Chlamydia Trachomatis and Human Papillomavirus Serostatus in Puerto Rican Women

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Objective: There is a high prevalence of human papillomavirus (HPV) infection in Puerto Rico, but little is known about the prevalence of *Chlamydia trachomatis* (CT) infection in healthy Puerto Rican women. Thus we aimed to evaluate the seroprevalence and association and the association between HPV and CT.

Methods: This was a secondary data analysis from a cross-sectional, population-based, study of HPV infection in women aged 16-64 years in Puerto Rico (2010-2013). Enzyme-linked immunosorbent assays (ELISA) were used to detect serum antibodies to CT and HPV. Logistic regression models were used to estimate the odds ratio (OR) for the association between HPV and CT serostatus.

Results: The study included 524 women; mean age was 42 years. Overall, 97 (18.5%) women were CT-seropositive, 251 (47.0%) were HPV seropositive, and 57 (10.9%) had antibodies for both CT and HPV. Women who were CT-seropositive were more likely (p<0.05) to also be seropositive to any HPV type ($OR_{adjusted}$: 1.7, IC 95% =1.1, 2.6), HPV 16/18 ($OR_{adjusted}$: 1.6, IC 95% =1.0, 2.6) and HPV 6/11 ($OR_{adjusted}$: 1.6, IC 95% =1.1, 2.6) than those CT-seronegative, after adjusting for possible confounding factors.

Conclusion: Given the association between CT and HPV seropositivity, longitudinal studies to evaluate whether CT infection influences HPV incidence and persistence in this group are warranted. [*P R Health Sci J 2020;39:28-33*]

Key words: CT, HPV, Serum, Women, Hispanics

Human Papillomaviruses (HPV) are a large group of DNA viruses that frequently infect cutaneous and mucosal sites (1). About 80% of sexually active people are infected at some point in their life with HPV (2). HPV infections, commonly acquired via sexual transmission, are associated with low and high grade intraepithelial lesions and development of cervical, vaginal, vulvar, anal, and oropharyngeal cancers (3, 4). While infection with HPV is common, most HPV infections clear within several months. Infections that persist, however, are associated with an increased risk for various neoplasias.

Identifying risk factors or cofactors that lead to HPV persistence is important not only to prevent cervical cancer but all HPV-related anogenital cancers. A limited number of studies have identified sexual behavior (5), and STDs (6, 7) as risk factors for HPV persistence. *Chlamydia trachomatis* (CT) is an intracellular bacterium that is also sexually transmitted. Infection with CT is one of the most frequently reported infections among American women (8). Several studies have suggested that CT may be associated with HPV persistence and the development of cervical intraepithelial neoplasia, thereby increasing the risk of cervical cancer (9, 10). Meanwhile, a recent meta-analysis showed that HPV and CT are strongly associated, in fact behaving as reciprocal risk factors, and suggesting that in women diagnosed with any of these infections, screening for the other infection could represent a preventive intervention for reproductive health morbidities, including cervical cancer (11). While studies have demonstrated an association between HPV and CT among women from other populations (11–13), no study to date, has evaluated the association between HPV and CT in Puerto Rican women. Research on the relationship of these infections is of particular relevance in Puerto Rico, given the high burden of HPV infection (14, 15) and cervical cancer documented in women in this population (16), and given the lack of population-based estimates on CT infection.

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Using data from a cross-sectional, population-based study of HPV infection in Puerto Rican women, the aims of this observational study were to: 1. Determine the seroprevalence of CT infection among young and middle-aged women from the San Juan metropolitan area; 2. Describe the sociodemographic, lifestyle, and clinical characteristics of the study sample according to their CT and HPV serostatus, and 3. Estimate the magnitude of association between seroprevalence of CT and HPV, after adjusting for a number of potentially confounding factors. While serology is used as an indicator of cumulative exposure, allowing us to quantify the seroprevalence of CT and HPV infections, serologic assays are not meant to diagnose these conditions, but to identify the burden of infection in the population and needs for future public health interventions (17).

Materials and Methods

Study design and setting

This study is a secondary analysis of data from a cross-sectional seroprevalence study (18). In this population-based study, the sampling frame used was based on the CENSUS tracts of the San Juan metropolitan area (19). The study consisted of a personal interview, a computer-assisted self-administered interview (ACASI), anogenital biological samples, and a blood sample from each participant. Study enrollment occurred in 2010-2013, and details of this study have been previously described in other sources (18).

Study population

The study's inclusion criteria were the following: women, age 16 to 64 years old, resident of selected households, sexually active, and not pregnant nor infected with human immunodeficiency virus (HIV) at the time of the study. Eligible women signed an informed consent form agreeing to participate in the study and gave permission to store serum samples for future tests related to the study of HPV. The current analysis included all women with HPV serology results who had not received the HPV vaccine and had sufficient stored serum for CT serology testing. A total of 566 women were originally enrolled, of which one had a problem with cervical sampling, seven were previously vaccinated against HPV, and 34 did not have satisfactory serum samples. Thus, the study population for this analysis consisted of 524 women.

Detection of HPV and CT

The primary outcome variables examined were HPV serostatus to HPV types 6, 11, 16 and 18, the types targeted by both the 4-valent HPV and 9-valent HPV vaccines (Gardasil and Gardasil 9, Merck and Co., Inc.). A multiplex ELISA (M4ELISA) was used as previously described to titer type-specific IgG antibodies to HPV L1 virus-like particles (VLPs). (20) Cut-off values for positive results were based on previously described findings.(21) Type-specific (positive or negative) and grouped outcomes were used. Results for seropositivity were categorized as: 1) any HPV (defined as: positive to HPV 6, 11, 16 or 18), 2) HPV 16/18 (defined as: positive to HPV 16 or 18) and 3), and HPV 6/11 (defined as: positive to HPV 6 or 11). The main independent variable in this study was CT serostatus, categorized as either positive or negative. The *Chlamydia trachomatis* IgG ELISA (Mybiosource, San Diego,CA) was used following the manufacturer's protocol and cut-off value for CT seropositivity.

Covariates

The covariates evaluated were study participant's age, education ($\leq$ 12 and > 12 years), marital status (single, married and divorced), medical insurance (no health insurance, Medicare or government health plan and private insurance), current family income (<$20,000 and $\geq$ $20,000), employment status, use of cigarettes (never, previously or currently), use of alcohol (never, previously or currently), history of anal, oral, or vaginal sex, use of condoms (ever or never), number of pregnancies ($\leq$ 2 and > 2), lifetime use of non-injected illicit drugs (ever or never), lifetime number of sexual partners, age of sexual initiation (>15 and $\leq$ 15 years), and use of sex for drugs and money (ever or never).

Statistical analysis

An initial epidemiological profile of the study group was performed using descriptive statistics and frequency distributions. To describe the association between HPV and CT, contingency tables were used. The significance analysis of these associations was performed with the chi-square test of homogeneity. To assess the strength of this association, the crude odds ratio (OR_{crude}) was estimated with 95% confidence intervals. Multivariate logistic regression models were used to estimate multivariable adjusted ORs ($OR_{adjusted}$) for HPV positivity with adjustment for covariates. Lifestyle and demographic variables were included in the multivariable model based on either a statistical relationship with CT, or if they had shown in the literature to be of importance for the associations of interest. To identify the potential confounders, we entered the covariates into the model and examined the extent to which the inclusion of the covariates changed the odds ratios (ORs). The final set of variables for statistical adjustment were selected using a combination of clinical judgment, and changes in the effect estimate >10%. Once the confounding variables were defined, an assessment of the first order interaction terms was conducted using the likelihood ratio test.

Results

Participant's characteristics

The participants' mean age was 42.4 years ± 13.3 SD. Overall, 65.3% had an academic degree higher than high school, 52.3% were married or living together, 46.2% had Medicare or government health plan, 58.8% had less than $20,000 per year of family income and 58.6% studied or

worked. Fifty-six percent of women had more than 2 pregnancies, 17.8% were current smokers and 41.0% had history of lifetime non-injected drug use. The mean number of sexual partners per year was 0.51±1.34 SD, 50.8% of women had one sexual partner on average every five years and 42.7% had more than four lifetime sexual partners. More than two-thirds (73.1%) of women had an age of sexual debut higher than 15 years old; 69.9% had ever engaged in anal sex and 94.9% had ever engaged in oral sex. Regarding other sexual practices, 25.2% of women never used condoms and 2.1% had ever practiced sex for drugs and/or money (Table 1).

The characteristics of the study population according to CT serostatus are also presented in Table 1. Based on the simple logistic models, current use of tobacco, history of non-injected drug use, increased number of sexual partners, younger age of sexual debut, anal sex history and history of condom use were all positively associated with CT seropositivity (P<0.05).

HPV and CT seroprevalence

Seropositivity to CT was 18.5%, while seropositivity to any of the four HPV types was 47.0% (31.7% for HPV 16/18 and 35.1% for HPV 6/11). Approximately 11% of women were seropositive for both CT and any HPV, 7.8% were seropositive to both CT and HPV 16/18, and 8.4 % were seropositive to both CT and HPV 6/11 (Figure 1). The seroprevalence of HPV 16/18, HPV 6/11, and any HPV was higher in women seropositive to CT than among those seronegative to CT (p-values<0.05, Figure 2).

Association between seroprevalence of HPV and CT

The results of our multivariate logistic regression model, which adjusted for age, average number of sexual partners and history of anal sex, suggest that CT-seropositive women were approximately 1.7 times more likely to be seropositive for any HPV type evaluated as compared with CT-seronegative women (OR:1.7, 95% CI= 1.1-2.6) (Table 2). Similar results were observed for HPV 16/18 (OR=1.6, 95% CI=1.0-2.6, P <0.05) and HPV 6/11 (OR:1.7, 95% CI=1.1-2.6). When analyzed individually, the associations were only significant for HPV 11 (OR:2.8, 95% CI= 1.7-4.7), and approached statistical significance for HPV 16 (OR:1.6, 95% CI=1.0-2.6, 0.05<p<0.10), after adjusting for potential confounders (data not shown).

Table 1. Demographic and lifestyle factors associated with CT serostatus among women aged 16-64 living in the San Juan metropolitan area of Puerto Rico. (n=524)

	Study population n (colum %)	Seropositive CT n [row %]	OR crude
Age			
≤ 42 years	254 (48.5)	55 [21.7]	1.0
>42 years	270 (51.5)	42 [15.6]	0.7 (0.4-1.0)**
Education			
≤ 12 years	182 (37.7)	52 [20.7]	1.0
> 12 years	342 (65.3)	45 [16.5]	0.5 (0.3-0.9)*
Marital status			
Single	119 (22.7)	27 [22.7]	1.0
Married	274 (52.3)	42 [15.3]	0.6 (0.4-1.1)**
Divorced	131 (25.0)	28 [21.4]	0.9 (0.5-1.7)
Health insurance			
No health insurance	51 (9.7)	10 [19.6]	1.0
Medicare, government health plan	242 (46.2)	53 [21.9]	1.2 (0.5-2.4)
Private insurance	231 (44.1)	34 [14.7]	0.7 (0.3-1.5)
Family income[a]			
<$20,000	281 (58.8)	56 [19.9]	1.0
≥$20,000	197 (41.2)	28 [14.9]	1.5 (0.9-2.5)
Employment status			
Work or study	307 (58.6)	61 [19.9]	1.0
Unemployed	165 (31.5)	31 [18.8]	0.9 (0.6-1.5)
Others	52 (9.9)	5 [9.6]	
Pregnancies[b]			
≤2 pregnancies	202 (44.2)	40 [19.8%]	1.0
>2 pregnancies	255 (55.8)	56 [22.0]	1.6 (1.0-2.5)**
Smoking history			
Never	248 (47.3)	39 [15.7]	1.0
Previously	183 (34.9)	33 [18.0]	1.2 (0.7-2.0)
Currently	93 (17.8)	25 [26.9]	2.0 (1.1-3.5)*
Alcohol use history			
Never	64 (12.2)	8 [12.5]	1.0
Previously	133 (25.4)	31 [23.3]	2.1 (0.9-4.9)**
Currently	327 (62.4)	58 [17.7]	1.5 (0.7-3.3)
Lifetime non-injected drug use[c]			
No	308 (59.0)	44 [14.3]	1.0
Yes	214 (41.0)	52 [24.3]	1.9 (1.2-3.0)*
Lifetime number of sexual partners			
≤4 partners	300(57.3)	42 [14.0]	1.0
>4 partners	224 (42.7)	55 [24.6]	2.0 (1.3-3.1)*
Age of sexual debut			
>15 years	383 (73.1)	55 [14.4]	1.0
≤15 years	141 (26.9)	42 [29.8]	2.5 (1.6-4.0)*
Anal sex history			
No	158 (30.1)	20 [12.7]	1.0
Yes	366(69.9)	77 [21.0]	1.8 (1.1-3.1)*
Oral sex history			
No	27 (5.1)	6 [22.2]	1.0
Yes	497 (94.9)	91 [18.3]	0.8 (0.3-2.0)
Condom use			
Never	132 (25.2)	15 [11.4]	1.0
Ever	392 (74.8)	82 [20.9]	2.1 (1.1-3.7)*
Sex for drugs and/ or money[d]			
Never	511 (97.9)	92 [18.0]	1.0
Ever	11 (2.1)	4 [36.4]	2.6 (0.7-9.1)

*P <0.05, ** 0.05<P<0.1, Missing data; a: n= 478; b: n= 522; c: n= 522; d: n= 522.

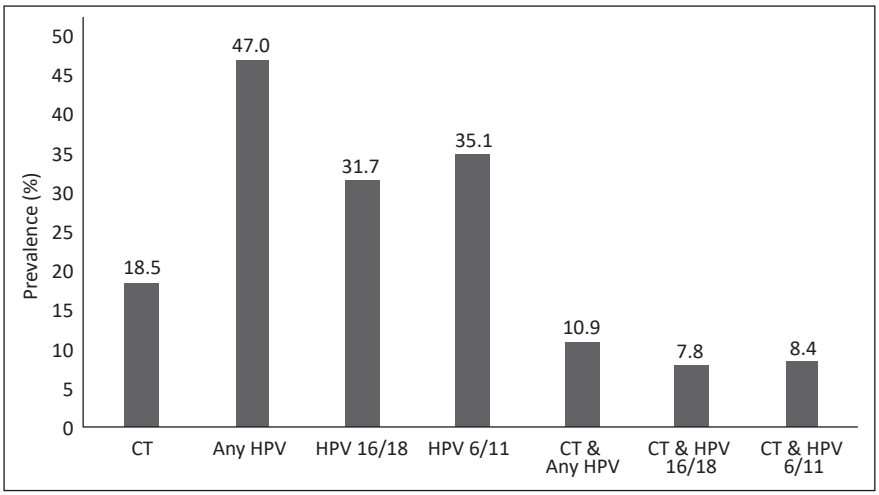

Figure 1. Seroprevalence of CT and HPV among women aged 16-64 years living in the San Juan metropolitan area of Puerto Rico (n=524).

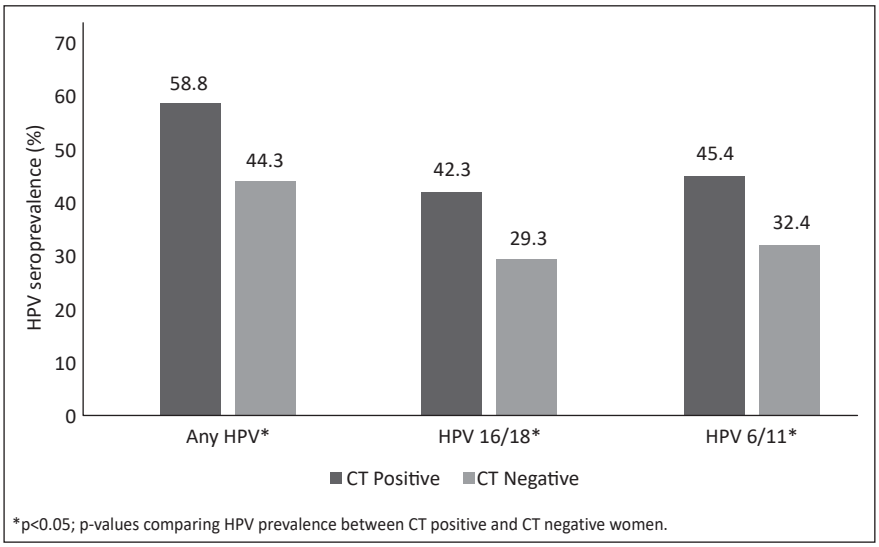

Figure 2. HPV seroprevalence among women living in the San Juan metropolitan area of Puerto Rico, according to CT antibody status (n=524).

Discussion

This is the first study to report the seroprevalence of CT in young and middle-aged Puerto Rican women. Approximately 1 in every 5 young and middle-aged women who resided in the metropolitan area of San Juan, Puerto Rico had serum antibodies to CT. Our findings also suggest an association between CT and HPV seropositivity (any HPV, HPV 16/18 and HPV 6/11).

HPV and CT seroprevalence

The frequency of CT seroprevalence found in this study is consistent with European studies that have reported CT seroprevalence rates of 10% (22) to 28% (23) in women aged 30 to 60 years. The seroprevalence of CT among healthy fertile women ranged between 17% and 19% in Rwanda and East Africa (24). We found that a greater proportion of women were seropositive to at least one of the four HPV types evaluated than to CT (47.0% versus 18.5%) and 10.9% were seropositive to both HPV and CT. Similar studies in the general population are limited. The CT seroprevalence of healthy control Taiwanese ages 30 to 64 years, in a nested case-control study of in situ or invasive cervical cancer, was 28.7% and HPV seroprevalence for HPV 6, 16, and 18 was 31.0%, 8.1%, and 14.8%, respectively (25). Similarly, the CT seroprevalence rates ranged from 8%-12% for healthy European women aged 35-75 years serving as controls in a nested case-control study of cervical cancer (23).

There is general agreement, based on serology and DNA detection, that CT is less prevalent than HPV. However, serology underestimates exposure to both CT and HPV, as not all individuals seroconvert. (26, 27) Infection with CT stimulates the synthesis of IgG antibodies, which are typically observed between 5–20 days of infection, and remain elevated for several weeks and then gradually decrease (26). It is estimated that approximately 70% of women seroconvert after having had a CT infection (28). In a previous study of CT seropositive women, seropositivity showed a decline of 18% over a period of four to seven years (29). Nonetheless, seropositivity for CT remains elevated for years and is influenced by antibiotic treatment and lack of subsequent re-infection (29).

Table 2. Association between CT and HPV serology among women aged 16-64 living in the San Juan metropolitan area of Puerto Rico. (n=524)

	Any HPV		HPV 16/18		HPV 6/11	
	OR Crude	OR Adjusted	OR Crude	OR Adjusted	OR Crude	OR Adjusted
CT serostatus						
Positive	1.8 (1.2-2.8)*	1.7(1.1-2.6)*	1.8 (1.1-2.8)*	1.6 (1.0-2.6)	1.7 (1.1-2.6)*	1.7 (1.1-2.6)*
Negative	1.00	1.00	1.00	1.00	1.00	1.00

‡Adjusted for age, lifetime number of sexual partners, and anal sex. ( ) 95% Confidence interval. *P <0.05

Association between seroprevalence of HPV and CT

Since CT and HPV share common risk factors for transmission, including sexual practices, it was not surprising that we found an association between seropositivity for CT and any HPV, in agreement with prior studies (13). A nested case-control study showed that CT serology was associated with a two-fold higher risk of cervical cancer only in HPV 16 seropositive women (6). The same study did not observe an association between CT serology and HPV 18 serostatus (6), consistent with our finding that CT serology was more closely associated with HPV 16 and was not associated with HPV 18 serology. A longitudinal study in Sweden found that women with a self-reported history of CT infection had a higher risk of having persistent cervical HPV-DNA compared to women without previous CT infection (30). A cross-sectional study of women from one private medical unit in southern Brazil found an association between HPV and CT with intraepithelial alterations in cervical samples, and indication that both are linked with early cervical carcinogenesis (31). Furthermore, a recent study found a strong association with past CT infection, indicated by serology, with the progression of cervical intraepithelial neoplasia grade 2 at 24 months of follow-up (32). In men, CT and HPV anogenital infection have also been associated (33, 34). A recent systematic review investigating the epidemiological data on the association of CT and CT-HPV co-infection on cervical cancer concluded that CT can be an independent predictor for cervical cancer risk, and that the prevalence of CT infection in cervical cancer patients varies according to the geographical area, detection method, serotype, and sampling number. The systematic review also indicated that the prevalence of CT infection was significantly higher among HPV-positive women compared with HPV-negative women. While this may be explained by shared risk factors for CT and HPV infections, it was also hypothesized that CT could indirectly impact cervical lesions by increasing the risk for HPV infection and persistence (35).

Study strengths and limitations

Our study had several strengths, among them, we evaluated serum antibodies for both CT and HPV. The literature has shown that the detection of antibodies in serum is usually better than DNA to assess cumulative exposure or exposure that may have occurred in prior years (36). Our study sample size was relatively large (n = 524) and was population-based. In addition, questionnaires on sociodemographic characteristics and sexual behavior allowed us to adequately assess and control for potential confounders. However, the study has several limitations that need be kept in mind in the interpretation of the study results. The study is representative only of women from the metropolitan area of San Juan, Puerto Rico, and sample size may have limited the power of HPV type specific analyses. Given the nature of our cross-sectional study design, we cannot make conclusions about temporality. In addition, since not all women seroconvert after CT and HPV infection, our results may be affected by information bias. Furthermore, some residual confounding may still be present in this study, since both CT and HPV are associated with sexual practices. Finally, our study evaluated the association of HPV and CT through serology, and indicator of cumulative exposure, and not of acute or active genital infection.

Conclusions

The results of this population-based sample of women aged 16-64 years in Puerto Rico demonstrate that there is an association between CT and HPV antibodies (any, 16/18 and 6/11), with type-specific significant associations for HPV type 11, followed by HPV 16. Prospective studies need to be performed to clarify the role of CT as a cofactor in the natural history of HPV, specifically in the acquisition and/or persistence of infection. These studies should consider not only serostatus of infections, but also the incidence and prevalence of acute and active genital infections over time. This would permit an evaluation of the viral clearance process, persistence and reinfection. Serotyping the CT infections should also be considered. Our study supports the notion that CT seropositivity is an indicator of higher risk behaviors that increase exposure to HPV. Finally, the results of our study suggest the importance of planning and evaluation of practices for the control of these infections. It supports the importance of increased use of the HPV vaccine as a prevention mechanism, and the need for cervical cancer and CT screening in this high-risk population.

Resumen

Objetivos: Hay una alta prevalencia de infección con el virus del papiloma humano (VPH) en Puerto Rico, pero muy poco se sabe sobre la prevalencia de infección con *Chlamydia trachomatis* (CT) en mujeres puertorriqueñas saludables. Por lo tanto, nuestro objetivo es evaluar la seroprevalencia y la asociación entre la de VPH y CT. Métodos: Este fue un análisis de datos secundarios de un estudio transversal, basado en población, de VPH en mujeres de Puerto Rico (2010-2013). El ensayo immunoabsorbente ligado a enzimas (ELISA, por sus siglas en inglés) fue usado para detectar anticuerpos de CT y VPH. Modelos de regresión logística fueron usados para estimar los odds ratio (OR) para la asociación del estado serológico entre VPH y CT. Resultados: El estudio incluyó 524 mujeres, la media de edad fue de 42 años. En total, 97 (18.5%) mujeres eran CT seropositivas, 251 (47.0%) eran mujeres VPH seropositivas, y 57 (10.9%) tenían anticuerpos para ambos CT y VPH. Las mujeres que eran CT-seropositivas fueron más dadas a ($p<0.05$) también ser seropositivas a cualquier tipo de VPH ($OR_{adjustado}$: 1.7, IC 95% =1.1, 2.6), VPH 16/18 ($OR_{adjustado}$: 1.6, IC 95% =1.0, 2.6) y VHP 6/11 ($OR_{adjustado}$: 1.6, IC 95% =1.1, 2.6) que aquellas CT-seronegativas, después de ajustar por posibles factores de confusión. Conclusión: Dada la asociación entre la seropositividad entre CT y HPV, estudios longitudinales que evalúen si la infección de CT influencia la incidencia y persistencia de HPV en este grupo son necesarios.

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