Juliana M. Serrano-Rodríguez, BS
UPR Comprehensive Cancer Center
Email: 99iserrano@cccupr.org
Phone:787-772-8300 ext.1250

Josué Pérez Santiago, PhD
UPR Comprehensive Cancer Center
Email: josue.perez22@upr.edu
Phone: 787-7728-8300 ext. 1219

The Alliance Hispanic Alliance for Clinical & Translational Research
2024 13th Scientific Day May 8
Centro Comprehensivo de Cancer

EPIDEMIOLOGICAL AND BIOLOGICAL DISPARITIES ASSOCIATED WITH OROPHARYNGEAL CANCERS IN HIV INFECTION

Authors: Juliana M. Serrano-Rodríguez, BS[1,2]; Carlos A. Solá-Morlá, BS[1,3]; Yakshi N. Ortiz-Maldonado, MS[1]; Gabriel Borges-Velez, PhD[1]; Jurelis Torres-Reyes, MS[1]; Jeannette L. Salgado-Montilla, MT MS[1]; Yabdiel A. Ramos-Velerio[4]; María M. Sanchez-Vazquez, MS[1]; Magaly Martinez-Ferrer, PhD[5]; Ana P. Ortiz-Martinez, MPH, PhD[1]; Ramon F. Gonzalez-Garcia, MPH, DDS[6]; Josué Pérez-Santiago, PhD[1,6]

Affiliations: [1]University of Puerto Rico Comprehensive Cancer Center, San Juan, PR, [2] University Ana G. Mendez, Carolina, PR, [3]School of Medicine - Universidad Central del Caribe, Bayamón, PR, [4]University of Puerto Rico – Rio Piedras Campus, San Juan,PR, [5]School of Phamacy, University of Puerto Rico Medical Sciences Campus, San Juan, PR, [6]School of Dental Medicine, University of Puerto Rico Medical Science Campus, San Juan, PR.

Abstract

- **Introduction**: Even with suppressive antiretroviral therapy, people with HIV (PWH) are disproportionately affected by HPV infection, a major factor for oropharyngeal cancers. Puerto Rico (PR) has disparities for both HIV infection and HPV-related malignancies, and has socio-economic disadvantages, which could further increase cancer risk.
- **Methods**: We collected saliva, oral rinse, sociodemographic, clinical and lifestyle variables, and evaluated periodontal disease (PD) status from 113 sexually active PWH. Oral rinse was analyzed for HPV infection and genotype. In a subset of participants (n=48), we characterized the oral bacteriome (16s rDNA), and quantified short-chain fatty acids (GC-MS). Analyses were performed using QIIME2 and R-statistical software.
- **Results**: The prevalence of oral HPV infection was 32%, of which more than 61% were high-risk genotypes, and HPV-18 was the most abundant (25.8%). There was also a high prevalence of PD of 83%. Higher alpha diversity measured by Shannon was found in HPV+ (p=0.056). Higher richness and phylogenetic diversity (p=0.012 and p=0.014), as well as lower evenness was associated with PD (p=0.025). Higher levels of butyrate and valerate were significantly associated with Shannon index in HPV+ PWH (r=0.53, p<0.05 and r=0.36, p<0.05 respectively). Higher levels of butyrate were significantly associated with higher microbial diversity in PD (r=0.28, p<0.05).
- **Conclusion**: Overall, we found specific prokaryotic profile and associated metabolites associated with HPV infection, which may suggest that the oral microbiome could influence the natural history of HPV infection via SCFA signaling.

Introduction

- Human papillomavirus (HPV) is the most common sexually transmitted disease worldwide and a major factor for oropharyngeal cancers, accounting for more than 70% of oropharyngeal cancers[1-2].
- Even with suppressive antiretroviral therapy (ART), people with HIV (PWH) are disproportionately affected by HPV infection, suggesting that ART may not fully recover oral HPV-specific immunity[3-4] .
- Periodontal disease (PD) is a chronic inflammatory condition associated with cancers in the oral cavity, and it is more prevalent in PWH.[5]
- Puerto Rico (PR) has significant disparities for both HIV infection and HPV-related malignancies, and has socio-economic disadvantages, which can potentially affect oral HPV and could further increase cancer risk[6-10].
- The oral microbiome can increase the risk of oral HPV infection and persistence; however, it has not been investigated in the context of HIV in PR.

Methods

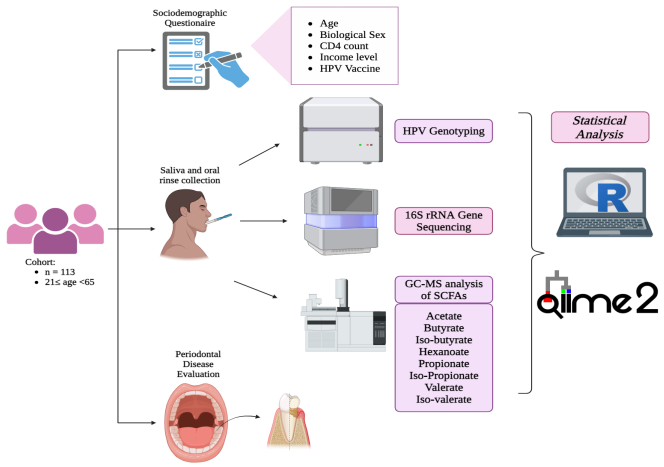

Figure 1: Study methodology. *We evaluated the composition of the oral microbiome (16s profiling) and levels of SCFA (GC-MS) in saliva of 113 PWH. Oral rinse samples were collected and analyzed for HPV genotyping (HPV+: n=36 and HPV-: n=77). Sociodemographic characteristics, lifestyle variables were collected through questionnaire. Participants also underwent a periodontal assessment following CDC/AAP guidelines. We performed microbial diversity and taxonomic analyses using QIIME2. Statistical analyses were performed in R software.*

Results

Table 1 – *Sociodemographic characteristics*

Variables	Total n	HPV+ n (%)	HPV- n (%)	p-value*
Biological Sex				**0.22**
Male	100	34 (34)	66 (66)	
Female	13	2 (15)	11 (85)	
Age (years)				**0.03**
Average ± sd	47 ± 11	50 ± 11	46 ± 11	
CD4 Absolute Count				**0.36**
Average ± sd	790 ± 297	832 ± 335	771 ± 278	
HPV Vaccine				**0.06**
Yes	22	3 (14)	19 (86)	
No	72	26 (36)	46 (64)	
Periodontal Assessment:				
- Periodontal Disease (PD)				**0.79**
Yes	94	31 (33)	63 (67)	
No	19	5 (26)	14 (74)	
- PD Severity				**0.15**
No	19	5 (26)	14 (74)	
Mild	3	2 (67)	1 (33)	
Moderate	59	15 (25)	44 (75)	
Severe	32	14 (44)	18 (56)	

Table 1: ***Demographic and clinical characteristics of study participants.*** *HPV+ subjects were significantly older than and HPV- subjects. There were no association of HPV status with biological sex, income level, CD4 counts, and PD. *P-value of a Chi-squared/Fisher Exact test or two tailed t-test.*

Figure 2 – *Prevalence of HPV and PD in PWH*

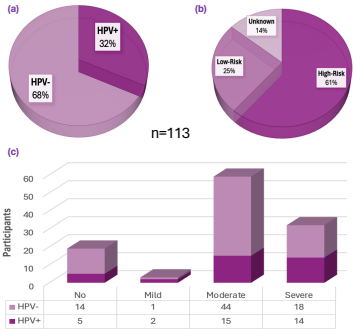

Figure 2: Prevalence of HPV and PD in PWH. ***(a)*** *Prevalence of HPV+ among PWH.* ***(b)*** *Higher prevalence of High-Risk HPV genotypes among PWH.* ***(c)*** *Distribution of PD severity*

Figure 3 – *Higher alpha diversity in HPV+ and PD*

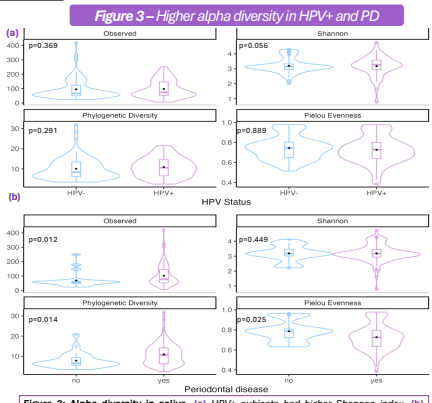

Figure 3: Alpha diversity in saliva. ***(a)*** *HPV+ subjects had higher Shannon index.* ***(b)*** *Subjects with PD had significantly higher phylogenetic diversity and richness but lower evenness.*

Figure 4 – *Association between SCFA levels and microbial diversity*

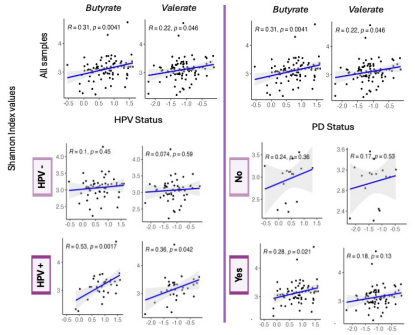

Figure 4: ***Pearson correlations between SCFA levels and Shannon Diversity index:*** *Butyrate and valerate levels were significantly correlated with microbial diversity. In HPV+, but not in HPV- individuals, butyrate and valerate levels significantly increased with the microbial diversity. Similarly, in subjects with PD, butyrate levels were significantly increased with microbial diversity. *Other SCFAs showed no significant correlations.*

Conclusion

- Overall, we found specific prokaryotic profile and associated metabolites associated with HPV infection, which may suggest that the oral microbiome could influence the natural history of HPV infection via SCFA signaling
- Higher alpha diversity in HPV infection and PD may be a result of microbial transfer from other anatomical compartments and colonization of opportunistic pathogens.
- Understanding the underpinning mechanisms of how the oral microbiome can facilitate HPV infection and persistence in PWH is essential to establish targets for early identification and personalized treatment approaches for oral HPV-related malignancies.

Acknowledgements

This project was supported by the National Cancer Institute: R21 CA264606 and diversity supplement, National Institute of General Medical Sciences (Center for the Promotion of Cancer Health Equity: P20GM148324, the National Institute on Minority Health and Health Disparities: RCMI Program U54 MD007600. We would also like to thank PR-CoNCRA and Hispanic Alliance for Clinical & Translational Research (U54 GM133807) for providing us with support in recruitment and specimen collection, and especially to our study participants.

References

1. Mehanna, H., et al., Prevalence of human papillomavirus in oropharyngeal and non-oropharyngeal head and neck cancer--systematic review and meta-analysis of trends by time and region. Head Neck, 2013. 35(5): p. 747-55.
2. Tanaka, T.I. and F. Alawi, Human Papillomavirus and Oropharyngeal Cancer. Dent Clin North Am, 2018. 62(1): p. 111-120.
3. Franzetti, M., E. Ricci, and P. Bonfanti, The Pattern of Non-AIDS-defining Cancers in the HIV Population: Epidemiology, Risk Factors and Prognosis. A Review. Curr HIV Res, 2019. 17(1): p. 1-12.
4. Lechner, M., et al. HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management. Nat Rev Clin Oncol. 2022 ; 19: 306-327. https://doi.org/10.1038/s41571-022-00603-7
5. Irani, S. Barati, I and Badiei, M. Periodontitis and oral cancer- current concepts of the etiopathogenesis. Oncol Rev, 2020. 14(1): p. 465.
6. Deren, S., et al., Addressing the HIV/AIDS epidemic among Puerto Rican people who inject drugs: the need for a multiregion approach. Am J Public Health, 2014. 104(11): p. 2030-6.
7. Ortiz, A.P., et al., Human papillomavirus-related cancers among people living with AIDS in Puerto Rico. Prev Chronic Dis, 2014. 11: p. E80.
8. Suarez, E., et al., Age-standardized incidence and mortality rates of oral and pharyngeal cancer in Puerto Rico and among Non-Hispanics Whites, Non-Hispanic Blacks, and Hispanics in the USA. BMC Cancer, 2008. 8: p. 128.
9. Dye, B.A., X. Li, and G. Thorton-Evans, Oral health disparities as determined by selected healthy people 2020 oral health objectives for the United States, 2009-2010. NCHS Data Brief, 2012(104): p. 1-8.
10. Kreimer, A.R., et al., Oral human papillomavirus infection in adults is associated with sexual behavior and HIV serostatus. J Infect Dis, 2004. 189(4): p. 685-98.