

UCSF

UC San Francisco Previously Published Works

Title

Prevalence, genotyping, and correlates of anogenital HPV infection in a population-based sample of women in Puerto Rico

Permalink

<https://escholarship.org/uc/item/1740j63r>

Authors

Ortiz, AP
Romaguera, J
Pérez, CM
[et al.](#)

Publication Date

2016-12-01

DOI

10.1016/j.pvr.2016.04.002

Peer reviewed



Prevalence, genotyping, and correlates of anogenital HPV infection in a population-based sample of women in Puerto Rico



A.P. Ortiz^{a,b,*}, J. Romaguera^c, C.M. Pérez^b, D. González^b, C. Muñoz^a, L. González^d, E. Marrero^a, G. Tortolero-Luna^{a,c}, E. Suárez^b, J. Palefsky^e

^a Cancer Control and Population Sciences Program, Comprehensive Cancer Center, University of Puerto Rico, United States

^b Department of Biostatistics and Epidemiology, Graduate School of Public Health, Medical Sciences Campus, University of Puerto Rico, United States

^c Department of OBGYN, School of Medicine, Medical Sciences Campus, University of Puerto Rico, United States

^d Puerto Rico Clinical and Translational Research Consortium, Medical Sciences Campus, University of Puerto Rico, United States

^e University of California, San Francisco (UCSF), United States

ARTICLE INFO

Article history:

Received 8 December 2015

Received in revised form

29 March 2016

Accepted 8 April 2016

Available online 26 April 2016

Keywords:

Anogenital HPV infection

Women

Hispanics

Puerto Rico

ABSTRACT

Background: Oncogenic HPV infection is associated to anogenital cancer. We estimate the prevalence and correlates of anogenital HPV infection among a population-based sample of women aged 16–64 years living in the metropolitan area of Puerto Rico.

Methods: 564 women completed face-to-face and computer assisted interviews and self-collected anal and cervical specimens. HPV DNA testing used MY09/MY11 consensus HPV L1 primers and beta-globin as an internal control for sample amplification. Positive specimens were typed by dot-blot hybridization.

Results: Weighted prevalence of cervical, anal, and cervical/anal co-infection was 29.4%, 38.6%, and 17.1%, respectively. The commonest oncogenic HPV types detected in the cervix and anus were: 68 (8% vs. 7%) and 16 (5.5% vs. 5.1%), correspondingly. Having ≥ 3 lifetime sexual partners (OR: 2.3; 95% CI: 1.5–3.5) and last year anal intercourse (OR: 1.6; 95% CI: 1.1–2.5) increased the odds of anogenital HPV infection. Cervical infection was independently associated to anal infection (OR: 3.0; 95% CI: 2.0–4.6).

Conclusions: Similar to others, our results confirm the burden of anogenital HPV infection in women and its relationship with sexual behavior. As vaccination increases, future studies should monitor changing trends in HPV infection in this population, and the relationship between anal and cervical HPV-related disease.

Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Background

Human papillomavirus (HPV) is mainly transmitted through sexual contact and it is common among the general population [1]. HPV genotypes are classified as High Risk (HR) or Low Risk (LR) types depending on their oncogenic potential, HR infections cause cervical and anal cancers [1–3]. The cervix and anus possess a transformation zone characterized by a metaplastic epithelial site, which make them susceptible for HPV infection [3]. HPV prevalence differs across geographical regions and depends on age distribution and sexual practices of the populations [4,5]. Despite the burden of HPV infection and its causal relationship with various cancers [1–3], there is no routine surveillance system for HPV.

Although HPV-16 is the most common HPV genotype at the time of cervical diagnosis of squamous cell carcinoma (SCC), HPV-18 is the type most strongly associated with adenocarcinoma [2]. Three vaccines have been licensed for the prevention of HPV infection and its related malignancies [6]. In order to assess the impact of HPV vaccination programs, it is essential to establish baseline estimates of the type-specific HPV prevalence in the general population [7–9].

Our group has documented a high burden of HPV-related cancers in Puerto Rico [10–13], as well as an elevated prevalence of high-risk sexual practices [14]. Having baseline information on the burden of cervical and anal HPV infections is important in order to measure the impact in the prevention and control of HPV infection and related malignancies in this population, which still has low vaccine uptake [15]. This study described the prevalence and correlates of cervical and anal HPV infections in a population-based sample of women living in the San Juan Metropolitan area (SJMA) of Puerto Rico.

* Correspondence to: University of Puerto Rico, Comprehensive Cancer Center & Department of Biostatistics and Epidemiology, Graduate School of Public Health, PO Box 365067, San Juan, PR 00936-5067, United States.

E-mail address: ana.ortiz7@upr.edu (A.P. Ortiz).

2. Methods

2.1. Study population

A detailed description of the design and methods of this study has been described elsewhere [16]. Briefly, 566 non-institutionalized women aged 16–64 years living in the SJMA of Puerto Rico participated in the study from August 2010 to May 2013. Participants were identified through a four-stage probability sample design of households in the SJMA: stage-1) systematic random selection of 50 census blocks groups; stage-2) random selection of one block from each census block group; stage-3) random selection of one segment of about 12–16 households on each census block was randomly selected; and stage-4) selection of one eligible woman per household. If more than one woman were eligible, selection was performed by simple random sampling. Women were not eligible to participate if they were HIV positive, pregnant, and/or were cognitive or physically impaired. All 566 participants signed the informed consent and completed study procedures. Of these, 564 provided adequate cervical and anal samples for HPV testing. All cervical specimens (100%) and 95% of anal specimens ($n=536$) were positive for the human β -globin, and thus suitable for HPV typing [16]. This study was approved by the Institutional Review Board of the Medical Sciences Campus, University of Puerto Rico.

2.2. Data collection procedures

After signing the informed consent, women completed a face-to-face interview and a self-administered questionnaire using an Audio Computer Assisted Self-Interview (ACASI) system. The face-to-face interview collected information on risk factors for anogenital HPV infection, including demographic and behavioral characteristics and reproductive and health history. The ACASI system was used to collect sensitive information on sexual practices, condom utilization, and drug use.

2.3. Biological specimens' collection

Anal and cervical specimens were self-collected. Each participant received a collection kit that included the necessary materials for self-collection. Additionally, staff personnel provided a verbal explanation and written instructions including diagrams, comparable to those used in past studies [17,18], to each participant. Upon completion of the study procedures, samples were stored at -70°C and shipped on dry ice to the University of California, San Francisco for HPV typing. After completing the study procedures, participants received educational material on HPV and HPV vaccine, and a monetary compensation for their time and effort.

2.4. Analysis of cervical and anal biological specimens

HPV DNA was purified from samples. HPV typing was performed using L1 consensus primer polymerase chain reaction (PCR) with MY09/MY11 primers sets and β -globin as an internal control for sample amplification. PCR products from positive samples were typed by dot-blot hybridization using 40 individual type-specific probes, including oncogenic HR HPV types as defined by the International Agency of Research on Cancer (IARC) (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) and non-oncogenic types LR (6/11, 26/69, 30, 32/42, 34, 53, 54, 57/2/27, 61, 62, 66, 67, 70, 71, 72, 73, 81, 82, 83, 84, 85, 86/87, 90/106, 97, 102/108, as well as 2 separate mixtures, mix1 contains 7/13/40/43/44/55/74/91, and mix2 contains 3/10/28/29/77/78/94 plus all those HPV types that hybridized only with the consensus probe). Samples that were positive for the consensus probe on the Linear Array (LA) HPV strip

were considered HPV positive and those that were negative for the consensus probe were considered HPV negative. Specimens with β -globin undetected were considered inadequate and were excluded from the analysis.

2.5. Statistical analysis

The variables cervical infection (yes/no) and anal infection (yes/no) were defined independently. In addition, participants were classified into one of four groups according to their cervical–anal HPV infection status: (1) no HPV infection in either site (Cervix–/Anus–), (2) HPV infection only in the anus (Cervix–/Anus+), (3) HPV infection only in the cervix (Cervix+/Anus–), and (4) HPV concurrent cervical/anal infection or co-infection (Cervix+/Anus+). The overall and type-specific HPV prevalence, for each group above, was estimated with 95% confidence intervals (95% CI) using a logistic regression model. In order to control for the effect of the sampling design on the prevalence estimation, a normalized weighting factor was considered in this model using the inverse probability of selection for each participant and the inverse probability of participation [16] as follows:

$$w_i = \frac{1/(f_1 \times f_2)}{\bar{w}}$$

where f_1 indicates the selection probability for each participant, f_2 is the rate of participation in each block, and \bar{w} is the mean final weight of the entire sample.

Meanwhile, the Kappa statistic was used to assess the concordance of the HPV types observed in the cervical and anal samples among women with co-infection. The chi-square statistic was used to assess differences in covariates across the four groups and an age-adjusted polytomous logistic regression model was used to quantify the magnitude of the association between cervical–anal HPV infection categories and covariates. Given the small sample size in each category, and thus limited statistical power for detecting differences in the groups HPV positive in different anatomical sites, a multivariate logistic regression model (MLRM) was also used to describe factors associated to any anogenital HPV infection, using those cervix–/anus– as the reference group. Furthermore, in order to assess the association between anal and cervical infection, another multivariate logistic regression model, adjusted by covariates significantly associated in the bivariate analysis to anal and cervical infection, was used. Variables that were significant ($p < 0.05$) in the bivariate analyses to the outcome variables for each case and those considered relevant based on the previous literature were included in the polytomous and MLRMs models to estimate the adjusted odds ratio (OR). The MLRMs were fitted using an estimable generalized equations approach for controlling the correlation between the measurements of women living in the same households block. Evaluation of interaction terms in these models was performed using the likelihood ratio test. The statistical package Stata (Version 13.0, College Station, TX, USA) was used to perform data management and all statistical analyses.

3. Results

3.1. Weighted HPV prevalence by anatomic site

The prevalence of cervical HPV infection (29.4%, 95% CI: 23.2–36.4%) was lower than anal HPV infection (38.6%, 95% CI: 30.1–47.9%). The prevalence of HR types in the cervix (8.4%, 95% CI: 5.6–12.6%) was lower than LR types (17.4%, 95% CI: 13.0–23.0%), while anal prevalence for HR and LR types was similar (12.5%, 95% CI: 8.4–18.3% and 12.3%, 95% CI: 8.7–17.3%, respectively). Meanwhile,

the weighted prevalence of HPV co-infection was 17.1% (95% CI: 12.6–22.8%), co-infection of HR types was 4.2% (95% CI: 2.1–8.2%) and of LR types was 6.4% (95% CI: 3.9–10.4%) (Table 1).

3.2. Distribution and concordance of HPV types

Among HPV infected women, 7% of cervical specimens and 15% of anal specimens were untyped. The commonest oncogenic HPV types detected in the cervix and anus were: 68 (8% vs. 7%) and 16 (5.5% vs. 5.1%), followed by 58 (4.5%) and 31 (3.5%) in the cervix and 51 (5.1%) and 18 (4.2%) in anus (Fig. 1). Among women with cervical and anal HPV co-infection (n=112), the highest prevalence of co-infection with HR types was for HPV 16 (4.5%), followed by 51 (2.7%) and 68 (2.7%); only 1.8% of women were co-infected with type 18. Meanwhile, for LR types, the highest prevalence of co-infection was for HPV 61 (4.5%), followed by HPV 62, 81, 82 and 83, all with 2.7%; only 0.9% was co-infected with HPV 6/11. Meanwhile, a high agreement percent (> 87%) was observed for each of the specific HPV types for which co-infection was detected (HR types: 16, 18, 51, 52, 56, 59 and 68, and LR types: 6/11, 32/42, 53, 54, 61, 62, 71, 72, 81, 82, 83, and Mix 1). Kappa estimates showed a marginal to good concordance (68: k=0.36, 16: k=0.56, and 51: k=0.47) for the most prevalent types in co-infected women; it was highest for HPV 82 (k=0.58) and 83 (k=0.65) (Data not shown).

3.3. Factors associated to anogenital HPV infection site

Among women with complete information on cervical and anal HPV infection status (n=536), 47% of them were negative to HPV in both anatomical sites, 21% were positive in both sites, 19% had only anal HPV infection, and 13% had cervical infection alone. Prevalence of HPV co-infection decreased with increasing age (Supplementary Table 1 and Fig. 2); women with co-infection were more likely to be younger (aged 16–34, 55%), had a lower annual family income (< \$20,000, 70%), had 3 or more lifetime sexual partners (87%), and were more likely to report current drug use (23%). Women with anal infection alone were more likely to have had anal sex in the last year (44%) and women with cervical infection alone reported to be current smokers (25%) (Supplementary Table 1).

The age-adjusted polytomous logistic regression model showed significant differences (p < 0.05) in the following characteristics: anogenital HPV infection status by age, education, marital status, health care coverage, age of sexual debut, lifetime number of sexual partners, last year anal sex, smoking and drug use (Table 2). Meanwhile, the fully adjusted multivariate logistic regression model showed that single women (adjusted odds ratio [OR_{adj}]=1.7, 95% CI: 1.0–2.7) and those divorced, separated or widowed (OR_{adj}=1.9, 95% CI: 1.2–3.1) were more likely to have anogenital HPV infection as compared to married women. In addition, the likelihood of HPV infection increased in women having 3 or more lifetime sexual partners (OR_{adj}=2.3, 95% CI: 1.5–3.5) and among women who had performed anal sex in the past 12 months (OR_{adj}=1.6, 95% CI: 1.1–2.5) (Table 2). Regarding the relationship between cervical and anal HPV infection, the covariate fully-adjusted logistic regression model showed that women with cervical HPV infection were more likely to have anal HPV infection (OR_{adj}: 3.0; 95% CI: 2.0–4.6) than those without cervical HPV infection, after adjustment by age, education, marital status, health care coverage, age of sexual debut, lifetime number of sexual partners, last year anal sex and drug use (p < 0.001; data not shown).

4. Discussion

This is the first study to describe the prevalence of anogenital

Table 1
Weighted prevalence of HPV Infection among women aged 16–64 years in the San Juan Metropolitan area, P.R. 2010–2013.

Site	n	Any		LR (with and without HR)		HR (with and without LR)	
		Prevalence (%) (95% CI)	Expected cases (95% CI)	Prevalence (%) (95% CI)	Expected cases (95% CI)	Prevalence (%) (95% CI)	Expected cases (95% CI)
Cervical (with and without anal infection)	564	29.4 (23.2–36.4)	107,480 (84,870–133,260)	17.4 (13.0–23.0)	63,650 (47,430–83,950)	8.4 (5.6–12.6)	30,890 (20,440–45,960)
Anal (with and without cervical infection)	536	38.6 (30.1–47.9)	141,170 (110,050–175,060)	12.3 (8.7–17.3)	45,110 (31,650–63,190)	12.5 (8.4–18.3)	45,840 (30,630–67,100)
Anal only (Cervical-/Anal+)	536	21.5 (14.1–31.3)	78,610 (51,730–114,380)	5.9 (3.7–9.4)	21,690 (13,480–34,410)	8.3 (5.1–13.4)	30,410 (18,490–48,930)
Cervical only (Cervical+/Anal-)	536	11.2 (7.7–15.9)	40,870 (28,220–58,220)	9.8 (6.6–14.2)	35,740 (24,300–51,770)	4.1 (2.5–6.6)	14,810 (8970–24,210)
Co-infection (Cervical+/Anal+)	536	17.1 (12.6–22.8)	62,550 (45,970–83,550)	6.4 (3.9–10.4)	23,420 (14,210–37,960)	4.2 (2.1–8.2)	15,440 (7780–30,010)

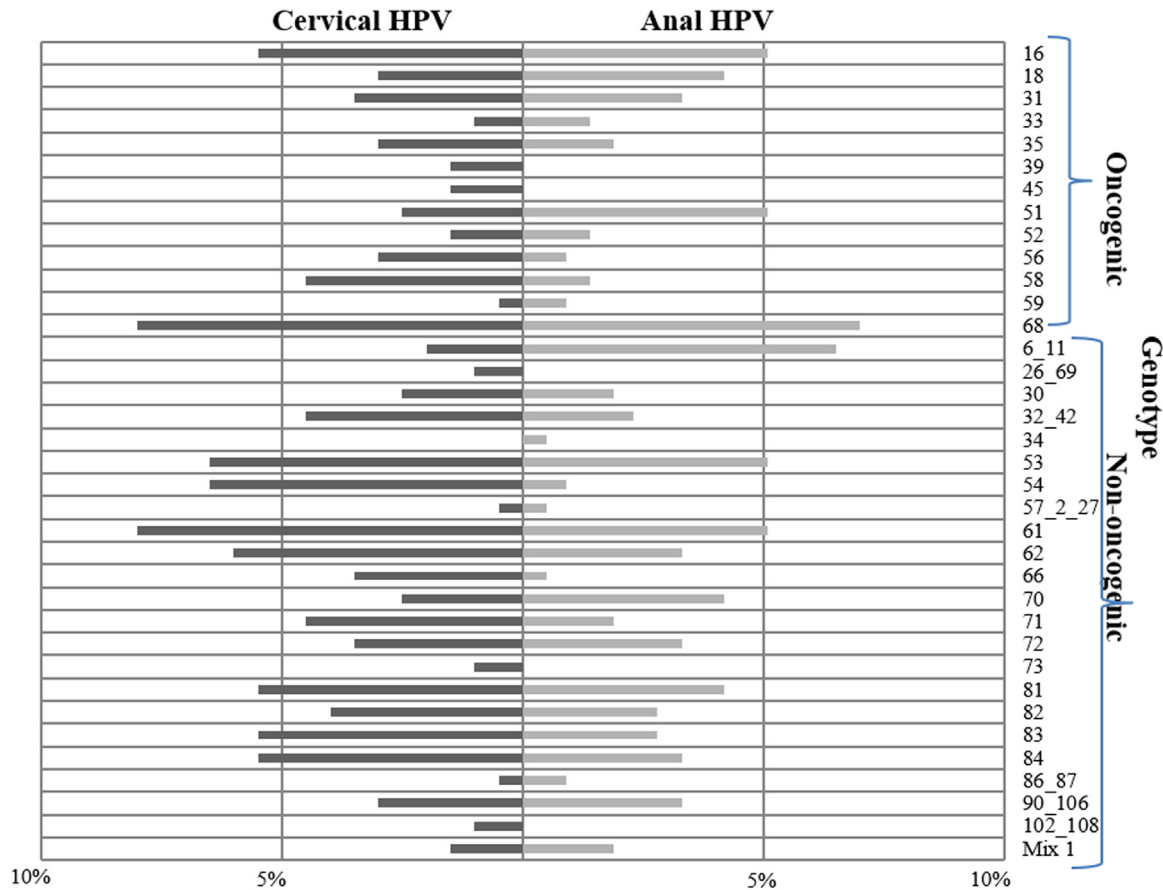


Fig. 1. Prevalence of HPV genotypes among positive women for each anatomical site.

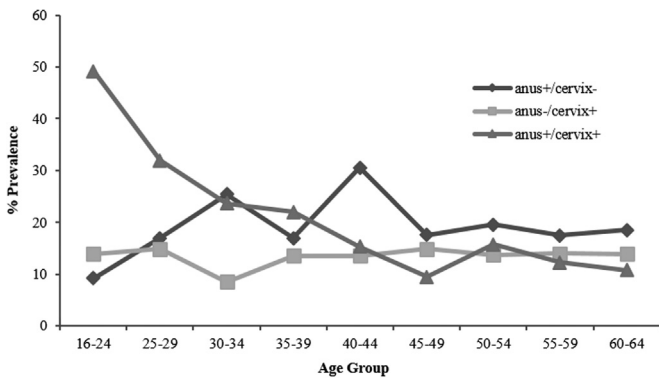


Fig. 2. Anogenital HPV infection by age group (n=536). Note: p-values for trend: anus+/cervix- = > 0.10; anus-/cervix+ = > 0.10; anus+/cervix+ = < 0.001.

HPV infection and the distribution of HPV genotypes among a population-based sample of Hispanic women living in Puerto Rico. Study results are of impact to this population, as they serve as baseline information on the burden of cervical and anal HPV infections, and will thus serve to monitor the impact of HPV vaccination in this population, as has been done in the USA with NHANES data [19]. Our results and their comparisons with other populations are summarized in Table 3. Overall, the prevalence of cervical HPV infection observed in our study in Puerto Rico (29.4%) was below the prevalence reported in the USA (NHANES, 2007–2010) among women aged 18–59 years (42%) [20]. Our estimate, when restricting the analysis to the 18–34 age group (48%, n = 174, data not shown), was similar to that reported in a clinic-based sample of women in that age group in Puerto Rico [17].

Meanwhile, our prevalence of cervical HPV infection is consistent with prior reports [21–23], although higher than others [24,25] (Table 3). Our results also showed a higher overall prevalence of LR HPV infection (17%) than HR infection (8%) in the cervix, similar to other studies [21,22], but contrary to others [23,24]. Regarding prevalence of anal HPV infection, our estimate (39%) is higher than that described in other reports [23,25,26], although similar prevalence was observed when compared to the clinic-based study in Puerto Rico, when restricting the analysis to the same age group (52%, n = 166, data not shown) [17]. Nonetheless, contrary to the cervix, the overall prevalence of HR and LR infections was similar in the anus (12%); the Hawaiian study reported an overall higher LR than HR infection [23]. It is important the future studies try to assess the reasons for the differences in HPV prevalence between the anus and the cervix, including the reasons for the differences in HR vs. LR types in different anatomical sites. For example, in cervix, HPV infection has been associated to vaginal pH and specific vaginal microbiota [27–29], thus, differences in vaginal and anal microbiota could also account for these differences; more research is warranted in this area.

Among other comparisons, the prevalence in our study of HPV co-infection (cervix and anus), and of infection only in the anus, were higher than the one reported in Hawaii (21% vs. 13% and 19% vs. 14%, respectively), although cervical infection alone was similar in both studies (13% vs. 14%) [23]. The prevalence of co-infection of younger women from Costa Rica (20%) was similar to ours, but they reported a lower prevalence of anal infection than cervical infection [26], contrary to our finding. These differences could be the result of the high prevalence of lifetime anal sex reported in our population (70%) vs. the low practice of this behavior in Hawaii (21%) and Costa Rica (21%) [23,26]. American Samoa reported

Table 2

Age-adjusted associations of cervical–anal HPV infection status with demographic, sexual, and lifestyle characteristics and magnitude of the association between anogenital infection and different variables.

Variables	Age-adjusted polytomous regression models ^a (n=536)				Multivariate logistic regression model ^b (n=564)
	Reference (Cervix-/Anus-)	Cervix-/Anus+ OR ^a (95% CI)	Cervix+/Anus- OR ^a (95% CI)	Cervix+/Anus+ OR ^a (95% CI)	Any Anogenital Infection OR ^b (95% CI)
Age					
16–34	1.0				1.0
35–49		0.9 (0.5–1.6)	0.8 (0.4–1.6)	0.3 (0.2–0.5)[†]	0.7 (0.4–1.1)
50–64		0.7 (0.4–1.3)	0.72 (0.4–1.4)	0.2 (0.1–0.4)[†]	0.7 (0.4–1.2)
Education					
≥ 12 years	1.0				1.0
< 12 years		1.8 (1.0–3.4)[‡]	1.6 (0.7–3.3)	2.5 (1.4–4.6)[†]	1.3 (0.7–2.3)
Marital status					
Married/LT	1.0				1.0
Div/Sep/widow		2.3 (1.3–4.1)[†]	4.5 (2.3–8.7)[†]	3.2 (1.7–6.1)[†]	1.9 (1.2–3.1)[†]
Single		1.2 (0.6–2.3)	2.3 (1.1–4.8)[†]	2.5 (1.4–4.5)[†]	1.7 (1.0–2.7)[†]
Health care coverage					
Private	1.0				1.0
Public		1.8 (1.1–3.0)[†]	2.1 (1.2–3.8)[†]	1.9 (1.2–3.1)[†]	1.5 (1.0–2.3)[‡]
None		1.2 (0.5–2.8)	2.2 (1.0–5.2) [‡]	0.9 (0.4–2.2)	1.1 (0.6–2.0)
Age of sexual debut					
≥ 15 years	1.0				1.0
< 15 years		1.7 (0.8–3.3)	1.2 (0.5–2.9)	2.2 (1.2–4.1)[†]	1.1 (0.6–1.9)
Lifetime sexual partners					
1–2	1.0				1.0
≥ 3		2.5 (1.5–4.3)[†]	1.9 (1.1–3.4)[†]	4.5 (2.4–8.3)[†]	2.3 (1.5–3.5)[†]
Last year anal intercourse					
No	1.0				1.0
Yes		2.2 (1.3–3.7)[†]	1.3 (0.7–2.4)	1.5 (0.9–2.4)	1.6 (1.1–2.5)[†]
Current drug user					
No	1.0				1.0
Yes		1.4 (0.7–2.9)	1. (0.6–3.2)	2.0 (1.1–3.8)[†]	1.3 (0.7–2.3)
Current smoking					
No	–				1.0
Yes		1.6 (0.9–3.0)	2.2 (1.1–4.1)[†]	1.6 (0.9–3.0)	0.8 (0.5–1.4)
Current drinking					
No	–				1.0
Yes		1.0 (0.6–1.6)	1.4 (0.8–2.4)	1.6 (0.9–2.6)[‡]	1.1 (0.7–1.6)
Lifetime same sex partner					
No	–				1.0
Yes		1.7 (0.7–4.2)	1.2 (0.4–3.7)	2.3 (1.0–5.3)[‡]	1.5 (0.7–3.2)

[†] $p < 0.05$.[‡] $0.05 < p < 0.1$.^a The age-adjusted Odds Ratio were estimated by a polytomous logistic regression model having women without infection as the reference category, analysis was performed among women with paired anal and cervical samples.^b The Odds Ratio was adjusted by all risk factors presented in the above MLRM column.

the lowest HPV co-infection rate (4%); however, this study did not include information on anal sexual behavior, because it was considered sensitive by the community members [25]. However, they report traditional cultural lifestyles and lower risk sexual practices, including higher age of sexual debut (20.5 years) [25]. We recognize that these and other comparisons with other populations need to be made with caution, as differences in study period, age of study groups, method for obtaining HPV samples, and

differences in HPV assays' methodology (HPV assays' sensitivity and detection estimates are influenced by differences in methodologies used: e.g.; method for genotyping, DNA purification method, PCR primers, and amplification techniques) might partially explain these variations.

With respect to the prevalence of specific HPV types, two of the commonest HPV HR genotypes found in our cervical samples (16 and 58) were also two of the most prevalent types reported in

Table 3
Anogenital HPV DNA prevalence (%) and commonest High Risk genotypes in women from different regions.

Setting	Study characteristics			HPV infection prevalence			Prevalence of commonest HR types in Puerto Rico		
	Study period	Age-group (years)	Study population	Sample size	Cervix	Anus	Cervix/Anus co-infection	Cervix	Anus
Puerto Rico	2010–2013	16–64	Population-based	564 (n=536 for anal)	29% (cervical only): 13%	39% (19% had anal only) 16%	17%	68 (8%), 16 (6%), and 58 (5%)* 16 and 53 (24% each)*	68 (7%), 16 (6%) and 51 (5%), 53 (17%)
American Samoa [25]	2008–2009	18+	Population and gynecologic clinics	211	10%	–	4%	–	–
USA NHANES [20]	2007–2010	18–59	Population-based	3738	42%	–	–	53 (6%) and 16 (5%)	–
New Mexico [22]	2007–2009	18+	Gynecology clinics	47,617	27%	–	–	16 (4%) and 51 (2%)	–
Costa Rica [26]	2004–2005	18–25	Control arm of clinical trial	2,107	37%	32%	20%	–	51 (15%) and 16 (13%)
Hawaii [23]	1999–2004	18+	Health clinics	2,372 (n=1,378 for anal)	29%	27% (14% had anal only)	13%	16 (12%), 53 (7%) and 58 (6%)*	16, 51 and 53 (7% each)
Colombia [24]	1993–1995	13–85	Census in four health districts	1859	15%	–	–	16 (16%) and 58 (6%)*	–
Costa Rica [21]	1993–1994	18+	Population-based	8514	27%	–	–	16 (13%) and 58 (8%)*	–

* among HPV positive women.

Costa Rica [21], and Colombia [24], consistent with the most common types described in Central and South America in women with normal cytology [4]. HPV genotype 16 was also one of the commonest found among women in other studies [20,22,23], but our most prevalent HR type, 68, was not as common in other populations. Similarly to our results in cervix, two of the commonest HR HPV types in our anal samples (16 and 51) were also common in Costa Rica [26]. It is important to highlight that in both anatomical sites, we found HPV types that are included in the three currently available HPV vaccines: Cervarix (HPV 16 and 18), Gardasil (HPV 6, 11, 16 and 18) and Gardasil 9 (6, 11, 16, 18, 31, 33, 45, 52 and 58). Nonetheless, HPV 68, our most common, is not currently included in any HPV vaccine. Although studies in other populations have found that HPV 16 and 18, and not 68, are found in most cervical and anal cancers [30], it is yet to be evaluated if the same is the case for Puerto Rico, and if these are the strongest types associated with cancer development in this population. Results of the most common HPV types identified in this population-based sample of women in Puerto Rico will help future studies determine if changes in the distribution of HPV types occur in this population with increasing uptake of HPV vaccination, as has been documented in young women in the USA [19].

Although both the cervix and anus shared the commonest oncogenic HPV types, the concordance evaluation in co-infected women showed a marginal to good concordance in the most prevalent types, which is similar to kappa values reported in a previous study carried in a clinical setting in Puerto Rico in self-collected samples (HPV 68 kappa: 0.38, 16 kappa: 0.52 and 51 kappa: 0.42) [17]. Since no information about previous infection of the same genotype in the alternate anatomical site is available due to the non-longitudinal nature of this study, no evidence of a common source or route of transmission could be established. Similar findings of the replication of the commonest genotypes in both anatomical sites were documented in a Belgium study, in their case with respect to HPV 16, 51, and 39 [31]. Meanwhile, we found a three-fold association between cervical and anal infection, which is consistent with Hawaiian [23] and American Samoa [25] results. Thus, the coexistence and association of anal and cervical HPV infections and the high frequency of the same genotypes on both anatomical sites evidences that both sites could share a similar risk of infection and may suggest a possible transmission between both sites [23,31,32]. This association also supports the biologic plausibility of the increased risk of anal cancer documented among women with gynecologic cancers [33]. Nonetheless, longitudinal studies are warranted in this population to further understand the mechanisms of HPV transmission and persistence in the anogenital area. Meanwhile, the relative high prevalence of HPV 16 in both anatomical sites could be explained by its lower clearance rate compared to other oncogenic HPV types [32,34] and by the clearance delay caused by the high frequency of anal sex intercourse, practiced in our study group [35].

Our results also support previous findings reported in Hawaii [23], such as the inverse association between age and HPV co-infection, but not with anal infection. The high prevalence of HPV co-infection at younger ages could be associated to riskier sexual behaviors in younger cohorts, as previously evidenced in Puerto Rico [14]. Conversely, we did not observe an inverse association between age and cervical infection alone as was observed in Hawaii [23]. The strongest risk factor for anogenital HPV infection in our study was increased number of lifetime sexual partners (≥ 3), which is consistent with findings reported in Hawaii [23] and in other populations [20,23–26]. This finding is aligned with data from the IARC, which evidences that the number of sexual partners is the main determinant of anogenital HPV infection [30]. Meanwhile, although previous findings have documented the association of younger age of sexual debut with increased HPV

prevalence in some [20,23], but not all studies [21,24]; this factor was only associated with co-infection in our study. Meanwhile, the association observed in our study between anogenital HPV infection and anal sexual intercourse in the last year evidences the relevance of anal intercourse in the risk of anal cancer development [36]; HR types have been detected in more than 80% anal cancer cases [30]. Furthermore, research has reported lower condom utilization during anal intercourse than during vaginal intercourse, which increased the risk of STD's in women [37].

4.1. Strengths and limitations

Among strengths, a previously validated self-collection methodology that showed good to excellent agreement between physician and self-collected samples was employed in our study [17,38], supporting the feasibility of using cervical and anal self-sampling methods in population-based studies. Likewise, the high response rate (99.6%) of women providing anal and cervical self-collected specimens represented a study's strength. As well, accurate prevalence HPV results were obtained from our population-based study, eliminating bias of testing performed on gynecological clinics, which could probably inflate HPV prevalence due to possible gynecological symptoms. However, our findings might not be generalizable to the entire Puerto Rican women population aged 16–64 years as the study sample was selected only from the San Juan Metropolitan area. In addition, concordance results among co-infected women (cervix and anus) should be taken with caution since the kappa statistic is affected by low prevalence, as it is the case for most of the genotypes evaluated.

5. Conclusions

As also observed world-wide, this study evidences that anogenital HPV infection in women from the San Juan Metropolitan area of Puerto Rico is common, and that for the most part, the greatest prevalent genotypes coincide with those reported in other populations. Our results are also consistent with previous studies confirming the relevance of sexual behavior in the risk for anogenital HPV infection and the strong association between cervical and anal HPV infection. Future studies should continue monitoring changing trends in HPV infection (including genotypes) in this population, and the relationship between anal and cervical HPV-related disease. Public health efforts should continue to focus on strengthening strategies for HPV-related cancer prevention for women and men in this population. These strategies should promote population awareness of HPV transmission and safer sexual behaviors, along with information about their impact on anogenital cancers. Educational intervention efforts should focus on the benefits of HPV vaccination and Pap test use combined with HR HPV screening, as the key for cancer prevention in this area.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.pvr.2016.04.002>.

References

- [1] J. Doorbar, W. Quint, L. Banks, I.G. Bravo, M. Stoler, T.R. Broker, M.A. Stanley, The biology and life-cycle of human papillomaviruses, *Vaccine* 30 (Suppl 5) (2012) F55–F70.
- [2] M. Tommasino, The human papillomavirus family and its role in carcinogenesis, *Semin. Cancer Biol.* 26 (2014) 13–21.
- [3] H. zur Hausen, Papillomaviruses and cancer: from basic studies to clinical application, *Nat. Rev. Cancer* 2 (2002) 342–350.
- [4] F.X. Bosch, A.N. Burchell, M. Schiffman, A.R. Giuliano, S. de Sanjose, L. Bruni, G. Tortolero-Luna, S.K. Kjaer, N. Munoz, Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia, *Vaccine* 26 (Suppl 10) (2008) K1–16.
- [5] J.S. Smith, A. Melendy, R.K. Rana, J.M. Pimenta, Age-specific prevalence of infection with human papillomavirus in females: a global review, *J. Adolesc. Health* 43 (2008), S5–25, S25.e1–41.
- [6] E. Petrosky, J.A. Bocchini Jr, S. Hariri, H. Chesson, C.R. Curtis, M. Saraiya, E. R. Unger, L.E. Markowitz, Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices, *Morb. Mortal. Wkly. Rep.* 64 (2015) 300–304.
- [7] X. Castellsague, T. Iftner, E. Roura, J.A. Vidart, S.K. Kjaer, F.X. Bosch, N. Munoz, S. Palacios, M. San Martin Rodriguez, L. Serradell, L. Torcel-Pagnon, J. Cortes, CLEOPATRE Spain Study Group, Prevalence and genotype distribution of human papillomavirus infection of the cervix in Spain: the CLEOPATRE study, *J. Med. Virol.* 84 (2012) 947–956.
- [8] L.E. Markowitz, S. Hariri, E.R. Unger, M. Saraiya, S.D. Datta, E.F. Dunne, Post-licensure monitoring of HPV vaccine in the United States, *Vaccine* 28 (2010) 4731–4737.
- [9] A.M. Johnson, C.H. Mercer, S. Beddows, N. de Silva, S. Desai, R. Howell-Jones, C. Carder, P. Sonnenberg, K.A. Fenton, C. Lowndes, K. Soldan, Epidemiology of, and behavioral risk factors for, sexually transmitted human papillomavirus infection in men and women in Britain, *Sex. Transm. Infect.* 88 (2012) 212–217.
- [10] A.P. Ortiz, M. Soto-Salgado, W.A. Calo, G. Tortolero-Luna, C.M. Perez, C. J. Romero, J. Perez, N. Figueroa-Valles, E. Suarez, Incidence and mortality rates of selected infection-related cancers in Puerto Rico and in the United States, *Infect. Agents Cancer* 5 (2010) 10-9378–5–10.
- [11] E. Suarez, W.A. Calo, E.Y. Hernandez, E.C. Diaz, N.R. Figueroa, A.P. Ortiz, Age-standardized incidence and mortality rates of oral and pharyngeal cancer in Puerto Rico and among non-Hispanics whites, non-Hispanic blacks, and Hispanics in the USA, *BMC Cancer* 9 (2009) 129-2407–9–129.
- [12] V. Colon-Lopez, A.P. Ortiz, M. Soto-Salgado, M. Torres-Cintron, J.J. Mercado-Acosta, E. Suarez, Anal cancer incidence and mortality in Puerto Rico, *P. R. Health Sci. J.* 32 (2013) 76–81.
- [13] V. Colon-Lopez, A.P. Ortiz, M. Soto-Salgado, M. Torres-Cintron, C.A. Pettaway, A. Puras-Baez, M. Martinez-Ferrer, E. Suarez, Penile cancer disparities in Puerto Rican men as compared to the United States population, *Int. Braz. J. Urol.* 38 (2012) 728–738.
- [14] A.P. Ortiz, M. Soto-Salgado, E. Suarez, M. del Carmen Santos-Ortiz, G. Tortolero-Luna, C.M. Perez, Sexual behaviors among adults in Puerto Rico: a population-based study, *J. Sex. Med.* 8 (2011) 2439–2449.
- [15] S. Reagan-Steiner, D. Yankey, J. Jeyarajah, L.D. Elam-Evans, J.A. Singleton, C. R. Curtis, J. MacNeil, L.E. Markowitz, S. Stokley, National, regional, state, and selected local area vaccination coverage among adolescents aged 13–17 years – United States, 2014, *Morb. Mortal. Wkly. Rep.* 64 (2015) 784–792.
- [16] A.P. Ortiz, E. Marrero, C. Munoz, C.M. Perez, G. Tortolero-Luna, J. Romaguera, N. Rodriguez, A. Gonzalez-Falero, J. Palefsky, E. Suarez, Methods in HPV surveillance: experiences from a population-based study of HPV infection among women in the San Juan metropolitan area of Puerto Rico, *P. R. Health Sci. J.* 34 (2015) 117–127.
- [17] A.P. Ortiz, J. Romaguera, C.M. Perez, Y. Otero, M. Soto-Salgado, K. Mendez, Y. Valle, M. Da Costa, E. Suarez, J. Palefsky, G. Tortolero-Luna, Human papillomavirus infection in women in Puerto Rico: agreement between physician-collected and self-collected anogenital specimens, *J. Low. Genit. Tract Dis.* 17 (2013) 210–217.
- [18] P.E. Gravitt, J.V. Lacey Jr, L.A. Brinton, W.A. Barnes, J.R. Kornegay, M. D. Greenberg, S.M. Greene, O.C. Hadjimichael, L. McGowan, R. Mortel, P. E. Schwartz, R. Zaino, A. Hildesheim, Evaluation of self-collected cervicovaginal cell samples for human papillomavirus testing by polymerase chain reaction, *Cancer Epidemiol. Biomark. Prev.* 10 (2001) 95–100.
- [19] L.E. Markowitz, G. Liu, S. Hariri, M. Steinau, E.F. Dunne, E.R. Unger, Prevalence of HPV after introduction of the vaccination program in the United States, *Pediatrics* 137 (2016) 1–9.
- [20] R. Shi, S. Devarakonda, L. Liu, H. Taylor, G. Mills, Factors associated with genital human papillomavirus infection among adult females in the United States, NHANES 2007–2010, *BMC Res. Notes* 7 (2014) 544-0500–7–544.
- [21] R. Herrero, P.E. Castle, M. Schiffman, M.C. Bratti, A. Hildesheim, J. Morales, M. Alfaro, M.E. Sherman, S. Wacholder, S. Chen, A.C. Rodriguez, R.D. Burk, Epidemiologic profile of type-specific human papillomavirus infection and cervical neoplasia in Guanacaste, Costa Rica, *J. Infect. Dis.* 191 (2005) 1796–1807.
- [22] C.M. Wheeler, W.C. Hunt, J. Cuzick, E. Langsfeld, A. Pearce, G.D. Montoya, M. Robertson, C.A. Shearman, P.E. Castle, New Mexico HPV Pap Registry Steering Committee, a population-based study of human papillomavirus genotype prevalence in the United States: baseline measures prior to mass human papillomavirus vaccination, *Int. J. Cancer* 132 (2013) 198–207.
- [23] B.Y. Hernandez, K. McDuffie, X. Zhu, L.R. Wilkens, J. Killeen, B. Kessel, M. T. Wakabayashi, C.C. Bertram, D. Easa, L. Ning, J. Boyd, C. Sunoo, L. Kamemoto, M.T. Goodman, Anal human papillomavirus infection in women and its relationship with cervical infection, *Cancer Epidemiol. Biomark. Prev.* 14 (2005) 2550–2556.
- [24] M. Molano, H. Posso, E. Weiderpass, A.J. van den Brule, M. Ronderos, S. Franceschi, C.J. Meijer, A. Arslan, N. Munoz, HPV Study Group HPV Study, Prevalence and determinants of HPV infection among Colombian women with normal cytology, *Br. J. Cancer* 87 (2002) 324–333.

- [25] B.Y. Hernandez, L.S. Ka'opua, L. Scanlan, J.A. Ching, L.E. Kamemoto, P. J. Thompson, X. Zhu, Y.B. Shvetsov, J. Tofaeono, V.T. Williams, Cervical and anal human papillomavirus infection in adult women in American Samoa, *Asia Pac. J. Public Health* 25 (2013) 19–31.
- [26] F.A. Castro, W. Quint, P. Gonzalez, H.A. Katki, R. Herrero, L.J. van Doorn, M. Schiffman, L. Struijk, A.C. Rodriguez, C. DelVecchio, D.R. Lowy, C. Porras, S. Jimenez, J. Schiller, D. Solomon, S. Wacholder, A. Hildesheim, A.R. Kreimer, Costa Rica Vaccine Trial Group, Prevalence of and risk factors for anal human papillomavirus infection among young healthy women in Costa Rica, *J. Infect. Dis.* 206 (2012) 1103–1110.
- [27] M.A. Clarke, A.C. Rodriguez, J.C. Gage, R. Herrero, A. Hildesheim, S. Wacholder, R. Burk, M. Schiffman, A large, population-based study of age-related associations between vaginal pH and human papillomavirus infection, *BMC Infect. Dis.* 12 (2012) 33–2334-12-33.
- [28] E.O. Dareng, B. Ma, A.O. Famooto, S.N. Akarolo-Anthony, R.A. Offiong, O. Olaniyan, P.S. Dakum, C.M. Wheeler, D. Fadrosh, H. Yang, P. Gajer, R. M. Brotman, J. Ravel, C.A. Adebamowo, Prevalent high-risk HPV infection and vaginal microbiota in nigerian women, *Epidemiol. Infect.* 144 (2016) 123–137.
- [29] J.E. Lee, S. Lee, H. Lee, Y.M. Song, K. Lee, M.J. Han, J. Sung, G. Ko, Association of the vaginal microbiota with human papillomavirus infection in a korean twin cohort, *PLoS One* 8 (2013) e63514.
- [30] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, Biological Agents: Human papillomaviruses, IARC Monogr. Eval. Carcinog. Risks Hum. 100B, 2012, pp. 255–313. Retrieve from (<http://monographs.iarc.fr/ENG/Monographs/vol100B/mono100B-11.pdf>).
- [31] K.W. D'Hauwers, T. Cornelissen, C.E. Depuydt, J. Bogers, A.R. Donders, E. Leuridan, P. Van Damme, W.A. Tjalma, Anal human papillomavirus DNA in women at a colposcopy clinic, *Eur. J. Obstet. Gynecol. Reprod. Biol.* 164 (2012) 69–73.
- [32] A.B. Moscicki, Y. Ma, S. Farhat, J. Jay, E. Hanson, S. Benningfield, J. Jonte, C. Godwin-Medina, R. Wilson, S. Shiboski, Natural history of anal human papillomavirus infection in heterosexual women and risks associated with persistence, *Clin. Infect. Dis.* 58 (2014) 804–811.
- [33] A.M. Saleem, J.K. Paulus, A.P. Shapter, N.N. Baxter, P.L. Roberts, R. Ricciardi, Risk of anal cancer in a cohort with human papillomavirus-related gynecologic neoplasm, *Obstet. Gynecol.* 117 (2011) 643–649.
- [34] N. Munoz, G. Hernandez-Suarez, F. Mendez, M. Molano, H. Posso, V. Moreno, R. Murillo, M. Ronderos, C. Meijer, A. Munoz, Instituto Nacional de Cancerologia HPV Study Group, Persistence of HPV infection and risk of high-grade cervical intraepithelial neoplasia in a cohort of Colombian women, *Br. J. Cancer* 100 (2009) 1184–1190.
- [35] Y.B. Shvetsov, B.Y. Hernandez, K. McDuffie, L.R. Wilkens, X. Zhu, L. Ning, J. Killeen, L. Kamemoto, M.T. Goodman, Duration and clearance of anal human papillomavirus (HPV) infection among women: the Hawaii HPV cohort study, *Clin. Infect. Dis.* 48 (2009) 536–546.
- [36] J.R. Daling, M.M. Madeleine, L.G. Johnson, S.M. Schwartz, K.A. SHERA, M. A. Wurscher, J.J. Carter, P.L. Porter, D.A. Galloway, J.K. McDougall, Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer, *Cancer* 101 (2004) 270–280.
- [37] L.S. Benson, S.L. Martins, A.K. Whitaker, Correlates of heterosexual anal intercourse among women in the 2006–2010 national survey of family growth, *J. Sex. Med.* 12 (2015) 1746–1752.
- [38] A.P. Ortiz, N. Alejandro, C.M. Perez, Y. Otero, M. Soto-Salgado, J.M. Palefsky, G. Tortolero-Luna, J. Romaguera, Acceptability of cervical and anal HPV self-sampling in a sample of hispanic women in Puerto Rico, *P. R. Health Sci. J.* 31 (2012) 205–212.