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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

**EPIDEMIOLOGY OF TRIPLE NEGATIVE BREAST
CANCER IN AZERBAIJAN**

Specialty: 3224.01 - “Oncology”

Field of science: Medicine

Applicant: **Aliyeva Shovkat Rustam-zal**

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The dissertation was performed at the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan.

Scientific supervisor: doctor of medical sciences, professor,
honored scientist, full member of ANAS
Aliyev Jamil Aziz

Official opponents: doctor of medical sciences
Tasdieq edir: **Soltanov Abulfaz Agasoltan**

Azərbaycan Respublikası Səhiyyə Nazarı
Milli Onkologiya Mərkəzi
ELM KATIBİ
Təbii elmlər üzrə doktoru dosent
Rufa Abdullayeva Hüseynova

doctor of medical sciences, professor
Karimov Muhammad Mammadali

doctor of medical sciences
Abbasov Firuz Arif

Dissertation Council FD 1.02 of the Higher Attestation Commission under the President of the Republic of Azerbaijan, operating on the basis of the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan.

Chairman of the dissertation council:

Doctor of medical sciences, professor,
Honored Scientist, Full member of ANAS
Aliyev Jamil Aziz

Academic Secretary of the Dissertation Council:

PhD in Medicine
Zeynalov Rashad Saleh

Chairman of the scientific seminar:

doctor of medical sciences, professor
Mardanli Fuad Aliovsat

THE RELEVANCE OF THE TOPIC

Breast cancer (BC) is the most common form of cancer among women. About 500000 women die from this disease every year, and the total number of new cases in the world every day is 1.67 million. In other words, every 20 seconds in the world a woman is diagnosed with BC, and every 5 minutes more than 3 women die from this pathology. The most cases are in the USA, Canada, France, Israel, Switzerland, the Baltic countries and the least in Japan. Occurs in the countries of Central Asia and Africa.^{1,2,3}

In 2015 in the Republic of Azerbaijan, 1751 new cases of BC were identified. The number of registered patients amounted to more than 10,000.^{4,5}

The study of immunohistochemical and molecular biological aspects has created fundamental changes in the assessment of treatment protocols and prognosis of BC.

In clinical practice and in numerous studies, “equivalents” of the genetic classification assigned by immunohistochemical (IHC) analyze are used to distinguish the types of breast cancer. Triple negative phenotype breast cancer (TN BC) is characterized by the absence or low expression of estrogen receptors (ER), progesterone (PR) in the tumor, as well as the absence of hyperexpression of HER2. Gene expression analysis shows that the molecular pattern of triple negative phenotype is similar to basal-like cancer (concordance rate - 70-90%). In addition,

¹ Горбачева, О. Ранний рак молочной железы: значение биологического подтипа опухоли для выбора хирургической тактики лечения (Обзор литературы) / О.Горбачева, В.Ивашков, В.Соболевский [и др.] // Вопросы онкологии, - 2018, т. 64, № 6, - с. 716-721.

² Давыдов, М.И. Онкология. Учебник. / М.И.Давыдов, Ш.Х.Ганцев, - Москва: ГЭОТАР-Медиа, - 2013. – 920 с.

³ Hyuna Sung, Philip S. Rosenberg, Wan-Qing Chen, и др. Female Breast Cancer Incidence among Asian and Western Populations: More Similar Than Expected. Journal of the National Cancer Institute. 2015. v. 7,- p.107.

⁴ Əliyev, C.Ə. III C mərhələli süd vəzi xərçəngində I xətt gəmsitabin+sisplatin və Antrasiklin±taksan tərkibli neoadyuvant polikimyaterapiyanın yaxın və uzaq nəticələri süd vəzi xərçənginin proqnostik və prediktiv təsnifatı, fərdiləşmiş müalicə / C.Ə.Əliyev, S.E.Rəhimzadə, L.A.Məlikova [və b.] Azərbaycan Onkologiya Jurnalı, - 2019. №1, - s. 22-31.

⁵ Vətənxə S.S. Azərbaycan Respublikasında süd vəzinin bədxassəli yenitörəmələrinin diaqnostik və kliniki-epidemioloji aspektləri: / tibb üzrə fəlsəfə doktoru dissertasiyası / - Bakı, - 2018. – 289 s.

as a basal-like "genetic" variant, TN BC is often associated with mutations in the BRCA genes: the frequency of these mutations in TN BC ranges from 16% to 42%.^{6,7,8}

The term "triple negative breast cancer phenotype" is used to describe a group of tumors with low or absence of estrogen, progesterone, and HER2 expression. TN BC is 10-17% of BC detected worldwide, about 200000 cases per year.^{9,10}

Unlike other subtypes of BC, patients with TN BC have a more aggressive course, characterized by early progression, high incidence of visceral metastases and metastases to the brain after treatment of the localized disease.^{11,12}

According to the systematized data, "triple"-negative cancer occurs in 15.0-30.0% of patients, at a relatively early age; characterized by high rates of BRCA1 gene mutations, an aggressive clinical course and a negative prognosis, and it ranks second in the frequency of relapses after organ-preserving operations on the breast (6.1%). Based on literature data, these tumors are larger in size, have a high metasta-

⁶ Əliyev, C.Ə. Hormon reseptor müsbət, HER2 mənfı metastatik süd vəzi xərcəngində hormonoterapiyanın metronom kimyaterapiya ilə birgə təyini və effektivliyi / C.Ə.Əliyev, S.E.Rəhimzadə, L.Ə.Məlikova [və b.] // Azərbaycan Onkologiya Jurnalı, - 2019. № 2, - s. 52-55.

⁷ Garrido-Castro, A.C. Insights into molecular classifications of triple-negative breast cancer: improving patient selection for treatment / A.C.Garrido-Castro, N.U.Lin, K.Polyak // Cancer Discov., 2019. № 9, - p. 176-198.

⁸ Lee, E. Progesterone levels, progesterone receptor gene polymorphisms, and mammographic density changes: results from the Postmenopausal Estrogen/Progestin Interventions Mammographic Density Study / E.Lee, S.A.Ingles, D.Van Den Berg [et al.] // J. für Menopause, - 2012, v. 19, № 3, - p. 302-310.

⁹ Lehmann, B.D. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies / B.D.Lehmann, J.A.Bauer, X.Chen [et al.] // J. Clin. Invest., - 2011, v. 121, - p. 2750-2767.

¹⁰ Пятницкий, И. Скрининг рака молочной железы: текущие достижения, перспективы и новые технологии / И.Пятницкий, О.Пучкова, В.Гомболевский [и др.] // Вопросы онкологии, - 2019, т. 65, № 5, - с. 664-671.

¹¹ El Sayed, R. Endocrine and Targeted Therapy for Hormone-Receptor-Positive, HER2-Negative Advanced Breast Cancer: Insights to Sequencing Treatment and Overcoming Resistance Based on Clinical Trials / R.El Sayed, L.El Jamal, S.El Iskandarani [et al.] // Frontiers in oncology, - 2019, v. 9, - 510 p.

¹² De Laurentis. Treatment of triple negative breast cancer (TNBC): current options and future perspectives / De Laurentis, D.Cianniello, R.Caputo [et al.] // Cancer Treat Rev., - 2010, v. 3, - p. 80-86.

sis potential, are more or less sensitive to chemotherapy protocols containing anthracyclines and taxanes; the survival rates of patients are relatively low. Due to the absence of a Target object, the only generally accepted method of systemic treatment is chemotherapy.^{13,14}

The parameters of the problem of “triple” - negative breast cancer in the Republic of Azerbaijan, the frequency of occurrence by regions have been studied very superficially or have not been studied at all. All listed confirm the relevance of the current study.

Research objects: The basis of the research was the data of 769 patients with a histologically verified TN BC diagnosis who underwent inpatient examination and treatment at the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan during 2015-2019, as well as the data obtained at the Department of Informatics and Statistics of the Ministry of Health of the Republic of Azerbaijan. For the study BRCA1, BRCA2 mutation, the genetic materials of 245 BC patients aged 21 to 87 who applied to National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan during 2015-2019 were analyzed.

The purpose of the research is to study the characteristics of the incidence of breast cancer in the administrative-territorial regions of the Republic of Azerbaijan, to determine the risk factors for the occurrence of the disease.

Research objectives:

1. Study of epidemiological features of TN BC in the population of breast cancer patients in the Republic of Azerbaijan
2. Study of morbidity indicators of “triple” -negative BC in different regions of the Republic;
3. Determination of mortality rates of patients with TN BC by regions;
4. Definition of important factors in the risk of developing TN BC.

¹³ Chavez, K.J. Triple negative breast cancer cell lines: one tool in search for better treatment of triple negative breast cancer / K.J.Chavez, S.V.Garimella, S.Lipkowitz // Breast Dis., - 2010, v. 32, № 1-2, - p. 35-48.

¹⁴ Liu, Y. Impact of polysomy 17 on HER2 testing of invasive breast cancer patients / Y.Liu, L.Ma, D.Liu [et al.] // Int J. Clin Exp Pathol., - 2013, v. 15, № 7, - p. 163-173.

Research methods

In the study, morbidity and mortality indicators of TN BC were analyzed in different administrative-territorial regions of Azerbaijan during 2015-2019. When analyzing the quantitative indicators of morbidity with TN BC, extensiveness, intensity, age-standardized, as well as attack rate, aggressiveness and 5-year survival rate were studied. Important factors in the risk of occurrence of TN BC have been identified.

Main provisions of the dissertation

1. The main epidemiological characteristics of triple negative breast cancer in different administrative regions of the Republic should be studied.

2. It is necessary to take into account the important risk factors of the occurrence of TN BC in regions with a high level of morbidity with this pathology.

3. Special oncological care for persons over 50 years of age is required by their doctors in the organization of preventive measures for TN BC.

Scientific novelty of the study

The results of the study determined the level of morbidity and mortality of TN BC in different administrative-territorial regions, and identified important risk factors for TN BC in the Republic of Azerbaijan. In addition, the economic regions with high and low TN BC morbidity and mortality rates were determined.

Practical significance of the study

The research findings will be the basis for developing the necessary measures for the initial diagnosis and prevention of this pathology in regions with a high incidence rate of TN BC. The results are also important in post-treatment prediction and selection of surveillance strategy.

Approbation of the dissertation:

The materials of the dissertation were presented at the scientific-practical conference of young scientists and specialists of the National Center of Oncology dedicated to the National Revival Day (Baku, 2017), at the 1st International Symposium on "Innovations in Surgery" (Baku, December 1, 2018), Materials of the scientific prac-

tical conference dedicated to the birthday of national leader H.A.Aliyev (Baku, 2018 and 2019), Scientific conference on Modern approach to diagnosis and treatment of malignant tumors" (Baku, May 3-5, 2019), International scientific - practical conference on Innovations in surgery (Minsk, November 1, 2019), XI congress of oncologists and radiologists of the CIS countries (Kazan, 2020), VI All-Russian conference on molecular oncology (Moscow, December 21-23, 2021), II International Karabakh-Applied Sciences Congress (Baku, November 8-10, 2021), at the XII congress of oncologists and radiologists of Eurasian and CIS countries (Nursultan, 2022).

The results of the dissertation were reported and discussed at the interdepartmental meeting of National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan (7 July, 2023 protocol No1), at the scientific seminar of the FD 1.02 Dissertation Council operating under NCO of the Ministry of Health of the Republic of Azerbaijan (3 November, 2023 protocol No2).

The main theoretical and practical provisions of the dissertation are reflected in 15 published scientific works. Scientific works on the topic of the study were published both in Azerbaijan (5 articles, 3 theses), and in foreign journals (3 article, 4 theses).

Application of the study

The results of the research are used in the lectures and practical work at the Oncology Department of Azerbaijan State Advanced Training Institute for Doctors named after A.Aliyev. Practical recommendations are used in the experimental work of the Department of General Oncology of the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan.

The organization in which the dissertation is carried out

The dissertation work was carried out at National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan.

The volume and structure of the dissertation

The dissertation is presented on 151 pages of typewritten text (206835 characters) consisting of an introduction (7976 characters), literature review (61957 characters), chapters of material and methods (26871 characters), 3 chapters of personal research (71224 characters), results (34631 characters), conclusions and practical recom-

mendations (4176 characters) and references (34400 characters). The list of references includes 166 sources. The dissertation contains 18 tables and 11 figures.

MATERIALS AND METHODS

Epidemiological analyses of "triple-negative" breast cancer among the female population of the Republic of Azerbaijan were based on patients aged 21 to 87 years with a histologically verified diagnosis of TN BC underwent inpatient examination and treatment at the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan during 2015-2019, as well as data obtained at the Informatics and Statistics Department of the Ministry of Health of the Republic of Azerbaijan.

The following indicators were mainly evaluated in the study:

- intensity indicator (per 100,000 population);
- extensiveness coefficient (%);
- standardized indicator (per 100,000 population);
- total mortality rate (per 1000 population);
- case fatality rate (in %);
- attack rate (per 100,000 population);
- aggressiveness rate;
- 5-year survival (%).

The above indicators are calculated according to the methodology proposed by the World Health Organization.

The standardized indicator of TN BC incidence was determined by the direct standardization method and consisted of three stages:

1. Calculation of the intensity indicator per 100,000 population
2. Calculation of average standards
3. Calculation of standardized indicators.

In order to achieve the goal, the Republic territory is divided into 11 economic-territorial regions, based on the recommendations of the National Academy of Sciences and the State Statistics Committee. Information about the number of population in the Republic was taken from the Informatics and Statistics Department of the Ministry of Health of the Republic of Azerbaijan.

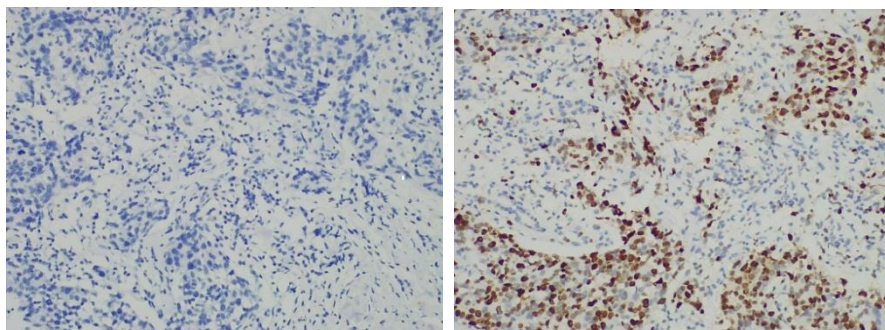


Figure 1. Histopathological images of "triple negative" breast cancer.

At the next stage of our research work, the BRCA1, BRCA2 mutation was studied in BC patients. In this regard, during 2015-2019, genetic materials of 245 patients with BC aged 21 to 87 years were analyzed. The isolation of genetic material from peripheral blood was carried out by the colony method.

In the research work, the factors that may lead to the development of TN BC were analyzed. In this regard, a special questionnaire was developed based on the medical histories and anamnesis of 136 patients with TN BC who were treated in National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan.

The questionnaire recorded the age of the patients, the age at the beginning of the menstrual cycle, the number of pregnancies and abortions in the anamnesis, the age of the first pregnancy, the duration of breastfeeding and the use of contraceptives.

Correlation analysis of the indicators of the health status of TN BC patients was performed using the EXCEL for Windows *xp* application program on a personal computer.

Research Results and Discussion

Morbidity and mortality rates of "triple-negative" breast cancer in the Republic of Azerbaijan

Breast cancer occupies the first place for the incidence of malignant tumors among female population of the Republic of Azerbaijan, and the extensiveness rate of "triple-negative" breast cancer in the Republic is 9.4%.

The analysis of statistical indicators of the incidence of "triple negative" breast cancer in the Republic was carried out. The extensiveness indicator in Baku is the highest among the regions, it amounted to 7.4%, which is 1.3 times less than the Republican indicator. The level of extensiveness of triple negative breast cancer was very low in the Guba-Khachmaz, Mountainous-Shirvan, Absheron economic regions and amounted to 1.3%, 1.7% and 2.2%, respectively. These indicators were 7.2, 5.5 and 4.2 times lower than the republican indicator, respectively. This figure was 2.5% in Nakhchivan, 2.9% in Sheki-Zagatala, 3.3% in Ganja-Gazakh, 4.5% in Lankaran and 6.4% in Aran. It should be noted that the extensiveness of "triple negative" BC for the country was 9.4% (Fig. 2).

The analysis of the extensiveness indicators showed that the highest extensiveness indicator in the Ganja-Gazakh economic region was recorded in the city of Naftalan (4.4%), and the lowest in the Goygol district (1.6%). This figure was 3.7% in Dashkasan, 3.4% in Gadabey, 3.3% in Samukh, 3.2% in Tovuz, 2.7% in Goranboy, and 2.7% in Shamkir district. In Agstafa, Gazakh regions and Ganja city, the extensiveness indicator was 3.0% and was equal to the overall regional indicator.

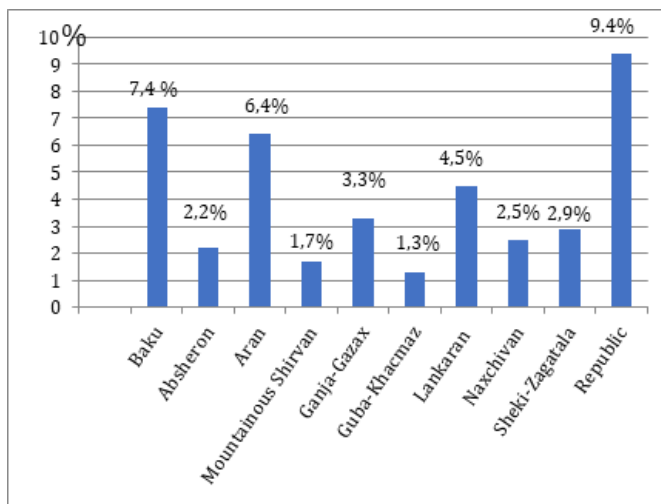


Figure 2. Extensiveness of "Triple negative" breast cancer in economic regions of the Republic of Azerbaijan (%)

In the Guba-Khachmaz economic region, high levels of the extensiveness of "triple negative" breast cancer were recorded in Khachmaz, Siyazan and Shabran regions, and the extensiveness indicator in these regions was 6.1%, 6.0% and 3.8%, respectively.

In the Lankaran economic region, the highest level of the extensiveness indicator of TN BC was recorded in Lerik district (6.3%), and the lowest level was recorded in Yardimli district (2.3%). In Lankaran region, this indicator was higher than the general regional indicator, it was 4.9%. In Jalilabad, Masalli and Astara regions, it was lower than the general regional indicator and was 4.0%, 3.2% and 3.0%, respectively.

In the study of the intensity indicator, the highest intensity indicator of "triple-negative" BC was recorded in Baku, and this figure was 11.7 ⁰/₀₀₀₀, which is 3.1 times higher than the general republican indicator.

The intensity index in Aran, Sheki-Zagatala, Lankaran and Ganja-Kazakh economic regions was higher than the republic index and was 6.7 ⁰/₀₀₀₀, 4.5⁰/₀₀₀₀, 4.1⁰/₀₀₀₀ and 4.0 ⁰/₀₀₀₀, respectively. In the Absheron, Nakhchivan, Guba-Khachmaz and Mountainous-Shirvan economic regions, the intensity indicator was lower than the republican indicator and was recorded as 3.4⁰/₀₀₀₀, 2.6⁰/₀₀₀₀, 2.2⁰/₀₀₀₀ and 1.9⁰/₀₀₀₀, respectively. The intensity index of "triple-negative" BC was 3.7 ⁰/₀₀₀₀ (Fig. 3).

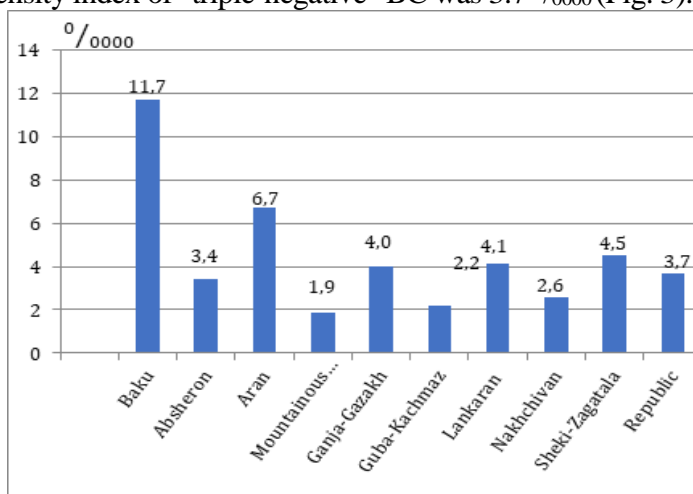


Figure 3. Intensity indicator of "Triple negative" breast cancer in economic regions of the Republic of Azerbaijan (⁰/₀₀₀₀)

As shown in the Figures 1 and 2, the highest extensiveness and intensity indicators among the regions of the republic were observed in Baku, and these indicators were 7.4% and 11.7⁰/₀₀₀₀, respectively.

The highest intensity indicator in the Guba-Khachmaz economic region was recorded in the Siyazan, and this figure was 3.2 times higher than the regional indicator (2.2⁰/₀₀₀₀), amounted to 7.2⁰/₀₀₀₀. In Shabran, this indicator is higher than the regional indicator, equal to 4.9⁰/₀₀₀₀. In Gusar and Khachmaz regions, the intensity index was low and was 1.5⁰/₀₀₀₀ and 0.7⁰/₀₀₀₀, respectively. The intensity index for the entire region was 2.2⁰/₀₀₀₀.

The statistical analysis showed that the attack rate is different in separate regions of the Republic. Thus, the highest attack rate was recorded in Baku and was 92.8⁰/₀₀₀₀, while the lowest attack rate was 4.1⁰/₀₀₀₀ and was recorded in Lankaran economic region. In the Aran, Ganja-Gazakh, Sheki-Zagatala and Absheron economic regions, the attack rates of "triple negative" BC were higher than the republican indicator (22.3⁰/₀₀₀₀), It was 49.8⁰/₀₀₀₀, 43.1⁰/₀₀₀₀, 42.4⁰/₀₀₀₀ and 28.8⁰/₀₀₀₀ respectively. This indicator was 15.0⁰/₀₀₀₀ in Guba-Khachmaz, 7.6⁰/₀₀₀₀ in Mountainous Shirvan, 6.6⁰/₀₀₀₀ in Nakhchivan and was lower than the republican indicator (Fig. 4).

It should be noted that the attack rate of triple-negative BC for the country was 22.3⁰/₀₀₀₀.

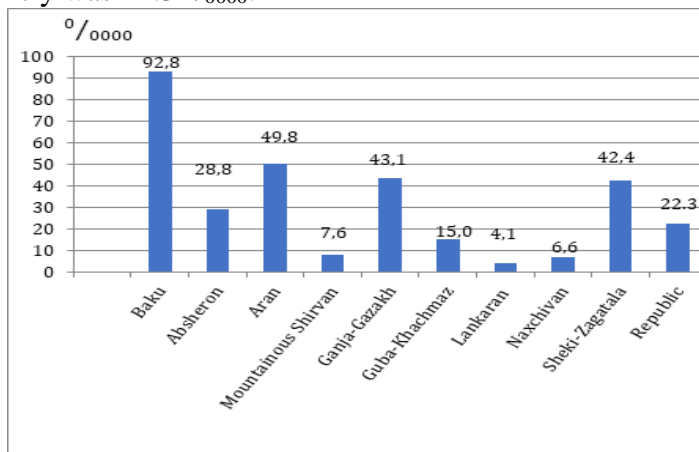


Figure 4. Attack rate of "triple-negative" breast cancer in economic regions of the Republic of Azerbaijan (per 10,000).

It is known that some errors are encountered in the analysis of mortality rates of malignant tumors. However, from an epidemiological point of view, the mortality rate is considered a valuable source of information about trends in the health status of the population. The case fatality rate is a measure of the severity of the disease.

Mortality indicators of "triple negative" BC were also calculated for separate economic regions of our republic. The mortality rate with this pathology was high mainly in Baku, Sheki-Zagatala and Aran economic regions and was $4.5^{0/0000}$, $3.8^{0/0000}$ and $3.3^{0/0000}$, respectively. The lowest mortality rate was in Guba-Khachmaz economic region, it was $1.1^{0/0000}$. In other regions, this indicator was Mountainous-Shirvan- $2.8^{0/0000}$, Ganja-Gazakh- $2.2^{0/0000}$, Lankaran $2.1^{0/0000}$, Nakhchivan- $2.0^{0/0000}$, Absheron- $1.7^{0/0000}$. For the country, the mortality rate from "triple-negative" BC was $1.5^{0/0000}$ (Fig. 5).

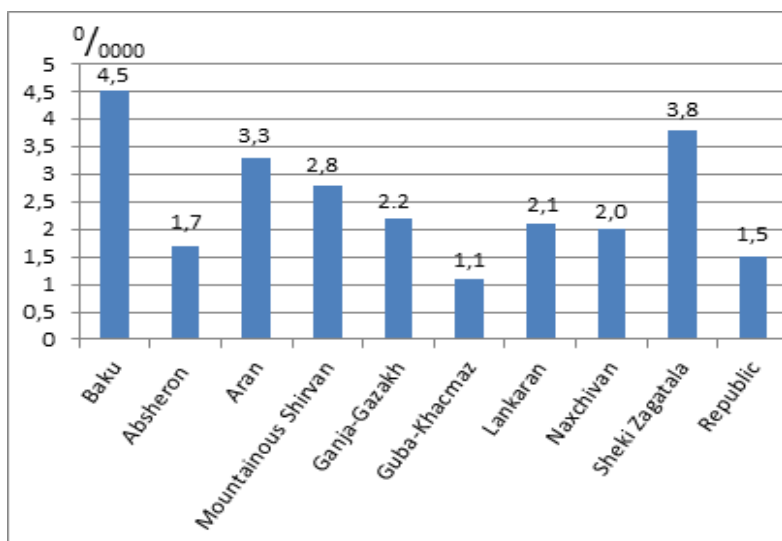


Figure 5. Mortality rate of "triple-negative" breast cancer patients in different regions of the Republic of Azerbaijan (0/0000).

The study showed that the mortality rate of TN breast cancer in many economic regions of the republic is relatively higher than the republican rate. The highest level of the case fatality rate was observed

in Sheki-Zagatala and Mountainous-Shirvan economic regions, and this figure was 35.7% and 33.3%, respectively, and was 2.9 and 2.7 times higher than the republican indicator, respectively. Also, this indicator was higher in the economic regions of Lankaran (22.1%), Nakhchivan (21.5%). It was 16.6% in Guba-Khachmaz, 15.4% in Ganja-Gazakh, and 14.2% in Baku. In the Aran and Absheron economic regions, this indicator was lower than the republican index (12.0%), and was 10.3% and 10.0%, respectively. The total case fatality rate of TN BC for the Republic is 12% (Fig. 6).

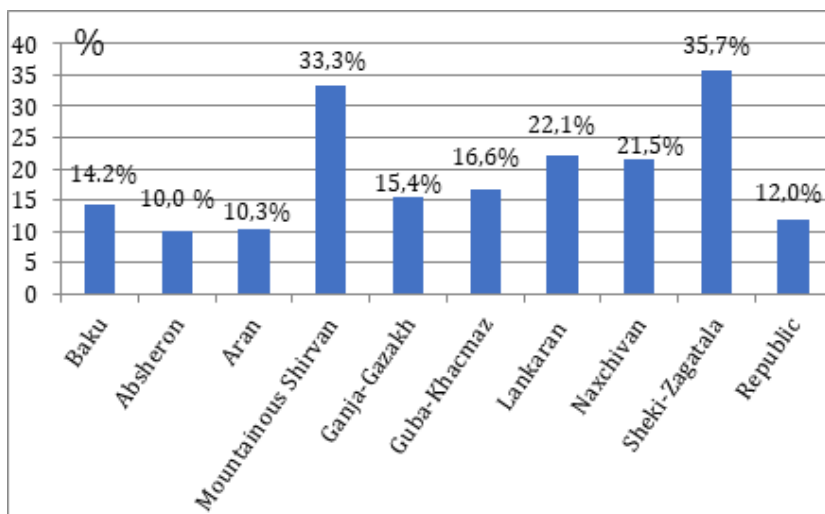


Figure 6. Case fatality rate of patients with "triple-negative" breast cancer in different regions of the Republic of Azerbaijan (in %).

One of the important factors determining the level and diversity of morbidity indicators is the availability of specialized care and the integrity of registration that is a disease aggressiveness index. Statistical analysis showed that the indicator of aggressiveness in Mountainous Shirvan economic region is quite high. Thus, the aggressiveness index in this region was 1.5 that is 3.8 times higher than the republican indicator. The total indicator for the country was 0.4. In other economic regions, aggressiveness index of TN BC is shown in the table below (Table 1).

Table 1

**Disease aggressiveness index of "triple-negative" breast cancer
in different regions of the Republic of Azerbaijan**

Regions	Disease aggressiveness index
Absheron	0,5
Baku	0,4
Lankaran	0,5
Mountainous Shirvan	1,5
Aran	0,5
Ganja-Gazakh	0,5
Shaki-Zaqatala	0,8
Guba-Khachmaz	0,5
Nakhchivan	0,8
Republic	0,4

Age standardization is an important statistical method to compare disease rates, or other health indicators, between populations. This method eliminates the effect of age structure on the comparable indicators of the disease. Standardization is necessary to compare two or more populations that differ in several key parameters such as age, race and socioeconomic status that independently affect mortality risk. In study, age standardized incidence rate of "triple negative" breast cancer were calculated. As shown in the table, this nosological form was not found in women aged 0-17 years. The highest rate was recorded in the 50-59 age group. After the age group of 50-59, a decrease in indicators was recorded. The age-standardized incidence rate of "triple negative" BC was 3.7 ‰.

It is important to note that "triple negative" BC was not recorded in women under the age of 18 during the study.

The increase in the incidence of "triple negative" BC mainly begins in the 30-39 age group. In most economic regions of the republic, the peak of the disease occurred in the 40-49 and 50-59 age groups. Only in Guba-Khachmaz and Nakhchivan economic regions, this indicator was recorded in the 60-69 age group. In the age group

of 70 and older, the age-standardized incidence rate for this nosological form was relatively low.

Table 2

Age-Standardized incidence rate of "triple negative" breast cancer in the Republic of Azerbaijan

Age	Intensity (⁰ /0000)	Average standard	Standardized rate (⁰ /0000)
0-17	-	24225,1	-
18-29	0,3	19668,0	0,06
30-39	2,2	15478,5	0,3
40-49	7,3	12769,1	0,9
50-59	8,7	14889,6	1,3
60-69	11,7	8441,4	1,0
70 <	3,4	4528,3	0,1
Σ	3,7	100000	3,7

Among the regions, the highest age-standardized incidence rate was recorded in Baku city, Sheki-Zagatala and Aran economic region, and these indicators were 6.1⁰/0000, 4.4⁰/0000 and 4.1⁰/0000, respectively.

In Baku this pathology are not found in women under 30 years of age. Age standardized incidence rate increases from the age of 30. The "peak" incidenc of the disease was recorded in the 50-59 age group, that the age standardized incidence rate was 2.4⁰/0000. Regardless of age, the age standardized incidence rate for the city was 6.1⁰/0000.

In the Sheki-Zagatala economic region, the incidence of this pathology was recorded from the 40-49 age group. The highest rate was observed in the 40-49 and 50-59 age groups, and the age-standardized rate for both age groups was 1.9⁰/0000. Starting from the 60-69 age group, a decrease in morbidity was observed, and its standardized indicator was 0.6⁰/0000. The age standardized incidence rate of "triple-negative" BC for the general region was 4.4⁰/0000.

In the Aran economic region, the highest incidence was recorded in the 50-59 age group (1.8⁰/0000). The age-standardized incidence rate of "triple negative" BC for the general region was 4.1⁰/0000, regardless of age.

Thus, epidemiological analysis of the incidence of TN BC in the Republic of Azerbaijan showed that the extensiveness indicator for the republic was 9.4%. The level of morbidity indicators of TN BC across the Republic is relatively high, the intensity indicator is 3.7⁰/0000, and the attack rate is 22.3⁰/0000. The "peak" incidence rate of TN BC occurs in the 50-59 age group, so the age-standardized incidence rate for the whole republic is 3.7⁰/0000. In many regions of the republic, the mortality and case fatality rate of TN BC were relatively higher than the republic indicator.

Detection of activating point mutations of BRCA 1/2 genes in breast cancer patients.

Breast cancer is a multi- factorial disease and its progression is closely related to both the influence of environmental factors and the individual characteristics of the genome. Heredity is a risk factor capable of causing the development of breast cancer. The share of breast cancer based on inherited mutations is between 5% and 10% of the total number of patients. Mutations in the BRCA1/2 genes account for 30% of all hereditary cases. According to modern understanding, BRCA1 and BRCA2 genes act as classic tumor suppressors. An international database consists of different mutational variants of BRCA1/2 genes with clinical significance from different regions and populations.

Currently, it is known that a number of activating mutations of the BRCA1/2 genes are found in all countries of Eastern Europe and Asia with different frequency of occurrence. The detection of mutations of these genes allows the implementation of targeted treatment and prevention options of BC depending on the individual genotype.^{15,16}

In the next stage of our study, the mutation of BRCA1 and

¹⁵ Dvorah A., Luna K., Israela L. et al. The Founder Mutations 185delAG and 5382insC in BRCA1 and 61 74delT in BRCA2 Appear in 60% of Ovarian Cancer and 30% of Early-Onset Breast Cancer Patients among Ashkenazi. American Journal of Human Genetics. 1997. v.60, -p.-505-514

¹⁶ Brenda B.J. Hermsen, Paul J. van Diest, Johannes B., et al. Low prevalence of (pre) malignant lesions in the breast and high prevalence in the ovary and Fallopian tube in women at hereditary high risk of breast and ovarian cancer. International Journal of Cancer. 2006, v.119, -p.1412-1418

BRCA2 genes was investigated among breast cancer patients. Detection of activating point mutations of BRCA 1/2 genes was performed in 245 patients diagnosed with breast cancer. In all cases, the diagnosis was confirmed morphologically. Patients were divided into 4 subgroups according to the criteria given in Table 3.

Table 3
Number of mutations detected in BRCA 1/2 genes in BC patients

№	The name of the subgroup	Number of patients	Mutation frequency	Age groups
1.	Family History: Breast cancer in 1st and 2nd degree blood relatives	132 (50,1%)	11/132 (10,6%)	35-87
2.	Age group: Patients under 35 years of age with and without a family history of breast cancer diagnosis	50 (19%)	5/50 (10%)	21-35
3.	Bilateral breast cancer	28 (10,6%)	3/28 (10,7%)	45-65
4.	Hormonal status: triple negative breast cancer	35 (13,3%)	4/35 (11,4%)	49-69
Total number of patients		245	23/245 (9,8%)	21-87

Taking into account the world literature and our personal experience, the selection of patients for the study was based on the following criteria: family history of oncology, age of the patient at the time of diagnosis, bilateral (synchronous, metachronous) BC.

The study was approved by the ethical committee of National Center of Oncology. The voluntary consent of all patients to be informed about these procedures was the absolute condition for inclusion in the examination.

Table 3 presents the subgroups, the number of patients in each group, the number of detected mutations, and the age groups of patients in each subgroup.

The most patients were observed in the subgroup with family

history. The age of all examined patients was 21-87 years old. The patients were tested for BRCA1/2 gene mutations. Testing was performed by genetic specialists as part of medical genetic counseling.

Activating point mutations were analyzed in each group of patients. The largest number of patients and women carrying BRCA1/2-mutations were in the family history group. Of 132 patients with BC, 11 were carriers of hereditary mutations: BRCA1 gene mutations were found in 10 women and BRCA2 gene mutation in one woman. The age of the patients was between 35 and 87 years.

As can be seen from the table 3, there were 50 patients (19%) in the group of women under 35 years of age, and BRCA1/2 mutations were detected in 5 of them (10%).

35 of the 245 patients in study were included in the TN BC subgroup. In 4 of them (11.4%), BRCA-1 and BRCA-2 gene mutations were detected.

Risk factors for Triple Negative Breast Cancer

Aggressive TN BC is one of the less common forms among breast cancer subtypes, accounting for approximately 10-20% of all BC. The main risk factors of TN BC include genetic predisposition, age, estrogen levels. Women with a family history of a first-degree relative (mother, daughter, sister) who underwent BC at a young age have a higher risk of TN BC. Disorders in the reproductive system in women, lack of births or births at a late age, endocrine-metabolic factors, genetic factors, BC in blood relatives (hereditary and familial BC), the presence of breast-ovarian cancer are considered risk factors of TN BC.

In the next stage of our research, factors that may lead to triple negative breast cancer progression have been analyzed. For this purpose, a special questionnaire was prepared based on the medical histories and anamnesis of 136 patients treated with the diagnosis of TN BC at National Center of Oncology of The Ministry of Health of The Republic of Azerbaijan. The questionnaire asked about the age of the patients, the age at the beginning of the menstrual cycle, the number of pregnancies and abortions in the anamnesis, the age of the first pregnancy, the duration of breastfeeding and the use of contraceptives.

The highest triple negative breast cancer incidence was record-

ed in the 50-59 and 60-69 age groups. The lowest incidence rate was recorded in the 17-29 and 30-39 age groups, which were 1.6% and 5.5%, respectively.

Table 4

Patient characteristics

Age of onset of menstrual cycle		
≤ 12	207 patients	27,2%
12-13	408 patients	53,7%
≥ 14	145 patients	19,1%
Number of pregnancies in the history:		
Not having any pregnancy:	61patients	8,1%
Abortion and miscarriage	543patients	71,2%
birth:		
1	67patients	8,8%
2	414patients	54,4%
more than 3	218patients	28,7%
First pregnancy age, years		
≤20	212patients	27,9%
21–24	246patients	32,3%
25–29	173patients	22,7%
≥30	123patients	8,8%
Breastfeeding period, months:		
Never:	61	8,1%
< 6	347	45,6%
6–11	212	27,9%
≥ 12	78	10,3%
Body weight		
Normal weight	201	26.5%
I Class obesity	352	46,3%
II Class obesity	140	18.4%
III Class obesity	67	8.8%

According to the gynecological anamnesis data of the studied TN BC patients, the menstrual cycle in women started mainly between the ages of 11 and 13. Thus, the menstrual cycle began in 207 women (27.2%) before the age of 12, in 408 women (53.7%) at the age of 12-13, and in 145 women (19.1%) after the age of 14. 67 patients (8.8%) had 1 birth, 414 patients (54.4%) had 2 births, and 218 patients (28.7%) had more than 3 births.

543 patients (71.2%) had abortions in their anamnesis. Among them, 151 patients (19.8%) had 1-3 abortions, 219 patients (28.7%) had 4-5 abortions, and 173 patients (22.8%) had more than 5 abortions. 61 patients (8.1%) had no history of pregnancy.

Most of the patients had their first pregnancy between the ages of 21-29 (55%). 212 patients (27.9%) had their first pregnancy before the age of 20, and 123 patients (8.8%) after the age of 30.

It is known that breastfeeding reduces the risk of developing breast cancer in women. 8.1% of the patients in the study never had a history of breastfeeding. 347 women (45.6%) had a history of breastfeeding for less than 6 months, 212 women (27.9%) had a history of 6-11 months, and 78 women (10.3%) had a history of breastfeeding for more than 1 year.

Overweight was recorded in 73.5% of the women included in our study. At this time, 46.3% of women had I class degree obesity, 18.4% had II class obesity, and 8.8% had III class obesity.

Thus, according to our results, factors such as early menarche, history of abortion and miscarriage, breastfeeding for less than 6 months, and overweight were more common in TN BC patients.

CONCLUSIONS

1. In the Republic of Azerbaijan, extensiveness indicator of TN BC is 9.4%. Among the regions of the republic, the highest extensiveness rate is recorded in Baku, and the lowest level is recorded in the Guba-Khachmaz economic region, and these figures were 7.4% and 1.3%, respectively. [4, 11]
2. The incidence indicators of TN BC in the Republic is relatively high, the intensity indicator is $3.7^0/0000$, and the attack rate is $22.3^0/0000$.

Among the regions, the highest intensity indicator was recorded in Baku - $11.7^{0}/_{0000}$, and the lowest in the Mountainous Shirvan economic region - $1.9^{0}/_{0000}$. The highest attack rate was recorded in Baku - $92.8^{0}/_{0000}$, and the lowest in Lankaran economic region - $4.1^{0}/_{0000}$. [8, 12]

3. The mortality and case fatality rate of TN BC in many regions of the republic were relatively higher than the republican indicator, and these indicators for the republic were $1.5^{0}/_{0000}$ and $12.0^{0}/_{0000}$, respectively. Among the regions, the highest mortality rate was in Baku - $4.5^{0}/_{0000}$, and the lowest was $1.1^{0}/_{0000}$ in Guba-Khachmaz economic region. The highest case fatality rate was recorded in Sheki-Zagatala - 35.7%, and the lowest in Absheron economic region - 10.0%. [2,15]
4. The peak incidence rate of TN BC in the republic occurs in the 50-59 age group, so the age standardized incidence rate for the whole republic is $3.7^{0}/_{0000}$. [10]
5. The frequency of activating point mutation of BRCA 1/2 genes in patients with breast cancer in Azerbaijan is 11.03%. Of the 245 patients we studied, 35 were diagnosed with TN BC, and BRCA-1 and BRCA-2 gene mutations were detected in 4 of them. [3,9]

PRACTICAL RECOMMENDATIONS

1. In the Republic of Azerbaijan, public health and social events should be held for prevention and early detection of TN BC among the population, and the use of mass media and social networks should be expanded to inform the population.
2. Health care services in economic regions with a high incidence of TN BC should be improved, human resources should be strengthened and the material and technical base should be upgraded to the level of modern standards.
3. Due to the high level of age standardized incidence rate of breast cancer in women over 50 years of age, those belonging to this age group should be given special oncological care by doctors of practical health.
4. In order to improve the quality of life, patients with TN BC are

firstly recommended to regularly engage in sports, aerobic exercises, and healthy nutrition. These factors will help patients to feel better.

5. Stress management is also important in this process. Relaxation techniques such as yoga, meditation or deep breathing techniques can be applied to patients.
6. It is possible to improve the quality of life by being surrounded by friends and family members who can provide social support, as well as by working with specialists in various fields such as psychological support, nutritional counseling, physiotherapy and medical social services to facilitate the treatment process.
7. Life expectancy and course of disease in TN BC vary depending on the stage of the cancer at diagnosis, response to treatment, and other personal factors. Early diagnosis and effective treatment certainly increase survival rates.

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LIST OF ABBREVIATIONS AND TERMS

TN - “Triple” negative

BC - breast cancer

ER - estrogen receptor

PR -progesteron receptor

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