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On the Issue of Early and Effective Diagnosis of Cervical Cancer (Literature Review)

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Abstract: The confirmation of the aetiological role of human papillomavirus (HPV) in the development of cervical cancer led to the fact that the diagnosis of papillomavirus infection along with cytological studies was considered to be an important element in screening and preventing this disease. Numerous studies have demonstrated that the HPV test has a much higher sensitivity for detecting cervical intraepithelial neoplasia than a cytological study. In this article, through expert analysis of research data for different countries and a comparative evaluation of the findings, we attempted to analyze the prevalence of cervical cancer among women and identify more modern and effective diagnostic methods.

Key words: Human papillomavirus · Cervical cancer · Screening · Papillomavirus infection

INTRODUCTION

The radical changes that took place in the country at the turn of the 20th and 21st centuries, which determined a new development vector of the Republic of Kazakhstan, are accompanied by radical changes in the social, economic, political and spiritual spheres of society and the consciousness of its citizens by innovative transformations in the healthcare system (Karpin and Novikova 2015). In accordance with the State Program for the Development of Healthcare "Salamatty Kazakhstan" (2011-2015) at the level of emergency, screening for early detection of factors of chronic non-infectious disease is conducted. 11 types of screening are approved, among them screening for early detection of precancerous and tumor diseases of the cervix [1].

The experience of the world's leading countries, in which screening for early detection of diseases, including cervical cancer, was launched in the late 80-90s of the last century, indicates that timely detection of risk factors for the development of chronic non-infectious disease contributes to a significant reduction in the incidence and mortality. The rationale for this study is that over the past 25 years, the screening strategy for cervical cancer has not changed. The lack of a screening program with the development of all organizational issues and monitoring of its implementation appears to be one of the main reasons for the lack of effective screening [2].

Based on the foregoing, it can be assumed that the data presented below will be of some practical interest for the specialists of the outpatient service and scientific workers.

The purpose of our study is to analyze the scientific literature on the prevalence and early detection of cervical cancer among women.

Cervical cancer is a form of malignant neoplasm, for the identification of which there is an established system of preventive examinations, there is a recognizable preclinical phase, a long stage of development and modern methods of effective treatment.

However, in Russia, the analysis of indicators of preventive work with the population indicates that only 28.3% of patients with cervical cancer from the number of primary identified was detected actively and the indicator of neglect for this visual form of cancer was noted in 38.9% of cases . According to the data of 2006, the incidence of cancer at the stage of in situ was on average in the country only in 16.7% of cases [2]. For comparison, in England in 2003, more than 20, 000 cases of carcinoma in situ were detected, which is approximately 10 times higher than the number of invasive forms of cervical cancer detected [3].

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Currently, among the screening programs conducted in various countries of the world, the cytology screening programs of the cervical cancer are the most effective, since cytology, as a method, allows detecting precancerous changes 3-5 years before the development of cervical cancer. A cytological test developed by Papanicolaou in 1940 and introduced into the practice of the United States, helped reduce the incidence of cervical cancer in the next 50 years by 75% [4]. As a result of the use of cytological screening in Russia for the period from 1980 to 1992, there was also a positive tendency to reduce the incidence of cervical cancer in the range of 37.1% [5]. The results of studies in Scandinavian countries showed a decrease in morbidity and mortality rates from cervical cancer following the introduction of organized screening programs, starting in the 1960s. In Finland, the program contributed to a 70-80% reduction in the incidence of this form of cancer, as well as a decrease in mortality. In Iceland, during the 20 years of screening, the incidence and mortality of cervical cancer decreased by 60%.

One of the main points in the development of cytological screening remains the problem of the screening frequency. The rational periodicity of cytological screening closely interacts with the coverage problem of the female population by screening activities. If the screening is carried out on an ongoing basis, the pathogenetic sequence is interrupted, which subsequently affects the reduction of morbidity and mortality from cervical cancer. In many countries, high rates of population turnover have been achieved, but in no European country, 100% coverage has been received [6]. Cytological screening is effective for those women who regularly participate in screening activities. Screening methods have limitations related to the sensitivity and specificity of the methods used [7]. So, for example, in detecting adenocarcinoma of the cervix, which is about 10% of all cervical cancers, the Papanicolaou test is less effective. This is due to the localization of adenocarcinoma above the cervical canal and with this test, this form of cancer is difficult to cover [8, 9]. The effectiveness of traditional screening for cervical cancer has now reached a plateau and can be confirmed by the fact that 40 women die from this form of cancer every day.

MATERIALS AND METHODS

Epidemiological studies in recent years have shown that an undeniable risk factor for precancerous changes and cervical cancer is a genital infection that causes changes in the cells of the cervical epithelium, which leads to the development of neoplasia. A revolutionary contribution to the disclosure of the mystery of the occurrence of cervical cancer was the work of H. zur Hausen and his colleagues who identified human papillomavirus DNA in the tissues of cervical cancer. The authors of the study showed that human papillomavirus viruses of high-risk - HPV types 16 and 18 are evaluated as the etiological factors of the occurrence of cervical intraepithelial neoplasias of types I-III) and cervical cancer [10]. Knowing the immediate causes of cell transformation process led to the creation of a vaccine and the possibility of vaccination against this group of viruses. The vaccination against papillomavirus infection forms the first line of protection against pre-tumor pathology and cervical cancer and cytological screening contributes to the early detection of a precancerous pathology of the cervix, caused by human papillomaviruses. Thus, the vaccine is a preventive drug and has no therapeutic effect [11]. At present, there is such a specific vaccine "GARDASIL", which has a protective effect against 4 types of human papillomaviruses. The vaccine belongs to the class of genetically engineered products and is a mixture in certain proportions of virus-like particles of types 6, 11, 16 and 18, which do not possess pathogenic properties. The immune system of humans perceives these particles as natural viruses and when in contact with the cells of the immune system, an immune response is beginning to emerge. This process leads to the formation of specific antibodies, creates a special pool of cells that circulate long in the body, which thus becomes protected. According to the results of the studies, the protective duration is at least 5 years, but there is evidence that an immunological memory is being formed. It is ideal to vaccinate children before sexual debut, that is before contact with the virus since antiviral protection is significantly higher in adolescents under 16 years old. Modeling studies according to cost-effectiveness rating combines both the vaccination process for girls aged 9 to 12 years and traditional cytological screening, starting at 25 years of age for women. At the present stage of the health care development, prevention of oncological diseases should not be considered only as a medical or economic problem. Now we need to take this problem as the basis of social responsibility [12].

The benign processes include endocervicosis, cervical erosion, leukoplakia, endometriosis, cicatricial changes of posttraumatic nature, precancerous conditions include dysplasia of varying severity, leukoplakia with atypia, erythroplakia [11].

At present, the causes of oncological diseases are well known, which makes it possible to prevent at least one-third of all cancers [13]. The main screening method for several decades is a cytological study of the cervical epithelium. However, up to 30% of cancers are thought to develop in women who have undergone cytological screening routinely [9]. Due to the limited sensitivity of the cytological method, false-negative results are registered even in the best screening programs. All this proves the need to search for new screening technologies, first of all, with the use of the HPV test.

Based on data obtained in many large international studies, the following recommendations were made on the use of the HPV test in cervical cancer screening [4]:

- In primary screening in women older than 30 years in combination with a cytological examination or as an independent test (in countries where cervical cytological screening programs are poorly organized);
- In the management of patients in a cytological study who are known to have identified atypical cells of uncertain significance (ASC-US, Atypical Squamous Cells of Undetermined Significance);
- For monitoring the therapy of cervical intraepithelial neoplasia (CIN, Cervical Intraepithelial Neoplasia) of high degree (CIN 2/3).

In many countries of Europe, America and Asia, positive experience has already been accumulated in the use of various methods of detecting HPV DNA in screening studies [5].

The problem of false-positive cytological findings (when a smear shows dysplasia where it does not actually exist) does not discredit the idea of cytological screening in general because in most cases, it is resolved by the price of relatively minimally invasive effects (cervical biopsy, repeated cytology after trial treatment). Nevertheless, in each case, this problem creates a number of inconveniences to the doctor and the patient:

- The need for a biopsy (cost, invasion, time);
- The need for repeated visits to the doctor;
- Negative psychological impact on the patient, associated with information about the possibility of developing cancer in her.

Even if the diagnosis of dysplasia is verified histologically, the probability of a dysplasia transition into cancer is less than 50%. However, at present, there are no reliable prognostic criteria for the further biological behavior of dysplasia at both the clinical and microscopic levels [14].

If consensus in medical tactics in relation to severe dysplasia and Ca in situ has already been reached, then with moderate and mild dysplasia, much depends on the opinion of the attending physician. He must compare the cytological conclusion, the clinical and colposcopic picture, the age of the patient and decide (ranging from observation without treatment to cone-shaped cervical excision). In this case, often a doctor faces a difficult choice because aggressive tactics are not always justified (especially in young patients) and unreasonably chosen expectant tactics threaten the development of cancer. The situation is aggravated by the fact that in this issue there is no unity of opinion among doctors, nor certain generally accepted standards (Salamatty Kazakhstan 2011).

The problem of false negative cytological conclusions in the adjusted system of cytological screening is leveled by the annual repetition of the cytological smear. However, in the case of a single cytological survey (when the patient was not covered by screening before), in some cases, additional guarantees of the absence of a neoplastic process are required.

The problem of false positive and false negative cytological conclusions is especially acute in relation to cells of the glandular epithelium. While cervical adenocarcinoma may not manifest at all in the cytological smear, the reasons for the pronounced changes in the cells of the glandular epithelium (even with the cytological picture of adenocarcinoma) may be reactive processes or endometriosis (Salamatty Kazakhstan 2011).

Among experts, there is no consensus on tactics for patients who are infected with HPV strains of high oncogenic risk, but there is no dysplasia in the cytological smear. The view that it is necessary to treat all carriers and contact persons, today has already discredited itself, because most of the carriers will never get cancer of the cervix [15].

To solve these problems, the following diagnostic algorithm for the cervical disease is proposed:

Standardized collection of cellular material from the cervix; Application of liquid cytology; immunocyto chemical study of the tumor marker r16tk4a.

Each of the listed items is discussed on the following pages of the article.

Material Selection: In the absence of visible pathology from the cervix of the uterus, a scraping for cytological examination is necessarily taken.

Given the absence of visible pathology, the material is taken from the entire surface of the cervix and from the cervical canal. Due to the fact that the cancer most often develops at the junction of the flat epithelium of the cervix with the cylindrical epithelium of the cervical canal, around the perimeter of the uterine throat (the so-called transformation zone), the scraping for material selection during screening must necessarily include this zone and the epithelium of the cervical canal [16].

The use of a special tool is of fundamental importance in this case and it guarantees the material selection from all the indicated zones and ensuring the information content of the preparation. The use of adapted tools is unacceptable, as this leads to a decrease in the effectiveness of screening, up to zero results.

Liquid Cytology: More than fifty years ago, Dr. Papanikolaou, in whose name was later called the method (test), developed a method for cytological examination of cervical canal cells by a smear on glass. The test is widely used in screening studies for the diagnosis of cervical cancer, precancerous and background states. In the Nordic countries, where screening studies are well organized, treatment of precancerous conditions and early forms of cancer has reduced the mortality from invasive cervical carcinoma by 50-70%. According to published data, in Finland in 1992 the incidence was reduced to 2.8 cases per 100, 000 women. In Russia, in 1998, 11, 937 new cases were detected, which was 15.3 per 100, 000 women, of whom 6.077 died. In England, according to the data for 1987/88. The incidence rate was 9 per 100, 000 women, the death rate in 1997 was 3.7 per 100, 000. About 4 million women per year underwent cytological screening of cervical smears. At present, the identification of a risk group in the cytological examination of cervical smears during preventive examinations and further observation allows one to catch the malignant process at the earliest stages [17].

A prerequisite for an accurate assessment of the morphology of cells in the smear is a well-made and well-colored smear. The effectiveness of cytological diagnosis is largely determined by the quality of preparation. At present, a new technology of cytopreparations, so-called liquid cytology, is becoming increasingly popular. An important technological feature of the liquid cytology (LC) method, which improves the quality of the study, is that the material under investigation is taken into a special stabilizing solution that ensures its preservation without destroying and losing cells. At the same time, all cellular material retains its morphological and immunocytochemical properties without changes. For the LC method, several systems are known: Cytospin, AutoCytePrep (CytoRich), LABONORD Easy Prep, Thin Prep [18].

In the last five years, a number of studies have been carried out in different countries comparing the efficacy of conventional techniques with the use of histological examination as a "gold standard" and evaluation of cytopreparations according to the TBS classification (The Bethesda System) for confirming diagnoses. Both polyclinic and inpatient departments that examined thousands of patients participated in the study. According to generalized data, the sensitivity of the traditional method varies in a wide range of values: 34.5-89 %; And for the LC method it has more stable values: 71.495 %. Accordingly, the specificity of methods was 36-76.9 % and 58-76.2 %. The authors of the studies summarized that the LC method is a more reliable laboratory test, reduces the amount of false negative results, reduces the number of unsatisfactory drugs for analysis and the time required for the cytologist to evaluate the drug [19].

The study of Papanikolaou smears obtained by the traditional method of collecting the material shows that not all, but only 6.5 to 18% of the cells taken are applied to the smear. In addition, many of these cells due to the poor application are difficult or impossible to analyze. There is no doubt that the traditional method of analyzing the cytological smear has a high diagnostic efficiency. Nevertheless, there is an opinion that the method has from 6 to 55% of false negative results. According to the Fahey review, the sensitivity of the traditional method is 55-65% and the specificity is 65-70% [20].

The reason for the majority (about 2/3) of false results, which reduces the quality of the laboratory's work, is the mistake of taking or transferring material for the preparation of smears. The material for cytological examination is obtained from the surface of the mucous membrane. Mucus, present in the material taken, prevents transfer to the smear cells and the material cannot be evenly mixed. The material can be unevenly distributed on the glass. When the material is transferred to the glass in a traditional way, cells from the whole region of the cervix may not enter the preparation. Drying and loss of cells adhering to the instrument significantly reduces the diagnostic informative value of micropreparations. The LC method allows excluding these negative factors [21].

However, routine staining of the smears gives us information about the state of the cervix for the time being, but it is not able to assess the oncogenic potential

of changes in cases where there is no cancer. Thus, the use of a cytological method alone is not sufficient for screening cervical cancer [22-24].

The advantage of liquid cytology is that it can produce up to 5-6 "serial" (i.e. identical in cellular composition) smears from a single material selection. It makes possible to apply additional research methods. For a long time, this additional method of investigation was used to determine the DNA of the human papillomavirus high oncogenic risk. However, it is now known that screening for HPV infection performed in women of the appropriate age can identify patients with a low risk of cervical cancer in the case of a negative test, but HPV PCR is useless for detecting patients at high risk of progression. To achieve this goal, we need a test to detect the manifestation of the oncogenic potential of the virus. Thus, our attention should be transferred from agent to owner [25].

The normal cell cycle consists of G1-, S-, G2- and M- phases. The epithelium of cervix is a dynamic tissue with constant cellular renewal. The kinase, which ensures the passage of the cell from G1 into the S phase of the cell cycle, is E2F. Normally, it is inactive, being in a bound state with the protein suppressor Rb (the product of the retinoblastoma gene).

The p16 protein (INK4a) controls the disengagement of the E2F-Rb complex, preventing uncontrolled proliferation of the cell. However, the synthesis of p16 (INK4a) is normally inhibited by the feedback mechanism. Thus, the concentration of this protein in a normal cell is extremely small, which is manifested by a negative immunocytochemical reaction [26].

The E7 protein of human papillomavirus HPV of high oncogenic risk when interacting with the product of the retinoblastoma gene leads to dissociation of the E2F-Rb complex [27].

E2F remains permanently active, stimulating unrestrained cell proliferation. P16 (INK4a) tries to contain this process, which leads to its uncontrolled synthesis. However, p16 is devoid of its target, which, in the absence of feedback, significantly increases its concentration in the cell. Immunocytochemically this is manifested by a positive response, which is a biomarker for the initiation of carcinogenesis in the cervical epithelium [28].

It was reliably shown that the expression of p16 is associated with low, moderate and severe dysplasia (with intraepithelial squamous lesions of the cervix of both high and low Grade, LSIL and HSIL according to the WHO classification), with p16 expression not occurring in flat epithelium without signs of dysplasia. At the same time, although there was a clear correlation between the detection of human papillomavirus DNA and dysplasia, there was also a large number of PCR-positive HPV cases (with episomal HPV localization) in which, with subsequent histological examination, there was no precancer and cancer. This phenomenon was confirmed by a negative immunocytochemical reaction to p16Tk4a in dysplastic cells [29].

RESULTS AND DISCUSSION

Application of the HPV Test in The Primary Screening of Cervical Cancer: A review of studies conducted to assess the diagnostic characteristics of the cytological survey and HPV testing showed that:

- The sensitivity of HPV testing (88-100%) significantly exceeds the sensitivity of cytological testing (34-86%);
- The specificity of HPV testing (82-97%) is only slightly inferior to the specificity of the cytological method (78-99%);
- The sensitivity and prognostic significance of a negative HPV test in combination with a negative cytological test result are close to 100% [10].

Relatively low specificity and prognostic significance of positive results are due to the fact that in most women the HPV infection is transient. However, the rate of spontaneous elimination of the virus in women older than 30 years is much lower, which increases the diagnostic efficiency of the HPV test. On this basis, screening with simultaneous use of the cytological test and the HPV DNA test is an alternative to cytological screening in the USA for women over 30 years of age [30].

In the case of negative results of both tests, the recommended screening interval is 3 years. For women with a negative cytological test result, but a positive test for oncogenic virus types, it is recommended to repeat both tests after 6-12 months: if the result of any test is positive in a second survey, the colposcopy is indicated [8].

An important argument of the supporters of using the HPV test in the primary screening is also that the high sensitivity and prognostic significance of the negative results allow significantly increasing the screening interval for women up to 5-7 years with a negative test for HPV DNA [31].

To increase the specificity of testing for HPV, several approaches are proposed. One of them is to use the cytological method as confirming in women with a positive test for viral DNA. Another approach is to identify a persistent HPV infection by re-testing at an interval of 6-12 months. The most effective method of establishing the persistence of HPV is the genotyping of the virus, which allows differentiating persistent infection from reinfection [8]. A high viral load is also considered as one of the criteria for a clinically significant infection that can develop into the disease. To increase the specificity of HPV testing, a number of molecular markers of dysplastic changes is proposed [32]. Obviously, however, before the introduction into clinical practice, all proposed markers must undergo a thorough clinical evaluation [33].

The HPV testing plays a special role in the initial screening of cervical adenocarcinomas - rare, but especially aggressive, neoplasias. Although the etiological role of HPV in the development of this disease is unambiguously undefined, it is shown that oncogenic types of HPV are mainly found in all cervical adenocarcinomas, mainly type 18 [34, 35]. Since cytological methods for detecting atypical cells of glandular epithelium have significant limitations, the inclusion of HPV testing in screening programs can increase the detection rate of cervical adenocarcinomas and previous defeats.

CONCLUSION

The clinical efficacy of the HPV test was also shown in cases of resolving the dubious results of cytology. Usually, for women with ASC-US an immediate colposcopy or a repeated cytology test are recommended; In the second case, when the same result is obtained, the colposcopy is performed. A study conducted in the United States with a view to evaluate existing algorithms for managing patients with atypia of an uncertain value, showed that in a real clinical situation, the HPV test can detect almost all cases of high-grade cervical lesions that are "hidden" behind the cytological diagnosis of atypia of undetermined significance (5-10%).

At the same time, the number of women referred for colposcopy and histology is halved, since the incidence of HPV detection in this group of patients is 50% (for comparison, after repeated cytological testing for colposcopy, up to 70% of patients are referred).

At present, there is a great interest in the use of the HPV test to control the treatment of high-grade cervical lesions. The main prerequisite for the application of the HPV test in this area of screening is that adequate treatment of cervical lesions also leads to the elimination of the virus and a positive test for the papilloma virus can serve as an early and accurate indicator of relapse. In addition, testing for the presence of viral DNA in combination with cytology reduces the number of visits to a doctor for women with negative results from both studies. In most countries that have cervical cancer screening programs, the standard post-treatment algorithm includes cytological studies every six months for the first two years and every year for the next 5 years.

An analysis of the effectiveness of papillomavirus test to control high-level therapy showed that among women whose treatment was considered successful, 84.2% had a negative test for papillomavirus after treatment, 15.8% - positive. Relevant indicators in cases of unsuccessful treatment were 17.2 and 82.8%.

At the present time, an algorithm with simultaneous application of the cytological test and the HPV test is proposed for consideration. It is expected that testing will be more reliable, since the test for viral DNA is more sensitive than the cytological method and the detection of the virus after treatment is associated with the risk of the disease recurrence.

Tests for detection and genotyping of HPV, based on methods of hybridization and polymerase chain reaction (PCR), began to be used more than 10 years ago. To date, a large number of methods for detecting and genotyping HPV have been described in the literature, however, it is obvious that only standardized tests meeting the specified sensitivity and specificity requirements and having passed clinical approbation can be used in screening programs.

In economically developed countries, commercial tests based on PCR and/or hybridization are recommended and successfully used to detect HPV of high carcinogenic risk and virus genotyping:

- Hybrid Capture 2 (Digene) - to detect 13 types of high-risk HPV;
- Amplicor® Human Papilloma Virus Test (Roche) - to identify 13 types of high-risk HPV;
- InnoLiPA HPV genotyping (Innogenetics) - to identify and differentiate 25 types of HPV;
- Linear Array HPV genotyping test (Roche) - to identify and differentiate 37 types of HPV.

HPV-tests are also developed and implemented on the basis of new technologies:

- Real-time PCR is a method for determining the concentration of a virus in the cervical epithelium; it is used in the Cobas TaqMan HPV test (Roche);
- NASBA (Nucleic Acid Sequence-Based Amplification) technology is used in the PreTect HPV-Proofer (NorChip) test to detect the full-length mRNA of the E6 and E7 HPV genes, whose presence in the clinical material is thought to be associated with an increased risk of neoplastic progression. The test is based on the amplification of RNA and is designed to detect the mRNA of five oncogenic HPV types (16, 18, 31, 33 and 45).

However, the high cost of these tests and equipment for their implementation, as well as the complexity and length of the analysis makes it difficult to widely implement them in the screening program in Kazakhstan. The standardization of domestic HPV tests will allow them to be used in the future as an inexpensive alternative for screening studies.

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