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EDITORIAL

Role of human papillomavirus in the pathogenesis of oral squamous cell carcinoma

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Abstract

Oral cancer is one of the most common cancers and it constitutes a major health problem particularly in developing countries. Oral squamous cell carcinoma (OSCC) represents the most frequent of all oral neoplasms. Several risk factors have been well characterized to be associated with OSCC with substantial evidences. While tobacco and alcohol are the primary risk factors for OSCC development, many epidemiological studies report a strong association with human papillomavirus (HPV) in a subset of OSCC. This article presents our current knowledge on the relationship between HPV and development of OSCC. HPVs are DNA viruses that specifically target the basal cells of the epithelial mucosa. Most experimental data are consistent with the hypothesis that HPV plays a causal role in oral carcinogenesis. Genotypes, such as HPV1 infect epidermal cells, whereas HPV6, 11, 16 and 18 infect epithelial cells of the oral cavity and other mucosal surfaces. Several studies have shown that there is an increased risk of head and neck cancer in the two major HPV 16 oncogenes E6 and E7 -positive patients. The presence of antibodies to HPV E6 and E7 proteins was found to be more associated with tumors of the oro-pharynx than of the oral cavity. However, HPV alone appears to be insufficient as the cause of OSCC but requires other co-factors. Although a viral association within a subset of OSCC has been shown, the molecular and histopathological characteristics of these tumors have yet to be clearly defined.

Key words: Human papillomavirus; Oral squamous cell carcinoma

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INTRODUCTION

Worldwide, oral cancer accounts for 2%-4% of all cancer cases. In some regions, such as Pakistan, oral cancer reaches the 10% of all cancers, and around 45% in India[1,2]. Within the EU the highest oral cancer incidence rates for males are found in France and Hungary (6%) and the lowest rates in Greece and Cyprus[3,4]. In 2009 over 300 000 new cases of oral and oropharyngeal cancer were diagnosed worldwide. During the same time period, over 7000 affected individuals died of these cancers[5]. Oral cancer includes a group of neoplasms affecting any region of the oral cavity, pharyngeal regions and salivary glands. However, this term is almost synonymous with oral squamous cell carcinoma (OSCC), which represents the most frequent of all oral neoplasms. It is estimated that more of 90% of all oral neoplasms are OSCC[6]. It is well established that a strong association exists between

genetic factors, environment and oral cancer. Several factors are involved in the pathogenesis of oral cancer, such as age, gender, ethnicity, lifestyle, genetic background, status of health and exposure to one or more oncogenic factors[7]. Tobacco use and alcohol consumption are well-known risk factors. Micronutrient deficiencies and poor oral hygiene[8-10] have also been associated with increased risk. However, the observation that several patients with oral cancer have not been exposed to these risk factors suggests that additional causes may promote oral carcinogenesis. Thus, other agents, such as viruses, are being investigated.

HUMAN PAPILLOMAVIRUS AND OSCC

The human papillomavirus (HPV) family consists of more than 100 genotypes, classified in accordance with the ability to infect and transform epithelial cells. HPVs are DNA viruses that specifically target the basal cells of the epithelial mucosa[11].

Genotypes, such as HPV1 infect epidermal cells, whereas HPV6, 11, 16 and 18 infect epithelial cells of the oral cavity and other mucosal surfaces. The ability of HPV to transform epithelial cells is divided into high-risk and low-risk types. Low-risk types are associated with development of benign lesions such as warts, while infections with high-risk types may progress to malignant lesions[12].

The HPV involvement in oral carcinogenesis was supported on the basis of the following evidences: (1) the strongly established etiological role of HPV in cervical SCC[13,14]; (2) the epithelial tropism of HPV; (3) the similarity between oral and genital epithelia[15]; and (4) the detection of HPV genotypes in samples of OSCC[16-20].

The HPV involvement in oral and oropharyngeal carcinogenesis was first proposed in 1983 by Syrjänen *et al*[16]. Her results showed that 40% of the laryngeal and oral cancers contained histological and morphological similarities with HPV-infected lesions, and 50% of the samples demonstrated HPV structural proteins by immunohistochemistry[21].

Since then, several studies have focused on HPV detection in oral cancer but results have been conflicting[22-24]. It was found that the prevalence of HPV detection varies broadly, depending on the population, on the location of the cancerous lesion, type of specimen, and detection method. By contrast, HPV was more frequently detected in OSCCs of the oropharynx and tonsil than at other head and neck sites[25-27]. However, in a systematic review that was performed by Syrjänen *et al*[28] it was suggested that a potentially important causal association between HPV (specifically HPV16) and OSCC exists. In a recent study the overall HPV prevalence was 10.5% in oral cavity carcinomas and was higher in female than in male cases. Ninety five percent of HPV-positive cases were infected by a single HPV type. HPV 16 was the most prevalent type and was found in 95.5% of HPV-positive oral cavity carcinoma cases[29].

Furthermore, other studies have proved the existence of a synergistic effect between HPV and alcohol. The risk of head and neck cancer was statistically significantly increased in heavy alcohol users detected with the virus, compared to that of HPV-negative cancer drinkers. Therefore, it has been proposed that alcohol can biologically modify mucosal tissue, increasing its permeability to viral infection, or by influencing the immune response to HPV[30].

It is believed that one of the major events of HPV-induced carcinogenesis is the integration of the HPV genome into a host chromosome. HPV genome integration often occurs near fragile sites of the human genome, but there are no apparent sites for integration and no evidence for insertional mutagenesis[31].

Slightly modifying Koch's postulates, in order to establish a relationship between a causative virus and a disease, four criteria are needed: (1) viral genome to be present in tumor lesions or in tumor cells; (2) virus must be isolated from a pathologic lesion and grown in culture; (3) cultured virus should cause disease when inoculated into a healthy organism; and (4) virus must be reisolated from the inoculated host and identified as being identical to the original specific causative factor. However, the use of Koch's postulates to establish disease causation does not fully apply to these phenomena, since the etiology of cancer is multifactorial[32]. In the contrary, other authors suggest that the incidence of HPV infection in the oral cavities of healthy population is very low and therefore other risk factors are most likely responsible to promote oral carcinogenesis[33].

GENITAL HPV INFECTION AND RISK OF OSCC

Several studies examined the incidence of second cancers after an initial diagnosis of ano-genital cancers[34,35] and have showed that there is an increased risk of head and neck cancer as well as other HPV-associated ano-genital cancers in the two major HPV 16 oncogenes E6 and E7 -positive patients. This association between HPV-associated anogenital cancers and head and neck cancer was further strengthened by two larger studies[36,37].

Additionally, the presence of antibodies to HPV E6 and E7 proteins was found to be more associated with tumors of the oro-pharynx than of the oral cavity[12].

A recent study has shown that besides the classical horizontal transmission during the sexual life, a vertical transmission occurs in approximately 20% of case HPV positive people. In these individuals, HPV-DNA is detected in amniotic fluid, foetal membranes, blood and placental trophoblastic cells, all suggesting HPV infection in utero, i.e. prenatal transmission[38].

HPV TESTING

HPV testing is critical for the estimation of HPV prevalence in various oral diseases. HPV testing is usually based

on PCR method. General or consensus primers targeting L1 gene are most frequently used for HPV detection because they are able to identify several HPV genotypes at the same time. Sampling techniques together with widely divergent PCR methods in different studies explain most of the variability in HPV prevalence among OSCC and control samples[29]. *In situ* hybridization and *in situ* oncogenic protein staining techniques have also increased sensitivity and specificity and are used for HPV testing. These techniques have allowed not only the detection of HPV in cytological smears or histopathological immunesections but also the determination of the topographic site of the infection[39]. According to recent studies, HPV-positive squamous cell carcinomas have intact *p16* gene and wild type *p53* compared to HPV negative ones[40]. Other authors have noted that a distinctive mark of the presence of HPV in oral cancer could be found in *p16* nuclear or cytoplasmic overexpression[41,42]. However, one goal of the scientific research is to find new biological markers able to identify the set(s) of genes involved in oral carcinogenesis.

HPV SEROLOGY

The immune response to HPV infection involves both the cell-mediated and humoral responses. However, serological evidence is circumstantial since it provides only data on prior exposure to HPV. Since not all patients with HPV-associated cancers have detectable HPV antibodies, serum antibody determination may be a limited biomarker for HPV infection and carcinogenesis. Serum antibodies to HPV capsid proteins (virus-like particles) are thought to be a marker of lifetime HPV infection[43,44]. Antibodies against HPV E6 and E7 proteins are associated with increased risk of HPV-associated cancer[45,46] but are rather linked more with tumors from the oro-pharynx than from the oral cavity[12].

The use of HPV viral load in oral biopsies in conjunction with serological markers may serve to identify a subset of HPV-associated oral cancers in which HPV is biologically active.

PROGNOSIS AND FAVORABLE OUTCOME

Several lines of evidence suggest that HPV-positive and HPV-negative HNSCC represent distinct subgroups with different biological, epidemiological and prognostic profiles[7,47]. Recent data suggest that a positive HPV status represents an important prognostic factor and is associated with a favorable outcome in head and neck cancer. Many studies confirmed that HPV-positive OSCC have a better prognosis compared with those that are HPV negative[48-51]. There is an approximate 30% absolute survival difference at 5 years (HPV-positive = 60% *vs* HPV-negative = 30%)[52]. The favorable outcome for patients harboring HPV-positive cancer cannot be easily explained. It has been proposed that HPV-positive cancer arises through a different mechanism or exhibits less genetic instability i.e., shows a lower degree of aneuploidy and a tendency to have fewer chromosomal aberrations, when compared to HPV-negative cancer[53]. In contrast, there appears to be a subgroup of HPV-positive patients whose clinical prognosis is worse than the typical HPV-positive patient. This subgroup has higher smoking rates, higher rates of *p53* mutations and higher expression of EGFR and Bcl-xL[27].

EXPERIMENTAL EVIDENCE

Experimental evidence regarding the role of HPV in oral carcinogenesis is limited both *in vitro* and in animal experimentation. The lack of suitable experimental animal models has hindered research into HPV cancers for many years. In one of the most significant studies it has been shown that oral keratinocytes could not be transformed by HPV alone but required further mutations in other oncogenes[54].

CONCLUSION

The vast amounts of epidemiological, molecular pathological and *in vitro* experimental data are consistent with the hypothesis that HPV does indeed have a causal role in oral carcinogenesis. However, HPV alone appears to be insufficient as the cause of OSCC but requires other co-factors. Although a viral association within a subset of OSCC has been shown, the molecular and histopathological characteristics of these tumors have yet to be clearly defined. Since HPV16 is involved in the development of some oral cancers, the implementation of a vaccine program for HPV 16 and 18 may prove to be beneficial in preventing not only cervical cancer, but possibly HPV16-positive oral cancers as well.

REFERENCES

1 **Landis SH**, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. *CA Cancer J Clin* 1999; **49**: 8-31, 1
2 **Siddiqui IA**, Farooq MU, Siddiqui RA, Rafi SMT. Role of toluidine blue in early detection of oral cancer. *Pak J Med Sci* 2006; **22**: 184-187
3 **Boyle P**, Ferlay J. Cancer incidence and mortality in Europe, 2004. *Ann Oncol* 2005; **16**: 481-488
4 **International Agency for Research on Cancer**. GLOBOCAN 2008: Cancer Incidence, Mortality and Prevalence Worldwide in 2008. Available from: URL: http://globocan.iarc.fr/
5 **Brinkman BM**, Wong DT. Disease mechanism and biomarkers of oral squamous cell carcinoma. *Curr Opin Oncol* 2006; **18**: 228-233
6 **Choi S**, Myers JN. Molecular pathogenesis of oral squamous cell carcinoma: implications for therapy. *J Dent Res* 2008; **87**: 14-32
7 **Llewellyn CD**, Johnson NW, Warnakulasuriya KA. Risk factors for oral cancer in newly diagnosed patients aged 45 years and younger: a case-control study in Southern England. *J Oral Pathol Med* 2004; **33**: 525-532
8 **Garrote LF**, Herrero R, Reyes RM, Vaccarella S, Anta JL, Ferbeye L, Muñoz N, Franceschi S. Risk factors for cancer of the oral cavity and oro-pharynx in Cuba. *Br J Cancer* 2001; **85**:

46-54
9 **Sánchez MJ**, Martínez C, Nieto A, Castellsagué X, Quintana MJ, Bosch FX, Muñoz N, Herrero R, Franceschi S. Oral and oropharyngeal cancer in Spain: influence of dietary patterns. *Eur J Cancer Prev* 2003; **12**: 49-56
10 **Talamini R**, Vaccarella S, Barbone F, Tavani A, La Vecchia C, Herrero R, Muñoz N, Franceschi S. Oral hygiene, dentition, sexual habits and risk of oral cancer. *Br J Cancer* 2000; **83**: 1238-1242
11 **zur Hausen H**, de Villiers EM. Human papillomaviruses. *Annu Rev Microbiol* 1994; **48**: 427-447
12 **Ragin CC**, Modugno F, Gollin SM. The epidemiology and risk factors of head and neck cancer: a focus on human papillomavirus. *J Dent Res* 2007; **86**: 104-114
13 **zur Hausen H**, de Villiers EM, Gissmann L. Papillomavirus infections and human genital cancer. *Gynecol Oncol* 1981; **12**: S124-S128
14 **Bosch FX**, Lorincz A, Muñoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol* 2002; **55**: 244-265
15 **Thompson IO**, van der Bijl P, van Wyk CW, van Eyk AD. A comparative light-microscopic, electron-microscopic and chemical study of human vaginal and buccal epithelium. *Arch Oral Biol* 2001; **46**: 1091-1098
16 **Syrjänen KJ**, Pyrhönen S, Syrjänen SM, Lamberg MA. Immunohistochemical demonstration of human papilloma virus (HPV) antigens in oral squamous cell lesions. *Br J Oral Surg* 1983; **21**: 147-153
17 **Gillison ML**, Koch WM, Capone RB, Spafford M, Westra WH, Wu L, Zahurak ML, Daniel RW, Viglione M, Symer DE, Shah KV, Sidransky D. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst* 2000; **92**: 709-720
18 **Smith EM**, Hoffman HT, Summersgill KS, Kirchner HL, Turek LP, Haugen TH. Human papillomavirus and risk of oral cancer. *Laryngoscope* 1998; **108**: 1098-1103
19 **Miller CS**, Johnstone BM. Human papillomavirus as a risk factor for oral squamous cell carcinoma: a meta-analysis, 1982-1997. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **91**: 622-635
20 **Schwartz SM**, Daling JR, Doody DR, Wipf GC, Carter JJ, Madeleine MM, Mao EJ, Fitzgibbons ED, Huang S, Beckmann AM, McDougall JK, Galloway DA. Oral cancer risk in relation to sexual history and evidence of human papillomavirus infection. *J Natl Cancer Inst* 1998; **90**: 1626-1636
21 **Syrjänen K**, Syrjänen S, Lamberg M, Pyrhönen S, Nuutinen J. Morphological and immunohistochemical evidence suggesting human papillomavirus (HPV) involvement in oral squamous cell carcinogenesis. *Int J Oral Surg* 1983; **12**: 418-424
22 **Cruz IB**, Snijders PJ, Steenbergen RD, Meijer CJ, Snow GB, Walboomers JM, van der Waal I. Age-dependence of human papillomavirus DNA presence in oral squamous cell carcinomas. *Eur J Cancer B Oral Oncol* 1996; **32B**: 55-62
23 **Miller CS**, White DK. Human papillomavirus expression in oral mucosa, premalignant conditions, and squamous cell carcinoma: a retrospective review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; **82**: 57-68
24 **Syrjänen SM**, Syrjänen KJ. HPV infections of the oral mucosa. In: Syrjänen KJ, Syrjänen SM, editors. Papillomavirus infections in human pathology. New York: John Wiley and Sons, 2000: 379-412
25 **Mellin H**, Friesland S, Lewensohn R, Dalianis T, Munck-Wikland E. Human papillomavirus (HPV) DNA in tonsillar cancer: clinical correlates, risk of relapse, and survival. *Int J Cancer* 2000; **89**: 300-304
26 **D'Souza G**, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, Westra WH, Gillison ML. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med* 2007; **356**: 1944-1956
27 **Ang KK**, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010; **363**: 24-35
28 **Syrjänen S**, Lodi G, von Bültzingslöwen I, Aliko A, Arduino P, Campisi G, Challacombe S, Ficarra G, Flaitz C, Zhou HM, Maeda H, Miller C, Jontell M. Human papillomaviruses in oral carcinoma and oral potentially malignant disorders: a systematic review. *Oral Dis* 2011; **17** Suppl 1: 58-72
29 **St Guily JL**, Jacquard AC, Prétet JL, Haesebaert J, Beby-Defaux A, Clavel C, Agius G, Birembaut P, Okaïs C, Léocmach Y, Soubeyrand B, Pradat P, Riethmuller D, Mougin C, Denis F. Human papillomavirus genotype distribution in oropharynx and oral cavity cancer in France--The EDiTH VI study. *J Clin Virol* 2011; **51**: 100-104
30 **Smith EM**, Ritchie JM, Summersgill KF, Hoffman HT, Wang DH, Haugen TH, Turek LP. Human papillomavirus in oral exfoliated cells and risk of head and neck cancer. *J Natl Cancer Inst* 2004; **96**: 449-455
31 **Ziegert C**, Wentzensen N, Vinokurova S, Kisseljov F, Einenkel J, Hoeckel M, von Knebel Doeberitz M. A comprehensive analysis of HPV integration loci in anogenital lesions combining transcript and genome-based amplification techniques. *Oncogene* 2003; **22**: 3977-3984
32 **Haverkos HW**. Viruses, chemicals and co-carcinogenesis. *Oncogene* 2004; **23**: 6492-6499
33 **Migaldi M**, Pecorari M, Forbicini G, Nanni N, Grottola A, Grandi T, Delle Donne G, Leocata P, Trovato D, Sgambato A. Low prevalence of human papillomavirus infection in the healthy oral mucosa of a Northern Italian population. *J Oral Pathol Med* 2012; **41**: 16-20
34 **Bjørge T**, Hennig EM, Skare GB, Søreide O, Thoresen SO. Second primary cancers in patients with carcinoma in situ of the uterine cervix. The Norwegian experience 1970-1992. *Int J Cancer* 1995; **62**: 29-33
35 **Rabkin CS**, Biggar RJ, Melbye M, Curtis RE. Second primary cancers following anal and cervical carcinoma: evidence of shared etiologic factors. *Am J Epidemiol* 1992; **136**: 54-58
36 **Frisch M**, Biggar RJ. Aetiological parallel between tonsillar and anogenital squamous-cell carcinomas. *Lancet* 1999; **354**: 1442-1443
37 **Hemminki K**, Dong C, Frisch M. Tonsillar and other upper aerodigestive tract cancers among cervical cancer patients and their husbands. *Eur J Cancer Prev* 2000; **9**: 433-437
38 **Syrjänen S**. Current concepts on human papillomavirus infections in children. *APMIS* 2010; **118**: 494-509
39 **Pannone G**, Santoro A, Papagerakis S, Lo Muzio L, De Rosa G, Bufo P. The role of human papillomavirus in the pathogenesis of head & amp; neck squamous cell carcinoma: an overview. *Infect Agent Cancer* 2011; **6**: 4
40 **Burns JE**, Baird MC, Clark LJ, Burns PA, Edington K, Chapman C, Mitchell R, Robertson G, Soutar D, Parkinson EK. Gene mutations and increased levels of p53 protein in human squamous cell carcinomas and their cell lines. *Br J Cancer* 1993; **67**: 1274-1284
41 **Gillespie MB**, Rubinchik S, Hoel B, Sutkowski N. Human papillomavirus and oropharyngeal cancer: what you need to know in 2009. *Curr Treat Options Oncol* 2009; **10**: 296-307
42 **Goon PK**, Stanley MA, Ebmeyer J, Steinsträsser L, Upile T, Jerjes W, Bernal-Sprekelsen M, Görner M, Sudhoff HH. HPV & amp; head and neck cancer: a descriptive update. *Head Neck Oncol* 2009; **1**: 36
43 **Kirnbauer R**, Hubbert NL, Wheeler CM, Becker TM, Lowy DR, Schiller JT. A virus-like particle enzyme-linked immunosorbent assay detects serum antibodies in a majority of women infected with human papillomavirus type 16. *J Natl Cancer Inst* 1994; **86**: 494-499
44 **Carter JJ**, Koutsky LA, Wipf GC, Christensen ND, Lee SK, Kuypers J, Kiviat N, Galloway DA. The natural history of human papillomavirus type 16 capsid antibodies among a

cohort of university women. *J Infect Dis* 1996; **174**: 927-936
45 **Meschede W**, Zumbach K, Braspenning J, Scheffner M, Benitez-Bribiesca L, Luande J, Gissmann L, Pawlita M. Antibodies against early proteins of human papillomaviruses as diagnostic markers for invasive cervical cancer. *J Clin Microbiol* 1998; **36**: 475-480
46 **Stanley M**. Antibody reactivity to HPV E6 and E7 oncoproteins and early diagnosis of invasive cervical cancer. *Am J Obstet Gynecol* 2003; **188**: 3-4
47 **Schlecht NF**. Prognostic value of human papillomavirus in the survival of head and neck cancer patients: an overview of the evidence. *Oncol Rep* 2005; **14**: 1239-1247
48 **Lindquist D**, Romanitan M, Hammarstedt L, Näsman A, Dahlstrand H, Lindholm J, Onelöv L, Ramqvist T, Ye W, Munck-Wikland E, Dalianis T. Human papillomavirus is a favourable prognostic factor in tonsillar cancer and its oncogenic role is supported by the expression of E6 and E7. *Mol Oncol* 2007; **1**: 350-355
49 **Lassen P**. The role of Human papillomavirus in head and neck cancer and the impact on radiotherapy outcome. *Radiother Oncol* 2010; **95**: 371-380
50 **Weinberger PM**, Yu Z, Haffty BG, Kowalski D, Harigopal M, Brandsma J, Sasaki C, Joe J, Camp RL, Rimm DL, Psyrri A. Molecular classification identifies a subset of human papillomavirus--associated oropharyngeal cancers with favorable prognosis. *J Clin Oncol* 2006; **24**: 736-747
51 **Licitra L**, Perrone F, Bossi P, Suardi S, Mariani L, Artusi R, Oggionni M, Rossini C, Cantù G, Squadrelli M, Quattrone P, Locati LD, Bergamini C, Olmi P, Pierotti MA, Pilotti S. High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. *J Clin Oncol* 2006; **24**: 5630-5636
52 **Gillison ML**. HPV and prognosis for patients with oropharynx cancer. *Eur J Cancer* 2009; **45** Suppl 1: 383-385
53 **Dahlstrand H**, Dahlgren L, Lindquist D, Munck-Wikland E, Dalianis T. Presence of human papillomavirus in tonsillar cancer is a favourable prognostic factor for clinical outcome. *Anticancer Res* 2004; **24**: 1829-1835
54 **Park NH**, Gujuluva CN, Baek JH, Cherrick HM, Shin KH, Min BM. Combined oral carcinogenicity of HPV-16 and benzo(a)pyrene: an in vitro multistep carcinogenesis model. *Oncogene* 1995; **10**: 2145-2153

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