EDITORIAL

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Human Papilloma Viruses in Oral Cancer – Review of the Literature

Rola wirusów brodawczaka ludzkiego w etiopatogenezie raków jamy ustnej – przegląd piśmiennictwa

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Abstract

Long-term examination of squamous head and neck region carcinoma (HNSCC) epidemiology for years assumed that this is a homogeneous group of tumors. Only in recent years have they noticed some significant differences in epidemiological trends within the given anatomical regions of this area. The examination of the viral background of the cancerogenesis in this area treated mouth and larynx as a single anatomical structure, which led to overstatement of the significance of the human papilloma virus (HPV) in the scope of oral cavity cancers. The HPV prevalence within oral cavity cancers is a lot lower compared to larynx cavity cancers. The latest research points to some positive aspects stemming from a viral infection in the case of larynx cancer (deescalation of adjuvant therapy, among others) which seems to be of no significant value in preventing and curing HPV (+) carcinoma of the oral cavity. The prevalence of HPV in male patients suffering from head and neck cancers led to the extension of the current HPV prevention program, based on the vaccination of females to prevent the development of urogenital cancers, to include the recommendation of the use of the quadrivalent vaccine among young men. The work below sums up the current research regarding the role of the human papilloma viruses in oral cavity cancers **(Dent. Med. Probl. 2014, 51, 3, 291–298)**.

Key words: cancer, oral cavity, etiology, HPV.

Streszczenie

Wieloletnie badania nad epidemiologią raków płaskonabłonkowych w obrębie głowy i szyi (HNSCC) zakładały, że jest to jednorodna grupa guzów. Uważano, że obecność wirusów brodawczaka ludzkiego (HPV) w tym umiejscowieniu dotyczy niepalących, niepijących, młodych (< 40 lat), białych mężczyzn o wysokim statusie społecznym i bardziej wrażliwych na chemio- i radioterapię. Dopiero w ostatnich latach zauważono znaczące różnice w trendach epidemiologicznych poszczególnych regionów anatomicznych w tej okolicy. Badania nad wirusowym podłożem kancerogenezy tego obszaru nie oddzielały od siebie regionu jamy ustnej od gardła, co w konsekwencji doprowadziło do przeszacowania rzeczywistego znaczenia wirusa HPV w nowotworach jamy ustnej. Wykrywalność HPV w rakach jamy ustnej jest o wiele mniejsza niż w rakach gardła. W świetle aktualnych badań pozytywne aspekty wynikające z infekcji wirusowej w rakach gardła (m.in. deeskalacja terapii adjuwantowej) wydają się nie mieć znaczenia w profilaktyce i terapii raków HPV (+) jamy ustnej. W pracy przedstawiono najbardziej współczesne badania dotyczące roli wirusa HPV w rakach jamy ustnej **(Dent. Med. Probl. 2014, 51, 3, 291–298)**.

Słowa kluczowe: jama ustna, rak, nowotwór, HPV, etiopatogeneza.

Globally, malignant oral cancers constitute only 2–4% of all cancers. In some countries, e.g. Pakistan and India, the number is significantly increasing and afflicts 10–40% of all oncological patients. From the countries of the European Union, malignant cancers of the oral cavity pose

the greatest problem in France and Hungary (6%). The most frequent form of oral cancer (ca. 90%) is squamous cell carcinoma. In spite of progress in the diagnostics and treatment of cancers, the five-year survival rate varies between 54% among white patients and 33% among black patients [1]. Alcohol and nicotine are considered the main risk factors for cancers of this region, contributing to the development of cancer in approximately 75% of patients. Other risk factors include age, sex, nationality, lifestyle, genetic predisposition, nutritional deficiency, poor oral hygiene, and health condition as well as viral and bacterial infections. At the beginning of the 1980s, the incidence of head and neck cancers in the USA and other developed countries began to decrease, which was associated with a declining number of smokers. Several years later there was an unexpected escalation of HNSCC incidence among young, non-smoking people with high social status and a healthy lifestyle, so an attempt to determine the role of viruses in the aetiology of HNSCC was undertaken.

In 1977, Harald zur Hausen et al. [1] reported that the human papillomavirus (HPV) is responsible for triggering neoplastic metaplasia in the cervix. In 2008 he was awarded the Nobel Prize in Physiology and Medicine for his multiannual studies. The similarity in histological structure between the mucous membrane of the genitals and of the upper tract of the respiratory and digestive systems forced the researchers to expand their studies to other regions of the body. Seven years later, in 1983, Syrjanen [acc. 2], using antibodies as a method to detect viral structural protein, published his first reports in which he reported that almost 20% of head and neck cancers are related to HPV infection.

In the last decade there has been a sharp increase in the number of studies concerning the viral aetiology of head and neck cancers. The differences in the histological characteristics of oral and oropharyngeal mucosa are great enough to treat them as two separate regions, which are significantly different in terms of biology. Current epidemiological studies have revealed that 35.6% of oropharyngeal cancers, 20.2% of oral cancers, 24.0% of laryngeal cancers and 29.6% of naso-sinus cancers are HPV-positive [1].

HPV and Head and Neck Cancers

Human papilloma viruses together with polio viruses constitute the Papovaviridae family. In 2004 the papilloma virus (PV) was subsumed under a separate family of Papillomaviridae. So far, over 200 types of papilloma viruses (PV) have been identified, 182 of which can be found in humans (HPV). HPV are nonenveloped, epitheliotropic DNA viruses with a diameter of approximately 55 nm, containing genetic material in the form of DNA, made up of ca. 8,000 base pairs. The genome may encode eight proteins: E1, E2, E4–E7, L1 and L2. It has been observed that different types of HPV may occur in several variants, differing in approximately 2% of the nucleotide sequence. Numerous epidemiological, etiological and molecular studies report that different variants of the same HPV are biologically different and can be associated with different pathological risk. In the majority of cases, HPV is responsible for benign epithelial proliferation, and only some types of the virus are capable of malignant transformation. The so-called early genes (E1–E8) become active immediately after the infection and shortly before DNA replication. The products of these genes are responsible for replication control, viral DNA expression and host-cell transformation. Late genes (L1–L2) code for structural proteins and are active in the last stages of the viral cycle [3]. It has been proven that the E7 protein, which controls cell growth and is responsible for the destruction of human epithelial cells is coded only by high-risk HPVs. In the majority of HPV (+) head and neck cancers, viral DNA, integrated into the DNA of a host cell, activates only two genes, E6 and E7, which are both responsible for the production of oncogenes.

There is a significant discrepancy in the proportion of HPV-associated head and neck cancers reported in different studies, e.g. because of a large group of smokers among patients suffering from malignant cancers of these areas. In the USA it has been estimated that 40–80% of oropharyngeal cancers are caused by HPV, whereas in Europe the incidence varies from 90% in Sweden, Holland and Great Britain to 20% in countries with a heavy consumption of nicotine. A significantly higher incidence of HPV (+) cancers has been observed by Asian centers, which is related to regional differences in the distribution of other risk factors. The incidence of HNSCC in the USA has decreased in recent years because of a decrease in nicotine dependence. Simultaneously, the incidence of HPV (+) oropharyngeal cancer is significantly increasing, affecting mainly young, educated, white male patients and is associated with their sexual practices [4]. In the USA, the statistics from the Surveillance, Epidemiology and End Results (SEER) survey revealed that the annual incidence of oropharyngeal cancers in the years 1973–2004 increased by 1–3% in the case of tongue root and by 0–6% in the case of tonsils, whereas the annual incidence of oral cancers decreased by 1–9%.

Human papillomavirus (HPV) is responsible for the majority of new infections among sexually transmitted diseases in the USA, the number of which is estimated at 20 billion [5]. It is assumed that 120,000 people aged 15–24 years become infected with HPV every day. Most of them will combat the virus on their own within two years, unaware that they had the infection. Sexual partners, who will have contact with them at that time, will be potentially exposed to the HPV infection.

HPV infection in the oral mucosa can be asymptomatic or may clinically manifest as: Heck's disease (focal epithelial hyperplasia), squamous cell papilloma (papilloma planoepitheliale), genital warts (condylomata acuminata), common warts (verruca vulgaris), lichen planus, leukoplakia, erythroplakia, verrucous carcinoma (Ackerman tumor) or squamous cell carcinoma (carcinoma planoepitheliale).

To formally confirm the role of a virus as an etiological factor of cancer, the so-called modification of Koch's postulates has to be fulfilled: 1. Viral infection precedes the development of cancer; 2. The viral genome is present in a tuberous lesion or in tumor cells; 3. There is an epidemiological relationship between the presence of the virus and the development of the cancer; 4. Viral proteins are able to perform the transformation of cells in vitro; and 5. The preventive vaccine against HPV eliminates squamous cell cancers of the oral cavity [2]. According to the authors of the modification, the last postulate can be proven only after at least 20 years of epidemiological observation.

Approximately 30 types of viral DNA have been isolated from lesions in the oral cavity: 1, 2, 3, 4, 6, 7, 10, 11, 13, 16, 18, 31, 32, 33, 35, 39, 45, 51, 52, 56, 57, 58, 59, 66, 69, 72, 73 [6]. The so-called low-risk viruses (i.e. 6, 11, 13, 32), associated with benign lesions in the oral cavity, which possess low potential for malignant transformation, predominate. On the other hand, such types of HPV as 16, 18, 31, 33 and 35, referred to as the high-risk HPV genotypes, are present in epithelial dysplasia and in squamous cell cancers. In unchanged oral mucosa the following types of HPV were detected: 2, 6, 7, 11, 13, 16, 18, 31, 33, 35. High-risk HPV is detected in oncological patients three times more often than in patients with benign lesions. HPV infects undifferentiated stem cells of the epithelium after injury or erosion.

HPV16 is the most frequently detected genotype in oral cancers. Studies performed in German and American centers estimate the incidence of HPV16 in HPV (+) oral cancers at 68.2% [7]. Only the studies performed in the Republic of South Africa [8] detected solely the presence of HPV18 with no reported case of HPV16. HPV18 or the coexistence of HPV16 and HPV18 infections was detected only rarely. HPV8, HPV31, HPV38 and HPV66 were also rarely detected [9].

HPV infection may have acute, chronic or latent character. Nevertheless, the details regarding the actual course of the infection remain unknown and are still under examination. Most HPV infections are self-limiting and resolve spontaneously in 12–24 months (the virus can be entirely removed from an organism or remain there in a latent form and be activated later). Only a small percentage of infections cause lesions in epithelium. Undoubtedly, HPV infection – both chronic and latent – is key to HPV-induced cancerogenesis [3]. In the context of HPV-induced cancerogenesis, a "hit-and-run" mechanism is being discussed. It seems that the presence of the virus is necessary only in the early stage, when the oncogenesis process is thought to be initiated, but it is probably no longer required in the subsequent stages of malignant neoplastic progression. There are ongoing studies to determine whether HPV is the main causative factor for the virus-mediated cancerogenesis of head and neck cancers, excluding oropharynx (a "bystander" infection).

The actual oncogenic potential of HPV in oral cancers is difficult to interpret because of the huge divergence in the available epidemiological studies. The incidence varies between 0 and 10%. Because of the relatively small group of patients that have been examined so far, diversified sample groups, small sample sizes (usually ca. 40 patients), significant differences in the sensitivity of tests and the use of tests that determine only one or two pathogens, caution when interpreting the results of epidemiological studies and drawing final conclusions is recommended. Additional difficulties arise due to the fact that the tongue, gums, base of the oral cavity, cheeks and hard palate are considered anatomical parts of the oral cavity, whereas the tongue root and soft palate are not. In some works, cancers of the tongue root, which is a part of the oropharynx, are taken into account in the assessment of HPV (+) planoepitheliale cancer of the oral cavity. However, it is known that the incidence of oropharyngeal HPV infections is much greater and, therefore, it may be significantly overestimated if HPV infections of the base of the tongue are taken into consideration.

Miller et al. [10], by performing a meta-analysis of patients treated in the years 1982–1997 in different centers, estimated the incidence of HPV-associated oral cancers at 46.5%. Cancers of the tonsil and the tongue root were also included in the analysis. So far, one of the most thorough analyses regarding the incidence of HPV-associated head and neck cancers was performed by

Isayeva et al. [11]. They summarized 60 publications and evaluated the results for 4,195 patients with oral cancer, showing that the incidence of HPV is approximately 20.2%. Kreimer [acc. 12] estimated the incidence of HPV-associated oral cancers at 23.5%. In some cases, a greater frequency of HPV (+) oral cancers was reported in men than in women (10.1% vs. 3.6%).

The summary prepared by Isayeva et al. [11] for the control group included 22 publications concerning 5,095 patients. HPV was detected in 6.9% of the patients. Significantly greater percentages were reported only by the investigators from India, Scandinavia and China [13–15]. The studies show that the incidence of HPV in the oral cavity increases with age and is detected in 3–5% of teenagers and in 5–10% of adults [16]. Studies performed on children aged 3–5 years in Japan showed that HPV16 was present in unchanged oral mucosa in 50% of patients [17]. Studies performed by Durzyńska [18] on Polish children aged 10–18 years revealed the presence of an active viral infection of the oral cavity in 1.08% of the 4,150 children who had been examined. The risk of HPV infection in women decreases with age, whereas men are equally susceptible to the infection at every stage of their lives. In their research, Swedes reported that in young women with cervical HPV infection the incidence of oral HPV infection is much greater [19]. Fakhry et al. [20] additionally showed that the virus present in the oral cavity of the examined women was different from the one found in the cervix. Studies performed on couples in the Republic of South Africa revealed that partners of women who tested positive for cervical HPV infection tended to have oral HPV infection [21]. The presence of HPV in children forced neonatologists and pediatricians to perform studies on the possibility of infecting a newborn with its mother's genital virus. It was shown that some mothers with an active infection transmit the virus to the child's mucous membrane, including oral mucosa [22]. At the same time, some authors stress that HPV-associated genome instability does not always lead to cancer. There are many factors involved in cancerogenesis, and HPV infection is only one of them. According to Syrjanen et al. [2], who examined 1,885 oncological patients and compared them to 2,248 healthy patients, the odds ratio (OD) of oral cancer in patients with HPV, in relation to a healthy population, equals 3.98. Patients suffering from immune deficiency (HIV) are 1.5 to 4 times more likely to suffer from HPV (+) head and neck cancer [23].

Polish scientific literature lacks studies related to the presence of HPV in patients suffering from oral cancers. The studies performed in the Lublin and Poznan centers were focused on head and neck cancers [24].

Huge discrepancies in the detection of various types of HPV in different studies may result from the choice of population, differences in the choice of sample material (formalin-fixed material, fresh biopsy specimen, fresh cells), different techniques of DNA isolation and, most importantly, different methods of testing, such as: immunohistochemistry, in situ hybridization, dot blot, Southern blot, PCR and ISH-AT. Some centers limit testing to the detection of HPV16, or sometimes HPV18, which significantly distorts the actual distribution of HPV in neoplastic lesions of the oral cavity. In the basic laboratory diagnostics, tests detecting 35 types of HPV are commonly available, but they are rarely used.

The test for the presence of antibodies against HPV in serum should be a commonly-used marker to monitor the progression of an infection and detect the recurrence of HNSCC in its early stage. The human body produces antibodies against the E6 and E7 viral proteins, and their concentration is a sensitive indicator of a viral infection. In the studies performed by Mork et al. [25] regarding oropharyngeal cancers, the risk of developing the disease is 14.4 times greater in patients with confirmed HPV16-L1 antibody. It is thought that the presence of antibodies can be detected more than 10 years before a cancer develops.

In most studies, the detection of HPV is based on the detection of the viral DNA by means of PCR. However, DNA only confirms the presence of a viral infection, it does not reveal anything about its actual transcriptional activity. Tests detecting the presence of HR-HPV-E6-E7 were only performed in a few centers, but studies performed on a group of 109 patients showed that, except for some DNA+/RNA+ patients, several patients were found to be DNA–/RNA+ and DNA+/RNA– [26].

In view of the current studies, it has been estimated that 20% of oral cancers and 60% of oropharyngeal cancers are caused by HPV, mainly the 11, 16 and 18 types. HPV16 seems to be the main viral genotype that occurs both in urogenital cancers and in head and neck cancers. Neoplastic metaplasia of oral mucosa is probably initiated in the same way as in genital cancers. In 2011, the International Agency for Research on Cancer (IARC), which classifies both chemical and biological carcinogens in humans, reported that there is sufficient evidence for a link between the HPV16 virus and oral cancer.

Gillison et al. [27] proposed a different biology and clinical manifestation of HPV (+) head and neck cancers, in comparison to HPV (–) head and neck cancers. Currently, head and neck cancer as-

sociated with HPV infection is treated as an independent nosological entity with a better prognosis than, for instance, nicotine and alcohol-related oral cancers. HPV (+) cancers of the oropharynx affect non-smoking, non-drinking, young (< 40), white men of high social status. Oropharyngeal HPV (+) cancers are more sensitive to chemo- and radiotherapy [28]. Clinically, oropharyngeal HPV (+) cancers are characterized in the TNM classification by a low T parameter and a high N parameter, with multilevel and cystic lymph node metastases. It is currently considered that the increased sensitivity to chemo- and radiotherapy of oropharyngeal HPV (+) cancers and a better prognosis is associated with a lack of exposure to nicotine and alcohol. Recent studies on the influence of HPV on the course of an adjuvant therapy are so advanced that some oncological centers have started to reduce the intensity of adjuvant therapy in oropharyngeal HPV (+) cancers [29]. Some authors have identified characteristic morphological features related to HPV (+) cancers, such as: lack of keratosis, low differentiation, cells with hyperchromatic nuclei, small amount of cytoplasm and visible mitotic activity.

In contrast to the key role of HPV in the development of oropharyngeal cancer, the role of the HPV infection in the development of oral cancer has not yet been adequately researched. Most probably, it is closely connected to sexual practices (mainly oral sex) and immunosuppression. Currently, it is considered that HPV requires other co-factors for the initiation of oncogenesis [30]. The role of HPV in the development of oral cancers is much more ambiguous than in the case of other head and neck cancers. Oral cancer in Southern Asia is an endemic disease with different aetiology than in European countries and the USA.

Few published works have aimed to determine how the presence of HPV influences the course of oral cancer. Kaminagakura et al. [31], Sugiyama et al. [32] and Smith et al. [33] monitored patients in different centers and failed to report greater survival rate in HPV (+) patients.

In the study performed on 333 patients at the Chang Gung hospital in Taoyuan, Lee et al. [34] evaluated the incidence rate of HPV at 21.3% and showed that the risk of distant metastases in patients with advanced oral HPV16 (+) cancer was three times greater than in HPV16 (–) patients. Their prognosis in the case of no adjuvant therapy was also worse. What is more, they required a more aggressive adjuvant treatment and had 2–3 times lower survival rate. HPV18 infection, rare in the case of pharyngeal cancers (about 10%), was reported in 32% of all advanced oral cancers. No difference in the survival rate between the HPV18 (–) and HPV18 (+) patients has been found.

Epidemiological studies suggest that HPV is associated with cancers in patients who do not smoke and do not drink alcohol. Most probably, there is increased risk of developing cancer in HPV (+) patients who drink alcohol and smoke. At the same time, it has been shown that long-lasting nicotinism and a large number of sexual partners predispose to HPV infection [35]. It has been estimated that the risk of developing oral cancer in smokers is 3.5 times greater for HPV (+) patients and 9.8 times greater for patients who abuse alcohol [33]. In terms of sexual practices, the risk factors for HPV (+) cancer in young men are the number of sexual partners and lesions on genitals. For women, the risk increases with the number of sexual partners. What is more, it is thought that some sexual practices, such as oral-anal contact, are associated with the risk of HPV (+) tumors [36].

In the prevention of head and neck cancers, the introduction of vaccination programs, formulated for urogenital cancers, is being considered. Vaccines against HPV decrease the incidence of benign as well as malignant lesions of the ano-genital system and, probably, oropharyngeal diseases. Currently, there are two vaccines available on the market: the quadrivalent HPV vaccine, Gardasil, which acts against HPV6, 11, 16 and 18; and the bivalent HPV vaccine, Cervarix, which acts against HPV16 and 18. In view of the current data, these two vaccines should be successfully used in the prevention of head and neck cancers, because HPV16 is the main type of virus that occurs in lesions of this region. Since 2006, Gardasil has been recommended in the USA for women aged 9–26 years, as a method of preventing genital cancer. In 2009 the recommendation was extended to the prevention of genital lesions in men. Recently it has also been recommended for the prevention of anal cancer (recommendation of the U.S. Food and Drug Administration). Clinical studies estimate the efficiency of vaccination at 98%. The bivalent vaccine is recommended for women to prevent benign and malignant urogenital lesions. Preventive medical examinations on head and neck region cancer incidence suggest the expansion of preventive vaccination to men. On the other hand, taking into account the direction in which the virus is transmitted, mainly from women to men and rarely in the opposite direction, numerous countries consider expanding the indications for the use of the vaccine to the prevention of not only cervical cancer, but also head and neck cancers.

Although persistent infection with high-risk HPV is responsible for a large proportion of cancers in female patients, in males, high-risk HPV types are responsible for a growing number of oral and pharyngeal cancers and a great part of anal and

penile cancers. In 2011, the Advisory Committee on Immunization Practices (ACIP) recommended that the quadrivalent human papillomavirus vaccine be used routinely in males. To achieve optimal effectiveness, the vaccine should be administered prior to the onset of sexual activity. The ACIP recommended routine use of Gardasil in boys aged 11–21 years old and approved the vaccination of males up to 26 years of age, in order to prevent genital warts and anal cancer. Based on mathematical models suggesting that male vaccination programs exceed the cost-effectiveness threshold, many European countries do not include men in their HPV vaccination programs, in contrast to the US (Centers for Disease Control and Prevention), Canada (Public Health Agency of Canada) and Australia (Australian Cancer Research Foundation). Instead, they focus on expanding coverage of HPV vaccination among women to promote immunization against HPV.

Recommendations formulated by the Polish Society of HPV Infections Prophylaxis are based on the WHO guidelines and were developed with the participation of the Polish Gynecological Society. Relying on the experience of other countries, the Head and Neck Cancer Prevention Program (introduced in 2011), which is a consolidation of works by specialists from such fields of medicine as oncology, otolaryngology, and oral and maxillofacial surgery, considers incorporating HPV vaccination into the Polish governmental prevention programs.

It is considered that Caesarean section should be performed in pregnant women with papillomatous lesions of the genitals, in order to prevent infection of the newborn.

Some researchers stress that features such as low differentiation, lack of keratosis, incidence in young patients, non-attributable to such risk factors as nicotine and alcohol, are characteristic for all cancers of viral aetiology. Current epidemiological studies on head and neck oncology are mainly aimed at the detection of HPV and dismiss other risk factors for the infection. However, it has been suggested by some researchers that the low detectability of HPV in oral cancers in patients with no history of alcohol or nicotine abuse points to a significant role of other oncogenic viruses, for example EBV, in the development of the disease [37].

In view of the large-scale European studies on the typology of HPV in HNSCC (head and neck squamous cell carcinoma), the decision regarding the implementation of a vaccine against the four types of HPV most frequently present in cervical cancer, as a preventive measure, seems premature. Given the fact that in numerous countries, different types of HPV predominate in the oral cavity, studies for the development of a vaccine encompassing the spectrum of HPV responsible for head and neck cancers should be initiated.

In view of the available studies on oropharyngeal cancers, several questions arise regarding the role of HPV in the development of oral cancers: 1. What is the actual incidence of HPV-associated oral cancers? 2. Are the clinical and biological features of HPV (+) oral cancers identical to HPV (+) oropharyngeal cancers? 3. Do patients with HPV (+) oral cancers require different treatment and postoperative protocols? 4. Does the presence of HPV influence the course of an adjuvant therapy? Since oral cancers are more common than oropharyngeal cancers, the answers to these questions are particularly important. However, the majority of them have received no unequivocal answer, which could be corrected by studies conducted on numerous, homogenous groups.

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