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CERVICAL CANCER: A MODERN VIEW OF THE PROBLEM

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Abstract
This scientific and analytical work presents modern global and local regional data regarding the incidence, mortality and five-year survival rate of such a common oncological pathology as cervical cancer. The issues of etiology and pathogenesis, features of distribution, clinical manifestations, modern principles of early diagnosis and prognosis results for future decades are covered in detail. The achieved successes and modern developing directions for the prevention of this pathology in the form of HPV vaccination and the screening programs used are carefully described. The epidemiological characteristics of this pathology in our republic are presented in the context of regions of the country.

Keywords: oncology, cervical cancer, epidemiology, incidence, human papilloma virus, screening, diagnostics, Pap test, smear for oncocytology, mortality, five-year survival rate, prognosis.

Cervical cancer (CC) is a disease that occurs as a result of malignant transformation of the epithelium of the cervix. Considering that this nosological form of malignant neoplasms refers to visually accessible localizations, the possibilities for its early detection are practically unlimited. For this, it is sufficient to correctly use accessible and informative methods of morphological and endoscopic diagnosis. In addition, timely detection and treatment of background and precancerous processes of the cervix can prevent the development of CC. It is known that CC is preceded for many years and even decades by precancerous lesions - cervical intraepithelial neoplasia (CIN). Timely diagnosis and treatment of CIN become the prevention of invasive CC. CIN initiates in the cervical transformation zone and is maintained by persistent infection caused by human papillomaviruses (HPV) of high carcinogenic risk. In 1980-1990, the connection between HPV and dysplasia and squamous cell cancer was clearly shown. Using hybridization methods, it was found that 80-100% of CC contain HPV DNA. A rough correlation was found between the frequency of CC and the detection of HPV in the population. Moreover, in squamous cell cancer, HPV type 16 was most often encountered (in more than 50% of cases), while HPV type 18 was more often associated with adenocarcinoma and poorly differentiated cancer. In 95% of cases, HPV is localized in the zone of transitional epithelium, where about 90% of dysplasias, which are classified as cervical precancer, occur. It is precancerous diseases, in which HPV types 16 and 18 are detected, that have the greatest risk of developing into invasive CC. Intraepithelial lesions are, in fact, stages of cervical carcinogenesis. Conventionally, three degrees are distinguished: CIN 1 (mild dysplasia); CIN 2 (moderate dysplasia); CIN 3 (severe dysplasia and pre-invasive cancer - carcinoma in situ, CIS). At the same time, there are two concepts of the occurrence of CC against the background of persistence of HPV of high carcinogenic risk. The first, classic, reflects the sequential change of CIN 1, 2, 3 to invasive cancer. The second, more recent one, suggests that CIN 2-3, which are severe intraepithelial lesions, can occur bypassing CIN 1 [1].

The diagnostic criteria for CC are as follows [2]: 1) complaints of acyclic bloody, watery, purulent discharge from the genital tract; pain in the lower abdomen and lumbar region of a pulling nature; bleeding due to menopause; 2) anamnesis: there are no pathognomonic

complaints; as a rule, the disease has a pronounced preinvasive stage, which can last from 1 year to 5 years or more; microinvasive cervical carcinoma is most often discovered during accidental presentation; the reason for women diagnosed with CC in stages Ib1-IIa2 to visit a gynecologist is bloody discharge from the genital tract; in later stages (IIb-IVa) there are complaints of pain in the lumbar region, lower abdomen; 3) physical examinations: gynecological examination (condition of the external genitalia; examination of the vagina and cervix on speculum (presence of vaginal infiltration, metastatic foci on the vaginal walls, size, condition of the cervix); presence of pathological discharge (purulent, bloody); bimanual examination (size and shape of the uterus; condition of the appendages; infiltration of the anterior and posterior vaginal fornix); 4) laboratory tests: cytological examination with Papanicolaou staining - PAP test (increase in cell size up to giant, change in the shape and number of intracellular elements, an increase in the size of the nucleus, its contours, different degrees of maturity of the nucleus and other elements of the cell, changes in the number and shape of nucleoli (pronounced cellular polymorphism, increase in cell size, pronounced hypochromia, large nuclei contain one or more nucleoli, there are glandular structures); from cancer cells in the form of rosettes, many cells in a state of mitosis); 5) instrumental studies: ultrasound of the pelvic organs (if CC is suspected, the size of the cervix will be normal or increased, its structure is heterogeneous, the condition of the uterus and ovaries is also assessed); magnetic resonance imaging of the pelvic organs (with CC, the size of the cervix will be normal or increased, its structure is heterogeneous, the condition of the uterus and ovaries is also assessed); computed tomography of the chest, abdominal cavity and pelvis (assessment of pelvic lymph nodes and retroperitoneal space, organic changes in the chest and abdominal organs); cystoscopy according to indications (for the purpose of diagnosing the germination of the tumor process into the bladder); sigmoidoscopy or colonoscopy according to indications (for the purpose of diagnosing the spread of the tumor process to the colon or rectum); skeletal scintigraphy (prescribed for suspected bone metastases); positron emission tomography of the whole body (performed to diagnose the extent of the tumor process or to assess the dynamics of the effectiveness of special treatment).

GLOBOCAN estimates that in 2020, there were 604,000 new cases and 342,000 deaths from CC worldwide, of which 80% occurred in low- and middle-income countries, mainly in sub-Saharan Africa, South-East Asia, and Latin America and the Caribbean [3].

As noted by Torres-Roman J.S. et al. [4], CC remains a major public health problem in low- and middle-income countries. Due to the high burden of this disease, in 2020 the World Health Organization (WHO) adopted a global strategy to decrease the number of new CC cases, with the aim of maintaining an incidence rate below 4 per 100,000 women. Currently, 29 of the 47 countries (and territories) in the Latin American and Caribbean region have implemented vaccination programs for girls and almost all countries have screening services in place, and while certain screening programs in the region achieve considerable coverage, the ambitious goals set by the CC elimination strategy have yet to be achieved. Researchers evaluated the mortality trends of CC among young women from 16 Latin American and Caribbean countries (and territories) and predicted mortality rates until 2030. Downward trends were observed in Chile, Colombia, Cuba, El Salvador, Mexico, Nicaragua, Panama, and Peru for the entire period; whereas Brazil, Argentina, Chile, and Costa Rica showed initial downward trends from − 0.9% to − 6.2% followed by significant upward trends from 2.5 to 4.8% (for the period~ 2006-2017). In the last 4 years of study (2014-2017), Paraguay and Venezuela had the highest mortality rates, whereas Puerto Rico had the lowest mortality. By 2030, authors projected that mortality for CC will increase in some countries that were examined. Colleagues considered CC mortality in young women only because of the lack of research in the Latin American and Caribbean region, which has focused on CC mortality in general. They point out that because HPV infection is the most important risk factor for CC, younger women are likely to have experienced higher rates of HPV infection compared to older women. The authors also note that CC mortality rates among young women in Latin America and the Caribbean are higher than in Eastern Europe. While Western and Southern Europe recorded rates below 2 deaths per 100 000 population in 2017, rates were below 6 deaths per 100 000 population in Northern and Eastern Europe. In conclusion, the researchers emphasize that most countries in Latin America and the Caribbean experienced a decline in mortality rates between 1997 and 2017. The variations of the mortality rates between countries during the last period of observation can be largely explained by the timing of implementation of nation-wide screening campaigns in different time periods and the variation of public health programs within each country, among others. Despite favorable downward trend, the mortality rate in some Latin America and the Caribbean countries remains high. HPV vaccination, screening, and early diagnosis and treatment are necessary to accelerate a rapid decline in CC mortality by 2030.

As noted by Abu-Rustum N.R. et al. [5], an estimated 13,960 new cases of carcinoma of the uterine cervix (ie, CC) will be diagnosed in the United States in 2023, and an estimated 4,310 people will die of the disease. Overall, CC rates are decreasing in the United States, although incidence remains high among Hispanic/Latino, Black, and Asian populations. In 2020, the global new cases of and deaths from CC were estimated to be 604,127 and 341,831, respectively. It is the fourth most common cancer in individuals assigned female at birth worldwide, with 85% of cases occurring in developing countries, where CC is a leading cause of cancer death in individuals assigned female at birth. Squamous cell carcinoma (SCC), adenocarcinoma (AC) or adenosquamous carcinoma (ASC) are the 3 common histologies of CC. SCC accounts for approximately 80% of all CCs and AC accounts for approximately 20%. In developed countries, the substantial decline in incidence and mortality of SCC of the cervix is presumed to be the result of effective screening and

higher HPV vaccination coverage, although racial, ethnic, and geographic disparities exist. However, AC and ASC of the cervix have increased over the past 3 decades, probably because cervical cytologic screening methods are less effective for AC/ASC because the lesions are located deeper than the ectocervix. The ASC subtype is rare and accounts for approximately 5% to 6% of all cervical carcinomas. Presently, there is no difference in treatment between SCC and AC/ASC CC subtypes, although the clinical features and prognosis of disease vary considerably between these subtypes. Persistent HPV infection is a major factor in the development of CC. The incidence of CC appears to be related to the prevalence of HPV in the population. In countries with a high incidence of CC, the prevalence of chronic HPV is approximately 10% to 20%, whereas in low-incidence countries it is 5% to 10%. Screening methods using HPV testing may increase detection of adenocarcinoma. Vaccination with HPV vaccines may also decrease the incidence of both SCC and AC. In 2020, the WHO updated the Female Genital Tumors classification of CC by subdividing the CC lesions into HPV-associated and HPV-independent tumors based on new pathologic findings. Among these subtypes, HPV-associated SCC is the most prevalent, with very rare occurrences of HPV-independent SCC. The HPV-independent AC subtype has a less favorable prognosis compared with HPV-associated AC. The NCCN CC Panel acknowledges that although the prior versions of the WHO classification discussed these tumors based on morphologic features, the integration of the immunohistochemical and molecular profiles has led to a better classification system, which is now adapted in the 2020 WHO Classification of Female Genital Tumors for CC.

Screening plays an important role in improving early diagnosis and treatment outcomes for CC. According to the Guidelines for Early Diagnosis of Cancer by Ilbawi A. et al. [6], screening aims to detect unrecognized cancer or its prior lesions in a typically healthy, asymptomatic population through tests (e.g., HPV test), screenings (e.g., visual inspection of VIA with acetic acid), or other procedures that can be applied quickly and are widely available to the target population. In screening, the target population is assessed for unrecognized cancer or precancer, and most people tested will not be diagnosed with the disease. Screening should be seen as a process and not as the performance of a specific test, examination, or procedure. The screening process includes a system of informing and inviting the target population to participate; administering the screening test; following-up with test results and referral for further testing among those with abnormal test results; ensuring timely pathologic diagnosis, staging and access to effective treatment with routine evaluation to improve the process. A screening programme encompasses the process from invitation to treatment and requires planning, coordination and monitoring and evaluation.

As pointed out by Pimple S.A., Mishra G.A. et al. [7], CC is highly preventable and can be easily treated if detected at early stages. However there is disproportionate high burden of CC incidence and mortality in low-middle income country settings that lack organized screening and prevention programs. Robust evidence for prevention and screening of CC is currently available. However there are barriers for country specific adoption and implementation. These pose unique challenges such as organizing prevention and screening services delivery through the current health infrastructure, access to screening facilities, follow-up management and adequate linkages for confirmatory diagnosis and subsequent treatment. Overall rates of CC screening and cancer screening among women remain suboptimal in many low- and middle-income countries.

Brisson M. et al. [8] demonstrate in their work that in May, 2018, WHO issued a global call to eliminate CC as a public health problem. To inform its global strategy to accelerate CC elimination, WHO created the CC Elimination Modelling Consortium (CCEMC) to examine the following key questions: what elimination threshold should be used; what prevention strategies can lead to elimination; when could elimination be reached for different countries; and how many cancers could be averted. The current working definition of elimination is an age-standardised CC incidence of four or fewer cases per 100 000 women-years. Alternative definitions, such as an incidence of ten or fewer cases per 100 000 women-years and an 80-90% reduction in incidence, have also been suggested. The only previous multicountry modelling study of CC elimination suggests that global elimination is possible through girls-only human papillomavirus (HPV) vaccination at 80-100% coverage with a perfectly effective 9-valent vaccine and twice-lifetime HPV-based screening. Herewith less than 30% of low- and middle-income countries have introduced HPV vaccination compared with more than 85% of high-income countries. Additionally, only about 20% of women in low- and middle-income countries have ever been screened for CC compared with more than 60% in high-income countries. Given that models necessarily include simplifying assumptions, the goal of the consortium is to use multiple models, taking into account their respective strengths and limitations, to illustrate the robustness of predictions. A systematic comparative modelling approach was used. To form the CCEMC, WHO selected three models that met the predefined eligibility criteria: HPV-ADVISE, Harvard, and Policy1-Cervix. The models projected reductions in CC incidence over time based on standardised HPV vaccination and cervical screening scenarios determined after consultations at various WHO technical expert, advisory group, and global stakeholder meetings. Three elimination thresholds were examined (CC incidence of four or fewer cases per 100 000 women-years, ten or fewer cases per 100 000 women-years, and ≥85% reduction in incidence). The three CCEMC models (HPV-ADVISE, Harvard, and Policy1-Cervix) have been used extensively to inform recommendations on cervical screening and HPV vaccination in Australia, Canada, the UK, the USA, and at a global level [8]. Although developed independently, the models have common features. First, they are transmission-dynamic models of HPV infection and the natural history of CC. Second, they include the following components: sexual behaviour and HPV transmission,

natural history of CC, vaccination, and screening, diagnosis, management, and treatment of cervical lesions and cancer. HPV transmission and cervical carcinogenesis are modelled for the HPV types in the 9-valent vaccine (HPV types 16, 18, 31, 33, 45, 52, 58) and other high-risk types. The models simulate type-specific HPV transmission through sexual activity, based on different risk groups and sexual mixing. The models reproduce the type-specific natural history of CC, from persistent HPV infection to CC via precancerous cervical lesions (cervical intraepithelial neoplasia grade 1 to 3). All models assume that HPV vaccines are prophylactic and capture post-vaccination herd effects. They can also simulate complex cervical screening and treatment algorithms at the individual level, by tracking and simulating each woman's screening history. Finally, all models were calibrated to highly stratified sexual behaviour and epidemiological data, validated to clinical trials or post-vaccination data, or both, and reproduce the age-specific CC incidence estimates from the Global Cancer Observatory (GLOBOCAN) 2018 for all 78 low- and middle-income countries.

A comparative modelling analysis by Brisson M. et al. [8], which includes projections from three independent transmission-dynamic models, provides consistent results predicting that CC can be eliminated as a public health problem by the end of the century, based on WHO's proposed elimination threshold (i.e., CC incidence of four or fewer cases per 100 000 women-years). This modelling study shows that girls-only HPV vaccination would lead to CC elimination in most low- and middle-income countries, if high coverage is reached (>90% coverage) and the vaccine provides long-term protection. However, countries with the highest CC incidence at present (>25 cases per 100 000 women-years), more than 90% of which are in sub-Saharan Africa, would not reach elimination by vaccination alone. To achieve CC elimination in all 78 low- and middle-income countries, these models predict that scale-up of both girls-only HPV vaccination and twice-lifetime screening is necessary, with 90% HPV vaccination coverage, 90% screening uptake, and long-term protection against HPV types 16, 18, 31, 33, 45, 52, and 58. If this global elimination strategy, which includes a combination of intensive scaling up of HPV vaccination and cervical screening, is implemented, the results suggest that CC elimination can be achieved in all countries by 2100. In doing so, CC incidence would be reduced by 97% and more than 74 million cases would be averted over the next century.

An interesting and important study was conducted by Simms K.T. et al. [9], who in their work modeled the global situation with CC for future decades depending on the coverage of the population with HPV vaccination and screening. In this study, the authors aimed to quantify the potential cumulative effect of scaled up global vaccination and screening coverage on the number of CC cases averted over the 50 years from 2020 to 2069, and to predict outcomes beyond 2070 to identify the earliest years by which CC rates could drop below two absolute levels that could be considered as possible elimination thresholds-the rare cancer threshold (six new cases per 100 000 women per year, which has been observed in only a few countries), and a lower threshold of four new cases per 100 000 women per year. In this statistical trend study and modeling, our colleagues conducted did a statistical analysis of existing trends in CC worldwide using high-quality cancer registry data included in the Cancer Incidence in Five Continents series published by the International Agency for Research on Cancer. Next, the authors used the comprehensive and extensively validated simulation platform, Policy1-Cervix, to do a dynamic multicohort modelled analysis of the impact of potential scale-up scenarios for CC prevention, in order to predict the future incidence rates and burden of CC. Data are presented globally, by Human Development Index (HDI) category, and at the individual country level. As a result of the study, the following conclusions were drawn. In the absence of further intervention, there would be 44.4 million CC cases diagnosed globally over the period 2020-2069, with almost two-thirds of cases occurring in low-HDI or medium-HDI countries. Rapid vaccination scale-up to 80-100% coverage globally by 2020 with a broad-spectrum HPV vaccine could avert 6.7-7.7 million cases in this period, but more than half of these cases will be averted after 2060. Implementation of HPV-based screening twice per lifetime at age 35 years and 45 years in all low- or middle-income countries with 70% coverage globally will bring forward the effects of prevention and avert a total of 12.5-13.4 million cases in the next 50 years. Rapid scale-up of combined high-coverage screening and vaccination from 2020 onwards would result in average annual CC incidence declining to less than six new cases per 100 000 individuals by 2045-2049 for very-high-HDI countries, 2055-2059 for high-HDI countries, 2065-2069 for medium-HDI countries, and 2085-2089 for low-HDI countries, and to less than four cases per 100.000 by 2055-2059 for very-high-HDI countries, 2065-2069 for high-HDI countries, 2070-2079 for medium-HDI countries, and 2090-2100 or beyond for low-HDI countries. However, rates of less than four new cases per 100 000 would not be achieved in all individual low-HDI countries by the end of the century. If delivery of vaccination and screening is more gradually scaled up over the period 2020-2050 (eg, 20-45% vaccination coverage and 25-70% once-per-lifetime screening coverage by 2030, increasing to 40-90% vaccination coverage and 90% once-per-lifetime screening coverage by 2050, when considered as average coverage rates across HDI categories), end of the century incidence rates will be reduced by a lesser amount. In this scenario, average CC incidence rates will decline to 0.8 cases per 100 000 for very-high-HDI countries, 1.3 per 100 000 for high-HDI countries, 4.4 per 100 000 for medium-HDI countries, and 14 per 100 000 for low-HDI countries, by the end of the century. At the same time, the researchers emphasize that more than 44 million women will be diagnosed with CC in the next 50 years if primary and secondary prevention programmes are not implemented in low- or middle-income countries. If high coverage vaccination can be implemented quickly, a substantial effect on the burden of disease will be seen after three to four decades, but nearer-term impact will require delivery of cervical screening to older cohorts who will not benefit from

HPV vaccination. Widespread coverage of both HPV vaccination and cervical screening from 2020 onwards has the potential to avert up to 12.5-13.4 million CC cases by 2069, and could achieve average CC incidence of around four per 100 000 women per year or less, for all country HDI categories, by the end of the century.

In our country, according to Decree of the Government of the Republic of Kazakhstan dated February 20, 2024 No. 102 [10], the list of diseases against which mandatory preventive vaccinations are carried out as part of the guaranteed volume of medical care at the expense of the republican budget includes routine preventive vaccinations against diseases caused by HPV (Annex 1). According to Annex 2 of this Resolution, girls aged 11 and 11.5 years will be vaccinated.

Now, as for this pathology in our republic. CC in the structure of all malignant tumors of both sexes of the population in 2022 took 6th place with a share of 5.51% (2021 - 4th place, 5.54%), in women - stable 2nd place - 9.7% (9.7%) [11].

The incidence rate per 100 thousand population increased from 9.4 to 9.92. In 10 regions of the republic, the incidence rate is higher than the national average: Pavlodar - 17.2 per 100 thousand people (2021 – 16.7) – the highest level, East Kazakhstan – 14.3 (10.8), North Kazakhstan – 14.3 (10.2), Atyrau – 13.2 (13.8), Zhetysu - 11.7, Karaganda - 11.7 (12.0), Abay - 11.1, Akmola - 11.1 (11.9), Mangistau - 11.1 (9.7), Kostanay - 10.8 (10.6) regions.

Low incidence rates in Zhambyl region - 5.8 per 100 thousand population (5.7), Turkestan region - 6.1 (5.2), Aktobe region - 8.3 (11.6), Kyzylorda region - 8.5 (8.2) areas.

CC in the structure of causes of death from malignant tumors of the population of both sexes in 2022 rose from 9th to 8th position, with a share of 4.6% (2021 - 4.3%), mortality from CC is stable at 3.1 per 100 thousand population (3.1).

The mortality rate from CC in 10 regions is higher than the national average: Akmola - 4.2 per 100 thousand population (2021 - 3.1) - maximum level, West Kazakhstan - 4.1 (4.8), Pavlodar - 3.8 (5.6), Almaty – 3.7 (2.5), Zhetysu – 3.7, Atyrau – 3.4 (4.0), East Kazakhstan – 3.3 (3.8), Karaganda - 3.2 (4.7), Kostanay - 3.2 (2.4) regions and Almaty city - 3.4 (2.9).

Below the national average mortality rate was registered in the Kyzylorda region - 1.7 (3.5) - the best result; North Kazakhstan - 2.0 (2.6), Aktobe - 2.2 (3.0), Turkestan - 2.3 (2.2), Mangystau - 2.8 (3.0), cities of Astana, Shymkent – and Abay region - 2.9 per 100 thousand population [11].

In 12 regions, a 100% level of morphological verification of the diagnosis is ensured. The lowest or worst indicator for the third year in a row was recorded in the Kyzylorda region - 94.3%. Below the national average, this figure was noted in Akmola - 98.8%, Atyrau - 98.9%, Kostanay - 98.9%, Mangistau - 97.6%, Pavlodar - 96.6% regions and Almaty city - 98.5 %.

In a number of regions, the frequency of diagnosis of stage I-II CC was lower than the national average (88.1%) - in Akmola - 76.2% - the worst result in the country, in Karaganda - 77.2%, Pavlodar - 81.3%, Zhetysu - 82.9%, Abay - 83.8%, Kostanay - 84.3%, Aktobe - 85.5%, West Kazakhstan - 85.7% regions. In the Atyrau region there is a 100% result.

The proportion of stage IV CC is higher than the republican average (2.7%) in the following regions: the worst result is in the Zhetysu region - 6.1%; next come: Karaganda - 5.1% (2021 - 5.6%), Akmola - 4.8% (2.3%), Kostanay - 4.5% (4.4%), North Kazakhstan - 3.9% (7.4%), Shymkent city - 3.8% (5.9%), Almaty - 3.7% (5.1%), Almaty city - 3.6% (1.8%), Zhambyl - 2.9% (0.0) regions. No advanced forms were registered in 3 regions. The lowest neglect is in the East Kazakhstan region - 1.0% (0.7%).

Indicators of late diagnosis of this pathology, as visually accessible localization (III-IV stages) are higher than the national average - 11.9% (15.4% in 2021) were noted in the Akmola region - 23.8% (2021 - 26.4 %) - worst result; Karaganda - 22.8% (35.2%), Pavlodar - 18.8% (20.8%), Zhetysu - 17.1% (24.2%), Abay - 16.2% (12.8%), Kostanay - 14.6% (15.6%), Aktobe - 14.5% (9.6%), West Kazakhstan - 14.3% (32.4%) regions. The least neglect is in the Mangistau region - 6.0% (20.8%).

Across the country, the five-year survival rate of patients with CC registered in 2018 was 59.9% in 2022, with a decrease from the level of 2021 (67.5% for those registered in 2017), and with a significant range in by region, from the maximum – 72.9% (2021 – 70.7%) in the North Kazakhstan region, to the minimum – 34.9% (64.4%) in the Atyrau region [11].

Next, regarding CC screening. CC screening is a periodic, comprehensive examination of women of a certain age group as part of a special medical program to prevent and reduce incidence and mortality from CC.

Type of screening - population. The purpose of screening is to identify pre-invasive diseases of the cervix with subsequent recovery. The screening method is a cytological examination of a smear for oncocytology from the cervix (traditional and liquid cytology) - Pap test. Interval - 1 time in 4 years. Target group: women aged 30-70 years who are not registered in the dispensary for CC. The expected results are a decrease in incidence and mortality from CC.

Screening steps:

1) Preparatory - formation of target groups, information support and invitation to screening. The preparatory stage is carried out by the nurses of the primary health care organization responsible for preventive measures and includes: annual compilation of a list of women subject to screening in the coming year by November 15 of the current year, followed by monthly correction; informing target groups of the female population about the need for screening; screening invitation; ensure timely screening.

2) Screening - filling out a statistical card of a preventive medical examination (screening) of an outpatient (form 025-08/y), a register of patients subject to cytological screening and taking material for cytological examination from the cervix. The screening examination of the target groups of the female population is carried out by a specially trained midwife of the primary health care organization.

3) The final one is obtaining the results of cytology, informing the woman and developing further management tactics, fill out accounting and reporting statistical documentation. Responsible for the final stage of screening is the obstetrician-gynecologist of primary health care [12].

Cytological screening of CC is a complex of organizational and medical measures aimed at early detection of precancerous and neoplastic diseases of this localization and at reducing the mortality of this cohort of patients. For traditional cytology, a smear containing 8-12 thousand cells of stratified squamous epithelium (including cells of metaplastic epithelium) is considered adequate; for liquid cytology - 5 thousand cells. For both methods, the number of cells of endocervical epithelium and/or metaplastic epithelium (from the transformation zone) must be at least 10 (single or in clusters). If more than 75% of the cells of the stratified squamous epithelium are covered with erythrocytes, leukocytes, etc., then the quality of the smear is considered unsatisfactory.

Interpretation of the results of a cytological study is carried out according to the Bethesda-terminology cytological system:

Intraepithelial changes and malignant processes are absent (NILM). This group includes cytological conclusions about the normal state of the epithelium, as well as the presence of various non-neoplastic diseases. Normally, squamous epithelial cells, groups of cells of columnar epithelium and metaplastic epithelium, a small number of leukocytes, and rod/mixed microflora are found in preparations. In the presence of non-neoplastic processes, their nature and, if possible, the cause are specified: atrophic changes, reactive changes associated with inflammation, including typical regeneration. In addition, the presence of microorganisms is indicated: Trichomonas vaginalis, fungi, morphologically corresponding to Candida spp., bacterial vaginosis, cellular changes corresponding to the defeat of Herpes simplex virus, squamous epithelial cells with atypia of unknown significance (ASC-US), squamous epithelial cells with atypia of unclear significance, not excluding the presence of a high degree of intraepithelial changes (ASC-H). Low-grade squamous intraepithelial changes (LSIL) include lesions associated with HPV and CIN I, high-grade squamous intraepithelial changes (HSIL) include CIN II, CIN III, carcinoma in situ and cases suspected of invasion, squamous cell carcinoma, cervical (glandular) epithelium with atypia of unknown significance, cells of the cervical (glandular) epithelium, possibly neoplasia, endocervical adenocarcinoma in situ, endocervical adenocarcinoma, endometrial adenocarcinoma, secondary adenocarcinoma, unclassified carcinoma, other malignant tumors.

There are certain features when taking material for oncocytology: firstly, the examined woman should be informed about the exclusion of sexual intercourse, vaginal manipulations, including douching, baths, tampons, etc. 2 days prior to sampling. Taking material for cytological examination is carried out by the midwife of the examination room of the department of medical examinations of the primary health care organization: the traditional method (2 glasses - with obligatory fixation in 96% alcohol, it is preferable to use glass slides with a polished edge, which are easily marked) or the liquid cytology method (one container with stabilizing liquid); the code or surname of the patient, identical to the code and surname in the form for sending material for cytological examination, should be clearly marked on the glasses or container [12].

At the same time, when using the traditional method, the biomaterial is delivered to the cytological laboratory as soon as possible after its collection in specialized containers for glass slides with 96% alcohol. If there are visible visual changes in the cervix, then the material is taken from the woman and, without waiting for the results, she is referred for an examination by an obstetrician-gynecologist.

A cytological study is carried out in centralized cytological laboratories at oncological institutions, where an archive of cytological preparations of patients involved in the screening examination is formed, regardless of the result, for a period of at least 10 years with the formation of a computer database.

What material and technical equipment is required to take material for a Pap test? It is as follows: soap and water for washing hands, a light source for cervical examination, a gynecological chair, a disinfected speculum and gloves, an Eyre spatula, a glass slide and a marking pen, a container with a stabilizing solution for liquid cytology, a fixative solution (96% alcohol), a container with warm water for lubricating and warming the vaginal mirrors, a 0.5% chlorine solution for disinfecting gloves and instruments, or another approved for this purpose. And, of course, the registration form itself.

For carrying out liquid cytology, you additionally need: a disposable cervix brush, a container with a stabilizing solution for liquid cytology, and a fixing solution.

At the same time, a smear for oncocytology cannot be taken: during menstruation, earlier than 48 hours after sexual contact or after using lubricants, vinegar or Lugol solution, tampons or spermicides, after vaginal examination or douching, and also during the treatment of genital infection.

The results of CC screening are as follows. In 2022, 771,282 women of the target group aged 30 to 70 years were examined during cytological screening (in 2021 - 757,454).

During cytological screening in 2022, 392 cases of CC were identified (319 in 2021). The detection rate increased from 0.42 to 0.51 per 1000 women examined [11].

High detection of CC during screening is ensured in Aktobe, Almaty, Atyrau (1.59 is the best result), East Kazakhstan, Kyzylorda, Pavlodar, North Kazakhstan, Turkestan regions and Shymkent city.

The detection rate in these regions ranges from 0.55 to 1.59 per 1000 women examined. Compared to 2021, there is an increase in detection in 10 regions, with the exception of Akmola, Aktobe, Zhambyl, Kostanay, Mangistau, North Kazakhstan regions and Shymkent city. The worst result in Astana city is 0.15 per 1000 women examined.

Cytologically, cervical precancer was detected in 1.16% of those examined (2021 – 0.99%). The detection rate of precancer below 0.6% (the planned indicator for 2022, according to the Comprehensive Plan) was noted in Aktobe, Karaganda and Kostanay regions.

A high proportion of stage I CC (70% or more) was detected in 6 regions of the country (in 8 in 2021): Kostanay, Mangistau (94.7% - best result), North Kazakhstan, Turkestan regions, cities of Almaty and Astana. Low levels of early detection of CC (below 50%) were not observed in any region.

Localized processes (stages I-II) were identified in 99.2% of all cases of detected cancer (96.5% in 2021). In the Akmola and Karaganda regions, cases of SS were identified not only in the localized, but also in the widespread stages of the process. A total of 3 cases of SS were identified in stage III and not a single case in stage IV (in 2021 - 11 and 0, respectively) [11].

Summarizing the above, we can conclude that cervical cancer occupies a significant place among all available nosological forms of malignant tumors. At the same time, despite the small percentage of patients detected at stages III and IV of the disease, as a visually accessible localization, taking into account a number of factors, early diagnostic indicators do not allow oncologists and gynecologists to "sleep peacefully." Variability, nonspecificity and veiledness of symptoms, its similarity with various non-tumor processes, leads to neglect of the tumor process. All this requires both oncologists and, first of all, primary health care workers and, of course, gynecologists to increase the level of oncological alertness, inform the population about early symptoms that may indicate this pathology or the onset of proliferative changes and carrying out high-tech diagnostic measures and, as a result, timely treatment. Patients at risk with precancerous diseases should undergo routine examination within the prescribed time frame. The development of screening technologies and methods of primary prevention in the form of vaccination of adolescent girls against HPV allows us to hope for a reduction in the incidence of this disease in the female population.

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