
THE ROLE OF HPV AS A RISK AND A PROGNOSTIC FACTOR IN HEAD AND NECK SQUAMOUS CELL CARCINOMA

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Summary

The aim of the study is to identify the risk factors and prognostic factors and to test whether the HPV presence is an independent factor of survival. 86 patients with oral/oropharyngeal cancer and 75 controls were enrolled. HPV DNA detection and typing was performed by PCR and reverse line blot hybridization. Risk factors and clinical data were analyzed together with the presence of HR HPV in the tissue. The exposure to tobacco and alcohol were the most significant risk factors. HPV DNA was detected in 61.6% of tumour tissue samples. The prevalence of HPV DNA was lower in oral than in oropharyngeal tumours, and higher in never smokers and never drinkers. HPV DNA presence was not related to gender, age, number of lifetime sexual partners or practice of oral-genital sex, size of tumour or presence of regional metastases. HPV positive patients had significantly better overall and disease specific survival rates than HPV negative patients. Analyses showed that prognostic factors were presence of HPV in the tumour, extra capsular spread and tumour size.

The most important risk factors are tobacco and alcohol consumption. A distinct subgroup of tumours has etiological relation to HPV. HPV was the most significant prognostic factor and possibly should be considered in treatment decisions.

Key words: HPV, oral cancer, oropharyngeal cancer, risk factors

INTRODUCTION

The incidence of oral/oropharyngeal tumours (ICD-10: C01–C06, C9–10) in the Czech Republic (CR) is relatively high: 12.2 /10⁵ for males and 3.1 /10⁵ for females. In contrast to laryngeal cancer, the incidence rates of oral cavity/oropharyngeal cancers have increased steadily in CR in recent years. Tobacco and alcohol consumption are considered to be the main risk factors in the aetiology of head and neck squamous cell carcinoma (HNSCC). However, the aetiology is multifactorial and genetic factors, diet,

occupational exposure and life style can also be implicated in the development of these cancers. High-risk human papillomavirus (HR HPV) infection is thought to play a role in a proportion of HNSCC. Distinct clinical and epidemiological characteristics have been found in patients with HR HPV positive tumours in different population. Molecular biology studies support the hypothesis that these cancers can be a consequence of HR HPV infection. The highest prevalence of HPV positive tumours in HNSCC is detected in the oropharynx and particularly in tonsils. Prognostic factors are important for treatment decisions as they help to adapt the therapy on a case-to-case basis. Some studies suggest that HPV presence favourably influences the prognosis. Traditionally nodal status, number of positive nodes, and presence of extra capsular spread are considered to be the most important prognostic factors in head and neck cancer.

The aims of our work were to find out the risk factors of oral/oropharyngeal cancer and to identify the differences between HPV positive and negative cases in the exposure to the traditional risk factors and in sexual behavior. Furthermore, the survival, prevalence and type of regional metastases in patients with HPV positive and negative tumours in the Czech population were compared, to identify prognostic factors and to find out whether the HPV presence is an independent factor influencing the survival.

MATERIALS AND METHODS

For the risk factors study 86 patients with a primary cancer of oral/oropharyngeal cancer and 75 controls were enrolled. The exposure to risk factors was elicited from questionnaires. The presence of HPV DNA was detected in tumor tissue and saliva of patients and in saliva taken from controls by means of polymerase chain reaction (PCR) and reverse line blot hybridization (RLB). Odds ratio was calculated by multivariate analysis to show the importance of different risk factors.

The prognostic factors study included 81 patients treated by surgery including the neck dissection for oral or oropharyngeal squamous cell cancer. A computerized medical report was completed for each patient. Analysis of the tumour specimen for the HPV DNA presence was done by the same method as above. Survival was measured in days from the date of diagnosis until death or until the date the patient was last known to be alive. Time-to-event measures were estimated by the Kaplan-Meier method. The significance of the difference in survival rates between the HPV positive and negative groups was analyzed by the log-rank test. Correlation between the variables and HPV positivity or survival was analyzed by implementing the logistic multivariate regression method.

RESULTS

The exposure to tobacco and alcohol were the most significant risk factors, others were lower education and higher number of lifetime sex partners. HPV DNA was detected in 61.6% of tumor tissue samples and in 48.8% of oral lavages of cases and in 9.3% of controls. In the control group, except for one sample, only LR or skin HPV types were detected. Among the HPV DNA positive tumours, 73.8% contained HPV16. The prevalence of HPV DNA was lower in oral (18.2%) than in oropharyngeal (68%) tumors, and higher in never smokers (100%) and never drinkers (77.8%). Within the group of cases HPV DNA presence was not related to gender, age, number of lifetime sexual partners or practice of oral-genital sex, size of tumour or presence of regional metastases.

HPV positive patients had significantly better both overall and disease specific survival rates than HPV negative patients ($P=0.0112$ and $P=0.0015$, respectively). In the multivariate Cox regression analyses, the improved survival of patients with HPV positive tumours was also confirmed in the presence of additional cofactors – alcohol and tobacco consumption, age, gender, tumour location, tumour grade, tumour size (T), incidence and extent of lymph node metastasis (N), number of positive nodes and ECS – in both models. The strongest significant prognostic factor of survival found in our study was the presence of HPV in the tumour. Gender, ECS and tumour size were identified as additional prognostic factors. The HPV presence seems to be associated with better prognosis and survival, while being a male and having one or more lymph nodes with ECS was found to be a factor, which significantly worsens the survival. A higher T classification also may increase the risk of dying.

CONCLUSIONS

The most important risk factors of oral/oropharyngeal cancer in the Czech population are tobacco and alcohol consumption. A distinct subgroup of tumors has probably etiological relation to HPV. HPV status is one of the most important prognostic factors for oropharyngeal cancer and should be considered also in clinical treatment decisions.

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