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Association of tobacco use and the presence of anal warts in people who attend the anal Neoplasia clinic in Puerto Rico

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ABSTRACT

Background: Limited research exists regarding the association between smoking and anal warts. In this study, we evaluated this association among a clinic-based Hispanic population in Puerto Rico.

Methods: Cross-sectional study among eligible patients seen at the Anal Neoplasia Clinic of the University of Puerto Rico Comprehensive Cancer Center (2016–2023) (n = 920). Sociodemographic and clinical variables were collected from medical records. Patients underwent a high-resolution anoscopy (HRA) during the clinical visit; physicians assessed anal condylomas on HRA. Poisson regression models with robust standard errors were used to evaluate the association between smoking and anal warts. Demographic and clinical factors were also assessed.

Results: The mean age of participants was 45.8 ± 13.1 years, 66.4 % were men, and 21.6 % were current smokers. While 10.8 % self-reported a history of anogenital condylomas, 18.9 % had anal condylomas on clinical evaluation. A higher prevalence of anal condylomas was observed among current smokers (PR = 1.28, 95 % CI: 0.94–1.75) in comparison to non-smokers in adjusted analysis, but this was not statistically significant. However, a higher prevalence of anal condylomas was observed among younger individuals (PR = 0.96, 95 % CI: 0.96–0.98) and individuals with anal high-grade squamous intraepithelial lesions (HSIL) as compared to those with benign histology (PR = 1.74. 95 % CI: 1.09–2.77).

Conclusions: Although current smoking seemed to be positively associated with anal condylomas in this high-risk Hispanic population, this finding was not statistically significant as the power to detect an association was limited. However, younger age and HSIL diagnosis were associated with a higher prevalence of anal condylomas.

1. Introduction

Genital warts, also medically known as condylomas, are caused by an infection with low-risk human papillomavirus (HPV); HPV types 6 and 11 cause approximately 90 % of genital warts (Centers for Disease Control and Prevention, "Basic Information about HPV and Cancer | CDC." https://www.cdc.gov/cancer/hpv/basic_info/index.htm (accessed Mar. 01, 2022; Allevato and Donatti, 2005). Given that HPV infection invades the cells of the basal layer of the epidermis and produces viral particles (Allevato and Donatti, 2005), warts do not have to be visible to be spread from one person to another during sexual intercourse (Clinic, 2022). It is estimated that approximately three months after infection, the individual can begin to develop lesions (Allevato and Donatti, 2005). Factors associated with the development of genital warts include having unprotected

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relationships with multiple sexual partners, having had another sexually transmitted infection, and becoming sexually active at an early age (Clinic, 2022).

Smoking is associated with anogenital HPV infection and is a known risk factor for HPV-associated cancers (Keller, Jan. 2022). Current smoking has also been associated with anal high-grade squamous intraepithelial lesions (HSIL), a precursor for anal cancer (Keller, Jan. 2022). Nonetheless, its association with the development of anogenital warts is still under study (Tyros et al., Jan. 2021), as studies have found conflicting results.

A cohort study conducted in New York reported that the incidence of clinically confirmed genital warts was almost three times higher in women who smoked compared to those who did not, for both HIV-positive and negative women (Feldman et al., Mar. 1997). Similarly, a longitudinal study carried out on Nordic women reported that smokers had a higher risk of self-reported genital warts compared to their counterparts (Hansen, Aug. 2010). Another study conducted on 2,835 men from the Multicenter AIDS Cohort Study reported that men who smoked had a 23 % higher risk of having diagnosed or self-reported external genital warts than non-smokers (Wiley et al., 2009). On the contrary, the Health in Men (HIM) prospective cohort study among homosexual men in Australia found no association between cigarette smoking and the incidence of self-reported genital or anal warts in their study population (Jin, Jul. 2007). Likewise, two population-based case-control studies among women (Habel, 1998) and men (Van Den Eeden et al., Jul. 1998) in Washington state did not find an association between smoking and incident or recurrent genital condylomas.

While research studies suggest an association of smoking with genital warts (Tyros et al., Jan. 2021), some studies are based on self-report information, results are still conflicting, and research specifically on anal warts is more limited. Research in this area in Puerto Rico, a territory of the United States of America with a Hispanic population, is virtually nonexistent. Thus, the primary aim of this study was to evaluate the association between smoking and anal condylomas in a clinic-based sample in Puerto Rico. As a secondary aim, we evaluated other correlates of anal condylomas in this population.

2. Methods

A cross-sectional analysis was performed using the data from the Anal Neoplasia Clinic (ANC) of the University of Puerto Rico Comprehensive Cancer Center. The ANC is a specialized clinic certified by the AIDS Malignancy Consortium and is one of the first centers to offer high-resolution anoscopy (HRA) in Puerto Rico (Ramos-Cartagena et al., 2020). Patients of the ANC come directly to the clinic (self-referred) or are referred by physicians/clinics from the community due to anal health concerns. Reasons for the visit include previous abnormal anal cytology, anal cancer symptoms, anal lesions (abnormal biopsy), anal warts, and others.

Physicians from the ANC are trained and certified in HRA and treatment of lesions by the AIDS Malignancy Consortium (Ramos-Cartagena et al., 2020). Additionally, the clinic performs anal cancer screening, diagnosis, and treatment to patients referred either for (1) abnormal cytology, (2) risk of anal cancer, (3) associated symptoms, or (4) concern about their anogenital health or anal cancer. The ANC creates a medical file for the patient that collects sociodemographic information, and behavioral and clinical characteristics through a medical history (baseline survey) and physical examination (Keller, Jan. 2022).

The study population includes all patients 18 years or older who received services at the ANC between September 2016 and May 2023 (n = 1,315). Those who had missing information on smoking (n = 145) and/or the presence of anal condylomas (n = 250) were excluded from the present analysis. The final sample size after all exclusion criteria was 920 (70.0 %) individuals. This study was approved by the Institutional Review Board of the University of Puerto Rico, Medical Sciences Campus.

2.1. Clinical evaluation

At the baseline appointment in the clinic, the physician performs anal cytology, and high-risk HPV testing through COBAS and HRA (Roche, "The cobas® HPV Test." https://diagnostics.roche.com/global/en/products/params/cobas-hpv.html (accessed Mar. 31, 2022). In addition, the patient undergoes a physical check-up in which the physician examines if there is vulvar or penile irritation, lumps, swelling, ulcers, scars, vesicles, condylomas, or abnormal discharge. Areas suspicious of neoplasia are biopsied and sent to the histopathology laboratory (Keller, Jan. 2022). During the HRA report, the physician examines other significant clinical findings, such as anal bleeding, hemorrhoids, fissures, fistula, scars, excoriation, and condylomas. For anal condylomas, clinical findings are reported and their location is specified as intra-anal (IA) or perianal (PA). In addition, penile and vulvar condylomas are documented in the medical record.

2.2. Study variables

Clinically assessed anal condylomas (yes/no) was our main outcome variable. Information gathered in the medical history was used to ascertain three definitions of smoking: history of smoking, current smoking, and smoking amount. History of smoking included current smokers (defined as individuals who reported being currently smoking at the moment of their visit to the clinic), previous smokers (defined as patients with a history of smoking but who reported that they were not smoking at the moment of the appointment) and never smokers (defined as individuals who reported to have never smoked in their life). Current smoking (yes/no) was also evaluated as a separate variable. The "yes" category included individuals who reported being current smokers during the visit, while the "no" category included those who were previous or never smokers. The number of cigarettes currently smoked per day was also used as a continuous and categorical (0, 1–10, 11 +) variable.

Demographic and clinical variables such as age (continuous and categorical, < 30, 30–39, 40–49, 50–59, 60 + years), sex at birth (male/female), HIV status (yes/no), anal histology (benign, low-grade squamous intraepithelial lesions (LSIL), HSIL) and HPV vaccination were assessed from the patient interview and clinical evaluation. Also, other variables like lifetime number of sexual partners (1–5, 6–25, 26–49, 50–99, 100 +), lifetime receptive anal intercourse (yes/no), and within the past 12 months (yes/no), self-reported history of genital condylomas, vulvar and penile condylomas at the clinical evaluation (yes/no), and sexual risk group (men who have sex with men (MSM), men who have sex with women (MSW), women) were considered in the analysis.

2.3. Statistical analysis

Descriptive statistics were used to evaluate the sociodemographic, behavioral, and clinical characteristics of the study participants. The proportion of patients who were current smokers and the percentage of patients with anal condylomas was estimated. Contingency tables were used to evaluate the association between current smoking, history of smoking (current, previous, and past), and daily smoking amount (0, 1–10, 11 + cigarettes) with anal condylomas, as well as the association of potential confounders with these variables.

Bivariate analysis was also conducted to evaluate the association between smoking and condylomas using the Pearson chi-squared test and Fisher's exact test. In addition, the associations between demographic (age), clinical (HIV status, histology results), and lifestyle variables (number of sexual partners, sexual risk group, history of anal sex) were also assessed on bivariate analysis. Variables included in the bivariate analysis were selected based on the literature review on risk factors for anal condylomas. Variables with a $p < 0.05$ in the bivariate analysis, as well as number of sexual partners in the past 12 months due to their relevance in the literature, were considered in the multivariable

regression models. To assess the magnitude of the association between each smoking variable and anal condylomas, the crude and covariate-adjusted prevalence ratio (PR) was estimated with 95 % confidence through Poisson regression, using the Taylor series linearization approach to calculate robust estimates of standard errors for the regression coefficients. In addition, another multivariable model was done to assess the relationship between demographic, clinical, and lifestyle factors with anal condylomas, based on the variables that were relevant to the bivariate analysis. Interaction terms were assessed using the likelihood ratio test. All the analyses were done using Stata for Windows, Version 17 (Stata Corporation, College Station, TX).

3. Results

3.1. Characteristics of the study population

The mean age of the patients from the ANC was 45.8 ± 13.1 years. Overall, 66.4 % of patients were men, 71.1 % were living with HIV, 21.6 % were current smokers, and 70.7 % reported having had receptive anal sex in their lifetime. While 10.7 % of participants self-reported the history of anogenital warts, 18.9 % had anal warts on the clinical evaluation. Among patients with condylomas, 46.5 % had intra-anal condylomas, 27.3 % *peri*-anal, and 26.2 % had both (Table 1). Additionally, 6.1 % of women had vulvar condylomas and 1.3 % of men had penile condylomas (data not shown).

3.1.1. Bivariate analysis

A higher prevalence of anal condylomas was observed in men (21.3 %) than in women (14.2 %), and in MSM (22.6 %) in comparison with MSW (7.4 %) and women (14.4 %) ($p < 0.05$). In addition, a higher prevalence of anal condylomas was observed in individuals aged < 30 years (33.6 %) and those aged 30–39 years (30.2 %), as compared to individuals from older cohorts ($p < 0.0001$). With respect to smoking, bivariate analysis did not show a higher prevalence of genital warts in current smokers versus non-smokers (22.6 % vs. 17.9 %, p-value = 0.132). Similarly, no significant difference in condyloma prevalence was observed by smoking status (p-value = 0.222) or number of cigarettes smoked per day (p-value = 0.879). Other variables associated with higher prevalence of anal condylomas in the bivariate analysis included HIV status, lifetime receptive anal intercourse (ever), and HSIL (Table 1). Although clinical information on vulvar and penile warts was available for a study sub-sample (199 women and 376 men), results also showed a strong association between having condylomas at these anatomical sites and having anal warts (Table 1).

3.1.2. Multivariable analysis

Multivariable regression modeling showed that although current smokers had a higher prevalence of anal condylomas (PR = 1.28, 95 % CI: 0.94–1.75), this result was not statistically significant in the adjusted analysis. Similarly, current (PR = 1.29, 95 % CI: 0.91–1.82) and previous (PR = 1.02, 95 % CI: 0.73–1.42) smokers did not show a significantly higher prevalence of anal condylomas when compared to individuals who have never smoke. Similar results were observed when evaluating the association between the number of cigarettes smoked per day (categorical and continuous variables) (Table 2). In the multivariable model constructed for factors associated with anal condylomas on the bivariate analyses, we observed that younger individuals (PR = 0.96, 95 % CI: 0.96–0.98) had a higher prevalence of anal condylomas than older individuals. In addition, individuals with HSIL had a higher prevalence of anal condylomas (PR = 1.74, 95 % CI: 1.09–2.77) in comparison to those with benign histology (Table 3). Moreover, individuals without HIV that attended the clinic had a lower prevalence of anal condylomas (PR = 0.60, 95 % CI: 0.44–0.80) in comparison to those with HIV.

Table 1
Factors associated with anal condylomas (clinical evaluation) in people who attend the Anal Neoplasia Clinic in Puerto Rico. (n = 920).

	Anal Condylomas (Clinical evaluation)			
	Overall	No	Yes	p-value
	n (%)	n (%)	n (%)	
Age (years)				
Mean (±SD)	45.8 (±13.1)	45.1 (±12.9)	39.9 (±12.6)	
<30	125 (13.6)	83 (66.4)	42 (33.6)	
30–39	199 (21.6)	139 (69.9)	60 (30.2)	
40–49	207 (22.5)	178 (86.0)	29 (14.0)	**<0.0001**
50–59	243 (26.4)	216 (88.9)	27 (11.1)	
60+	146 (15.9)	130 (89.0)	16 (11.0)	
Sex at birth				
Male	611 (66.4)	481 (78.7)	130 (21.3)	**0.01**
Female	309 (33.6)	265 (85.8)	44 (14.2)	
Sexual Risk Group [a]				
MSW	54 (6.0)	50 (92.6)	4 (7.4)	**0.001**
MSM	553 (60.5)	428 (77.4)	125 (22.6)	
Women	306 (33.5)	262 (85.6)	44 (14.4)	
Current Smoking				
No	721 (78.4)	592 (82.1)	129 (17.9)	0.132
Yes	199 (21.6)	154 (77.4)	45 (22.6)	
Smoking status				
Never	394 (42.8)	319 (81.0)	75 (19.0)	0.222
Previous	327 (35.6)	273 (83.5)	54 (16.5)	
Current	199 (21.6)	154 (77.4)	45 (22.6)	
Smoking Amount (cigarettes per day)[b]				
Mean (±SD)	10.2 (±7.6)	8.4 (±6.9)	10.0 (±5.3)	
0	736 (83.2)	603 (81.9)	133 (18.1)	0.879
1–10	101 (11.4)	81 (80.2)	20 (19.8)	
11+	48 (5.4)	40 (83.3)	8 (16.7)	
HIV Status [c]				
Negative	264 (28.9)	545 (84.1)	103 (15.9)	**0.001**
Positive	648 (71.1)	196 (74.2)	68 (25.8)	
Histology[d]				
Benign	145 (16.8)	126 (86.9)	19 (13.1)	
LSIL	355 (41.2)	295 (83.1)	60 (16.9)	**0.019**
HSIL	362 (42.0)	279 (77.1)	83 (22.9)	
HPV Vaccine [e]				
No	751 (86.7)	616 (82.0)	135 (18.0)	0.159
Yes	115 (13.3)	88 (76.5)	27 (23.5)	
Lifetime number of sexual partners[f]				
1–5	262 (28.9)	222 (84.7)	40 (15.3)	
6–25	299 (33.0)	233 (77.9)	66 (22.1)	
26–49	90 (9.9)	73 (81.1)	17 (18.9)	0.252

(*continued on next page*)

Table 1 (*continued*)

	Anal Condylomas (Clinical evaluation)			
	Overall	No	Yes	p-value
50–99	109 (12.0)	91 (83.5)	18 (16.5)	
100+	147 (16.2)	115 (78.2)	32 (21.8)	
Number of sexual partners in the last 12 months[g]				
0	222 (25.3)	192 (86.5)	30 (13.5)	0.066
1–10	577 (65.9)	460 (79.7)	117 (20.3)	
11+	77 (8.8)	60 (77.9)	17 (22.1)	
Receptive Anal Intercourse (ever) [h]				
No	264 (29.3)	228 (86.4)	36 (13.6)	**0.007**
Yes	637 (70.7)	501 (78.7)	136 (21.3)	
History of Condyloma (Self-reported)				
No	821 (89.2)	687 (83.4)	134 (16.32)	**<0.0001**
Yes	99 (10.8)	59 (59.60	40 (40.4)	
Vulvar condylomas (n = 309 women) [i]				
No	187 (93.9)	163 (87.2)	24 (12.8)	**<0.001***
Yes	12 (6.1)	1 (8.3)	11 (91.7)	
Penile condylomas (n = 611 men) [j]				
No	371 (98.7)	271 (73.0)	100 (27.0)	**0.022***
Yes	5 (1.3)	1 (20.0)	4 (80.0)	
Condyloma location (n = 174 persons with condylomas) [k]				
Perianal	47 (27.3)	—	—	
Intraanal	80 (46.5)	—	—	——
Both	45 (26.2)	—	—	

Excluded missing value [a] 5, [b] 35, [c] 8, [d] 58, [e] 54, [f] 13, [g] 44, [h]19, [i] 110, [j] 235, [k] 2. *Fisher exact test was used. Abbreviations: HIV, human immunodeficiency virus; HSIL, High grade squamous intraepithelial lesion; LSIL, Low-grade squamous intraepithelial lesion; HPV, human papillomavirus; MSM, men who have sex with men.

Table 2
Prevalence ratio of smoking with anal condylomas, Anal Neoplasia Clinic, Puerto Rico.

	n	Crude PR (95 % CI)*	Adjusted PR (95 % CI)*
Current smoking			
No	867	1.00	1.00
Yes		1.22 (0.88–1.66)	1.28 (0.94–1.75)
Smoking status			
Never		1.00	1.00
Previous	867	0.86 (0.62–1.19)	1.02 (0.73–1.42)
Current		1.14 (0.81–1.60)	1.29 (0.91–1.82)
Smoking Amount (cigarettes per day, categorical)			
0		1.00	1.00
1–10	835	1.13 (0.75–1.74)	1.28 (0.85–1.92)
11+		0.82 (0.41–1.66)	1.10 (0.54–2.21)
Smoking amount (cigarettes per day, continuous)	822	1.00 (0.98–1.03)	1.01 (0.99–1.04)

* Poisson regression models evaluating the association of each smoking variable with anal condylomas. For the Adjusted PR, models were adjusted by age (years; continuous), sexual risk type, HIV status, and number of sexual partners (last 12 months). Analyses are based on individuals with complete information on the variables evaluated.

Table 3
Prevalence ratio of factors associated with anal condylomas, Anal Neoplasia Clinic, Puerto Rico*.

	n	Crude PR (95 % CI)*	Adjusted PR (95 % CI)*
Age (years)	816	**0.97 (0.95–0.98)**	**0.96 (0.96–0.98)**
Sexual Risk Group			
MSW		1.0	1.0
MSM	816	**3.59 (1.18–10.88)**	2.16 (0.72–6.53)
Women		2.35 (0.76–7.31)	1.88 (0.62–5.69)
HIV Status			
Negative		1.0	1.0
Positive		**0.59 (0.44–0.79)**	**0.60 (0.44–0.80)**
Histology			
Benign	816	1.0	1.0
LSIL		1.20 (0.73–1.98)	1.16 (0.71–1.89)
HSIL		**1.79 (1.12–2.88)**	**1.74 (1.09–2.77)**
Number of sexual partners (12 months)			
0		1.0	1.0
1–10	816	**1.38 (0.95–2.02)**	0.84 (0.57–1.24)
11+		1.52 (0.87–2.63)	0.74 (0.42–1.31)

*Crude and multivariable Poisson regression models evaluating factors associated with anal condylomas. Analyses based on individuals with complete information on the variables evaluated.

4. Discussion

To our knowledge, this is the first study to evaluate the association of tobacco use and anal condylomas in Puerto Rico, and among the first studies exclusively in a Hispanic population. This is of relevance as while previous research efforts have evaluated the association between smoking and anogenital warts, findings are still somewhat conflicting, few studies have evaluated Hispanic populations, and there is limited literature that focuses specifically on anal warts.

Concerning the study population, we observed that the prevalence of current smoking in our study population was 21.6 %, much higher than that observed in the general population of Puerto Rico (9.6 %) (Centers for Disease Control and Prevention and National Center for Chronic Disease Prevention and Health Promotion, "BRFSS Prevalence Trends Data,", 2015). Additionally, the prevalence of clinically confirmed anal condylomas among study subjects was 18.9 %, although only 10.7 % of participants self-reported a history of genital condylomas; suggesting that 16.2 % of those who presented condylomas in the clinical evaluation did not know their existence. This is consistent with the fact that condylomas might be invisible to the naked eye, and affected individuals may be unaware of their infection status(Das, Sep. 2020).

In the present study, current smokers (PR = 1.28, 95 % CI: 0.94–1.75) had a higher prevalence of having anal condylomas when compared with non-smokers; however, this finding was not statistically significant. Similarly, no significant association was observed when comparing previous smokers (PR = 1.02, 95 % CI: 0.73–1.42) and current smokers (PR = 1.29, 95 % CI: 0.91–1.82) versus individuals who have never smoked. Similarly, the HIM prospective cohort study observed no association between cigarette smoking and the incidence of self-reported genital or anal warts in their study population of MSM in Australia(Jin, Jul. 2007).

While studies specifically for anal warts are limited, smoking has been associated with an increased risk of being diagnosed with genital condylomas in large population studies (Tyros et al., Jan. 2021; Hansen, Aug. 2010). Munk et al., conducted a population-based cross-sectional study involving 22,900 men aged 18–45 years in Denmark. This study collected self-reported clinically diagnosed genital warts and reported that 31.0 % of the population was currently smoking. They showed that men who were current or former smokers had an increased risk for self-reported genital warts (OR = 1.4, CI 95 %: 1.30–1.60) (Munk et al., Dec. 2012). A cross-sectional study conducted among a university population

(n = 9,259) in Italy compared the prevalence of self-reported genital warts, which were subsequently confirmed by a clinical evaluation. This study showed that men who currently smoked had higher odds of self-reported genital warts (OR = 4.6, 95 % CI: 2.05–10.3) than those who did not smoke (Cocchio et al., 2018).

Additionally, other studies have shown that the greater the number of cigarettes per day, the greater the risk. For example, a retrospective case-control study in Australia showed that people who smoked 11 or more cigarettes per day had a higher risk (OR = 1.9, CI 95 %: 1.00–2.30) of developing genital warts than people who smoked 1–10 cigarettes per day (OR = 1.3, CI 95 %: 1.00–1.80) (Wen et al., 1999). Furthermore, a case-control study in the Czech Republic reported a 0.5 higher risk in men and 3.0 in women who smoked more than 10 cigarettes per day than those who smoked 2–10 cigarettes per day (Petráš and Adámková, Jul. 2015). In our study, we did not see a higher prevalence of anal condyloma by cigarette consumption (PR = 1.01, 95 % CI: 0.99–1.04). Moreover, when categorizing the variable, we did not observe differences between individuals who consume 1–10 cigarettes per day (PR = 1.28, CI 95 %: 0.85–1.92) and 11 + per day (PR = 1.10, CI 95 %: 0.54–2.21), compared to the non-smokers.

Tobacco use is a known risk factor for HPV-associated cancers. There is a gradient in which, the greater the amount of tobacco, the greater the damage. As Wiley, D. J. and contributors mentioned in their study on men, the causal pathway between HPV and smoking is complex and multidimensional (Wiley et al., 2009). Although anogenital warts, caused mainly by HPV 6 and 11, are rarely malignant, it has been seen that smoking can affect multiple metabolic pathways (Wiley et al., 2009). Smoking may influence the incidence and persistence of HPV infections by suppressing local immune function, increasing excessive cell proliferation, protein turnover, unregulated proinflammatory factors, or induced host DNA damage resulting in increased susceptibility to infection (Schabath et al., Jan. 2012). In addition, smoking decreases the ability to phagocytose or destroy bacteria and eliminate dead cells (Schabath et al., Jan. 2012).

Our study showed that younger individuals had a higher prevalence of anal condylomas in this clinic-based Hispanic population. This is consistent with ample research on the epidemiology of anogenital warts. In the systematic review by Patel et al., the incidence of anogenital warts peaked among women aged 24 years or less and between men aged 25 and 29 years (H. Patel, M. Wagner, P. Singhal, and S. Kothari, "Systematic review of the incidence and prevalence of genital warts," BMC Infect Dis, vol. 13, no. 1, Jan., 2013). Similarly, the study by Jin et al. showed that the incidence of genital warts and anal warts was significantly associated with younger ages in HIV-negative homosexual men (Jin, Jul. 2007). Likewise, in the study by Petráš and Adámková in the Czech Republic, the highest incidence in patients with a history of genital warts was in the age group of 21 to 25 years (Petráš and Adámková, Jul. 2015). Our study also showed that individuals diagnosed with HSIL had a higher prevalence of anal condylomas in comparison to those without lesions. This result is consistent with a longitudinal study (SPANC) among gay and bisexual men aged 35 years and older, in Sydney, Australia, that found that anal warts were strong predictors for high-grade anal lesions (OR = 1.69 95 % CI: 1.16–2.46) (Goddard, Oct. 2020). Moreover, a Danish nationwide longitudinal study, that assessed factors associated with the progression of anal high-grade lesions to anal cancer, reported an increased risk of anal cancer among those with a history of genital warts (Faber et al., Oct. 2022) Finally, our results showed that people with HIV had a lower prevalence of anal condylomas in comparison to those without HIV. We hypothesize that this result is mainly because 13.3 % of people without HIV came to our clinic due to anal condylomas versus only 1.5 % of people with HIV ($p < 0.001$, data not shown). Also, a higher proportion of people with HIV than HIV-negative individuals (34.5 % vs. 13.4 %, respectively) were excluded from the study due to missing information on condylomas or smoking. Both situations could lead to selection bias, potentially resulting in an inaccurate estimation of the relationship between HIV and condylomas.

Among study limitations, the cross-sectional study design does not allow us to assess causality, while reduced sample size and limited power may have restricted our ability to detect a significant association between smoking and anal warts. Limited power is reflected in the confidence intervals range and by the fact that the number of recent sexual partners is only borderline significantly to anal condylomas. In addition, the study was constrained in its ability to evaluate the dose–response relationship between frequency (every day, some days, never) and years of tobacco use, and anal warts, due to incomplete data on these variables. This study may also be affected by information bias, as smoking and sexual activity were self-reported. Moreover, when comparing individuals who were included in the study to those who were excluded due to missing information on smoking or anal condylomas, we observed differences by age and HIV status, but not for sex at birth, number of partners (last 12 months), and histology. Thus, the observed differences between eligible and non-eligible individuals, the referral process, and reasons for patients to attend the ANC (e.g., due to anal health concerns) could lead to selection bias, potentially affecting the internal validity of the study and generalizability of findings to the general population of Puerto Rico.

5. Conclusions

Although current smoking seemed to be positively associated with anal condylomas in this cross-sectional study among a high-risk Hispanic population, this finding was not statistically significant, and the power to detect an association was limited. However, a higher prevalence of anal condylomas was observed among individuals with younger age and with HSIL. For future studies, it is recommended to use longitudinal designs, and a larger sample size to increase limited power, and further evaluate the time and frequency of smoking exposure. These studies should consider Hispanic individuals, due to their low representation in the scientific literature within this research area. Education should continue to be promoted among clinic-based high-risk populations about the risks of tobacco use as well as the importance of HPV vaccination to reduce the risk of HPV-associated disease.

Ethics.

The University of Puerto Rico Institutional Review Board granted ethical approval for this study (IRB #: A1810215).

Précis: While the higher prevalence of anal condylomas was observed among current smokers in this cross-sectional study, no statistically significant association was observed. However, younger age and HSIL were associated with increased prevalence of this condition.

CRediT authorship contribution statement

Tanialy Rivera-Santiago: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis. **Jeslie M. Ramos-Cartagena:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Claudia Amaya-Ardila:** Visualization, Formal analysis. **Cristina Muñoz:** Writing – review & editing, Project administration, Investigation. **Humberto M. Guiot:** Writing – review & editing, Project administration, Investigation. **Vivian Colón-López:** Writing – review & editing, Project administration, Investigation. **Miriam Matos:** Writing – review & editing, Project administration, Investigation. **Maribel Tirado-Gómez:** Writing – review & editing, Project administration, Investigation. **Ana Patricia Ortiz:** .

Declaration of competing interest

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Data availability

Data will be made available on request.

References

Allevato, M.A., Donatti, L.B., 2005. VERRUGAS GENITALES dr miguel angel. Educación Continua.

Centers for Disease Control and Prevention and National Center for Chronic Disease Prevention and Health Promotion, "BRFSS Prevalence & Trends Data," 2015. https://www.cdc.gov/brfss/brfssprevalence/. (accessed May 22, 2022).

Centers for Disease Control and Prevention, "Basic Information about HPV and Cancer | CDC." https://www.cdc.gov/cancer/hpv/basic_info/index.htm (accessed Mar. 01, 2022).

Mayo Clinic, "Verrugas genitales - Síntomas y causas - Mayo Clinic," Jan. 14, 2022. https://www.mayoclinic.org/es-es/diseases-conditions/genital-warts/symptoms-causes/syc-20355234 (accessed Apr. 23, 2022).

S. Cocchio, C. Bertoncello, T. Baldovin, A. Buja, S. Majori, and V. Baldo, "Self-reported genital warts among sexually-active university students: A cross-sectional study," *BMC Infect Dis*, vol. 18, no. 1, Jan. 2018, doi: 10.1186/S12879-018-2954-7.

Das, S., Sep. 2020. Human Papillomavirus Infection: Management and Treatment. Human Papillomavirus. https://doi.org/10.5772/INTECHOPEN.92397.

Faber, M.T., Frederiksen, K., Palefsky, J.M., Kjaer, S.K., Oct. 2022. A nationwide longitudinal study on risk factors for progression of anal intraepithelial neoplasia grade 3 to anal cancer. Int. J. Cancer 151 (8), 1240. https://doi.org/10.1002/IJC.34143.

Feldman, J., Chirgwin, K., Dehovitz, J., Minkoff, H., Mar. 1997. The association of smoking and risk of condyloma acuminatum in women. Obstet. Gynecol. 89 (3), 346–350. https://doi.org/10.1016/S0029-7844(97)00011-2.

Goddard, S.L., et al., Oct. 2020. Prevalence and association of perianal and intra-anal warts with composite high-grade squamous intraepithelial lesions among gay and bisexual men: Baseline data from the study of the prevention of anal cancer. AIDS Patient Care STDS 34 (10), 436–443. https://doi.org/10.1089/APC.2020.0067/ASSET/IMAGES/LARGE/APC.2020.0067_FIGURE1.JPEG.

H. Patel, M. Wagner, P. Singhal, and S. Kothari, "Systematic review of the incidence and prevalence of genital warts," *BMC Infect Dis*, vol. 13, no. 1, Jan. 2013, doi: 10.1186/1471-2334-13-39.

L. A. HABEL, S. K. VAN DEN EEDEN, K. J. SHERMAN, B. MCKNIGHT, A. STERGACHIS, and J. R. DALING, "Risk factors for incident and recurrent condylomata acuminata among women. A population-based study," *Sex Transm Dis*, vol. 25, no. 6, pp. 285–292, Jul. 1998, doi: 10.1097/00007435-199807000-00003.

Hansen, B.T., et al., Aug. 2010. Association between smoking and genital warts: longitudinal analysis. Sex. Transm. Infect. 86 (4), 258–262. https://doi.org/10.1136/STI.2009.038273.

Jin, F., et al., Jul. 2007. Risk factors for genital and anal warts in a prospective cohort of HIV-negative homosexual men: The HIM study. Sex. Transm. Dis. 34 (7), 488–493. https://doi.org/10.1097/01.OLQ.0000245960.52668.E5.

Keller, K., et al., Jan. 2022. Association of smoking with anal high-risk HPV infection and histologically confirmed anal high-grade squamous intraepithelial lesions among a clinic-based population in Puerto Rico. Cancer Treat Res Commun 30. https://doi.org/10.1016/j.ctarc.2021.100503.

Munk, C., Nielsen, A., Liaw, K.L., Kjaer, S.K., Dec. 2012. Genital warts in men: A large population-based cross-sectional survey of Danish men. Sex. Transm. Infect. 88 (8), 640–644. https://doi.org/10.1136/SEXTRANS-2012-050512.

Petráš, M., Adámková, V., Jul. 2015. Rates and predictors of genital warts burden in the czech population. Int. J. Infect. Dis. 35, 29–33. https://doi.org/10.1016/J.IJID.2015.04.002.

J. M. Ramos-Cartagena, C. M. Pérez, H. M. Guiot, C. P. Amaya-Ardilla, M. Tirado-Gómez, and A. P. Ortiz, "Assessment of Anal Cancer Screening Tools in Detecting High-Grade Anal Squamous Intraepithelial Lesions in Women," *J Low Genit Tract Dis*, vol. 24, no. 1, 2020, doi: 10.1097/LGT.0000000000000497.

Roche, "The cobas® HPV Test." https://diagnostics.roche.com/global/en/products/params/cobas-hpv.html (accessed Mar. 31, 2022).

Schabath, M.B., Villa, L.L., Lazcano-Ponce, E., Salmerón, J., Quiterio, M., Giuliano, A.R., Jan. 2012. Smoking and human papillomavirus (HPV) infection in the HPV in men (HIM) study. Cancer Epidemiol. Biomark. Prev. 21 (1), 102–110. https://doi.org/10.1158/1055-9965.EPI-11-0591.

Tyros, G., Mastraftsi, S., Gregoriou, S., Nicolaidou, E., Jan. 2021. Incidence of anogenital warts: epidemiological risk factors and real-life impact of human papillomavirus vaccination. Int. J. STD AIDS 32 (1), 4–13. https://doi.org/10.1177/0956462420958577.

Van Den Eeden, S.K., Habel, L.A., Sherman, K.J., Mcknight, B., Stergachis, A., Daling, J. R., Jul. 1998. Risk factors for incident and recurrent condylomata acuminata among men a population-based study. Sex. Transm. Dis. 25 (6), 278–284. https://doi.org/10.1097/00007435-199807000-00002.

Wen, L.M., Estcourt, C.S., Simpson, J.M., Mindel, A., 1999. Risk factors for the acquisition of genital warts: Are condoms protective? Sex. Transm. Infect. 75 (5), 312–316. https://doi.org/10.1136/STI.75.5.312.

Wiley, D.J., Elashoff, D., Masongsong Emmanuel, V., Harper, D.M., Gylys, K.H., 2009. Smoking Enhances Risk for New External Genital Warts in Men - ProQuest. Int. J. Environ. Res. Public Health 6 (3), Mar.