PAPILLOMA VIRUS AND POTENTIALLY MALIGNANT DISORDERS OF ORAL CAVITY

PAPILLOMA VIRUS E LESIONI DELLA MUCOSA ORALE. INFEZIONE E AUMENTO DEL POTENZIALE DI DEGENERAZIONE MALIGNA

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Parole chiave: Papilloma virus umani, lesioni potenzialmente maligne, prevenzione del carcinoma orale
Abstract

**Background:** Oral cancer has been associated with several risk factors such as smoking, alcohol, irritants and irradiation. The presence of HPV in oral cancers suggests that HPV may play a similar role in transforming the oral epithelia.

**Objectives:** A significant association was appreciated between infection with human papillomavirus (HPV), squamous cell carcinoma and potentially malignant disorder of the oral cavity, such as leukoplakia, erythro-leukoplakia erythroplakia. This review will attempt to focus on relevant characteristics of HPV, analyze its role in oral cancer and discuss some emerging developments.

**Methods:** From the critical analysis of the current literature, many studies evaluating different markers of exposure and viral activity in tumors were collected. Several studies have investigated the prevalence of HPV in these cancers, but the prevalence of HPV detection varies broadly, depending on the population, combination of sub-sites, typology of specimen and method of detection.

**Results:** The majority of HPV-related cancers contain HPV DNA integrated into the host cell genome and express only two viral genes, E6 and E7, both of which encode oncoproteins. Data appearing in the literature have provided strong evidence that HPVs may be the cause of a defined subset of head and neck cancers and also an indicator of improved survival.

**Conclusions:** While the role of HPV infection in the onset of cervix cancer is now well established, there is little information on the prevalence, determinants and natural history of the infection in the oral mucosa, and further studies are needed to clarify the potential role of HPV in the onset of oral cancer.

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**Introduzione:** L’insorgenza del cancro orale è stata associata a diversi fattori di rischio, quali tabagismo, alcool, sostanze irritanti e radiazioni.

**Obiettivi:** E’ stata evidenziata una significativa associazione tra infezione da papillomavirus umano (HPV), carcinoma orale a cellule squamose e, anche se in modo variabile, lesioni potenzialmente maligne della cavità orale, quali leucoplakia, eritro-leucoplakia eritroplakia. Questo articolo ha lo scopo di descrivere le caratteristiche principali dell’HPV e analizzare il suo ruolo nello sviluppo del carcinoma.

**Metodi:** Dall’analisi critica della letteratura corrente, sono stati selezionati diversi studi volti a valutare il grado di esposizione e l’attività virale in alcuni tumori. Diversi studi hanno analizzato la prevalenza dell’HPV in questi tumori, ma i risultati sono contrastanti, essendo collegati alla popolazione dello studio, al tipo di analisi e di prelievo.

**Risultati:** La maggior parte delle neoformazioni maligne correlate ad infezione da HPV, contengono DNA virale integrato nel corredo genetico della cellula ed esprimono due geni virali, E6 ed E7, che codificano entrambi per oncoproteine. Dati presenti in letteratura, hanno evidenziato che l’HPV possa essere l’agente causale di uno specifico tipo di tumore della testa e del collo e anche un indicatore di prognosi.

**Conclusioni:** Mentre il ruolo dell’infezione da HPV nell’insorgenza della cervice uterina è oggi ben accertato, scarse sono le informazioni sulla prevalenza, i determinanti e la storia naturale dell’infezione della mucosa orale, e altri studi sono necessari per chiarire il potenziale ruolo oncogeno dell’HPV nell’insorgenza del carcinoma orale.
Background
The oral and oropharyngeal cancer is a major public health problem worldwide. In Italy, with about 4000 new cases a year, the epidemiological trend stood on constant values, without improvements in the last two decades. Tobacco use and alcohol abuse are the two main causal factors with an incidence of approximately 90% of cases. Other causal factors found are dietary deficiencies (especially as regards the lack of a suitable supply of vitamins, antioxidants and micronutrients) and poor oral hygiene (1-10).

Objectives
In recent years, we investigated the role of the Human Papilloma Viruses (HPVs) in the oral oncogenesis. The Human papilloma viruses (HPVs) are a diverse group of viral agents belonging to the Papillomaviridae family. About 200 different genotypes of human HPVs genotypes are classified into high-risk (HPV 16, 18, 31, 33, etc.), associated with malignant and potentially malignant lesions and low-risk genotypes (including HPV 2, 4, 6, 11, 13, 32), most commonly associated with benign manifestations (common warts, condylomas) (2-3).
The aim of this article is to describe the main features of HPV infection in the oral cavity and analyze its role in the development of oral cancer.

Methods
From the critical analysis of current literature, a number of studies assessing the degree of exposure and viral activity in some cases of oral cancers have been selected. Several studies have analyzed the prevalence of HPV in these tumors, but results are not clear, given the connection between the study population, the type of analysis and sampling (16.17 to 20).
Oncogenic action of this group of viruses, and in particular of some types, precisely defined high-risk, has now been proven within the carcinomas of the uterine cervix, in particular the viral proteins E6 and E7 are responsible for oncogenic action through the inactivation of protein elements underlying the regulation of the cycle of cell replication as the p53 and pRB (4-8).
The association between HPV and squamous cell carcinoma was initially described by Syrjänen et al, in 1983. The results have shown that HPV could be involved in the onset of certain types of carcinoma. In the last years, the literature has provided evidence that HPV can be an independent risk factor for squamous cell carcinoma (15,16).
HPV-associated oral lesions may be benign, potentially malignant or malignant. Benign lesions are exophytic, sessile or pedunculated, with a smooth or "cauliflower" white or pink surface (Fig. 1 and 2).

Figure 1 - Benign HPV lesion located on the back of the tongue. The lesion is whitish and sessile
They can be single, multiple or grouped and are asymptomatic, chronic and sometimes regress spontaneously. Literature refers the prevalence of genotypes HPV 6 and 11 in the normal mucosa, as well as in benign lesions associated with HPV such as squamous papilloma and condyloma acuminatum, instead HPV genotypes 2 and 57 are found in common warts. The potentially malignant epithelial lesions which may be associated with HPV are mainly leukoplakia and lichen planus, in which there is a hyperkeratosis of the epithelium, with a characteristic whitish appearance that cannot be removed (Fig. 3).

The HPV genotypes characteristically associated with this type of lesions are HPV 16 and 18 and it is possible that the superinfection of initially degenerate epithelial cells can promote the progression of malignant transformation, but mechanisms remain unknown. Oral cancer is primarily associated with HPV 16 (12), it lacks a well-defined clinical appearance but, in general, any mucosal injury persistent, hard at palpation and covered with ulcerated or atrophic mucosa must be considered suspect (Fig. 4).
In general, a definite diagnosis cannot be performed with the unique clinical examination of any injury. It is therefore essential to consult a specialist for further examination based on the nature of the lesion, performing, if necessary, a biopsy for histological analysis.

The presence of HPV infection is easily investigated performing a cell sample through one sterile brush which collects in a totally painless way cells of the more superficial epithelial layers. Once fixed, the presence of viral DNA is investigated from sampling. HPV infection is transmitted through contact with individuals or with infected areas of the body (such as the warts in hands). The virus is transmitted primarily through vaginal or anal sexual contact with partners carriers of virus. The risk of being infected then increases with an increase in the number of sexual partners. Even other types of sexual activities (oral or manual) can be routes of transmission, but in rare cases.

Results
The latest observations about HPV infection of the oral mucosa reveal that the risk of developing an oropharyngeal carcinoma in HPV-16 infected individuals is increased 14-fold, supporting the interesting hypothesis that HPV infection may precede the onset of oropharyngeal carcinoma up to 10 years or more (9,13).

The importance of these observations is even greater if we consider the characteristics of oral oncogenesis. Indeed, in the developmental process of an oral cancer, in about 50% of cases the disease presents with Potentially Malignant Epithelial Lesions, whose course is often subclinical and non-specific. The oral squamous cell carcinoma associated with HPV-16 has a much better prognosis, regardless of the type of treatment it is subjected to, with low incidence of recurrence and mortality (6,11,19). The use of the vaccine appears to prevent HPV infection not only in the genital mucosa, but also in oral mucosa. The impact of current HPV vaccines on the incidence of persistent oral infections has to be identified yet. Although vaccination currently involves only the female population, immunogenetic studies have shown that the vaccine induces a strong immune response also in male subjects, which is important if we consider that cancer associated with HPV is prevalent in the male population.

Conclusions
About 75% of the world population have been or will be infected by HPV (14). Where a precancerous or malignant lesion is detected, even in patients without the usual risk factors (young, non-smoking), it is of crucial importance to investigate the possible superinfection with HPV, in order to draw from this presence a predictive outcome for these lesions, and guide their treatment and follow up according to their higher degenerative risk.
References


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