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ORIGINAL ARTICLE

Ki-67 expression in triple-negative breast cancer and its correlation with age

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ABSTRACT

Purpose of the study. To analyze the correlation between the proliferative activity of atypical cells in triple-negative breast cancer (BC) and patient age.

Patients and methods. The study included 80 women with a newly diagnosed BC, in whom a triple-negative surrogate molecular genetic subtype was identified based on histological and immunohistochemical examination with assessment of hormone receptor expression and Ki-67. Statistical analysis was performed using Statistica 13.5.0.17 software (TIBCO Software Inc.). The Shapiro-Wilk test was applied to assess the normality of the distribution. Correlation between variables was evaluated using the Kendall tau rank correlation coefficient.

Results. The median age of patients was 53.9 years (95 % confidence interval [CI]: 50.0–57.8) (Fig. 3). Among them, 65 % of patients were younger than 50 years and 35 % were older. The median proliferative activity, assessed by Ki-67 expression according to the St. Gallen Consensus (2009), was 76.4 % (95 % CI: 73.28–79.66). However, this indicator varied depending on patient age. The analysis revealed a correlation between Ki-67 expression level and patient age, with a Kendall tau coefficient of −0.449 ($p < 0.05$), corresponding to a weak-to-moderate negative association.

Conclusion. The analysis showed that the degree of Ki-67 expression correlates with the age at breast cancer onset. Thus, there is a tendency toward higher proliferative activity of cancer cells in younger patients.

Keywords: breast cancer, triple negative, Ki-67

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Compliance with ethical standards: the study was carried out in compliance with the ethical principles set in the World Medical Association Declaration of Helsinki (1964, revised in 2013). The research was approved by the Joint Problem Commission of the P. A. Hertsen Moscow Oncology Research Institute – branch of the National Medical Research Radiological Center (extract from the meeting protocol No. 2 dated 03/15/2024). Informed consent was obtained from all study participants

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Экспрессия Ki-67 при трижды негативном раке молочной железы, возрастные особенности

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РЕЗЮМЕ

Цель исследования. Проанализировать степень корреляции между уровнем пролиферативной активности атипичных клеток трижды негативного рака молочной железы (РМЖ) и возрастом пациента.
Пациенты и методы. В исследование было включено 80 женщин с впервые установленным диагнозом РМЖ, у которых по результатам гистологического и иммуногистохимического исследования с оценкой экспрессии гормональных рецепторов и Ki-67 был установлен трижды негативный суррогатный молекулярно-генетический подтип РМЖ. Статистический анализ выборки проводился с применением программного обеспечения Statistica 13.5.0.17 software (TIBCO Software inc.). Для оценки нормальности распределения признака, применялся критерий Шапиро-Уилка (Shapiro-Wilk). Степень корреляции между признаками оценивалась с применением коэффициента корреляции Кенделла (Kendall tau rank correlation coefficient).
Результаты. Медиана возраста у пациентов в полученной выборке составляла 53,9 лет (95 % доверительный интервал [ДИ] 50,0–57,8). Среди них 65 % пациентов были моложе, а 35 % – старше 50 лет. Медианный уровень пролиферативной активности, оцененный по уровню экспрессии Ki-67 по шкале St. Gallen Consensus (2009 г.) составил 76,4 % (95 % ДИ 73,28–79,66). Однако значение данного показателя варьировало в зависимости от возраста пациентов. При проведении анализа выявлено, что существует корреляция между уровнем экспрессии Ki-67 и возрастом пациента, коэффициент корреляции Кенделла составил –0,449 ($p < 0,05$), что соответствует слабой-умеренной отрицательной связи.
Заключение. В ходе проведенного анализа выявлено, что степень экспрессии Ki-67 коррелирует с возрастом дебюта РМЖ у пациента. Таким образом, имеется тенденция к более высокой пролиферативной активности раковых клеток у молодых пациентов.

Ключевые слова: рак молочной железы, трижды-негативный рак, Ki-67

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено Объединенной проблемной комиссией при Московский научно-исследовательский онкологический институт им. П. А. Герцена – филиал ФГБУ «Национальный медицинский исследовательский центр радиологии» Министерства здравоохранения Российской Федерации (выписка из протокола заседания № 2 от 15.03.2024 г.). Информированное согласие получено от всех участников исследования

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BACKGROUND

Breast cancer (BC) is a malignant tumor arising from the luminal epithelium of the terminal ductal lobular units and represents one of the most common oncological diseases worldwide [1].

In Russia, in 2023, breast cancer accounted for 22.5 % of all newly diagnosed cancers in women, corresponding to 12.3 % of the total population or 84,299 cases in absolute numbers. Such a high incidence also explains the significant contribution of breast cancer to cancer-related mortality, which was 15.9 % or 18,580 deaths in 2023. Nevertheless, there are clear positive trends in the diagnosis and treatment of breast cancer: compared with 2013, the mortality growth rate decreased by 16.2 % [2].

One of the reasons for the decline in mortality is the early detection of malignancies, as well as the development and implementation of innovative therapeutic approaches, including those based on the genetic characteristics of tumors. A particularly effective advancement has been the introduction of surrogate molecular genetic subtyping of breast cancer into routine clinical practice. Indeed, "breast cancer" is an umbrella term that encompasses a heterogeneous group of tumors with distinct genetic and transcriptomic features [3–5]. Based on genetic research, four intrinsic subtypes of breast cancer have been identified: luminal A, luminal B, HER2-enriched, and basal-like. Each subtype is distinguished by its specific expression profile of estrogen receptors, progesterone receptors, and HER2/neu receptors.

However, from both technical and economic perspectives, genetic testing of every tumor remains difficult to implement in daily practice. Therefore, an immunohistochemical (IHC) approach was developed as a surrogate for genetic testing, based on the assessment of hormone receptor expression and proliferative activity (Ki-67 index). Using this method, five surrogate molecular subtypes are distinguished: luminal A, luminal B HER2-negative, luminal B HER2-positive, HER2-enriched, and triple-negative [1, 6, 7]. These subtypes allow clinicians to select the most appropriate treatment strategy [7].

Among all subtypes, triple-negative breast cancer (TNBC) is characterized by the most aggressive clinical course and the highest mutational burden [8–10]. Due to severe alterations in the genetic apparatus, TNBC cells lack expression of estrogen, progesterone, and HER2/neu receptors (Fig. 1), which greatly limits therapeutic options, as both hormone therapy and anti-HER2 targeted therapy (e. g., trastuzumab) are ineffective [8, 9, 11]. The overall prevalence of TNBC is about 10–15 %, but it varies by age. According to Anders, et al., 34.3 % of breast cancers in women younger than 40 years had a basal-like phenotype, compared with 17.9 % in women over 65 years [12]. It is also well established that early-onset breast cancer is a strong negative prognostic factor, being associated with larger tumor size, higher rates of lymph node involvement, more aggressive histological features, and increased recurrence rates, both after breast-conserving surgery and mastectomy [9, 13].

We hypothesize that the aggressive course of the disease in younger patients is related not only to the higher proportion of the triple-negative phenotype compared with older patients, but also to the fact that age at disease onset itself may be an independent prognostic factor influencing tumor biology.

Purpose of the study: To analyze the correlation between the proliferative activity of atypical cells in triple-negative breast cancer and patient age.

PATIENTS AND METHODS

In this retrospective study, we analyzed data from 80 patients (medical records and pathomorphological reports) who received treatment at the P. A. Herzen MNIOI – Branch of the National Medical Research Radiological Center. Inclusion criteria were: female sex, age over 18 years, a confirmed diagnosis of breast cancer with ≥ T1a stage, histological subtype – invasive carcinoma of no special type (ICD-O: 8500/3), and triple-negative surrogate molecular subtype. Exclusion criteria were: pregnancy, severe comorbid conditions, history of malignant tumors, and the presence of BRCA1/2 mutations, determined by RT-PCR (DTPrime4; DNA-Technology). According to the medical records, all patients underwent diagnostic biopsy followed by morphological and immunohistochemical examination using the following monoclonal antibodies: anti-Estrogen Receptor (ER, clone SP1, Ventana), anti-Progesterone Receptor (PgR, clone 1E2, Ventana), anti-HER2/NEU (clone 4B5, Ventana), and anti-Ki-67 (clone 30–9, Ventana) on the Ventana Benchmark XT universal staining system with the ultra-View Universal DAB Detection Kit (Ventana).

Tumor grade was assessed according to the Nottingham Histologic Score (Table 1).

The surrogate molecular genetic profile and the proliferative activity grade were determined in accordance with the recommendations of the WHO and the College of American Pathologists using the Allred scoring system (Table 2) [7, 14]. A triple-negative phenotype was defined as an Allred score of ≤ 2 for ER and PR, as well as the absence of HER2/neu expression (Table 3). For the assessment of proliferative activity, at least 1000 tumor cells were analyzed. Counting was performed across the entire tumor material, with special attention to "hot spots" (Figs. 2–5) [15].

Based on the results of the immunohistochemical study, the surrogate molecular genetic subtype was determined according to the hormonal receptor expression profile (Table 4).

Table 1. Nottingham Histologic Grading System

Показатель	Score		
	1	2	3
Tubule formation	< 10 %	10–75 %	> 75 %
Nuclear pleomorphism	Mind	Moderate	Marked
Mitotic count*	≤ 12	12–24	> 25
Total score	3–5	6–7	8–9
	Grade 1	Grade 2	Grade 3

Note: * – mitotic count is determined in hot spots across 10 high-power fields, adjusted for the field area (values are given for a field diameter of 0.65 mm)

Table 2. Evaluation of Estrogen and Progesterone Receptor Expression by the Allred Scoring System

Proportion of expression	Positive cells, %	Intensity/ Score
0	0	No staining / 0
1	< 1	Weak /1
2	1 – 10	Moderate /2
3	11 – 33	Strong / 3
4	34 – 66	
5	≥ 67	

Note: The final score = proportion score + intensity score. 0–2 – negative result, 3–8 – positive result

Table 3. Assessment of HER2/neu Expression

HER2/статус	Criteria
Negative	No staining, or incomplete and weak membrane staining observed in ≤ 10 % of tumor cells
Negative	Incomplete weak membrane staining observed in ≥ 10 % of tumor cells
Equivocal	Weak to moderate complete membrane staining in ≥ 10 % of tumor cells, or complete intense membrane staining in ≤ 10 % of tumor cells
Positive	Complete intense membrane staining in > 10 % of tumor cells

Statistical analysis

Statistical analysis was performed using Statistica software version 13.5.0.17 (TIBCO Software Inc.). The Shapiro-Wilk test was applied to assess the normality of distribution. The degree of correlation between variables was evaluated using the Kendall tau rank correlation coefficient.

STUDY RESULTS AND DISCUSSION

In all breast tissue samples of the patients (n = 80), a morphological pattern of invasive carcinoma of no special type (NST), grade G3 according to the Nottingham grading system (Bloom-Richardson modification), was identified. Breast microfragments with pathologically altered tissue (tissue and cellular atypia of the parenchyma) showed clusters of pleomorphic atypical cells (> 300), forming solid structures. The cytoplasm of these cells appeared as a thin rim; their nuclei, displaying polymorphism, were eccentrically located, round in shape, with irregular ("moth-eaten") nuclear membranes. The stromal component demonstrated a weak desmoplastic reaction (Fig. 1).

In the immunohistochemical analysis of samples from patients with breast cancer (n = 80), no Her2/neu membrane staining of atypical cells was detected. ERα and PR according to the Allred score: 0 (PS) + 0 (IS) = 0 (TS) (Immunoreactivity score – negative). The status (ER, PR, Her2/neu) was defined as triple-negative breast cancer (Fig. 2). At the same time, immunohistochemical reactions with antibodies to Ki-67 demonstrated pronounced nuclear immunostaining of tumor cells (Fig. 2). The median proliferative activity level, assessed by Ki-67 expression according to the St. Gallen Consensus scale (2009), was 76.4 % (95 % confidence interval [CI] 73.28–79.66) (Fig. 3). However, the value of this indicator varied depending on the patients' age.

The median age of patients in the studied cohort was 53.9 years (95 % confidence interval [CI] 50.0– 57.8) (Fig. 4). Among them, 65 % of patients were younger and 35 % were older than 50 years. In all patients, breast carcinoma corresponded to a high grade of malignancy (grade 3). The distribution by disease stage is presented in Table 5. Statistical analysis of the correlation between Ki-67 expression level and patient age showed a Kendall's tau coefficient of –0.449 (p < 0.05), indicating a weak-to-moderate negative correlation.

According to the results of our study, it was found that the degree of proliferative activity of triple-negative breast cancer has a negative correlation with patient age, i. e., in younger women, tumor cells exhibit higher proliferative activity. Taking into account the charac-

Table 4. Surrogate molecular genetic subtypes of breast cancer

Surrogate molecular genetic subtype	Characteristics	Prevalence
Luminal A	ER-positive PR-positive HER2-negative Ki-67 ≤ 20 %*	55 %
Luminal B, HER2-negative	ER-positive HER2-negative and at least one of the following: Ki-67 ≥ 30 % PR < 20 % (percentage of expressing cells)	15 %
Luminal B, HER2-positive	ER-positive HER2-positive Ki-67 any PR any	
HER2-enriched	ER-negative PR-negative HER2-positive	15–20 %
Triple-negative	ER-negative PR-negative HER2-negative	10–15 %

Note: * – the threshold values of Ki-67 may vary depending on the institutional guidelines [1, 15]. ER – estrogen receptor; PR – progesterone receptor

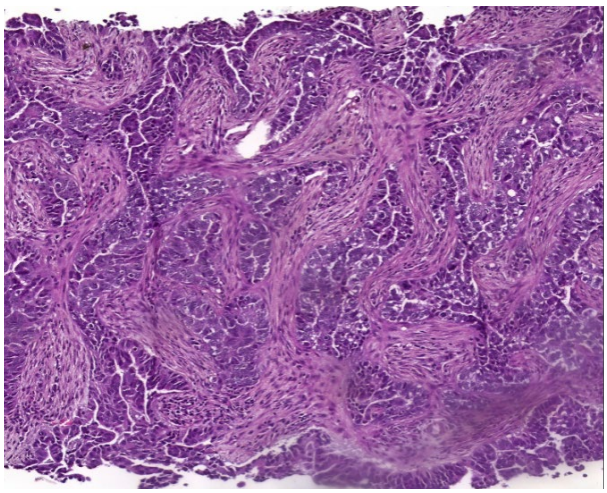

Fig. 1. Patient T., 58 years old. Invasive breast carcinoma of no special type, G3 according to the Nottingham grading system (Bloom-Richardson modification). Staining: hematoxylin and eosin, magnification ×200

teristics of our cohort namely, the absence of estrogen and progesterone receptor expression in tumor cells we can exclude the influence of these hormones on proliferative activity. However, in our opinion, thyroid hormones may play an important role, since one of their functions is the regulation of cellular proliferative activity at different sites [16]. It is known that triiodothyronine levels decrease linearly with age, and there are studies indicating that the use of tyrosine kinase inhibitors, i. e., drug-induced hypothyroidism, is associated with improved survival in patients with non-thyroid solid malignant tumors [17, 18]. This hypothesis is supported by the study of Tawfik, et al., which demonstrated that breast carcinoma cells are capable of capturing T3, which in turn stimulates their proliferative activity [19].

The result obtained in our study can be explained not only by the influence of the macroorganism on tumor biology [20], but also by the genetic characteristics of triple-negative breast cancer. For example, when analyzing data from The Cancer Genome At-

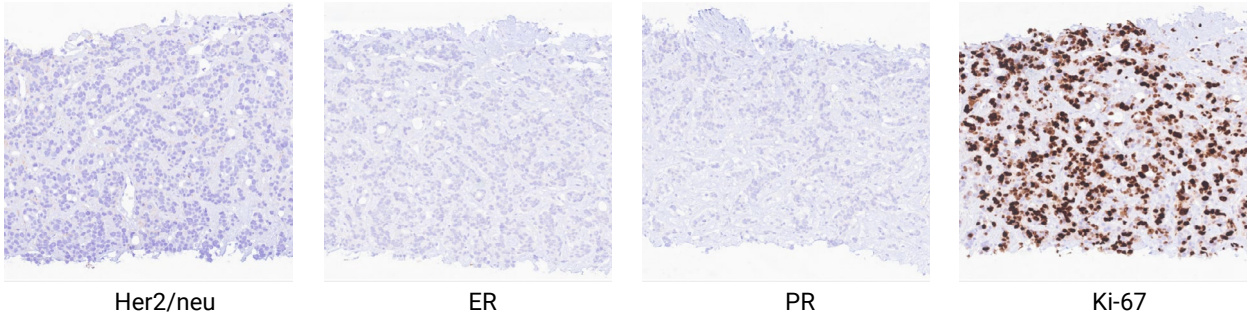

Fig. 2. Patient T., 58 years old. Invasive breast carcinoma of no special type, G3 according to the Nottingham grading system (Bloom-Richardson modification); immunophenotype – triple-negative. Immunohistochemical staining with antibodies, counterstaining with hematoxylin and eosin, magnification ×200

Table 5. Distribution of patients by disease stage according to TNM classification (UICC, 8th edition, 2018)

Disease stage	Number of patients (%)
Stage IA	4 (5 %)
Stage IB	0
Stage IIA	44 (55 %)
Stage IIB	8 (10 %)
Stage IIIA	4 (5 %)
Stage IIIB	8 (10 %)
Stage IIIC	12 (15 %)
Stage IV	0

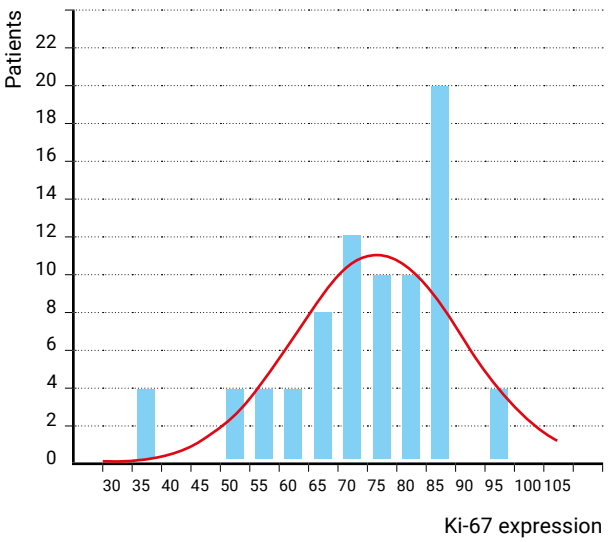

Fig. 3. Level of Ki-67 expression in triple-negative breast cancer

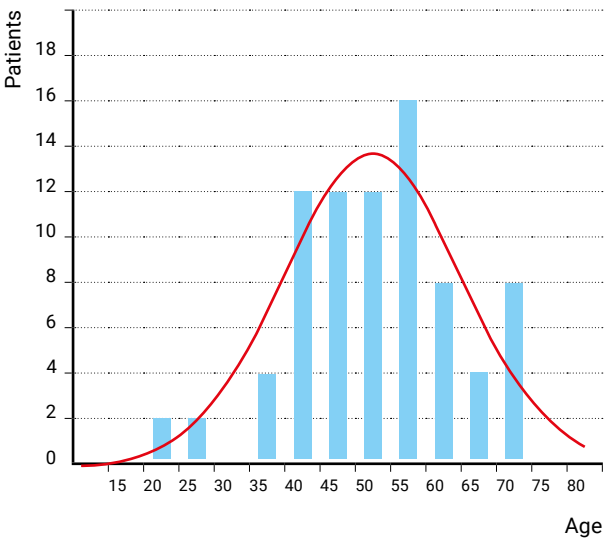

Fig. 4. Age characteristics of the cohort

las in the TCGA-BRCA (Breast invasive carcinoma) cohort using the Oncomatrix tool, a higher frequency of *TP53* mutations can be observed in patients younger than 45 years 42.6 % compared to 37.7 % in women older than 45 years (Figs. 6, 7) [21]. It is well established that TP53 mutations are associated with increased tumor proliferative activity [22]. Thus, according to published data, when comparing p53-mutant and p53-wt breast carcinomas, the Ki-67 index was on average 16 % higher in p53-mutant tumors (51.77 ± 24.53 vs. 35.81 ± 19.54) [23]. We hypothesize that the higher frequency of *TP53* mutations in younger women is one of the key factors determining both the greater proliferative activity of the tumor and the higher incidence of triple-negative breast cancer. From a clinical standpoint, higher proliferative activity represents a factor negatively affecting patient prognosis and relapse-free survival.

Main outcome of the study. In the course of the analysis of triple-negative breast cancer, a statistically significant negative correlation was revealed between the level of proliferative activity of tumor cells and patient age. The Kendall-tau coefficient was −0.449 ($p < 0.05$), which corresponds to a weak-to-moderate negative association.

CONCLUSION

In patients with triple-negative breast cancer, a weak-to-moderate negative correlation was identified between the proliferative activity index, assessed by the percentage of Ki-67-positive tumor cells, and the age at onset. A high mitotic potential was observed in younger women, which suggests that age may serve as an independent prognostic factor. The phenomenon is most likely associated with a higher frequency of *TP53* mutations, as well as age-related and physiological features of the tumor microenvironment. However, this hypothesis requires further confirmation through large-scale prospective studies employing molecular biological and molecular genetic methods.

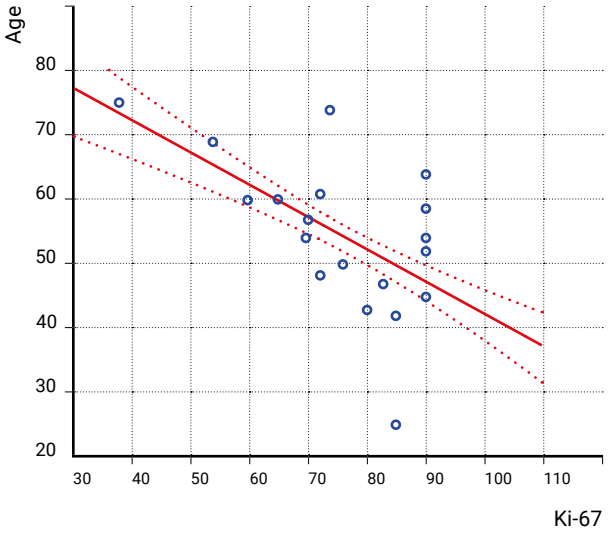

Fig. 5. Scatter plot of Ki-67 expression by age in patients with triple-negative breast cancer

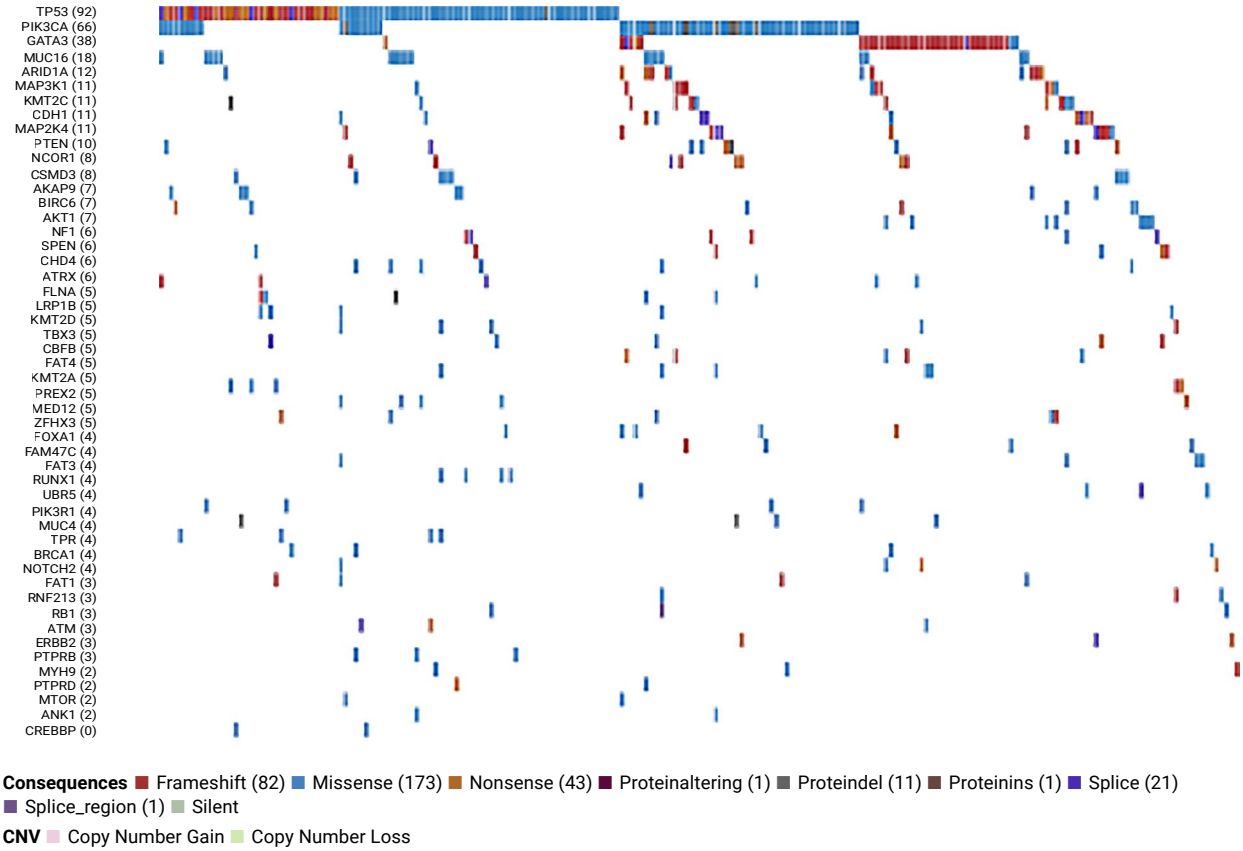

Fig. 6. Mutational profile of breast cancer patients. Age < 45 years

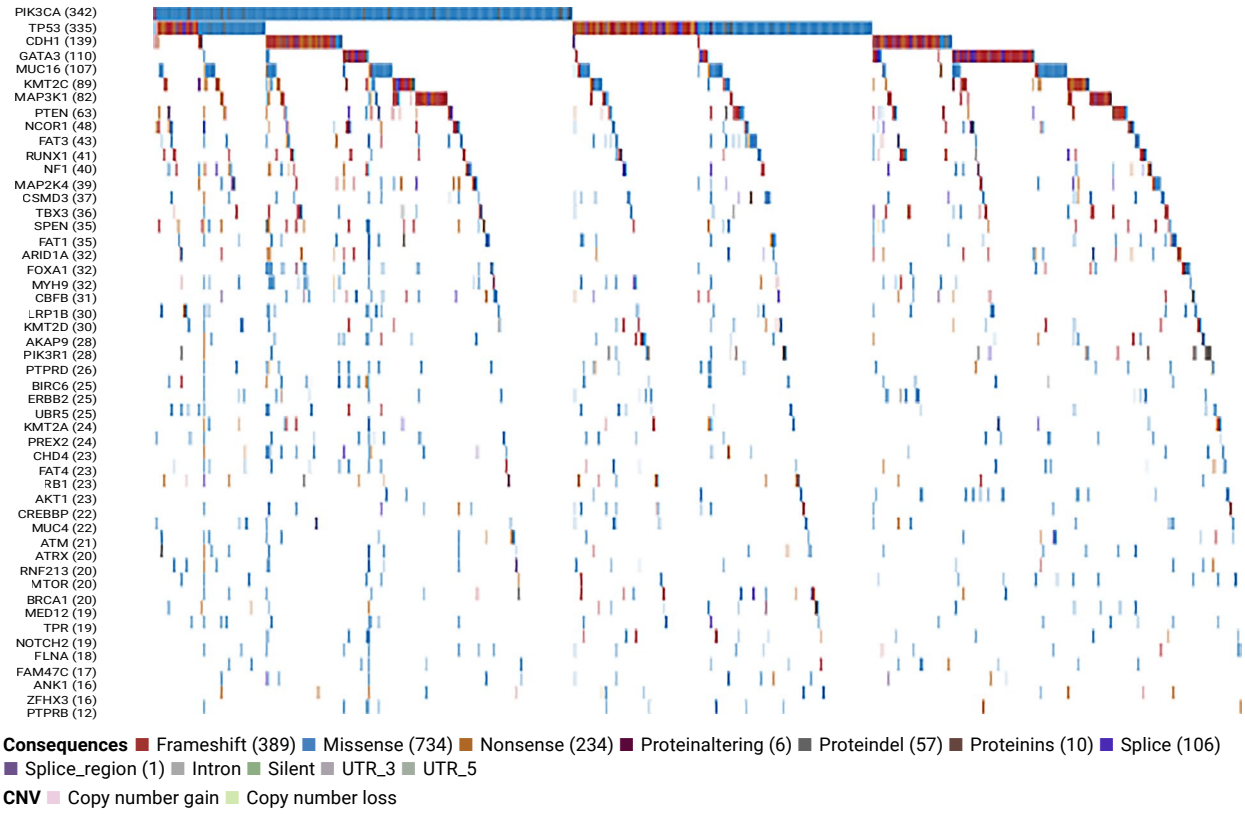

Fig. 7. Mutational profile of breast cancer patients. Age ≥ 45 years

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