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Human papillomavirus as an important factor in the development of oropharyngeal cancer - modern diagnostics and new therapeutic methods

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Abstract

Background. The article focuses on epidemiological trends observed globally over the past few decades, which demonstrate a dynamic increase in the incidence of HPV-positive OPC. A significant part of the paper is a discussion of the latest therapeutic and diagnostic methods, enabling the dynamic development of clinical management.

Aim. The aim of this article was to present the current state of knowledge regarding the impact of HPV infection on the development of OPC.

Material and methods. The review methodology included an analysis of 28 publications retrieved from the PubMed database, selected based on their currency and relevance to the research topic. The article primarily includes work published between 2018 and 2024, with the largest possible number of participants included.

Results. HPV-associated OPC is currently one of the fastest-growing types of head and neck cancer worldwide. HPV types 16 and 18 are responsible for the majority of cases. The disease typically has a better prognosis than its HPV-negative counterparts, which is due to the different tumor biology. The introduction and widespread use of HPV vaccinations is a key element of global prevention, potentially significantly reducing the number of new cases in the future.

Conclusions. Despite the dynamically developing knowledge about the HPV virus, we still need new diagnostic and therapeutic techniques to more effectively treat patients with OPC.

Key words: HPV, OPC, vaccination

Introduction

Human papillomavirus (HPV) infection has become a significant risk factor for the development of oropharyngeal carcinoma (OPC) in recent years [21]. In contrast to well-known risk factors such as smoking and alcohol abuse, HPV infection, especially types

16 and 18, is gaining importance as a cause of head and neck cancers, especially in developed countries [22]. Changes in sexual behavior, including an increase in the number of sexual partners, contribute to an increased risk of infection with this virus [23]. Therefore, understanding the relationship between HPV infection and OPC becomes crucial for developing effective preventive and therapeutic strategies.

HPV is a virus with a double-stranded circular DNA genotype belonging to the Papillomaviridae family. There are about 100 types of HPV viruses, including 16 groups divided into cutaneous and mucosal types depending on their affinity for specific tissues. The HPV virus is divided into non-oncogenic types - 6 and 11, mainly responsible for the formation of warts and condyloma acuminata [24] and oncogenic types - 16,18,31,33,35,39,45, involved in the development of cervical, anal, penile or oral and pharyngeal mucosal cancer [25]. It is estimated that 4.5% of cancers in the world are associated with HPV infection, and about half of adults during their lives are at least once in a lifetime be infected.[1] Infection most often occurs at a young age during sexual intercourse, but most infections are asymptomatic and are fought off by the immune system.[26]

Viral replication depends on the transcriptional mechanisms of the host. In the initial stage of infection, the virus enters the basal layer and then, thanks to early genes, causes hypertrophy of the basal layer, increasing the number of cells in the spinous and granular layers, leading to the formation of papillomatosis. The entire process takes about 3-4 months. The cells of the basal layer differentiate, leading to the release of specific nuclear factors, which facilitates transcription of viral genes. As infected cells mature, the expression of viral genes increases. In mature, differentiated cells, late genes that encode structural proteins are activated and when the cell reaches the apical layer, it dies and the virus is released. [27]

The host's immune response is important in preventing infection. A special role is played by antibodies against the L1 protein of the HPV envelope, which is the most important element of protective vaccinations, and specific IgG antibodies prevent infection after vaccination. [28]

Epidemiology

The correlation between persistent high-risk HPV infection and the development of oral squamous cell carcinoma has been known for a long time. It is estimated that up to 70% of throat cancer cases are related to HPV 16 infection [2]. At the

same time, we see a significant increase in the number of cases of oral and throat cancer, and it is also believed that the frequency of HPV+ OPC has the fastest growth rate of all HPV+ cancers. [6] In both the UK and the USA, the incidence of OPC in men has exceeded the incidence of cervical cancer in women. [7] It is estimated that in the United States, OPC is the most common cancer associated with HPV infection. [3]. In the United States alone, approximately 15,800 cases of HPV-related OPC are diagnosed each year. [17] Increasingly, cases concern people under 45 years of age [4] without risk factors such as alcohol abuse or smoking and with a better prognosis in terms of survival [5]. The problem is the lack of screening for the presence of HPV in the oral cavity compared to the widespread screening for cervical cancer, which is also, in most cases, induced by HPV.

Vaccination

The primary method of preventing HPV-related infections and cancers is HPV vaccination. Six studies with a total of 15,240 participants were included in a meta-analysis, which showed that vaccinated individuals were 46% less likely to develop oral HPV infection. A second meta-analysis, including 4 studies and a total of 13,285 participants, showed that oral HPV infection was 80% less likely to occur. [9] At the same time, therapeutic vaccinations are being developed to treat established cancer. These vaccinations target oncogenes E6 and E7. These include ADXS-HPV11-001, which uses genetically modified L.monocytogenes bacteria to induce immunity against E7 [10]. MEDI0457 (INO-3112) is an E6 and E7 vaccine, a TA-CIN vaccine developed for the treatment of squamous intraepithelial neoplasia [11]. Additionally, the PDS0101 vaccine consisting of the immune-activating cationic lipid R-DOTAP and HLA-nonrestricted HPV16 peptides, which has been shown to induce CD8+ T cells in vivo. [12] However, data are still lacking in the context of their role in the treatment of HPV+ oral cancer.

Diagnostics

Currently, molecular tests are performed to detect HPV DNA using the PCR method; however, the mere presence of the virus's genetic material does not indicate that cancer has started, because most infections resolve spontaneously. mRNA tests of E6 and E7 oncogenes [8] are used in the diagnosis of persistent infection, which allows for the detection of the beginning of oncogenesis and reduces the probability of false positive results. However, it is estimated that P16 determination with HPV DNA has higher sensitivity

than RNA testing alone [13]. Antibodies against HPV E6 have an additional application. Studies show that up to 85% of patients with HPV OPC are seropositive at the time of diagnosis, and the level of antibodies decreases after treatment. [14]

Treatment

HPV-related OPC responds better to radiotherapy and chemotherapy than cancers of other etiologies and is associated with a better prognosis. The risk of death is 28% lower, and the risk of disease recurrence is 49% lower in patients with HPV-positive OPC compared to patients with non-HPV OPC. [20]. Additionally, these tumors increasingly affect young people with no medical history. For this reason, research is being conducted to enable the patient to be cured with the least radical method possible. The method used in patients with HPV OPC is a combination of intensity-modulated radiotherapy (IMRT) in combination with cisplatin. Additionally, the NCCN 2024 and ESMO 2020 guidelines use cetuximab - a monoclonal antibody against the epidermal growth factor receptor (EGFR).

The study by Bonner et al. demonstrated a significant improvement in survival with the addition of cetuximab in patients with locally advanced OPC, with no increase in radiation-related adverse events [15]. A 5-year follow-up of 67 patients with recurrent/metastatic OPC demonstrated an increase in OS compared to chemotherapy with cetuximab of 35,7% vs. 12,5%, respectively (hazard ratio [HR] 0.38; 95% CI 0.13-1.05). [19]

An additional option for HPV+ patients is transoral robotic surgery (TORS). TORS allows surgery to be performed through the mouth, eliminating the need for large incisions in the neck. This leads to less postoperative pain, shorter recovery time, and smaller scars. With maximum precision, TORS can help preserve speech and swallowing function. The study included 96 people with stage 3 and 4 HPV+ OPC cancer, 30 (group A) treated with TORS, and 66 (group B) with IMRT. There was no statistically significant difference in survival outcomes (group A: overall survival 97%, progression-free survival 83%; group B: OS 98%, PFS 86%) or toxicity between groups. [16] Drugs such as pembrolizumab (Keytruda) and nivolumab (Opdivo) are examples of drugs that can be used to treat some head and neck cancers, including those associated with HPV. Preliminary results suggest that patients with HPV-positive OPC may have better responses to immunotherapy compared with patients with HPV-negative cancer. 52 patients with stage III-IV resectable HNSCC received neoadjuvant nivolumab (26 HPV-positive, 26 HPV-negative). Neoadjuvant nivolumab was found to be safe and induced regression in HPV-positive (23.5%) and HPV-negative (5.9%) tumors [18].

Discussion

HPV is a significant risk factor for OPC, and the number of HPV+ OPC patients is a huge challenge for today's oncology. The development of science has contributed to more accurate diagnostic and therapeutic methods in this group of patients, and therapies are still being developed. It is important to counteract HPV infections, where education and wide access to vaccinations play a key role in prevention. The direction of further research should be the improvement of diagnostic and therapeutic methods and the development of new therapies that improve patients' prognosis.

Conclusions

Despite the dynamically developing knowledge about the HPV virus, we still need new diagnostic and therapeutic techniques to more effectively treat patients with OPC.

Disclosure

Author's contribution:

Conceptualization: Joanna Madoń, Marta Czechowicz, Patryk Gadziński
Methodology: Joanna Madoń, Marta Czechowicz, Patryk Gadziński
Formal analysis: Joanna Madoń, Marta Czechowicz, Patryk Gadziński
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Writing - review and editing: Joanna Madoń, Marta Czechowicz, Patryk Gadziński
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References

[1]- Roman BR, Aragones A. Epidemiology and incidence of HPV-related cancers of the head and neck. J Surg Oncol. 2021 Nov;124(6):920-922. doi: 10.1002/jso.26687. Epub 2021 Sep 23. PMID: 34558067; PMCID: PMC8552291.

[2]-Yom SS. HPV and oropharyngeal cancer: etiology and prognostic importance. Semin Cutan Med Surg. 2015 Dec;34(4):178-81. doi: 10.12788/j.sder.2015.0182. PMID: 26650695.

[3]- Timbang MR, Sim MW, Bewley AF, Farwell DG, Mantravadi A, Moore MG. HPV-related oropharyngeal cancer: a review on burden of the disease and opportunities for prevention and early detection. Hum Vaccin Immunother. 2019;15(7-8):1920-1928. doi: 10.1080/21645515.2019.1600985. Epub 2019 May 7. PMID: 31050595; PMCID: PMC6746516.

[4]- Cerar J, Bryant KB, Shoemaker SE, Battiato L, Wood G. HPV-Positive Oropharyngeal Cancer: The Nurse's Role in Patient Management of Treatment-Related Sequelae. Clin J Oncol Nurs. 2020 Apr 1;24(2):153-159. doi: 10.1188/20.CJON.153-159. PMID: 32196001.

[5]-You EL, Henry M, Zeitouni AG. Human papillomavirus-associated oropharyngeal cancer: review of current evidence and management. Curr Oncol. 2019 Apr;26(2):119-123. doi: 10.3747/co.26.4819. Epub 2019 Apr 1. PMID: 31043814; PMCID: PMC6476447.

[6]- Lechner M, Liu J, Masterson L, Fenton TR. HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management. Nat Rev Clin Oncol. 2022 May;19(5):306-327. doi: 10.1038/s41571-022-00603-7. Epub 2022 Feb 1. PMID: 35105976; PMCID: PMC8805140.

[7]-Lechner M, Jones OS, Breeze CE, Gilson R. Gender-neutral HPV vaccination in the UK, rising male oropharyngeal cancer rates, and lack of HPV awareness. Lancet Infect Dis. 2019 Feb;19(2):131-132. doi: 10.1016/S1473-3099(18)30802-8. Epub 2019 Jan 30. PMID: 30722999.

[8]-Ndiaye C, Mena M, Alemany L, Arbyn M, Castellsagué X, Laporte L, Bosch FX, de Sanjosé S, Trottier H. HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis. Lancet Oncol. 2014 Nov;15(12):1319-31. doi: 10.1016/S1470-2045(14)70471-1. Epub 2014 Oct 16. Erratum in: Lancet Oncol. 2015 Jun;16(6):e262. doi: 10.1016/S1470-2045(15)70270-6. PMID: 25439690.

[9]-Tsentemeidou A, Fyrmpas G, Stavrakas M, Vlachtsis K, Sotiriou E, Poutoglidis A, Tsetsos

N. Human Papillomavirus Vaccine to End Oropharyngeal Cancer. A Systematic Review andMeta-Analysis. Sex Transm Dis. 2021 Sep 1;48(9):700-707. doi: 10.1097/OLQ.0000000000001405. PMID: 34110733.
[10]-Cory L, Chu C. ADXS-HPV: a therapeutic Listeria vaccination targeting cervical cancers expressing the HPV E7 antigen. Hum Vaccin Immunother. 2014;10(11):3190-5. doi: 10.4161/hv.34378. PMID: 25483687; PMCID: PMC4514130.
[11]- Hasan Y, Furtado L, Tergas A, Lee N, Brooks R, McCall A, Golden D, Jolly S, Fleming G, Morrow M, Kraynyak K, Sylvester A, Arif F, Levin M, Schwartz D, Boyer J, Skolnik J, Esser M, Kumar R, Bagarazzi M, Weichselbaum R, Spiotto M. A Phase 1 Trial Assessing the Safety and Tolerability of a Therapeutic DNA Vaccination Against HPV16 and HPV18 E6/E7 Oncogenes After Chemoradiation for Cervical Cancer. Int J Radiat Oncol Biol Phys. 2020 Jul 1;107(3):487-498. doi: 10.1016/j.ijrobp.2020.02.031. Epub 2020 Mar 7. PMID: 32151670; PMCID: PMC7705948.
[12]- Smalley Rumfield C, Pellom ST, Morillon Ii YM, Schlom J, Jochems C. Immunomodulation to enhance the efficacy of an HPV therapeutic vaccine. J Immunother Cancer. 2020 Jun;8(1):e000612. doi: 10.1136/jitc-2020-000612. PMID: 32554612; PMCID: PMC7304848.
[13]-Broglie Däppen MA. HPV-assoziierte Oropharynxkarzinome: Update zu Diagnose und Management [Update for Diagnosis and Management of HPV-Driven Oropharyngeal Cancer]. Praxis (Bern 1994). 2020 Jul;109(9):697-703. German. doi: 10.1024/1661-8157/a003484. PMID: 32635845.
[14]- Zhang Y, Waterboer T, Haddad RI, Miles BA, Wentz A, Gross ND, Fakhry C, Quon H, Lorch JH, Gourin CG, Clayburgh D, Misiukiewicz KJ, Richmon JD, Andersen PE, Posner MR, D'Souza G. Human papillomavirus (HPV) 16 antibodies at diagnosis of HPV-related oropharyngeal cancer and antibody trajectories after treatment. Oral Oncol. 2017 Apr;67:77-82. doi: 10.1016/j.oraloncology.2017.02.004. Epub 2017 Feb 15. PMID: 28351584; PMCID: PMC5788011.
[15]-Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, Raben D, Baselga J, Spencer SA, Zhu J, Youssoufian H, Rowinsky EK, Ang KK. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol. 2010 Jan;11(1):21-8. doi: 10.1016/S1470-2045(09)70311-0. Epub 2009 Nov 10. Erratum in: Lancet Oncol. 2010 Jan;11(1):14. PMID: 19897418.
[16]- Zorzi SF, Agostini G, Chu F, Tagliabue M, Pietrobon G, Corrao G, Volpe S, Marvaso G,

Colombo F, Cossu Rocca M, Gandini S, Gaeta A, Ruju F, Alterio D, Ansarin M. Upfront transoral robotic surgery (TORS) versus intensity-modulated radiation therapy (IMRT) in HPV-positive oropharyngeal cancer: real-world data from a tertiary comprehensive cancercentre. Acta Otorhinolaryngol Ital. 2022 Aug;42(4):334-347. doi: 10.14639/0392-100X-N2144. Epub 2022 Aug 8. PMID: 35938555; PMCID: PMC9577690.
[17] -Viens LJ, Henley SJ, Watson M, Markowitz LE, Thomas CC, Thompson TD, Razzaghi H, Saraiya M. Human Papillomavirus-Associated Cancers - United States, 2008-2012. MMWR Morb Mortal Wkly Rep. 2016 Jul 8;65(26):661-6. doi: 10.15585/mmwr.mm6526a1. PMID: 27387669.
[18] -Ferris RL, Spanos WC, Leidner R, Gonçalves A, Martens UM, Kyi C, Sharfman W, Chung CH, Devriese LA, Gauthier H, Chiosea SI, Vujanovic L, Taube JM, Stein JE, Li J, Li B, Chen T, Barrows A, Topalian SL. Neoadjuvant nivolumab for patients with resectable HPV-positive and HPV-negative squamous cell carcinomas of the head and neck in the CheckMate 358 trial. J Immunother Cancer. 2021 Jun;9(6):e002568. doi: 10.1136/jitc-2021-002568. Erratum in: J Immunother Cancer. 2021 Aug;9(8):e002568corr1. doi: 10.1136/jitc-2021-002568corr1. PMID: 34083421; PMCID: PMC8183204.
[19]-Oridate N, Takahashi S, Tanaka K, Shimizu Y, Fujimoto Y, Matsumoto K, Yokota T, Yamazaki T, Takahashi M, Ueda T, Hanai N, Yamaguchi H, Hara H, Yoshizaki T, Yasumatsu R, Nakayama M, Shiga K, Fujii T, Mitsugi K, Takahashi K, Nohata N, Gumuscu B, Lerman N, Tahara M. First-line pembrolizumab with or without chemotherapy for recurrent or metastatic head and neck squamous cell carcinoma: 5-year follow-up of the Japanese population of KEYNOTE-048. Int J Clin Oncol. 2024 Dec;29(12):1825-1839. doi: 10.1007/s10147-024-02632-x. Epub 2024 Oct 9. PMID: 39382718; PMCID: PMC11588814.
[20]- Adelstein DJ, Ridge JA, Gillison ML, Chaturvedi AK, D'Souza G, Gravitt PE, Westra W, Psyrri A, Kast WM, Koutsky LA, Giuliano A, Krosnick S, Trotti A, Schuller DE, Forastiere A, Ullmann CD. Head and neck squamous cell cancer and the human papillomavirus: summary of a National Cancer Institute State of the Science Meeting, November 9-10, 2008, Washington, D.C. Head Neck. 2009 Nov;31(11):1393-422. doi: 10.1002/hed.21269. PMID: 19787782.
[21]-Hennessey PT, Westra WH, Califano JA. Human papillomavirus and head and neck squamous cell carcinoma: recent evidence and clinical implications. J Dent Res. 2009 Apr;88(4):300-6. doi: 10.1177/0022034509333371. PMID: 19407148; PMCID: PMC3317947.
[22]-Garbuglia AR. Human Papillomavirus in Head and Neck Cancer. Cancers. 2014;

6(3):1705-1726. https://doi.org/10.3390/cancers6031705
[23]-Farsi NJ, El-Zein M, Gaied H, Lee YC, Hashibe M, Nicolau B, Rousseau MC. Sexual behaviours and head and neck cancer: A systematic review and meta-analysis. CancerEpidemiol. 2015 Dec;39(6):1036-46. doi: 10.1016/j.canep.2015.08.010. Epub 2015 Sep 12. PMID: 26372414.
[24]- Mlynarczyk-Bonikowska B, Rudnicka L. HPV Infections—Classification, Pathogenesis, and Potential New Therapies. International Journal of Molecular Sciences. 2024; 25(14):7616. https://doi.org/10.3390/ijms25147616
[25]- Muñoz N, Bosch FX, de Sanjosé S, Herrero R, Castellsagué X, Shah KV, Snijders PJ, Meijer CJ; International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003 Feb 6;348(6):518-27. doi: 10.1056/NEJMoa021641. PMID: 12571259.
[26]- Christopoulos P, Papadias K, Panoulis K, Deligeoroglou E. Human papilloma virus in adolescence. Clin Exp Obstet Gynecol. 2008;35(4):248-51. PMID: 19205436.
[27]- Graham SV. The human papillomavirus replication cycle, and its links to cancer progression: a comprehensive review. Clin Sci (Lond). 2017 Aug 10;131(17):2201-2221. doi: 10.1042/CS20160786. PMID: 28798073.
[28]- Kiamba EW, Goodier MR, Clarke E. Immune responses to human papillomavirus infection and vaccination. Front Immunol. 2025 Jun 16;16:1591297. doi: 10.3389/fimmu.2025.1591297. PMID: 40589751; PMCID: PMC12206648.