients are presented in table 1. Genotyping protocols were the same [31]. Briefly, after microdissection of archival tumor tissue samples and isolation of nucleic acids, fragments of the *PIK3CA* exons 7, 9, and 20 with mutant hotspots were studied using high resolution melting analysis of PCR amplicons (HRMA). The most frequent *PIK3CA* molecular defects (p.E542K, p.E545K, p.H1047R, p.H1047L, p.H1047Y) were analyzed using allele-specific PCR (AS-PCR). If melting curves deviated outside the ranges of the five mutation types detected by AS-PCR, Sanger sequencing was performed. Digital droplet PCR (ddPCR) was used to verify the borderline AS-PCR results.

Mutation rates in different BC subgroups were compared using the exact Fisher's test. The age at diagnosis of primary tumor in patients with different *PIK3CA* status was compared using the Mann–Whitney U-test. The relationship between the *PIK3CA* status and the degree of tumor differentiation was compared using the Cochrane–Armitage test for trends.

Results

PIK3CA mutations were detected in 220/694 (32%) of HR+/HER2- BCs. The three most frequent mutations accounted for 190/220 (86%) cases: p. E542K (38/220, 17%), p.E545K (40/220, 8%), H1047R (112/220, 51%). Three more mutations were observed more than once: p.H1047L (8/220, 4%), p.Q546K (5/220, 2%), and p.C420R (3/220, 13%); other mutations were detected in individual cases. In total, 4 mutations were detected in *PIK3CA* exon 7, 88 mutations were detected in exon 9 and 123 mutations were detected in exon 20. In addition, five double mutations were found (see table 2).

Table 1 demonstrates the results of the analysis of associations between *PIK3CA* mutations and their location (helical or kinase domain) and BC clinical and morphological features. *PIK3CA* mutations were less frequently observed in patients with a large primary tumor (>5 cm, T3 involving neighboring anatomical structures, T4), 147/410 (36%) vs 47/182 (26%); p=0.0177. *PIK3CA* mutations were more common in luminal A subtype vs luminal B, (51/130 (39%) vs 105/366 (29%), respectively; p=0.0283), and in tumors with a low vs high proliferation index, 66/171 (39%) vs 76/266 (29%); p=0.0362. We observed a tendency of an increased percentage of *PIK3CA*-mutant tumors

Table 2. Identified mutations in the *PIK3CA* gene

Mutation	Number of cases
Exon 7 (n=4)	
C420R	3/220 (1.3%)
L422W	1/220 (0.5%)
Exon 9 (n=88)	
E542K	38/220 (17%)
E542A	1/220 (0.5%)
E545K	40/220 (18%)
E545Q	1/220 (0.5%)
E545G	1/220 (0.5%)
Q546K	5/220 (2.3%)
Q546P	1/220 (0.5%)
Q546R	1/220 (0.5%)
Exon 20 (n=123)	
H1047R	112/220 (50.9%)
H1047L	8/220 (3.6%)
H1047Q	1/220 (0.5%)
H1047Y	1/220 (0.5%)
H1047L	1/220 (0.5%)
Double mutations (n=5)	
H1047R+E418K	1/220 (0.5%)
G1049R+C420R	1/220 (0.5%)
H1047R+C420R	1/220 (0.5%)
M1043V+N1044Y	1/220 (0.5%)
E545Q+H1047R	1/220 (0.5%)

in more highly differentiated BCs, p=0.08. Assessing relapsing, we compared the spreading of *PIK3CA* mutations in late-relapsed initially local BCs ("indolent") and early-relapsed localized tumors ("aggressive"). *PIK3CA* kinase domain mutations were associated with late relapses of local tumors, i.e. with indolent BCs, 7/8 (88%) vs 11/26 (42%); p=0.0425. Tumors from patients with predictors of cancer hereditary syndrome (young age, <45), multiple primary tumors, family history of BC or ovarian cancer) were found to have fewer *PIK3CA* positive cases 55/215 (26%) vs 165/479 (34%); p=0.0218. Finally, the samples received from the national republics where non-Slavic ethnic groups (Republic in the North Caucasus, Tatarstan, Bashkortostan) dominated showed the lower percentage of *PIK3CA*-positive neoplasm compared to samples from the regions, populated mostly by Slavs: 16/71 (23%) vs 190/590 (32%) (p=0.1048). The distribution of mutation types among *PIK3CA*-positive BCs was also different in these categories of patients, with the predominance of kinase domain mutations in presumably non-Slavic patients, 102/181 (56%) vs 14/16 (88%), p=0.0165.

Discussion

The study analyzed a large cohort of Russian patients with HR+/HER2- aBC who received any line of anti-cancer therapy in Dec 2020 to June 2021. In general, the percentage and structure of the detected mutations correspond to the world data [8, 32]. The detected frequency of *PIK3CA* mutations (32%) was numerically lower than in some large multicenter studies, for example, in the work by P. Rajadurai et al., 2021 (808/1995, 41%) [33]. This difference may be attributed to the distinct distribution of transcriptional BC subtypes: for example, in the TCGA cohort, the frequency of *PIK3CA* mutations reached 45% in luminal A cancers (n=225), and was only 29% in luminal B tumors (n=126). We determined the transcriptional subtypes by surrogate IHC markers and also noted a significant difference between luminal A (51/130, 39%) and luminal B (105/366, 29%) carcinomas (p=0.028). At the same time, the proportion of luminal A tumors in our cohort was somewhat low (130/596, 22%) if compared to a large European study (4036/9415, 43%) [34].

Interestingly, although no specific clinical features of the *PIK3CA* status in receptor-positive BCs were observed in Russian patients in general, the observed trend towards a lower percentage of *PIK3CA*-associated tumors and the predominance of kinase domain mutations in presumably non-Slavic patients (Tatars, Bashkirs, and especially North Caucasian representatives). Similar interethnic differences in the percentage of *PIK3CA* mutations, the nature of which remains unknown, occur, for example, between European and African-American descents in the US [28, 29].

A number of the associations we found confirmed previously published data; e.g. the association of *PIK3CA* mutations and a low proliferative index, luminal B subtype, and a high differentiation have been repeatedly reported [8]. As for the evidence of the association of *PIK3CA* mutations with the size of the primary tumor, it is quite contradictory; an association with large tumors and a connection of *PIK3CA* helical domain damage with the small size of the primary focus has been reported [25, 35]. The reported association between the presence of *PIK3CA* mutations and the late relapse of large local BCs is interesting. It can be noted that some authors explain the favorable prognostic role of *PIK3CA* mutations in the early stages of BC by the high expression of immune-stimulating cytokines by such tumors and pronounced infiltration by CD8+ lymphocytes [19, 36]. It is possible that the long-term asymptomatic persistence of micrometastatic foci consisting of *PIK3CA*-positive tumor cells is caused by their relatively high immunogenicity.

We have revealed a low percentage of *PIK3CA* mutations among BCs with predictors of hereditary cancer, which included young age, multiple primary tumors, or cancer in family history. At least one of these predictors was present in 215/694 (31%) cases. Obviously, the percentage of "true" monogenic tumor syndromes is small in this group, especially considering that the BRCA1-associated hereditary BCs, the most frequent in Russia, is usually a triple-negative cancer subtype which was excluded from our study.

It should be noted in conclusion that some of the results of our study, including the possible interethnic differences in the structure of *PIK3CA* mutations in BC, deserve further investigation.

Disclosure of Interest. The authors declare that they have no competing interests.

Authors' contribution. The authors declare the compliance of their authorship according to the international ICMJE criteria. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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