Sex differences in risk factors for oral and pharyngeal cancer among Puerto Rican adults

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## Abstract

Background: Oral and pharyngeal cancer (OPC) is a frequent type of cancer in Puerto Rico, with the risk being higher in men relative to women. We assessed differences in OPC risk factors implicated in these sex disparities.

Methods: We analyzed data of 740 adult participants (40-65 years) from the San Juan Overweight Adults Longitudinal Study (SOALS). A comprehensive questionnaire was administered to collect information on sociodemographic characteristics, cigarette smoking, binge drinking, oral high-risk HPV infection, fruit and vegetable consumption, sexual behavior, and oral hygiene practices. A full-mouth periodontal examination was also performed. Sixteen OPC known and potential risk factors were evaluated. Crude and adjusted prevalence ratio (PR) estimates for individual OPC risk factors, by sex, were calculated using log-binomial regression.

Results: Compared to women, men had significantly increased prevalence of several OPC risk factors including current smoking (PR: 1.91, 95% Confidence interval [CI]: 1.35-2.70), binge drinking (PR: 1.92, 95% CI: 1.31-2.84), and severe periodontitis (PR: 2.05, 95% CI: 1.47-2.85).

Conclusions: Men were significantly more likely than women to have risk factors for OPC. Cancer prevention and control efforts should focus on sex-specific interventions that help reduce this disparity.



## Keywords

sex; risk factors; oral HPV; periodontitis, Hispanics, Puerto Rico

## Cover Page Footnote

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# Sex Differences in Risk Factors for Oral and Pharyngeal Cancer among Puerto Rican Adults

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## ABSTRACT

**Background:** Oral and pharyngeal cancer (OPC) is a frequent type of cancer in Puerto Rico, with the risk being higher in men relative to women. We assessed differences in OPC risk factors implicated in these sex disparities.

**Methods:** We analyzed data of 740 adult participants (40-65 years) from the San Juan Overweight Adults Longitudinal Study (SOALS). A comprehensive questionnaire was administered to collect information on sociodemographic characteristics, cigarette smoking, binge drinking, oral high-risk HPV infection, fruit and vegetable consumption, sexual behavior, and oral hygiene practices. A full-mouth periodontal examination was also performed. Sixteen OPC known and potential risk factors were evaluated. Crude and adjusted prevalence ratio (PR) estimates for individual OPC risk factors, by sex, were calculated using log-binomial regression.

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**Keywords:** Sex; Risk factors; Oral HPV; Periodontitis, Hispanics, Puerto Rico

## INTRODUCTION

Oral and pharyngeal cancer (OPC) is rising in the US (Siegel, Miller, & Jemal, 2020). These malignancies occur most often in the tongue, tonsils, oropharynx, gums, floor, and other

parts of the mouth. The most common risk factors for OPC are oral infection with high-risk Human Papilloma Virus (HPV) (Herrero, 2003; Smith et al., 2004), history of heavy smoking and alcohol use (Hayes et al., 1999; Mashberg, Boffetta, Winkelman, & Garfinkel, 1993), low intake of fruits and vegetables (Kreimer et al., 2006), drinking "maté" (Goldenberg, 2002), chewing "betel quid or gutka" (Ho, Ko, Yang, Shieh, & Tsai, 2002), older age (Hussein et al., 2017), UV light (lip cancer) (Grant, 2014), weakened immune system (Gillison, 2009), and periodontitis (Ortiz et al., 2018). Other controversial risk factors that have been suggested in the literature include use of mouthwash with high alcohol content and poor oral hygiene practices (Gandini, Negri, Boffetta, La Vecchia, & Boyle, 2012). Recent increases in the incidence of oropharyngeal cancer in the US have been attributed to HPV infection (Martel, Plummer, Vignat, & Franceschi, 2017). High-risk sexual behaviors are known to facilitate HPV infection and persistence, thus could be also be considered potential risk factors (Smith et al., 2004).

Considerable sex differences exist in the risk of multiple cancer types, including OPC (Warnakulasuriya, 2009), with men having a greater risk than women (Weatherspoon, Chattopadhyay, Boroumand, & Garcia, 2015). While the excess risk for these malignancies in men as compared with women has been attributed to a male predominance of its risk factors (Siegel et al., 2015), particularly alcohol and tobacco consumption (Agaku, King, & Dube, 2014; Nolen-Hoeksema, 2004; Slade et al., 2016), the basis for these sex disparities remains unknown (Edgren, Liang, Adami, & Chang, 2012). In addition, a limited number of studies have explored sex differences of less conventional OPC risk factors, such as mouthwash use and tooth brushing (Gandini et al., 2012; Schulze & Busse, 2016). Oral hygiene behavior appears to be worse among men (Schulze & Busse, 2016), and daily tooth brushing may lower the risk of OPC (Moreno-López et al., 2000).

In Puerto Rico, OPC was the fourth most diagnosed cancer among Puerto Rican men from 2010-2014, accounting for 4% of all incident cases of cancer. In contrast, OPC accounted for 1.2% of all newly diagnosed cancers among women (Zavala-Zegarra et al., 2017). While higher incidence rates of OPC have been observed in adults in Puerto Rico compared with those in the US (Suárez et al., 2009), these differences have been inconsistently observed across studies (Weatherspoon et al., 2015). Men and women in Puerto Rico are also at higher risk of dying from OPC when compared to Hispanics living in the US (Suárez et al., 2009). Given the sex disparity in OPC occurrence in Puerto Rico and other populations, this cross-sectional study examined sex differences in behavioral, lifestyle, and clinical risk factors for this malignancy in a sample of middle-aged Hispanic adults. Understanding sex differences in the risk factor occurrence in this population will help determine target areas for OPC prevention efforts in the future.

## METHODS

### Study Design and Study Subjects

This study was based on a secondary analysis of data from a cross-sectional study on oral HPV infection(Ortiz et al., 2018), which recruited participants from the follow-up visit of the San Juan Overweight Adults Longitudinal Study (SOALS), a cohort of 1,214 overweight or obese Hispanic adults aged 40-65 years living in the San Juan metropolitan area. Detailed descriptions of this study have been published elsewhere (Joshipura et al., 2018; Pérez et al., 2013). A total of 740 adults, who came to the SOALS follow-up examination visit between September 2014 and May 2016, were included in this study. Participants who did not complete

HPV collection, periodontal examination, or had unsatisfactory HPV laboratory test results were excluded for this analysis, for a final analytic sample of 740 adults. This study was approved by the Institutional Review Board of the University of Puerto Rico Medical Sciences Campus.

Data Collection

Comprehensive questionnaires were administered in person to assess risk factors for OPC. Data on age at first sexual contact and oral sex, number of sexual partners (lifetime and past-year), and number of oral sex partners (lifetime and past-year) were collected using the audio computer-assisted self-interview (ACASI) methodology, which has been successfully used to collect sensitive behavioral risk factor data (Ortiz et al., 2015). Through an interviewer-administered questionnaire, participants also provided information on socio-demographic and behavioral characteristics including age, sex, marital status, years of education, annual income, smoking status, alcohol consumption, fruit and vegetable intake, and oral hygiene indicators (frequency of use of tooth brushing, dental floss, and dental cleaning device). Participant's weight and height were also collected by trained staff to determine body mass index (BMI).

Oral mouthwash samples for oral HPV testing followed the methodology used in the National Health and Nutrition Examination Survey (NHANES) (CDC, 2010). For HPV typing, PCR products were typed by dot-blot hybridization using specific probes and two separate mixtures, including oncogenic (high-risk) and non-oncogenic HPV types (Ortiz et al., 2018). Periodontitis was assessed by clinical measurements of probing pocket depth (PD) and clinical attachment loss (CAL) at six sites for all teeth, excluding the third molars. The Centers for Disease Control and Prevention/American Academy of Periodontology working definition was used to classify participants into severe periodontitis, moderate periodontitis, and mild or no periodontitis (Page & Eke, 2007).

Study Variables

Demographic and clinical characteristics included age, marital status, education, family income, and BMI. With the information collected, 16 OPC known and potential risk factors (yes/no) were defined. Known risk factors included: current smoking, binge drinking, oral infection with high-risk HPV types, severe periodontitis, and consumed fruits and vegetables less than one time per day. Potential risk factors included: <14 years at first sex, <14 years at first oral sex, ≥10 lifetime sexual partners, ≥3 recent sexual partners, lifetime oral sex, ≥3 lifetime oral sexual partners, past year oral sex, ≥3 recent oral sexual partners, tooth brushing <2 times/day, dental floss use <2 times/day, and use of other dental cleaning devices < 2 times/day. Total number of risk factors was also evaluated.

Statistical Analysis

The distribution of OPC risk factors between men and women was compared using the chi-square test statistic. Crude and adjusted prevalence ratio (PR) estimates for individual OPC risk factors by sex were calculated using log-binomial regression. All models controlled for sociodemographic characteristics (age, marital status, and family income) because of their hypothesized and observed associations with sex and OPC risk factors. All models were not controlled for BMI, given its lack of association with the OPC risk factors under investigation. All statistical analyses were performed using Stata version 16 (StataCorp LLC, College Station, TX).

## RESULTS

The mean age of study participants was 53.6±6.4 years, less than one-third were men, and over half had less than 12 years of education and an annual income below $20,000. Mean BMI was high in both women (33.7±6.4) and men (32.6±6.2). The prevalence of OPC risk factors differed by sex. Men had higher prevalence than women of current smoking (26.5% vs. 15.5%), binge drinking (22.6% vs. 11.9%), severe periodontitis (30.4% vs. 16.4%), and infrequent tooth brushing (10.8% vs. 6.3%) ($p<0.05$). In addition, men were more likely to report sex-related risk factors, including early age of sexual debut, higher number of sexual partners, and lifetime and recent oral sex practices (Table 1).

**Table 1.** Characteristics of study participants according to sex

| **Characteristics** | **Female (n=536) n (%)** | **Male (n=204) n (%)** | **P-value** |
|---|---|---|---|
| ***Demographic and clinical characteristics*** | | | |
| Age (years) | | | |
| 40-49 | 169 (31.5) | 68 (33.3) | 0.64 |
| 50-64 | 367 (68.5) | 136 (66.7) | |
| *Mean±SD* | 53.6 ± 6.6 | 53.3 ± 6.7 | 0.61 |
| Married/Cohabitating | 218 (40.7) | 114 (55.9) | <0.001 |
| High school education or less | 292 (54.5) | 111(54.4) | 0.99 |
| Family income < $20,000 | 303(67.5) | 93 (54.7) | 0.003 |
| Body mass index (kg/m$^2$) – *Mean±SD* | 33.7 ± 6.4 | 32.6 ± 6.2 | 0.035 |
| ***Risk factors for OPC*** | | | |
| Current smoking | 83 (15.5) | 54 (26.5) | 0.001 |
| Binge drinking | 64 (11.9) | 46 (22.6) | <0.001 |
| Any oral HPV infection | 21 (3.9) | 21 (10.3) | 0.001 |
| Oral high-risk HPV infection | 2 (0.4) | 3 (1.5) | 0.103 |
| Severe periodontitis | 88 (16.4) | 62 (30.4) | <0.001 |
| Intake of fruits and vegetables less than once per day | 326 (61.3) | 141 (69.5) | 0.039 |
| ***Potential risk factors for OPC*** | | | |
| <14 years at first sex | 23 (4.3) | 29 (14.2) | <0.001 |
| <14 years at first oral sex | 17 (3.6) | 12 (6.2) | 0.15 |
| ≥10 lifetime sexual partners | 80 (15.6) | 101 (54.6) | <0.001 |
| ≥3 recent sexual partners | 88 (16.4) | 54 (26.5) | 0.002 |
| Lifetime oral sex | 453 (84.7) | 187 (92.1) | 0.008 |
| ≥3 lifetime oral sexual partners | 17 (3.2) | 86 (42.2) | <0.001 |
| Past year oral sex | 253 (47.2) | 151 (74.0) | <0.001 |
| ≥3 recent oral sexual partners | 5 (0.9) | 11 (5.4) | <0.001 |
| Tooth brushing <2 times/day | 34 (6.3) | 22 (10.8) | 0.04 |
| Use of dental floss <2 times/day | 373 (69.7) | 177 (87.2) | <0.001 |
| Use of other dental cleaning devices <2 times/day | 366 (68.3) | 146 (71.9) | 0.33 |
| **Number of risk factors - *Mean ± SD*** | 4.3 ± 0.1 | 6.4 ± 0.2 | <0.001 |

After adjusting for age, marital status, and family income, men were more likely than women to be current smokers (PR: 1.91, 95% CI: 1.35-2.70), binge drinkers (PR: 1.92, 95% CI:

1.31-2.84), and to have severe periodontitis (PR: 2.05, 95% CI: 1.47-2.85) (Table 2). With respect to other potential risk factors related to sexual practices that facilitate HPV infection, men were significantly more likely than women to have ≥ 10 sexual partners (PR=3.65, 95% CI: 2.71-4.91), be <14 years old at the time of their first sexual encounter (PR=3.27, 95% CI: 1.88-5.71), and have had oral sex in the past 12 months (PR=1.49, 95% CI: 1.22-1.83). In terms of oral hygiene practices, men were significantly less likely to brush their teeth (PR=1.81, 95% CI: 1.05-3.13) and use dental floss on a regular basis (PR=1.23, 95% CI: 1.03-1.48) (Table 2).

**Table 2.** Crude and multivariable-adjusted prevalence ratios (95% CI) for individual OPC risk factors according to sex* (n=740)

| Outcome variables | Crude PR (95% CI) | Adjusted PR (95% CI)* |
|---|---|---|
| *OPC risk factors* | | |
| Current smoking | **1.70 (1.21-2.40)** | **1.91 (1.35-2.70)** |
| Binge drinking | **1.89 (1.29-2.76)** | **1.92 (1.31-2.84)** |
| Any oral HPV infection | 2.63 (1.43-4.81) | 2.80 (1.52-5.17) |
| Oral high-risk HPV infection | 3.98 (0.66-24.02) | 4.39 (0.72- 26.82) |
| Severe periodontitis | **1.85 (1.33-2.56)** | **2.05 (1.47-2.85)** |
| Consumed fruit and vegetables less than once per day | 1.13 (0.93-1.38) | 1.13 (0.93-1.39) |
| *Potential OPC risk factors* | | |
| <14 years at first sex | **3.31 (1.92-5.73)** | **3.27 (1.88-5.71)** |
| < 14 years at first oral sex | 1.70 (0.81-3.56) | 1.73 (0.82-3.66) |
| ≥10 lifetime sexual partners | **3.51 (2.62-4.70)** | **3.65 (2.71-4.91)** |
| ≥3 recent sexual partners | **1.61 (1.15-2.26)** | **1.86 (1.32-2.61)** |
| Lifetime oral sex | 1.09 (0.91-1.29) | 1.09 (0.91-1.28) |
| ≥3 lifetime oral sexual partners | **13.29 (7.90-22.36)** | **14.08 (8.34-23.8)** |
| Oral sex past 12 months | **1.57 (1.28-1.91)** | **1.49 (1.22-1.83)** |
| ≥3 recent oral sexual partners | **5.78 (2.00-16.6)** | **6.33 (2.18-18.4)** |
| Tooth brushing <2 times/day | 1.70 (0.99-2.91) | **1.81 (1.05-3.13)** |
| Dental floss <2 times/day | **1.25 (1.05-1.50)** | **1.23 (1.03-1.48)** |
| Dental cleaning devices <2 times/day | 1.05 (0.87-1.28) | 1.04 (0.86-1.27) |

*Adjusted for age, marital status, and family income. Reference category=Female sex

## DISCUSSION

The results of this cross-sectional study among Hispanic adults living in Puerto Rico demonstrate that men were significantly more likely than women to have known OPC risk factors examined, including current smoking, binge drinking, and severe periodontitis. In terms of poor oral hygiene, men were less likely to brush their teeth and use dental floss on a regular basis. Our findings are consistent with the results of other studies, which have shown that men are more likely to have these risk factors (Gandini et al., 2012; Schulze & Busse, 2016). The Behavioral Risk Factor Surveillance System (BRFSS) data for 2017 for Puerto Rico showed that men had a higher prevalence of current smoking (16.9%) than women (6.4%) and were more likely to report binge drinking (20.5%) than women (6.8%). Previous studies have also found that men appear at greater risk for destructive periodontal disease than women (Krüger, Hansen, Kasaj, Moergel, & Moergel, 2013; Ortiz et al., 2018). A study of the prevalence of oral HPV infection in the United States (2009-2010) found that men (10.1%) had a significantly higher

prevalence than women (3.6%) for any oral HPV infection (Gillison et al., 2012). Cumulative evidence show that women are more likely to receive professional dental care, comply with recommended oral health treatment, and have higher oral health literacy, as well as present with lower levels of plaque, calculus, and bleeding on probing than men (Niessen, Gibson, & Kinnunen, 2013).

Other potential OPC risk factors evaluated in this study included sexual practices. Oral sexual behaviors are responsible for the acquisition of HPV or other pathogens that may be associated with OPC development. In this study, men were almost twice as likely as women to initiate sexual activity before age 14 and more likely to report more than 10 sexual partners in their lifetime. These findings are consistent with population-based studies of sexual practices in Puerto Rico (Ortiz et al., 2011). Our results were also similar to the NHANES (2009-2010) study where 37.4% of men and 17.1% women report more than 10 lifetime sexual partners (D'Souza et al., 2014).

Previous studies have described that the influence of social and cultural factors on harmful behaviors is compounded by stressors stemming from neighborhood characteristics, including a high prevalence of drug and alcohol abuse and overall effects of poverty (Cruz, Shulman, Kumar, & Salazar, 2007). It is important to recognize that male sex and increasing age are considered the most important OPC risk factors. However, this disparity may be related to sex differences in both the frequency and severity of established OPC risk factors.

The strengths of the present study include the evaluation of multiple known OPC risk factors including smoking, alcohol abuse, and oral high-risk HPV infection. Furthermore, periodontitis and oral HPV testing were assessed using standard validated clinical methods. However, the possibility of residual confounding cannot be excluded. We failed to evaluate UV light exposure, which could be an important risk factor for this population given the geographic location of Puerto Rico. Also, given that study population focused on overweight and obese Puerto Ricans living in the San Juan Metropolitan area, the extrapolation of study findings to underweight and normal weight adults is limited. Furthermore, results regarding risk factor occurrence may not be generalizable to the entire population of Puerto Rico. Despite these limitations, to the best of our knowledge, this is the first study to evaluate sex differences in OPC risk factors in a group of adults living in Puerto Rico. Results of this study may help to further understand sex differences in OPC occurrence and may help guide areas for targeted intervention efforts.

## CONCLUSION

Study results evidence increased prevalence of OPC risk factors in men in Puerto Rico, supporting the increased risk of this malignancy in the male population. Our findings suggest that cultural lifestyle factors are mostly related to the sex gap in OPC risk factor prevalence. Nonetheless, future studies should evaluate if differences exist in men and women regarding their oral bacterial profiles. Most of these risk factors could be prevented. Further longitudinal research is needed to characterize potential sex-specific interactions between various risk factors and risk of developing OPC. In addition, OPC prevention and control efforts should consider these sex differences in developing possible sex-specific interventions. Oral health professionals should be aware of these differences and continue to promote health education in men and women regarding the reduction of risk factors. Given that the HPV vaccine is approved by the

U.S. Food and Drug Administration (FDA) for prevention of oral and pharyngeal cancer it should continue to be promoted in Puerto Rico as a cancer prevention strategy.

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