

## HUMAN PAPILLOMAVIRUS AND ORAL CANCER: SYSTEMATIC REVIEW

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### ABSTRACT

**Aim:** The cause-and-effect relationship between human papillomavirus (HPV) in oral cavity carcinomas and potentially malignant lesions continues to be controversial. The main objective of this work is to demonstrate this cause-effect relationship between HPV and oral cavity cancers as well as to identify the types of HPV involved in malignant oral diseases.

**Materiels and methods:** Our research was conducted using PubMed via Medline, Science Direct and SciVerse Scopus and we have selected studies that date back 10 years. Eligible studies included case-control clinical studies and cross-sectional studies. Our work is based on 20 clinical studies, 3 of which are cross-sectional and 17 are case-control studies.

**Results:** Of the 20 studies selected, 14 of 20 studies confirm that HPV is an important causative factor for the development of oral carcinomas, especially high-risk HPVs, HPV16 and HPV18, while 6 studies suggest that there is no relationship between the presence of HPV and oral malignant lesions.

**Conclusion:** The results suggest a significant causal association between HPV and oral carcinomas, but this does not preclude the need for prospective studies on young non-alcoholic-tobacco patients.

**Keywords:** Human Papillomavirus, Etiology, Oral Cavity, Lesion, Tumor.

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### INTRODUCTION

Cancers of the oral cavity include all the malignant tumors of the oral and labial mucosa and are the 6 th largest cancer in the world with an incidence of 275,000 cases / year. [1,2]

In Morocco, during the years 2005, 2006 and 2007, the Cancer Registry of the Greater Casablanca region recorded 11,923 cases in all localities combined, cancer of the oral cavity occupies the 16 th place with 1.6% in men and 2.3% in women. [3]

Alcohol and tobacco are known as the 2 identified toxicants (9 times out of 10 in alcohol-tobacco subjects) [4,2], yet their absence in young patients with carcinomas, [5] involves other Risk factors, contributing to the development of oral carcinomas, namely HPV, particularly oncogenic genotypes. [6] The human Papillomavirus belongs to the family of Papillomaviridae, a small double-helix DNA virus not wrapped with an icosahedral structure composed of 72 capsomers and about 55 nm in diameter. [7,8]

Today, 200 genotypes, of which more than 120 have been discovered in humans and 25 are associated with oral lesions [9], such as HPV 16 and 18 known to be oncogenic, sometimes found in non-alcoholic subjects -tabagic carriers of oral-pharyngeal carcinomas. [10]

According to a comparative clinical study conducted at the Pardubice regional hospital in the Czech Republic on a sample of 46 non-smoking patients, 24 of whom were diagnosed with squamous cell carcinoma of the oral cavity and 22 with squamous cell carcinoma of the oropharynx, 21/46 who is the equivalent of 45.65% of non-smoking patients with squamous cell carcinoma of the oral cavity and oropharynx were HPV-positive. [11]

In this study, we propose to carry out a systematic review of the literature with the following objectives:

- Focus on the presence of a causal relationship between HPV and oral cancers.
- Identify the types of HPV involved in malignant

oral diseases and Establish the epidemiological and diagnostic characteristics of oral cancers associated with HPV.

**MATERIELS AND METHODS**

**Electronic search**

A systematic literature search at Pubmed via MEDLINE, Science Direct and SciVerse Scopus from 2006 to 2016 was conducted without any language restriction by entering the following terms: Human papillomavirus, HPV, Papillomaviridae, Cancer (s), Oral cancer (s) , Carcinoma (s), Oral carcinoma (s), Mouth neoplasm (s), Squamous cell carcinoma, Verrucous carcinoma, Adenocarcinoma, Oral cavity, Mouth

All abstracts were independently reviewed by two pre-selected standardized examiners. When the article was deemed relevant by both examiners, the complete documents were obtained and evaluated.

**Inclusion criteria**

Studies on the relationship between HPV infection and oral cavity cancers were included in this systematic review when they met the following criteria:

- Articles with a publication date between 2006 and 2016.
- Cross-sectional clinical studies
- Clinical case-control studies
- Clinical studies conducted on living humans interested in oral HPV infections and HPV induced malignancies in the oral cavity.

**Exclusion criteria**

Other studies were excluded at the basis of the following criteria:

- Articles with a publication date prior to 2006.
- Articles that have experimented with animals or treated cancers due to human papillomavirus infection in parts of the human body other than the oral cavity
- Case series
- Case Reports

**Table I** lists all the articles selected for our systematic review.

Thus, in **Table** , we present all of results obtained following the critical reading of the selected articles with the following items: age, sex, sample size, favorite site of oral cancer, histological type, degree of differentiation, tumor classification, detection methods of oral cancer, risk factor, results and

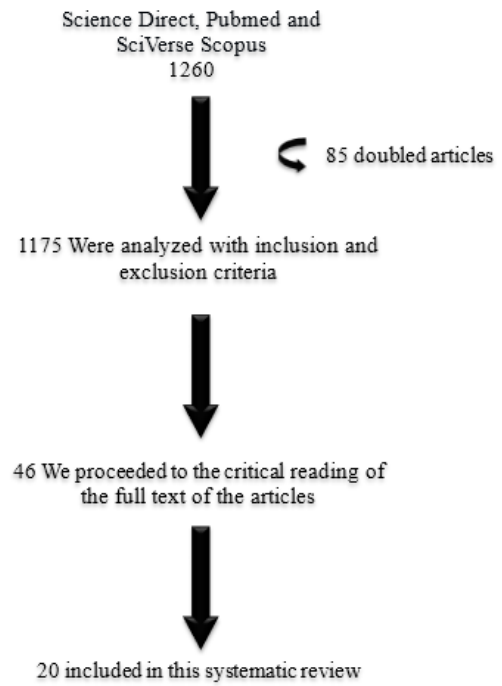
- Articles which do not correspond to the objectives of our work, which are the basis for the reading of the abstracts and for the critical reading of the full text.

**RESULTS**

We recall that the querying of the MEDLINE (Pubmed), SciVerse Scopus and Direct Science databases via the keyword combinations made it possible to identify, respectively, 266, 966 and 28 articles published between 2006-2016.

At the end of this stage, the number of articles obtained after elimination of duplicates and reading of titles and abstracts by application of the inclusion and exclusion criteria was 46 articles.

We then proceeded to the critical reading of the full text of the articles; 20 articles with a sufficient methodological quality and corresponding to the subject of our study were included definitively. (Figure 1)



**Figure 1 : Selection process of the studies included in this systematic review**

conclusions. Results of the 20 studies selected, 14 of 20 studies confirm that HPV is an important causative factor for the development of oral carcinomas, especially high-risk HPVs, HPV16 and HPV18, while 6 studies suggest that there is no relationship between the presence of HPV and oral malignant lesions

**Table I : Summary table of selected articles.**

| N° | Author  | Title  | Journal   | Country     | Year |
|----|---|--|---|-------------|------|
| 1  | Vicente José Villagómez-Ortiza, Diana Estela Paz-Delgadilloa, Ivan Marino-Martínezb, Luis Angel Cesenas-Falconc, Anabel Sandoval-de la Fuentea, Alfonso Reyes-Escobedo  | Prevalence of human papillomavirus infection in squamous cell carcinoma of the oral cavity, oropharynx and larynx  | Cirugia y Cirunajos                                   | Mexico      | 2016 |
| 2  | Pintos Javier, Black Martin J, Sadeghi Nader, Ghadirian Parviz, Zeitouni Anthony G, Viscidi Raphael P, Herrero Rolando, Coutle Francois, Franco Eduardo L.  | Human papillomavirus infection and oral cancer: A case-control study in Montreal, Canada   | Oral Oncology   | Canada      | 2007 |
| 3  | Luo C.W, Roan C.H., Liu CJ.   | Human papillomaviruses in oral squamous cell carcinoma and pre-cancerous lesions detected by PCR-based gene-chip array   | International journal of Oral & Maxillofacial surgery | Taiwan      | 2006 |
| 4  | Petito Guilherme, Aparecida dos Santos Carneiro Megmar, De Rabello Santos Silvia Helena, Teodoro Cordeiro Silva Antonio Marcio, Alencar Rita de Cassia, Gontijo Antonio Paulo, Aparecida Saddi Vera   | Human papillomavirus in oral cavity and oropharynxcarcinomas in the central region of Brazil   | Brazilian Journal of Otorhino-Laryngolo-Gyoriginal    | Brazil      | 2016 |
| 5  | McCord Christina, Xu Jing, Xu Wei, Qiu Xin, McComb Richard John, Perez-Ordóñez Bayardo, and Bradley Grace   | Association of high-riskhuman papillomavirus infection with oral epithelial dysplasia  | Oral And Maxillofacial Pathology                      | Canada      | 2013 |
| 6  | Suyamindra S Kulkarni, Sujayendra S Kulkarni, Priyanka P Vastrad, Bhushan B Kulkarni, Amruta R Markande, G.S.Kadacol, S.V.Hiremath, S.Kaliwal, B.R.Patil,Pramod B Gai   | Prevalence and Distribution of High Risk Human Papillomavirus (HPV) Types 16 and 18 in Carcinoma of Cervix, Saliva of Patients with Oral Squamous Cell Carcinoma and in the General Population in Karnataka, India | Asian Pacific Journal of Cancer Prevention            | India       | 2011 |
| 7  | Nasrollah Saghravarian, Kiarash Ghazvini, Shahab Babakoohi, Alireza Firooz & Nooshin Mohtasham  | Low prevalence of high risk genotypes of human papilloma virus in normal oral mucosa, oral leukoplakia and verrucous carcinoma   | Acta Odontologica Scandinavica                        | Iran        | 2011 |
| 8  | Vieira de Spindula-Filho José, Divino da Cruz Aparecido, Ferreira Oton-Leite Angélica , Carvalho Batista Aline , Rodrigues Leles Claudio, Gonçalves Alencar Rita de Cassia, Aparecida Saddi Vera , Mendonça Elismauro Francisco                                     | Oral squamous cell carcinoma versus oral verrucous carcinoma: an approach to cellular proliferation and negative relation to human papillomavirus (HPV)  | Tumor Biol  | Brésil      | 2010 |
| 9  | Lee S. Y., Cho N. H., Choi E. C., Baek S. J., Kim W. S., Shin D. H., Kim S.-H.  | Relevance of human papillomavirus (HPV) infection to carcinogenesis of oral tongue cancer  | International journal of Oral & Maxillofacial surgery | Korea       | 2010 |
| 10 | Laprise Claudie, Madathil Sreenath A., Allison Paul, Priya Abraham, Anantharam Raghavendran, Shahul Hameed P., ThekkePurakkal Akhil-Soman,Genevieve Castonguay, Coultée François, Schlecht Nicolas F., Rousseau Marie-Claude, Nicolau Eduardo L. Franco and Belinda | No role for human papillomavirus infection in oral cancers in a region in southern India 2015  | International Journal of cancer                       | India       | 2015 |
| 11 | Lucas-Roxburgh Rebecca, Benschop Jackie, Dunowska Magdalena, Perrott Matthew  | Prevalence of human papillomaviruses in the mouths of New Zealand women  | New Zealand Médical Association Journal               | New Zealand | 2015 |
| 12 | Li-Li Gan, Hao Zhang, Ji-Hua Guo, Ming-Wen Fan  | Prevalence of Human Papillomavirus Infection in Oral Squamous Cell Carcinoma: a Case-control Study in Wuhan, China   | Asian Pac J cancer Prev                               | China       | 2014 |

|    |   |   |   |        |      |
|----|---|---|---|--------|------|
| 13 | Ginawi Ibrahim A. M, Mahgoub Ebtihag A, Ahmed Hussain G   | Immunophenotyping of HPV Types 16 and 18 among Sudanese Patients with Oral Lesions  | Oman Medical Journal                                      | Sudan  | 2012 |
| 14 | Kaminagakura Estela, Lina Villa Luisa, Andreoli Maria Antonieta, Sobrinho Joao Simao, Vartanian Jose Guilherme, Soares Fernando Augusto, Nishimoto Ines Nobuko, Rocha Rafael and Kowalski Luiz Paulo    | High-risk human papillomavirus in oral squamous cell carcinoma of young patients  | International journal of cancer                           | Brasil | 2012 |
| 15 | Kristoffersen.A.K, Enersen.M, Kverndokk.E, Sundeb.P.T, Landin.M, Solheim.T., Olsen.I, Grinde.B  | Human papillomavirus subtypes in oral lesions compared to healthy oral mucosa   | Journal of clinical virology                              | Norway | 2012 |
| 16 | Palmieri.A, Scapoli.L, Martinelli.M, Pezzetti.F, Girardf.A, Spinelli.G, Lucchese.A, Carinci.F   | Incidence Of low risk Human Papillomavirus In Oral Cancer: A Real Time PCR Study On 278 Patients                            | International Journal of Immunopathology And Pharmacology | Italy  | 2011 |
| 17 | Kalavathy Jayapal Elango, Amritha Suresh, Elango Murugaian Erode,Lakshmi Subhadradevi, Hiran Kattilaparambil Ravindran, Subramania Kulathu Iyer, Sundaram Karimassery Rama Iyer, Moni Abraham Kuriakose | Role of Human Papilloma Virus in Oral Tongue Squamous Cell Carcinoma  | Asian Pacific Journal of Cancer Prevention                | India  | 2011 |
| 18 | Shuichi Fujita, Masachika Senba, Atsushi Kumatori, Tomayoshi Hayashi,Tohru Ikeda, Kan Toriyama  | Human Papillomavirus Infection in Oral Verrucous Carcinoma: Genotyping Analysis and Inverse Correlation with p53 Expression | Pathobiology  | Japan  | 2008 |
| 19 | Anaya-Saavedra Gabriela, Ramirez-Amador Velia, Irigoyen-Camacho Ma. Esther, Garcia-Cuellar Claudia Ma., Guido-Jiménez Miriam, Méndez-Martinez Rocio, Garcia-Carranca Alejandro                          | High Association of Human Papillomavirus Infection with Oral Cancer:A Case-Control Study                                    | Archives of Medical Research                              | Mexico | 2008 |
| 20 | Gonzalez Joaquin V, Gutierrez Rafael A, Keszler Alicia, Del Carmen Colacino Lidia Maria V.Alonio, Teyssie Angelica R , Picconi Maria Alejandra  | Human papillomavirus in oral lesion   | Medicina  | Mexico | 2007 |

**Table 2 : Summaries of the selected research work.**

| N° | Age                        | Sex               | Sample size | Histologic type                                | Degree of differentiation  | Tumor classification   | Detection methods | Risk factor  | Results   | Conclusions  |
|----|----------------------------|-------------------|-------------|--|--|--|-------------------|--|---|--|
| 1  | Avr 58 years [39-92] years | M : 32<br>W : 13  | 45          | Squamous cell carcinoma                        | NM   | *Stage I :15.6%<br>*StageII :22.2%<br>*Stage III :24.2%<br>*StageIV :37.8 %<br>* The two HPV positive cancers of the larynx are stage I and II | PCR               | *Tobacco : 49%<br>*Alcohol : 36%<br>*Periodontal disease:76%<br>*Betel : Absent<br>*Oral sex : Absent  | * <b>HPV+</b> : 4.4%<br>* <b>Types</b> : HPV11<br>* <b>Site</b> :Tonsils  | * Low prevalence of HPV infection in squamous cell carcinoma.<br>* Need for prospective studies on young patients.   |
| 2  | [25-84] Years              | M : 143<br>W : 58 | 201         | Squamous cell carcinoma                        | NM   | NM   | PCR               | *Tobacco :<br>Never :23.55%<br>Former :45.2%<br>Recent :31.3%<br>*Alcohol :<br>Non-drinkers :10.65%<br>1-80ml/d :25.15%<br>81-400ml/d :29.25%<br>>401ml/d :34.95%<br>*Periodontal disease :<br>Absent<br>*Betel : Absent<br>*Oral sex : Absent | * <b>HPV+</b> : Cases :19.4% and controls :4.7%<br>* <b>Types</b> :<br>- Cases :<br>HPV16 :1.4%, HPV84 : 1.4%, HPV16+31 : 1.4%<br>HPV16+35 : 1.4%, HPV16+39+53: 1.4%<br>HPV16+51+55: 1.4%, HPV6+16+39+53: 1.4%<br>- Controls :<br>HPV11 : 1.4%, HPV55 : 1.4%, HPV58 : 2.8%,<br>HPV66 : 1.4%<br>* <b>Site</b> :<br>Tonsils<br>-Cases :12.5% and Controls :4.6%<br>Other sites :<br>-Cases :6.9% and Controls :4.6% | * Strong causal association between HPV infection and tonsil's cancer.<br>* The presence or absence of an etiological link is less clear for other cancers |
| 3  | [20-74] years              | M : 145<br>W :42  | 187         | Squamous cell carcinoma<br>Verrucous carcinoma | -Verrucous : 8%<br>-Well differentiated: 45 %<br>-Moderately differentiated : 39%<br>-Little differentiated : 8% | Determined for the groupe of HPV+ carcinom a:<br>StageII : 38.5%<br>Stage III : 15.4%<br>Stage IV : 46.2%                                      | PCR               | Determined for the group of carcinoma and Potentially malignant lesions:<br>- Squamous cell carcinoma:<br>*Tobacco : 96%<br>*Alcohol : 96%<br>*Betel : 98%<br>*Periodontal disease :Absent   | * <b>HPV +</b> : Cases : Carcinomas : 25.49%, Potentially malignant lesions: 30.43% and Controls : 13.33%<br>* <b>Types</b> :<br><i>High risk HPV</i><br>-Cases : Carcinomas : 21.57% and Potentially malignant lesions: 10.87%<br>-Controls : 8.89%<br><i>Low risk HPV:</i><br>-Cases : Carcinomas : 3.92% and Potentially malignant lesions: 19.57%<br>-Controls : 4.44%  | * High prevalence of high-risk HPV in squamous cell carcinoma.<br>* High prevalence of low-risk HPV in potentially malignant lesions                       |

|          |  |                  |     |                         |  |   |           |   |  |   |
|----------|--|------------------|-----|-------------------------|--|---|-----------|---|--|---|
|          |  |                  |     |                         |  |   |           | <p>*Oral sex : Absent</p> <p>- Potentially malignant lesions:</p> <p>*Tobacco : 97.8%</p> <p>*Alcohol : 95.6%</p> <p>*Betel : 100%</p> <p>*Peridental disease :Absent</p> <p>*Oral sex : Absent</p> | <p><b>*Site:</b></p> <p>Determined for the group of carcinomas:<br/>Tongue:5.9%, Oral mucosa :7.8% , Gum :7.8, Lips :2% and Floor of the mouth :2%</p>   |   |
| <b>4</b> | Avr 58 years <59 years :45 >60 years :37 | M :64<br>W : 18  | 82  | Squamous cell carcinoma | -Moderately to well differentiated : 84.2%<br>-Little differentiated: 15.8%                            | T1+T2 :42.7%<br>T3+T4 : 57.2%<br>N :Yes :51.2%<br>No:48.8%<br>M :Yes :1.2%<br>No :98.8% | PCR       | <p>*Tobacco : 78%</p> <p>*Alcohol : 70.8%</p> <p>*Betel :Absent</p> <p>*Periodontal disease :Absente</p> <p>*Oral sex : Absent</p>  | <p>*<b>HPV+</b> : 25.6%</p> <p>*<b>Types :</b></p> <p>HPV 16 :33.3%</p> <p>HPV18 : 14.3%</p> <p>Other types :42.4%</p> <p>*<b>Site :</b></p> <p>Oral cavity :47.4%</p> <p>Oropharynx :52.6%</p>  | <p>* High prevalence of HPV in men over the age of 78 tobacco users and alcohol.</p> <p>* Importance of vaccination against HPV in the control of the oral cavity and oropharynx.</p> |
| <b>5</b> | Avr 58 [15-84] years                     | M : 46<br>W : 31 | 77  | NM                      | Determined for HPV Positive cancer .<br>-Well differentiated : 51.9%<br>-Little differentiated : 48.1% | NM  | PCR + IHC | NM  | <p>* <b>HPV+ :</b> 9.1%</p> <p>*<b>Types :</b> High risk HPV</p> <p>*<b>Site :</b></p> <p>Floor of the mouth:71.4%</p> <p>Other sites :28.6%</p>   | <p>* Association of high-risk carcinoma in situ</p>   |
| <b>6</b> | NM                                       | NM               | 490 | Squamous cell carcinoma | NM   | NM  | PCR       | NM  | <p>*<b>HPV+</b> : 96.7%</p> <p>*<b>Types :</b> HPV 16 : 89.7% and HPV18 : 86.2 %</p> <p>*<b>Site :</b> Cervix</p> <p>-----</p> <p>*<b>HPV+</b> : 70.6%</p> <p>*<b>Types :</b> HPV 16 : 45.8% and HPV 18 : 54.2%</p> <p>*<b>Site :</b>oral cavity</p> | <p>* Importance of vaccination against oral and cervical infection by HPV 16 and 18.</p>  |

|    |   |   |     |  |    |   |     |   |  |  |
|----|---|---|-----|--|----|---|-----|---|--|--|
| 7  | Avr 59.6<br>±11.21<br>years                                       | M : 32<br>W : 27                                  |     | Leukoplakia<br>Verrucous carcinoma             | NM | NM  | PCR | NM  | * <b>HPV+</b> :5.1%<br>* <b>Types</b> : Co-infection : HPV16+18 : 100%<br>* <b>Site</b> : Mandibular vestibule   | * No significant relationship between HPV infection and oral verrucous carcinoma.<br>* Need for more studies.  |
| 8  | Mentioned for the cases<br><65years : 36.85%<br>>65 years: 63.15% | Mentioned for the cases:<br>M :63.5%<br>W :36.5 % | 56  | Squamous cell carcinoma<br>Verrucous carcinoma | NM | Tx-Tis :32.53%<br>T1-T2 :41%<br>T3-T4 :46.97%                                 | PCR | Determined for cases :<br>*Tobacco : 63.5%<br>*Alcohol : 62%<br>*Betel : Absent<br>*Periodontal disease : Absent<br>*Oral sex :Absent   | * <b>HPV+</b> : 0%   | * Absence of correlation between HPV infection and verrucous or squamous cell carcinoma.   |
| 9  | NM  | NM  | 61  | Squamous cell carcinoma                        | NM | Stage I : 29%<br>Stage II : 44%<br>Stage III : 8 %<br>Stage IV :19%           | PCR | NM  | * <b>HPV+</b> : Cases :36% and controls :4%<br>* <b>Types</b> :<br>-Cases : HPV16 : 85% and others : 15.3%<br>-Controls : NM<br>* <b>Site</b> : Tongue | * Consideration of HPV 16 as a factor responsible for squamous cell carcinoma of the tongue.<br>* Association of HPV16 to the depth of the invasion. |
| 10 | Avr 60.7<br>±11.5<br>years  | M: 400<br>W : 321                                 | 721 | Squamous cell carcinoma                        | NM | Stage I : 9.7%<br>Stage II : 10.25%<br>Stage III : 49.05%<br>Stage IV: 30.95% | PCR | *Tobacco: Cases : 10.9% and Controls :20.3%<br>*Alcohol : Cases :22.75% and Controls:25.5%<br>*Betel : Cases :100% and Controls :100%<br>*Oral sex : Cases : 40.65% and Controls :51.1%<br>*Periodontal disease :Absent | * HPV+ : 0%  | * HPV is not a major risk factor in oral carcinogenesis according to the study sample.   |

|    |               |                  |     |                                     |  |  |                       |   |  |   |
|----|---------------|------------------|-----|-------------------------------------|--|--|-----------------------|---|--|---|
| 12 | [18-55] years | M: 170<br>W: 98  | 268 | Squamous cell carcinoma             | NM   | Stage I-II : 90.5%<br>Stage III-IV : 9.5%                            | PCR                   | *Tobacco :<br>-Cases : 50%<br>-Controls : 19.1%<br>*Alcohol :<br>-Cases : 35.5%<br>-Controls : 8.8%<br>*Betel : Absent<br>*Periodontal disease : Absent<br>*Oral sex : Absent | *HPV + : Cases :27.5% and Controls :2.9%<br>*Types :<br>HPV16 : Cases :19.5% and Controls :0%<br>HPV18 : Cases :7.5% and Controls :2.9%<br>Co-infection 6+18 : Cases :0.5% and Controls:0%<br>*Site:NM   | * High binding of HPV with oral cancer.<br>* Individualization of HPV as an independent risk factor leading to oral carcinogenesis.<br>* Synergistic effect of tobacco and alcohol. |
| 13 | Avr 46 years  | M: 30<br>W: 30   | 60  | Carcinome épidermoïde               | Well differentiated : 66%<br>Moderately differentiated : 26%<br>Little differentiated : 8%       | NM   | IHC                   | NM  | *HPV+ : Cases :20% and controls :0%<br>*Types : Cases :<br>HPV16: 50%, HPV18 : 40% and HPV 16+18 : 10%<br>*Site : NM   | * Presence of etiological link between HPV 16 and 18 and cancers of the oral cavity.<br>* Need for confirmation of results by PCR   |
| 14 | [20-82] years | M : 81<br>W : 33 | 114 | Squamous cell carcinoma             | Well differentiated : 62.58%<br>Moderately differentiated : 28.2%<br>Little differentiated 8.95% | T1-T2 : 40.15%<br>T3-T4 :59.85%<br>N0 : 44%<br>>N0 :55%<br>M0 : 100% | PCR +<br>ISH +<br>DBH | *Tobacco : 73.7%<br>*Alcohol :53.4%<br>*Betel : Absent<br>*Periodontal disease : Absent<br>*Oral sex : Absent   | *HPV+ :19.2%<br>*Types :<br>HPV16 : Cases : 68.2% and Controls :31.8%<br>HPV16+18 : Cases1.7% and controls :0%<br>*Site :NM  | * High prevalence of HPV at high risk, especially HPV16 which is a factor in oral cancer in young patients.   |
| 15 | [20-89] years | M : 42<br>W : 48 | 150 | Leukoplakia Squamous cell carcinoma | NM   | NM   | PCR                   | NM  | *HPV+ :<br>-Cases: Loukoplakia:64% and Squamous cell carcinoma : 16%<br>- Controls : Normal mucosa : 56 %<br>*Types :<br>-Cases : Leukoplakia : HPV6 :28%, HPV11 : 46.4%, HPV6+11 :17.9% and Squamous cell carcinoma :NM<br>- Controls : HPV6 : 52.4%, HPV11 : 33.3%, HPV6+11 :9.5% and HPV 16 : 4.8%<br>*Site : Oral cavity | * Absence of role of HPV in the development of oral leukoplakia or oral epidermoid carcinoma.   |



|    |  |                    |     |                         |  |   |           |  |   |   |
|----|--|--------------------|-----|-------------------------|--|---|-----------|--|---|---|
| 16 | NM   | NM                 | 56  | Squamous cell carcinoma | NM   | Determined for the HPV+ carcinoma:<br>T1 : 54.5%<br>T2 : 36.4%<br>T4 : 9.1%<br>N0 : 72.7%<br>Nt : 27.3% | PCR       | NM   | * <b>HPV+</b> : Cases : 5.1% and Controls :1.6%<br>* <b>Types</b> :<br>-Cases : HPV16 : 45.5%, HPV11 : 45.5% and HPV6 : 9.1%<br>- Controls : HPV 16 : only one case<br>* <b>Site</b> :<br>-Cas : Tongue :36.4%, Cheek : 45.5% and Floor of the mouth :18.2%<br>- Controls: Only one HPV 16 on the cheek | * Absence of relationship between HPV 6 and 11 and oral malignant lesions.<br>* Association of low-risk HPV with benign lesions.              |
| 17 | 55.1<br>±12.75<br>years for men<br>29.5<br>±14.25<br>years for women | M :76<br>W :30     | 106 | Squamous cell carcinoma | Well differentiated : 57%<br>Moderately differentiated : 37%<br>Little differentiated : 6% | Stage I : 32%<br>Stage II : 18%<br>Stage III : 22%<br>Stage IV : 28 %                                   | PCR + IHC | *Present :<br>-Cases : 50%<br>-Controls : 54%  | * <b>HPV+</b> : Cases :50% and Controls :67%<br>* <b>Types</b> : Cases : HPV16 : 48 % and Controls : HPV16 : 0%<br>* <b>Site</b> : Tongue   | * Positive correlation between HPV infection and oral cancer  |
| 18 | Avr 71.3 years   | M: 19<br>W: 14     | 33  | Verrucous carcinoma     | NM   | NM  | PCR       | NM   | * <b>HPV+</b> : Cases : 48% and Controls :70%<br>* <b>Types</b> :<br>-Cases : HPV6 : 39%, HPV11 : 4%, HPV 18 : 43%, HPV33 : 4%, HPV74 : 9%, HPV6+11:35%<br>- Controls :HPV6 : 50%, HPV11 : 10%, HPV18 : 70%, HPV6+18 : 50%<br>* <b>Site :NM</b>   | * Participation of multiple infections with HPV at risk and low risk in the histogenesis of oral squamous cell carcinoma.                     |
| 19 | Avr 62 years   | M : 165<br>W : 145 | 310 | Squamous cell carcinoma | Well differentiated : 48.4 %   | Stage III et IV : 74.2 %  | PCR       | *Tobacco :<br>-Cases :61.6% and Controls :52%<br>*Alcohol :<br>-Cases :21% and Controls :30%<br>*Betel : Absent<br>*Periodontal disease :Absent<br>*Oral sex :Absent | * <b>HPV +</b> : Cases : 43.5% and controls : 17.3%<br>* <b>Types</b> :<br>-Cases : HPV16 :55.6%, HPV18 :18.5%, HPV33 :7.4%, HPV35 :3.7%<br>- Controls : HPV16 :34.9%, HPV18 :11.6%, HPV33 :2.3%<br>HPV35 :0%, HPV31 :4.7%, HPV 52 :2.3%<br>* <b>Site :NM</b>   | * High association between HPV 16 and 18 and cancers of the oral cavity.<br>* Confirmation of significant association of tobacco and alcohol. |

|    |    |                  |     |  |    |    |              |                    |  |   |
|----|----|------------------|-----|--|----|----|--------------|--------------------|--|---|
| 20 | NM | M : 53<br>W : 64 | 137 | Squamous cell carcinoma<br>Verrucous carcinoma | NM | NM | PCR +<br>DBH | * Absent from most | <p><b>*HPV+ :</b><br/>-Cases : Benign lesions HPV associated :91%, Benign lesions HPV non-associated :12.5%, Potentially malignant lesions :51.5% and Cancers :60%</p> <p><b>*Types :</b><br/>-Cases :<br/>Benign lesions HPV associated :HPV16 : 15.8%, HPV13 : 5.3%, HPV11 : 15.8%, HPV6 : 10.5%, HPV11+16 : 1.3%<br/>ND :1.3%</p> <p>Benign lesions HPV non-associated :HPV16 :1.3%<br/>Potentially malignant lesions : HPV16 : 12.1%, HPV11 :9.1%, HPV6 : 6.1%, HPV18 : 3%, HPV11+16 : 12.1%, HPV16+18: 3% and ND: 6.1%<br/>Cancers : HPV6: 4%, HPV11: 8%, HPV16: 24%, HPV11+16: 16%, HPV16+18: 4% and HPV6+11+16:4%</p> <p><b>*Site:</b> Oral mucosa, Tongue , Floor of the mouth, Trine, Upper lip, Palate and Gum</p> | <p>* High frequency detection of HPV in potentially malignant lesions and cancerous lesions.<br/>* Etiological role of HPV in at least one subset of carcinomas of the oral cavity.</p> |
|----|----|------------------|-----|--|----|----|--------------|--------------------|--|---|

\* Avr :Average \*M: Men \*W: Women \*HPV : Human Papillomavirus \*PCR : Polymerase chain reaction\*ISH :In situ hybridization \*IHC :Immunohistochemie \* ND : Non determined \* DBH : Dot blot hybridization \*NM :Non mentioned

## DISCUSSION

We initially exclude the study of Luccas-Roxburgh Rebecca and al. which was conducted on a 100% female sample [12].

Oral HPV infection can affect all ages and both sexes. The average age of onset of the disease in our studied cases was 49.31 years ranging from 18 to 92 years, which differs from the results reported in the study Gordon A. Pringle (2014) considering the age range between 14 and 69 years [13].

A study in a Indian population, oral carcinogenesis were found principally on the tongue. This location is justified by a few risk factors, namely "Betel" [14-16].

In terms of the site of choice, oral carcinogenesis is much more prevalent in the tongue, this location is justified by a few risk factors, namely "Betel", betel nutters are very numerous in the Indian population [14-16].

In the present systematic review, the studies which have mentioned the degree of differentiation of carcinomas and their tumor classification show a high degree of differentiation and therefore a good prognosis of HPV-induced carcinomas, as well as the predominance of extended carcinomas with absence Lymph nodes and non-metastatic. According to Mirghani.H, HPV-induced carcinomas respond better to the treatment which supports their good prognosis. No correlation between HPV infection and tumor classification was reported [17]. In order to detect HPV, several methods have been used, either individualized or combined, namely PCR, in situ hybridization, immunohistochemistry, and Dot blot hybridization, yet PCR remains the most used method given its specificity of 100% and sensitivity of 94%, HPV typing was done by immunohistochemistry or Dot Blot Hybridization several types were detected.

According to Munoz et al, there are two groups of HPV viruses, high-risk and low-risk, high-risk HPV, such as HPV 16 and 18, that integrate their DNA into cellular DNA to That the expression of the oncogene E6 and E7 takes place in the host genome, which leads to the suppression of p53 and Rband tumor suppressor factors and therefore therefore the induction of malignant diseases [18].

On the basis of our results, a predominance of HPV16 and 18 infection and occasionally HPV16 + HPV18 co-infection were noted in more than 60% of the studies, all studies of these two types conclude with presence of an etiological role between HPV and HPV-dependent oral cancers, however, the authors strongly support their etiological role in oral carcinogenesis and suggest to individualize them as viral risk factors for HPV-dependent oral cancers, Absence of alcohol-smoking in the study of

Gonzalez Joaquin and al. confirm their etiological role in the oral carcinogenesis. In addition to HPV 16 and HPV 18, the presence of other types of HPV strongly marked our results [19].

According to the classification, HPV 11 and HPV 6 are low risk HPVs that were found much more in controls and associated with benign lesions, HPV 13 was also found in carcinomas according to the study of Rebecca Roxburg Lucas, yet it is not on the high-risk HPV list. 16

HPV 74 which is not a high-risk HPV has been found in cases in the Shuichi Fujita study, which confuses the possibility of oncogenic potency [20].

Thus, the presence of HPV 31, 35 and 58 which are high-risk HPVs in the controls prompts us to ask about the possibility of development of HPV-induced carcinomas even in the controls carrying the virus free of Carcinomas.

Studies of the existence of risk factors reveal the existence of different risk factors: tobacco, alcohol, betel, periodontal disease and oral sex, yet the study by Gonzalez Joaquin and al. was carried out on a sample without risk factors. A lot of HPV types have been found in both cases and controls, which has allowed HPV to be individualized as a risk factor leading to oral carcinogenesis [19].

The results of this study suggest a significant causal association between HPV and oral carcinomas, especially high-risk HPVs, HPV16 and HPV18, but there is still a great deal of research to be conducted on young non-alcoholic tobacco patients in order to fully understand the mechanism of the papillomavirus and to be able to hope to prevent the disease as well as early screening to reduce oral HPV lesions.

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