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DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF EPSTEIN-BARR VIRUS AND HUMAN PAPILLOMAVIRUS ASSOCIATED WITH THROAT CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Pharyngeal cancer (PC) is a malignant neoplasm in the oropharynx and nasopharynx associated with Epstein-Barr viruses (EBV) and human papillomavirus (HPV). Both viruses have oncogenic potential, affecting the pathogenesis of PC.*

EBV, which infects more than 90% of the population, can cause various benign and malignant diseases. HPV, especially types 16 and 18, is the main oncogenic factor of oropharyngeal cancer (OPC). The E6 and E7 proteins produced by HPV disrupt the action of tumor suppressors p53 and Rb, which leads to uncontrolled cell proliferation.

EBV activates latent proteins and regulates the immune response, whereas HPV affects cell cycle control by inactivating p53 and Rb. HPV-induced PC has a better prognosis compared to EBV-associated cancer due to higher sensitivity to treatment.

The study aimed to *systematize literature data on assessing the diagnostic and prognostic significance of EBV and HPV associated with PC and improve programs for early diagnosis and primary prevention of head and neck tumors.*

Methods: *Since 2015, a literature review has been conducted on the study's keywords in the PubMed and MedLine databases.*

Results: *Studies show that EBV and HPV are important in the diagnosis and prognosis of PC. The EBV presence in tumor cells can mark a more aggressive course of the disease. However, in some cases, it is associated with better treatment results. Patients with HPV-positive tumors have better prognoses and a more favorable response to treatment compared to HPV-negative cases. Both viruses play an important role in the pathogenesis of PC, and their diagnosis and characterization can significantly affect treatment tactics and prognosis of the outcome of the disease.*

Conclusion: *EBV and HPV play key roles in the pathogenesis of RG, but their mechanisms of action and clinical outcomes differ. EBV is more often associated with nasopharyngeal cancer, and HPV is associated with OPC. The latter is more common in Western countries and has a more favorable prognosis. Future research should focus on developing more effective prevention, diagnosis, and treatment methods for these viruses.*

Keywords: *Epstein-Barr virus (EBV), human papillomavirus (HPV), pharyngeal cancer, diagnostics.*

Introduction: Pharyngeal cancer (PC) applies to malignant neoplasms (MNO) in the oropharynx and nasopharynx. Epstein-Barr virus (EBV) and human papillomavirus (HPV) are the main infectious agents associated with developing these tumors. EBV, a member of the family of herpesviruses, and HPV, a member of the family of papillomaviruses, have different effects on the pathogenesis of PC, but both have a significant oncogenic potential.

These viruses are the most common cause of infectious oncological diseases. HPV and EBV are associated with 38% of all virus-associated STDs [1]. The majority of virus-associated types of cancer develop after a long latent period, which can take from 15 to 40 years [2].

The preferred way of transmission of VEB is airborne. Today, it has become known that organ transplantation and blood transfusion can also contribute to the spread of EBV [2,3].

According to data for 2019, HPV caused 620,000 cases of cancer among women and 70,000 among men. Cervical diseases account for 93% of all HPV-associated STDs in women. In 2022, cervical cancer was the fourth leading cause of cancer and death among women, with 660,000 new cases and approximately 350,000 deaths worldwide [4]. HPV is associated with more than 90% of cases of cervical cancer and about 70% of cases of oropharyngeal cancer (OPC).

According to estimates from the International Agency for Research on Cancer (IARC), 10% of cancer cases worldwide are caused by viral infections [5].

EBV and HPV have been classified as high-risk group 1 (certainly established) human carcinogens. EBV is etiologically associated with Burkitt's lymphoma, extranodal NK/T-cell lymphoma (i.e., nasal type), Hodgkin's lymphoma, nasopharyngeal carcinoma (NA), and lymphoepithelioma-like carcinoma [6].

EBV, first identified in 1964, is associated with several NCDs, including nasopharyngeal carcinoma (NPC). RNG is one of the most common head and neck tumors, espe-

cially in endemic areas such as China, Southeast Asia, and North Africa. EBV causes the transformation of epithelial cells of the nasopharynx through the activation of latent proteins, such as latent membrane protein-1 (latent membrane protein 1, LMP1), which acts as an oncogene, activating the NF-kB and JAK/STAT signaling pathways. These molecular processes lead to a decrease in apoptosis and an increase in cell proliferation and cell migration.

The study aimed to systematize literature data on assessing the diagnostic and prognostic significance of EBV and HPV associated with PC and improve programs for early diagnostics and primary prevention of head and neck tumors.

Materials and methods: A literature review of scientific and clinical studies from PubMed and MedLine databases was conducted under the main keywords and phrases: "Epstein-Barr virus associated with PC," "human papillomavirus associated with PC," "diagnostic and prognostic significance of Epstein-Barr virus and human papillomavirus." Filters were used in the search procedure: publication date from 2015 to the present.

Results: Presumably, a specific combination of the EBV variant and a specific person exists. A eucocyte antigen allows the proliferating epithelial cells to evade immune control [7]. The histological subtypes of nasopharyngeal squamous cell carcinoma (NPC) and the suspected etiological factors vary by geographic region. According to the WHO classification of head and neck tumors, NPCs are classified into 3 main types: keratinizing squamous cell carcinoma (KC), non-keratinizing carcinoma (NKC), and basaloid squamous cell carcinoma. NPC can be divided into differentiated and undifferentiated forms. In endemic areas with high incidence, up to 99.6% of NPC tumors belong to the KC subtype. It is more strongly associated with EBV positivity than other subtypes. In non-endemic areas with low incidence, the prevalence of the NKC subtype is significantly lower, while the prevalence of KC is higher than in endemic regions. [8].

In comparison, in non-endemic areas with low incidence, the prevalence of subtypes (NKC) is significantly lower, whereas the prevalence (KC) is higher than in endemic areas.

High-risk HPV infection is thought to be one of the etiological factors causing NPC in Caucasian people. In one of the studies, patients with HPV-positive and EBV-positive tumors had a significantly higher overall survival rate than patients with EBV/HPV-negative tumors [9, 10].

Previous studies of viral infections in NPCs have mainly reported small and heterogeneous groups of patients treated at 1 or 2 facilities. Thus, data on the predictive value of EBV and HPV in NPCs are limited. This retrospective population-based study aimed to describe the status of EBV and HPV in cases of Finnish NPC and to link them to histopathological subtypes of NPC and patient survival.

There is evidence of a relationship between HPV and oral cavity cancer. According to the results of the study, "Prevalence of HPV-induced oral cavity and OPC in Kazakhstan and its prognostic significance," conducted at Kazakh Research Institute of Oncology and Radiology JSC (Almaty, Kazakhstan), the analysis of HPV incidence among patients with malignant neoplasms of the oral cavity and oropharynx in the Republic of Kazakhstan is of great clinical importance, since the HPV presence in the tumor is a favorable prognostic sign of the course of the disease. The highest survival rates in patients with oropharyngeal and oral malignancies associated with HPV (93%) are explained by a higher response to chemotherapy and radiation therapy compared to patients without HPV (82%). The presence of a high level of p16 protein proliferative activity in oropharyngeal and oral cavity tumors is also associated with HPV infection and can be used as a marker for the diagnostics of HPV-associated tumors at these locations. These results will develop methods for early diagnostics and improve methods for primary prevention of laryngeal cancer.

Discussion: Why does the virus cause cancer? Viral infections are one of the most common causes of infectious cancers, accounting for 12-15% of all cases. HPV and EBV are associated with 38% of all virus-associated malignancies. Most types of cancer associated with viruses develop after a long latency period that can last from 15 to 40 years [2, 11, 12].

Oncogenic viruses include various groups of DNA and RNA viruses, which are important but not always sufficient for the occurrence of all types of malignant tumors [2]. A common feature is that cancer develops only in a few people infected with viruses for a long time and only after many years of chronic infection [4, 13].

Both viruses have different mechanisms of influence on cellular processes. EBV mainly acts through the activation of latent membrane proteins and the regulation of the immune response, whereas HPV alters the control of the cell cycle through the inactivation of p53 and Rb. Studies show that HPV-induced OPC has a better prognosis than cancers associated with EBV or classic risk factors. This is due to the higher sensitivity of HPV-positive tumors to treatment (especially to chemoradiotherapy).

Currently, the main confirmation of the viral nature of tumors is the detection of the virus or its components in tumor cells using monoclonal analysis. This method allows for the confirmation of a chronic infection that precedes malignant transformation and the detection of viral oncogenes that contribute to the start of the tumor process.

Viral carcinogenesis is divided into two main types: direct and indirect. The direct mechanism is that once infected, the virus persists in the cell as an independent genetic element, either as an eposome (as it occurs in herpes viruses) or integrates into the host genome (e.g.,

in retroviruses or hepatitis B virus). It can lead to inactivation of the p53 and pRB genes, genomic instability, increased mutations, changes in telomere length, disruption of cellular polarity, and the formation of miRNA. An indirect mechanism involves chronic inflammation and oxidative stress in normal cells caused by the production of pro-inflammatory cytokines by infected cells (e.g., in hepatitis C virus), resulting in prolonged antigenic stimulation. Viruses can also induce immunosuppression in surrounding tissues by destroying or impairing the function of CD8+ lymphocytes (e.g., in HIV, EBV, or KSHV) [13-15].

HPV belongs to the *Papillomaviridae* family. To date, more than 100 types of these viruses are known to be involved in the development of various diseases. They are divided into two groups: low and high-risk ones. Low-risk subtypes 6 and 11 cause cutaneous and anogenital warts and upper respiratory tract papillomatosis, rarely leading to malignancy. Subtypes 16 and 18 are at high risk and are more likely to be associated with the development of malignant tumors. Type 16 is mainly associated with OPC (up to 95%) and invasive cervical cancer (up to 70%), and type 18 is associated with squamous cell carcinoma of various sites. HPV is transmitted through contact and sexual routes. A characteristic feature of this virus is its ability to persist in the body for a long time without obvious clinical signs.

Antibodies to HPV can be found in 50-60% of infected people. The natural process of HPV-associated tumors usually takes 10 to 30 years from the time of initial infection. The pathogenesis of tumor progression against the background of HPV infection includes changes in the expression of viral oncogenes at different stages of the disease and the accumulation of mutations in the host genome. Clinically, this is manifested by such epithelial changes as CIN-1, CIN-2, and CIN-3. The main oncoproteins are E6 and E7. They must maintain a malignant state as they inactivate the retinoblastoma and p53 genes. This is important because such inactivation increases p16INK4A (cyclin-dependent kinase 2A inhibitor/tumor suppressor 1), a marker of oncogenic HPV infection [13, 16].

A literature review shows significant fluctuations in the HPV incidence in the oral cavity and pharyngeal diseases, which range from 0 to 100% in different studies. For example, a comprehensive analysis of 60 studies conducted in different regions of the world showed that more than 25% of malignant head and neck tumors are associated with HPV infection [16, 17].

EBV associated with RNG (???) is diagnosed by detecting specific antibodies to EBV, such as EBNA1 and VCA. PCR to detect EBV DNA in tumor tissue is also a standard diagnostic method. For HPV associated with laryngeal cancer, PCR detects HPV DNA, and immunohistochemical methods are used to find E6 and E7 proteins [18].

One of the main methods to combat HPV-related diseases is primary prevention in the form of vaccination against this virus.

A nine-valent vaccine was approved in 2014. It covers five additional HPV types (31, 33, 45, 52, and 58). In June 2020, the FDA expanded the indications for the use of this vaccine to allow its use for the prevention of OPC and other head and neck tumors. These indications were approved under an accelerated procedure based on the proven efficacy of the vaccine in preventing anogenital diseases associated with HPV. The vaccine is recommended for women and men aged 9 to 45 years. The World Health Organization states that modern HPV vaccines (types 16/18) can prevent more than 90% of HPV-induced OPC cases[2, 16, 19].

Traditional treatments for head and neck cancer include surgery, radiotherapy, and chemotherapy. However, new approaches have been developed for virus-associated tumors. HPV, including its types 16 and 18, is one of the main causes of cervical, oropharyngeal, anal, vaginal, labia, and penile cancers. The most effective method to reduce morbidity and mortality from these tumors is vaccination. The bivalent Cervarix vaccine, designed to protect against types 16 and 18, and the quadrivalent Gardasil vaccine, which protects against types 16, 18, 6, and 11, are used in medical practice. The main goal of vaccination was to prevent precancerous and cancerous changes in the cervix caused by HPV. In countries where vaccination of adolescent girls was introduced 5-10 years ago (for example, Australia and Denmark), there is a 90% decrease in HPV infection among vaccinated people, as well as a 90% decrease in genital warts and an 85% decrease in the detection rate of CIN2-3. It will take longer for vaccination to reduce the incidence of cervical cancer since the risk of developing this cancer increases 15-20 years after the onset of viral carriage. Nevertheless, the already available data confirm the high efficiency of vaccine prophylaxis [19].

The importance of HPV vaccination for our country can hardly be overestimated. Reduction of the incidence and, accordingly, mortality from such widespread tumors as cervical cancer and OPC is impossible without the use of preventive measures, one of which is vaccination. In the absence of screening programs and early diagnostics of malignant tumors associated with HPV, vaccination is an economically viable method to prevent these diseases in the Republic of Kazakhstan. Oncologists shall make every effort to include the HPV vaccine in the national vaccination schedule.

Conclusion: EBV and HPV play key roles in the pathogenesis of RG, but their mechanisms of action and clinical outcomes differ. EBV is more often associated with nasopharyngeal cancer, and HPV is associated with OPC. The latter is more common in Western countries and has a more favorable prognosis. Future research should focus on developing more effective prevention, diagnosis, and treatment methods for these viruses.

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АҢДАТПА

ЭПШТЕЙН-БАРР ВИРУСЫНЫҢ ЖӘНЕ ЖҰТҚЫНШАҚ ҚАТЕРЛІ ІСІКПЕН БАЙЛАНЫСТЫ АДАМ ПАПИЛЛОМАВИРУСЫНЫҢ ДИАГНОСТИКАЛЫҚ ЖӘНЕ БОЛЖАМДЫҚ МАҢЫЗЫ: ӘДЕБИЕТКЕ ШОЛУ

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Сәйкестік: *Бұл Өзектілігі: Жұтқыншақтың қатерлі ісігі (ЖҚІ) – Эпштейн-Барр (ЭБВ) және адам папиллома вирустарымен (АПВ) байланысты ауыз-жұтқыншақ пен мұрын-жұтқыншақ аймағындағы қатерлі ісіктер (МЖҚІ). Екі вирустың да онкогендік потенциалы бар, олар ЖҚІ патогенезіне әсер етеді.*

Халықтың 90% – астамын ЭБВ жұқтырған және ол әртүрлі қатерсіз және қатерлі ауруларды тудыруы мүмкін. АПВ, әсіресе 16 және 18 типтері, ауыз-жұтқыншақ қатерлі ісігінің (АЖҚІ) негізгі онкогендік факторы болып табылады. АПВ өндіретін Е6 және Е7 ақуыздары p53 және Rb ісік супрессорларының әсерін бұзады, бұл жасушалардың бақылаусыз көбеюіне әкеледі.

ЭБВ жасырын ақуыздарды белсендіреді және иммундық жауапты реттейді, ал АПВ p53 және Rb инактивациясы арқылы жасуша циклін басқаруға әсер етеді. ЭБВ байланысты АЖҚІ қарағанда АПВ туындаған АЖҚІ жақсы болжамға емдеуге сезімталдығы жоғары болғандықтан ие болып саналады.

Зерттеудің мақсаты *– бас және мойын ісіктерінің ерте диагностикасы мен бастапқы алдын алу бағдарламаларын жақсарту үшін ЭБВ және АПВ байланысты ЖҚІ диагностикалық және болжамдық маңыздылығын бағалау үшін әдебиет деректерін жүйелеу.*

Әдістері: *2015 жылдан бастап PubMed және MedLine дерекқорларында зерттеудің негізгі сөздері бойынша әдеби шолу жүргізілді.*

Нәтижелері: *Зерттеулер ЭБВ және АПВ ЖҚІ диагностикасы мен болжауында маңызды екенін көрсетеді. Ісік жасушаларында ЭБВ болуы аурудың агрессивті ағымының белгісі бола алады, бірақ кейбір жағдайларда емдеудің жақсы нәтижелерімен де байланысты. Емделушілердегі АПВ оң ісіктері мен АПВ теріс ісіктері жағдайлармен салыстырғанда оң ісіктері жақсы болжамдар және емдеуге қолайлы жауап береді. Екі вирус та ЖҚІ патогенезінде маңызды рөл атқарады және олардың диагностикасы мен сипаттамасы емдеу тактикасына және аурудың нәтижесін болжауға айтарлықтай әсер етуі мүмкін.*

Қорытынды: *ЭБВ және АПВ ЖҚІ патогенезінде шешуші рөл атқарады, бірақ олардың әсер ету механизмдері мен клиникалық нәтижелері әртүрлі. ЭБВ көбінесе МЖҚІ — мен, ал АПВ АЖҚІ-мен байланысты, соңғысы батыс елдерінде жиі кездеседі және қолайлы болжамды көрсетеді. Болашақ зерттеулер осы вирустардың алдын-алу, диагностикалау және емдеудің тиімді әдістерін жасауға бағытталуы керек.*

Түйінді сөздер: *Эпштейн-Барр вирусы (ЭБВ), адам папилломавирусы (АПВ), жұтқыншақ қатерлі ісігі, диагностика.*

АННОТАЦИЯ

ДИАГНОСТИЧЕСКАЯ И ПРОГНОСТИЧЕСКАЯ ЗНАЧИМОСТЬ ВИРУСА ЭПШТЕЙНА-БАРР И ВИРУСА ПАПИЛЛОМЫ ЧЕЛОВЕКА, АССОЦИИРОВАННЫХ С РАКОМ ГЛОТКИ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Рак глотки (РГ) представляет собой злокачественные новообразования в области ротоглотки и носоглотки, которые имеют связь с вирусами Эпштейна-Барр (ВЭБ) и папилломы человека (ВПЧ). Оба вируса обладают онкогенным потенциалом, влияя на патогенез РГ.*

ВЭБ, которым инфицировано более 90% населения, может вызывать различные доброкачественные и злокачественные заболевания. ВПЧ, особенно типы 16 и 18, является основным онкогенным фактором рака ротоглотки (РРГ). Белки Е6 и Е7, продуцируемые ВПЧ, нарушают действие супрессоров опухолей p53 и Rb, что приводит к бесконтрольной пролиферации клеток.

ВЭБ активизирует латентные белки и регулирует иммунный ответ, тогда как ВПЧ влияет на контроль клеточного цикла через инактивацию p53 и Rb. РРГ, вызванный ВПЧ, имеет лучший прогноз по сравнению с раком, ассоциированным с ВЭБ, из-за более высокой чувствительности к лечению.

Цель исследования *– систематизация данных литературы для оценки диагностической и прогностической значимости ВЭБ и ВПЧ, связанных с РГ, для улучшения программ ранней диагностики и первичной профилактики опухолей головы и шеи.*

Методы: *Проведен литературный обзор по ключевым словам исследования в базах данных PubMed и MedLine с 2015 года.*

Результаты: *Исследования показывают, что ВЭБ и ВПЧ имеют важное значение диагностике и в прогнозировании РГ. Наличие ВЭБ в опухолевых клетках может служить маркером более агрессивного течения болезни, однако в некоторых случаях ассоциируется с лучшими результатами лечения. Пациенты с ВПЧ-положительными опухолями имеют лучшие прогнозы и более благоприятный ответ на лечение по сравнению с ВПЧ-отрицательными случаями. Оба вируса играют важную роль в патогенезе РГ, и их диагностика и характеристика могут существенно повлиять на тактику лечения и прогнозирование исхода заболевания.*

Заключение: *ВЭБ и ВПЧ играют ключевую роль в патогенезе РГ, однако их механизмы действия и клинические исходы различаются. ВЭБ чаще ассоциируется с РНГ, а ВПЧ – с РРГ, причем последний чаще встречается в западных странах и демонстрирует более благоприятный прогноз. Будущие исследования должны быть направлены на разработку более эффективных методов профилактики, диагностики и лечения этих вирусов.*

Ключевые слова: *вирус Эпштейна-Барр (ВЭБ), вирус папилломы человека (ВПЧ), рак глотки, диагностика.*

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