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HUMAN PAPILLOMAVIRUS IN THE ETIOLOGY OF HEAD AND NECK CARCINOMAS

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Background. For more than 20 years, infection with the human papillomavirus (HPV) has been of a matter of interest not only to gynecologists but also to maxillofacial surgeons and othorhinolaryngologists. HPV is generally known to be involved in cervical cancer. Recently, there are many clinical studies pointed out the potentially dangerous connection between HPV infection and head and neck carcinomas (HNC). HPV infection was identified as a possible etiological factor in 15–30% of HNC.

Methods. Aim of this article is to summarize the recent knowledge about the HPV infection with regards to etiology of head and neck cancer.

Results. It has been proven that HPV infection is related to development of head and neck cancer and that the sexual behavior has played an important role in the viral transmission. HNC of viral etiology have been observed mostly in younger people; their curability is difficult and prognosis serious.

Conclusion. Beside the well known correlation between developing of new head and neck cancer and bad habits (smoking, alcohol abuse, poor oral hygiene etc.) we should take into consideration the sexual promiscuity and alternative sexual practices. Vaccination against cervical cancer, recommended to young women, should be extended to their male partners to prevent the virus transmission and decrease the HNC incidence.

INTRODUCTION

HNC are diseases of disproportionate occurrence globally. The number of newly reported cases is estimated to be around 500,000 yearly worldwide. Traditionally, the highest incidence is in the countries of South East Asia (35–45% of the overall number of malignant tumors, 15 incidences of disease for every 100,000 inhabitants). In the Czech Republic, the percent of carcinomas of the oral cavity and oropharynx average approximately 2% of the overall number of malignant diseases (about 5.5 cases of disease per 100,000 inhabitants). In the USA, the mortality rate is between 2–4 cases of disease per 100,000 inhabitants (about 12,000 new patients per year), with a morbidity rate of approximately 5,000 people per year. Approximately 40% of those with the disease survive five years, a result that has remained unchanged for 30 years, despite advances in treatment and diagnostics[1–2]. Apart from the high mortality rate for HNC, quality of life which is often very problematic for patients with advanced oncological disease in the area of the head and neck is very important.

In the USA, there has been a definite decrease in the incidence of oropharyngeal malignancies in recent years, probably due to the decrease in number of smokers[3] in connection with an energetic anti-smoking campaign. However, this positive trend is to a marked degree compensated for by increased incidence of HNC among young men, non-smokers and non-drinkers [4–6]. In this context, there is on- going greater attention being paid to the role of HPV in the development of oropharyngeal carcinomas.

HPV

The human papillomavirus belongs to the Papovaviridae family. Roughly 100 serotypes can be found on the skin, mucous membranes of the genitals, anal opening, oral cavity, and oro- and hypopharynx. Individual serotypes have been divided into three groups according to their seriousness: low risk (e.g. *Condylomata acuminata*) – HPV types 6 and 11 belong here, intermediate, and high risk. From the perspective of HNC, HPV types 16, 18, 31, 33, and 45 are in the high risk group. These are viruses with double stranded DNA and roughly 8000 nucleotides, coding: 7 early (E) genes (E1–7), 2 L genes (late genes), and LCR. Of these, the most frequently detected type in HNC is HPV 16 occurring in 90–95% (ref.[7–13]). From the perspective of maxillofacial surgery, the most frequent representative for HPV+ tumors is type 16, followed by the markedly smaller group of 18 and 33.

Virus Detection

For detecting the virus in the mucous membrane, PCR (an oral cavity swab and/or wash[14]) is used most often for high sensitivity. Another option is histopathological detec-

tion of HPV from common samples of paraffin-embedded or deep frozen tumor tissue. A number of studies point to the significance of *in situ* hybridization using a signal amplification system, which is a relatively inexpensive method with the possibility of visualizing individual copies of HPV 16 in infected cells[15,16,17].

Among the designated types, HPV 16 is, at 90–95%, the one most often detected in cases of HNC[7–13]. The presence however of the virus alone in swabs is not a an indicator of a HPV+ tumor. Only the expression of viral oncogenes within the tumor cells plus the presence of antibodies to HPV 16 E6 and E7 in the serum of HPV+ HNC patients is unambiguously conclusive.

Many studies have demonstrated the causal connection between HPV seropositivity and the development of tumors in the oral cavity[15,18–20]. The prospective study by Mork et al.[8] shows a 14 times greater risk of developing an oropharyngeal tumor in people testing positive for the presence of HPV 16.

The Pathophysiology of Tumor Formation

In connection with the formation of a malignant tumor, Hanahan and Weinberg[15] described alteration in six physiological processes characteristic for malignant growths:

1. Autonomy in growth signals
2. Disturbed apoptosis
3. Insensitivity to anti-growth signals
4. Unlimited replication
5. Angiogenesis
6. Invasion and metastasizing

Primarily two of the so-called early genes (E6 and E7) are responsible for the malignant conversion of the HPV+ tumor cells; these genes are considered to be the most important oncogenes in this context. E6 reacts with tumor suppressor gene p53 and with this event, the path is opened to malignant transformation. On the other hand, E6 still reacts with the proapoptotic protein BAK and in this way, prevents apoptosis of the afflicted cells.

The E7 gene binds to the so-called pRB gene in the E2F-pRB complex; by loosening this binding it is possible for E2F to steer the cell towards the S phase and proliferation.

The discovery of mRNA for tumors of the oral cavity testifies to transcriptional activity, mainly of HPV 16 (ref.[21]). Integration of the viral genome into the genome of the tumorous cells is an indicator of the involvement of HPV in tumorigenesis[21].

L1 and L2 code viral capsid proteins. L1 and/or L2 can separately combine viral capsid proteins such that they are morphologically and immunologically similar to natural virions, naturally without viral DNA. This is the basis of prophylactic HPV vaccines.

The Transmission of Infection

Mucosal lesions subject to HPV infection are classed with the sexually transmitted diseases (STD) and found on the cervix, perianally as well as in the mouth. Transmission occurs via the close contact of mucous membranes, primarily during sexual intercourse. Slight injuries in the mucous membrane serve as an entry gate for HPV, which thus works into the basal layer of the epithelium[22]. Individual virions wander into the keratinocyte, whose stem cells are the primary goal of the papillomavirus infection[23]. The majority of HPV positive carcinomas have been found in the area of the oropharynx and tonsils (in up to 50% of the overall number of cases), a fact which is explained by the easier route of invasion for the virus into the basal layer of the epithelium of the tonsillar crypts[24]. There is also a difference in the incidence of HPV positive carcinomas in smokers and non-smokers. HPV 16 has been found to occur in 57.1% of smokers and in 22.5% of non-smokers[13]. D´Souza[25] found a relatively close relationship between HPV+ carcinomas in non-smokers, in relation to both antibodies and directly within the individual's tumor, contradicting both alcohol and smoking as causative in these cases. They found no evidence of any synergy between HPV infection and other causative factors of HNC. The risk of the manifestation of HPV+ oral carcinoma is demonstrably influenced by alternative sexual practices and sexual promiscuity.

Characteristics of Patients with an HPV+ Tumor

HPV+ tumors display characteristic histopathological and clinical differences to HPV– tumors. HPV+ tumor patients are more often younger, between 40–60 years of age than HPV– (ref.[17,15,26]). A number of studies call attention to the prevalence of men versus women, in an approximate ratio of 3 to 1[15,17].

Gillison et al.[17] report HPV positive patients as predominantly Caucasians with higher education and a good economic background. The most important factor, they noted was the number of sexual partners. D'Souza[25] recorded an increased risk of HPV for a number of life time partners more than 26 for vaginal intercourse and more than 6 for oral sex. Smith[20] showed that more than 4 partners in the period before the formation of the tumor indicated an increased risk of tumor of the oral cavity as opposed to the oropharynx (85% vs. 50%, $p = 0.07$). The presence of high risk HPV tends to be lower for patients who are smokers. Another risk factor is high risk HPV positivity in husbands whose partners have abnormal Pap smears or dysplasia of the cervix in their medical history. However, they found no other demographic risk, risky sexual practices, or lesions on the genitals or in the oral mucous membrane which were characteristic for HPV+ patients. In an overview of these patients, Smith[20] came to the conclusion that apropos the development of HPV positive tumors of the head and neck, the group of younger patients who listed a larger number of sexual partners and more risky alternative sexual practices in their questionnaire was more at risk. The results of this study testify to a divergent age distribution: HPV+ tumors are found predominantly in younger patients (≤ 55 yrs.).

Poorly differentiated tumors with locoregional metastasis into the lymphatic nodes predominate in HPV+ carcinomas[17,27–29]. It seems that HPV in the oral cavity produces nearly exclusively spinocellular mucosal carci-

nomas, while in the anogenital area, it can lead to the formation not only of spinocellular carcinoma, but also adenocarcinomas or small cell carcinomas of the cervix.

The prognosis for HPV+ carcinomas of the oral cavity and oropharynx, after combined treatment, appears somewhat better than for HPV negative tumors. This refers mainly to the disease-free and overall survival – primarily for oropharyngeal carcinomas[30]. This reality is explained by the lower probability of occurrence of 11q13 gene amplification, which is considered to be a factor underlying faster and more frequent recurrence of the disease[31–34].

The latest demographic studies across continents aimed at studying geographical differences in incidence of HPV+ tumors of the head and neck[35]. The prevalence of HPV+ spinaliomas of the oral cavity were the same in Europe as in North America (around 16%); however but in Asia it was 33%. In contrast, the highest prevalence of HPV+ oropharyngeal carcinomas was in North America (47%) in comparison with Europe (28%). The situation in Asia was not monitored.

Perhaps the most important condition for eradicating malignant tumors is prevention. In the case of HPV+ oropharyngeal carcinomas, this is above all about appropriate sexual education. The younger generation has taken recourse to oral sex to a greater degree as a safe sexual practice in the age of the AIDS pandemic[15]. This in turn increases the risk of introducing the virus into the oropharynx. However, perhaps the most important prevention. remains vaccination – not only for girls, but also boys. Vaccination of both boys and men in target groups could decrease the incidence of oral cancer by 25% and cancer of the tonsils by up to 50% (ref.[21]).

CONCLUSION

The role of HPV viruses of the high risk group in the development of HNC is beyond doubt. Individual studies differentiate the representation of numbers of HPV+ carcinomas within the overall number of tumors of the head and neck. More extensive studies comprising more than 100 cases show that the number of HPV+ carcinomas is between 10–45% (ref.[36]); however, individual localities were not specified in this study.

Eradicating the HNC by vaccination will be impossible but decreasing the total number of HNC could be the reason why to extent the vaccination to the younger generation in both genders.

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