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Might Oral Human Papillomavirus (HPV) Infection in Healthy Individuals Explain Differences in HPV-Attributable Fractions in Oropharyngeal Cancer? A Systematic Review and Meta-analysis

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Background. Differences in oral human papillomavirus (HPV) prevalence and contrasts in HPV-attributable fractions (AFs) in oropharyngeal cancer (OPC) have not been evaluated in depth.

Methods. A systematic review was performed to identify studies in which at least 50 healthy individuals were tested for oral HPV infection. Information on sex, age, tobacco/alcohol consumption, sex practices, specimen collection, HPV detection, and population type was extracted. Prevalences were pooled using random-effects models for meta-analyses of binomial data. Correlations were assessed by the Spearman test.

Results. Forty-eight reports comprising 28 544 individuals fulfilled inclusion criteria. Global oral HPV prevalence was 4.9%. Estimates were highest in Europe, although regional differences were not statistically significant. HPV16 prevalence was 1.0% globally, and regional differences became statistically significant. A lifetime history of >6 sex partners showed a higher risk of oral HPV infection. The age-specific HPV distribution revealed a prevalence of ≥5% over 40 years of age and a lower prevalence at younger ages. There was no association between oral HPV prevalence and HPV-AFs or age-standardized rates (ASRs) of OPC, genital HPV in healthy women, or tobacco use.

Conclusions. Differences in HPV-AFs or ASRs of OPC cannot be explained by differences in the prevalence of oral HPV infection across healthy populations. Consistent research on determinants of oral HPV prevalence, acquisition, clearance, and persistence is warranted.

Keywords. Oral; HPV infection; healthy population; head and neck cancer; meta-analysis.

Persistent oral human papillomavirus (HPV) infection is thought to be causally linked to the increasing rates of oropharyngeal cancer (OPC) in some regions of the world [1–5]. These rising trends have been observed in regions where tobacco consumption decreased [6] while the lifetime number of sex partners and the proportion of people with a history of performing oral sex increased over time [7–9]. HPV-attributable fractions (AFs) in cases of OPC are very heterogeneous, with the highest HPV-AFs observed in the United States and Northern Europe, young patients, and recent calendar periods [10–14]. Sex differences are also observed, with higher HPV-AFs in males or females, depending on the region [10–16].

Contrary to the high number of prevalence surveys on cervical HPV infection conducted in the past 20 years, equivalent surveys on oral HPV infection prevalence in healthy individuals are scarce. The first global estimate on the prevalence of oral infection derives from a systematic review published in 2010 [17] that conducted a simple pooling of 18 studies involving 4581 cancer-free subjects with an estimated overall oral HPV prevalence of 4.5%. The most frequently detected HPV type was HPV16 (1.3%). Two more recent systematic reviews with meta-analyses aimed to evaluate risk factors for oral HPV infection [18] and to synthesize data on the prevalence, incidence, clearance, and persistence of oral HPV infection in healthy population [19]. The estimated prevalences of oral HPV infection overall and due to HPV16 were 5.5% and 1.0%, respectively [18], and 7.7% and 1.4%, respectively [19]. All of those reviews

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included high-risk populations, such as female sex workers and sexually transmitted diseases clinic attendees [17, 18] or men who have sex with men and women who had gynecological lesions [18, 19], and had several limitations, such as the inability to provide age-specific prevalence and the underrepresentation of regions such as Asia, Latin America, and Africa. Moreover, none of the studies evaluated in detail the epidemiological differences in oral HPV infection across populations and the extent to which such differences can explain differences in HPV-AFs in OPC.

Therefore, we aimed to conduct a new systematic review applying sound meta-analysis techniques to provide age-, sex-, and type-specific global and regional estimates of the prevalence of oral mucosal alpha-type HPV infection in healthy individuals and to evaluate the potential influence and predictive value of oral HPV infection in healthy individuals on the estimated HPV-AFs and of OPC age-standardized rates (ASRs) at regional and national levels once differences in potential cofactors were considered.

METHODS

Search Strategy, Selection Criteria, and Data Extraction

The National Institutes of Health PubMed and Scopus search engines were used to identify articles that reported results of HPV testing of oral specimens collected from healthy individuals. Search criteria involved publication from 1 January 1995 through 19 May 2015 and the keywords "oral" AND ("papillomavirus" OR "HPV"). All articles reporting data on oral HPV prevalence in healthy individuals were selected. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses), MOOSE (Guidelines for Meta-analyses and Systematic Reviews of Observational Studies), and GATHER (Guidelines for Accurate and Transparent Health Estimates Reporting) checklists were followed [20–22]. The following exclusion criteria were used: studies involving subjects vaccinated against HPV, individuals with HPV-related pathology, and other high-risk populations (ie, prostitutes, drug users, partners of individuals of any HPV-related pathology, men who have sex with men, immunosuppressed populations, individuals recruited in sexually transmitted clinics); studies involving pregnant women or infants and children (age ≤13 years); studies that had HPV test results for <50 subjects and did not use DNA-based HPV testing methods; studies that did not provide information on the sex distribution of participants; commentaries; and systematic reviews. Cross-references were also reviewed to identify additional sources. When duplicate reports were identified, the one that had the largest sample size or presented more-detailed information was selected. For studies including multiple geographic locations, the data were separated by country, if possible.

Data were extracted by 2 investigators (M. M. and M. T.) independently and then reviewed by 2 investigators (L. B. and L. A.) for discrepancies. Covariates and categorization are described in Supplementary Table 1*a*. When possible, separate data on overall and type-specific HPV positivity were extracted by sex, country, age group, tobacco and alcohol consumption, oral sex practice, and lifetime number of sex partners. Additionally, authors were contacted to provide information on overall and type-specific HPV prevalence, disaggregated by sex and age groups, if such information was not included in the publication.

Statistical Analyses

We primarily focused on mucosal alpha-type HPV for overall estimates of oral infection, given the low prevalence of nonalpha types detected in head and neck cancer (HNC) [23, 24]. Thus, the estimation of the prevalence of cutaneous and nonalpha oral HPV infection was performed as a secondary objective of the meta-analysis. Overall oral HPV DNA prevalence includes all individuals with positive results of a broad-spectrum alpha-mucosal HPV DNA test. High-risk oral HPV DNA prevalence data comprised HPV DNA–positive cases involving ≥1 established high-risk type (ie, HPV16/18/31/33/35/39/45/51/52/56/58/59) [25]. The HPV DNA type–specific prevalence was estimated for types 6, 11, 16, 18, 26, 31, 33, 34, 35, 39, 40, 42, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, and 89 by dividing the number of cases positive for a specific type by the total number of cases tested for the specific type. Meta-analyses were conducted using *metaprop*, a statistical procedure in Stata 15, developed at the Unit of Cancer Epidemiology (Sciensano, Brussels) [26]. A random-effects model including Freeman-Tukey arcsine transformation of the prevalence was used to normalize variance. 95% confidence intervals (CIs) were computed around study-specific and pooled prevalences, based on the score-test statistic. The percentage of total variation because of interstudy heterogeneity was evaluated with the I^2 measure [27]. Sample size effects were evaluated by visual inspection of funnel plots, and plot asymmetry was assessed formally with the Egger test with R (version 3.2.3) [28]. A sample size calculation established 500 as the minimum number of tested individuals needed to produce an estimate. The data available from studies did not allow estimation of the prevalence of multiple infections. Countries were classified by income level, according to the United Nations classification [29]. Age-specific prevalences were transformed into 10-year age groups. Intrastudy relative risks (RRs) were pooled with the *metan* command in Stata 15 [30]. We planned to perform subgroup meta-analyses and meta-regression to explain interstudy heterogeneity [31] (Supplementary Figure 1). However, exploratory analyses using linear or logistic models revealed its unfeasibility because of the lack of data equally stratified for multiple covariates. Correlation analyses between our estimates of oral HPV infection and HPV-AFs in OPC [12, 13, 32, 33], ASRs of OPC in 2018 [34], and HPV-related HNC in 2012 [13], genital HPV in healthy women (Bruni et al,

unpublished data), and tobacco use in 2006 [6] were explored with the Spearman and Kendall τ tests.

RESULTS

A total of 2577 abstracts from the National Institutes of Health PubMed search engine and 2728 from the Scopus search engine, published between 1 January 1995 and 19 May 2015, were identified with the search strategy. After removing duplicates, 3226 abstracts were reviewed for inclusion, and 181 full-text articles were assessed for eligibility. A total of 56 studies were initially evaluated (Supplementary Figure 2). However, when performing the analysis by type of study, a statistically significant much higher overall oral HPV prevalence was obtained for studies in which subjects were controls unmatched to patients with cancer, as compared to studies in which subjects were age-matched controls, or individuals from a general population who were recruited in population-based surveys (Supplementary Figure 3). A sensitivity analysis was then performed by excluding the 8 studies in which individuals were unmatched controls, and these studies were excluded for further analyses because this group might be nonrepresentative of the general population. Thus, 48 studies contributing data for 28 544 healthy individuals were considered for the final analyses (Supplementary Table 2).

The estimated overall oral HPV prevalence of alpha mucosal types worldwide was 4.9% (95% CI, 3.7%–6.1%), with 1477 individuals positive for oral HPV infection, and ranged from 0.0% (95%CI .0%–3.7%) to 24.1% (95%CI 18.2%–31.1%). High heterogeneity was observed (I^2 = 94.7%; P < .001). Estimates were highest in Europe (6.5% [95% CI, 3.4%–10.5%]; 142 of 1967 individuals), followed by North America (5.1% [95% CI, 3.6%–6.8%]; 928 of 15 324 individuals), Latin America (4.6% [95% CI, 2.2%–6.7%]; 320 of 6635 individuals), and Asia (3.1% [95% CI, .7%–6.8%]; 58 of 3849 individuals), although differences between regions were not statistically significant (Figure 1A). Restriction of the analysis to high-risk HPV types revealed a prevalence of 2.6% (95% CI, 1.7%–3.5%; 686 of 23 286 individuals) globally (Figure 1B).

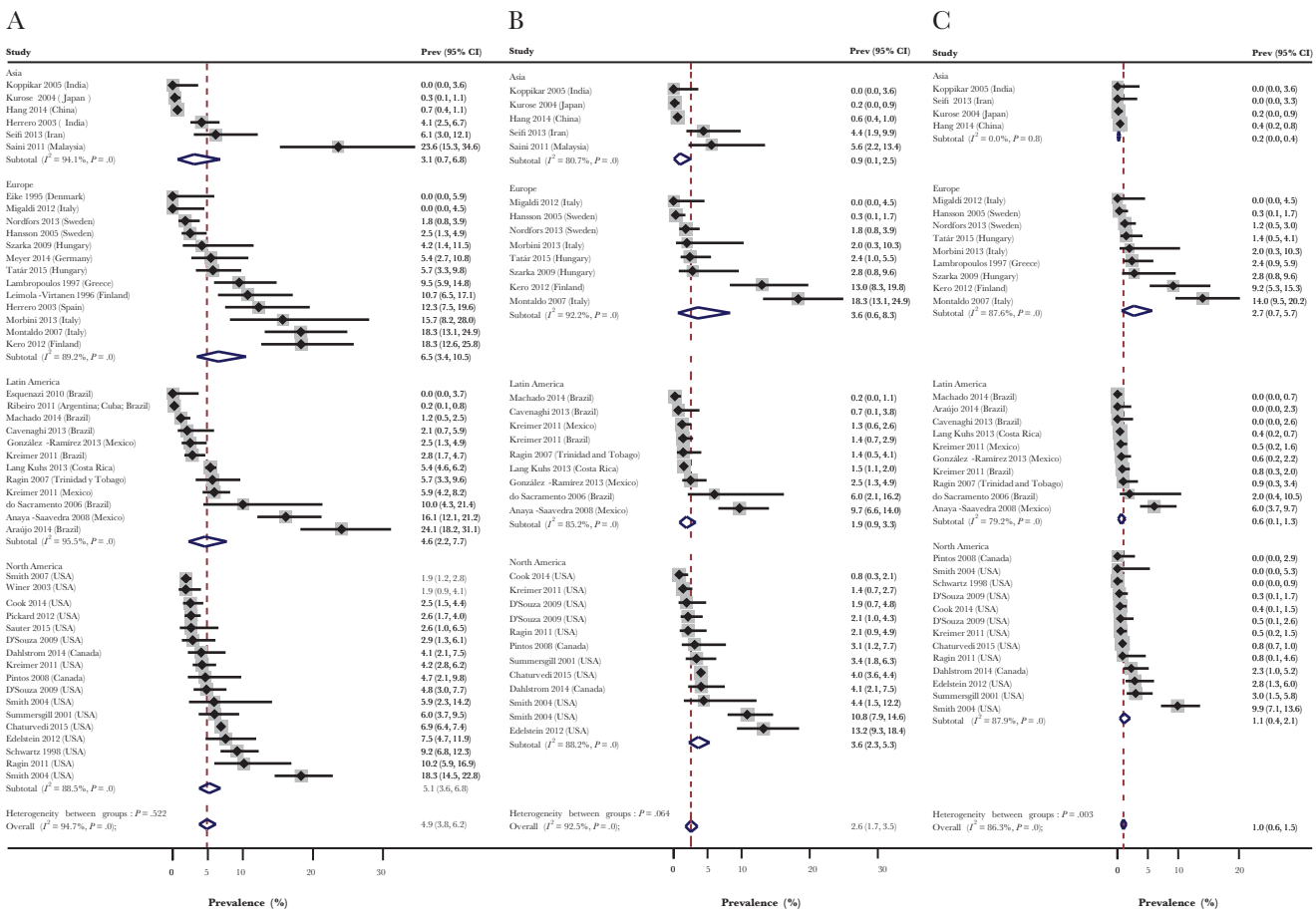

Figure 1. Prevalence of oral human papillomavirus (HPV) infection overall (*A*), due to high-risk types (*B*), and due to HPV16 (*C*), by region. Regional estimates and heterogeneity between groups have been estimated only for regions with >500 individuals. However, the global estimates include all studies testing >50 individuals. CI, confidence interval.

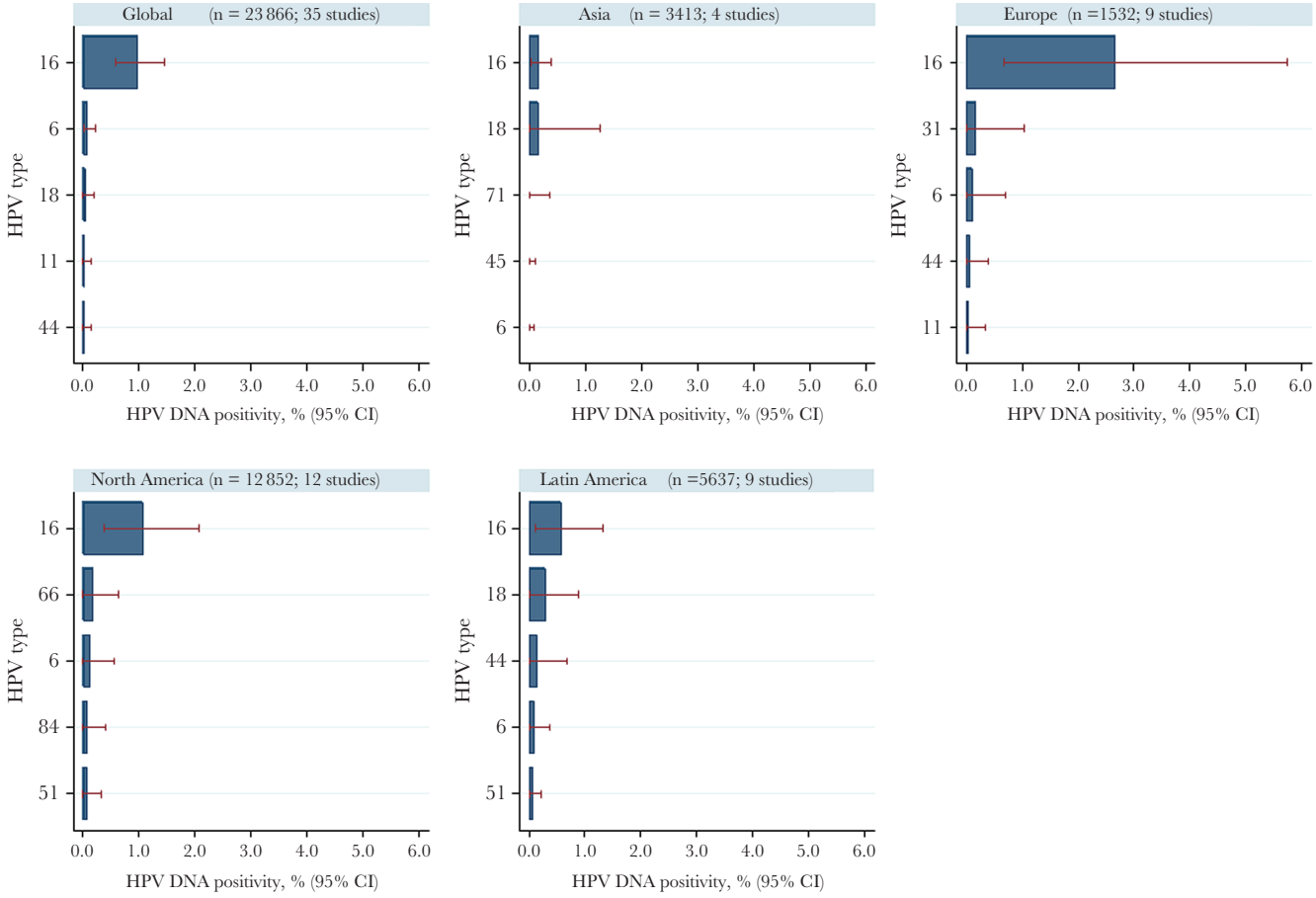

Figure 2. Distribution of oral human papillomavirus (HPV) types, by region. CI, confidence interval.

HPV16 was the most common type in all regions, with a worldwide prevalence of 1.0% (95% CI, .6%–1.5%; 242 of 23 866 individuals), and differences between regions were statistically significant (Figures 1C and 2). The next-most-common types were substantially less frequent and varied by region.

Figure 3 shows the pooled overall prevalence of oral HPV infection, stratified by country. Studies with the highest number of participants came from the United States, Costa Rica, and China. In the subregional analysis, Southern Europe was noted as the subregion with the highest overall estimates (9.5% [95% CI, 3.3%–18.1%]; $P < .001$; Table 1 and Supplementary Figure 5). In the analysis stratified by income, high-income regions showed a higher HPV16 HPV prevalence than middle-income regions ($P = .048$), whereas low-income regions were not represented in this meta-analysis (Table 1).

The prevalence of cutaneous and oral nonalpha HPV infection was lower than that of mucosal types, with estimated values of 1.8% (95%CI .6%–3.6%; based on 12 studies) and 0.7% (95%CI .1%–1.9%; based on 5 studies), respectively.

Age-specific information on the oral overall HPV prevalence was available for 27 publications contributing data for 11 493 individuals. The age group of <30 years had the highest number of observations (Figure 4). The age group of 50–59 years showed the highest prevalence estimates (7.5% [95%CI 4.8%–10.5%]), and observed differences between age groups were statistically significant ($P = .002$).

Table 1 summarizes estimates of the prevalence of oral infection overall, due to high-risk HPV types, and due to HPV16, stratified by select variables. HPV16 estimates differed by study design, with case-control studies having higher estimates than other designs. The highest overall HPV prevalence was observed in studies with the highest proportion of smokers in the sample. Statistically significant differences between estimates for all types, high-risk types, and HPV16, stratified by the proportion of participants who performed oral sex, were also observed. Finally, higher estimates of the overall prevalence of infection were noted when the when mean age of the study population was 25–39 years or >55 years as compared to <25 or >39 years. Other variables, such as last year of testing, proportion of male participants, or proportion of participants with a high lifetime number of sex partners, did not show statistically significant differences in the prevalence of oral infection overall, due to high-risk HPV types, or due to HPV16. Twenty-seven of 48 studies presented information on oral overall HPV prevalence stratified by sex. The prevalence

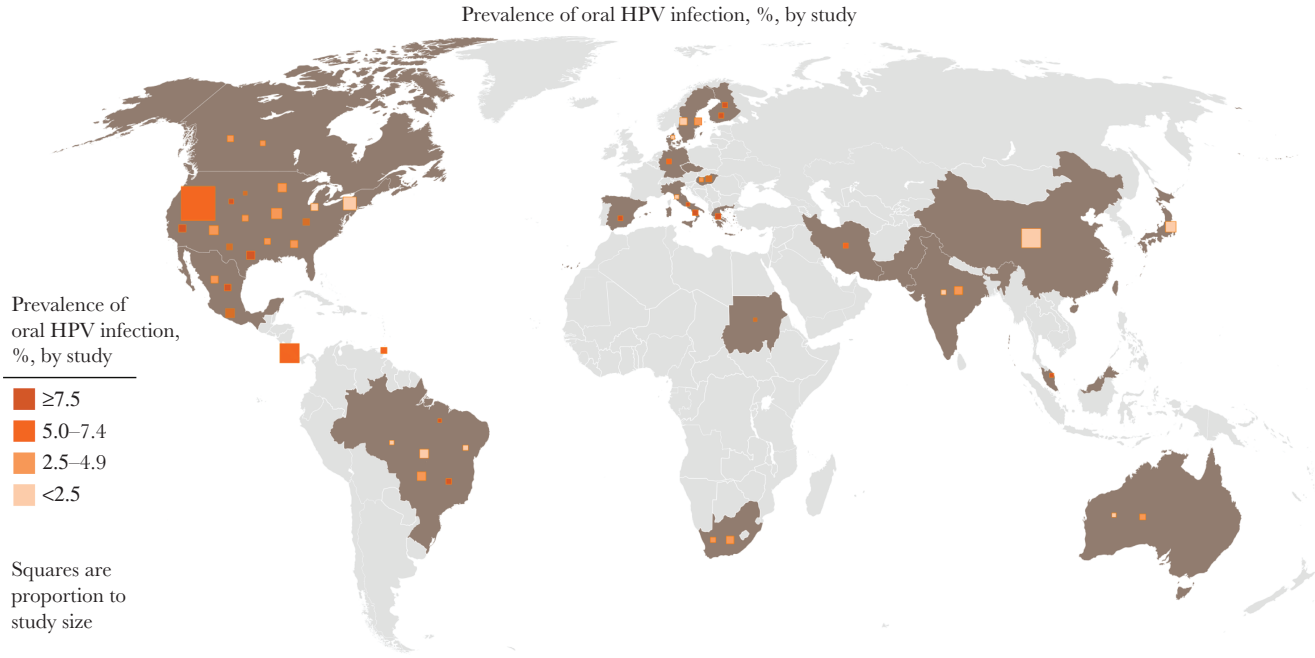

Figure 3. Distribution of studies on the overall prevalence of oral human papillomavirus (HPV) infection, by country. Each square corresponds to a study included in the meta-analysis. The size of the squares is proportional to the size of the study. The distribution of the squares within each country is arbitrary and does not correspond to the recruitment area of the studies.

of oral HPV infection in men and women was similar, with worldwide estimates of 4.3% (95%CI 2.7%–6.4%) and 3.8% (95%CI 2.6%–5.2%), respectively. When stratifying by type of study (ie, studies including only men, only women, or both sexes), estimates were similar, with the exception of slightly higher estimates in women for studies only testing women (Supplementary Table 3). Men in North America had double the risk of oral HPV infection as compared to women (RR, 2.0 [95%CI .99–4.0]; Table 2). A history of tobacco consumption was associated globally with a higher risk of oral HPV infection (RR, 1.4 [95% CI, .9–2.4]), although this association did not reach statistical significance. An increased RR for having a high versus low lifetime number of sex partners was observed globally (2.27 [95%CI 1.34–3.85]) but not for ever performing versus never performing oral sex.

Sample size effects, suggestive of publication bias, were observed, with a higher prevalence of infection reported in smaller studies (Supplementary Figures 8 and 9). Correlation analyses between the prevalence of oral infection overall, due to high-risk types, or due to HPV16 and HPV-AFs in OPC, ASRs of OPC in 2018, and HPV-related HNC in 2012, genital HPV in healthy women, and tobacco use, stratified by country or region, did not show any correlation pattern (Figure 5 and Supplementary Table 4).

DISCUSSION

We are the first to present data on the prevalence of oral HPV infection with respect to several covariates, including age group, in healthy individuals. We used strict inclusion criteria to obtain a sample as representative as possible of the general population and to avoid bias and reduce heterogeneity. The most-appropriate meta-analytical techniques [26] were chosen, to provide robust estimates of oral HPV prevalence in the general populations. Associations between oral HPV and HPV AFs in OPC, ASRs of OPC in 2018, and HPV-related HNC in 2012, genital HPV in healthy women, or tobacco use, stratified by country and region, were explored for the first time with correlation analyses.

Globally, we estimated the prevalence of alpha mucosal oral HPV infection among healthy individuals to be 4.9% overall and the prevalences due to high-risk HPV and HPV16 to be 2.6% and 1.0%, respectively. HPV16, which is present in >90% of HPV-driven OPCs, was the most frequent type everywhere and the only one presenting statistically significant differences between regions, with Europe presenting the highest estimates. The age-specific prevalence presented a sigmoid pattern, reaching its peak among individuals aged 50–59 years. Differences in the prevalence oral HPV infection stratified by sex were observed only in North America. Having a high lifetime number of sex partners showed an increased RR for having oral HPV infection, but having a history of performing oral sex did not.

Correlation analyses did not show any association between oral HPV and HPV-AFs in OPC, ASRs of OPC, and HPV-related HNC, genital HPV in healthy women, or tobacco use.

Global estimates were similar to those of earlier systematic reviews [17, 18], despite their inclusion of high-risk individuals.

Table 1. Prevalence of Oral Human Papillomavirus (HPV) Infection Overall, Due to High-Risk Types, and Due to HPV16, by Select Variables

Variable	Studies, No.[a]	Participants, No.[b]	Oral HPV Prevalence, % (95% CI)					
			Overall	*P*[c]	High-Risk Types	*P*[c]	HPV16	*P*[c]
Overall	48	28 544	4.9 (3.7–6.1)		2.6 (1.7–3.5)		1.0 (.6–1.5)	
Region				*P-value*[c] = .522		*P-value*[c] = .064		***P-value*[c] = .003**
Latin America	11	6635	4.6 (2.2–7.7)		1.9 (.9–3.3)		0.6 (.1–1.3)	
North America	16	15 324	5.1 (3.6–6.8)		3.6 (2.3–5.3)		1.1 (.4–2.1)	
Asia	6	3849	3.1 (.7–6.8)		0.9 (.1–2.5)		0.2 (.0–.4)	
Europe	13	1967	6.5 (3.4–10.5)		3.6 (.6–8.3)		2.7 (.7–5.7)	
Subregion				***P-value*[c] = .001**		***P-value*[c] = .001**		***P-value*[c] = .045**
North America	16	15 324	5.1 (3.6–6.8)		3.6 (2.3–5.3)		1.1 (.4–2.1)	
Central America	4	4051	6.6 (3.5–10.7)		3.0 (1.0–5.9)		1.2 (.2–3.2)	
South America	6	1474	4.4 (.6–10.9)		0.9 (.0–2.7)		0.1 (.0–.7)	
Americas[d]	1	898	0.2 (.1–.8)		…		…	
Eastern Asia	2	3197	0.6 (.3–.9)		0.5 (.3–.7)		0.4 (.2–.6)	
Southern Asia	3	580	2.7 (.2–7.3)		…		…	
Northern Europe	5	978	4.9 (.9–11.5)		3.3 (.0–11.0)		2.3 (.0–7.6)	
Southern Europe	5	579	9.5 (3.3–18.1)		…		…	
Income				*P-value*[c] = .552		*P-value*[c] = .087		***P-value* = .048**
High income	31	18 171	5.2 (3.8–6.7)		3.3 (2.0–4.9)		1.4 (.7–2.3)	
Upper middle income	16	8959	5.3 (3.1–8.0)		1.8 (1.0–2.8)		0.5 (.2–1.0)	
Lower middle income	2	516	2.4 (.0–7.5)		…		…	
Study population				*P-value*[c] = .516		*P-value*[c] = .833		*P-value*[c] = .827
Age-matched controls	14	6782	5.4 (3.0–8.3)		2.8 (1.1–5.1)		1.1 (.1–2.8)	
Convenient samples from general population	14	4686	3.8 (2.6–5.2)		2.1 (1.1–3.3)		0.9 (.3–1.7)	
Convenient samples from outpatients	14	4072	5.8 (2.8–9.7)		2.6 (.6–5.7)		1.1 (.1–2.8)	
General population	7	13 004	4.8 (1.7–9.2)		3.2 (1.0–6.7)		0.7 (.3–1.3)	
Study design				*P-value*[c] = .332		*P-value*[c] = .057		***P-value*[c] = .020**
Case-control	9	2967	4.8 (1.4–9.9)		4.3 (1.1–9.3)		1.5 (.0–5.5)	
Clinical trial	1	2926	5.4 (4.6–6.2)		1.5 (1.1–2.0)		0.4 (.2–.7)	
Cohort	11	8020	3.6 (2.1–5.4)		3.0 (1.2–5.4)		1.0 (.4–1.9)	
Cross-sectional	28	14 631	5.5 (4.0–7.2)		2.1 (1.1–3.3)		0.8 (.4–1.5)	
Male sex, %				*P-value*[c] = .439		*P-value*[c] = .089		*P-value*[c] = .107
0–5	7	4309	5.1 (3.3–7.3)		1.4 (1.0–1.8)		0.3 (.1–.6)	
6–50	17	4303	4.2 (2.1–6.9)		3.7 (.7–8.5)		1.8 (.0–5.4)	
51–95	15	13 192	6.5 (4.4–9.1)		3.9 (.6–9.6)		2.2 (.0–9.8)	
>95	9	5643	4.2 (2.2–6.8)		2.6 (1.1–4.6)		0.9 (.3–1.7)	
Tobacco use, %				***P-value*[c] = .029**		*P-value*[c] = .668		*P-value*[c] = .953
6–50	20	17 325	6.0 (4.5–7.8)		3.1 (1.9–4.5)		1.0 (.6–1.6)	
51–95	9	4428	7.0 (2.7–13.1)		2.3 (.3–5.8)		0.8 (.0–2.8)	
Unknown	21	6691	3.2 (2.0–4.7)		2.0 (.7–3.9)		1.1 (.2–2.4)	
Alcohol use, %				*P-value*[c] = .565		*P-value*[c] = .934		*P-value*[c] = .578
6–50	9	4704	4.3 (1.4–8.6)		2.1 (.4–4.8)		0.5 (.0–1.5)	
51–95	8	1678	6.4 (3.1–10.7)		2.6 (.2–7.0)		0.8 (.0–4.1)	
Unknown	32	22 031	4.4 (3.3–5.6)		2.4 (1.5–3.4)		1.0 (.5–1.5)	
Oral sex performance, %				***P-value*[c] = .001**		***P-value*[c] = .001**		***P-value*[c] = .043**
0–5	1	2535	0.7 (.4–1.0)		0.6 (.3–.9)		0.4 (.2–.7)	
6–50	5	3548	7.3 (2.8–13.6)		3.6 (.4–9.5)		1.6 (.0–7.2)	
51–95	10	11 673	5.7 (3.6–8.3)		4.7 (1.9–8.4)		1.0 (.3–2.3)	
Unknown	34	10 788	4.5 (3.2–6.1)		2.1 (1.2–3.2)		0.9 (.4–1.6)	
High lifetime no. of sex partners, %				*P-value*[c] = .161		*P-value*[c] = .074		*P-value*[c] = .352
6–50	4	1307	6.5 (4.1–9.5)		4.7 (.5–12.6)		0.6 (.0–1.7)	
51–95	3	9833	8.6 (3.9–14.8)		6.1 (2.6–10.8)		3.1 (.2–8.5)	
Unknown	41	17 404	4.5 (3.2–5.9)		2.1 (1.3–3.0)		0.9 (.4–1.6)	
Collection method				*P-value*[c] = .754		*P-value*[c] = .350		*P-value*[c] = .361
Brush/swab	21	6605	5.1 (2.7–8.1)		2.0 (.8–3.7)		1.0 (.3–1.9)	

Table 1. Continued

Variable	Studies, No.[a]	Participants, No.[b]	Oral HPV Prevalence, % (95% CI)					
			Overall	*P*[c]	High-Risk Types	*P*[c]	HPV16	*P*[c]
Oral rinse	9	5139	4.2 (2.4–6.4)		2.4 (1.0–4.3)		1.1 (.1–2.7)	
Oral rinse and gargle	7	13 698	4.0 (2.7–5.6)		1.6 (.6–2.9)		0.5 (.3–.8)	
Brush/swab and oral rinse, gargle, or saliva	9	2824	5.3 (2.5–9.0)		5.0 (1.4–10.4)		0.8 (.0–2.6)	
Anatomic site				*P-value*[c] = .481		*P-value*[c] = .752		*P-value*[c] = .183
Oral mucosa	31	12 087	5.1 (3.5–7.1)		2.7 (1.5–4.3)		1.2 (.5–2.1)	
Oral and oropharyngeal mucosa	15	16 087	4.3 (2.9–6.0)		2.5 (1.4–3.9)		0.7 (.3–1.1)	
Last year of testing				*P-value*[c] = .663		*P-value*[c] = .356		*P-value*[c] = .142
2006	22	9535	5.2 (3.3–7.4)		3.3 (1.4–5.9)		1.6 (.4–3.3)	
2013	26	19 009	4.6 (3.2–6.3)		2.2 (1.3–3.3)		0.7 (.4–1.0)	
Age, y, mean				***P-value*[c] = .003**		*P-value*[c] = .257		*P-value*[c] = .367
<25	11	4835	2.8 (1.8–3.9)		2.3 (.6–4.9)		0.8 (.2–1.9)	
25–39	9	4889	8.6 (5.4–12.5)		4.9 (2.0–9.0)		1.8 (.3–4.2)	
40–54	13	14 234	3.9 (1.7–6.8)		1.4 (.4–3.0)		0.4 (.2–.8)	
>55	8	1597	6.5 (2.9–11.3)		2.1 (.3–5.1)		1.0 (.0–2.9)	
Unknown	10	2989	4.7 (1.6–9.2)		4.1 (.9–9.1)		1.2 (.0–4.1)	
DNA assessment				*P-value*[c] = .209		*P-value*[c] = .314		*P-value*[c] = .108
Yes	38	24 190	4.5 (3.3–5.9)		2.3 (1.4–3.4)		0.8 (.4–1.2)	
No	10	4354	6.5 (3.7–9.9)		3.6 (1.3–6.9)		2.1 (.4–4.7)	
>100 samples				*P-value*[c] = .242		*P-value*[c] = .848		
Yes	40	26 634	5.2 (3.9–6.6)		2.6 (1.7–3.6)		1.0 (.6–1.5)	
No	9	1910	3.1 (1.2–5.8)		2.4 (.6–5.1)		…	

Abbreviation: CI, confidence interval.

[a]Data are for studies contributing data on the overall prevalence of oral HPV. Studies contributing data on oral high-risk HPV or HPV16 prevalences are not shown.

[b]Data are for individuals tested for overall oral HPV. The number tested for oral high-risk HPV or HPV16 are not shown.

[c]For heterogeneity between groups within the variable. Groups with <500 cases have been excluded.

[d]Data are for 1 study, which included individuals from Argentina, Cuba, and Brazil and for which country-specific data were not specified.

However, our estimates are substantially lower than the most recently published estimate of 7.7% [19].

In agreement with Kreimer et al [17], we observed a similar overall prevalence for men and women. However, Shigeishi et al [18] and Tam et al [19] found a higher oral HPV prevalence in men than in women, as was observed in the US population-based National Health and Nutrition Examination Survey (NHANES) [35, 36], which represents the most robust estimate of oral HPV prevalence presented to date. Repeatedly, estimates from the United States have been generalized to the global population, because the most relevant insights of HPV-related OPC natural history mainly come from the United States [37]. Indeed, the United States contributed 52% of individuals included in the meta-analysis (Figure 3). Discrepancies on HPV prevalence with respect to sex between the US and global estimates are also observed in OPC [11, 12, 15].

Such discrepancies could be partially explained by differences in exposure to other risk factors, such as tobacco and alcohol use, or to differences in sexual behavior [14], as well as by other differences between studies. However, after exploring several meta-analytical strategies (Supplementary Figure 2), we could not adjust prevalence estimates by means of meta-regression, because of a lack of statistical power. Many studies defined and stratified covariates unequally, and few reported thoroughly stratified data. This is a general limitation inherent to meta-analyses of aggregated data extracted from published studies. To address this limitation, a meta-analysis of individual participant data should be performed.

If our results were accurate, immunological differences due to previous exposure to anogenital HPV infection or to differences in transmission effectiveness from men to women versus women to men could also explain the observed differences. A US study examining sex-based differences in risk factors for oral HPV infection observed that men but not women had a higher risk of HPV infection as the number of recent oral sex partners increased, whereas women but not men had a decreased risk of oral HPV infection as the lifetime number of vaginal sex partners increased [38]. Correlation analyses were performed to explore these hypotheses, as well as whether differences in HPV AFs or ASRs in OPC or HPV-related HNC could be explained by differences on oral HPV prevalence across healthy populations. However, we did not find any significant correlation suggesting that the observed differences were due to methodological and age differences between studies or to more-complex

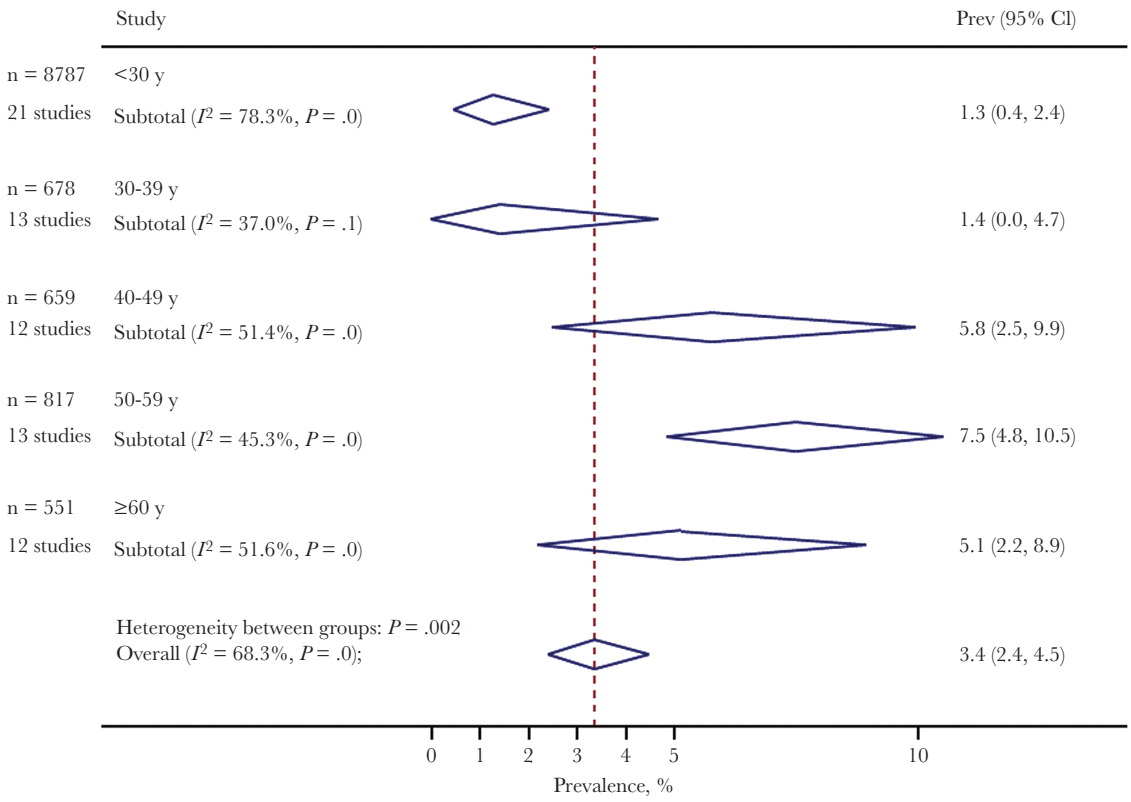

Figure 4. Age-specific prevalence of oral human papillomavirus infection overall. CI, confidence interval.

interactions between competing factors and determinants of clearance and persistence. Noteworthy, the gap between oral HPV infection and onset of HPV-related OPC may reach up to 20 years, and, thus, cohort effects may also play a role. A recent systematic review of the incidence and clearance of oral HPV infection noted that estimates varied notably between regions [39]. Previous data showed that male sex, older age, current smoking [40], some medications with immunomodulatory effects [41], and HPV16 integration [42] may play a role in oral HPV persistence in healthy individuals.

When comparing oral HPV by region, differences in overall estimates were not statistically significant. However, regional differences were statistically significant for HPV16 estimates, with the highest prevalences observed in Europe and North America, in line with what is observed in OPC.

In the age-specific analysis, the highest prevalence was observed at ages >50 years (Figure 4), following a sigmoid curve. When we performed an alternative analysis using the mean age of the study population instead of age-specific prevalences (Table 1), we found a bimodal pattern, although most of the CIs overlapped, and in our view the age-specific prevalence provides a more-robust estimate.

We made a special effort to retrieve information on a large collection of potential determinants in each study, such as risk factors, study design, or technical details of specimen collection and HPV testing methods. In contrast to a previous meta-analysis [19], we did not observe an increased prevalence with time, despite observing increased time trends in HPV-related OPC in some regions of the world [3, 4, 11]. The long clinical latency between HPV infection and oncogenesis could explain such discrepancies. Although oral brush or swab samples were previously found to provide insufficient DNA quality as compared to oral rinse and gargle specimens [43–46], we did not observe a higher HPV prevalence in oral rinse or gargle specimens than in brush or swab samples. However, a large study evaluating HPV prevalence in tonsil brushings and gargle specimens in cancer-free patients suggested that gargle specimens are not representative of the HPV prevalence in the tonsil [46].

Although few studies presented data stratified by sex, tobacco use, alcohol use, and sexual behavior, we could pool RRs by using a random-effect model. Globally, only a high lifetime number of sex partners showed a significantly higher risk of oral HPV infection. However, this finding mainly came from North American studies. A tendency of a higher risk of oral HPV infection was observed in ever smokers. We did not observe a higher RR of oral HPV infection among people with a history of performing oral sex as compared to those with no such history (Table 2), but oral HPV prevalences in studies with a higher proportion of individuals with a history of performing oral sex did show statistically significant higher prevalences

Table 2. Relative Risk of Oral Human Papillomavirus Infection Due to Any Type, by Risk Factor

Risk Factor	Studies, No.	Variable		Relative Risk (95% CI)
Sex		Male	Female	Male vs Female
Global	34	13 090	11 410	1.2 (.74–1.9)
Africa	3	289	193	0.7 (.1–7.1)
Asia	5	3152	616	1.1 (.5–2.4)
Europe	9	607	718	0.8 (.5–1.3)
Latin America	7	1893	3528	1.3 (.5–3.5)
North America	13	7149	6355	2.0 (1.0–4.0)[a]
Tobacco use		Yes	No	Yes vs No
Global	11	1566	2636	1.4 (.9–2.4)
Africa	2	69	106	1.2 (.3–4.5)
Asia	4	300	872	1.5 (.2–9.1)
Europe	1	80	34	0.8 (.3–2.1)
Latin America	0	…	…	…
North America	5	430	673	1.6 (.6–4.0)
Alcohol use		Yes	No	Yes vs No
Global	6	535	1286	1.3 (.7–2.4)
Africa	2	112	63	1.3 (.2–11.5)
Asia	4	158	1049	2.3 (.3–19.8)
Europe	1	94	20	1.3 (.3–5.3)
Latin America	0	…	…	…
North America	1	171	154	1.1 (.4–3.0)
Oral sex performance		Yes	No	Yes vs No
Global	8	2218	735	1.2 (.6–2.6)
Africa	2	54	121	1.2 (.3–4.4)
Asia	2	46	136	1.4 (.4–4.9)
Europe	…	…	…	…
Latin America	1	370	131	1.8 (.2–15.0)
North America	3	445	215	1.4 (.2–14.2)
Lifetime no. of sex partners		High	Low	High vs Low
Global	5	585	731	2.3 (1.3–3.9)
Africa	1	9	3	…[a]
Asia	1	2	4	…[a]
Europe	1	13	75	1.7 (.6–5.5)
Latin America	1	220	119	1.1 (.1–11.8)
North America	3	341	530	2.6 (1.4–4.8)

Abbreviation: CI, confidence interval.

[a]There were no positive cases for either variable.

(Table 1). A previous systematic review found that subjects with a history of tobacco use or performing oral sex had a significantly increased risk of oral HPV infection [18]. Higher risks of oral HPV infection in smokers have also been observed in large population-based studies, such as the NHANES in the United States [35] or the HIM study in Brazil, Mexico, and the United States [47].

Our study had some limitations. The large variability in the methods of specimen collection and processing and the small sample sizes of the studies limited the unequivocal assessment of the prevalence of oral HPV in healthy population. High heterogeneity was observed in most analyses, although we stratified by several covariates. However, the main strength of meta-analyses lies on their use as a comparative rather than a synthetic exercise [48], because statistical techniques cannot compensate for fundamental limitations of the input data but can help to identify patterns in study results and sources of heterogeneity. Another limitation was the unavailability of covariate-specific prevalence data. Moreover, overall and type-specific information on HPV infection was unequally distributed across the globe, with certain regions, especially Africa and Oceania, contributing only a few studies, including small series. We did not assess DNA extraction method as a covariate, but D'Souza et al found that different DNA purification methods showed different oral HPV prevalences [49]. A total of 34% of articles did not specify any recruitment period, and surrogate measures such as publication year could not be as precise as needed to assess time trends.

Our evaluation of the epidemiological landscape of oral HPV infection across different populations does not support that differences in HPV AFs in OPC could be explained by difference in oral HPV prevalence across healthy populations.

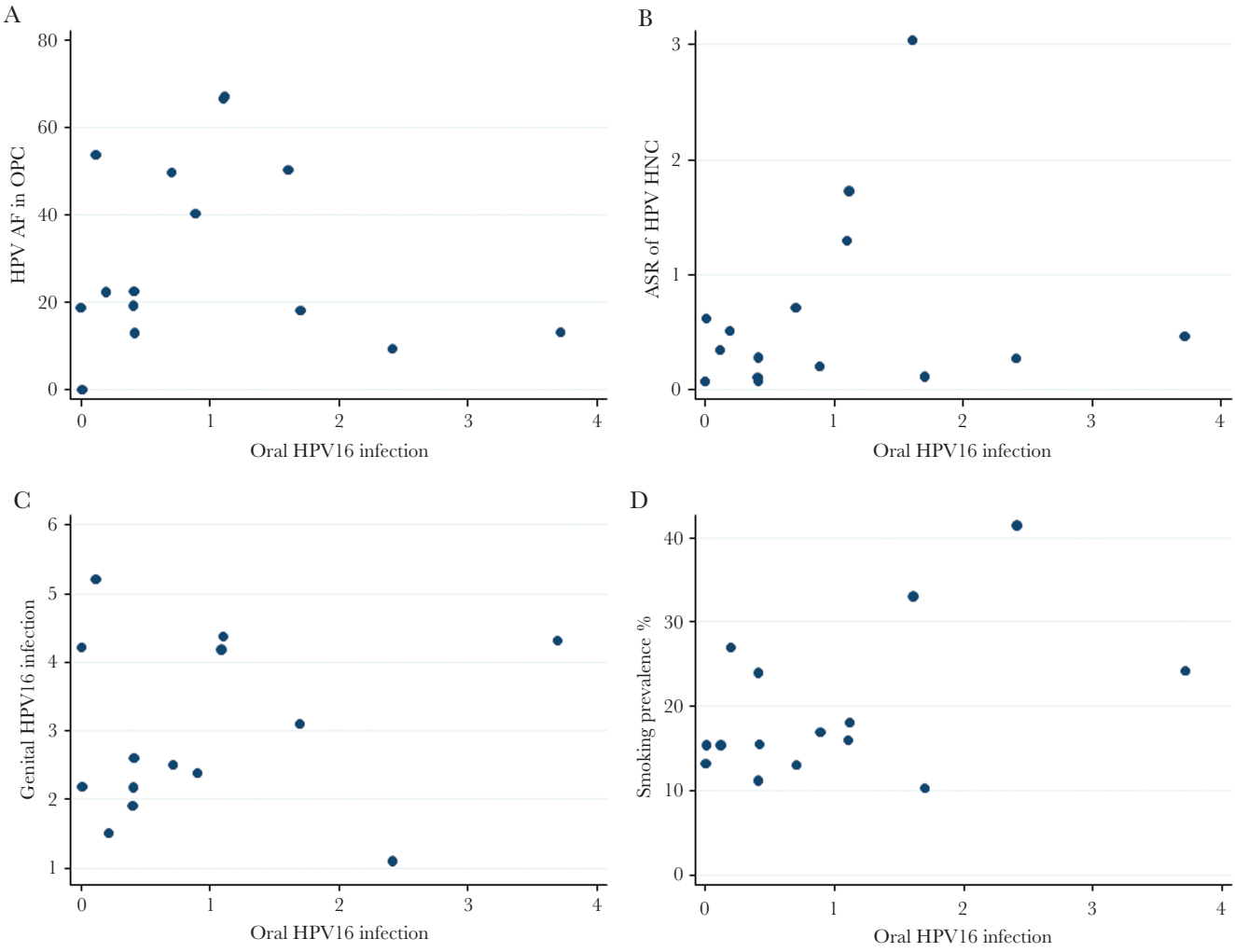

Figure 5. Correlation between oral human papillomavirus type 16 (HPV16) infection and HPV-attributable fraction (AF) of oropharyngeal cancer (OPC) (A), age-standardized incidence rate (ASR) of HPV-associated head and neck cancer (HNC) (B), genital HPV16 infection in healthy women (C), and smoking prevalence (D), by country . Countries with outlying estimates were excluded. Estimates for HPV-AFs were derived from Castellsagué et al [12] for all regions except North America, Southern Africa, Northern Africa, and Australia and New Zealand AFs. For North America, AFs were derived from Jordan et al [32]; for Southern and Northern Africa, AFs were derived from de Martel et al [13]; and for Australia and New Zealand, AFs were derived from Hong et al [33]. Estimates of ASRs of HPV-related HNC in 2012 were derived from de Martel et al [13]. Estimates for genital HPV prevalence in healthy women were derived from Bruni et al (unpublished data). Estimates for tobacco use in 2006 were derived from Ng et at [6].

There is a need for more-detailed information from large and well-designed studies to make definitive conclusions on the determinants of HPV AFs in OPC, since its assessment from aggregated reports is challenging and because assessment via average parameters is prone to ecological fallacy. New developments of screening techniques for HPV-related HNC call for the identification of high-risk populations, with a view to optimizing prevention [50]. Thus, consistent research on the determinants of the prevalence, acquisition, clearance, and persistence of oral HPV infection is warranted to fill the gaps in knowledge of the HPV-related natural history of OPC.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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M. M., L. A., and L. B. designed the study. M. M., L. B., and M. T. did the literature searches and designed the data-extraction form. M. M. and M. T. extracted the data. L. B. and L. A. cross-checked the data extraction. L. M., M. M., M. A., and L. B. did the statistical analyses. L. B. and M. A. supervised the statistical

analyses. M. M. wrote the manuscript. All authors critically revised subsequent drafts and read and approved the submitted version.

Disclaimer. The funding sources had no role in the data collection, analysis, or interpretation of the results.

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References

1. Mehanna H, Beech T, Nicholson T, et al. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer–systematic review and meta-analysis of trends by time and region. Head Neck **2013**; 35:747–55.
2. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol **2011**; 29:4294–301.
3. Hammarstedt L, Lindquist D, Dahlstrand H, et al. Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer. Int J Cancer **2006**; 119:2620–3.
4. Hong AM, Grulich AE, Jones D, et al. Squamous cell carcinoma of the oropharynx in Australian males induced by human papillomavirus vaccine targets. Vaccine **2010**; 28:3269–72.
5. Arbyn M, de Sanjosé S, Saraiya M, et al. EUROGIN 2011 roadmap on prevention and treatment of HPV-related disease. Int J Cancer **2012**; 131:1969–82.
6. Ng M, Freeman MK, Fleming TD, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. JAMA **2014**; 311:183–92.
7. Heck JE, Berthiller J, Vaccarella S, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Int J Epidemiol **2010**; 39:166–81.
8. Ryser MD, Rositch A, Gravitt PE. Modeling of US human papillomavirus (HPV) seroprevalence by age and sexual behavior indicates an increasing trend of HPV infection following the sexual revolution. J Infect Dis **2017**; 216:604–11.
9. Stenhammar C, Ehrsson YT, Åkerud H, Larsson M, Tydén T. Sexual and contraceptive behavior among female university students in Sweden - repeated surveys over a 25-year period. Acta Obstet Gynecol Scand **2015**; 94:253–9.
10. Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of human papillomavirus-positive head and neck squamous cell carcinoma. J Clin Oncol **2015**; 33:3235–42.
11. Ndiaye C, Mena M, Alemany L, et al. HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis. Lancet Oncol **2014**; 15:1319–31.
12. Castellsagué X, Alemany L, Quer M, et al.; ICO International HPV in Head and Neck Cancer Study Group. HPV involvement in head and neck cancers: comprehensive assessment of biomarkers in 3680 patients. J Natl Cancer Inst **2016**; 108:djv403.
13. de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer **2017**; 141:664–70.
14. Castellsagué X, Mena M, Alemany L. Epidemiology of HPV-positive tumors in Europe and in the World. Recent Results Cancer Res **2017**; 206:27–35.
15. Combes JD, Chen AA, Franceschi S. Prevalence of human papillomavirus in cancer of the oropharynx by gender. Cancer Epidemiol Biomarkers Prev **2014**; 23:2954–8.
16. Leemans CR, Snijders PJF, Brakenhoff RH. The molecular landscape of head and neck cancer. Nat Rev Cancer **2018**; 18:269–82.
17. Kreimer AR, Bhatia RK, Messeguer AL, González P, Herrero R, Giuliano AR. Oral human papillomavirus in healthy individuals: a systematic review of the literature. Sex Transm Dis **2010**; 37:386–91.
18. Shigeishi H, Sugiyama M. Risk factors for oral human papillomavirus infection in healthy individuals: a systematic review and meta-analysis. J Clin Med Res **2016**; 8:721–9.
19. Tam S, Fu S, Xu L, et al. The epidemiology of oral human papillomavirus infection in healthy populations: a systematic review and meta-analysis. Oral Oncol **2018**; 82:91–9.
20. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol **2009**; 62:1006–12.
21. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for

reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA **2000**; 283:2008–12.
22. Stevens GA, Alkema L, Black RE, et al.; The GATHER Working Group. Guidelines for accurate and transparent health estimates reporting: the GATHER statement. Lancet **2016**; 388:e19–23.
23. Félez-Sánchez M, Vergara M, de Sanjosé S, Castellsagué X, Alemany L, Bravo IG; VVAPO/RIS HPV TT study groups. Searching beyond the usual papillomavirus suspects in squamous carcinomas of the vulva, penis and head and neck. Infect Genet Evol **2016**; 45:198–204.
24. Agalliu I, Gapstur S, Chen Z, et al. Associations of oral α-, β-, and γ-human papillomavirus types with risk of incident head and neck cancer. JAMA Oncol **2016**. doi: 10.1001/jamaoncol.2015.5504.
25. World Health Organization. IARC monographs on the evaluation of carcinogenic risks to humans: volume 100B-biological agents. Lyon: International Agency for Research on Cancer, **2012**.
26. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health **2014**; 72:39.
27. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ **2003**; 327:557–60.
28. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ **1997**; 315: 629–35.
29. Population Division, Department of Economic and Social Affairs, United Nations Secretariat. World population prospects: the 2005 revision. New York, NY: United Nations, **2005**.
30. Harris R, Bradburm M, Deeks J, Harbord RM, Altman DG, Sterne JAC. metan: fixed- and random-effects meta-analysis. Stata J **2008**; 8: 3–26.
31. Harbord R, Higgins JP. Meta-regression in Stata. Stata J **2013**; 8: 493–519.
32. Jordan RC, Lingen MW, Perez-Ordonez B, et al. Validation of methods for oropharyngeal cancer HPV status determination in US cooperative group trials. Am J Surg Pathol **2012**; 36:945–54.
33. Hong AM, Grulich AE, Jones D, et al. Squamous cell carcinoma of the oropharynx in Australian males induced by human papillomavirus vaccine targets. Vaccine **2010**; 28:3269–72.
34. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin **2018**; 68:394–424.
35. Gillison ML, Broutian T, Pickard RK, et al. Prevalence of oral HPV infection in the United States, 2009-2010. JAMA **2012**; 307:693–703.
36. McQuillan G, Kruszon-Moran D, Markowitz LE, Unger ER, Paulose-Ram R. Prevalence of HPV in adults aged 18–69: United States, 2011–2014. NCHS data brief, no 280. Hyattsville, MD: National Center for Health Statistics, **2017**.
37. Chung CH, Bagheri A, D'Souza G. Epidemiology of oral human papillomavirus infection. Oral Oncol **2014**; 50:364–9.
38. D'Souza G, Wentz A, Kluz N, et al. Sex differences in risk factors and natural history of oral human papillomavirus infection. J Infect Dis **2016**; 213:1893–6.
39. Wood ZC, Bain CJ, Smith DD, Whiteman DC, Antonsson A. Oral human papillomavirus infection incidence and clearance: a systematic review of the literature. J Gen Virol **2017**; 98:519–26.
40. Beachler DC, Sugar EA, Margolick JB, et al. Risk factors for acquisition and clearance of oral human papillomavirus infection among HIV-infected and HIV-uninfected adults. Am J Epidemiol **2015**; 181:40–53.
41. Lam JO, Sugar EA, Cranston RD, et al. The association of medication use with clearance or persistence of oral HPV infection. Cancer Causes Control **2016**; 27:1491–8.
42. Lorenzi A, Rautava J, Kero K, et al. Physical state and copy numbers of HPV16 in oral asymptomatic infections that persisted or cleared during the 6-year follow-up. J Gen Virol **2017**; 98:681–9.
43. Rogers NL, Cole SA, Lan HC, Crossa A, Demerath EW. New saliva DNA collection method compared to buccal cell collection techniques for epidemiological studies. Am J Hum Biol **2007**; 19:319–26.
44. Chai RC, Lim Y, Frazer IH, et al. A pilot study to compare the detection of HPV-16 biomarkers in salivary oral rinses with tumour p16(INK4a) expression in head and neck squamous cell carcinoma patients. BMC Cancer **2016**; 16:178.
45. Herrero R, Castellsagué X, Pawlita M, et al.; IARC Multicenter Oral Cancer Study Group. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. J Natl Cancer Inst **2003**; 95:1772–83.
46. Combes JD, Dalstein V, Gheit T, et al.; SPLIT study group. Prevalence of human papillomavirus in tonsil brushings and gargles in cancer-free patients: The SPLIT study. Oral Oncol **2017**; 66:52–7.
47. Kreimer AR, Pierce Campbell CM, Lin HY, et al. Incidence and clearance of oral human papillomavirus infection in men: the HIM cohort study. Lancet **2013**; 382:877–87.
48. Greenland S. Can meta-analysis be salvaged? Am J Epidemiol **1994**; 140:783–7.
49. D'Souza G, Sugar E, Ruby W, Gravitt P, Gillison M. Analysis of the effect of DNA purification on detection of human papillomavirus in oral rinse samples by PCR. J Clin Microbiol **2005**; 43:5526–35.
50. D'Souza G, McNeel TS, Fakhry C. Understanding personal risk of oropharyngeal cancer: risk-groups for oncogenic oral HPV infection and oropharyngeal cancer. Annals Oncol **2017**; 28:3065–9.