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Kattakhodjaeva Mahmuda Hamdamovna
doctor of medical sciences, professor
Karshieva Elnora Elbekovna
Independent researcher
Toshkent Davlat Dental Institute

MODERN CONCEPTS ABOUT ETIOPATHOGENETIC ASPECTS OF PRECANCEROUS CERVICAL DISEASES APPEARANCE (LITERATURE REVIEW)

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ABSTRACT

This paper presents data on the etiopathogenetic mechanisms of emergence and development of precancerous cervical diseases. This review covers the latest data from epidemiological studies, molecular research methods and histological methods. It also presents data on the etiology of precancerous cervical disease - Chl. Trachomatis and the effect of nicotine on the course and condition of the disease. Several serotypes of cervical precancerous lesions were detected based on microbiological methods of research, which also reveals the mechanisms of occurrence and course of cervical precancerous lesions.

Keywords: human immunodeficiency virus; cervical precancerous disease; dysplasia; molecular mechanisms.

Каттаходжаева Махмуда Хамдамовна
д.м.н, профессор
Каршиева Эльнора Элбековна
Независимый соискатель
Тошкент Давлат Стоматология институти

СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ ОБ ЭТИОПАТОГЕНЕТИЧЕСКИХ АСПЕКТАХ ВОЗНИКНОВЕНИЯ ПРЕДРАКОВЫХ ЗАБОЛЕВАНИЙ ШЕЙКИ МАТКИ (ОБЗОР ЛИТЕРАТУРЫ)

АННОТАЦИЯ

В данной статье приводятся данные по этиопатогенетических механизмах возникновения и развития предраковых заболеваний шейки матки. Представленный обзор охватывает последние данные эпидемиологических исследований, данные молекулярных методов исследований и гистологических методов. Также приводятся данные по этиологии предрака шейки матки - Chl. Trachomatis и влиянию никотина на течение и состояние данного заболевания. Обнаружено несколько серотипов предрака шейки матки по данным микробиологических методов исследований, что также раскрывает механизмы возникновения и течения предрака шейки матки.

Ключевые слова: предрак шейки матки; дисплазия; молекулярные механизмы; вирус иммунодефицита человека

Kattaxodjaeva Mahmuda Hamdamovna
Tibbiyot fanlari doktori, professor
Qarshieva Elnora Elbekovna
Mustaqil tadqiqotchi
Toshkent Davlat stomatologiya institute

BACHADON BO'YNI O'SMA OLDI KASALLIKLARINING KELIB CHIQISHIDA ZAMONAVIY ETIOPATOGENETIK ASPEKTLAR HAQIDA TUSHUNCHA (ADABIYOT SHARHI)

ANNOTATSIYA

Ushbu maqolada bachadon bo'yni saraton kasalliklari paydo bo'lishi va rivojlanishining etiopatogenetik mexanizmlari to'g'risida ma'lumotlar keltirilgan. Ushbu sharh epidemiologik tadqiqotlarning so'nggi ma'lumotlarini, molekulyar tadqiqot usullari va gistologik usullarning ma'lumotlarini o'z ichiga oladi. Shuningdek, u bachadon bo'yni o'sma kasalligi etiologiyasi to'g'risida ma'lumot beradi - Chl. Traxomatis va nikotinning ushbu kasallikning borishi va holatiga ta'siri. Mikrobiologik tadqiqot usullari bo'yicha bachadon bo'yni saratonining bir nechta serotiplari topilgan bo'lib, ular bachadon bo'yni saratonining paydo bo'lishi va rivojlanish mexanizmlarini ham ochib beradi.

Kalit so'zlar: bachadon bo'yni saratoni; displazi; molekulyar mexanizmlar; OITS virusi

Relevance. The first studies on the epidemiology of cervical cancer were published back in the nineteenth century Rigoni-Stern in 1842. They published the results of the study of causes of death in 1760-1830 in Verona. He noted that cervical cancer is more common in married women and widows and that nuns and virgins have almost no cervical cancer. This fact led the scientist to conclude that cervical cancer may have an infectious origin. Later, F. Gagnon (1950), studying medical records in Montreal and Quebec, discovered that nuns had almost no cervical cancer. F. Gagnon associated this fact with low cervical inflammation in nuns [4,8,9,16]. Virgins of the cervix have been confirmed histopathologically and cancer is extremely rare. Many epidemiological studies have focused on the role of cervical cancer, early sexual debut, early pregnancy, frequent change of sexual partners, and sexually transmitted infections.

Research objective. To study the emergence and development of precancerous diseases of the cervix and to generalize data on the etiopathogenetic mechanism of their occurrence.

Patients with cervical cancer, in comparison with the control group, started sexual life earlier [2, 7, 12]. Often, change of sexual partners and first childbirth at a young age play a negative role in the emergence of cervical cancer [12,14,16].

A number of epidemiological and clinical and statistical studies demonstrate the role of poor socioeconomic status and low educational attainment [8,11,13]. On the contrary, other authors believe that cervical cancer, education and economic situation are not important [6,14,15,16].

The carcinogenic effect of abortion is the mechanical trauma of endocervix with subsequent infection. The trauma of the cervix and its further deformation is the cause of damage to the physiological barrier. Cervical mucus is not trapped in the channel, which is accompanied by a decrease in local immunity and further infection [7,9,10,14]. Lesions with a high risk of cervical cancer often form tension and ectropionics against the background of the cervical scar. Disruption of innervation, reception and cervical tropism leads to birth trauma (abortion) [8].

Oral contraception, especially in the presence of cervical infection, correlates with cervical ectopy [6,7,10,11]. This increases the risk of adenocarcinoma in drugs and metaplasia is detected.

The infection process after an injury is very important in the pathogenesis of cervical cancer [5,6,12]. Appleby P. and others believe that the use of hormonal contraceptives does not affect the

development of dysplastic processes and cervical cancer. There is a correlation between hormonal, immunosuppressive therapy and cervical cancer [13,15,16].

The impact of tobacco smoking on the risk of malignancies has been carefully studied. The results of epidemiological and experimental studies have recognized that tobacco smoking is a carcinogenic factor for humans and is a risk factor for cancer of any localization [10].

The dependence of cervical cancer and intraepithelial neoplasia on smoking has been revealed.

Smoking plays the role of carcinogenesis promoter in cervical epithelium infected with HPV, especially in flat cell cancer [11]. Intensive smoking reduces immune protection, and nicotine plays a co-carcinogenic role in promoting the carcinogenic effects of viral infection in CIN and cervical cancer. Studies have found nicotine and its derivatives in the cervical mucosa, and smoking-related damage to the DNA of the cervical epithelium has been found [11,12,14,16] by Appleby P. et al. (2006), Gadducci A. et al. (2011) believe that nicotine acts as an accompanying carcinogenic factor [11,14]. In urogenital chlamydia occurs flat cell desquamation of the cervical epithelium with the formation of right or pseudo-erosion, marked edema, swelling of the mucous membrane abundant blood supply, tissue looseness, which creates favorable conditions for infection with HPV, associated dysplasia and cervical cancer [1,5,8,9,10]. Chl. Trachomatis is an obligate intracellular parasite, has tropism to the cylindrical epithelium, forming a primary lesion of the mucous membrane of the cervix, where it can persist for a long time, causing various pathological changes in the endocervical. International studies have found that women with similar risk factors for cervical dysplasia are often found in people infected with the immunodeficiency virus. Cervical injuries are an etiological factor in the metaplastic process of the cervix. Cervical injury is not an etiological factor of carcinoma but is itself a subsequent chronic infection. 83% of cervical lesions accompanied by inflammatory processes. Urogenital trichomoniasis causes a slow inflammatory process on the mucous membrane of the cervix. Toxic effect of trichomoniasis on the cells of the epithelium, provoking disruption of epithelial maturation and its partial destruction.

Chronic cervical erosion by trichomonade and their etiology in the presence of additional risk factors capable of malignant transformation [12].

Role of HPV as a carcinogenic factor in intraepithelial neoplastic processes. Viral etiology of neoplasia is the most complicated issue of modern oncology. In most cases, neoplasia cannot be associated with carcinogenic factors. The viral etiology of cervical cancer is closely related to studies of different localizations. The first time Rigoni-Stern suggested the theory of the infectious origin of cervical cancer in 1842. For the first time in 1903, Borrel and Bosk proposed a theory of the viral origin of tumors, Rous, Kidd (1938), Friedewald (1941) believe that viruses increase the effect of carcinogenic factors.

Data from experimental studies of virileology first obtained by L.A. Silber (1945) and then by Horsfall (1963) and Southam (1964) suggested that viruses act on the gene of normal cells and affect the conversion of cells into cancers. The role of viruses in cancer transformation is different from that of viruses when an infection occurs. After the transformation of normal cells into a tumor, viruses do not influence the reproduction and growth of the tumor (9, 12,13,16). The central etiological factor for intraepithelial cancer and precancerous tumors of cervical lesions is HPV with a high carcinogenic risk (6,7,8,9). HPV is a group of viruses that confirms their inducing role in human tumor formation in vivo [11,16].

In dysplasia and cervical cancer, the genetic material HPV is detected in 90-95% of samples. Currently, more than 79 types of HPV are known to possess their specific properties [13,14].

More than 30 types can infect reproductive tract [11, 12] All types of HPV associated with neoplasia can be roughly divided into 2 groups: The "high risk" found in malignant tumors and the "low risk" found in benign cervical lesions and rarely in invasive cancer. High-risk viruses are HPV16,18,31,33 which increase the risk of cervical cancer by a factor of 20-150, and HPV-6,1 [13,14] and "low risk".

Persistent infection mediated by HPV-KR increases the risk of cervical cancer (cancer) by a factor of 10-20 and the onset of severe intraepithelial cervical neoplasia by a factor of 100 in

uninfected women [6,8,14,15]. Studies show that women infected with oncogenic HPV types have a risk of progression of pre-existing low-level intraepithelial dysplasia (LSIL) to severe (HSIL) [1,4,6 12,13]. According to Guan P. (2012), Daily L.R. (2014), LSIL and HSIL are significant markers for oncogene infection and complete HPV [5,6,7]. At the same time, the validity of the diagnosis of precancerous lesions and cervical cancer in HPV-infected patients requires additional extensive examination [10, 11].

The lifetime risk of HPV infection ranges from 50-90% [9]. Infection occurs in most cases soon after the sexual debut [1], the peak of which was recorded in women younger than 25 [4]. However, with the integration of episomal HPV patients of this age, the virus is eliminated in most patients with HPV [7]. Progress of chronic infection to the condition of different localization. The first time a malignant neoplasm passes through some intermediate stages usually takes 10 to 20 years [10,12]. In the primary role of HPV in the development of cervical neoplasia and the high prevalence of this infection in the population, HPV screening is an essential area of early diagnosis of socially significant cervical diseases [8, 9, 10, 13]. The widespread detection of HPV in the population without regard to the nature of the course of infection leads to an erroneous diagnosis and determines the overly aggressive therapeutic and surgical tactics of a gynecologist and oncologist [4,5].

Of particular importance are various retrospective and prospective studies aimed at revealing the importance and interrelation of new risk factors affecting the persistence of HPV [2,4,5]. According to M.S. Afanasyev (2004), papillomavirus infection in the form of mixed associations is found in 71% of cases. Most often accompanied by bacterial vaginosis (26.6%), candidiasis vulvovaginitis (32%), herpes virus (18.4%), mycoplasma (18.1%) and chlamydia (18%), which affect the genital tract, cause a background of vaginal microflora changes, is characterized by a decrease in the frequency and number of obligate representatives and excessive growth of opportunistic vaginal biocenosis [10,12].

To establish the theory of "virus is an etiological factor", several factors must be combined:

1) a continuously integrated or episomal form of DNT virus is detected in tumor cells;

2) viral genes cloned in vitro may be capable of nascent malignant tumors;

3) a regular expression of the viral gene in tumor cells;

4) in nature, similar viruses that cause tumors should also be detected;

5) epidemiological studies must prove the relationship between the tumor process and the identified genetic material of the virus [1,3,4,5].

In cervical cancer, cell transcriptions of the viral genome are very important, and preservation of the viral genome plays an important role in the proliferation of cells of cervical cancer [15].

The process of HPV replication and the subsequent transformation of cells induced by it are in some way related to the process of epithelium differentiation. The production of cellular growth factor stimulates the expression of E6 and E7 genes and the proliferation of the epithelium. Differentiation and maturation of flat epithelial cells are absent due to the suppression of native protein shell synthesis. Cellular renewal of the epithelial layer is also impaired in the subsequent stage of infection, which is based on proliferation and structural reorganization of epithelial cells at the beginning of basal and parabasal layers [2,5,9,14]. Modern molecular genetic studies using PCR 95-100% of cases of cervical cancer cells are detected by the virus genome [5,6,8,9]. At present, more than 100 types of HPV have been detected; more than 70 of them have been studied and described in detail. Some types of human papillomavirus were found to infect only certain types of epithelium causing characteristic changes. There are many works devoted to the detection of different variants of virus genotypes and malignant transformation of cervical warts [2,6].

Of all types of the virus, only 34 human papillomas affect the anogenital zone. HPV affects the basal layer of the flat epithelium (mainly affects the transition zone of the flat epithelium into the cylindrical epithelium).

Kurtz (1993) and Schiffman (1994), pathomorphological changes caused by the papilloma virus and classified as 1) benign atypia; 2) LSIL (Low-grade - Flat intraepithelial lesions) or CIN-I

(cervical intraepithelial neoplasia) - mild dysplasia of the flat epithelium without signs of colocytosis; 3) HSIL - (High Degree Flat Intraepithelial Lesions) or CIN-II-Medium Dysplasia; 4) Severe Dysplasia or Intraepithelial Cancer (in situ) - CIN-III (1,5,6,7)

The discussion on the classification of dysplastic and preinvasive cancers continues to this day. Dysplasia by the degree of severity is divided into three degrees and intraepithelial cancers are separated into a separate group [10]. The groups of dysplasia based on virological and pathomorphological criteria are not homogeneous.

It is not certain that dysplasia of different degree is a sequential stage of carcinogenesis [16].

The oncogenic potential of different types of HPV in terms of ability to cause dysplastic processes and cervical cancer in low and high risk groups. Depending on the power of transformation, the types of HPV cancers are 6.11, 42, 43, 44 low, while 16, 18, 48, 56 types of high-risk groups. Types HPV 6 and 11 contribute to the emergence of spiky condoms in mild to moderate dysplasia is very rare in cervical cancer. In cervical cancer HPV types 16 and 18 are most often detected, with HPV 16 50-70%, HPV18 10-20%, other types of HPV are extremely rare [2,4,6,8] HPV 16 type 21% of cases are found with CIN-I, 57% of cases - with CIN-II-III. HPV 16 and 18 types 67-93% of cases are associated with cervical cancer type 18 occurs twice as often as type 16 (11,13) HPV 18, associated with adenocarcinoma, has a high oncogenic potential, the tumor is rapidly progressing, and usually, the differentiation of the tumor is low, the prognosis is usually poor (11,13). HPV is widespread and has high oncogenic potential (11). The team of authors believes that the single effect of the papillomavirus in cells is not sufficient for cancer development. When HPV-dependent carcinogenesis requires additional cofactors. Factors such as immortality and transformation, which ensure cell division and differentiation, are also involved in the process of carcinogenesis [1,4,6] Some authors believe that HPV viruses increase cervical proliferative activity, violate the apoptosis mechanism, change the genetic code of epithelium and are additional carcinogenesis of the cervix [4,7,8] Risk factors are: not an etiological factor for cancer development, together with some other factors increases the risk of cancer. For a carcinogenic factor to work, it is necessary to influence additional exogenous and endogenous factors [2,6,7].

HPV infection and cervical dysplastic processes are related to sexual life, education and the effectiveness of the screening program [1,11,16]. Thus, all risk factors can be divided into two groups - controlled and uncontrolled risk factors [9,12].

Controlled risk factors include early onset of sexual activity (up to 17-18 years of age), frequently changing sexual partners and multiple sexual partners (3 or more) [4,6] disorderly sexual intercourse increases the risk of infection and dysplastic processes, thereby increasing the risk of cervical cancer by a factor of 5-7.5 [11,12]. Dysplastic processes occur mainly in married women, especially those born again. Uncontrolled risk factors include genetic changes.

Morphological foundations of cervical cancer pathologies. Numerous clinical studies confirm that the transformation of the normal cervical epithelium into cancer can be diagnosed in advance by special methods. Only 2-11% of cancer cases occur in intact epithelium [2, 6, 10].

In order to understand the pathological process of processes, it is necessary to know the normal histological structure of endo and ectocervical. Normally, the mucous membrane of the cervix consists of the cover epithelium and stroma. In the vaginal part of the cervix of women of reproductive age, age consists of an unroot, highly differentiated flat epithelium with complex functional features. The multi-layer covering flat cervical epithelium has 4 layers: superficial, intermediate, parabasal and basal [1,5,7].

The surface layer cells are polygonal with clear contours. Cell diameter is 35-50 microns; the edges of the cytoplasm are sometimes curved. The nuclei are small in size, laid out in the center, with painted cytoplasm. Surface layer cells are easily peeled, intermediate layer cells are round and oval, less surface layer of cells (20-35 microns), cytoplasm, on the contrary, more than surface layer cells, more basic than their cells. The cell nucleus is larger than the surface layer cells. Cells are mostly found one by one. Parabasal cells of 15-18 microns in size, with transparent borders, in cytological preparations are revealed in pre- and postmenopausal period. Cell cytoplasm in the form

of a thin basophilic bezophile, strongly colored. The cell nucleus is located in the center. Cells are mostly located alone, very rarely in groups.

Cells of the basal layer are 15-20 mm in size, mostly rounded, sometimes oval cells. Cell nuclei are large, intensely colored, surrounded by a thin border of basophilic stained cytoplasm [4,5,6,8]. The ratio of epithelium cells to layer change depending on age, the phase of the menstrual cycle of a woman. Women in the pre-menstrual and post-menstrual periods are mainly found in cells of the intermediate, parabasal and basal layers. Fragments of the flat epithelium, red blood cells, leukocytes and single neutrophils can also be found in the smears. Sometimes epithelial cells of the upper parts (endometrium, uterine tubes) of the genitals, epithelial cells, various bacterial flora, sperm cells. In smears from the cervical canal cells of the cylindrical epithelium are found. In pathocytological smears on cells of cylindrical form and epithelium of rounded shape and are located in complexes. The appearance of the epithelium depends on the projection of the cell in cytological smears. Epithelial cells of the cervical canal in the lateral projection of a rectangular shape with uneven fields. Cell nuclei are round or oval, basophilic. Cell cytoplasm in the form of a thin edging is located at the base of the cells. When the study of single-layer formation on the top or bottom of the cells, tightly adjoining each other cells resemble honeycombs. The cell nucleus is in the center of cells [6,7,9].

The type of invasive cancer is flat cell cancer with cornification, flat cell cancer without cornification, adenocarcinoma, dimorphic flat cell carcinoma and undifferentiated cancer [4,5,7].

Background diseases that create a background for cancer development contribute to the process. In many untreated cases, precancerous diseases develop into cancer [3,5,7].

According to many authors, the process of malignant transformation of the cervical epithelium goes through several successive stages - dysplasia, in situ cancer, invasive cancer. In some cases, in dysplasia without progressing to the stage of in situ cancer, invasive cancer develops.

Conclusions: Summarizing the above, we can say that the etiopathogenetic mechanisms of emergence and development of precancerous diseases of the cervix are not fully understood and require further in-depth study.

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