



INFECTIOUS DISEASE

Cervical, oral and anal Human papillomavirus infection in women attending the Dermatology Unit of a regional reference hospital in Genoa, Italy: a prevalence study

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Keywords

Human papillomavirus infection • Prevalence • Cervical infection • Anal infection

Summary

Human papillomavirus (HPV) infection is the most common sexually transmitted infection (STI) worldwide. In women with genital infection, the virus can be transmitted by sex to the oral cavity of their partners and then to their own oral cavity. The aim of the present study was to establish the prevalence of cervical/anal/oral HPV infection in women attending the Dermatology Unit of the Policlinico San Martino of Genoa, the regional reference hospital in Liguria, Italy.

Methods. Between January 2016 and December 2018, the female patients attending the STI center (cases) and those requiring a full body skin examination for skin cancer screening ("supposed" healthy population: controls) were recruited. Cervical/anal/oral samples were collected with ThinPrep liquid based cytology preparation system: polymerase chain reaction for HPV and cytologi-

cal evaluation were performed. Overall, 85 cases and 31 controls were recruited.

Results. Cervical HPV infection was detected in 60% of the cases and 48% of the controls; anal HPV infection in 44% of the cases and 26% of the controls. Cervical and anal HPV infection resulted associated, especially in the control group. Moreover, 32% of the cases and 29% of the controls proved HPV positive in the oral cavity. In the cases of our series, prevalence of cervical, anal and oral HPV infection was higher compared with the controls.

Conclusions. The high prevalence of anal-oral infections and the frequent association between anal and cervical infections, provide reason to suggest HPV screening also in the anal and oral regions, which may represent HPV reservoirs and grounds for cancer development.

Introduction

Human papillomavirus (HPV) infection is the most common sexually transmitted infection (STI) worldwide and a causative agent for cancer of the cervix uteri, vagina, vulva, penis, anus and oropharynx [1]. Especially women pay a high price for HPV infection: the majority of cancers attributable to HPV worldwide are cervical cancers representing the fourth most common cause of death from cancer in women [1]. After establishing infection, HPV can spread from one region of the body to another anatomically close area: indeed, patients with genital infection have an increased risk of anal infection. Moreover, in women with genital infection, the virus can be transmitted by sex to the oral cavity of their partners and then to their own oral cavity [1, 2].

Data on the prevalence of genital HPV infection are disparate, depending on demographic, geographic and clinical factors of the studied populations. The different prevalence of genital HPV infection among countries and even among regions of the same countries is influenced by migration, sexual behavior, type of

cervical lesion in women sampled, and diagnostic methods.

In 2014, the Center for Disease Control and Prevention (CDC) estimated the prevalence of cervical HPV infection of any type (both high and low risk genotypes) at 42.7% in a nationally representative US population [3]; similarly, an Italian studies from Southern Italy found overall prevalences of HPV infections of 45% in pregnant women during the first trimester [4]; a recent report from southern Mexico observed a higher prevalence of genital HPV infection (54.2%) among 7313 females aged 14-97 years: the cohort included women who had no intraepithelial lesions, women with low-grade and high grade squamous intraepithelial lesions, and women with cervical cancer [5]. In our previous study involving patients attending the STI clinic and healthy subjects, we found an overall prevalence of genital HPV infection of 50%, with a slightly higher prevalence in STI patients (51%) than in the healthy population (43%) [6].

Data on the prevalence of anal and oral HPV infection and their association with genital HPV infection in Italian women are few.

The present study aimed to establish the prevalence of HPV infection not only in cervical but also in anal and oral samples collected in the women attending the Dermatology Unit of the Policlinico San Martino, Genoa, the regional reference hospital in Liguria, Italy.

Methods

Between January 2016 and December 2018, the female patients attending the Dermatologic Unit of the Policlinico San Martino, Genoa, were asked to participate in the study, after giving written informed consent. The patients attending the STI outpatient clinic were recruited as “cases”, since we assumed they could be at moderate-high risk of HPV infection; the age-matched patients attending the Dermatology Unit for skin cancer screening were recruited as “controls”, since they could represent a supposed healthy population from the point of view of STI. Inclusion criteria were: to be over 18 years old and to show no overt clinical signs of ano-genital/oral/cutaneous HPV infection. Exclusion criteria were: age under 18, presence of cutaneous, ano-genital and/or oral warts, or having undergone treatment for warts in the last 6 months. Cervical, anal, oral samples were collected through a cytobrush by F.D. and G.C. in the STI outpatient clinic; samples were stored using the ThinPrep liquid based cytology preparation system, as previously described [7]. Polymerase chain reaction (PCR) for HPV and cytological evaluation were performed at the Pathology Unit of the Galliera Hospital, Genoa.

STATISTICAL ANALYSIS

Data from cases and controls were statistically compared using the Fisher's exact test and chi-square test, considering a p-value < 0.05 as significant.

Results

Overall, 116 female patients were recruited: 85 cases (median age: 37 years, [interquartile range 25-46 years]) and 31 controls (median age: 38 years, [interquartile range 27-42 years]).

Cervical HPV infection was detected in 66 of the total 116 recruited women (57%), 60% of the cases (17 low-risk [LR] HPV, 34 high-risk [HR] HPV) and 48% of the controls (5 LR-HPV, 10 HR-HPV).

In the anal region, 45 of the 116 women (39%) proved positive for HPV: they were 44% of the cases (18 LR-HPV, 19 HR-HPV) and 26% of the controls (4 LR-HPV, 4 HR-HPV).

In the oral cavity, 36 of the 116 women (31%) proved positive for HPV: they were 32% of the cases (14 LR-HPV, 13 HR-HPV) and 29% of the controls (4 LR-HPV, 5 HR-HPV).

Cytological results are detailed in Table 1. The difference in the prevalence of cervical, anal and oral HPV infection among cases and controls was not statistically significant ($p > 0.05$).

Overall, simultaneous HPV infection in the anal site (regardless to genotype) was detected in 30 of the 66 women with cervical HPV infection (45%). Considering the healthy subjects, among the 15 women with cervical HPV, 7 had also anal HPV infection

Tab. 1. Citological findings in HPV positive STI patients (cases) and apparently healthy subjects (controls).

	Cases			Controls			All 116 patients		
	85 STI patients			31 supposed healthy subjects					
	HPV+			HPV+			HPV+		
site of infection	global positivity	HR-HPV	LR-HPV	global positivity	HR-HPV	LR-HPV	global positivity	HR-HPV	LR-HPV
cervix	51 (60%)	34 (12 normal cytology, 21 L-SIL, 1 H-SIL)	17 (3 normal cytology, 14 L-SIL)	15 (48%)	10 (1 normal cytology, 9 L-SIL)	5 (5 L-SIL)	66 (57%)	44 (38%)	22 (19%)
anus	37 (44%)	19 (19 normal cytology)	18 (19 normal cytology)	8 (26%)	4 (4 normal cytology)	4 (4 normal cytology)	45 (39%)	23 (20%)	22 (19%)
oral cavity	27 (32%)	13 (13 normal cytology)	14 (14 normal cytology)	9 (29%)	5 (5 normal cytology)	4 (4 normal cytology)	36 (31%)	18 (15.5%)	18 (15.5%)

STI sexually transmitted infections; HR-HPV high-risk HPV; LR-HPV low risk HPV; L-SIL low-grade squamous intraepithelial lesion; H-SIL high-grade squamous intraepithelial lesion. In the group of cases, cervical and anal HPV infections were not statistically associated ($p > 0.05$); conversely, in the control group, cervical and anal HPV infection resulted significantly associated ($p = 0.0154$ at Fisher's exact test).

(47%) versus 1 of the 16 (6%) women that were cervical HPV-negative. Considering the STIs women, anal HPV infections were detected in 23 of the 51 (45%) women with cervical HPV infection versus 14 of the 34 (41%) women that were cervical HPV negative. Therefore, in the control group, cervical and anal HPV infection resulted significantly associated ($p = 0.0154$ at Fisher's exact test); conversely, in the group of cases, cervical and anal HPV infections were not statistically associated ($p > 0.05$).

Oral HPV infection was detected in 16 of the 66 women with cervical HPV infection (29%) and in 18 of the 45 women with anal HPV (40%). Oral-cervical and oral-anal HPV infection were not statistically associated ($p > 0.05$) using chi-square test.

Discussion

As we have previously observed in a cohort of male and female patients [7], in the STI women of the present series, the prevalence of cervical, anal and oral HPV infection (regardless of genotype) was only slightly higher (respectively 60, 44, 32%) than in the "presumed" healthy women (48, 26, 29%), without statistically significant difference between the two groups.

The prevalence of HR-HPV genital infection in this study resulted in line (38%) with one of our previous works (39%) [7] but definitely lower than that reported in a similar recent study from Czech Republic (53%) [8]. According to our work, the Czech authors observed that all HPV infections occurred more often in cases than in controls and found a frequent association between cervical and anal HPV infection (especially in the group of cases) [8].

Another recent study from Hungary showed a cervical HR-HPV infection prevalence of 11.1% among 4,000 eligible samples from a screening target population of women without histories of hysterectomies, immunosuppression and/or operations or samplings that affected the cervix [9], confirming the different prevalence in very close geographical areas.

Also in extra-European studies, the overall prevalence of genital HPV infection in women varies widely, especially based on the population studied. A study from Ghana recruiting women who had never attended cervical screening prior to the study, found a prevalence of 37.2%, with 31% of women carriers of HR-HPV infections [10]. A work from Nigeria investigating prevalence and concordance of cervical, vulval, oral and anal HPV infection among female sex workers showed a very high prevalence and concordance of HPV infections in these sites: 88% in the vulva, 84% in the cervix, 75% in the anus and 24% in the oral cavity [11].

Regarding the association between cervical and anal HPV infection, more than 10 years ago Goodman et al. found that it appears common for anal and cervical HPV infections to occur simultaneously. The high

degree of genotype-specific concordance between sites suggests that the cervix (or vagina) and anus may serve as reservoirs for HPV infection for the other anatomic sites [12]. Another study including 304 female sex workers in Amsterdam found a strong and significant concordance in vaginal and anal HR-HPV infection: logistic regression analyses demonstrated that having an anal HR-HPV infection was a risk factor for vaginal HR-HPV infection; likewise, vaginal HR-HPV infection was a risk factor of anal HR-HPV infection [13].

According to these studies [11-13], our work suggests that the presence of HPV genital infection in women is a risk factor for detection of HPV in the anal region. Although sexual intercourse is the primary route of anal infection, several authors have found that a history of anal intercourse is not the single risk factor for incident anal HR-HPV infection or anal cancer, suggesting alternative routes of transmission, including non-penetrative sex or inoculation through fomites or vaginal discharge. Concomitant HPV infection in different anatomical sites (cervix-vagina-anus, for example) might be due to viral shedding between contiguous anatomic structures and/or to autoinoculation through fingers [12, 14] or unhygienic practices, as the use of sex toys [15]. Also during hygienic practices the virus can spread from the vagina to contiguous regions such as the anus.

Therefore, the presence of HPV infection in an anatomic site suggests the need for a screening protocol in multiple anatomic sites. For example, in a subject with genital HPV infection associated with premalignant lesion of the cervix should also be taken into account the possible presence of HPV infection in other sites and offered the opportunity to screen for HPV DNA and premalignant lesions of the anus.

Unfortunately, despite the evidence of the association among cervical, anal, and oral HPV infections in women and men, to date, the Center for disease Control and Prevention (CDC) states that data are insufficient to recommend routine anal HPV infection and cancer screening among populations at risk for anal cancer (persons with HIV infection, men who have sex with men and those having receptive anal intercourse). However, the last CDC guidelines on STI treatment admit that certain clinical centers perform anal cytology to screen for anal cancer among high risk populations, followed by high resolution anoscopy (HRA) for those with abnormal cytological findings; the CDC guidelines report also that "HRA can be useful for diagnosis of high grade-squamous intraepithelial lesions (H-SIL), to monitor response to therapy or to conduct surveillance of H-SIL for evidence of progression" [16].

Conclusions

In conclusion, despite the limitation of the small sample size of our study, our data confirm the wide circulation of HPV not only in the genital sites but also

in the anal and oral ones; we therefore emphasize the need to improve the screening protocols for preventing HPV related cancers not only in the cervix but also in multiple anatomic sites, especially the anus.

Our results underlie the diffuse lack of awareness on this subject among the general population that is often unaware of having contracted a STI and highlight the urgent need of effective information campaigns [17]. The increase of knowledge on STIs to educate to sexual health through the rules of safe sex, the early diagnosis of STIs through screening tests for discovering asymptomatic infections, and prevention strategies (as anti-HPV vaccination) especially in high risk populations as the prison inmates [18], should all be encouraged by institutions like health services and schools.

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Conflict of interest statement

The authors have no conflict of interest nor funding sources to declare.

Authors' contributions

F.D. and G.C. conceived of the presented idea; A.H. developed the theory and performed the computations; A.H. and A.P. verified the analytical methods; all the authors discussed the results and contributed to the final manuscript. The manuscript has been approved by all authors.

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