Papilloma virus and oral lesions. Infection and increased risk of potential malignant transformation. A systematic review

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Abstract

Background: oral cancer has been associated with several risk factor, such as smoking, alcohol, irritants and irradiation. The presence of HPV in oral cancers suggests that HPV may play a similar role in transforming oral epithelia. Objectives: a significant association was appreciated between infection with human papillomavirus (HPV), squamous cell carcinoma and potentially malignant disorders 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 published in the literature have provided strong evidence that HPV may be the cause of a defined subset of head and neck cancers and also an indicator of improved survival. Discussion: 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.

KEY WORDS: human papillomavirus 16, precancerous condition, oral cancer.

Background

Oral and oropharyngeal cancer are a major public health problem worldwide. In Italy, with about 4000 new cases a year, the epidemiological trend has remained constant, without any 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 identified are dietary deficiencies (especially as regards the lack of a suitable supply of vitamins, antioxidants and micronutrients) and poor oral hygiene (1-2).

Objectives

In recent years, we investigated the role of the Human Papilloma Viruses (HPVs) in oral oncogenesis. Human Papilloma Viruses (HPVs) are a diverse group of viral agents belonging to the Papillomaviridae family. About 200 different genotypes of human HPVs 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) (3-4). The aim of this article is to describe the main features of HPV infection in the oral cavity as well as analyze its role in the development of oral cancer, through a revision of the available literature.

Materials and methods

From the critical analysis of current literature (2000-2014), a number of studies assessing the degree of exposure and viral activity in some cases of oral cancers have been selected. Several studies analyzed the prevalence of HPV in these tumors, but the results are not clear, given the connection between the study population, the type of analysis and sampling. Only clinical trials available on the platform of the U.S. National Library of Medicine National Institutes of Health (PubMed) were taken into consideration. We used HPV and Oral Cancer
as keywords. From 41 proposed results, those related to cancer of the oral cavity and oropharynx were selected.

Results

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 (5-8). 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 few years, the literature has provided evidence that HPV can be an independent risk factor for squamous cell carcinoma (9, 10). Case-control studies such as the one performed in 2008 by Pintos J et al (9), show that infection from high-risk HPV is associated with 19% of cases and 5% of controls. In particular, viral DNA has been reported in 43% of cases of cancer of tonsil and base of tongue, with an odds ratio of 19:32. Analysis of oral cancers not involving tonsil area resulted in an odds ratio of 2.14. These results led the authors to conclude that oral cancer might have a less clear causative link with human papilloma virus infection than tonsillar one. The same conclusion was previously acheived by Herrero of the International Agency for Research on Cancer (11), who detected viral DNA in 3.9% of oral cancers and in 18.3% of oropharynx carcinomas in a multivariate analysis conducted on the results of a multicenter case-control study with a total of 1670 cases. Moreover, the study pointed out that the presence of HPV was less detectable in smokers while it appeared more frequent in individuals with multiple sexual partners. In 2008, Anaya-Saavedra G (12) published a case-control study of 62 cases of oral cancer and 248 healthy controls from Mexican population (1:4), and noted an infection with high-risk HPV (strain 16 and 18) detecting an OR of 6.2 in 43.5% of cases. A more recent study (13) reports that a low fraction of oral cancers are attributable to high-risk strains of HPV (13). The study carried out on 409 oral carcinomas revealed that only 5.9% were associated with HPV16 and other high risk HPVs. 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 (Figs 1-2). They can be single, multiple or grouped and are asymptomatic, chronic and sometimes regress spontaneously. Literature reports 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 (14), 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).
the world population has been or will be infected by HPV is prevalent in the male population. About 75% of genetic studies have shown that the vaccine induces a strong immune response also in male subjects, which has to be identified yet. Although vaccination cur- rently involves only the female population, immuno- suppressions may be anticipated to HPV infection not only in genital mucosa, but also in oral mucosa. The impact of current oral squamous cell carcinoma associated with HPV-16 whose course is often subclinical and non-specific. The latest observations about HPV infection of the oral mucosa revealed that the risk of develop- ing an oropharyngeal carcinoma in HPV-16 infected individuals has a 14-fold increase, supporting the inter- esting hypothesis that HPV infection may precede the onset of oropharyngeal carcinoma up to 10 years or more (15, 16). 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 oropharyngeal squamous cell carcinoma associated with HPV-16 has a much better prognosis, regardless of the type of treatment it is exposed to, and at a low incidence of recurrence and mortality (17). The use of the vaccine seems to prevent HPV infection not only in 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. About 75% of the world population has been or will be infected by HPV (18). Where a precancerous or malignant lesion is detected, even in patients without the usual risk fac- tors (young, non-smoking), it is of crucial importance to investigate the possible superinfection with HPV, in or- der to draw from this presence a predictive outcome for these lesions, and guide their treatment and follow up according to their higher degenerative risk.

Discussion

In general, a definite diagnosis cannot be performed with the unique clinical examination of any injury. Therefore, it is 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 by 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 infected areas of the body (such as the warts in hands). The virus is transmitted primarily through vaginal or anal sexual contact with partners who are carriers of virus. Therefore, the risk of being infected increases with the 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. The latest observations about HPV infec- tion of the oral mucosa revealed that the risk of develop- ing an oropharyngeal carcinoma in HPV-16 infected individuals has a 14-fold increase, supporting the inter- esting hypothesis that HPV infection may precede the onset of oropharyngeal carcinoma up to 10 years or more (15, 16). 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 oropharyngeal squamous cell carcinoma associated with HPV-16 has a much better prognosis, regardless of the type of treatment it is exposed to, and at a low incidence of recurrence and mortality (17). The use of the vaccine seems to prevent HPV infection not only in 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. About 75% of the world population has been or will be infected by HPV (18). Where a precancerous or malignant lesion is detected, even in patients without the usual risk fac- tors (young, non-smoking), it is of crucial importance to investigate the possible superinfection with HPV, in or- der 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


