SPECIAL ARTICLE

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The Significance of Human Papillomaviruses in Head and Neck Cancer Development

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ABSTRACT

Head and neck cancers (HNC) are a heterogeneous group of diseases. Histopathological, these are head and neck squamous cell carcinoma (HNSCC) epithelium of the skin, mucosa of the upper aerodigestive tract, pharynx and larynx. HNSCC is the fifth leading cause of cancer worldwide. The most important risk factors are alcohol and smoking. In the recent years, the studies have been conducted in order to prove the role of HPV in HNSCC carcinogenesis. The prevalence of HPV in HNSCC is 30%. HPV is often detected in biological materials of males. People with HPV positive HNSCC respond better to treatment and have a better treatment outcome than patients with no proven HPV. In the future, HPV should be the marker that will influence the choice of therapy in patients with HNSCC, but also the factor that will indicate the outcome of this malignancy in the human population.

Key words: HPV, head and neck cancer, diagnosis

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Introduction

According to the modified Borst´s definition „Tumor is local, atypical, autonomous and continual growth tissue".[1] Head and Neck cancer (HNC) are heterogeneus group of diseases. Histopathologically, these are head and neck squamous cell carcinoma (HNSCC) epithelium of the skin, mucosa of the upper aerodigestive tract, pharynx and larynx.[2]HNSCC is the fifth leading cause of cancer worldwide.[3] It is estimated that the annual occurrence of HNSCC is around 560.000 new cases, with the deadly outcome of 301.000 people.[4] In recent decades, the risk of HNSCC has increased in developing countries.[5] In the Unitated States (US), the increased incidence of HNSCC among young people, men and whites was recorded.6,7 According to SEER Database (Cancer statistics rewiew 1975-2010),[8] the illness rate in white and black women and men during 2010was 10.79:100.000, while the mortality was 2.47:100.000. HNSCC is more frequent in older men (>65 yeras of age), and it often affects pharynx,[9] tongue and tonsils.[5]

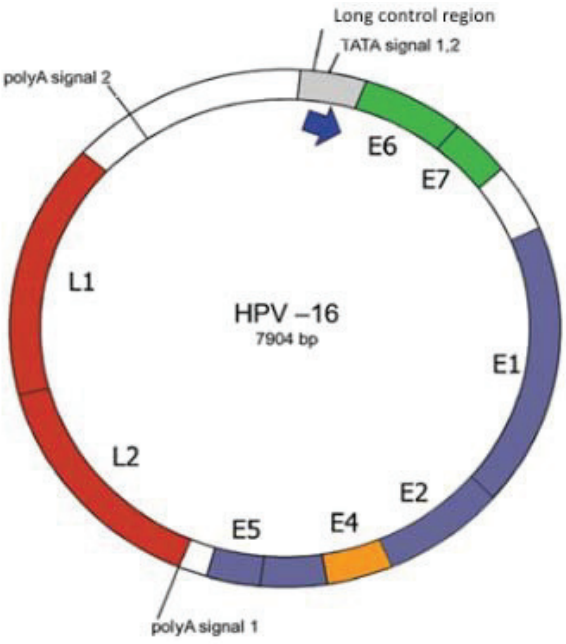
Human Papillomaviruses and HNSCC

Various factors are included in etiopathogenesis of the head and neck carcinoma. In 75%, the most important

risk factors are alcohol and smoking (over 20 cigaretas per day).[7] In recent years, studies referring to the involvement of HPV in HNSCC pathogenesis, have been conducted.[8]

HPVs are a group of double stranded, nonenveloped DNA viruses. HPV genome is consisted of circular DNA with the length of 8000bp. It is divided into: E region (early) with gene for E6 i E7 oncoproteines, E2 transcriptional factor, helicasa gene E4,E5, E1 i E2 genes; L region (late) which encodes capsid proteins L1 i L2; LCR (long control region) for viral replication and gene expression (Figure 1.).

Figure 1. HPV genome (taken from Hadžisejdić, Ita, Magdalena Grce, and Blaženka Grahovac. "Humani papiloma virus i karcinom cerviksa: mehanizmi karcinogeneze, epidemiologija, dijagnostika i profilaksa." Medicina Fluminensis 46.2 (2010): 112-123.



There are more than 150 HPV types grouped in low (6, 11, 40, 42, 43 i 44) and high (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 i 68) risk viruses.HPV is a virus that causes hyperplastic, papilomatosis and mamilla changes on squamos epithelium of skin and mucosa.9It can be present in healthy oral mucosa. HPV is well established cause of cervical cancer,[5] and due to the similarity of mucosa of anogenital and oropharngeal tissue, it is based on correlation between HPV and HNSCC.

In high-risk HPV infection, E6 and E7 oncogenes cause degradation of p53 and retinoblastoma (Rb) tumor suppresor genes,inducing genomic instablity, reducing the cell´s ability to respond to cell proliferation and DNA damage, leading to genetic instability so that they interfere with controlling spots of cell cycle and hence they prevent apoptosis, causing the futher mutation accumulation and the absence of DNA reparation. The low-risk types of HPV display a low affinity towards domestic supressing genes so these infections are self-limiting and without consequences.[4]

The prevalence of HPV in HNSCC is around 30%. This is the consequence of different geographical sites, sample size, diet, sexual bahaviour, various detection techniques for HPV. A variability in detection of HPV can be the result of different sampling methods such as biopses, oral rinses, scrapes, fresh tissue or formalin-fixed parrafin embedded tissue (FFPE).[4]

Gillison and colleagues10found HPV in 25% of HNSCC, with the most comon type being HPV 16. Patients with HPV-positive tumours had better survival rate compared to people with HPV-negative tumours. The clinical and histopathological presentation of HPV positive was distinct compared to HPV-negative cancers. HPV-positive cancers were characterized by lower tumor size,nonkeratinizing and poor tumor differentiation.10

Oral and oropharingeal squamous cell cancers are the sixth most common malignancy worldwide. The major incidence rate was shown in India and Southeast Asia due to the risk factor betel quid-chewing.[11] During 2008, around 400.000 patients with orofacial cancer was registered, with the deadly outcomeof 223.000.[11] Study which included 23 countries showed the highest incidence of oropharyngeal cancers in France, Slovakia and the United Kingdom.[10]

In recent years, the incidence of HPV-positive oropharyngeal cancers is increasing, but is decreasing for other head and neck cancers.[12] Results from the study conducted in the US showed that theHPV type 16 was the leading cause of oral infection.[12] The fact was that the number of HPV-positive cancers increased in patients who had denied the alcohol and tobacco consuption.[7]

According to Kreimer et al.[13], the incidence of HPV in HNSCC was 23.5% for oral cavity cancer, 24% for laryngeal cancer, where in the cancer prevalence was similar in both sexes. Murray et al.[14] found the HPV to be more common in precancerous lesions (leukoplakia, lichen, etc.). Murray et. colleagues[9] detected HPV in 25% of patients with oropharyngeal cancers, while the study from Asia confirmed the incidente of oral cavity carcinoma to be 66%-100%.[9] This leads us to the conclusion that combination of HPV, dietary habits and genetic predis-

position leads to formation of malignancies.The results of these studies differ from the data obtained by the research in South Africa, where the incidence of HPV-positive oral cavity cancer ranged from 0% to 11.9%.[12]

In theirmeta-analysis, Termine and colleagues3 reported that the prevalence of HPV in the oral cavity carcinoma was 38.1%, the result which was reached by the analysis of 47 studies that included analysis of samples for 3583 patients worldwide.

In recent years, number of base tongue and tonsilascancers isincreasingm, and in more than 70% of cases is more common in men.The decrease in smoking tendency is found among these patients too.[15] Kreimer et al13 reported that the prevalence of HPV in oropharyngeal cancer in North America was 47%, 46% in Asia and 28% in Europe.This diversity can be linked to the method of sampling, method for HPV detection in biological material, but it depends on anatomical localization of the sample. It has beenproven that HPV is detected in fresh tissue in significantly higher percent then intissues embedded in paraffin.[4] DNA of tissues embedded in paraffin are eventually fragmented, and in such condition, it is difficult to prove it. Therefore, it is recommended to use tissue embedded in paraffinfor five years the most. In order to avoid errors in the analysis rate of HPV prevalence for head and neck tumors, it is important to know the anatomical part the tissue samples originate from. In the study conducted in Slovenia on the sample of 62 patients, in which the presence of HPV was proven in 8.4% of patients, the detection was performed by Polymerase chain reaction(PCR) from paraffin blocks.[16] PCR method can not determine whether HPV is integrated into the human genome or in episomal form. Therefore, Reverse transcription polymerase chain reaction (RT-PCR), which indicates the activity of the virus,should be performed to confirm its association with malignant alteration of cells.[4]This is technically demanding and time-consuming method, which is why HPV is often detected with conventional PCR methods and nested PCR. Often, this is the reason for false-positive results and there is a risk of contamination with HPV from the surrounding healthy tissue. Following types of HPV: 2, 6, 7, 11, 13, 16, 18, 31, 33 and 35 were discovered in healthy oral cavity mucous. Significance of HPV presence in healthy mucosa is unknown for now. 24 different HPV types - 1, 2, 3, 4, 5, 6, 7, 10, 11, 13, 16, 18, 31, 32, 33, 35, 39 , 45, 51, 52, 55, 56, 57, 58, 59, 66, 69, 72 and 73 were detected in benign and malignant head and neck lesions.[16]

It has already been noted that, in the last 20 years, the incidence of the oral cavity and oropharynx cancer has increased, while the trend of smoking has decreased. Due to the above mentioned, the studies were conducted in order to confirm the link between tobacco and HPV with HNSCC. The increased incidence of oral cancers, usually in men younger than 60 years, who did not belong to the group of high risk patients was noted,[7] which could be linked to the change of sexual behavior.

HPV in HNSCC is an important prognostic marker that can indicate the outcome of treatment. Regardless to interdisciplinary approach to treatment, the mortality rate fot this disease has not changed for the last 40 years. According to some studies, five-year survival ranges from 40% to 50%.[3] Therefore, in the future, HPV may be the factor that influences the choice of therapy. There is also a new RNA-scope test, HPV test techniques and in situ hybridization, which detects E6 / E7 mRNA of up to 18 high-risk types. This test is not for the clinical use. There is a correlation among p16 expression and HPV positive oropharyngeal cancer. However, according to some authors, p16 is not reliable to be specific for the oncogenesis caused by HPV.

Conclusion

Currently, HPV is the most important etiological cause of cervical cancer, but this has not been proven for HNSCC yet.Regardless of this, in the future, HPV should certainly be the marker that will affect the choice of therapy in patients with HNSCC, and also the factor that will indicate the outcome of this malignancy in the human population.

References

1. Gavrić M. Maksilofacijalna hirurgija. Beograd: Draganić, 2001.
2. Marur, Shanthi, et al. "HPV-associated head and neck cancer: a virus-related cancer epidemic." The lancet oncology 11.8 (2010): 781-789. http://dx.doi.org/10.1016/S1470-2045(10)70017-6
3. Termine N, Panzarella V, Falaschini S, Russo A, Matranga D, Lo Muzio L, Campisi G. HPV in oral squamous cell carcinoma vs head and neck squamous cell carcinoma biopsies: a meta-analysis (1988-2007). Ann Oncol. 2008 Oct;19(10):1681-90. http://dx.doi.org/10.1093/annonc/mdn372 PMid:18558666
4. Cartwight, S.J. (2014) A Review of Literature Pertaining to Head and Neck Squamous Cell Carcinoma with Emphasis on the Role of the Human Papilloma Virus. International Journal of Otolarygology and Head and Neck surgery, 3, 279-292.
5. Elwood JM, Youlden DR, Chelimo C, Ioannides SJ, Baade PD. Comparison of oropharyngeal and oral cavity squamous cell cancer incidence and trends in New Zealand and Queensland, Australia. Cancer Epidemiol. 2014 Feb;38(1):16-21. http://dx.doi.org/10.1016/j.canep.2013.12.004 PMid:24445141

6. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, Jiang B, Goodman MT, Sibug-Saber M, Cozen W, Liu L, Lynch CF, Wentzensen N, Jordan RC, Altekruse S, Anderson WF, Rosenberg PS, Gillison ML. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011 Nov 10;29(32):4294-301.
http://dx.doi.org/10.1200/JCO.2011.36.4596 PMid:21969503 PMCid:PMC3221528

7. Benson E, Li R, Eisele D, Fakhry C. The clinical impact of HPV tumor status upon head and neck squamous cell carcinomas. Oral Oncol. 2014 Jun;50(6):565-74.
http://dx.doi.org/10.1016/j.oraloncology.2013.09.008 PMid:24134947 PMCid:PMC4391706

8. Venuti A, Paolini F. HPV detection methods in head and neck cancer. Head Neck Pathol. 2012 Jul;6 Suppl 1:S63-74.
http://dx.doi.org/10.1007/s12105-012-0372-5 PMid:22782225 PMCid:PMC3394157

9. Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 7th ed. St. Louis: Mosby; 2002.

10. Gillison ML, Koch WM, Capone RB, Spafford M, Westra WH, Wu L, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancer. J. Natl Cancer Inst. 2000;92:709-20.
http://dx.doi.org/10.1093/jnci/92.9.709

11. Chocolatewala NM, Chaturvedi P. Role of human papilloma virus in the oral carcinogenesis: an Indian perspective. J Cancer Res Ther 2009;5:71-7.
http://dx.doi.org/10.4103/0973-1482.52788 PMid:19542661

12. Ferlay J, Shin HR, Bray F, et al: Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 127:2893-2917, 2010.
http://dx.doi.org/10.1002/ijc.25516 PMid:21351269

13. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck cell carcinomas worldwide: a systematic review. Cancer Epidemiol Biomarkers Prev. 2005;14(2):467-75.
http://dx.doi.org/10.1158/1055-9965.EPI-04-0551 PMid:15734974

14. Syrjanen S, Lodi G, von Bultzingslowen I, Aliko A, Arduino P, Campisi G et al. Human papillomaviruses in oral carcinoma and oral potentially malignant disorders: a systematic review. Oral Dis. 2011;17 Suppl 1:58-72.
http://dx.doi.org/10.1111/j.1601-0825.2011.01792.x PMid:21382139

15. Ramqvist T, Grün N, Dalianis T. Human papillomavirus and tonsillar and base of tongue cancer. Viruses. 2015 Mar 20;7(3):1332-43.
http://dx.doi.org/10.3390/v7031332 PMid:25803099 PMCid:PMC4379573

16. Kansky AA, Poljak M, Seme K i sur. Human papillomavirus DNA in oral squamous cell carcinomas and normal oral mucosa. Acta Virol 2003;47:11-6. PMid:12828338

Značaj humanih papiloma virusa u nastanku karcinoma glave i vrata

SAŽETAK

Karcinomi glave i vrata su heterogena grupa oboljenja. Histopatološki, to su planocelularni karcinomi pločasto slojevitog epitela (engl. HNSCC) kože glave i vrata, sluznica gornjeg aerodigestivnog trakta, farinksa i larinksa. HNSCC je peti najčešći maligni tumor kod ljudi širom svijeta. U najvećem broju slučajeva HNSCC se dovodi u vezu sa konzumacijom alkohola i duvana. Poslednjih godina rađena su istraživanja čiji je cilj bio dokazati ulogu humanih papiloma virusa (HPV) u karcinogenezi HNSCC. Prevalenca HPV-a u HNSCC je oko 30%. HPV je češće detektovan u biološkom materijalu osoba muškog pola. Osobe sa HPV pozitivnim HNSCC bolje reaguju na terapiju i imaju povoljniji ishod liječenja u odnosu na pacijente kod kojih nije dokazan HPV. U budućnosti, HPV treba da bude marker koji će uticati na izbor terapije kod oboljelih od HNSCC, ali i faktor koji će ukazati na ishod ovog malignoma kod pacijenata.

Ključne riječi: HPV, karcinom glave i vrata, dijagnostika