Реферати

ИСПОЛЬЗОВАНИЕ ЗДОРОВЬЕСБЕРЕГАТЕЛЬНЫХ ОБРАЗОВАТЕЛЬНЫХ ТЕХНОЛОГИЙ В ПРОФЕССИОНАЛЬНОЙ ДЕЯТЕЛЬНОСТИ ВРАЧА СЕМЕЙНОЙ МЕДИЦИНЫ

Емец А.В.

Анализ исследований при подготовке специалистов семейной медицины осуществляется на основе инновационных подходов. В тоже время исследования проблемы укрепления здоровья, формирование у них культуры здоровья с помощью здоровье-сберегательных образовательных технологий свидетельствует о попытках ученых обосновать теоретико-методологические и методические мероприятия определенного феномена, определить понятие терминологического спектра данной проблемы, выяснитьпути ее решения в современных социокультурных условиях.

Ключевые слова: семейная медицина, здоровье сберегательные технологии.

THE USE OF HEALTH SAVING EDUCATIONAL TECHNOLOGIES IN PROFESSIONAL ACTIVITIES OF DOCTOR OF DOMESTIC MEDICINE

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Analysis of research in the training of specialists in family medicine is based on innovative approaches. In too time of research of problem of strengthening of health, forming for them cultures of health bymeans of health saving educational technologies testifies to the attempts of scientists to ground the theoretical, methodological and methodical measures of a certain phenomenon, define the concept of terminological spectrum of this problem, to find out ways of her decision in modern sociocultural terms.

Key words: family medicine, health saving technologies.

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CERVICAL CANCER: TRIGGERING FACTORS

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The relevance of the study of cervical carcinogenesis is due to the high incidence of the papillomavirus infection among young women (up to 95%), which oncogeneicity has been proven to date. The **purpose** of the present study was the analysis of the findings of recent studies on the triggers of cervical cancerogenesis. The author emphasizes the findings of immunocytochemical study of cervical cells for the detection of toll-like receptors (TLR 3,4,7,8), nitric oxide synthase (iNOS), the NF-kB p 65 transcription factor, which are the controllers of the cellular cycle. The dysfunction of these enzymes leads to carcinogenesis. The analyzed publications indicated that the TLR 3, 4, 7, 8, iNOS and NF-kB p 65 expressions in the epithelial cells of cervical cancer significantly exceeded the one in the benign HPV-cells and disease-free specimens ($p<0,005$). Thus, the TLR/NO signal path is involved in the pathogenesis of cervical cancer and is subject to study. Another point of the presented review is the effect of the folates on DNA-methylation and the expression of tumor suppressor of the FHIT (Frigile Histidine Triad) protein, which inhibits the cervical neoplasia. The studies were conducted on the CaSki (16 HPV-positive) and C33A (16 HPV-negative) cellular lines in women with CIN and carcinoma. It has been established that the higher the grade of the cervical lesions the more elevated the level of FHIT-methylation was, whilst the level of the RBC folate was decreasing. Thus, the deficiency of folates is one of the links of cervical carcinogenesis that should be considered by clinicians. The publications also reported on the HPV–L1capsid protein as a marker of the tension of the local cervical immunity, induced by the HPV infection. The capsid test in combination with and quantitative HPV-test of cervical specimens can be used as a criterion for the effectiveness of conservative therapy in CIN.

Keywords: cervical cancerogenesis, toll-receptors, nitric oxide synthase, folates, papillomavirus.

Nowadays, cervical cancer (CC) is regarded as one of the most common cases amongst all gynecologic malignant tumors worldwide, thus, obtaining the top place in this category of oncologic diseases accordingly. The incidence rate of CC is accounted for 2,1 per 100 000 women (in Western Europe) and 20 per 100 000 (in Eastern Europe and Central Asia) [7]. Approximately 50% (12 700 among 25 700 women) with CC die every year in these regions [24]. The aim of the present study was the analysis of the findings of recent studies on the triggers of cervical cancerogenesis. Human papillomavirus (HPV) is the main factor for triggering the CC and has been widely studied worldwide [24]. Since HPV is a sexually transmitted infection (STI), CC is classified as a preventable disease, thereby, targeted educational sources available for all layers of the population, timely screening and appropriate interventions were found to be perfect tools in the reduction of the burden of CC. There is a consistently uneven pattern affiliated with the scope of screening, early diagnosis, and timely cure stipulated by numerous issues, thus, screening rates are conducted less frequently in low socioeconomic and low resource regions taking into account certain ethnic and age variations. For instance, black American females tend to develop advanced stages of CC more often than their white counterparts due to their ethnic and cultural peculiarities. While handling CC, there are two certain interventions distinguished, and affiliated with primary and secondary prevention. The term "primary prevention" of the CC implies the implementation of national programs for vaccination against HPV in

adolescents before sexual intercourse, as well as awareness of parents and adolescents about the advisability of this vaccination.

The year 2006 was marked by a breakthrough in oncological practice, due to the fact that the vaccination for CC has become available. To date, two vaccines are used: the quadrivalent vaccine Gardasil (Netherlands) and the bivalent Cervarix vaccine (Belgium). The composition of the vaccines includes the purified structural proteins HPV L1, which form the type specific for HPV virus-like particles [2]. It is well known that vaccines induce the formation of virus neutralizing antibodies that attach to the virus capsid and block the penetration of the virion into the host cell [20]. In this case, protection against the virus is induced by the incorporation of class G immunoglobulins. It has been reported about an increase in IgA and IgG levels after vaccination of women with persistent form of latent papillomavirus infection of the cervix [2, 4]. Therefore, HPV immunization lowered CC death rates in the low-income countries where routine screening is not available or rare but yet has not become a common practice and has not acquired wide approval amongst women [9]. Secondary prevention of CC is the conduct of adequate screening, which consists of a PAP test and a HPV test. The combined (co-test) has almost 100% sensitivity to CIN. Cervical screening is needed at least once every 3 years for women aged 21-65 years. The conduct of cervical screening and the interpretation of its results should be brought into line with national consensus. Correct cervical screening can reduce the frequency of squamous cell cancer of the cervix, but does not affect the incidence of adenocarcinoma, so it is necessary to use as a screening biomarkers p16 and Ki67, liquid cytology, the viral capsid L1 (capsid-test), quantitative papillomaviral load of cervical mucosa [3, 23]. The scientific world has moved far enough in the researches connected with the determination of the ways of CC development and identification of the most probable causative factors in CC pathogenesis. As it was mentioned before, HPV plays a pivotal role in the mechanism of oncogenesis in cervical epithelium. Let's consider some of them.

The L1 capsid protein is a viral nuclear protein that encapsidates the HPV DNA to build new infectious particles. Previous studies in the immune-competent patients have shown that detectable L1 protein in Low grade squamous intraepithelial lesion smears is associated with remission in 60-75% of cases [11]. Immunocytochemical detection of HPV-L1 pritein could present prognostic information about the evolution of early dysplastic cervical lesions and can be useful in predicting their oncogenic potential [25]. The HPV L1 protein expression is closely related to spontaneous regression of the disease. But HPV-16 infection is related to persistent disease or progression to high-grade lesions in patients with CIN1 [28]. The combination of HPV L1 and p16INK4a has been a higher diagnostic accuracy than L1 or p16INK4a alone in diagnosis of cervical lesions [12]. In this study, 52 patients of reproductive age with papillomavirus infection and precancerous changes in the cervix were involved. The standard survey included standard cervical screening, an additional quantitative HPV test and an immunocytochemical test for the viral capsid protein L1. The examination was carried out twice: before treatment and after conservative medical treatment before surgery.

The efficacy of anti-inflammatory and immunotropic therapy as preoperative preparation was assessed. It was found out that in 67.6% of cases the viral load of HPV of cervical tissue increased after immunomodulation. At the same time, the CIN morphological regression in 56.5% and the positive L1 test in 69.6% were recorded, which indicates the natural clearance of HPV, and therefore the positive therapeutic effect of conservative preoperative therapy. Thus, the capsid L1-test and quantitative HPV-test should be included in the management plan of patients with CIN, in order to avoid unreasonable surgical manipulations [3]. Autoimmune protection provides the elimination of HPV in the carriers of the virus to 90%. The carcinogenic potential of HPV is realized only in 1% of infected patients [10, 17]. Given the obligate epitheliality of HPV, the cellular immunity of peripheral blood is not regarded as leading in antiviral protection. [21]. Attention is focused on the role of congenital local immunity associated with the mucous membrane of the cervix. Therefore, exploring the role of local cervical immune regulation factors in HR-HPV infection is of great significance and clinical value. Toll-like receptors (TLRs) are the most distinctive pathogenic pattern recognition receptors involved in the defense against infection in humans. In addition, TLRs are widely expressed in a variety of human malignant tumor tissues [1].

In recent years, the microenvironment of tumors has become hot topic in cancer research. Nitric oxide (NO) is one of the key components in tumor microenvironment formation caused by a chronic infection [29]. Indicated nitric acid oxide synthase (iNOS) is the main enzyme for synthesis from NO. This enzyme is highly expressed in many species. Malignant tumors, leading to catalytic synthesis, have a large amount of NO. In turn, NO promotes tumor angiogenesis, as well as invasion of tumor cells and metastases [13, 29].

Indeed, high expression of iNOS in cervical cancer positively correlates with tumorigenicity and lymph node metastasis [6]. The binding of TLR to its specific ligand shown for triggering the signal transduction cascades, activates nuclear factor kappa B (NF-κB), regulate iNOS and mediate. There is no secretion through the factor of myeloid differentiation 88 (MYD88) or supporting TIR adapter interferon-β

(TRIF) [27]. But, TLR / NO signaling pathway involved in pathogenesis of cervical cancer caused by infection with HR-HPV remains unclear. This study aims to investigate the role of TLR / NO a signaling pathway in HR-HPV-positive cervical cancer. Immunocytes and epitheliocytes of the female reproductive tract express "surprising" signal Toll-like receptors (TLR) [14, 17]. Each of the TLR binds to a specific ligand after it enters the cell. The recognition of bacterial structures occurs through the activation of TLR 1, 2, 4, 5 and 6, nucleic acids - TLR 3, 7, 8 and 9, proprietary and single-stranded viral RNA - TLR 7 and 8. TLR 3 plays a key role in the antiviral immune response, which is able to recognize double-stranded RNA viruses [5, 6, 13, 29, 30]. Recent studies have shown that TLR also play a role in the onset of tumor processes [14]. The expression of the mRNA of all 11 TLRs was detected in the cervical cancer cell line HeLa. It has also been shown that the expression of TLR5 and TLR 9 progressively increases depending on the degree of cervical dysplasia, reaching a maximum in cancer invasion [15] and can be used as a marker of squamous cell carcinoma of the cervix. It is known that Toll-receptors take an active part in the elimination of HPV from the body, but the human papillomavirus in the process of evolution has acquired the phenomenon of "escape" from the immunological defense of the human body. There are studies that show that type 16 HPV inhibits the expression of Toll-like type-9 receptors on epithelial cells and dendritic cells, and the presence of certain polymorphic loci of TLR9 gene (A2848G) and TLR3 (Phe-412 Leu) predisposes to chronicization of the process [18]. As a result, therapeutic vaccines loaded with adjuvants capable of activating Toll-like receptors expressed on the surface of dendritic cells have been developed. Developed and introduced therapeutic vaccines [4]. There are new tests that claim that HPV may switch on TLR /nitric oxide (NO) signaling pathways. The tests were conducted on the three categories of patients: HR-HPV-positive females and CC, HR-HPV-positive patients with an intact cervix and HR-HPV-negative controls. Quantitative reverse transcription PCR was employed as the method for the detection of expressions of key TLR/NO pathway genes (TLR3/4/7/8, NF-B p65, and iNOS) in the epithelial cells of the cervix. It was distinguished that NO concentration in cervical canal of CC group was found to be substantially higher than in the rest categories of subjects. Positive rates of iNOS in cervical tissues in the CC group, HR-HPV group, and controls was reflected in the proportion of 72,1%, 28,2%, and 3,1%, accordingly. Also, CC group produced higher levels of TLR3, TLR4, TLR7, TLR8, NF-B p65, and iNOS in cervical epithelial cells than in other categories of patients. Having weighed all obtained data, it was inferred that TLR/NO signaling pathway may be considered as an important pathogenetic factor of CC developed on the background of HR-HPV infection [18, 19].

It is a well-known fact that aberrant DNA methylation is detected in various types of human cancer. Thereby, folate plays a pivotal role in the growth and sufficient division of cells as it is directly involved in methyl groups' supplementation for DNA methylation reactions. Thus, fragile histidine triad (FHIT) is considered to be a neoplasm suppressor gene that is in majority of cases silenced in CC and precancer pathologies. Another research studied promoter hypermethylation in CC together with its epigenetic silencing at mRNA/ protein levels. There was a hypothesis claiming that all changes in folate intake provoking modulation of DNA methylation may be determined as a close connection with malignant tumors genesis.

The main purpose of the given research was to estimate the impact of folate on FHIT gene methylation and expression in the course of cervical malignant neoplasm. There were women selected for the tests in which, red blood cell (RBC) folate levels, FHIT gene methylation status, and mRNA and protein expression levels were examined. Amongst the subjects, there were females with the normal cervix (NC), those with cervical intraepithelial neoplasm (CIN1, CIN2-3) and cervical squamous cell carcinoma (SCC) sufferers, accordingly. The methylation status of FHIT gene and its mRNA and protein expression levels were determined in CaSki (HPV16 positive) and C33A (HPV16 negative) CC cells that underwent cure with various concentrations of folate [8, 19]. Thus, obtained outcome allowed underlining the fact that FHIT gene methylation rate enhanced with the aggravation of cervix pathology, meanwhile, RBC folate levels, FHIT mRNA, and protein expression levels declined. Hence, on the background of growing concentration of folate, the proliferation inhibition rate, apoptosis rate, and FHIT protein and mRNA expression levels went up, on the other hand, the scope of FHIT gene methylation steadily went down in CaSki or C33A cell lines. Basing on the results of the given experiments, it can be inferred that folate deficiency, FHIT gene promoter hypermethylation and decreased expression were closely affiliated with CC. The most important findings here is the proof of the fact that folate was responsible for the enhancement of apoptosis and inhibition of the cervical cell growth, being involved in FHIT gene methylation control and expression. To sum up, corresponding intake of folate supporting natural DNA methylation status is an efficacious approach in the prevention of CC; furthermore, the treatment based on demethylation may lead to the development of a new strategy for CC therapy [18, 19]. Therefore, taking into account the analysis of the publications, new trends in the diagnosis and prevention of cervical carcinogenesis can be identified. It is advisable to use immunochemical testing of cervical cells for TLR 3,4,7,8, p65 and iNOS as a marker of cervical malignancy,

and the TLR / NO signal pathway should be considered a pathogenetic factor of carcinogenesis in the presence of HPV infection. The test for the viral capsid protein L1 is considered as a marker of local immunity of the cervical mucosa infected with VC-HPV and, accordingly, as a marker for the progression of precancerous changes in the endothelial and ectocervix. A capsid test in conjunction with the quantitative viral load of cervical specimens can be used not only to differentiate the degrees of cervical intraepithelial lesions, but also as a measure of the effectiveness of conservative cervical precancer therapy.

***Perspectives of further research**. An in-depth study of the pathogenesis of cervical carcinogenesis needs to be continued because there is no single view of the management of patients with cervical pathology, whose malignancy is increasing and "getting younger".*

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Реферати

ЦЕРВІКАЛЬНИЙ РАК: ТРИГЕРНІ ФАКТОРИ
Крутікова Е. І.

Актуальність вивчення пускових механізмів цервікального канцерогенезу зумовлена високою частотою папіломавірусної інфекції серед молодих жінок (до 95%), онкогенність якої доведена на сьогодняшній день. Проаналізовані джерела вказували на експресію TLR 3, 4, 7, 8, iNOS и NF-kB p 65 в епітеліоцитах раку шийки матки, яка значно перевищувала аналогічну в доброякісних клітинах-носіях папіломавірусу і здорових зразках (p<0,005). Сигнальный шлях TLR/NO залучений у патогенез цервікального раку і підлягає вивченню. Наступний аспект даного огляду присвячений впливу фолатів на ДНК-метилювання і експресії пухлинного супресору білка FHIT (Frigile histidine triad), який пригнічує неоплазию шийки матки. Дослідження проводились на клітинних лініях CaSki (HPV 16 позитивних) та C33A (HPV 16 негативних) жінок з CIN та карциномою. З'ясовано, що при підвищенні тяжкості ураження шийки матки відповідно підвищувався рівень метилювання FHIT, тоді як рівень фолату ерітроцитів (RBC) знижувався. Тобто, дефіцит фолатів являється одним із ланчюгів цервікального канцерогенезу, що необхідно враховувати клініцистам. Наведені також дані про капсидний білок HPV–L1, як про маркер напруження локального цервікального імунітету на фоні папіломавірусної інфекції. Капсидний тест у купі з кількісним HPV-навантаженням цервікальних зразків може бути використаний як крітерій ефективності консервативної терапії CIN.

Ключові слова: цервікальний канцерогенез, толл-рецептори, синтетаза оксиду азоту, фолати, папіломавирус.

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ЦЕРВИКАЛЬНЫЙ РАК: ТРИГГЕРНЫЕ ФАКТОРЫ
Крутикова Э. И.

Актуальность изучения пусковых механизмов цервикального канцерогенеза обусловлена высокой частотой папилломавирусной инфекции среди молодых женщин (до 95%), онкогенность которой доказана на сегодняшний день. Проанализированные источники указывали, что экспрессия TLR 3, 4, 7, 8, iNOS и NF-kB p 65 в эпителиоцитах рака шейки матки значительно превышала таковую в доброкачественных клетках-носителях папилломавируса и здоровых образцах (p<0,005). Сигнальный путь TLR/NO вовлечён в патогенез цервикального рака и подлежит изучению. Другой аспект данного обзора посвящён влиянию фолатов на ДНК-метилирование и экспрессию опухолевого супрессора белка FHIT (Frigile histidine triad), который подавляет неоплазию шейки матки. Исследования проводились на клеточных линиях CaSki (HPV 16 позитивных) и C33A (HPV 16 негативных) у женщин с CIN и карциномой. Выяснено, что по мере повышения тяжести поражения шейки матки повышался уровень метилирования FHIT, тогда как уровень фолата эритроцитов (RBC) снижался. Таким образом, дефицит фолатов является одним из звеньев цервикального канцерогенеза, что необходимо учитывать клиницистам. Приведены также данные о капсидном белке HPV–L1, как о маркере напряжения локального цервикального иммунитета на фоне папилломавирусной инфекции. Капсидный тест в совокупности с количественной HPV-нагрузкой цервикальных образцов может использоваться как критерий эффективности консервативной терапии CIN.

Ключевые слова: цервикальный канцерогенез, толл-рецепторы, синтетаза оксида азота, фолаты, папиломавирус.

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CURRENT MORPHOLOGICAL ACHIEVEMENTS IN UNDERSTANDING OF URINARY BLADDER PATHOLOGIES AND THEIR DETAILED ANALYSIS

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The paper presents the analysis of the current studies of the urinary bladder pathologies that occur in the clinical practice. The novel theories of the UB damage and the disorders of the urodynamics are impressive by its complexity and diversity. Understanding the causes and ways of the development of UB pathological processes is crucial in the correct and timely diagnosis and further therapeutic management, resulting in the improving of patient's quality of life. In particular, the analysis and study of some of the discoveries made by the scholars that form an understanding of the development of inflammatory, nonplastic and dysfunctional pathology of the bladder is presented. The paper highlighted the differential diagnosis of the inflammatory pseudotumor, pathogenesis of the overactive bladder, clinical and morphological picture of rare malignant tumors. The role of the advanced morphological studies in the diagnosis of the UB disease is emphasized.

Keywords: urinary bladder, urological pathology, overactive bladder, obstruction, inflammation, tumors, environmental pollution.

Generally, the pathology of the urinary bladder (UB) is often accompanied by its dysfunction and/or different types of complications. We have analyzed and described some of the discoveries made by the scientists, which contribute to understanding of the development of urinary bladder pathology. Inflammation of the UB is the common problem with the developed diagnostic and treatment protocols; however, the inflammatory process may have specific features. In this respect the case of inflammatory pseudotumor of the UB has been reported. The patient complained of the abdominal pain and hematuria. The CT and MRI showed the thickening of the wall of the organ, and cystoscopy test detected a neoplasm. After its removal the histological study showed proliferation of myofibroblastic spindle cells and mixed cellular infiltration (lymphocytes, neutrophils and eosinophils). Scientists emphasize the importance of the detailed differential