

Supplementary file 1 (S1) - Oral Bacteria, Virus and Fungi in Saliva from Adult Subjects with Oral Squamous Cell Carcinoma

Table S1. Data extracted and collected from the included studies that had carried out a histopathologic analysis of OSCC-tissue lesions. Studies: first Author, year and journal of publication, reference, number and design of included studies, meta-analysis, assessed quality, funding (if any). Population characteristics: sample size, mean age, gender ratio, country of origin of the sample, risk factor and history of OPMD, history of malignancies, other comorbidities and ongoing treatments. OSCC characteristics: macroscopic features, location, staging and grading, microscopic features, first diagnosis (primary site/metastatic lesion), time to onset, chemotherapy (yes/no), radiotherapy (yes/no). Intervention: number of sample(s), method(s) of sample collection, microorganisms identification technique, target. Outcome(s): type(s) of phylum, genus and species of bacterium, type(s) and genotype of virus, type(s) and species of fungus detected, number or percentage of OSCC positive case.

STUDIES	POPULATION		INTERVENTION	OUTCOME(S)		
	Characteristics	OSCC		Bacteria	Viruses	Fungi
First Author, year	Sample size: n. ...of case/n. ... of control	Macroscopic features:	Sample(s):			
<i>Journal of publication</i>	Mean age: ... y.o.; range ...-...	Location:				
	Gender ratio: M/F					
Reference	Country: (origin of the sampling)	Staging: Grading:	Method(s) of sample collection:	Type(s) of bacterium: n. .../ % of OSCC case	Type(s) of virus: n. .../ % of OSCC case	Type(s) of fungus: n. .../ % of OSCC case
Studies: n.		Microscopic features:		Type(s) of bacterium species detected:		
Type n.	Risk factors for OSCC:		Microorganisms identification technique:		Genotype(s) of virus detected:	Type(s) of fungi species detected:
	History of OPMD:	First Diagnosis (metastatic lesion/primary site):				
Meta-analysis	Time to OPMD onset:	Time to onset:	Target:			
	Previous history of malignancies:	Chemotherapy:				
Assessed quality	Other comorbidities:	Radiotherapy:				
Funding (if any)	Other ongoing treatments:					
Ayuningtyas, 2022	Sample size: n.136+MD of case/n.92+MD of the healthy control group/n.107+MD of OPMD control group	Macroscopic features: MD Location: MD	Sample(s): n.136+MD			Than the healthy control group
<i>Pathophysiology</i>	Mean age: MD	Staging: MD Grading: MD	Method(s) of sample collection: Biopsy n.61 Swab n.50	-	-	↑ Candida: n.MD of OSCC case
Studies: n.5	Gender ratio: MD	Microscopic features: MD				
RCSS n.2	Country:		Biopsy and Swab n.25+MD			Than the OPMD control group
CSS n.2	India n.80	First Diagnosis: MD				
PS n.1	Egypt n.31	Time to onset: MD				

No Meta-analysis	Argentina n.25 Taiwan n.MD	Chemotherapy: MD Radiotherapy: MD	Microorganisms identification technique: Culture n.136+MD IHC: n.MD	↑ Candida: n.MD of OSCC case
Critically Low quality	Risk factors for OSCC: MD History of OPMD: MD Time to OPMD onset: MD		Target: MD	Type(s) of fungi species detected: MD
No Funding	Previous history of malignancies: MD Other comorbidities: MD Other ongoing treatments: MD			
	Sample size: n.294 of case Mean age: MD Gender ratio: MD			Than the healthy control group
Bronzato D.J., 2020	Country: USA n.52 China n.40	Macroscopic features: MD Location: N/D oral cavity n.161; gingiva n. MD; tongue n. MD; cheek n. MD; oral floor n. MD; mandible n. MD; buccal mucosa n. MD.	Sample(s): n.294 Method(s) of sample collection: Biopsy n.125 Swab n.146 Biopsy and Swab n.20 Sterile paper point n.3	Fusobacteria: ↑ Fusobacterium: n.132 of OSCC case Type(s) of Fusobacterium species detected: F. nucleatum; F. naviforme; F. periodonticum; F. canifelinum; F. oral taxon (A71, 203, 370); F. necrophorum; F. gonidiaformans; F. simiae.
Arch Oral Biol	India n.40 Germany n.33 Hungary n.31 Wales n.30 Sri Lanka n.27 Japan n.21 Yemen n.N/D			–
Studies: n. 13 CCS n.13	Saudi Arabia n.N/D	Staging: MD Grading: MD Microscopic features: MD	Microorganisms identification technique: Culture n.142 PCR n.152	–
Meta-analysis				
Moderate quality	Risk factors for OSCC: MD History of OPMD: MD Time to OPMD onset: MD Previous history of malignancies: MD Other comorbidities: MD Other ongoing treatments: MD	First Diagnosis: MD Time to onset: MD Chemotherapy: MD Radiotherapy: MD	Target: 16S rDNA n.42 16S rRNA n.107 MD n.145	Type(s) of Fusobacterium nucleatum subspecies: F. nucleatum ssp. nucleatum; F. nucleatum ssp. vicentii; F. nucleatum ssp. polymorphum; F. nucleatum ssp. animalis.
This study was supported by CAPES, FAPESP and CNPq.				
Chaitanya N.C., 2016	Sample size: n. N/D of case/n. 3212 of the healthy control group	Macroscopic features: MD Location: tongue n. MD buccal mucosa n. MD dentoalveolar complex n. MD	Sample(s): n. N/D Method(s) of sample collection: Serum analysis n. MD Biopsy n. MD	Than the healthy control group – ↑ HPV: n.N/D of OSCC case
J Cancer Res Ther	Mean age: MD Gender ratio: MD Country: MD			–
Studies: n. 11				

CCS n.11		oral floor n. MD	Brush n. MD	20.34% OSCC of the tongue	
Meta-analysis	Risk factors for OSCC: MD			8.70% OSCC of the oral floor	
Critically Low quality	History of OPMD: MD	Staging: MD	Microorganisms identification technique: N/D	8.00% OSCC of the dentoalveolar complex	
No Funding	Time to OPMD onset: MD	Grading: MD		5.00% OSCC of the buccal mucosa	
	Previous history of malignancies: MD	Microscopic features: MD		Genotype(s) of HPV detected: MD	
	Other comorbidities: MD	First Diagnosis: MD	Target: HPV DNA n.MD		
	Other ongoing treatments: MD	Time to onset: MD			
		Chemotherapy: MD			
		Radiotherapy: MD			
Christianto S., 2022		Macroscopic features: MD			
<i>Laryngoscope</i>	Sample size: n.3065 of case	Location: MD	Sample(s): n.3065	↑ HPV: n.672 (prevalence 21.92) of OSCC case	
Studies: n. 22	Mean age: MD			Genotype(s) of HPV detected:	
CS n.22	Gender ratio: 2155M/720F/190 N/D	Staging: Stage I (n.134)	Method(s) of sample collection: MD	HPV-16: n.82	
Meta-analysis	Country: MD	Stage II (n.173)	Microorganisms identification technique: PCR n.1800	HPV-6, -11, -16, -18, -26, -31, -32, -33, -34, -35, -37, -39, -40, -42, -43, -44, -45, -51, -52, -53, 54, -55, -56, -58, -59, -61, -62, -66, -67, -68, -69, -70, -71, -72, -74, -81, -82: n.N/D	-
Critically Low quality	Risk factors for OSCC: MD	Stage III (n.172)	IHC n.779		
No Funding	History of OPMD: MD	Stage IV (n.551)	ISH n.264		
	Time to OPMD onset: MD	Stage MD (n.2303)	PCR/IHC/ISH n.N/D		
	Previous history of malignancies: MD	Grading: MD			
	Other comorbidities: MD	Microscopic features: MD			
	Other ongoing treatments: MD	First Diagnosis: MD	Target: MD		
		Time to onset: MD			
		Chemotherapy: MD			
		Radiotherapy: MD			
de Carvalho Melo, 2021	Sample size: n.383 of case	Macroscopic features: MD	Sample(s): n.383		
<i>Braz J Otorhinolaryngol</i>	Mean age: N/D y.o.; range 19-92 y.o.	Location: tongue n.9;	Method(s) of sample collection: Biopsy n.225 MD n.158	HPV: n.16 of OSCC case	
Studies: n.5	Gender ratio: 218M/165F	dentoalveolar complex n.1; MD n.373.		Genotype(s) of HPV detected:	
CCS n.5	Country: USA n.113			HPV-16: n.14 HPV-18: n.2 NS	-
No Meta-analysis	Greece n.53	Staging: MD	Microorganisms identification technique: N/D		
	Chile n.80	Grading: MD			
	China n.137	Microscopic features: MD			
		First Diagnosis: MD			
	Risk factors for OSCC: Tobacco n.2 of OSCC HPV+	Time to onset: MD	Target:		

No Funding	Alcohol n.2 of OSCC HPV+ History of OPMD: MD Time to OPMD onset: MD Previous history of malignancies: MD Other comorbidities: MD Other ongoing treatments: MD	Chemotherapy: MD Radiotherapy: MD	E6 mRNA n.MD E7 mRNA n.MD		
	Sample size: n.N/D of case/n.N/D of the healthy control group Mean age: MD Gender ratio: MD Country: Japan n.N/D Taiwan n.N/D India n.N/D China n.N/D South Africa n.N/D Sudan n.N/D Finland n.N/D Italy n.N/D Spain n.N/D Germany n.N/D Hungary n.N/D Czech Republic n.N/D The Netherlands n.N/D	Macroscopic features: MD Location: tongue n.12 Staging: In situ OSCC (n.7) Stage II (n.12) Grading: MD Microscopic features: MD	Sample(s): n.N/D Method(s) of sample collection: MD Microorganisms identification technique: PCR: n.940 In situ PCR: n.220 Nested PCR: n.290 RT-PCR: n.59 PCR dot blot: n.198 Differential PCR: n.60 IHC: n.635 ISH: n.864 Radioactive ISH: n.117 DNA sequencing: n.64 Single strand conformation polymorphism: n.60		
de Lima, 2014 <i>J Bras Patol Med Lab</i>				↑ HPV genome: n.555 of OSCC case	
Studies: n.37 MD n.37				Genotype(s) of HPV detected: HPV-6, -11, -16, -18, -31, -33: n.N/D	-
No Meta-analysis				↑ EBV: n.236 of OSCC case	
Critically Low	Serbia n.N/D USA n.N/D	First Diagnosis: MD Time to onset: MD			
No Funding	Venezuela n.N/D Brazil n.N/D Argentina n.N/D	Chemotherapy: MD Radiotherapy: MD	Target: HPV DNA: n.640 p16: n.193 p53: n.496 p21: n.33 pRb: n.112 BCL-2: n.43 hTERT: n.35 C-MYC: n.60 EBV genome: n.601		
	Risk factors for OSCC: Tobacco and alcohol n.36 History of OPMD: MD Time to OPMD onset: MD Previous history of malignancies: MD Other comorbidities: MD				

Other ongoing treatments: MD				
		Sample(s): n.2665		
		Method(s) of sample collection:		
		Biopsy n.2530		
		Brush n.135		
		Microorganisms identification technique:		
		PCR: n.1016		
		In situ PCR: n.102		
		PCR Southern blot: n.411		
		RT-PCR Southern blot: n.40		
		Real time qPCR: n. 158		
		qPCR: n.128		
		Real time RT-PCR: n.35		
		Nested PCR: n.708		
		PCR ELISA: n.79		
		IF: n.85		
		IHC: n.721		
		ISH: n.179		
		RNA ISH: n.668		
		Radioactive RNA ISH: n.4		
		DNA ISH: n.142		
		RNA microarray: n.151		
		NASBA: n.9		
		Target:		
		EBV: n.471		
		EBNA1: n.458		
		EBNA2: n.444		
		LMP gene: n.33		
		LMP1: n.716		
		LMP2: n.4		
		EBER: n.535		
		EBER1: n.295		
		BZLF1: n.240		
		BNLF1: n.127		

				BNRF1: n.16 BNFR1 n.60 BMLF1: n.16 BHRF1: n.9 BARF0: n.10 IR-1 region: n.36 IR-3 region: n.1 71 EBV fragments: n.57 BamHI W: n.974 BamHI L: n.103 MD n.31	
			Sample(s): n.199	Than the healthy control group	
			Method(s) of sample collection: Biopsy n.104 Swab n.95	↑ Fusobacteria: ↑ Fusobacterium	
	Sample size: n.199 of case/n.201 of the healthy control group			Type(s) of Fusobacterium species detected:	
Gopinath, 2019	Mean age: 60,85 y.o.; range MD	Macroscopic features: MD	Microorganisms	F. nucleatum ssp.	
	Gender ratio: MD		identification technique:	polymorphum	
	Country:	Location:	DNA isolation kit n.30	F. naviforme	
<i>Crit Rev Oncol Hematol</i>	United Kingdom n.10	tongue n.39	Incubation in Proteinase K and DNA purification kit		
	USA n.64	MD n.160	n.10	↑ Spirochaetes	
Studies: n.7	Yemen n.20	Staging: MD	Incubation in Proteinase K and DNA easy kit n.15	↑ Proteobacteria:	
CCS n.7	Sri Lanka n.25	Grading: MD	Gentra Puregene Tissue kit n.25	↑ Campylobacter	-
	China n.80	Microscopic features: MD	QIAamp DNA Stool mini kit n.39	Type(s) of Campylobacter species detected:	
No Meta-analysis	Risk factors for OSCC: N/D	First Diagnosis: MD	QIAamp DNA Mini kit n.80	C. Oral taxon 44	
Low quality	History of OPMD: MD	Time to onset: MD	Target:	↑ Pseudomonas	
	Time to OPMD onset: MD	Chemotherapy: MD	16s rRNA: n.10	Type(s) of Pseudomonas species detected:	
No Funding	Previous history of malignancies: MD	Radiotherapy: MD	V1-V3 region: n.45	↑ Pseudomonas aeruginosa	
	Other comorbidities: MD		V4-V5 region: n.90	↑ Ralstonia	
	Other ongoing treatments: MD		V4 region: n.54	Type(s) of Ralstonia species detected:	
				Ralstonia insidiosa	
				↑ Bacteroidetes:	

					<p>↑ Capnocytophaga</p> <p>↓ Actinobacteria:</p> <p>↑ Corynebacterium</p> <p>↑ Atopobium</p> <p>↑ Actinomyces</p> <p>↑ Rothia</p> <p>↑ Micrococcus</p> <p>↑ Clavibacter michiganensis</p> <p>Type(s) of Clavibacter michiganensis species detected:</p> <p>Clavibacter michiganensis tellarius</p> <p>↓/↑ Firmicutes:</p> <p>↑ Enterococcus</p> <p>↑ Gemella</p> <p>Type(s) of Gemella species detected:</p> <p>Gemella haemolysans</p> <p>Gemella morbillorum</p> <p>↑ Streptococcus</p> <p>Type(s) of Streptococcus species detected:</p> <p>S. salivarius</p> <p>S. oral taxon 058</p> <p>S. gordonii</p> <p>S. parasanguinis</p> <p>↑ Johnsonella</p> <p>Type(s) of Johnsonella species detected:</p> <p>Johnsonella ignava</p> <p>↑ Peptostreptococcus:</p> <p>Type(s) of Peptostreptococcus species detected:</p> <p>Pepetosptreptococcus stomatis</p>	
Guo, 2018	Sample size: n.1275 of case Mean age: MD	Macroscopic features: MD Location: MD	Sample(s): n.1275	-	↑ HPV: n.190 (prevalence 14.9%) of OSCC case	-

<i>Front Oncol</i>	Gender ratio: MD Country: China n.1275	Staging: MD Grading: MD Microscopic features: MD	Method(s) of sample collection: Biopsy n.1275	p < 0.001	
Studies: n.11 MD n.11	Risk factors for OSCC: MD		Microorganisms	Genotype(s) of HPV detected: HPV-16: n.190	
Meta-analysis	History of OPMD: MD Time to OPMD onset: MD	First Diagnosis: MD Time to onset: MD	identification technique: PCR: n.921+N/D		
Critically Low	Previous history of malignancies: MD	Chemotherapy: MD Radiotherapy: MD	ISH: n.N/D		
This study was supported by the National Natural Science Foundation of China (No.81703298).	Other comorbidities: MD Other ongoing treatments: MD		Target: HPV-16: n.1275		
	Sample size: n.513 of case/n.354 of the healthy control group Mean age: MD Gender ratio: 39M/44F/430MD		Sample(s): n.513		
Gupta, 2020	Country: Japan n.58	Macroscopic features: MD Location: MD	Method(s) of sample collection: Swab n.58 Biopsy n.455	↑ Than the healthy control group (prevalence 31.92%)	
<i>Clin Oral Investig</i>	Sri Lanka n.53 India n.60			Proteobacteria: Helicobacter	
Studies: n.7 CSS n.7	Iran n.83 Germany n.191 China n.68	Staging: MD Grading: MD Microscopic features: MD	Microorganisms identification technique: PCR: n.128 RT-PCR: n.58 Culture: n.131 Giemsa: n.68 IHC: n.274 ELISA: n.121	Type(s) of Helicobacter species detected: ↑ Helicobacter pylori: n.165 (prevalence 32.16%) of OSCC case	-
No Meta-analysis		First Diagnosis: MD Time to onset: MD Chemotherapy: MD Radiotherapy: MD			
Low quality	Risk factors for OSCC: Betel chewers n.44				
No Funding	History of OPMD: MD Time to OPMD onset: MD Previous history of malignancies: MD Other comorbidities: MD Other ongoing treatments: MD		Target: MD		
Haghshenas, 2022	Sample size: n.69 of case/n.57 of the healthy control group Mean age: MD	Macroscopic features: MD Location: MD	Sample(s): n.69	-	Than the healthy control group (prevalence 0.00%)

<i>Iran J Public Health</i>	Gender ratio: MD Country: MD	Staging: MD Grading: MD Microscopic features: MD	Method(s) of sample collection: Biopsy n.69	↑ HPV: n.20 (prevalence 28.99%) of OSCC case
Studies: n.2 CCS n.2	Risk factors for OSCC: MD History of OPMD: MD Time to OPMD onset: MD	First Diagnosis: MD Time to onset: MD	Microorganisms identification technique: N/D	Genotype(s) of HPV detected: HPV-16: n.5 HPV-18: n.2 MD n.13
Meta-analysis	Previous history of malignancies: MD	Chemotherapy: MD Radiotherapy: MD		
Critically Low	Other comorbidities: MD Other ongoing treatments: MD		Target: MD	
This study was supported by the Mazandaran University of Medical Sciences (IR.MAZUMS.REC.1399.8657).				
Hobbs, 2006	Sample size: n.1873 of case/n.2437 of the healthy control group Mean age: MD Gender ratio: MD Country: MD	Macroscopic features: MD Location: N/D oral cavity n.1656 Tonsil n.217	Sample(s): n.1873 Method(s) of sample collection: Biopsy n.322 Serum analysis n.1551	↑ HPV: n.314 (prevalence 16.76%) of OSCC case
<i>Clin Otolaryngol</i>				
Studies: n.15 MD n.15		Staging: MD Grading: MD Microscopic features: MD		n.219 (13.22%); N/D oral cavity n.95 (43.78%); tonsil
Meta-analysis	Risk factors for OSCC: MD History of OPMD: MD Time to OPMD onset: MD	First Diagnosis: MD Time to onset: MD	Microorganisms identification technique: N/D	Genotype(s) of HPV detected: N/D
Critically Low	Previous history of malignancies: MD	Chemotherapy: MD Radiotherapy: MD	Target: N/D	
No Funding	Other comorbidities: MD Other ongoing treatments: MD			
Huybrechts, 2020	Sample size: n.724 of case/n.1188 of the healthy control group Mean age: MD Gender ratio: MD Country: MD	Macroscopic features: MD Location: MD	Sample(s): n.724	↑ Bacteroidetes: ↑ Capnocytophaga
<i>Cancer Epidemiol Biomarkers Prev</i>				
Studies: n.13 CS n.2 CCS n.11	Risk factors for OSCC: MD	Staging: MD Grading: MD Microscopic features: MD First Diagnosis: MD	Method(s) of sample collection: Biopsy n.724	↑ Fusobacteria: ↑ Fusobacterium Firmicutes: ↑ Dialister

No Meta-analysis	History of OPMD: MD Time to OPMD onset: MD Previous history of malignancies: MD Other comorbidities: MD Other ongoing treatments: MD	Time to onset: MD Chemotherapy: MD Radiotherapy: MD	Microorganisms identification technique: N/D Target: MD	↑ Peptostreptococcus ↑ Parvimonas
Low quality				
This study was supported by the Intramural Research Program of the National Cancer Institute at the National Institutes of Health and by the Research Foundation-Flanders 12h1519N.				
Kreimer, 2005	Sample size: n.2642 of case Mean age: MD Gender ratio: MD Country: United Kingdom n.39 Germany n.53 Switzerland n.15 Italy n.38+N/D Slovenia n.55 The Netherlands n.105 France n.12 Spain n.2+N/D Canada n.53 USA n.832 Finland n.28+N/D Norway n.N/D Sweden n.N/D North Ireland n.N/D Poland n.N/D India n.473 Taiwan n.103	Macroscopic features: MD Location: MD Staging: MD Grading: MD Microscopic features: MD First Diagnosis: MD Time to onset: MD Chemotherapy: MD Radiotherapy: MD	Sample(s): n.2642 Method(s) of sample collection: Biopsy n.2642 Microorganisms identification technique: PCR n.2642 Target: MD	HPV: n.796 (prevalence 23.5%) of OSCC case HPV prevalence in - Europe: 16.0% - North America: 16.1% - Asia: 33.0% - Other: 18.1% ↓ Than the oropharyngeal SCCs group (prevalence 35.6%) and the laryngeal SCCs group (prevalence 24.0%) Genotype(s) of HPV detected: HPV-6: n.59 (7.41%) HPV-11: n.31 (3.89%) HPV-16: n.423 (53.34%) HPV-18: n.212 (26.73%)

						Japan n.306 China n.85 Korea n.76 Venezuela n.50 Cuba n.N/D Australia n.N/D Sudan n.N/D Risk factors for OSCC: MD History of OPMD: MD Time to OPMD onset: MD Previous history of malignancies: MD Other comorbidities: MD Other ongoing treatments: MD	HPV-16 and -18: n.44 (5.55%) HPV-31: n.3 (0.38%) HPV-32: n.1 (0.13%) HPV-33: n.14 (1.76%) HPV-35: n.1 (0.13%) HPV-39: n.0 (0.0%) HPV-44: n.1 (0.13%) HPV-45: n.0 (0.0%) HPV-51: n.0 (0.0%) HPV-52: n.0 (0.0%) HPV-53: n.1 (0.13%) HPV-56: n.2 (0.25%) HPV-57: n.1 (0.13%) HPV-58: n.1 (0.13%) HPV-59: n.0 (0.0%) HPV-68: n.1 (0.13%) HPV-73: n.0 (0.0%) HPV-81: n.1 (0.13%) HPV-82: n.0 (0.0%)
							↑ Oral yeast: MD n./% of OSCC case
Mallika, 2020	Sample size: MD	Macroscopic features: MD	Sample(s): MD				
	Mean age: MD	Location: MD	Method(s) of sample collection:			↑ HPV: MD n./% of OSCC case	
<i>Trans Cancer Res</i>	Gender ratio: MD	Staging: MD	Biopsy n.MD	Proteobacteria:			Candida: MD n./% of OSCC case
	Country: MD	Grading: MD	Swab n.MD	Helicobacter		Genotype(s) of HPV detected:	case (two studies of OSCC patients undergoing radiotherapy; one study of OSCC patients undergoing chemotherapy)
Studies: n.8		Microscopic features: MD	Brush n.MD	Type(s) of Helicobacter species detected:		HPV-16 n.MD	
CCS n.8	Risk factors for OSCC: MD			↑ Helicobacter pylori		HPV-18 n.MD	
	History of OPMD: MD	First Diagnosis: MD	Microorganisms				
No Meta-analysis	Time to OPMD onset: MD	Time to onset: MD	identification technique:			HHV-6: NS	
	Previous history of malignancies: MD	Chemotherapy: yes (one study)	Culture n.MD				
Moderate quality	Other comorbidities: MD	Radiotherapy: yes (two studies)	IHC n.MD			EBV: NS	
	Other ongoing treatments: MD		ISH n.MD				
No Funding			PCR n.MD				
			Target: MD				Type(s) of fungi species detected: MD

					↑ HPV: n.627 (prevalence 46.5%) of OSCC case p < 0.001	
					Genotype(s) of HPV detected: HPV-2: n.3 HPV-3: n.1 HPV-4: n.2 HPV-6: n.52 HPV-10: n.16 HPV-11: n.37 HPV-13: n.1 HPV-16: n.285 HPV-18: n.115 HPV-31: n.3 HPV-33: n.9 HPV-57: n.1 HPV-6 and -11: n.27 HPV-16 and -18: n.49 HPV-6, and 11 and 16 and 18: n.1 HPV-6 and -16 and -18: n.3 HPV-31 and -33 and -35: n.6 N/D: 16	
Miller, 2001	Sample(s): n.N/D					
Oral Surg Oral Med Oral Pathol Oral Radiol Endod	Sample size: n.N/D of case Mean age: MD Gender ratio: MD Country: MD	Macroscopic features: MD Location: MD	Method(s) of sample collection: Biopsy n.N/D			
Studies: n.80 MD n.80	Risk factors for OSCC: MD History of OPMD: MD	Staging: MD Grading: MD Microscopic features: MD	Microorganisms identification technique: N/D ISH/IP/IF n.608 N/D Southern blot/dot blot/filter blot hybridization n.321 PCR n.1154	-		-
Meta-analysis	Time to OPMD onset: MD Previous history of malignancies: MD	First Diagnosis: MD Time to onset: MD				
Critically Low quality	Other comorbidities: MD Other ongoing treatments: MD	Chemotherapy: MD Radiotherapy: MD				
No Funding	Target: HPV DNA: n.2083					
					LR-HPV: p < 0.001 HR-HPV: P < 0.001 (prevalence 23.71%)	
Muthusamy, 2023	Sample size: n.373 of case/n.326 of healthy control group/n.73 of OPMD group Mean age: MD Gender ratio: MD Country: MD	Macroscopic features: MD Location: MD	Sample(s): n.373	Fusobacteria: ↑ Fusobacterium p = 0.05	↑ EBV: MD n./% of OSCC case p < 0.0001	
Cureus		Staging: MD Grading: MD Microscopic features: MD	Method(s) of sample collection: Blood analysis n.50 Biopsy n.211 Biofilm sampling n.21 Brush n.91	Firmicutes: ↑ Streptococcus p = NSS	HSV-1: MD n./% of OSCC case p = NSS	-
Studies: n.6 CCS n.6						
Meta-analysis	Risk factors for OSCC: MD	First Diagnosis: MD				

Critically Low quality	History of OPMD: MD Time to OPMD onset: MD Previous history of malignancies: MD Other comorbidities: MD Other ongoing treatments: MD	Time to onset: MD Chemotherapy: MD Radiotherapy: MD	Microorganisms identification technique: PAP technique n.50 Culture n.21 Nested PCR n.120 ELISA n.132 PCR n.50 Target: Herpes Select-1 n.132 16s RNA n.50	Bacteroidetes: ↑ Prevotella p = NSS ↑ Porphyromonas p = NSS Proteobacteria: ↑ Neisseria: p= NSS	
This study was supported by Indian Council of Medical Research (ICMR) under Nurturing Clinical Scientist (NCS) scheme HRD/Head-NCS-2019-02.					
Nandi, 2021	Sample size: n.1639 of case/n.206 of the healthy control group	Macroscopic features: MD	Sample(s): n.1639		
<i>Cancer Treat Res Commun</i>	Mean age: N/D y.o.; range MD Gender ratio: 955M/377F/307MD	Location: tongue n.156 MD n.1483	Method(s) of sample collection: N/D		
Studies: n.19 CCS n.19	Country: India n.1639	Staging: MD Grading: MD	Microorganisms identification technique: PCR/p16-IHC n.216 ISH n.31 IHC n.30 PCR/ISH n.45 PCR n.1317	-	↑ HPV: n.553 of OSCC case
No Meta-analysis	Risk factors for OSCC: MD	Microscopic features: MD			Genotype(s) of HPV detected: MD
Critically Low quality	History of OPMD: MD Time to OPMD onset: MD Previous history of malignancies: MD Other comorbidities: MD Other ongoing treatments: MD	First Diagnosis: MD Time to onset: MD Chemotherapy: MD Radiotherapy: MD	Target: MD		
No Funding					
Rahman, 2023	Sample size: n.1109 of case/n.211 of the healthy control group/n.150 of the OPMD group	Macroscopic features: MD	Sample(s): n.1109		HPV-EBV coinfection: n.95 of OSCC case p < 0.01
<i>Mol Oral Microbiol</i>	Mean age: MD Gender ratio: MD	Location: tonsil n.16 oral floor n.30 Buccal mucosa n.27 tongue n.74 palate n.16 (soft n.10/MO n.6) lip n.11	Method(s) of sample collection: Biopsy n.1109	-	HPV: n.31 of OSCC case
Studies: n.15 CCS n.5 NRS n.10	Country: USA n.61 Poland n.53		Microorganisms identification technique: PCR n.968		Genotype(s) of HPV detected: MD
Meta-analysis					

Critically Low	Sweden n.17 Norway n.20	MD n.935	ISH n.141	
No Funding	United Kingdom n.20 Sudan n.20 India n.20 Sri Lanka n.20 Yemen n.18	Staging: MD Grading: MD Microscopic features: MD	Target: MD	
	Risk factors for OSCC: MD History of OPMD: MD Time to OPMD onset: MD Previous history of malignancies: MD Other comorbidities: MD Other ongoing treatments: MD	First Diagnosis: MD Time to onset: MD Chemotherapy: MD Radiotherapy: MD		
Ramos, 2020				↑ Firmicutes: ↑ Dialister ↑ Catonella
Oral Maxillofac Surg	Sample size: n.124 of case/n.20 of the healthy control group/n.27 of the control group with oral fibroepithelial polyp	Macroscopic features: MD	Sample(s): n.124	↑ Peptostreptococcus ↑ Peptococcus ↑ Filifactor ↑ Parvimonas
Studies: n.4 CCS n.1 MD n.3	Mean age: MD Gender ratio: N/D Country: MD	Location: tongue n.39 MD n.85	Method(s) of sample collection: Biopsy n.64 Swab n.40 Swab and Biopsy: n.20	↓ Bacteroidetes: ↑ Capnocytophaga
No Meta-analysis				
Critically Low quality	Risk factors for OSCC: Tobacco: n.N/D Alcohol: n.N/D	Staging: MD Grading: MD Microscopic features: MD	Microorganisms identification technique: MiSeq n.85 Ion torrent n.39	↑/↓ Fusobacteria: ↑ Fusobacterium
This study was supported by the National Council for Scientific and Technological Development (CNPq) (Project:211309/2013-3) and the Foundation for	History of OPMD: MD Time to OPMD onset: MD Previous history of malignancies: MD Other comorbidities: MD Other ongoing treatments: MD	First Diagnosis: MD Time to onset: MD Chemotherapy: MD Radiotherapy: MD	Target: V4 region n.39 V1-V3 region n.45 V4-V5 region n.40	Type(s) of Fusobacterium species detected: ↑ F. nucleatum ssp. polymorphum
				Proteobacteria: ↑ Campylobacter Pseudomonas Type(s) of Pseudomonas species detected:

Research Financial Support in the State of Rio de Janeiro (FAPERJ) (Project: E26/ 1033.001/2012).	↑ <i>Pseudomonas aeruginosa</i>				Actinobacteria: ↑ <i>Atopobium</i>
Shaikh, 2015 <i>Cancer Epidemiol</i> Studies: n.45 CSS n.N/D CCS n.N/D Meta-analysis Low quality This study was supported by the Griffith University of Australia.	Sample size: n.4893 of case Mean age: 56.80 y.o.; range 22- 94 y.o. Gender ratio: MD Country: India n.1293 Pakistan n.48 Bangladesh n.34 Sri Lanka n.96 Malaysia n.109 Thailand n.32 China n.183 Hong Kong n.31 Taiwan n.535 South Korea n.167 Japan n.843 Australia n.1522	Macroscopic features: MD Location: buccal mucosa n.433 gingiva n.196 tongue n.679 oral floor n.96 palate n.64 (hard n.1/soft n.5/MD n.59) tonsil n.1587 lip n.114 N/D oral cavity n.2353	Sample(s): n.4893 Method(s) of sample collection: Biopsy n.4893 Microorganisms identification technique: PCR n.4209 Southern blot PCR n.224 Slot blot PCR n.15 Nested PCR n.27 ISH n.102 PCR and ISH: n.244 RT-PCR and IHC: n.52 In situ PCR and ISH n.20 Target: HPV genome: n.N/D	↑ HPV: n.1627 of OSCC case n.146 (33.72%): buccal mucosa n.59 (30.10%): gingiva n.219 (32.25%): tongue n.29 (30.21%): oral floor n.20 (31.25%): palate n.489 (30.81%): tonsil n.19 (16.67%): lip n.646 (27.45%): N/D oral cavity Genotype(s) of virus detected: HPV-6, -8, -11, -16, -18, - 22, -31, -32, -33, -35, -38, - 39, -44, -45, -51, -52, -53, - 54, -58, -59, -61, -66, -67, - 68, -69, -70, -75, -76: n.N/D	-
	Risk factors for OSCC: Tobacco n.171+N/D Tobacco not smoked n.N/D Alcohol n.N/D History of OPMD: MD Time to OPMD onset: MD Previous history of malignancies: MD Other comorbidities: MD Other ongoing treatments: MD	Microscopic features: MD First Diagnosis: MD Time to onset: MD Chemotherapy: MD Radiotherapy: MD			
	Sample size: n.686 of case/n. 412 of the healthy control group Mean age: MD	Macroscopic features: MD Location: MD Staging: MD	Sample(s): n.686 Method(s) of sample collection:	↑ EBV: n.332 of OSCC case p = 0.002	-

Studies: n.13 CCS n.13	Gender ratio: MD Country: South Africa n.138 Netherland n.36 China n.81 India n.103 Japan n.186 Sweden n.29 Egypt n.22 Spain n.5 Hungary n.65 USA n.21	Grading: MD Microscopic features: MD	Biopsy n.686 Microorganisms identification technique: PCR n.562 Nested PCR n.34 ISH n.36 IHC n.33 RT-qPCR n.21 Target: EBV DNA n.218 EBV DNA BamHIW n.275 EBV DNA EBNA2 n.150 EBV RNA EBER1 n.21 EBV protein n.22	
Meta-analysis Moderate quality No Funding	Risk factors for OSCC: MD History of OPMD: MD Time to OPMD onset: MD Previous history of malignancies: MD Other comorbidities: MD Other ongoing treatments: MD			
Shen, 2023 <i>Arch Oral Biol</i> Studies: n.2 CCS n.2 No Meta-analysis High quality This study was supported by the China-Japan Friendship Hospital Research Project Foundation [grant	Sample size: n.25 of case/n.15 of the healthy control group/n.17 of the OPMD control group Mean age: 56.25 y.o.; range MD Gender ratio: MD Country: USA n.16 Malaysia n.9 Risk factors for OSCC: MD History of OPMD: MD Time to OPMD onset: MD Previous history of malignancies: MD Other comorbidities: MD Other ongoing treatments: MD	Macroscopic features: MD Location: MD Staging: MD Grading: MD Microscopic features: MD First Diagnosis: MD Time to onset: MD Chemotherapy: MD Radiotherapy: MD	Sample(s): n.25 Method(s) of sample collection: Swab n.25 Microorganisms identification technique: Incubation Proteinase K & DNA easy kit n.16 DNA extraction kit n.9 Target: 16s rRNA n.25 V4 region n.16 RFLP gene n.9	Than the healthy and the OPMD control group Fusobacteria: ↑ Fusobacterium ↑ Proteobacteria: ↑ Neisseria ↓ Firmicutes: ↑ Gemella ↑ Granulicatella Actinobacteria: ↓ Rothia Than the healthy control group

number 2020-1-QN-2].			↑ Bacteroidetes ↓ Firmicutes: ↓ Streptococcus ↓ Veillonella ↑/↓ Actinobacteria Than the OPMD control group ↓ Bacteroidetes ↓ Fusobacteria		
			Sample(s): n.349		
Sivakumar, 2020	Sample size: n.349 of case/n.205 of the healthy control group	Macroscopic features: MD	Method(s) of sample collection: Biopsy n.349		
<i>Transl Cancer Res</i>	Mean age: MD Gender ratio: MD Country: MD	Location: MD			
Studies: n.7 CCS n.7		Staging: MD Grading: MD	Microorganisms identification technique:	Than the healthy control group (prevalence 20.0%)	
	Risk factors for OSCC: MD	Microscopic features: MD	IHC n.61	-	
Meta-analysis	History of OPMD: MD		ISH n.20	↑ EBV: n.161 (prevalence 46.13%) of OSCC case	
	Time to OPMD onset: MD	First Diagnosis: MD	PCR n.190		
Low quality	Previous history of malignancies: MD	Time to onset: MD	N/D n.78		
No Funding	Other comorbidities: MD	Chemotherapy: MD	Target:		
	Other ongoing treatments: MD	Radiotherapy: MD	LMP-1 n.61		
			EBV DNA n.60		
			EBNA-2 n.150		
			N/D n.349		
Su Mun, 2021	Sample size: n.280 of case/n.191 of the healthy control group	Macroscopic features: MD	Sample(s): n.280	Than the healthy control group	
<i>Int J Environ Res Public Health</i>	Mean age: MD	Location: MD			
	Gender ratio: MD	Staging: MD	Method(s) of sample collection:	Fusobacteria: -	
	Country:	Grading: MD	Biopsy n.280	↑ Fusobacterium	
Studies: n.7	Yemen n.20	Microscopic features: MD		Type(s) of Fusobacterium	
CCS n.7	Sri Lanka n.25	First Diagnosis: MD		species detected:	
		Time to onset: MD			

No Meta-analysis	China n.135 USA n.100	Chemotherapy: MD Radiotherapy: MD	Microorganisms identification technique: DNA isolation kit n.20 Gentra Puregene Tissue kit n.25 QIAampFast DNA Stool Mini kit n.61 TIANamp Swab DNA kit n.50 MD n.124 Target: V1-V3 region n.45 V3-V4 region n.135 MD n.100	↑ F. oral taxon 204 ↑ F. parvimonas ↑ F. nucleatum ↑ F. nucleatum ssp. polymorphum Leptotrichia: Type(s) of Leptotrichia species detected: ↓ Leptotrichia oral taxon 225 Actinobacteria: ↑ Mobiluncus ↑/↓ Actinomyces ↓ Rothia Type(s) of Rothia species detected: ↓ Rothia dentocariosa ↓ Rothia mucilaginosa ↑ Atopobium ↓ Propionibacterium Corynebacterium Type(s) of Corynebacterium species detected: ↓ Corynebacterium matruchotii ↓ Arthrobacter ↓ Microbacterium Defferibacteraceae: ↓ Mucispirillum Proteobacteria: ↑ Brevundimonas ↑ Aeromonas ↑ Frateuria ↑ Caulobacter ↑ Pseudomonas Type(s) of Pseudomonas species detected:
High quality	Risk factors for OSCC: Betel nut chewers n.N/D			
This study was supported by the International Medical University of Malaysia.	Tobacco n.N/D Shammah (smokeless tobacco) n.N/D Alcohol n.N/D History of OPMD: MD Time to OPMD onset: MD Previous history of malignancies: MD Other comorbidities: MD Other ongoing treatments: MD			

↑ *Pseudomonas aeruginosa*
Aggregatibacter
Type(s) of Aggregatibacter
species detected:
↑ Aggregatibacter segnis
↑ Campylobacter
Type(s) of Campylobacter
species detected:
↑ *C. concisus*
↑ *C. rectus*
↑ Citrobacter
Type(s) of Citrobacter species
detected:
↑ Citrobacter koseri
↓ Lautropia
Type(s) of Lautropia species
detected:
↓ Lautropia mirabilis
↓ Sphingomonas

Firmicutes:
↓/↑ Streptococcus:
Type(s) of Streptococcus
species detected:
↑ *S. dysgalactiae*
↓ *S. parasanguinis*
↓ *S. mitis*
↓ *S. oralis*
↓ *S. sp oral taxon 423*
↓ *S. sp oral taxon 070*
↓ *S. sp oral taxon 431*
↓ *S. agalactiae*
↓ Staphylococcus
Type(s) of Staphylococcus
species detected:
↓ Staphylococcus epidermidis
↑ Peptostreptococcus
Type(s) of Peptostreptococcus
species detected:

				↑ Peptostreptococcus stomatis Granulicatella Type(s) of Granulicatella species detected: ↓ Granulicatella adicens ↓ Granulicatella elegans ↓ Paenibacillus ↑ Parvimonas Gemella: Type(s) of Gemella species detected: ↑ Gemella morbillorum Bacteroidetes: ↑ Capnocytophaga Type(s) of Capnocytophaga species detected: ↑ Capnocytophaga leadbetteri ↑ Prevotella Type(s) of Prevotella species detected: ↑ Prevotella salivae ↑ Prevotella loeschii ↑ Prevotella intermedia Porphyromonas Type(s) of Porphyromonas species detected: ↑ Porphyromonas cationiae ↓ Porphyromonas gingivalis
Syrjänen, 2011	Sample size: n.1885 of case/n.2248 of the healthy control group	Macroscopic features: MD Location: MD	Sample(s): n.1885	HPV: n.634 of OSCC case $p < 0.00001$ Genotype(s) of virus species detected: HPV-16: n.222 $p < 0.00001$
Oral Dis	Mean age: MD Gender ratio: MD Country: MD	Staging: MD Grading: MD	Method(s) of sample collection: Brush n.697 Biopsy n.1043 Biopsy and Brush n.145	
Studies: n.33 CCS n.33		Microscopic features: MD		
Meta-analysis	Risk factors for OSCC: MD History of OPMD: MD Time to OPMD onset: MD	First Diagnosis: MD Time to onset: MD Chemotherapy: MD	Microorganisms identification technique:	

Critically Low quality	Previous history of malignancies: MD Other comorbidities: MD	Radiotherapy: MD	PCR n.1821 ISH n.64		
No Funding	Other ongoing treatments: MD		Target: MD		
	Sample size: n.3238 of case Mean age: MD Gender ratio: MD Country: Finland n.91 USA n.1082 Spain n.42 Japan n.606 Taiwan n.29 Brazil n.69		Sample(s): n.3238		
Termine, 2008	Slovenia n.62 South Africa n.271 The Netherlands n.35	Macroscopic features: MD Location: MD	Method(s) of sample collection: Biopsy n.3238		↑ HPV: n. 1090 of OSCC case p = 0.000
Studies: n.47 MD n.47	Sudan n.88 Hungary n.79 Korea n.42	Staging: MD Grading: MD	Microorganisms	-	-
Meta-analysis	Venezuela n.116 Greece n.100 China n.113 Sweden n.134	Microscopic features: MD First Diagnosis: MD Time to onset: MD Chemotherapy: MD Radiotherapy: MD	identification technique: ISH: n.370 PCR: n.2681 N/D ISH or PCR: n.187		Genotype(s) of HPV detected: HPV-6, -11, -16, -18, -22, -31, -33, -35, -38, -58, -68, -70: n.MD
Critically Low quality	India n.213 Italy n.66		Target: MD		
No funding	Risk factors for OSCC: MD History of OPMD: MD Time to OPMD onset: MD Previous history of malignancies: MD Other comorbidities: MD Other ongoing treatments: MD				
Yang, 2019	Sample size: n.758 of case Mean age: MD Gender ratio: MD Country: China n.758	Macroscopic features: MD Location: MD	Sample(s): n.758		HPV: n.55/7.2% of OSCC case
Medicine (Baltimore)		Staging: Stage I-IV (n.327)	Method(s) of sample collection: Biopsy n.758	-	- Type(s) of HPV detected: HPV-18: n.55

Studies: n.6 CSS n.6	Risk factors for OSCC: MD History of OPMD: MD Time to OPMD onset: MD	Stage III-IV (n.333) Stage N/D (n.98) Grading: MD Microscopic features: MD	Microorganisms identification technique: PCR n.704 ISH n.54	p = 0.011	
Meta-analysis	Previous history of malignancies: MD Other comorbidities: MD	First Diagnosis: MD Time to onset: MD	Target: L1 region of HPV-18 gene n.533		
Moderate quality	Other ongoing treatments: MD	Chemotherapy: MD Radiotherapy: MD			
No Funding					
				Than the healthy control group	
Yu, 2023					
<i>Heliyon</i>			Sample(s): n.30	Fusobacteria	
Studies: n.2 CCS n.2	Sample size: n.30 of case/n.26 of the healthy control group Mean age: 52.3 y.o.; range MD Gender ratio: MD Country: MD	Macroscopic features: MD Location: MD	Method(s) of sample collection: Biopsy n.30	↑ Fusobacterium: p=0.000	
Meta-Analysis		Staging: MD Grading: MD	Microorganisms	↑ Proteobacteria: ↓ Haemophilus p= 0.000	
Moderate quality	Risk factors for OSCC: MD History of OPMD: MD Time to OPMD onset: MD Previous history of malignancies: MD Other comorbidities: MD Other ongoing treatments: MD	Microscopic features: MD First Diagnosis: MD Time to onset: MD Chemotherapy: MD Radiotherapy: MD	identification technique: N/D next-generation sequencing technology n.30	– – ↓ Actinobacteria: ↓ Rothia	
This study was supported by Grant from Qingdao Medical Talents Training Program [VYQ2020Y02].			Target: V4 region n.10 V1-V3 region n.20	↓ Firmicutes: ↓ Streptococcus p= 0.032	
				↓ Bacteroidetes: ↑ Prevotella: NSS	
Zhu, 2012	Sample size: n.610 of case/n.259 of healthy control group Mean age: MD y.o.; range MD Gender ratio: MD Country: China n.610	Macroscopic features: MD Location: MD Staging: MD Grading: MD Microscopic features: MD	Sample(s): n.610 Method(s) of sample collection: MD Microorganisms identification technique: PCR n.544 Dot-blot hybridization n.66	Than the healthy control group	
<i>PLoS One</i>				↑ HPV: n.354 of OSCC case p < 0.00001	
Studies: n.18 CCS n.18				– –	
Meta-analysis	Risk factors for OSCC: MD History of OPMD: MD	First Diagnosis: MD Time to onset: MD		Type(s) of HPV detected: HPV-16: n.169	

Critically Low quality	Time to OPMD onset: MD Previous history of malignancies: MD	Chemotherapy: MD Radiotherapy: MD	Target: MD	p < 0.00001 MD: n.185
No Funding	Other comorbidities: MD Other ongoing treatments: MD			

Abbreviations: number, "n."; years old, "y.o."; percentage, "%"; greater than, ">"; missing data, "MD"; not defined, "N/D"; not statistically significant, "NSS"; not significant, "NS"; p-value, "p"; male, "M"; female, "F"; case-control study, "CCS"; cohort study, "CS"; cross-sectional study, "CSS"; retrospective cross-sectional study, "RCSS"; prospective study, "PS"; non-randomized study, "NRS"; Oral Squamous Cell Carcinoma, "OSCC"; Oral Potentially Malignant Disorder, "OPMD"; United States of America, "USA"; polymerase chain reaction, "PCR"; real time polymerase chain reaction, "RT-PCR"; quantitative polymerase chain reaction, "qPCR"; immunohistochemistry, "IHC"; in situ hybridization, "ISH"; enzyme-linked immunosorbent assay, "ELISA"; immunofluorescence, "IF"; immunoperoxidase, "IP"; nucleic acid sequence based amplification, "NASBA"; Papanicolaou technique, "PAP technique"; Messenger Ribonucleic Acid, "mRNA"; Ribosomal Ribonucleic Acid, "rRNA"; RiboNucleic Acid, "RNA"; DeoxyriboNucleic Acid, "DNA"; Ribosomal DeoxyriboNucleic Acid, "rDNA"; subspecies, "ssp."; Fusobacterium, "F."; Campylobacter, "C."; Streptococcus, "S."; restriction fragment length polymorphism, "RFLP"; Human Papilloma Virus, "HPV"; Low Risk Human Papilloma Virus, "LR-HPV"; High Risk Human Papilloma Virus, "HR-HPV"; Herpes Simplex Virus, "HSV"; Epstein Barr Virus, "EBV"; Epstein Barr Nuclear Antigen, "EBNA"; Epstein Barr Encoding Region, "EBER"; Latent Membrane Protein, "LMP"; human telomerase reverse transcriptase, "hTERT"; B-cell lymphoma 2, "BCL-2"; Bahm HI N fragment rightward open reading frame, "BNRF"; Bahm HI A fragment rightward open reading frame, "BARF"; Bahm HI H fragment rightward open reading frame, "BHRF"; Bahm HI N fragment leftward open reading frame, "BZLF"; BahmHI M fragment leftward open reading frame, "BMLF"; BahmHI Z fragment leftward open reading frame, "BZLF"; positive, "+"; increased, "↑"; decreased, "↓"; not investigated, "-".