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Human Papillomavirus-Associated Oropharyngeal Carcinoma: Trends in Epidemiology and Methods for Detecting the Virus in a Tumor

Nurov Jamshid Raxmatovich
Bukhara state medical institute, department of oncology and medical radiology

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ABSTRACT

Oropharyngeal squamous cell carcinoma (OSCC) has traditionally been associated with exposure to tobacco smoke and alcohol. However, in the past 30 years, despite a decrease in the prevalence of smoking, there has been a stabilization and subsequent increase in the incidence of OSCC. This rate increased mostly among middle-aged white men (including never-smokers or quitters). This cohort differs from the usual OSCC patients, elderly people with a long history of smoking or drinking. This increase in the incidence of OSCC is currently associated with human papillomavirus (HPV) infection. HPV is transmitted sexually, and oral-genital contact can lead to HPV infection of the mouth and oropharynx. There are many types of HPV, but the vast majority of HPV-associated cases of OSCC are caused by type 16 virus. This review discusses the epidemiology of HPV-associated OSCC, the prevalence of HPV infection of the oral cavity and/or oropharynx, and methods for detecting the virus in tumor cells.

RELEVANCE

Head and neck cancer is one of the most common forms of cancer. In the structure of mortality from cancer, it takes 8th place. Epidemiological studies show an increase in the incidence of oropharyngeal squamous cell carcinoma (OSCC), especially in the tonsils and root of the tongue. According to US statistics, in 1973 about 18% of all cases of head and neck cancer were oropharyngeal cancer, and in 2004 the incidence of cancer of this localization increased to 31%. Recent studies have revealed that a significant number of cases of OSCC worldwide are associated with human papillomavirus (HPV) infection. The role of HPV in increasing the prevalence of OSCC in the US and Europe is discussed [1].

More than 100 different types of HPV have been identified, 15 of which are thought to be high risk factors for OSCC. HPV type 16 is found in over 90% of cases of HPV-associated OSCC. HPV infection as an independent risk factor for the development of OSCC must be taken into account along with smoking and alcohol consumption [1]. Sexual transmission of HPV is suspected in patients with OSCC (oral-genital contact).

Trends in the epidemiology of human papillomavirus-associated oropharyngeal squamous cell carcinoma The typical patient with HPV-associated OSCC is a nonsmoking, middle-aged Caucasian male of high socioeconomic status who has oral-genital sex with multiple sexual partners [2] . OSCC patients infected with HPV tend to be younger than non-infected OSCC patients [1]. In 2008, the US National Cancer Institute analyzed SEER (Surveillance, Epidemiology, and End Results) registry data from 1973 to 2004 and concluded that the

incidence of OSCC increased in a certain age group - among middle-aged people. Since 2000, it has grown by 10% per year. Among people younger than 40 years and older than 59 years, the incidence of OSCC did not change significantly [3].

V. Mehta et al. also used the SEER registry to compare the incidence of OSCC across different age groups, but at a later time period (1973 to 2006). They found that the proportion of patients aged 40–59 increased from 35% to 45%, while the proportion of patients aged 60–79 decreased from 52% to 40% [4].

In men, HPV infection of the oral cavity and oropharynx is found more often than in women. This may be due to the structure of the mucous membrane of the genital organs of women, on which the viral load is greater than on the mucous membrane of the genital organs of men. Therefore, during oral sexual contact with a woman, a man receives a greater viral load than vice versa.

L.M. Brown et al. also revealed an increase in the incidence of OSCC among Caucasian men, due to which the pre-existing racial differences in the incidence of OSCC almost leveled out [5]. At the end of the 80s of the XX century. among African-American men, the incidence of OSCC was 2 times higher than among Caucasians, but the increase in the incidence of OSCC among white men and its decrease among African-American men led to the alignment of these indicators [3].

HPV-infected OSCC patients are less likely to smoke: 30% of them are non-smokers (less than 5% of non-smokers among non-HPV-infected OSCC patients) [6]. Patients with HPV-associated OSCC are also less likely to consume alcohol compared to OSCC patients not infected with HPV or patients with other head and neck squamous cell carcinoma [7].

Over the past few decades, a decrease in the average age of first sexual contact and an increase in the average number of sexual partners have been revealed, which increases the likelihood of HPV infection [8]. The risk of HPV-induced infection of the oral cavity and oropharynx increases in proportion to the number of sexual partners [9]. Patients with OSCC associated with HPV probably have more than 8-10 sexual partners, and possibly more than 4 partners with whom they had oral-genital sex [10-13]. However, lifestyle features are considered only predictors of HPV status in patients with OSCC [14]. Considering the prevalence of HPV infection of the oral cavity and oropharynx (about 7%), it can be argued that in most cases of HPV infection, cancer does not develop, since HPV is usually eliminated by the immune system. Delayed elimination of HPV may be a risk factor for OSCC.

By 2020, the predicted incidence of HPV-associated OSCC will exceed the incidence of cervical cancer, and by 2030, it is expected that half of the cases of head and neck cancer will be associated with HPV [15]. In North America, Europe, and Australia, there has been an increase in the incidence of OSCC associated with HPV [15, 16]. A similar trend has not been clearly identified in South America, Africa, and Asia, but large population-based studies that would use a clear classification of cancer by location have not been conducted in these regions, and differences in sexual culture and an increase in prevalence smoking may mask the trend under discussion.

The vague classification of oropharyngeal tumors and the presence of transitional cases may lead to an incorrect definition of OSCC. The list of OSCC localizations is constantly changing: some types of oropharyngeal cancer were previously erroneously classified as oral cavity cancer (mostly cancers of the root of the tongue, which are often coded as cancer of the tongue) [17, 18].

Among carcinomas of all oropharyngeal localizations, OSCC of the tonsils and root of the tongue is most clearly associated with HPV, and the proportion of cancers of these localizations

in the overall structure of OSCC increases [17].

Human papillomavirus association with tonsil cancer

The tonsils are the most common localization of OSCC. By the end of 2002, 432 patients with tonsil cancer had been screened for HPV DNA. The detection rate of HPV DNA was 51% [19].

In 18 studies conducted in different countries, the frequency of detection of HPV DNA in patients with tonsil cancer varies from 12.6% to 90.9% [19] (see table). Only in 1 report the detection rate was <20%, in 9 publications <50%, and in 4 papers it exceeded 80%. In the study by A. Venuti et al. the frequency of detection of HPV DNA was significantly higher in tonsil cancer than in tumors of other areas of the head and neck. Viral load was also higher in tonsil cancer. A high copy number of HPV DNA was observed in this region, which indicates a high probability of viral carcinogenesis [20]. In recent decades, several studies have demonstrated an increase in the incidence of tonsil cancer [19, 21].

A. Ryerson et al. found that the incidence of HPV-associated tonsil cancer increased in the United States between 1998 and 2003 [22]. Similar results were obtained in Greece for the period 1986-2007. In tonsil cancer, HPV type 16 was more common than HPV types 6, 18, 33, 35, and 58. HPV type 16 is found in approximately 40% of tonsil carcinomas [19]. HPV-positive tumor status is associated with female sex and young age [19, 23]. In a study by H. C. Hafkamp et al. HPV detection rate also correlated with low differentiation, small tumor size, and locoregional metastasis [24].

Methods for the detection of human papillomavirus in carcinoma cells

Differences in data on the prevalence of HPV-associated tumors may be due to the imperfection of methods for detecting HPV [25], which may contribute to an increase in the frequency of false positive results. Despite this, the frequency of HPV-associated squamous cell carcinoma of the oropharynx consistently remains the highest among carcinomas of other sites — the oral cavity, larynx, or lower pharynx [26].

The association of HPV with oropharyngeal cancer has been proven by detecting HPV DNA in OSCC cells and by detecting anti-HPV antibodies (seropositivity). In oropharyngeal tumor cells, HPV DNA was detected 7.7 times more often (hazard ratio (RR) 7.7; 95% CI 4.0–15.0) than in carcinoma cells of other localizations. It was also found that in patients with a positive serological test for the presence of HPV type 16, the risk of developing oropharyngeal cancer was 14 times higher compared with that in patients with a negative result (RR 14.4; 95% CI 3 .6–58.1) [1]. Seropositivity is not an accurate criterion for past HPV infection, as the likelihood of false negative results is high. Currently, there is no sufficiently sensitive and specific test to detect a previous HPV infection if the virus has been eliminated from the primary site of infection. HPV is detected in 65–100% of the adult population in the oral cavity, genital area, or anal area [27, 28].

For the diagnosis of HPV, 2 methods are used - polymerase chain reaction (PCR) and fluorescent in situ hybridization. Both methods have advantages and disadvantages. Several HPV-specific PCR tests have been approved for clinical use, but are not available in all laboratories. The application of the method requires special skills, as well as laboratory conditions to avoid contamination. Detection of HPV using fluorescent in situ hybridization proves the presence of the virus genome by detecting microRNA or DNA in the tumor cell nucleus and is a highly specific test, but less sensitive than PCR. This method does not differentiate between integrated and non-integrated genomes [29]. In the studies included in the review by C. Gronh0j Larsen et al., when using PCR, 49.6% of tumors were HPV-positive, when using fluorescent in situ hybridization - 59.8%, and when using sequential use of 2 methods — 52.9% [30].

Correlation of overexpression of p16 protein and detection of human papillomavirus in oropharyngeal carcinoma

The presence of HPV DNA is not enough for a clear qualification, since HPV infection may be biologically inactive and may not cause malignant cell transformation. Immunohistochemical determination of p16 protein expression is often used as a surrogate biomarker to detect HPV infection and viral oncoprotein activity.

An increase in the expression of the p16 protein appears as a compensatory mechanism for uncontrolled cell division, which is mediated by the inactivation of the pRb protein. The p16 protein plays a key role in the regulation of the cell cycle, being a product of the tumor growth suppressor gene CDKN2A (cyclin-dependent kinase inhibitor 2A, inhibitor of cyclin-dependent kinase 2A). The p16 protein is expressed on the surface of HPV-positive OSCC cells. Most HPV-negative tumors lack the p16 protein [31, 32].

In the presence of transcriptionally active HPV, the hypophosphorylated retinoblastoma protein (pRb) binds to the HPV E7 oncoprotein, which allows the E2F transcription activator to be constitutionally active and effectively block the negative feedback of the free pRb protein on the p16 gene. This is how p16 is overexpressed. Regardless of treatment options, patients with OSCC and p16 overexpression have a better prognosis and clinical outcomes [33].

Immunohistochemical determination of the degree of p16 expression is an affordable procedure, the cost of which is significantly less than the cost of HPV-specific tests [34].

Unified approaches to the determination of p16 overexpression have not been developed. C. Gronh0j Larsen et al. studied the method for determining p16 protein expression in HPV-positive and HPV-negative OSCC by immunohistochemical staining of tumor tissues [30]. They analyzed 39 studies: in 22, the PCR method was used, in 6, the method of immunohistochemical staining of histological material, in 11, both methods were used sequentially. HPV-positive tumor status was established in 52.2% of cases. In 17 studies, staining of 5-69% of tumor cells was used as a criterion for overexpression of p16, and in 7 studies, staining of 70% of cells. 15 studies used a verbal system to assess HPV status. Thus, high heterogeneity was revealed in the diagnosis of HPV and the determination of overexpression of the p16 protein.

A correlation between the presence of HPV and overexpression of p16 has been observed in studies in which staining of more than 70% of tumor cells was the criterion. Verbal determination of p16 expression had a significantly lower number of false positive results, but the sensitivity of this method was lower. In studies where staining of 5–69% of cells was used as a criterion for p16 overexpression, lower sensitivity was also demonstrated. It was also concluded that morphological examination is not enough to establish the presence of HPV, although HPV-positive OSCC is often described as cancer without keratinization or basal cell carcinoma [30].

The American College of Pathologists recently proposed an algorithm for detecting p16 protein expression to detect high oncogenic risk HPV infection. All patients with OSCC should be tested for the presence of HPV by immunohistochemical analysis of p16 expression, and additional methods for detecting HPV can be applied at the request of the pathologist and/or oncologist or when participating in a clinical trial. Expression of p16 in 70% or more of tumor cells with moderate and intense nuclear and cytoplasmic staining is considered a surrogate marker for the presence of HPV in the tumor. Such HPV testing by a surrogate marker should be performed in patients with metastatic squamous cell carcinoma with an undiagnosed primary focus in the neck and in the presence of metastatic lymph nodes in the neck. It has been found that smoking history does not affect the need to establish HPV status [36]. Since 2017, the International Union Against Cancer (IUAC) and the American Joint Committee on Cancer (AJCC) in the TNM

classification of the 8th revision propose to use for p16 -positive OSCC separate staging system [37].

CONCLUSION

The occurrence of OSCC has traditionally been associated with exposure to tobacco smoke and alcohol, but in the past 30 years there has been an increase in the incidence of OSCC among middle-aged white men, including those who have never smoked or quit smoking. This trend is explained by exposure to HPV, which is transmitted through oral-genital sexual contact. The vast majority of HPV-associated cases of OSCC are caused by type 16 virus.

The studies demonstrate the difficulties of HPV diagnostics and accompanying analysis — immunohistochemical analysis of p16 expression, since a single criterion for p16 overexpression — the exact percentage of stained and non-stained tumor cells — has not been developed. This number varies from 5 to 75%. Some studies use less specific verbal criteria, such as "diffuse and strong nuclear and cytoplasmic staining" [34, 35]. This may present a problem, as varying degrees of staining may correlate differently with the HPV status of the tumor. Staining patterns should clearly separate a transcriptionally active HPV infection from an inactive one. In clinical practice, this can play an important prognostic role. However, since 2017, IUAC and AJCC in the 8th revision of the TNM classification have proposed using a separate staging system for p16-positive OSCC, and p16 expression, which detects 70% or more of tumor cells with nuclear and cytoplasmic staining of moderate and intense , consider as a surrogate marker of HPV in the tumor.

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