Oral human papillomavirus (HPV) prevalence and genotyping among healthy adult populations in the United States and Europe: results from the PROGRESS (PRevalence of Oral hpv infection, a Global aSSessment) study

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Summary

Background HPV-related oropharyngeal squamous cell carcinoma (OPSCC) is increasing in incidence, yet there are few well-designed oral HPV epidemiology studies in general populations. This study assessed oral HPV prevalence and risk-factors among a general population in Europe and the United States (US).

Methods The cross-sectional study was conducted between November 2020 and July 2023 in 105 dental offices in France, Germany, Spain, the United Kingdom (UK) and US. Participants were aged 18–60 and visiting dental clinics for routine examination. Participants provided oral gargle specimen for HPV DNA and genotyping and completed behavioral questionnaires. HPV DNA detection and genotyping was performed using SPF10/DEIA/LiPA25 at central laboratories.

Findings Of 7674 participants, mean (SD) age was 40.0 (11.9), and 45.8% were males. Among men, any oral HPV prevalence ranged between countries from 6.6% to 15.0% and 1.8%–4.5% for high-risk (HR) types. Among women, any oral HPV prevalence ranged between countries from 3.6% to 6.8% and 0.2%–2.1% for HR types. HR infection among men was associated with older age (AOR 1.04; 95% CI: 1.02, 1.06); marijuana use (AOR 1.92; 95% CI: 1.19–3.11); increasing number of lifetime female oral sex partners; and by country, residing in the UK compared to Spain (AOR 2.89; 95% CI: 1.30–6.43). HR infection among women was associated with lifetime marijuana use (AOR 2.33; 95% CI: 1.18–4.60) and by country, residing in France compared to Spain (AOR 4.46; 95% CI: 1.26–15.77).

Interpretation Oral HPV burden was highest among older men who may be at risk of developing OPSCC.

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Keywords: Oral human papillomavirus; Prevalence; Risk factors

Research in context

Evidence before this study

We searched PubMed with no language restrictions for publications comparing prevalence of oral HPV infection across Europe and the United States. The search was undertaken starting at study conceptualization in January 2019 using the terms "oral" AND ("papillomavirus" OR "HPV"). We identified one study that used systematic review to report global and regional oral HPV prevalence, but findings are limited by the heterogeneity in the methods of HPV specimen collection and processing as well as small sample sizes, which makes cross-country comparison difficult.

Added value of this study

The motivation for this study draws from the need to use homogenous HPV specimen collection and processing methods to compare oral HPV prevalence in Europe and the US. Having robust estimates of oral HPV prevalence, including factors associated with having a prevalent infection, can support the development of effective HPV prevention efforts. Our study recruited 7674 participants in 105 dental offices in France, Germany, Spain, the United Kingdom and United States, used a standard study protocol across all sites, and HPV DNA processing was conducted in central laboratories. We found a global prevalence of 7.4% for any oral HPV infection and 2.0% for high-risk types. While oral HPV prevalence differed by country, a key similarity across countries is that prevalence was higher in men than women. Our evidence represents some of the most robust estimates of oral HPV infection and associated factors in the published literature to date.

Implications of all the available evidence

A proportion of the general population, particularly males, has a prevalent oral HPV infection; persistent high-risk oral HPV infections can lead to increased risk of developing oropharyngeal cancer. Oral HPV prevalence differs by country even when using homogenous HPV sampling and testing methods, highlighting the need for country-specific HPV prevention efforts.

Introduction

Head and neck cancer (HNC) is the sixth most frequent cancer worldwide with over 870,000 new cases and 440,000 deaths in 2020.[1] Head and neck squamous cell carcinoma (HNSCC) is the most common type of HNC; its incidence is increasing and predicted to rise to 1.08 million new cases per year by 2030.[2] Human papillomavirus (HPV) is a cause of a subset of HNSCC, particularly oropharyngeal squamous cell carcinoma (OPSCC).[3] HPV-attributable fractions (HPV-AFs) in cases of OPSCC are heterogeneous by geographic region, with HPV-AFs ranging from less than 10% in some world regions to more than 80% in the United States (US) and Northern Europe.[4–6] Differences by sex have also been observed, with higher HPV-AFs in men compared to women, depending on the region.[6–8] These differences may reflect temporal, geographical, and sociodemographic changes in smoking and sexual behavior.

Having robust oral HPV prevalence estimates may help explain the heterogeneity in HPV-AF and could support the development of effective prevention efforts. A systematic review by Mena et al. (2019) reported a global oral HPV prevalence of 4.9%.[9] Estimates were highest in Europe (6.5%) followed by North America (5.1%), although regional differences were not statistically significant.[9] Prevalence was highest among 50–59-year-olds and among men in North America. Findings from Mena et al. (2019), like other systematic reviews of oral HPV prevalence estimates, are limited by small sample sizes, differences in study populations and heterogenous approaches to specimen collection, processing, and testing which make it challenging to compare prevalence across countries.[10] The HPV Infection in Men (HIM) study is an additional large-scale study comparing oral HPV prevalence in Brazil, Mexico and the US and found a prevalence of 8.7%, 10.0% and 7.6% respectively, but is limited by focusing on men.[11]

As such, the burden of oral HPV infection is poorly quantified across countries and factors associated with oral HPV in the general population are not well understood. To address this, the PROGRESS (Prevalence of Oral HPV Infection, a Global Assessment) study assessed oral HPV prevalence and associated factors among a large sample of the general adult population within the US and Europe using homogeneous methodology that includes standardized field work and lab controls as well as highly sensitive HPV DNA detection technique.[12]

Methods

Study design and participants

PROGRESS is a cross-sectional study assessing oral HPV infection in the US, France, Germany, Spain, and the UK. Detailed description of study design and methodology, including HPV testing procedures and sample size calculations has been published,[12] as has the US prevalence, genotyping and risk-factor analysis.[13]

Eligible participants were men and women aged 18–60 years accessing routine dental care who provided written informed consent. All participants diagnosed with or who had suspicion of HNC were excluded.

Written consent was obtained from participants and participant data were pseudonymized in the US and anonymized in Europe. The study protocol was approved by Central Ethics Committees including the *Comite de Protection des Personnes* (CPP) Ouest VI, Health Research Authority and the Health and Care Research Wales (HCRW), the Western Institutional Review Board (WIRB), and by the corresponding Institutional Review Board/Ethics Committee (IRB/EC) at dental site level when required.

Site recruitment and site initiation

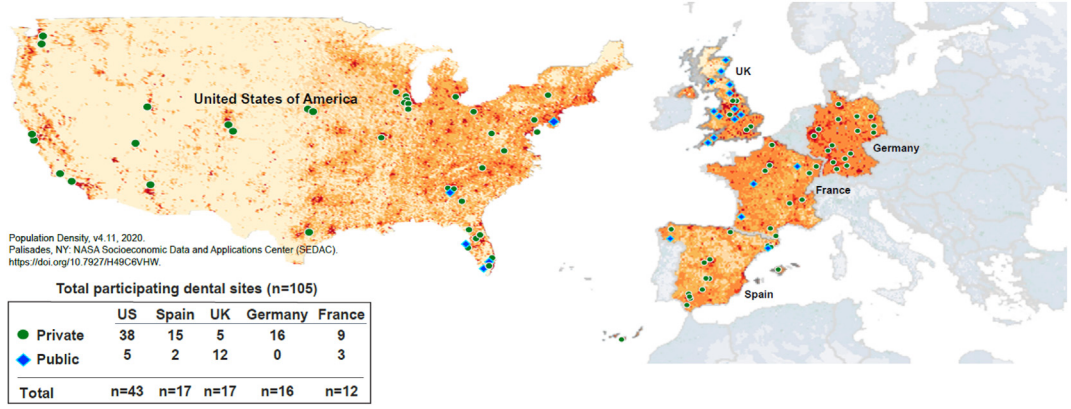
The 2020 IQVIA OneKey™ database was used to recruit dental sites. OneKey™ is a database of healthcare providers that is updated on a continuous basis through government and non-government industry sources. In 2020, information about PROGRESS and an invitation to participate was sent to all dentists listed in the database via email. Through this convenience sampling, 105 dental sites dispersed throughout each country were recruited: 43 in the US, 12 in France, 16 in Germany, and 17 in both Spain and the UK (Fig. 1). Dental sites used targeted sampling to recruit roughly equal distribution of participants based on sex and age group.[12] Eligible participants within sex and age groups consecutively presenting for dental care were consented until the sample size for that clinic was reached. Dentists and study support staff were trained on the study protocol, study procedures, and specimen collection protocols to ensure consistent methodology across all participating sites.

Data collection and study procedures

Data were collected from November 2020 to July 2023 (Fig. 2). Participants underwent HPV sampling via oral rinse and gargle (ORG) using LongSpin® prior to all dental procedures and completed a self–administered questionnaire in the local language of each country (Fig. 3). The self-administered questionnaire assessed socio-demographics, medical history, and other factors associated with HPV.[10] Dentists assessed oral health by counting the number of missing teeth and identifying presence of gingivitis and/or periodontitis for each participant. Dentists obtained HPV vaccination status by asking participants whether they had been vaccinated against HPV. Details of the ORG sampling process and participant- and dentist-collected data are described elsewhere.[12]

HPV testing

Samples were analyzed at the Catalan Institute of Oncology (ICO) in Barcelona, Spain and the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida, US. ICO analyzed 27.9% of samples (n = 2144) and Moffitt analyzed 72.1% of samples (n = 5530). HPV DNA detection and genotyping was assessed by SPF10/DEIA/LiPA25.[4,12,14] Interlaboratory quality control (QC) between both labs was performed by retesting 50% of HPV-positive samples and a random selection of HPV-negatives: 162 samples previously tested at ICO



Total participating dental sites (n=105)

	US	Spain	UK	Germany	France
Private	38	15	5	16	9
Public	5	2	12	0	3
Total	n=43	n=17	n=17	n=16	n=12

***Fig. 1:* Distribution of participating dental clinical sites (n = 105)**. The 43 US sites represent 21 out of 52 states: Arizona, California, Colorado, Florida, Georgia, Illinois, Maryland, Montana, Nebraska, New Jersey, New York, North Carolina, Michigan, Ohio, Pennsylvania, Texas, Utah, Virginia, Washington, West Virginia, and Wisconsin. The 17 Spanish sites represent 8 of 17 autonomous communities: Andalusia, Balearic Islands, Canary Islands, Castilla–La Mancha, Catalonia (Cataluña or Catalunya), Galicia, Madrid, and Navarre. The 17 UK sites represent 3 of the 4 UK countries (Scotland, Wales and England). Within England, sites represented 7 of the 9 administrative regions: East Midlands, London, North East, North West, South West, West Midlands and Yorkshire and The Humber; three sites in Scotland (Aberdeen, Dundee and Glasgow) and one site in Wales (Cardiff). The 16 German sites represent 10 of 16 federal states: Baden-Württemberg, Bavaria, Berlin, Brandenburg, Hamburg, Hesse, Lower Saxony, North Rhine-Westphalia, Rhineland-Palatinate and Saxony. The 12 French sites represent 7 of 13 metropolitan regions: Auvergne-Rhône-Alpes, Centre-Val de Loire, Grand Est, Hauts-de-France, Île-de-France (Paris Region), Nouvelle-Aquitaine and Occitanie.

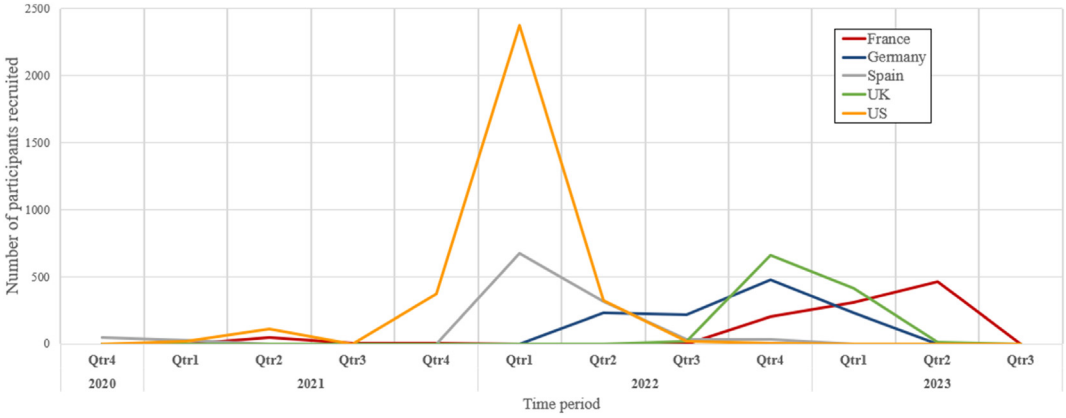


Fig. 2: **Data collection timeline**.

were re-tested at Moffitt and 161 samples previously tested at Moffitt were retested at ICO, and resulted in 85.8% concordance (Cohen Kappa index 0.7; 95% CI: 0.6–0.8) and 82.6% concordance (Cohen Kappa index 0.6; 95% CI: 0.5–0.8), respectively. Retested samples were representative of all countries and geographical areas in the study.

Statistical analysis

Statistical analyses were performed with SAS® statistical software packages. A sample was considered positive for any HPV genotype if it tested PCR-DEIA-positive. A sample was considered high-risk (HR) if any of 12 types were detected: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59, as recommended by the International Agency

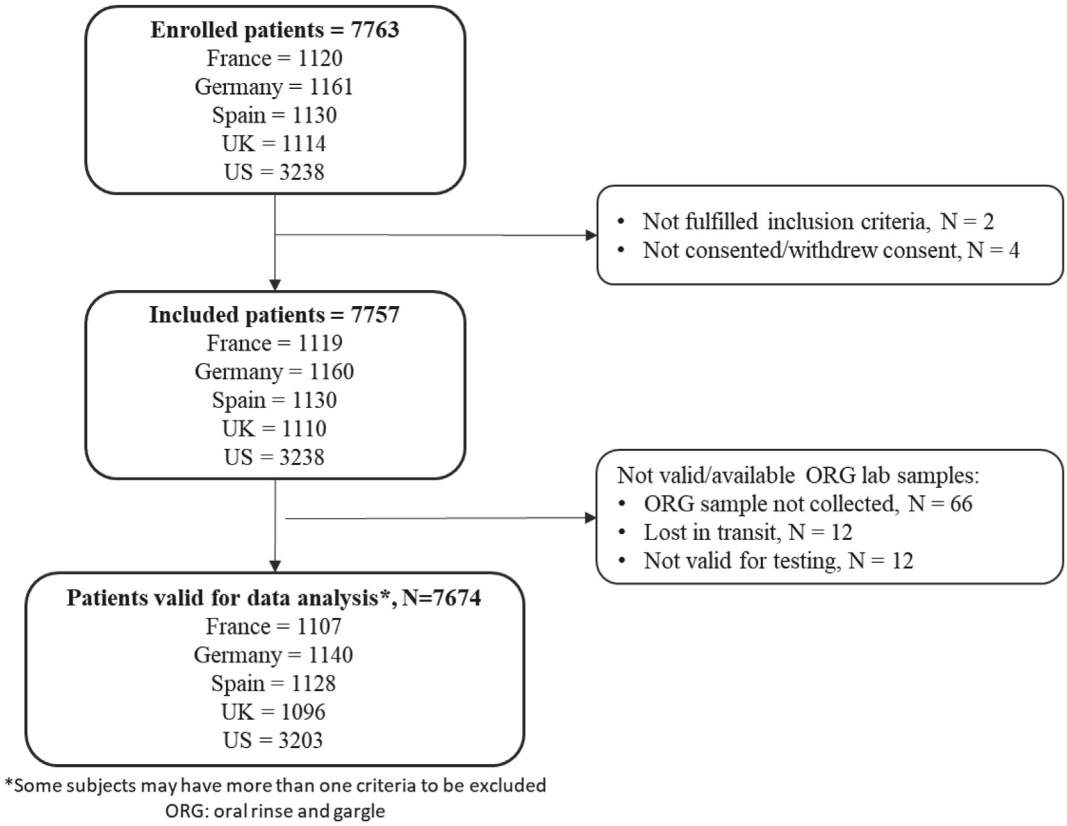


Fig. 3: **Patient flow chart including patient enrollment, eligibility and exclusion criteria and country of origin**.

for Research on Cancer (IARC) based on their epidemiological association with cervical cancer.[15] Despite no genotype classification for non-cervical cancer, this categorization is consistent with other oral HPV studies.[16] A sample was considered low-risk (LR) if: 1) ≥1 LR types were detected: 6, 11, 34, 40, 42, 43, 44, 53, 54, 66, 68/73, 70, or 74; or 2) it was PCR-DEIA-positive but did not hybridize to one of 25 probes (i.e., untypable).

Oral HPV prevalence was estimated for any HPV type (PCR-DEIA positive), specific HPV genotypes, grouped infections (HR, LR, and 9-valent vaccine types [6,11,16,18,31,33,45,52, and 58]), untypable HPV and concurrent infections. Any oral HPV prevalence was calculated by dividing the number of PCR-DEIA positive study participants by the total number of study participants. Prevalence was calculated in this way for each of the 25 individual HPV types, HR-HPV, LR-HPV, and HPV types included in the 9-valent vaccine, untypable HPV and concurrent infections.

Prevalence estimates were calculated including 95% confidence interval (CI) calculated using Wilson score method and stratified by age, gender, and country. We examined how HR and LR prevalence differed among men and women by socio-demographics, medical history, and behavioral characteristics. Bivariate and multivariable analyses of associated factors were stratified by participant gender due to differences in oral HPV prevalence and OPSCC by sex described in the literature.[6–9]

Proportions were compared using Chi-squared tests or Fisher's Exact tests when expected cell sizes were <5. Post-data collection we identified that German participants may have misunderstood the survey questions "lifetime number of female sex partners" and "number of new female sex partners in the prior 6 months" and as a result not distinguish between female and male sex partners. For these two survey questions, the term "sexualpartnerinnen" was used, which formally refers to female sexual partners. However, some Germans have recently began using a gender-neutral term for sexual partner, "partner:in" that refers to all sexes. Therefore, while "sexualpartnerinnen" technically referred to female sex partners, it may have been mistaken for "sexualpartner:in" which addresses both sexes. As a result, the data for those two questions from the German database were considered possibly invalid. Bivariate analyses for these variables exclude German data (Table 2 footnote 4). As these variables were significant at the bivariate level, but they could not be included in the global multivariable models, sensitivity analyses were conducted to explore the impact of excluding these two variables from the multivariable analysis. In this sensitivity analysis, multivariable models without German data were conducted and included variables with a significance level of <0.1, which included "lifetime number of female sex partners" and "number of new female sex partners in the prior 6 months." Both variables were removed from the model during the backward elimination process due to their low significance, suggesting that it was acceptable to exclude them in the global multivariable model.

In the final analyses, four multivariable logistic regression models estimated adjusted odds ratios (AORs) and 95% CIs for factors associated with HR and LR-only infection among men and women compared with HPV negative. In cases of concurrent infections (when more than 1 genotype was detected), the sample was classified as HR if one of the infections detected was an HR genotype. Factors to be included in the model were defined based on clinical and statistical significance. Age and country were forced to be included in the model. Due to the high number of potential confounders, factors, other than those identified based on clinical significance, were assessed based on the p-value obtained in univariate analysis. Factors with a significance level <0.1 in the univariate analysis were considered for inclusion in multivariable models by a backward elimination method. Variables included in the model after this process with a p-value<0.05 were considered in the final model. A backward elimination approach was used considering availability of prior information about the relationship between possible risk factors associated to oral HPV infection and with the purpose to reduce the number of predictors, reducing possible challenges with multicollinearity, and to resolve overfitting of the model due to limited number of HPV positive subjects.[17] Variance Inflation Factor (VIF) was used to assess collinearity between predictors. All predictors included in the model were categorized, except age that was included as a continuous variable. Linearity of age was confirmed using visual inspection and potential adjustment of prevalence of HR and LR HPV infection by age (continuous variable) was evaluated using restricted cubic splines with 5 knots (5th, 27.5th, 50th, 72.5th, and 95th percentiles of age distribution). A complete case analysis was used for regression models and subjects with missing data were excluded from the analysis. The approach was applied due to the random distribution of missing values, the limited number of missing values in each of the models (between 5% and 15%) and the lack of auxiliary variables to apply multiple imputation approaches.

Role of funding source

In collaboration with the external investigators, employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc, (Rahway, NJ, USA), the sponsor and funder of the study, were involved in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

A total of 7674 participants were recruited. The distribution of sociodemographic, medical history and

behavioral characteristics are described in Table 1. The US had the highest percentage of lifetime marijuana users (58.2%) and France the lowest (46.3%). Heavy alcohol consumption was highest in Germany (20.4%) and lowest in the US and France (both 7.8%). Periodontitis/gingivitis was highest in France (43.8%) and lowest in the US (23.5%).

UK had the highest proportion of participants missing ≥5 teeth (28.7%). There was a higher proportion of UK participants with ≥26 lifetime female oral sex partners (3.9% vs 2.3% in France, 3.2% in Germany, 3.1% in Spain, and 3.3% in the US). Self-reported HPV vaccination was highest among participants in Germany (4.8%) and lowest in the UK (2.1%).

Regarding differences by sex, a higher proportion of women were never-smokers compared to men (63.7% vs 57.3%). A higher proportion of men compared to women had used marijuana in their lifetime (59.0% vs 47.4%), had heavy alcohol use (14.8% vs 7.7%), had periodontitis/gingivitis (34.2% vs 27.2%), and had ≥26 female oral sex partners in their lifetime (6.9% vs 0.2%; $p < 0.0001$ for all). Self-report HPV vaccination was 5.8% among women compared to 1.3% among men.

Oral HPV infection prevalence

Prevalence of all HPV genotypes, HR genotypes, HPV-16 and 9-valent vaccine types were stratified by country, age and sex (Fig. 4 and Supplemental Table A). Overall, prevalence of any oral HPV was 7.4%, 2.0% for HR types, 0.6% for HPV-16, and 1.5% for 9-valent types. Prevalence of untypable genotypes was 4.2% overall, and comprised 4.3%, 4.2%, 3.5%, 2.9%, and 2.8% of samples in the Germany, UK, France, US, and Spain, respectively (data not shown). Concurrent infections were detected in 38 participants: 15 in the US, 9 in France, 6 in the UK, 5 in Germany and 3 in Spain; 30/38 were among males and 32/38 included a HR -genotype (data not shown).

Among men, prevalence of any oral HPV infection ranged between countries from 6.6% to 15.0%, 1.8%–4.5% for HR genotypes, 0.2%–1.6% for HPV-16, and 0.7%–3.6% for 9-valent-types (Fig. 4 and Supplemental Table A). Prevalence was lowest in Spain and highest in the UK for all, HR and HPV-16 genotypes, and lowest in Spain and highest in France for 9-valent-types. Among women, prevalence of any oral HPV infection ranged between countries from 3.6% to 6.8%, 0.2%–2.1% for HR genotypes, 0.0%–0.4% for HPV-16, and 0.2%–1.7% for 9-valent-types. Prevalence was lowest in Spain and highest in UK for any HPV, lowest in Germany and highest in France for HR and 9-valent-types, and lowest in Germany and highest in US for HPV-16.

Among all countries, prevalence of any oral HPV and HR-HPV was approximately twice as high in men than women (Supplemental Table B): 15.0% vs 6.8% in the UK, 11.7% vs 6.0% in France, 9.4% vs 4.8% in Germany, 6.6% vs 3.6% in Spain, in Europe, and 9.3% vs 4.8% in the US, among men and women respectively for any infection, and 4.5% vs 1.2% in the UK, 3.8% vs 2.1% in France, 3.1% vs 0.2% in Germany, 1.8% vs 0.5% in Spain, in Europe and 3.3% vs 1.0% in the US among men and women, respectively for HR-HPV.

Oral HPV genotype distribution

Among oral HPV-positive men (n = 353), HPV-16 was the most commonly detected genotype in UK (10.5%), Germany (9.5%), and US (12.0%; Fig. 5 and Supplemental Table B). HPV-18 and HPV-39 were the most commonly detected genotypes among men in France and Spain (8.9% and 11.1%, respectively). Among HPV-positive women (n = 213), the most detected genotypes by country were: HPV-18 in France (13.2%), HPV-53 in Germany (7.1%), HPV-16, HPV-31, HPV-33, HPV-44, HPV-51 and HPV-53 in Spain (4.8%), HPV-53 in UK (10.0%) and HPV-16 and HPV-44 in the US (8.1%; Fig. 5 and Supplemental Table C).

Prevalence of HR and LR oral HPV infection by socio-demographics, medical history, and risk behaviors

Prevalence of oral HR and LR HPV by socio-demographic, medical and behavioral characteristics, stratified by sex, are presented separately in Tables 2 and 3. In multivariable analyses (Table 4), oral HR-HPV risk among males was independently associated with age (AOR 1.04; 95% CI: 1.02–1.06); lifetime marijuana use (AOR 1.92; 95% CI: 1.19–3.11); higher number of lifetime oral sex partners (≥26), compared with no partners (AOR 2.10; 95% CI: 0.95–4.61), with an increasing trend with the number of partners; and residing in other countries compared with Spain, especially in the UK (AOR 2.89; 95% CI: 1.30–6.43). Oral HR-HPV risk among women was associated to lifetime marijuana use (AOR 2.33; 95% CI: 1.18–4.60) and residing in France, UK and USA, compared to Spain (AOR 4.46; 95% CI: 1.26–15.77, AOR 2.26; 95% CI: 0.56–9.08 and AOR 1.69; 95% CI: 0.49–5.82, respectively). Oral LR-HPV among males was independently associated with age (AOR 1.04; 95% CI: 1.03–1.06); previous STI diagnosis in past 6 months (AOR 3.05; 95% CI: 1.68–5.54); ≥5 missing teeth, compared to no missing teeth (AOR 1.44; 95% CI: 0.95–2.12), and residing in other countries compared with Spain, especially in the UK (AOR 2.11; 95% CI: 1.26–3.52). Oral LR-HPV among women was significantly associated with age (AOR 1.05; 95% CI: 1.03–1.06); prior diagnosis of STI in past 6 months (AOR 2.93; 95% CI: 1.34–6.39); and residing in countries other than Spain, especially in the UK (AOR 2.1; 95% CI: 1.1–3.9). Supplemental Table D and Supplemental Figure A describe results obtained from univariable regression models using restricted cubic splines for age.

Variables	Country of residence					Participant sex	
	France N = 1107	Germany N = 1140	Spain N = 1128	UK N = 1096	US N = 3203	Men N = 3511	Women N = 4163
Participant sex (n = 7674)							
Male	477 (43.1%)	553 (48.5%)	548 (48.6%)	506 (46.2%)	1427 (44.6%)	–	–
Female	630 (56.9%)	587 (51.5%)	580 (51.4%)	590 (53.8%)	1776 (55.4%)	–	–
Self-Identified race (n = 7257)							
White	887 (84.8%)	1037 (94.6%)	1024 (94.6%)	878 (82.6%)	2184 (73.6%)	2753 (82.5%)	3257 (83.1%)
Black or African American	43 (4.1%)	7 (0.6%)	12 (1.1%)	41 (3.9%)	274 (9.2%)	169 (5.1%)	208 (5.3%)
Asian	18 (1.7%)	24 (2.2%)	1 (0.1%)	103 (9.7%)	287 (9.7%)	201 (6.0%)	232 (5.9%)
Native Hawaiian or Other Pacific Islander	3 (0.3%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	10 (0.3%)	10 (0.3%)	4 (0.1%)
Other or mixed-race	95 (9.1%)	27 (2.5%)	46 (4.2%)	41 (3.9%)	214 (7.2%)	205 (6.1%)	218 (5.6%)
Age (years; n = 7674) [Mean (SD)]	41.0 (11.9)	40.1 (11.8)	40.2 (11,4)	39.8 (11.9)	39.6 (12.1)	40.0 (12.0)	40.0 (11.8)
18–30	262 (23.7%)	276 (24.2%)	261 (23.1%)	279 (25.5%)	880 (27.5%)	899 (25.6%)	1059 (25.4%)
31–40	251 (22.7%)	295 (25.9%)	297 (26.3%)	287 (26.2%)	783 (24.4%)	865 (24.6%)	1048 (25.2%)
41–50	304 (27.5%)	285 (25.0%)	310 (27.5%)	269 (24.5%)	756 (23.6%)	876 (25.0%)	1048 (25.2%)
51–60	290 (26.2%)	284 (24.9%)	260 (23.0%)	261 (23.8%)	784 (24.5%)	871 (24.8%)	1008 (24.2%)
Education level (n = 7421)							
<12th grade/Everything up through vocational school	507 (46.6%)	673 (60.0%)	579 (52.2%)	488 (46.0%)	648 (21.3%)	1378 (40.3%)	1517 (37.9%)
Some college	76 (7.0%)	55 (4.9%)	110 (9.9%)	140 (13.2%)	596 (19.6%)	455 (13.3%)	522 (13.1%)
College graduate	506 (46.5%)	394 (35.1%)	421 (37.9%)	434 (40.9%)	1794 (59.1%)	1588 (46.4%)	1961 (49.0%)
Marital status (n = 7498)							
Single/divorced/separated/widowed	439 (40.2%)	427 (38.2%)	446 (40.2%)	462 (43.1%)	1246 (40.1%)	1401 (40.7%)	1619 (39.9%)
Married or cohabiting	653 (59.8%)	691 (61.8%)	663 (59.8%)	609 (56.9%)	1862 (59.9%)	2041 (59.3%)	2437 (60.1%)
Employment status (n = 7486)							
Employed full-time	742 (68.4%)	804 (71.8%)	763 (68.8%)	656 (61.5%)	2297 (73.9%)	2759 (52.4%)	2503 (47.6%)
Employed part-time	163 (15.0%)	247 (22.1%)	154 (13.9%)	217 (20.4%)	379 (12.2%)	275 (23.7%)	885 (76.3%)
Not employed	180 (16.6%)	68 (6.1%)	192 (17.3%)	193 (18.1%)	431 (13.9%)	406 (38.2%)	658 (61.8%)
Cigarette pack years (n = 6935)							
Never smoker (0 pack-years)	522 (52.7%)	409 (44.0%)	516 (48.6%)	515 (55.3%)	2248 (74.4%)	1842 (57.3%)	2368 (63.7%)
Light smoker (>0–20 pack-years)	377 (38.1%)	434 (46.7%)	459 (43.2%)	341 (36.6%)	690 (22.8%)	1108 (34.5%)	1193 (32.1%)
Moderate smoker (>20–40 pack-years)	76 (7.7%)	73 (7.9%)	76 (7.2%)	69 (7.4%)	64 (2.1%)	215 (6.7%)	143 (3.8%)
Heavy smoker (>40 pack-years)	15 (1.5%)	13 (1.4%)	11 (1.0%)	7 (0.8%)	20 (0.7%)	50 (1.6%)	16 (0.4%)
Lifetime marijuana use (yes; n = 7015)	476 (46.3%)	444 (47.0%)	559 (52.0%)	471 (49.5%)	1755 (58.2%)	1920 (59.0%)	1785 (47.4%)
Marijuana use in past 6 months (yes; n = 7001)	111 (10.8%)	113 (12.0%)	103 (9.7%)	114 (12.0%)	677 (22.5%)	616 (19.0%)	502 (13.4%)
Alcohol consumption in last 30 days (yes; n = 6089)							
None	271 (31.0%)	47 (5.5%)	223 (25.9%)	185 (25.8%)	1006 (36.1%)	719 (25.3%)	1013 (31.2%)
Low	534 (61.2%)	638 (74.1%)	515 (59.9%)	444 (61.9%)	1561 (56.1%)	1706 (60.0%)	1980 (61.1%)
High	68 (7.8%)	176 (20.4%)	122 (14.2%)	88 (12.3%)	218 (7.8%)	420 (14.8%)	249 (7.7%)
Weakened immune system[a] (yes; n = 7005)	55 (5.5%)	30 (2.8%)	45 (4.6%)	36 (3.9%)	113 (3.7%)	124 (3.8%)	155 (4.1%)
Diagnosed with STI in past 6 months[b] (yes; n = 7253)	20 (1.9%)	6 (0.5%)	13 (1.3%)	14 (1.4%)	128 (4.2%)	97 (2.9%)	84 (2.1%)
Self-report HPV vaccination status (vaccinated; n = 6678)	42 (4.0%)	52 (4.8%)	37 (3.4%)	20 (2.1%)	95 (3.9%)	43 (1.3%)	203 (5.8%)
Number of missing teeth[c] (n = 7665) [Median (IQR)]	2.0 [0.0, 4.0]	2.0 [0.0, 4.0]	1.0 [0.0, 4.0]	2.0 [0.0, 5.0]	4.0 [0.0, 4.0]	3.0 [0.0, 4.0]	3.0 [0.0, 4.0]
0	434 (39.3%)	425 (37.3%)	427 (37.9%)	311 (28.9%)	843 (26.4%)	1119 (31.9%)	1321 (31.8%)
1–3	269 (24.4%)	213 (18.7%)	357 (31.7%)	336 (30.7%)	430 (13.5%)	769 (21.9%)	836 (20.1%)
4	186 (16.9%)	251 (22.0%)	74 (6.7%)	135 (12.3%)	1278 (40.0%)	814 (23.2%)	1110 (27.6%)
≥5	215 (19.5%)	251 (22.0%)	270 (23.9%)	314 (28.7%)	646 (20.2%)	807 (23.0%)	889 (21.4%)
Presence of gingivitis or periodontitis[c] (yes; n = 7665)	484 (43.8%)	294 (25.8%)	371 (32.9%)	408 (39.9%)	750 (23.5%)	1201 (34.2%)	1129 (27.2%)
Lifetime number female sex partners[d] (n = 6035)							
0	529 (51.6%)	N/A[d]	524 (49.3%)	552 (53.2%)	1549 (53.2%)	335 (12.3%)	2819 (85.1%)
1–5	261 (25.4%)	N/A[d]	284 (26.7%)	202 (19.5%)	701 (24.1%)	1049 (38.5%)	399 (12.0%)

(Table 1 continues on next page)

Variables	Country of residence					Participant sex	
	France N = 1107	Germany N = 1140	Spain N = 1128	UK N = 1096	US N = 3203	Men N = 3511	Women N = 4163
(Continued from previous page)							
6–25	190 (18.5%)	N/A[d]	189 (17.8%)	219 (21.1%)	472 (16.2%)	988 (36.5%)	82 (2.5%)
≥26	46 (4.5%)	N/A[d]	65 (6.1%)	64 (6.2%)	188 (6.5%)	350 (12.9%)	13 (0.4%)
Number of new female sex partners in last 6 months[d] (n = 5884) [Median (IQR)]	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.0 [0.0, 0.0]	0.0 [0.0, 1.0]	0.0 [0.0, 0.0]
0	832 (82.5%)	N/A[d]	797 (82.7%)	886 (88.2%)	2602 (89.5%)	1919 (73.6%)	3198 (97.6%)
1	141 (14.0%)	N/A[d]	109 (11.3%)	85 (8.5%)	222 (7.6%)	495 (19.0%)	62 (1.9%)
≥2	36 (3.6%)	N/A[d]	58 (6.0%)	33 (3.3%)	83 (2.9%)	194 (7.4%)	16 (0.5%)
Lifetime number of female oral sex partners (n = 7048)							
0	664 (64.7%)	550 (53.3%)	582 (54.7%)	601 (58.5%)	1709 (59.0%)	576 (18.1%)	3530 (91.3%)
1–5	241 (23.5%)	321 (31.1%)	294 (27.6%)	233 (22.7%)	756 (26.1%)	1554 (48.8%)	291 (7.5%)
6–25	98 (9.5%)	128 (12.4%)	155 (14.6%)	154 (15.0%)	337 (11.6%)	833 (26.2%)	39 (1.0%)
≥26	24 (2.3%)	33 (3.2%)	33 (3.1%)	40 (3.9%)	95 (3.3%)	219 (6.9%)	6 (0.2%)
Number of new female oral sex partners in last 6 months (n = 7065)							
0	931 (89.6%)	921 (88.8%)	905 (86.8%)	934 (91.3%)	2756 (94.3%)	2635 (82.2%)	3812 (98.7%)
1	83 (8.0%)	91 (8.8%)	88 (8.4%)	59 (5.8%)	116 (4.0%)	402 (12.5%)	35 (0.9%)
≥2	25 (2.4%)	25 (2.4%)	50 (4.8%)	30 (2.9%)	51 (1.7%)	167 (5.2%)	14 (0.4%)
Lifetime number of male sex partners (n = 7086)							
0	486 (46.7%)	509 (49.1%)	525 (49.1%)	488 (47.4%)	1353 (46.5%)	2951 (90.2%)	410 (10.7%)
1–5	326 (31.3%)	311 (30.0%)	360 (33.7%)	255 (24.8%)	840 (28.9%)	151 (4.6%)	1941 (50.9%)
6–25	197 (18.9%)	187 (18.0%)	164 (15.3%)	235 (22.8%)	589 (20.2%)	97 (3.0%)	1275 (33.4%)
≥26	32 (3.1%)	30 (2.9%)	20 (1.9%)	52 (5.0%)	127 (4.4%)	71 (2.2%)	190 (5.0%)
Number of new male sex partners in last 6 months (n = 6832) [Median (IQR)]	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]
0	815 (81.7%)	877 (87.5%)	760 (81.3%)	873 (88.3%)	2561 (88.0%)	3159 (96.8%)	2727 (76.4%)
1	139 (13.9%)	96 (9.6%)	130 (13.9%)	87 (8.8%)	259 (8.9%)	42 (1.3%)	669 (18.7%)
≥2	43 (4.3%)	29 (2.9%)	45 (4.8%)	29 (2.9%)	89 (3.1%)	62 (1.9%)	173 (4.8%)
Lifetime number of male oral sex partners (n = 5075)							
0	558 (69.1%)	566 (83.6%)	564 (53.6%)	520 (60.9%)	1469 (87.2%)	3068 (97.3%)	609 (31.7%)
1–5	181 (22.4%)	82 (12.1%)	381 (36.2%)	222 (26.0%)	154 (9.1%)	38 (1.2%)	982 (51.1%)
6–25	60 (7.4%)	27 (4.0%)	92 (8.7%)	93 (10.9%)	53 (3.1%)	29 (0.9%)	296 (15.4%)
≥26	8 (1.0%)	2 (0.3%)	15 (1.4%)	19 (2.2%)	9 (0.5%)	18 (0.6%)	35 (1.8%)
Number of new male oral sex partners in last 6 months (n = 6957)							
0	901 (88.2%)	957 (92.6%)	894 (87.7%)	930 (91.2%)	2656 (92.7%)	3212 (97.5%)	3126 (85.3%)
1	85 (8.3%)	53 (5.1%)	81 (7.9%)	65 (6.4%)	159 (5.6%)	30 (0.9%)	413 (11.3%)
≥2	35 (3.4%)	23 (2.2%)	44 (4.3%)	25 (2.5%)	49 (1.7%)	52 (1.6%)	124 (3.4%)
Sexual behavior[e] (n = 6317)							
Heterosexual	743 (83.4%)	844 (89.1%)	892 (90.6%)	787 (85.8%)	2210 (85.8%)	2594 (89.2%)	2882 (84.6%)
Same sex	15 (1.7%)	17 (1.8%)	30 (3.0%)	30 (3.3%)	51 (2.0%)	93 (3.2%)	50 (1.5%)
Bisexual	133 (14.9%)	86 (9.1%)	63 (6.4%)	100 (10.9%)	316 (12.3%)	222 (7.6%)	476 (14.0%)

HPV, human papilloma virus; IQR, interquartile range; STI, Sexually Transmitted Infection. [a]Weakened immune system defined as participant reporting a blood disease, blood cancer, auto-immune disease or HIV, or if they were receiving corticosteroids, chemotherapy, biologic therapy or other immunosuppressants. [b]STI were defined as participant reporting having been diagnosed with at least one of the following: syphilis, gonorrhea, genital herpes, chlamydia, genital warts/condyloma, anal warts, skin warts (not on the genitals or anus), and/or trichomoniasis. [c]Data were reported by dentists after performing oral exam. [d]Data for female sexual partners in Germany is not included in the analysis due to possible misinterpretation of the questions by responders. [e]Participants were classified as engaging in *heterosexual* behavior if they were men who reported sex with ≥1 female sex partner and 0 male sex partners in their lifetime, or if they were women who reported sex with ≥1 male sex partner and 0 female sex partners in their lifetime; participants were classified as engaging in *same-sex* behavior if they exclusively reported sex in their lifetime with ≥1 person of their same sex. Participants were classified as engaging in *bisexual* behavior if they reported sex in their lifetime with ≥1 male and ≥1 female.

Table 1: **Characteristics of subjects by country of residence and sex (n = 7674).**

Discussion

Among 7674 adults attending dental clinics for routine care in France, Germany, Spain, UK, and US, 7.4% had a prevalent oral HPV infection and 2.0% had a prevalent HR infection. Our study demonstrates a higher burden of oral HPV in men than women, which is consistent with the higher number of HPV-related OPSCC cases in males.[8] HR-HPV prevalence was 2- to 4-fold higher among men compared with women in each country. Hypothesized explanations for higher oral HPV in men

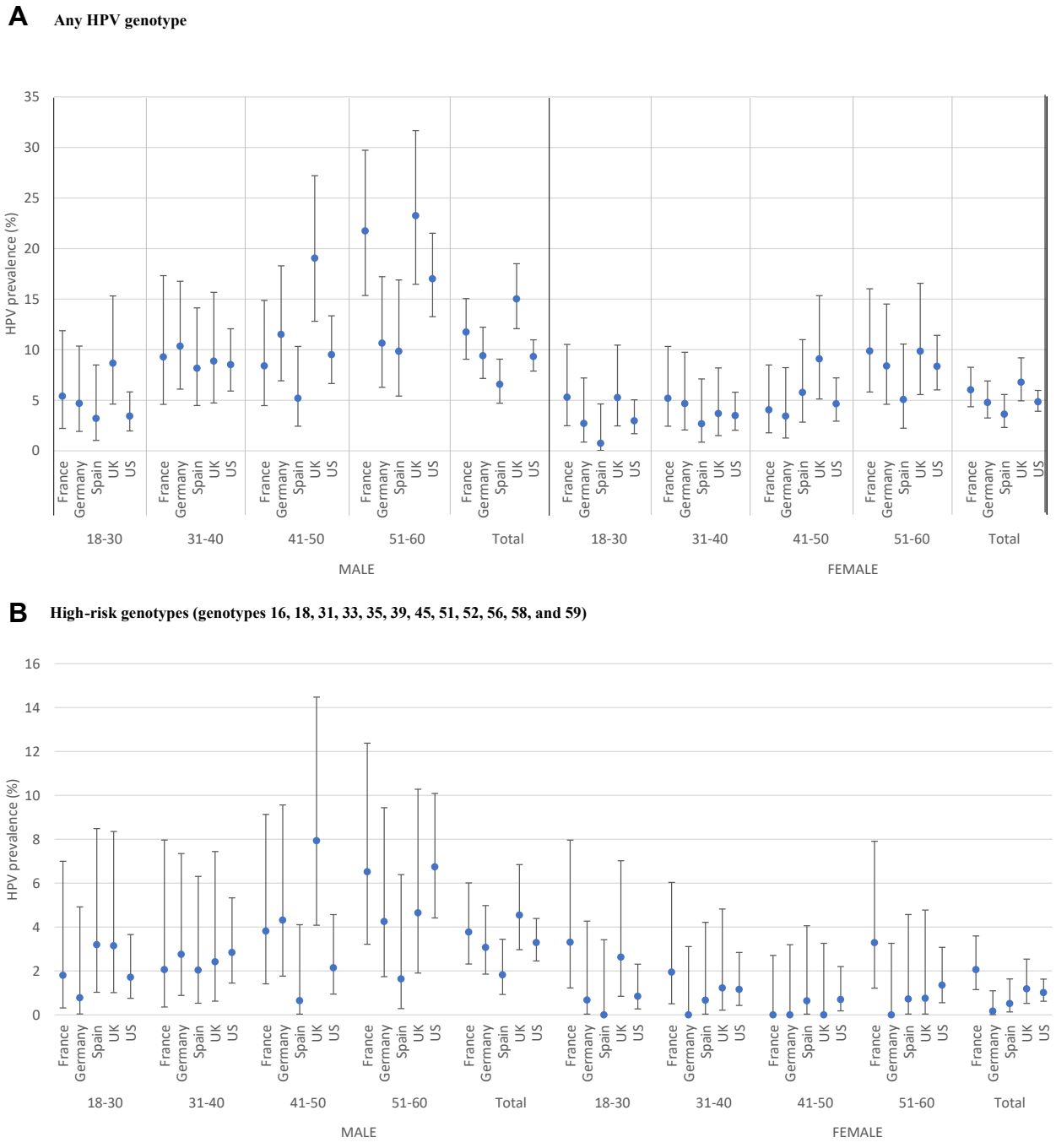


Fig. 4: **Prevalence of oral HPV infection stratified by sex and age. A. Any HPV genotype. B. High-risk genotypes (genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59). C. HPV-16 genotype. D. 9-valent vaccine genotypes (genotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58).**

include: 1) men have more sex partners and stronger associations between sexual behavior and HPV infection,[18,19] 2) orogenital HPV transmission is higher from women-to-men than men-to-women,[20] and 3) women have a more robust immune response to HPV compared with men.[21] As a result, men may remain susceptible to HPV acquisition and persistent infection across their lifespan.[22] Findings highlight the need to increase HPV prevention efforts among males worldwide.

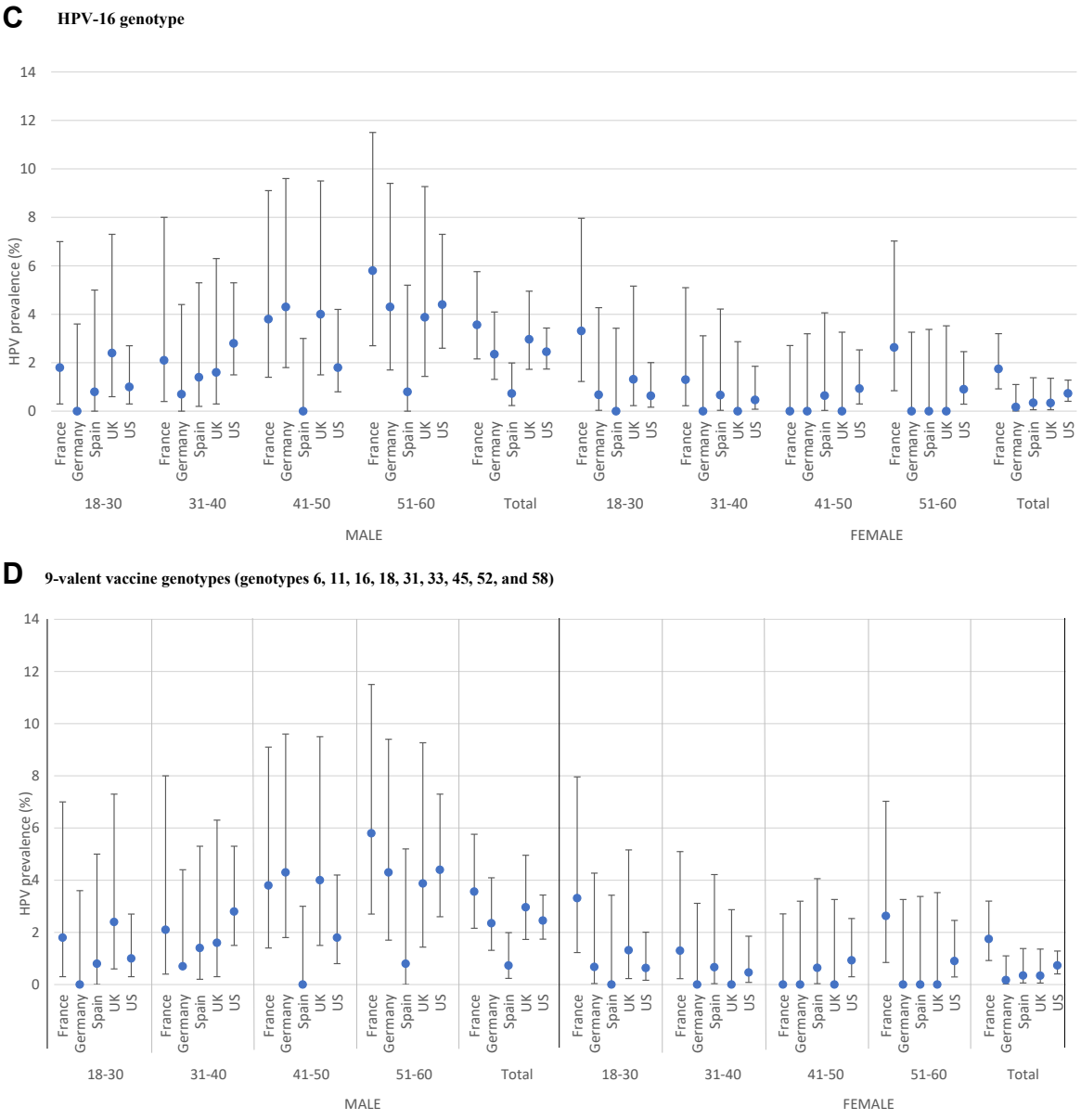
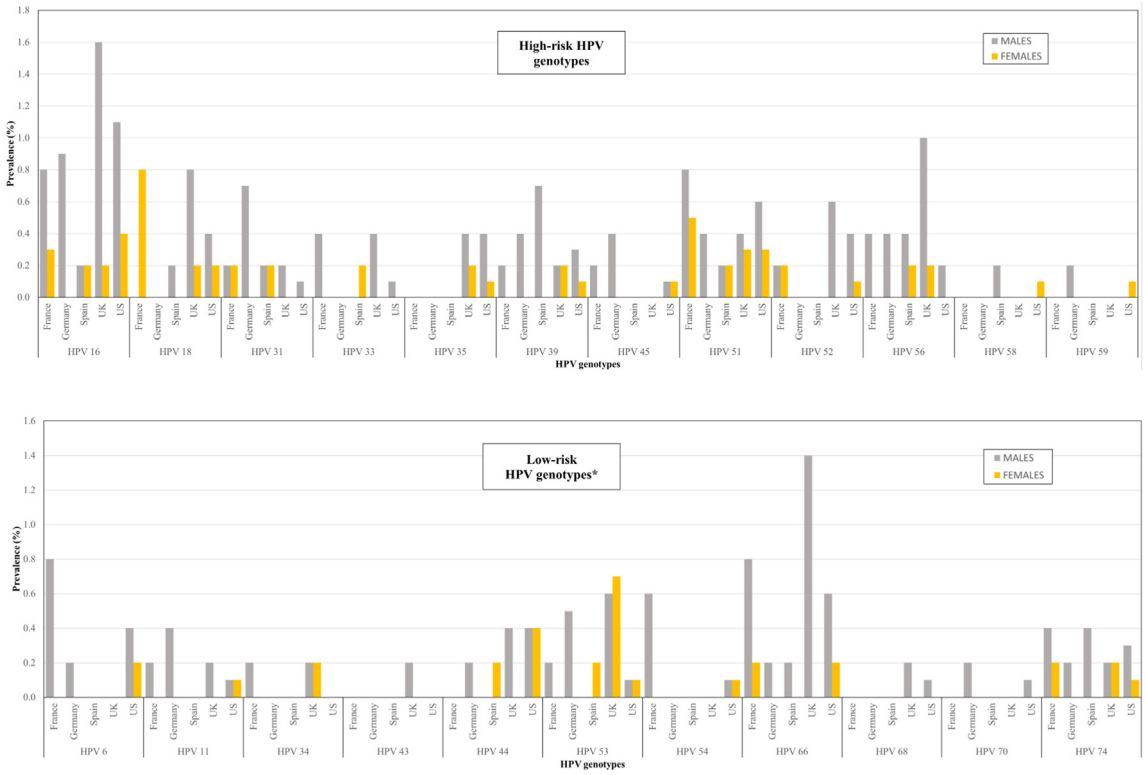


Fig. 4: Continued.

Older age was independently associated with HR and LR infection in men and LR infection in women. Approximately one in five men aged 51–60 in France, UK, and US, and one in 10 men aged 51–60 in Germany and Spain had a prevalent oral HPV infection. Approximately one in 10 women aged 51–60 in France, Germany, UK, and US, and 1 in 20 women aged 51–60 in Spain had a prevalent oral HPV infection. Higher prevalence of oral HPV among older adults has been previously reported and may be due to increased HPV exposure, infection and/or persistence with age, potential loss of immune control, and/or reactivation of latent HPV infections.[10] These findings are in line with studies reporting a shifting burden of HPV-OPSCC towards older adults.[23,24] Since there is no routine screening for OPSCC, programs and policy will need to address OPSCC prevention and management of older patients. Conversely, in the HR-HPV multivariable model among women, women aged 41–50 had decreased odds of HR infection, but this finding must be interpreted with caution given only 4 women aged 41–50 had an HR infection. Nonetheless, studies with



*LR HPV40 and HPV42 were removed from the figure because no participants tested positive for them.

***Fig. 5:* HPV genotype distribution stratified by sex**. *LR HPV40 and HPV42 were removed from the figure because no participants tested positive for them.

larger sample sizes of women with HR infections are needed to understand if this finding is replicated.

Measures of sexual activity were associated with oral HPV infection, which is in line with the published literature.[10] Having a high number of female oral sex partners was associated with HR-HPV infection among men and recent STI diagnosis was associated with higher odds of having LR-HPV among men. While studies have found oral sex to be a primary independent risk factor for oral HPV,[10] our study found this relationship with HR but not LR-HPV, and among men but not women. Data from the HPV Infection in Men (HIM) study also found oral sex behaviors to be associated with HR infection only, and posited that this could be due to differing modes of transmission, such as direct from oral sex for HR-HPV compared to auto-transmission for LR-HPV.[16] Research is needed to further elucidate why oral sex may be a risk factor for HR but not LR oral HPV, and why sexual behaviors may be independent risk factors for oral HPV among men but not women.

To our knowledge, this is the first study reporting an independent relationship between marijuana-use and oral HPV. Gillison et al. (2012) reported that oral HPV prevalence was higher among former and current marijuana users, but marijuana use was no longer significant after introduction of sexual behavior variables into multivariable models.[7] The literature is mixed on the relationship between marijuana-use and HPV-driven OPSCC.[25,26] Findings from the present analysis may be explained by the hypothesis that cannabis modulates the immune system by acting on immune cell receptors, decreasing immunity, and thereby increasing susceptibility to infections.[27] The inconsistent data concerning marijuana-use and its association with both oral HPV infection and OPSCC may also be indicative of confounding between smoking behaviors and sexual practices, though our study found no significant interactions between these variables.

A unique contribution of our study was the inclusion of dentist-assessed oral health variables. Indicators of poor oral health were associated with LR HPV in men. Data from the HIM study also found indicators of poor oral health to be independent risk factors for LR oral HPV infection among men.[16] The association between oral health and HPV may be explained by dental disease and oral HPV sharing similar risk factors, such as smoking behaviors.[10,28] Additionally, it is possible that

Variables	Men N = 3273			Women N = 3992		
	HR HPV positive N = 115	HPV negative N = 3158	p-value	HR HPV positive N = 42	HPV negative N = 3950	p-value
Country						
Germany	17 (3.3%)	501 (96.7%)	0.10	1 (0.2%)	559 (99.8%)	0.013
Spain	10 (1.9%)	512 (98.1%)		3 (0.5%)	559 (99.5%)	
France	18 (4.1%)	421 (95.9%)		13 (2.1%)	592 (97.9%)	
UK	23 (5.1%)	430 (94.9%)		7 (1.3%)	550 (98.7%)	
USA	47 (3.5%)	1294 (96.5%)		18 (1.1%)	1690 (98.9%)	
Self-identified race						
White	95 (3.7%)	2466 (96.3%)	0.32	31 (1.0%)	3081 (99.0%)	0.11
Black or African American	6 (5.5%)	144 (4.8%)		2 (1.0%)	198 (99.0%)	
Asian	2 (1.0%)	193 (99.0%)		1 (0.4%)	229 (99.6%)	
Native Hawaiian or Other Pacific Islander	0 (0.0%)	10 (100.0%)		0 (0.0%)	4 (100.0%)	
Other or mixed-race	7 (3.6%)	189 (96.4%)		6 (2.9%)	204 (97.1%)	
Age						
18–30 years	18 (2.1%)	858 (97.9%)	0.0001	14 (1.3%)	1024 (98.7%)	0.11
31–40 years	22 (2.7%)	788 (97.3%)		11 (1.1%)	1008 (98.9%)	
41–50 years	29 (25.2%)	786 (24.9%)		4 (0.4%)	994 (99.6%)	
51–60 years	46 (6.0%)	726 (94.0%)		13 (1.4%)	924 (98.6%)	
Education level						
≤12th grade	51 (4.0%)	1219 (96.0%)	0.38	13 (0.9%)	1429 (99.1%)	0.031
Some college	12 (10.8%)	414 (13.4%)		11 (2.2%)	489 (97.8%)	
College graduate	48 (3.2%)	1446 (96.8%)		17 (0.9%)	1875 (99.1%)	
Marital status						
Single/divorced/separated/widowed	54 (4.1%)	1267 (95.9%)	0.10	23 (1.5%)	1528 (98.5%)	0.033
Married or cohabiting	57 (3.0%)	1833 (97.0%)		18 (0.8%)	2320 (99.2%)	
Cigarette pack years						
Never smoker (0 pack-years)	51 (2.9%)	1682 (97.1%)	0.0009	24 (1.1%)	2252 (98.9%)	0.69
Light smoker (>0–20 pack-years)	40 (3.9%)	987 (96.1%)		11 (1.0%)	1136 (99.0%)	
Moderate smoker (>20–40 pack-years)	9 (4.7%)	183 (95.3%)		2 (1.6%)	123 (98.4%)	
Heavy smoker (>40 pack-years)	6 (14.0%)	37 (86.0%)		0	14 (100.0%)	
Lifetime marijuana use						
No	32 (2.6%)	1212 (97.4%)	0.011	13 (0.7%)	1881 (99.3%)	0.016
Yes	77 (4.3%)	1707 (95.7%)		26 (1.5%)	1685 (98.5%)	
Marijuana use in last 6 months						
No	87 (3.5%)	2367 (96.5%)	0.87	30 (1.0%)	3089 (99.0%)	0.068
Yes	21 (3.7%)	549 (96.3%)		9 (1.9%)	467 (98.1%)	
Alcohol consumption during the last 30 days						
None	20 (3.0%)	644 (97.0%)	0.18	11 (1.1%)	967 (98.9%)	0.68
Low	53 (3.3%)	1542 (96.7%)		16 (0.8%)	1877 (99.2%)	
High	20 (5.0%)	377 (95.0%)		3 (1.3%)	235 (98.7%)	
Weakened immune system[a]						
No	100 (3.4%)	2801 (96.6%)	0.29	36 (1.0%)	3436 (99.0%)	0.21
Yes	6 (5.3%)	108 (94.7%)		3 (2.0%)	144 (98.0%)	
Diagnosed with STI in past 6 months[b]						
No	103 (94.5%)	2918 (97.5%)	0.066	36 (1.0%)	3654 (99.0%)	0.043
Yes	6 (5.5%)	76 (2.5%)		3 (3.9%)	73 (96.1%)	
Number of missing teeth[c]						
0	31 (2.9%)	1034 (97.1%)	0.083	14 (1.1%)	1278 (98.9%)	0.67
1-3	25 (3.5%)	689 (96.5%)		6 (0.7%)	800 (99.3%)	
4	23 (3.0%)	753 (97.0%)		14 (1.3%)	1045 (98.7%)	
≥5	36 (5.0%)	680 (95.0%)		8 (1.0%)	820 (99.0%)	
Presence of periodontitis/gingivitis[c]						
No	60 (2.8%)	2120 (97.2%)	0.0008	26 (0.9%)	2895 (99.1%)	0.093
Yes	55 (5.0%)	1036 (95.0%)		16 (1.5%)	1048 (98.5%)	

(Table 2 continues on next page)

Variables	Men N = 3273			Women N = 3992		
	HR HPV positive N = 115	HPV negative N = 3158	p-value	HR HPV positive N = 42	HPV negative N = 3950	p-value
(Continued from previous page)						
Lifetime number female sex partners[d]						
0	10 (3.1%)	310 (96.9%)	0.0020	25 (0.9%)	2675 (99.1%)	0.039
1–5	20 (2.0%)	965 (98.0%)		9 (2.1%)	377 (97.7%)	
6–25	41 (4.5%)	869 (95.5%)		2 (2.6%)	74 (97.4%)	
≥26	19 (6.0%)	298 (94.0%)		0	11 (100.0%)	
Number of new female sex partners last 6 months[d]						
0	55 (3.1%)	1727 (96.9%)	0.057	36 (1.2%)	3027 (98.8%)	1.00
1	25 (5.4%)	438 (94.6%)		0	60 (100.0%)	
≥2	7 (3.8%)	177 (96.2%)		0	14 (100.0%)	
Lifetime number of female oral sex partners						
0	13 (2.4%)	528 (97.6%)	<0.0001	31 (0.9%)	3351 (99.1%)	0.051
1–5	30 (2.1%)	1425 (97.9%)		7 (2.5%)	273 (97.5%)	
6–25	42 (5.5%)	723 (94.5%)		1 (2.8%)	35 (97.2%)	
≥26	16 (8.0%)	185 (92.0%)		0 (0.0%)	6 (100.0%)	
Number of new female oral sex partners last 6 months						
0	77 (3.1%)	2375 (96.9%)	0.021	39 (1.1%)	3613 (98.9%)	1.00
1	17 (4.5%)	358 (95.5%)		0 (0.0%)	34 (100.0%)	
≥2	11 (7.0%)	147 (93.0%)		0 (0.0%)	13 (100.0%)	
Lifetime number of male sex partners						
0	93 (3.4%)	2666 (96.6%)	0.028	5 (1.3%)	386 (98.7%)	0.11
1–5	5 (3.6%)	134 (96.4%)		13 (0.7%)	1856 (99.3%)	
6–25	3 (3.4%)	86 (96.6%)		16 (1.3%)	1209 (98.7%)	
≥26	7 (11.5%)	54 (88.5%)		4 (2.3%)	169 (97.7%)	
Number of new male sex partners last 6 months						
0	102 (3.5%)	2843 (96.5%)	0.11	26 (1.0%)	2579 (99.0%)	0.20
1	1 (2.6%)	38 (97.4%)		9 (1.4%)	633 (98.6%)	
≥2	5 (8.8%)	52 (91.2%)		4 (2.4%)	162 (97.6%)	
Lifetime number of male oral sex partners						
0	95 (3.3%)	2770 (96.7%)	0.71	6 (1.0%)	577 (99.0%)	0.14
1–5	1 (2.7%)	36 (97.3%)		5 (0.5%)	941 (99.5%)	
6–25	0 (0.0%)	26 (100.0%)		5 (1.8%)	280 (98.2%)	
≥26	1 (6.3%)	15 (93.8%)		1 (3.0%)	32 (97.0%)	
Number of new male oral sex partners last 6 months						
0	102 (3.4%)	2892 (96.6%)	0.16	30 (1.0%)	2965 (99.0%)	0.22
1	0 (0.0%)	25 (100.0%)		6 (1.5%)	390 (98.5%)	
≥2	4 (8.2%)	45 (91.8%)		3 (2.5%)	117 (97.5%)	
Sexual behavior[e]						
Heterosexual	82 (3.4%)	2331 (96.6%)	0.14	22 (0.8%)	2743 (99.2%)	0.016
Same sex	2 (2.4%)	83 (97.6%)		1 (2.0%)	48 (98.0%)	
Bisexual	12 (6.0%)	189 (94.0%)		10 (2.2%)	444 (97.8%)	

HPV, human papilloma virus; HR, high-risk; STI, Sexually Transmitted Infection. HR genotypes include genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. [a]Weakened immune system defined as participant reporting a blood disease, blood cancer, auto-immune disease or HIV, or if they were receiving corticosteroids, chemotherapy, biologic therapy or other immunosuppressants. [b]STI were defined as participant reporting having been diagnosed with at least one of the following: syphilis, gonorrhea, genital herpes, chlamydia, genital warts/condyloma, anal warts, skin warts (not on the genitals or anus), and/or trichomoniasis. [c]Data were reported by dentists after performing oral exam. [d]Data for female sexual partners in Germany is not included in the analysis due to misinterpretation of the question by respondents. [e]Participants were classified as engaging in *heterosexual* behavior if they were men who reported sex with ≥1 female sex partner and 0 male sex partners in their lifetime, or if they were women who reported sex with ≥1 male sex partner and 0 female sex partners in their lifetime; participants were classified as engaging in *same-sex* behavior if they exclusively reported sex in their lifetime with ≥1 person of their same sex. Participants were classified as engaging in *bisexual* behavior if they reported sex in their lifetime with ≥1 male and ≥1 female.

Table 2: **Bivariate analysis of high-risk (HR) HPV infection.**

missing teeth facilitates the penetration of oral HPV into the epithelium and causes infection in basal cells by inducing inflammation in the gingival mucosa and microscopic lesions.[29]

When comparing countries, oral HPV prevalence was consistently higher in men than women. HPV-16 was the most detected genotype among men in Germany, UK and US. By contrast, prevalence differed

Variables	Men N = 3396			Women N = 4121		
	LR HPV positive N = 238	HPV negative N = 3158	p-value	LR HPV positive N = 171	HPV negative N = 3950	p-value
Country						
Germany	35 (6.5%)	501 (93.5%)	0.0011	27 (4.6%)	559 (95.4%)	0.23
Spain	26 (4.8%)	512 (95.2%)		18 (3.1%)	559 (96.9%)	
France	38 (8.3%)	421 (91.7%)		25 (4.1%)	592 (95.9%)	
UK	53 (11.0%)	430 (89.0%)		33 (5.7%)	550 (94.3%)	
USA	86 (6.2%)	1294 (93.8%)		68 (3.9%)	1690 (96.1%)	
Self-identified race						
White	192 (7.2%)	2466 (92.8%)	0.013	145 (4.5%)	3081 (95.5%)	0.059
Black or African American	19 (11.7%)	144 (88.3%)		8 (3.9%)	198 (96.1%)	
Asian	6 (3.0%)	193 (97.0%)		2 (0.9%)	229 (99.1%)	
Native Hawaiian or Other Pacific Islander	0 (0.0%)	10 (100.0%)		0 (0.0%)	4 (100.0%)	
Other or mixed-race	9 (4.5%)	189 (95.5%)		8 (3.8%)	204 (96.2%)	
Age						
18–30 years	23 (2.6%)	858 (97.4%)	<0.0001	21 (2.0%)	1024 (98.0%)	<0.0001
31–40 years	55 (6.5%)	788 (93.5%)		29 (2.8%)	1008 (97.2%)	
41–50 years	61 (7.2%)	786 (92.8%)		50 (4.8%)	994 (95.2%)	
51–60 years	99 (12.0%)	726 (88.0%)		71 (7.1%)	924 (92.9%)	
Education level						
≤12th grade	108 (8.1%)	1219 (91.9%)	0.096	75 (5.0%)	1429 (95.0%)	0.11
Some college	29 (6.5%)	414 (93.5%)		22 (4.3%)	489 (95.7%)	
College graduate	94 (6.1%)	1446 (93.9%)		69 (3.5%)	1875 (96.5%)	
Marital status						
Single/divorced/separated/widowed	80 (5.9%)	1267 (94.1%)	0.062	68 (4.3%)	1528 (95.7%)	0.79
Married or cohabiting	151 (7.6%)	1833 (92.4%)		99 (4.1%)	2320 (95.9%)	
Cigarette pack years						
Never smoker (0 pack-years)	109 (6.1%)	1682 (93.9%)	0.0045	92 (3.9%)	2252 (96.1%)	<0.0001
Light smoker (>0–20 pack-years)	81 (7.6%)	987 (92.4%)		46 (3.9%)	1136 (96.1%)	
Moderate smoker (>20–40 pack-years)	23 (11.2%)	183 (88.8%)		18 (12.8%)	123 (87.2%)	
Heavy smoker (>40 pack-years)	7 (15.9%)	37 (84.1%)		2 (12.5%)	14 (87.5%)	
Lifetime marijuana use						
No	89 (6.8%)	1212 (93.2%)	0.56	83 (4.2%)	1881 (95.8%)	0.98
Yes	136 (7.4%)	1707 (92.6%)		74 (4.2%)	1685 (95.8%)	
Marijuana use in last 6 months						
No	179 (7.0%)	2367 (93%)	0.55	131 (4.1%)	3089 (95.9%)	0.22
Yes	46 (7.7%)	549 (92.3%)		26 (5.3%)	467 (94.7%)	
Alcohol consumption during the last 30 days						
None	55 (7.9%)	644 (92.1%)	0.38	35 (3.5%)	967 (96.5%)	0.46
Low	111 (6.7%)	1542 (93.3%)		87 (4.4%)	1877 (95.6%)	
High	23 (5.8%)	377 (94.3%)		11 (4.5%)	235 (95.5%)	
Weakened immune system[a]						
No	200 (6.7%)	2801 (93.3%)	0.45	153 (4.3%)	3436 (95.7%)	0.54
Yes	10 (8.5%)	108 (91.5%)		8 (5.3%)	144 (94.7%)	
Diagnosed with STI in past 6 months[b]						
No	205 (6.6%)	2918 (93.4%)	0.0011	156 (4.1%)	3654 (95.9%)	0.020
Yes	15 (16.5%)	76 (83.5%)		8 (9.9%)	73 (90.1%)	
Number of missing teeth[c]						
0	54 (5.0%)	1034 (95.0%)	<0.0001	29 (2.2%)	1278 (97.8%)	<0.0001
1-3	55 (7.4%)	689 (92.6%)		30 (3.6%)	800 (96.4%)	
4	38 (4.8%)	753 (95.2%)		51 (4.7%)	1045 (95.3%)	
≥5	91 (11.8%)	680 (88.2%)		61 (6.9%)	820 (93.1%)	

(Table 3 continues on next page)

Variables	Men N = 3396			Women N = 4121		
	LR HPV positive N = 238	HPV negative N = 3158	p-value	LR HPV positive N = 171	HPV negative N = 3950	p-value
(Continued from previous page)						
Presence of periodontitis/gingivitis[c]						
No	128 (5.7%)	2120 (94.3%)	<0.0001	106 (3.5%)	2895 (96.5%)	0.0010
Yes	110 (9.6%)	1036 (90.4%)		65 (5.8%)	1048 (94.2%)	
Lifetime number female sex partners[d]						
0	15 (4.6%)	310 (95.4%)	0.018	119 (4.3%)	2675 (95.7%)	0.078
1–5	64 (6.2%)	965 (93.8%)		13 (3.3%)	377 (96.7%)	
6–25	78 (8.2%)	869 (91.8%)		6 (7.5%)	74 (92.5%)	
≥26	33 (10.0%)	298 (90.0%)		2 (15.4%)	11 (84.6%)	
Number of new female sex partners last 6 months[d]						
0	137 (7.4%)	1727 (92.7%)	0.57	135 (4.3%)	3027 (95.7%)	0.24
1	32 (6.8%)	438 (93.2%)		2 (3.2%)	60 (96.8%)	
≥2	10 (5.4%)	177 (94.7%)		2 (12.5%)	14 (87.5%)	
Lifetime number of female oral sex partners						
0	35 (6.2%)	528 (93.8%)	0.16	148 (4.2%)	3351 (95.8%)	0.55
1–5	99 (6.5%)	1425 (93.5%)		11 (3.9%)	273 (96.1%)	
6–25	68 (8.6%)	723 (91.4%)		3 (7.9%)	35 (92.1%)	
≥26	18 (8.9%)	185 (91.1%)		0 (0.0%)	6 (100.0%)	
Number of new female oral sex partners last 6 months						
0	183 (7.2%)	2375 (92.8%)	0.81	160 (4.2%)	3613 (95.8%)	0.56
1	27 (7.0%)	358 (93.0%)		1 (2.9%)	34 (97.1%)	
2+	9 (5.8%)	147 (94.2%)		1 (7.1%)	13 (92.9%)	
Lifetime number of male sex partners						
0	192 (6.7%)	2666 (93.3%)	<0.0001	19 (4.7%)	386 (95.3%)	0.0052
1–5	12 (8.2%)	134 (91.8%)		72 (3.7%)	1856 (96.3%)	
6–25	8 (8.5%)	86 (91.5%)		50 (4.0%)	1209 (96.0%)	
≥26	10 (15.6%)	54 (84.4%)		17 (9.1%)	169 (90.9%)	
Number of new male sex partners last 6 months						
0	214 (7.0%)	2843 (93.0%)	0.77	122 (4.5%)	2579 (95.5%)	0.93
1	3 (7.3%)	38 (92.7%)		27 (4.1%)	633 (95.9%)	
≥2	5 (8.8%)	52 (91.2%)		7 (4.1%)	162 (95.9%)	
Lifetime number of male oral sex partners						
0	203 (6.8%)	2770 (93.2%)	0.42	26 (4.3%)	577 (95.7%)	0.74
1–5	1 (2.7%)	36 (97.3%)		36 (3.7%)	941 (96.3%)	
6–25	3 (10.3%)	26 (89.7%)		11 (3.8%)	280 (96.2%)	
≥26	2 (11.8%)	15 (88.2%)		2 (5.9%)	32 (94.1%)	
Number of new male oral sex partners last 6 months						
0	218 (7.0%)	2892 (93.0%)	0.15	131 (4.2%)	2965 (95.8%)	0.96
1	5 (16.7%)	25 (83.3%)		17 (4.2%)	390 (95.8%)	
≥2	3 (6.3%)	45 (93.8%)		4 (3.3%)	117 (96.7%)	
Sexual behavior[e]						
Heterosexual	181 (7.2%)	2331 (92.8%)	0.25	117 (4.1%)	2743 (95.9%)	0.72
Same sex	8 (8.8%)	83 (91.2%)		1 (2.0%)	48 (98.0%)	
Bisexual	21 (10.0%)	189 (90.4%)		22 (4.7%)	444 (95.3%)	

HPV, human papilloma virus; LR, low-risk; STI, Sexually Transmitted Infection. Non-HR genotypes include genotypes 11, 34, 40, 42, 43, 44, 53, 54, 66, 68, 73, 70, 74 and untypable. [a]Weakened immune system defined as participant reporting a blood disease, blood cancer, auto-immune disease or HIV, or if they were receiving corticosteroids, chemotherapy, biologic therapy or other immunosuppressants. [b]STI were defined as participant reporting having been diagnosed with at least one of the following: syphilis, gonorrhea, genital herpes, chlamydia, genital warts/condyloma, anal warts, skin warts (not on the genitals or anus), and/or trichomoniasis. [c]Data were reported by dentists after performing oral exam. [d]Data for female sexual partners in Germany is not included in the analysis due to misinterpretation of the questions by responders. [e]Participants were classified as engaging in *heterosexual* behavior if they were men who reported sex with ≥1 female sex partner and 0 male sex partners in their lifetime, or if they were women who reported sex with ≥1 male sex partner and 0 female sex partners in their lifetime; participants were classified as engaging in *same-sex* behavior if they exclusively reported sex in their lifetime with ≥1 person of their same sex. Participants were classified as engaging in *bisexual* behavior if they reported sex in their lifetime with ≥1 male and ≥1 female.

Table 3: **Bivariate analysis of low-risk (LR) HPV infection.**

	Category	OR	95% CI	AOR	95% CI	p-value	Global p-value
HR HPV infection among men (n = 2801/3273, 14.4% missing)							
Age	Years	1.04	1.02–1.06	1.04	1.02–1.06	<0.0001	<0.0001
Lifetime marijuana use	No	*REF*		*REF*	*REF*		0.0079
	Yes	1.71	1.12–2.60	1.92	1.19–3.11	0.0079	
Lifetime number of female oral sex partners	0	*REF*		*REF*	*REF*		0.017[c]
	1–5	0.86	0.44–1.65	0.68	0.35–1.33	0.26	
	6–25	2.36	1.25–4.44	1.48	0.76–2.89	0.25	
	≥26	3.51	1.66–7.44	2.10	0.95–4.61	0.066	
Country	Spain	*REF*		*REF*	*REF*		0.11
	Germany	1.74	0.79–3.83	1.94	0.83–4.51	0.13	
	France	2.19	1.00–4.79	1.97	0.85–4.61	0.12	
	UK	2.74	1.29–5.82	2.89	1.30–6.43	0.0095	
	USA	1.86	0.93–3.71	1.68	0.80–3.50	0.17	
HR HPV infection among women (n = 3605/3,992, 9.7% missing)							
Age	Years	1.00	0.97–1.02	1.00	0.97–1.03	0.97	0.97
Lifetime marijuana use	No	*REF*		*REF*	*REF*		0.015
	Yes	2.23	1.14–4.36	2.33	1.18–4.60	0.014	
Country	Spain	*REF*		*REF*	*REF*		0.015
	Germany	0.33	0.04–3.22	0.41	0.00–4.03	0.45	
	France	4.09	1.16–14.44	4.46	1.26–15.77	0.020	
	UK	2.37	0.61–9.22	2.26	0.56–9.08	0.25	
	USA	1.99	0.58–6.76	1.69	0.49–5.82	0.41	
LR HPV infection among men (n = 3213/3,396, 5.4% missing)							
Age	Years	1.05	1.04–1.06	1.04	1.03–1.06		<0.0001
Diagnosed with STI in past 6 months[a]	No	*REF*		*REF*	*REF*		0.0003
	Yes	2.81	1.59–4.98	3.05	1.68–5.54	0.0003	
Number of missing teeth[b]	0	*REF*		*REF*	*REF*		0.025[c]
	1–3	1.53	1.04–2.25	1.11	0.74–1.66	0.62	
	4	0.97	0.63–1.48	0.74	0.47–1.18	0.20	
	5 or 5+	2.56	1.81–3.64	1.44	0.98–2.12	0.062	
Country	Spain	*REF*		*REF*	*REF*		0.046
	Germany	1.38	0.82–2.32	1.37	0.80–2.35	0.25	
	France	1.78	1.06–2.98	1.55	0.90–2.66	0.12	
	UK	2.43	1.49–3.95	2.11	1.26–3.52	0.0043	
	USA	1.31	0.83–2.05	1.30	0.81–2.10	0.28	
LR HPV infection among women (n = 3648/4,121, 11.5% missing)							
Age	Years	1.04	1.03–1.06	1.05	1.03–1.06		<0.0001
Diagnosed with STI in past 6 months[a]	No	*REF*		*REF*	*REF*		0.0068
	Yes	2.57	1.22–5.42	2.93	1.34–6.39	0.0059	
Lifetime number of male oral sex partners	0	*REF*		*REF*	*REF*		0.044[c]
	1–5	0.79	0.47–1.32	0.77	0.45–1.32	0.35	
	6–25	0.84	0.49–1.44	0.80	0.45–1.39	0.42	
	≥26	2.04	1.04–4.03	1.72	0.85–3.49	0.13	
Country	Spain	*REF*		*REF*	*REF*		0.12
	Germany	1.50	0.82–2.76	1.47	0.75–2.89	0.26	
	France	1.31	0.71–2.43	1.42	0.73–2.74	0.30	
	UK	1.86	1.04–3.35	2.06	1.09–3.89	0.026	
	USA	1.25	0.74–2.12	1.20	0.67–2.14	0.55	

HPV, human papilloma virus; HR, high-risk; LR, low-risk; STI, Sexually Transmitted Infection. HR genotypes include genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. Non-HR genotypes include genotypes 11, 34, 40, 42, 43, 44, 53, 54, 66, 68, 73, 70, 74 and untypable. [a]STI were defined as participant reporting having been diagnosed with at least one of the following: syphilis, gonorrhea, genital herpes, chlamydia, genital warts/condyloma, anal warts, skin warts (not on the genitals or anus), and/or trichomoniasis. [b]Data were reported by dentists after performing oral exam. [c]p-value reported for ordinal variables correspond to the trend.

Table 4: **Multivariable regression model for factors associated with HR and LR HPV infection among men and women.**

across countries, and tended to be lowest in Spain and Germany and highest in the UK and France. There was also no common dominant genotype detected among women across countries. It is possible that higher prevalence in France is driven by a higher proportion of participants reporting bisexual behavior, heavy smoking and gingivitis and in UK by a higher proportion of participants reporting high number of sex partners and periodontitis, all of which have been associated with HPV infection.[10] In Germany and Spain, the lower prevalence may be driven by a higher proportion of participants reporting heterosexual sex and fewer with poor oral health. Further research is required to elucidate why differences in oral HPV prevalence occurred. However, findings highlight that there is heterogeneity in oral HPV prevalence and genotype distribution across Western European countries, which merit further country-specific HPV prevention efforts.

Findings from this study must be interpreted considering limitations. While the 105 dental sites represented many regions in each country, they were recruited via convenience sample, limiting generalizability of findings. Furthermore, the study's dental settings might introduce bias toward participants with higher socioeconomic levels because of their potential for better access to dental care.[30] Dentists collected self-reported HPV vaccination data which were not verified by medical records. Given the age distribution of participants in the present study, most participants were in age cohorts unlikely to have received HPV vaccination; in fact, self-report HPV vaccination rates were <5% in all countries. Due to limitations of self-report vaccination data and the low number of participants who self-reported as vaccinated, we did not stratify oral HPV prevalence by self-report vaccination status. While lifestyle and sexual behavior information was self-collected directly from participants to reduce social desirability bias, some variables related to sex, alcohol and smoking had missing data, which may also impact the identification of risk factors for HPV. Additionally, data were partially collected during time periods with stay-at-home orders associated with COVID-19 prevention programs (see Fig. 2). Studies worldwide reported decreases in sexual behavior during the COVID-19 pandemic.[31–35] Therefore, the current study may underestimate oral HPV prevalence. Participants in the US will be followed for a total of 24-months, which will allow the identification of any changes in prevalence post-pandemic. The study might miss the impact of unmeasured cofounding factors associated with HPV. To minimize this risk the list of potential predictors factors was exhaustively defined based on prior evidence and scientific guidance provided by HPV experts. Despite limitations, PROGRESS has several important strengths. PROGRESS is a large study spanning five countries, 105 clinical sites, all of which followed a standardized protocol, and included a large sample size of 7674 participants. Samples were collected using ORG samples, a more robust approach compared to tonsil brushings, and tested using SPF10 PCR-DEIA-LiPA25, which has high analytic sensitivity necessary to detect viral load in oral samples.[36] Findings represent some of the most robust estimates of oral HPV prevalence and risk factors in the US and Europe. Oral HPV infection is prevalent across the US and Europe, with increased prevalence among older men who may be at increased risk of developing OPSCC. HPV prevention efforts are critical to preventing OPSCC among men in the long-term.

Contributors

AG, MF, TW, HaM, HiM, CR, YC, NL, ML, MP, LA, EM, and MAP conceptualized the study and designed the study methodology. AG, BS, SP, LA, and MAP provided study materials, reagents, materials, lab samples, and instrumentation. BQ, GC, ML and MT contributed to data collection. MP, BQ, and ES led data curation, coding, and visualization; AG, MF, YC, MP, BQ, LA, MAP and ES contributed to data analysis and AG, MP, LA and MAP contributed to data validation. AG, BQ, LA, MAP, BS, GC and SP had access and verified the data. AG, MF, TW, HaM, HiM, CR, YC, NL, ML, MP, BQ, GC, SP, LA, EM, MAP and JS contributed to study supervision. GC, MF, NL, ML, MT, EM, and JS contributed to project administration. All co-authors contributed to manuscript drafting, reviewing and editing, and all authors approved the final version of the report.

Data sharing statement

Data from this study will not be made available to others.

Declaration of interests

MF, YC, JS and CR are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, USA and receives stock as part of long-term incentive. EM is an employee of MSD France, Pueaux, France. AG reports grants and consulting fees from MSD during the conduct of the study. TW reports personal fees from MSD during the conduct of the study. HaM reports personal and consulting fees from MSD during the conduct of the study. HiM reports personal fees from MSD during the conduct of the study, and other from AstraZeneca, MSD, Warwickshire Head Neck Clinic Ltd. and Docspert Ltd outside of the submitted work, participates on advisory boards with Seagen, Nanobiotix and MSD and has a leadership role on the Head and Neck International Group. HiM is a National Institute for Health Research (NIHR) Senior Investigator. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care. MT, ML, NL, PM and ES are employees of IQVIA, Real-World Solutions which received financial support from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, USA for the execution of this study. MAP's, LA's, GC's, BP's and SP's department, Cancer Epidemiology Research Program, has received sponsorship for grants from MSD, Roche, GSK, IDT, Hologic, and Seegene.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.103018.

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