

## A RETROSPECTIVE STUDY OF ORAL AND OROPHARYNGEAL CARCINOMA IN THE WESTERN SICILY POPULATION

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### ARTICLE INFO

*Article history:*

Received 07 Sep2022

Accepted 15 Oct 2022

Published 20 Oct 2022

**Keywords:**

Oral cancer, oropharynx cancer, papilloma, squamous cell, Head and Neck squamous cell carcinomas

### ABSTRACT

The main risk factors of oral/oropharyngeal carcinomas (OPCs) are smoking and alcohol. Recently, another risk factor has been identified: Human Papilloma Virus (HPV). This study is aimed to define demographic and clinical data of OPC in western Sicilian native population and their correlation with HPV. A retrospective study was carried out on 112 patients with OPC: 66.96% were males and 55.36% were over 65; 75% smoked more than 20 cigarettes/day; 64.28% did not drink alcohol. HPV was detected in 48/112 patients: 54.17% were females and 41.67% were under 65; the most affected subsite was palatine tonsil. Statistically significant association between age (over 65), gender (female), anatomical subsite (palatine tonsil) and HPV-related carcinoma was found. Our study confirmed a significant diffusion of OPCs in western Sicilian population and the crucial role of HPV. In our opinion, it's mandatory to search for HPV in biopsy sample to schedule the best therapeutic protocol.

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### 1. Introduction

To date, head and neck carcinomas represent the sixth most frequent among all cancers worldwide. In particular, oral and oropharyngeal cancers (OPC) are growing in incidence<sup>1</sup>. Alcohol and smoking are the most frequent risk factors for squamous cell carcinoma. In the last 15 years, cancer studies have begun to pay attention to a "new" risk factor: Human Papilloma Virus infection (HPV)<sup>2,3</sup>. It is known that sexually transmitted HPV infection is responsible for cervical cancer<sup>4</sup>, however it isn't the same in its role and prevalence in oral and / or oropharyngeal cancer related to high-risk sexual behaviour. The epidemiological data reveals the increase in incidence of oral and oropharyngeal squamous cell carcinoma despite a general reduction in smoking habits, as well as frequent involvement of a younger population (under 65 years of age)<sup>5,6</sup>. Males are more often affected, probably due to a greater exposure to risk factors (smoking and alcohol); however, recent studies show an increased incidence on females due to an increase in smoking habits<sup>7</sup>.

In general, the prognosis of these tumours is poor and depends above all on the anatomical subsite involved and on early diagnosis, even if the new therapeutic strategies specific for HPV allow to guarantee a better survival rate for HPV-positive tumours compared to HPV-negative ones<sup>8</sup>.

The aim of this study is to define demographic and clinical data in oral and oropharyngeal carcinoma in the western Sicilian native population and their correlation with HPV positivity.

### 2. Material and methods

*Study design*

We carried out a retrospective study on a cohort of 131 patients with oral or oropharyngeal squamous cancer recruited in our Unit from January 2015 to January 2020. This study was approved by the Ethical Committee (approval number 11/2020) and informed consent was obtained from each patient in accordance with the Helsinki declaration.

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DOI: 10.3269/1970-5492.2022.17.31

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Inclusion criteria were: (1) histological diagnosis of primary squamous cell carcinoma of the oral cavity (gingiva, hard palate, cheek mucosa, oral tongue, retromolar trigone, floor of the mouth) and/or oropharynx (palatine tonsils, base of the tongue, soft palate), (2) microbiological examination of the specimen to assess the presence of HPV infection, (3) age over 18 years, (4) possibility of acquiring the patient's personal information and habits, (5) western Sicilian natives.

Exclusion criteria were: (1) other synchronous and/or previous head or neck cancers, (2) previous chemotherapy, RT and/or head or neck surgery.

#### Study protocol

After patients' selection, the following parameters were evaluated: age at diagnosis, gender, tumour site, tobacco/alcohol consumption, presence or absence of HPV in the specimen. About "tobacco use" parameter, the patients were divided in three groups: non-smokers, light smokers and those smoking more than 20 cigarettes per day. For "alcohol abuse", the patients were divided in three groups: non-drinkers, drinkers of more or less than 4 drinks per day, considering that any drink, regardless of type, contains about 14 grams of ethanol<sup>10</sup>.

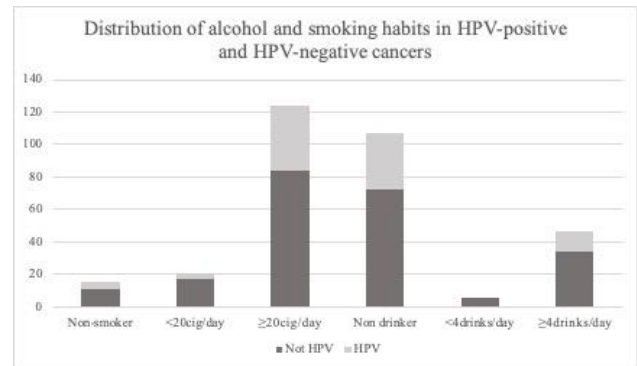
#### Statistical analyses

EPI-Info™ software was used for statistical analyses. Odd ratio and the associated 95% confidence interval (CI) were calculated to measure the possible association between variables. To assess the presence or absence of association between the dichotomous nominal variables, the Fisher's exact test was performed with two-tailed p-value <0.05. Chi-square was calculated if all expected cell frequencies are equal to or greater than 5. P-value <0.05 was considered statistically significant.

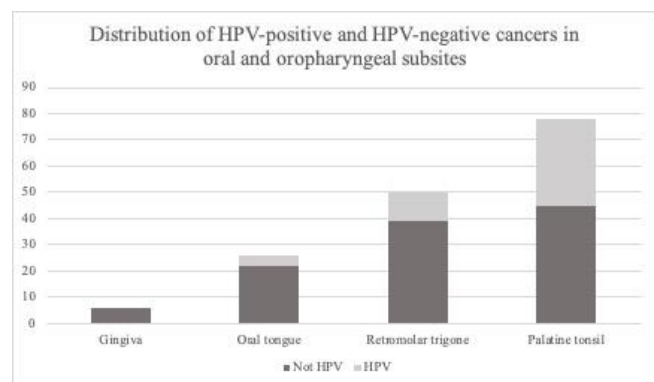
### 3. Results

#### Study population

The demographic and clinical characteristics of 112 enrolled patients are described in Table 1. The analysis showed that most patients (66.96%) were male and elderly (over 65 years), with a mean age of 63.9 years. In addition, 75% of patients smoked more than 20 cigarettes per day and only 9.82% of the cohort did not smoke. The data regarding alcohol abuse is different. In fact, only a small percentage was a heavy drinker ( $\geq 4$  drinks/day) (30.36%), while the majority did not drink alcohol daily (64.28%) (Figure 1). Among the patients included in the study, squamous cell carcinoma was found more frequently in the oral cavity (gingiva, oral tongue and retromolar trigone) rather than in the oropharynx (palatine tonsils). The most affected site by the carcinoma was the palatine tonsils (40.18%), followed by the retromolar trigone (34.82%), the oral tongue (19.64%) and the gingiva (5.36%) (Figure 2). The positivity for HPV in the sample, both by histology and immunochemistry, was limited to a few cases (48/112 patients). Moreover, none of enrolled patients had been vaccinated for HPV.



**Figure 1. Distribution of alcohol and smoking habits in HPV-positive and HPV-negative cancers**



**Figure 2. Distribution of HPV-positive and HPV-negative cancers in oral and oropharyngeal subsites**

#### HPV-positivity and demographic characteristics

48/112 (42.86%) patients tested positive for HPV on histological and immunochemistry examination (Table 1). In particular, 28/48 (58.33%) patients were under 65 years at the time of diagnosis and a correlation between the variable "age at diagnosis" and the onset of HPV-related carcinoma was found (odd ratio 2.67, p-value 0.0196). As regards to the distribution of carcinoma based on gender, in our casuistry a higher incidence in females (54.17%) and a statistically significant association between gender and onset of HPV-related carcinoma (odd ratio 5.69, p-value 0.0001) were found. Therefore, in our population, the HPV-positivity related to "age at diagnosis" and "gender" is distributed differently compared to what emerged in the global evaluation of oral and oropharyngeal carcinomas: the carcinoma was more frequent in males over 65 years, but the HPV-related carcinoma was more frequent in females under 65.

With reference to tobacco and alcohol consumption, in order to state the possible correlation with HPV-related carcinoma, patients were grouped into two categories: "smokers" vs "non-smokers", "drinkers" vs "non-drinkers". The statistical survey did not reveal any association between tobacco and the onset of HPV-related carcinoma (odd ratio 0.74 and p-value 0.75) and between alcohol and the onset of HPV-related carcinoma (odd ratio 1.96 and p-value 0.1463). Therefore, although they represent risk factors for the onset of OPC, in our experience, they don't represent a factor affecting the onset of HPV-related carcinoma.

The study of our sample showed that 35/48 patients did not usually drink alcohol and that 40/48 patients were heavy smokers ( $\geq 20$  cigarettes / day) (Figure 1).

Parameters	N° patients (%)	HPV prevalence (%)	OR (95% CI)	p-value
<b>Age at diagnosis (years)</b>				
≤65	50 (44.64)	28 (58.33)	<b>2.67</b> (1.2-5.7)	<b>&lt;0.05</b>
>65	62 (55.36)	20 (41.67)		
Mean age	63.9			
Minimum	49			
Maximum	85			
<b>Gender</b>				
Female	37 (33.04)	26 (54.17)	<b>5.69</b> (2.4-13.4)	<b>&lt;0.001</b>
Male	75 (66.96)	22 (45.83)		
<b>Tobacco use</b>				
Non-smoker	11 (9.82)	4 (8.33)	0.74 (0.2-2.6)	n.s.
Smoker	101 (90.18)	44 (91.67)		
<20 cigarettes/day	17 (15.18)	4 (8.33)		
$\geq 20$ cigarettes/day	84 (75)	40 (83.34)		
<b>Alcohol abuse</b>				
Non-drinker	72 (64.28)	35 (72.92)	1.96 (0.8-4.4)	0.15
Drinker	40 (35.72)	13 (27.08)		
<4 drinks/day	6 (5.36)	0 (0)		
$\geq 4$ drinks/day	34 (30.36)	13 (27.08)		
<b>Tumour site</b>				
- Oral cavity	67 (59.82)	15 (31.25)	<b>9.53</b> (3.9-22.8)	<b>&lt;0.001</b>
Gingiva	6 (5.36)	0 (0)		
Oral tongue	22 (19.64)	4 (8.33)		
Retromolar trigone	39 (34.82)	11 (22.92)		
- Oropharynx	45 (40.18)	33 (68.75)		
Palatine tonsil	45 (40.18)	33 (68.75)		
<b>HPV detection</b>				
Yes	48 (42.86)			
Not	64 (57.14)			
<b>Total</b>	<b>112 (100)</b>	<b>48 (42.86)</b>		

**Table 1. Patients' characteristics**

#### HPV-positivity and anatomical subsites

In HPV-related carcinoma a greater involvement of the palatine tonsil (68.75%) compared to other anatomical sites was found with a statistically significant higher risk of HPV-related tumour in the oropharynx rather than in the oral cavity (odd ratio 9.53, p-value <0.001).

## 4. Discussion

Oral cavity and oropharynx are very frequent sites of squamous cell carcinoma in the head and neck<sup>11,12,13</sup>. More frequently it affects elderly males<sup>14</sup>. Smoking and alcohol are the main risk factors. Tobacco smoke is classified as group 1 carcinogen by the international agency for research in cancer<sup>15</sup>. The smoking-associated risk is correlated to the number of cigarettes smoked per day as demonstrated also in our study where 75% of the patients included smoked more than 25 cigarettes per day. Alcohol consumption also has a dose-dependent association with the onset of OPC<sup>16</sup>. However, in our cohort, only 30.36% were heavy drinkers. Combined tobacco and alcohol consumption increases the risk of OPC by 35 times<sup>17</sup>.

In recent decades, another risk factor has been identified: HPV infection<sup>18</sup>. HPV-positive tumours usually occur in younger subjects, predominantly in males<sup>19-20</sup>. Our sample shows a different epidemiological data: OPC

occurs mainly in males (66.96%) over 65 (55.36%); however, HPV-positive OPC were more frequent in young females. The study also demonstrated the presence of a statistically significant correlation between female gender and HPV-related cancer. Our study also looked for a correlation or synergic action of HPV and alcohol or tobacco consumption, but no relationship was found. D'Souza<sup>21</sup> suggests that risk factors act with two different pathways: HPV determines genomic instability, alcohol and / or smoking have a carcinogenic action.

The most affected anatomical subsites from the OPC are the tongue and the palatine tonsil<sup>1</sup>. In case of HPV-related tumours, literature reports frequent involvement of the oropharynx, in particular of the palatine tonsil<sup>22-23</sup>. Similarly, in our sample, the most affected sites were in order: the palatine tonsil (40.18%), the retromolar trigone (34.82%) and the oral tongue (19.64%). HPV was most often detected in palatine tonsil carcinoma. Several hypotheses have been suggested to explain why the oropharynx is most often affected by HPV infection: according to some authors, HPV infection occurs in the presence of microtrauma of the mucosa that allows virus penetration; according to other authors, the tonsillar crypts play as reservoir for HPV and the presence of lymphoid tissue promotes HPV infection and allows HPV to evade the immune system<sup>11, 24</sup>.

The main limit of our study is the modest sample size which could not be representative of the general population, although much data is consistent with what is reported in the literature. In addition, none of the enrolled patients had been vaccinated for HPV: this made it possible to avoid a bias in the evaluation of the prevalence of HPV infection in OPCs. However, at the same time, it highlighted a very important epidemiological data: the low diffusion of HPV vaccination in the western Sicilian population and the lack of knowledge of its role in the OPCs' prevention<sup>25</sup>.

OPCs are characterized by high mortality and low survival rates<sup>7</sup>. HPV-related tumours have a better prognosis than HPV-negative ones, with a better response to therapy<sup>8</sup>. For this reason, it is important to search for the virus in biopsy sampling to provide the best therapeutic strategy and ensure the highest survival rate to the patient.

## 5. Conclusions

Oral and oropharyngeal carcinomas are among the most frequent head and neck cancers and are characterized by a poor prognosis. The study on the Western Sicilian population confirmed the large prevalence of OPCs and the increasingly important role of HPV in their onset. For this reason, a deep and complete knowledge of OPCs enables to make an early diagnosis, to act promptly and to ensure a high survival rate for the patient, as well as to spread the importance and necessity of HPV vaccination, both for women and men<sup>26-28</sup>.

## References

1. Dalianis T. Human papillomavirus and oropharyngeal cancer, the epidemics, and significance of additional clinical biomarkers for prediction of response to therapy (Review). Int J Oncol. 2014;44(6):1799-805.

2. El-Mofty SK. Human papillomavirus (HPV) related carcinomas of the upper aerodigestive tract. *Head Neck Pathol.* 2007;1(2):181-5.
3. International Agency for Research on Cancer (IARC). IARC Monographs on the evaluation of carcinogenic risk to humans. France: Lyon; 2007;90.
4. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol.* 1999;189(1):12-9.
5. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 2011; 29(32):4294-301.
6. Ramqvist T, Dalianis T. Oropharyngeal cancer epidemic and human papillomavirus. *Emerg Infect Dis.* 2010;16(11):1671-7.
7. Moro JDS, Maroneze MC, Ardenghi TM, Barin LM, Danesi CC. Oral and oropharyngeal cancer: epidemiology and survival analysis. *Einstein (Sao Paulo).* 2018 Jun 7;16(2):eAO4248.
8. Oguejiofor KK, Hall JS, Mani N, Douglas C, Slevin NJ, Homer J et al. The prognostic significance of the biomarker p16 in oropharyngeal squamous cell carcinoma. *Clin Oncol.* 2013;25(11):630-8.
9. Chen ZW, Weinreb I, Kamel-Reid S, Perez-Ordenez B. Equivocal p16 immunostaining in squamous cell carcinoma of the head and neck: staining patterns are suggestive of HPV status. *Head Neck Pathol.* 2012;6(4):422-429.
10. O'Keefe EL, Di Nicolantonio JJ, O'Keefe JH, Lavie CJ. Alcohol and CV Health: Jekyll and Hyde J-Curves. *Prog Cardiovasc Dis.* 2018;61(1):68-75.
11. Chi AC, Day TA, Neville BW. Oral cavity and oropharyngeal squamous cell carcinoma--an update. *CA Cancer J Clin.* 2015;65(5):401-21.
12. Saraniti C, Gallina S, Verro B. NBI and Laryngeal Papillomatosis: A Diagnostic Challenge: A Systematic Review. *Int J Environ Res Public Health.* 2022;19(14):8716. Published 2022 Jul 18. doi:10.3390/ijerph19148716
13. Melo BAC, Vilar LG, Oliveira NR, Lima PO, Pinheiro MB, Domingueti CP et al. Human papillomavirus infection and oral squamous cell carcinoma - a systematic review. *Braz J Otorhinolaryngol.* 2020;S1808-8694(20)30209-3.
14. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin.* 2015;65(1):5-29.
15. International Agency for Research on Cancer (IARC). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. List of classifications by cancer sites with sufficient or limited evidence in humans. France: Lyon; 2020;128.
16. International Agency for Research on Cancer (IARC). IARC Section 2.2: Cancer of the oral cavity and pharynx. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Alcohol Consumption and Ethyl Carbamate. France. 2010;96: 237-329.
17. Tribius S, Hoffmann M. Human papilloma virus infection in head and neck cancer. *Dtsch Arztebl Int.* 2013;110(11):184-190.
18. Elrefaey S, Massaro MA, Chiocca S, Chiesa F, Ansarin M. HPV in oropharyngeal cancer: the basics to know in clinical practice. *Acta Otorhinolaryngol Ital.* 2014;34(5):299-309.
19. Chaturvedi AK, Graubard BI, Broutian T, Pickard RKL, Tong ZY, Xiao W et al. NHANES 2009-2012 Findings: Association of Sexual Behaviors with Higher Prevalence of Oral Oncogenic Human Papillomavirus Infections in U.S. Men. *Cancer Res.* 2015;75(12):2468-2477.
20. Saraniti C, Speciale R, Gallina S, Salvago P. Prognostic role of resection margin in open oncologic laryngeal surgery: survival analysis of a cohort of 139 patients affected by squamous cell carcinoma. *Braz J Otorhinolaryngol.* 2019;85(5):603-610. doi:10.1016/j.bjorl.2018.04.012
21. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med.* 2007;356(19):1944-56.
22. Saraniti C, Greco G, Verro B, Lazim NM, Chianetta E. Impact of Narrow Band Imaging in Pre-Operative Assessment of Suspicious Oral Cavity Lesions: A Systematic Review. *Iran J Otorhinolaryngol.* 2021;33(116):127-135. doi:10.22038/ijorl.2021.51485.2746
23. Mena M, Frias-Gomez J, Taberna M, Quiros B, Marquez S, Clavero O et al. Epidemiology of human papillomavirus-related oropharyngeal cancer in a classically low-burden region of southern Europe. *Sci Rep.* 2020; 10:13219.
24. Mirghani H, Amen F, Moreau F, Lacau St Guily J. Do high-risk human papillomaviruses cause oral cavity squamous cell carcinoma? *Oral Oncol.* 2015;51(3):229-36.
25. Verro B, Gallina S, Saraniti C. Papillomavirus Infection and Prevention: How Much Does the Sicilian Population Know? An Observational Study. *Int J Environ Res Public Health.* 2022;19(17):11032. Published 2022 Sep 3. doi:10.3390/ijerph191711032
26. Trucchi C, Amicizia D, Tafuri S, Sticchi L, Durando P, Costantino C, Varlese F, Silverio BD, Bagnasco AM, Ansaldi F, Icardi G. Assessment of Knowledge, Attitudes, and Propensity towards HPV Vaccine of Young Adult Students in Italy. *Vaccines (Basel).* 2020 Feb 7;8(1).
27. Restivo V, Costantino C, Amato L, Candiloro S, Casuccio A, Maranto M, Marrella A, Palmeri S, Pizzo S, Vitale F, Amodio E. Evaluation of the Burden of HPV-Related Hospitalizations as a Useful Tool to Increase Awareness: 2007-2017 Data from the Sicilian Hospital Discharge Records. *Vaccines (Basel).* 2020 Jan 26;8(1).
28. Palmeri S, Costantino C, D'Angelo C, Casuccio N, Ventura G, Vitale F, Pojero F, Casuccio A. HPV vaccine hesitancy among parents of female adolescents: a pre-post interventional study. *Public Health.* 2017 Sep;150:84-86.