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ANALYSIS OF THE ROLE OF THE BRCA1 AND BRCA 2 GENES AS A PREDICTOR OF OVARIAN CANCER. PREVALENCE OF OVARIAN CANCER IN THE REPUBLIC OF UZBEKISTAN.

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Abstract:
According to the World Health Organization, ovarian cancer accounts for 4-6% of malignant tumors in women and ranks seventh in frequency. According to the International Agency for Research on Cancer, more than 165 thousand new cases of ovarian cancer are registered annually in the world, and more than 100 thousand women die from malignant ovarian tumors. If the proportion (%) of ovarian cancer in the oncological incidence of women in all countries of the world is approximately the same, then the incidence rate per 100 thousand female population (%) is significant.
To date, the contingent of patients with malignant neoplasms in the Republic of Uzbekistan, namely with ovarian cancer, is 4.2%. Despite the improvement of diagnostic methods, the provision of modern medical equipment, the introduction of screening programs, the proportion of actively diagnosed patients, as well as patients with stages 1 and 2 of the tumor process, remains quite low, in particular with visual malignant neoplasms.

Keywords: ovarian cancer, incidence of rural and urban population, Uzbekistan

OBJECTIVE:

To study the features of the distribution of OC on the territory of the Republic, among the urban and rural population.
The study of factors that play a starting role in the occurrence of ovarian cancer.
Study of the prevalence of BRCA1 and BRCA2 genes and their polymorphic variants in patients with ovarian cancer
Measures to prevent the risk of developing ovarian cancer based on the presence of predictor genes.

MATERIALS AND METHODS:

The incidence of OC in the Republic was studied for the period from 2015 to 2019. Information about first-time cases was compiled on the basis of data from the cancer registry of the Republican Cancer Research Center of the Republic of Uzbekistan. On the numerical composition of the population of the republic and regions, data were used from the official website of the State Committee of the Republic of Uzbekistan. The calculation of intensive and standardized indicators was carried out according to the methodological recommendations of the Moscow Research Institute of Oncology. P.A. Herzen.
Based on intensive and standardized indicators, the incidence rates of OC were determined. The latter were calculated on the average number of cases over 4 years (2015-2019). Standardized indicators were calculated in a direct way, while using the world standard for the age distribution of the population, which is recommended by the IARC and used in the monograph Cancer Incidence in Five Continents. Statistical processing of the material was carried out using Excel 2010, Statistica 6.0. The assessment of the significance of differences was carried out according to the Student's criteria based on the t u p indicators. A p value <0.05 was considered statistically significant.

RESULTS:

In the course of our study and calculation of standardized indicators, the prevalence of ovarian cancer in the Republic of Uzbekistan for 2015-2019 per 100,000 population is: 2015-4302, 2016-4018, 2017-3871, 2018-3918, 2019-4213 patients with cancer ovaries. At the same time, the proportion of patients who were registered in the institutions of Uzbekistan for 5 years or more from the moment the diagnosis of OC was established at the end of the reporting year in 2015-2019,% of neoplasms from the number of those registered was: 2015-45.3%, 2016-43%, 2017-42%, 2018-39.1% 2019-40.3%. It should also be noted that the mortality of patients from malignant neoplasms in the Republic for 2015 was 314 patients, 2016 - 412,

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2017 - 416, 2018 - 463, 2019 - 371 patients with OC. Mortality of patients within a year from the moment of diagnosis of a malignant neoplasm (from among patients registered for the first time in the previous year) in Uzbekistan in 2015-0.2; 2016-0.5; 2017-0.5; 2018-0.6; 2019-0.5. Information on the treatment of ovarian cancer first registered in 2019 and subject to treatment included: 1) patients who completed specialized treatment 453, with 53.3% of those newly diagnosed; 2) patients who received radical treatment - 12.8%, palliative - 3.8%, high-tech - 1.8%. 3) patients who received only drug therapy 20.8%, combined 61.0%.

We also studied the factors that play a triggering role in the occurrence of ovarian cancer. These include: early (before 12 years) menarche and / or late (after 55 years) menopause, late (after 30 years) first birth and nulliparous women, age over 50 years, family history (especially in direct relatives in premenopause), BRCA-1 gene mutations; BRCA-2. It is important to note that in addition to trigger factors, there are also modifying factors such as: obesity, abortion, late first pregnancy, oral contraceptive use in patients with BRCA, long-term hormone replacement therapy, physical inactivity, smoking, alcohol abuse, chemical, physical and biological factors (ionizing, radiation, trauma, chemical carcinogens).

We studied the BRCA genes (Breast Cancer gene), which include BRCA1 and BRCA2, the first of which is located in the long arm of chromosome 17 at position 21.31, and the second is located in the long arm of chromosome 13 at position 13.1. More than 2,000 variants of pathogenic mutations in the BRCA1 and BRCA2 genes are currently known. In addition, these genes are quite large - 24 and 27 exons, respectively. Therefore, a complete analysis of the BRCA1 and BRCA2 gene sequences is a laborious, costly, and time-consuming process.

However, some nationalities are characterized by a limited range of significant mutations (the so-called "founder effect"). Thus, in the population of Russian patients of Slavic origin, up to 90% of detected pathogenic BRCA1 variants are represented by only three mutations: 5382insC, 4153delA, 185delAG. This fact makes it possible to significantly accelerate the genetic testing of patients with signs of hereditary OC. These genes have many polymorphic variants, each of which is responsible for the manifestation of a particular mutation in target cells. For example: In cancer patients of the Slavic population, as well as the Ashkenazi ethnic group, pathogenic variants 185delAG, T181G, 4153delA, 5382insC in the BRCA-1 gene and 1528delAAAA, 1099SX C>G, 6174delT, 9318delAAAA in the BRCA-2 gene are most often detected. The population frequency of occurrence of these common mutations is quite low (no more than 1%). The detection of these mutations is usually associated with an increased risk of developing ovarian cancer. The BRCA-1 185delAG, 5382insC, and BRCA-2 6174delT variants are associated with an increased risk of ovarian cancer with long-term oral contraceptive use. The BRCA-1 variant 185delAG or 5382insC corresponds to more unfavorable histological malignancy of the tumor. BRCA-1 and BRCA-2 polymorphisms are not strictly specific for OC. The pathological BRCA-2 genotype increases the risk of stomach, colon, endometrial, pancreas, bladder, biliary tract, and melanoma. In connection with the above data, we have identified those cases when it is necessary to pass an analysis to detect BRCA1 and BRAC2 mutations:

1) Patients under 45 with a diagnosis of ovarian cancer.
2) Patients under the age of 50 with OC, if there is at least one in the family
a close blood relative with such a diagnosis.
3) Also in the event that a patient under 50 years old with OC has a family
cancer history unknown.
4) Patients with OC under the age of 60 years - if, according to the results
Histological examination of the tumor is triple-negative (there is no expression of markers ER, PR, HER2).
5) All patients diagnosed with ovarian cancer and breast cancer.
6) If a man is diagnosed with breast cancer.
7) If prostate cancer is diagnosed (with a Gleason score> 7) if there is at least one relative with OC and breast cancer aged less than 50 years or if there are at least two relatives with OC and breast cancer, pancreatic cancer or prostate cancer.
8) If a relative has a BRCA1 or BRCA2 mutation

PREVENTION MEASURES WILL BE:

Monthly self-examination from the age of 18, clinical examination of the ovaries (ultrasound or magnetic resonance imaging) from the age of 25 + screening from the age of 45-65, male carriers of a mutation in the BRCA1 / 2 genes are recommended to undergo an annual clinical examination of the mammary glands starting from the age of 35. From the age of 40, it is advisable to perform a screening examination of the prostate gland.

In our Republic, OC is treated by the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology (RSNPMTSOR) and its branches in the regions.

On April 4, 2017, the President of the country signed the Decree "On measures to further develop the oncological service and improve oncological care for the population of the Republic of Uzbekistan for 2017-2021". According to this program, the reorganization of the RSNPMTSOR and its branches in the regions,

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modernization and equipping with new modern equipment (including party mammographs) has begun. Doctors undergo specialization and improvement in leading oncological centers in Russia, Europe, Korea, India and other countries.

The Soglom Avlod Uchun Foundation conducts preventive examinations among women of different age categories with the involvement of doctors of various specialties, including gynecologists and mammologists. It should be noted with regret that at present in our country there are no funds that fully deal with cancer patients, as well as a large-scale volunteer movement.

Decree of the President of the Republic of Uzbekistan No. 5130 dated May 27, 2021 "ON FURTHER IMPROVEMENT OF THE SYSTEM OF PROVIDING HEMATOLOGICAL AND ONCOLOGICAL SERVICES TO THE POPULATION" prevention of cancer among the population using a mobile mammograph and ultrasound machines in all branches, including in Tashkent of the Republican Specialized Oncological and Radiological Scientific and Applied Medical Center is conducted in these areas for the early detection of dangerous tumors. May 8th is recognized worldwide as Ovarian Cancer Awareness (OC) Month.

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