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Human papillomavirus and its influence on head and neck cancer predisposition

Wirus brodawczaka ludzkiego i jego wpływ na predyspozycję do nowotworów głowy i szyi

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Summary

Human papillomavirus (HPV) is a virus often infecting humans. It is often present on skin or mucous membranes. These diverse DNA viruses are often linked to many various benign and malignant neoplastic lesions. Over 40 types of HPV are transmitted through sexual contact and infect the anogenital region which might be secondly transmitted to the oral mucous. Over 150 HPV viruses are defined according to the invaded site. Oral papillomas are marked with numbers 6, 7, 11, 16 and 32. Squamous cell papilloma is often found in laryngeal epithelial tumor associated with HPV-6 and HPV-11 and also HPV-16 in oral squamous cell carcinoma (OSCC). In the last 15 years OSCC has become more common in children and young adults. The role of HPV virus causing oral squamous cell carcinomas is more often realized, but people's lack of knowledge and risky sexual behavior is still the main factor in growing HPV infections.

Keywords: **Human papillomavirus • squamous cell carcinoma • HPV infections • oral cavity**

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Introduction

The oral cavity is a specific part of the human body. Because of its architecture and localization often many lesions and pathological changes can be diagnosed. Quite often the oral cavity is the first place of manifesting general diseases, such as leukemia or diabetes.

Because of dangerous sexual behavior HPV infection might spread to the oral cavity and oropharyngeal regions. Sexually transmitted infections (STI) are related to HPV infections. Schwartz et al. reported that increasing number of sexual partners, young age and a history of genital warts are related to higher prevalence of transmission of HPV positive head and neck squamous cell carcinoma (HNSCC) in oral and oropharyngeal regions [47]. Studies performed by Mork et al. show that higher exposure to HPV-16 dramatically increases risk of squamous cell carcinoma (SCC)

[38]. Many authors worldwide are studying the nature of HPV virus and its relation to oral SCC.

HPV virus can be present in healthy people, despite age, gender or other factors. It is also worth noting that syndromes and diseases with less or lack of immunodeficiencies are also considered to be related not only to HPV infections, but also HSV (herpes simplex virus), EBV (Epstein-Barr virus) and others.

HPV virus is also related to human immunodeficiency virus (HIV) [14]. Beachler et al. performed a study on 379 HIV-positive and 266 at-risk HIV-negative individuals and tested for 36 types of HPV DNA with PGMY09/11 (primary PCR, polymerase chain reaction) primers and reverse line blot hybridization [3]. Studies showed that oral HPV prevalence was higher in HIV-positive individuals. It may depend on the stage of HIV infection. During those studies the authors found that oral HPV-16 was the most commonly discovered, and more often in HIV-negative (16%) than HIV-positive participants (8%). In a cross-sectional study the most common detected oncogenic HPV was 16, 59 and 33, and non-oncogenic was HPV: 55, 62 and 53 types. This relation may differ in geographical regions and cultural findings. Individual habits should also be considered.

Studies performed by Gillison et al. on 5579 participants in the USA showed that HPV-16 prevalence was 1.0% and oral HPV was 6.9% [15]. During studies a 30-second oral rinse and gargle with mouth wash was used. HPV was detected using PCR (polymerase chain reaction) and type-specific hybridization. HPV prevalence was higher among men than women aged 50 to 64 years old. Another important issue is that HPV infection was more common in sexually experienced individuals than among sexually inexperienced. Therefore patient's age, number of partners and sexual experience are among the main factors responsible for HPV infections related to sexual transmission. Nevertheless, uneducated young people are still considered the high-risk group [6,58].

Tobacco and alcohol along with HPV are related to head and neck squamous-cell carcinomas (HNSCC). A synergistic effect that might occur after combining both factors might increase the number of HNSCC. The well-known rate of all factors may vary depending on region, sexual behaviors or might be related to a combination of risk factors. Various authors discuss the potential role of HPV, since it cannot form an SCC on its own [4].

It seems that not only tobacco and alcohol might be related to SCC of the oral and oropharyngeal region. Both studies from the USA and Europe show that average age of sexual debut has decreased while the number of sexual partners has increased over the years. Studies made by Agius in 2010 [1] seem to confirm this. Tendencies to perform oral sex between men and women vary in age, but younger and middle-aged both men and women seem to have over 45% more oral sex than older people [18]. HPV infection normally takes more than 10 years to progress from simple infection, sexual behavior changes to potential malignancy [7,13]. Therefore sexual education should take place in younger patients and inform about potential threats of having more than one sexual partner. Women with cervical HPV infection have higher oral HPV prevalence than others, while according to Kreimer oral HPV-16 presence is found in 1.3% of healthy adults [26].

Kreimer et al. studies performed on 1688 young and healthy men aged from 18 to 74 suggest that several types of HPV are related to different risk factors [27]. In the study Roche Linear Array was used and about 12 types of HPV were recognized. Oral HPV-16 was the most commonly detected and was detected in 1.3% of all studied individuals. HPV-16 is rarely present in younger ages, and was probably related to current tobacco use.

HPV-related HNSCC remains not fully described. Occurrence and localization of viral infections are still studied. Many authors claim that personal life and life style are very important factors of HPV-related HNSCC [51,57].

Oral SCC

Oral squamous cell carcinoma (OSCC) and nasopharyngeal carcinoma (NPC) are commonly related to HPV infection and/or EBV virus (Epstein-Barr Virus). Variables of SCC might be present in the oral or nasopharyngeal region, but not so common at both sites at the same time. According to the newest studies, evidence shows that high-risk HPV-16 has a specific role in the main cause of oropharyngeal SCC. According to Marur et al., pharyngeal tonsils, soft palate and posterior third of the tongue are more common for squamous cell carcinoma [35]. More than 65% of oropharyngeal cancers are HPV positive, and because of that might have better prognosis than those that are HPV negative. Oral SCC is on the other hand more common on the anterior two thirds of the tongue, mouth floor, alveolus, gingiva, hard palate and buccal and labial mucosa [9, 31]. Place of occurrence might vary depending on exposure to risk factors in different anatomical parts of the oral cavity. Some studies have shown that HPV positive testing may vary in oropharyngeal sites and non-oropharyngeal sites [44]. The International Agency for Research on Cancer (IARC) concludes that the role of HPV in non-pharyngeal HNSCC in the general population is less certain. Only lesser HPV influence might be correlated with oral cavity SCC [19]. Because of different opinions on HPV involvement in OSCC, a conclusion can be made that it might be related to occurrence in different geographic regions.

In cohort analysis of 47 patients suffering from OSCC performed by Sagredo et al., no HPV genomic DNA was detected [45]. It might be a fact that HPV infection is temporary and related to malignant and premalignant lesions. On the other hand, OSCC was found on the tongue, mouth floor, oropharynx, gingiva and buccal mucosa. The authors

used a simple method to diagnose, with use of a cytological brush swabbed in the oral cavity and use of a single kit using the PCR method and targeting the L1 region of the viral genome.

HPV virus has many types and sub-types, but mostly HPV-16 is the most common type of HPV related to OSCC. Other sub-types can also be found in the oropharyngeal region.

Oral squamous-cell carcinoma in the mouth floor is related to HPV-16. Simonato et al. studies performed on mouth floor SCC using nested polymerase chain reaction (nPCR) seem to confirm that HPV-DNA is related to OSCC, and was presented in 17.2% within 29 paraffin-embedded specimens of mouth floor SCC [49]. All were diagnosed in men with clinical stage of III–IV lesions, but due to low presence of virus, it seems that it does not have a role on its own to induce an SCC, which might lead to a suggestion that only all risk factors combined together are related to OSCC. Nevertheless, a small amount of patients suffering from OSCC do not use either tobacco or alcohol, and tumors are with unknown etiology. Studies have shown that patients with HPV-DNA-positive tumors have 59% reduction in risk of cancer death compared to HPV-DNA-negative tumor patients. Moreover, HPV is more common in oropharynx SCC during more advanced clinical stages. In our opinion, based on the literature HPV could be a potential co-factor taking part in OSCC prognosis.

Gillison and Lowy conclude that in addition to alcohol and tobacco, HPV is an important agent for some HNSCC [17]. Indian research performed by Mondal et al. indicates that low levels of mtDNA (mitochondrial DNA, detected using PCR study with detection for GSTM1-GSTT1 polymorphism) content in tumors related to tobacco-betel quid chewing suggest an important marker in diagnosing invasive OSCC [36]. On the other hand, Song reported that microRNA in HPV is an important factor of OSCC, and microRNA polymorphisms may modify the association between HPV-16 and OSCC risk [52]. These findings may lead to a conclusion that microRNA may modify the risk of HPV-16 related oral SCC in patients with oropharyngeal SCC and in never smokers. Only in some cases mostly HPV-16 might be found in HNSCC. A higher amount of copies mostly can be found in the oropharynx region (posterior lingual and palatine tonsils) [52]. HPV-associated HNSCC are more frequent in non-smoking and in younger patients than in HNSCC not associated with HPV [50]. Vargas-Ferreira et al. stated that oral SCC is the fifth most common cancer type, and tobacco and alcohol are the main etiological factors, but at least 15-20% of all OSCC occurs in patients without any risk factors [48, 59]. Some etiology of OSCC still remains unknown, but HPV-related infections seem to be more related to women or bisexuals [22, 54]. Nevertheless, HPV infections are a very important factor related to oral SCC. PCR diagnostics should be routinely performed in patients with SCC.

Geographic regions and genetic predispositions are considered as important factors in HPV infections.

Oral cavity cancer in Taiwan is common in middle aged men. Huang et al. in a group of 103 patients tried to find relations with HPV infection and OSCC. 30.1% of patients were positive for HPV infections with HPV-16 in about 51.6% and HPV-18 in 22.6% [21]. According to studies, HPV-16 was not related to tumor aggressiveness, risk exposure or treatment outcome, but HPV-18 showed statistically more cases with second primary cancers (SPC). A very important issue is that HPV infections noted by Huang in head and neck cancers may be different among anatomical subsites of diseases and HR-HPV-18 (high-risk) has a 42.9% potential of occurrence of secondary primary tumors in OSCC.

Studies performed by Chow et al. in a 30-year time frame show that in patients younger than 20 years SCC were diagnosed in three to fourteen patients [61]. In laryngeal tumors more of them were positive for HPV-16, and were treated with radical surgical resection with radio- or chemotherapy. In fewer cases in children EBV virus was present. Children receiving bone marrow transplant (BMT) developed SCC earlier than those without BMT. Because of more cases with nasopharyngeal carcinomas (NPC) found in younger women, a potential epidemic should be considered [29, 40]. Very rare tumors in children are still a diagnostic and clinical problem. In patients with any history of immunosuppression, tumors, radiotherapy or even genetic predisposition to malignancies, it is very important to perform biopsies early. In younger patients some authors claim to have found relations between HPV and spinocellular carcinoma of the mouth, although Praetorius HPV-DNA research studies on oral spinocellular carcinoma (CEC) might suggest some differences [43]. Education of children on sexual behavior and early vaccination seems to be a rational way of decreasing HPV infections.

The region of head and neck is anatomically different from other parts of the human body. Because of the presence of many anatomical structures, and also the upper part of the digestive and respiratory system a careful examination should be performed in order to properly diagnose and evaluate this region.

Cancers of the upper aero-digestive tract (UADT) are involved in relation to HPV. Anantharaman et al. in the ARCAGE study performed on 1496 cancer patients and 1425 control group patients tried to associate specific HPV antibodies [2]. HPV-16L1 was most common in oral and oropharyngeal cancer, HPV-16E6 antibodies were present in 30.2% of oropharyngeal cases and just 0.8% of control subjects. Combined E6 and E7 antibodies seropositivity was rare. HPV-18 was associated with oropharyngeal cancer and HPV-6 with laryngeal cancer. In the study 47 tumors were positive for HPV-DNA, with 93.6% of HPV-16, HPV-31 4.2%, HPV-33 12.8%, HPV-35 4.2% and HPV-66 2.1%. HPV-16 E6 antibodies in UADT seem to be an important marker in identifying HPV-16 DNA.

Another condition related to HPV infection is recurrent respiratory papillomatosis (RRP). HPV-6 and HPV-11 along

larynx and/or vocal cords can cause RRP. It is well known for many benign growths in the middle and lower part of the respiratory tract. According to Larson et al., it is present in 0.504 per 100 000 cases [28]. Papillomas tend to grow inside the vocal tract slowly, and despite their surgical removal they tend to grow back slowly over a period of years. RRP can be fatal because it may cause respiratory obstruction. In juveniles RRP is common in children under five years of age, and might be related to vertical transmission from older parents or family members. RRP present in older people is observed from 20-40 years old and might be HPV-related non-cervical disease and has not been included in a vaccine [11]. HPV vaccines to prevent non-cervical HPV-related cancers are still not tested and it is not yet confirmed if they are helpful in for example HNSCC [16].

Patients suffering from HNSCC are at risk of second primary malignancies (SPM). The most common sites of diagnosed SPM are head and neck or lungs and esophagus [30]. Studies performed by Morris et al., in the past twenty years, suggest that the SPM site for patients with oral cavity and oropharynx SCC was head and neck, and for patients with laryngeal and hypopharyngeal cancer it was the lung [39]. Nowadays because of many HPV-related infections, risk of SPM related to SCC oropharyngeal is very low in any subsites. Despite that, complete surgical evaluation of each anatomical region should be performed. The authors used the data from The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) from years 1975 to 2006, gathering a total of 75 087 occurrences of HNSCC. The study shows that SPM risk was highest for index hypopharyngeal cancers. The authors hypothesize that patients with HPV-associated oropharyngeal SCC may have lower SPM risk [53].

Molecular studies performed in HPV virus and its influence on SCC seem to explain more often the nature of the virus, its structure and presence of antibodies. Immunohistochemical findings are very important factors related to proper treatment. Due to those studies, often performed chemotherapy and radiotherapy in SCC can be more accurate.

Lopes et al. made an attempt to establish the prevalence and relations of HPV-16 and HPV-18 subtypes in oral SCC in a study group of 142 using PCR and Q-PCR (type-specific quantitative PCR) [33]. During this study two files containing HPV-16 and two with HPV-18, but only two with HPV-16 had moderate viral loads with 51 and 91 viral copies per cell respectively and were positive for HPV DNA virus. Other cases had very low viral loads and lacked HPV DNA tumor cells. Because of that, Lopes et al. suggest that oncogenic HPV is uncommon in oral SCC, but only high viral loads were positive by consensus PCR. Because of little evidence that high-risk HPV is related to oral SCC, routine testing for oral cancers related to HPV is not justified, but vaccination against HPV against oropharyngeal cancers might show some protection; therefore any protection for oral cancers is in vain. Marur et al., on the other hand, emphasize that oropharyngeal cancer is distinct with P53 degradation, retinoblastoma RB pathway inactivation and P16 upregulation, but tobacco-related oropharyngeal cancer is characterized by TP53 mutation and downregulation of CDKN2A encoding P16 [35]. Therefore HPV-positive HNSCC seems to be more responsive to chemotherapy and radiation than HPV-negative disease. P16 could be useful as a marker for HPV status, but only after proper patient life style evaluation can direct laboratory and immunohistochemical diagnoses be performed.

The molecular profile of HPV-related HNSCC is different in HPV positive and negative HNSCC. TP53 protein and E6 oncoprotein are common with HPV-related HNSCC along with high levels of p16 tumor-suppressor protein. In HPV-negative cases p16 is not fully expressed. Klussmann et al. discovered that high prevalence of p16 protein correlates strongly with presence of HPV during PCR testing, and is evidence of the presence of HPV DNA in a diagnosed tumor [23]. Molecular findings in various studies show that despite many findings, HPV virus still has a lot of unknown variables. The molecular role of HPV in pathogenesis of oropharyngeal squamous-cell carcinoma was investigated by D'Souza et al. in a study group consisting of 100 patients with newly diagnosed oropharyngeal cancer and 200 control patients without cancer [8]. Many sex partners, especially a high amount of oral sex partners, was associated with oropharyngeal cancer and was significantly high with HPV-16 infection. Any oral infections with any of 37 types of HPV were seropositive for the HPV-16 L1 capsid protein. This protein was also associated with subjects with a history of tobacco and alcohol use and among those without such history. In addition, tobacco and alcohol seem to be the main factors of HNSCC but HPV-16 infection can additionally lead to it. Increasing cancers of tonsils and tongue base are related to increasing sexual practices. Vaccination of young boys and girls should lead in future to decrease of HPV-16 infections.

In most cases the standard PCR protocol is used in order to find and diagnose HPV infection, but other methods are also used quite often. Because of methods' limitations, their costs and patient acceptance, not always can better diagnostic methods be performed.

Studies by Morbini et al. performed on 56 patients diagnosed with head and neck neoplastic and preneoplastic lesions suggest high sensitivity of the Genotyping Extra assay (SPF10 LiPA), which is a great alternative for recognizing and identifying viral types of HPV in patients with head and neck cancers [37]. Tumor tissues or oral exfoliated cells can be used in order to diagnose HPV. The authors used buccal scrapes and prepared them for analysis. DNA HPV assay allows one to detect high-risk (HR), low-risk (LR) and unclassified types of HPV. HPV DNA was identified in larynx, tongue, oropharynx, mouth floor and hypopharynx with overall infection of high-risk HPV being 96.43%. The study shows that this diagnostic method is highly effective in identification and characterization of DNA HPV presented in selected cases. HR HPV infections

in head and neck can be more precisely diagnosed than when using other standard PCR methods.

All over the world, national research teams are working on HPV infection related cancers. From a practical point of view, it seems to be a great idea, because of geographical and cultural differences.

A Swedish study performed on 160 samples from patients diagnosed in 2000-2008 in Stockholm performed by Du et al. suggested that HPV-16 is associated with both cervical and tonsillar cancer lesions are variants of amino acid sequence of E6 oncoprotein [12]. Diagnosis of tonsillar squamous cell carcinoma (TSCC), cervical cancer (CC) and cervical samples (CS) shows that E6 variant R10G in HPV-16 was observed in TSCC but not in patients with CC. Studies revealed that special variants of HPV-16 especially L83V differ geographically but its prevalence is higher in TSCC compared to CC and CS. Quite an important factor is disease-free survival (DFS), defined as time from date of diagnosis to last known occasion that the patient was disease-free or the date of disease recurrence.

Greek studies performed by Kouvousi et al. on 45 patients suffering from OSCC revealed that HPV-DNA was detected in 11.1% and HR-HPV in 6.7% of OSCC [25]. In 64 cytological samples 35 were from tongue, and the lowest number, 3, from buccal mucosa, which seems to be in line with WHO findings. E6/E7 mRNA expression from HR-HPV types (16, 18, 31, 33 and 45) was found in 8.9% of samples. Still HPV-16 is the most commonly found and in this case was present in 3 out of 5 cases. Protein findings in HPV-related infections might lead to discovery of new vaccines. Poljak's review of 20 years of human papillomavirus research shows that L2 protein of HPV-16 at lysine 35 regulates the expression of a small ubiquitin-related modifier, which shows the complex interactions between HPV and host cell machinery [41]. This might lead to development of treatment focused on viral infections and HPV-induced cancers. Still more studies are taking place, but at this place lesions of cervical cancers with high-grade CIN and expression of HPV E7 are targeted with HPV therapeutic vaccines. Perhaps due to this study oral HPV and its cancerous predispositions might be cured.

Oral leukoplakia related to tobacco and alcohol is also related to HPV infections. In etiology of leukoplakia other infectious diseases and other irritant factors should be considered. The study by Majmumder et al. on XRCCI polymorphisms in DNA repair loci might modulate risk of tobacco-related leukoplakia and cancer in HPV patients, but further studies need to be performed. HPV infections significantly increase leukoplakia in HPV non-infected individuals [34].

Genetic findings and gene therapy related findings are still not yet fully used, although their value in successful therapy is very important. Gene expression profiles in HPV positive and negative oropharyngeal cancer in 119 patients with primary OSCC made by Lohavanichbutr et al. show that DNA HPV-16 virus was found in 34.5% in all studied cases [32]. Higher prevalence of HPV was found in oropharyngeal cancer than in oral cavity cancer, and no difference between gene expressions in positive and negative forms of HPV. Those findings also reported chemosensitivity to some chemotherapeutic agents used for treatment of HNSCC. Treatment of oropharyngeal cancer based on HPV status and efficacy of *cisplatin, 5-fluorouracil, paclitaxel* and irradiation seems to be one way to properly manage patients with SCC.

The WHIM syndrome (warts, hypogammaglobulinemia, infections, myelokathexis) seems to be related to OSCC. This very rare syndrome is an example of the possibility that many diseases might have multi-symptomatic representation. Cipriani et al. reported WHIM syndrome related to HPV SCC in two siblings [5]. WHIM is an autosomal dominant disease related to chemokine receptor CXCR4 mutation, and influences the immune function. Some studies have shown that WHIM syndrome might be related to oral HPV that would have further risk in OSCC.

I seem that not only standard therapies are accurate in threatening viral diseases. In studies performed on mice, some authors are researching different possible therapies. According to studies performed by Taguchi et al., using traditional Japanese herbal medicine, *Juzen-taiho-to* (JTT) and *Hochu-ekki-to* (HET), with combined *Lactobacillus* vaccine immunized orally in mice, they achieved an adjuvant effect on the mucosal type 1 immune responses to human HPV E7 [55].

Conclusions

HPV testing for cervical cancer is very common. Testing for oral HPV in the oral cavity should be associated with HPV-HNSCC, but still no adequate way of testing and diagnosis may be found. Many authors claim that standard PCR methods are useful, but few cases seem to make the difference. HPV-16 is well known as a factor strongly related to HNSCC, but so far no accurate vaccine or treatment is fully known to minimize or reduce its occurrence. So far only HPV-16 vaccine on the female genital tract is effective [10, 24]. Public awareness in patients of HPV and oral cancers is increasing slowly. Local dentists and general practitioners should inform each patient about dangerous sexual behavior and methods of oral care and regular routine dental check-ups. Knowledge and education of patients should be an important factor in preventing HPV and other viral infections. Oral cancer screening for oral and oropharyngeal cancer should be performed regularly, and reduction of alcohol and tobacco should be advised [20, 42, 46, 56, 60]. Some presented oral diseases or lesions might be correlated with HPV infections; therefore extended and precise diagnostics and patient evaluation should be performed. Patient's education, routine check-ups, and promotion of safe sexual behaviors should be implemented.

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