ANTICANCER RESEARCH *40*: 2219-2223 (2020)
doi:10.21873/anticanres.14183

Prevalence of Cervico-vaginal High-risk HPV Types and Other Sexually Transmitted Pathogens in Anogenital Warts Patients

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Abstract. *Aim: To investigate the prevalence of cervico-vaginal co-infection with high-risk (HR) HPV types and other sexually transmitted pathogens (STPs) in women with anogenital warts (AGWs). Patients and Methods: In this cross-sectional study, cervico-vaginal smears of women with AGWs were examined with real-time polymerase chain reaction for the presence of HR-HPV types and common STPs. Women with recent cervical HPV infection and general population were used for comparisons. Results: A total of 689 women participated in the study. Among the examined groups, higher rates of cervico-vaginal co-infection with HR-HPV types and other STPs collectively were recorded in women with AGWs (p=0.0049 and p<0.004, respectively). Within the AGWs group, cervical co-infection with HR-HPV types was detected more often in women with recurrent disease (p<0.001). Conclusion: The higher rates of cervico-vaginal co-infection with HR-HPV types and common STPs in women with AGWs may affect their risk for cervical carcinogenesis and the natural course of their disease.*

Human papillomavirus (HPV) infection is the most common sexually transmitted infection globally. More than 100 HPV types have been identified, amongst which approximately 40 infect the anogenital area. Chronic infection with high-risk (HR) HPV types may lead to anogenital precancers and cancers. The strongest oncogenic activity within HR-HPV types is attributed to HPV 16 and HPV 18 (1, 2), primarily through the loss of genome stability (3, 4, 5).

In contrast to the carcinogenic potential of HR-HPV types, low-risk (LR) HPV types, primarily 6 and 11, are mostly implicated in the development of anogenital warts (AGWs) (6). Although benign in nature, AGWs confer a remarkable psychological burden on patients and considerable economic cost on health care systems, due to their tendency to recur after treatment (7, 8). Interestingly, co-infection with HR-HPV types has been frequently detected in tissue samples from AGWs (9-14). This may underlie the biological mechanism accounting for the increased risk of anogenital cancers in patients with AGWs (15). In contrast, little is known on the prevalence of HR-HPV types in cervical scrapings of patients with AGWs (16-17).

As far as the other sexually transmitted pathogens (STPs), namely Chlamydia trachomatis, *Mycoplasma genitalium, Ureaplasma parvum/Ureaplasma urealyticum (Ureaplasma spp), and Mycoplasma hominis*, are concerned, women with cervical HPV infection seem to exhibit higher rates of their presence, compared to those without HPV infection (18-22). Of note, this link may promote the HPV-driven cervical carcinogenesis (22). On the other hand, data on the other STPs infection rates in women with AGWs remain sparse.

Taken together, despite the reassuring nature of LR-HPV types recognized in the vast majority of women with AGW, their risk for cervical cancer may be exaggerated if cervical co-infection with HR-HPV types and other STPs is documented. To shed more light on that, we aimed to assess the prevalence of both HR-HPV types and other STPs in

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Key Words: High-risk HPV, smoking, anogenital warts, sexually transmitted infection, *Mycoplasma genitalium, Mycoplasma hominis, Ureaplasma spp*.

cervico-vaginal scrapings from female patients with AGWs, compared to that in women with recent cervical HPV infection and a control group.

Patients and Methods

The study included women aged 18-45 years presented to the Sexually Transmitted Infection Unit and the Outpatient Clinics of "Andreas Sygros" hospital for Skin and Venereal Diseases from May 2016 to May 2018. “Andreas Syngros” hospital, the major hospital in Greece dedicated to Dermatology and Venereology, is part of the public health system. The hospital serves the greater area of Athens and its suburbs and is a referral center for southern Greece. The Institutional Review Board of the hospital consented to the use of biological specimens of the participants for research purposes, according to World Medical Association Declaration of Helsinki guidelines (Study Approval Code: 1617004952).

Participants of the study were split into 3 groups. All women with AGWs were assigned to the first group (“AGWs group”). Women with a history of cervical HPV infection within the last year, as evidenced by PAP smear results, were included in the second group (“Cervical HPV group”), while those who visited the hospital for their routine dermatologic check-up consisted the third group (“Control group”). Women in the latter group should have documented a negative PAP smear within the last year and declined a history of sexually transmitted infections. Current pregnancy, menopause and history of a positive HIV or syphilis serology served as the exclusion criteria. All participants provided written informed consent for their participation in the study.

Cervico-vaginal specimen collection. Cervico-vaginal cell scrapings were collected by a clinician using a cytobrush. The scrapings were placed in a liquid-based cytological transport medium (Thin- Prep PreservCyt Solution; Hologic, Inc. Ltd., Manchester, UK) and stored at 4˚C until prepared for HPV and STPs molecular analyses.

HPV genotyping analysis. Molecular analyses for STPs and HPV types were performed at the Molecular Biology Diagnostic Center 'Bioiatriki', Athens, Greece. US Food and Drug Administration (FDA)-approved Roche Cobas® HPV test (Roche Molecular Systems, Pleasanton CA, USA) was applied for HPV testing. The current automated qualitative in vitro test detects 14 HR-HPVs. In detail, the method separately detects HPV16 and HPV18 combined with a set of 12 other HR-HPVs types together (31,33,35,39,45,51,52,56,58,59,66,68). DNA extraction was based on the COBAS 4800 Sample Preparation kit (Roche Molecular Systems). Pre-analytic procedure included specimens’ digestion under denaturation in specific conditions (Cobas® 4800 Sample pre-Buffer with heating, Roche Molecular Systems). B-globin DNA was used as internal control. According to the protocol, 3 ml liquid-based cytological sample was obtained by the semi-automated device, followed by amplification of target DNA based on a multiplex real-time polymerase chain reaction (RT-PCR) on a thermo-lightcycler and nucleic acid hybridization (Cobas® 4800 HPV Amplification/Detection Kit, Roche Molecular Systems).

STPs analysis. For STPs analysis, a combination of synchronous four multiplex RT-PCR reactions were performed using 5 μl of the already isolated and extracted DNA described above. All multiplex RT-PCRs were performed on the same thermocycling program (denaturation-amplification-extension) by applying the thermocycler, according to the manufacturer’s instructions. More specifically, the four RT-PCRs detected *Chlamydia trachomatis, Mycoplasma genitalium, Ureaplasma parvum/Ureaplasma urealyticum (Ureaplasma spp)*, and *Mycoplasma hominis*. The RT-PCR reaction uses an algorithm program of SACACE (Sacace Biotechnologies Srl, Como, Italy).

Statistical analysis. Multiple statistical analyses were carried out using the statistical package SPSS v.21.00 (IBM Corporation, Somers, NY, USA). Data were expressed as mean±S.D for quantitative variables and as frequencies (percentages) for qualitative variables. The Kolmogorov–Smirnov test was utilized for normality analysis of the quantitative variables. Comparison between the 3 groups in relation to the categorical variables was performed using the Chi-square test or z-test with Bonferroni correction. All tests were two-sided and statistical significance level was set at $p<0.05$.

Results

In total, 689 women participated in this study; of those, 196 were included in the “AGWs group”, 315 in the “Cervical HPV group” and 178 in the “Control group”. The mean age of the patients was 32 years (range=18-45 years). Women in the “AGWs group” were younger, compared to those in the “Cervical HPV group” and “Control group” (mean age in years: 30.4 *vs*. 32.4 *vs*. 33, respectively, $p=0.005$, Table I). Smoking status was also different across the 3 groups. The “AGWs group” comprised significantly more smokers, as compared to the “Cervical HPV group” and the “Control group” (52% *vs*. 37% *vs*. 22%, respectively, $p=0.001$, Table I).

Overall, a significant proportion of the study participants (25.25%) were positive for HR-HPV in cervico-vaginal HPV DNA analysis. The higher rate of HR-HPV infection was detected in the “AGWs group”, in comparison with the “Cervical HPV group” and the “Control group” (34.2% *vs*. 29.2% *vs*. 8.4%, respectively, $p=0.0049$, Table II). Women with recurrent AGWs, as defined by the presence of 2 or more episodes within the last 6 months, were more frequently diagnosed with cervico-vaginal HR-HPV types, as opposed to the remaining population of the “AGWs group” (63% *vs*. 25.3%, respectively, $p<0.001$, Table III).

The overall prevalence of the other STPs was 50.8% (Table II). Patients in the “AGWs group” exhibited significantly higher rates of other STPs infection, as compared to “Cervical HPV group” and the “Control group” (70.9% *vs*. 47.8% *vs*. 33.8%, respectively, $p<0.004$). In detail, 45.9% of patients in the “AGWs group” were diagnosed with *Ureaplasma spp*, 16.3% with *M. hominis* and 4.1% with *M. genitalium*. In contrast with the Chlamydia trachomatis co-infection rates which were similar across the study groups, co-infection with *Ureaplasma spp*, *M. hominis* and *M. genitalium* was more common in the “AGWs group”.

Table I. *Socio-demographic characteristics of patients.*

Cases (n=689)	AGWs group n=196	Cervical HPV group n=315	Control group n=178	*p*-Value
Age (mean)	30.41±8.3	32.43±7.8	33.08±9.32	**0.005**
Smoking status				
Yes (n=257)	102 (52%)	116 (37%)	39 (22%)	**0.001**
No (n=432)	94 (48%)	199 (63%)	139 (78%)	

AGW: Anogenital warts. Bold values denote significance.

Table II. *Prevalence of HR-HPV and STPs in different groups.*

Cases (n=689)	AGWs group (n=196)	Cervical HPV group (n=315)	Control group (n=178)	*p*-Value
Mycoplasma genitalium				**0.005**
Positive (n=11)	8 (4.1%)	2 (0.6%)	1 (0.6%)	
Negative (n=678)	188 (95.9%)	313 (99.4%)	177 (99.4%)	
Mycoplasma hominis				**0.005**
Positive (n=62)	32 (16.3%)	19 (6%)	11 (6.2%)	
Negative (n=627)	164 (83.7%)	296 (94%)	167 (93.8%)	
Ureaplasma spp				**0.005**
Positive (n=250)	90 (45.9%)	117 (37.1%)	43 (24.2%)	
Negative (n=439)	106 (54.1%)	198 (62.9%)	135 (75.8%)	
Chlamydia				0.652
Positive (n=27)	9 (4.6%)	13 (4.1%)	5 (2.8%)	
Negative (n=662)	187 (95.9%)	302 (95.9%)	173 (97.2%)	
HR-HPV				**0.0049**
Positive (n=174)	67 (34.2%)	92 (29.2%)	15 (8.4%)	
Negative (n=515)	129 (65.8%)	223 (70.8%)	163 (91.6%)	

HR-HPV: High-risk HPV sub-types (16/18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). AGW: Anogenital warts. Bold values denote significance.

Table III. *Prevalence of HR-HPV in patients with AGWs.*

Cases (n=196)	Single episode (n=150)	Recurrent AGWs (n=46)	*p*-Value
HR-HPV			**0.001**
Positive (n=67)	38 (25.3%)	29 (63%)	
Negative (n=129)	112 (74.7%)	17 (37%)	

HR-HPV: High-risk HPV sub-types (16/18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). AGW: Anogenital warts. Bold values denote significance.

Discussion

According to our findings, the prevalence of cervico-vaginal HR-HPV and other STPs co-infections in women with AGWs is higher, as opposed to that in women with recent cervical HPV infection and the general population. To our knowledge, the present is among the first studies that focused specifically on female patients with AGWs and used the above populations for comparisons in cervico-vaginal HR-HPV and other STPs co-infection rates.

The "AGWs group" included significantly more smokers, compared to both the "Cervical HPV group" and the "Control group". Smoking has been already shown to increase the incidence of AGWs (23), so the difference in the number of smokers between the "AGWs group" and the "Control group" was expected. However, the surprisingly different rates of smoking between the "AGWs group" and the "Cervical HPV group" underscores the need of further research to elucidate the possibly more deleterious role of smoking in AGWs development *per se*.

Approximately, one third of cervico-vaginal scrapings in the "AGWs group" were tested positive for HR-HPV, a percentage markedly different to that in the "Cervical HPV group" and "Control group". Past studies (8-14) estimated HR-HPV types in tissue samples from AGWs ranging from 11.6% to 53% (11, 14). Nonetheless, scant data exist when testing for HR-HPV types restricted to cervico-vaginal smears of patients with AGWs. A study from South Korea on 18 patients reported that 50% of cervical scrapings were infected with HR-HPV types (18), while a slightly higher rate was found by researchers in Ireland (16). Although, our rate of 34.2% is considerably lower compared to the aforementioned studies, it is strikingly similar to what was reported (33%) in an older study from Greece which included 100 patients with AGWs (17). Collectively, the discordance between our findings and those reported in the South Korean and Irish studies may be attributed to the intrinsic population characteristics, as well as the differences in sample size.

The association of AGWs with increased rates of cervico-vaginal HR-HPV infection is intriguing. As a result, women with AGWs, a traditionally considered benign disease, may have higher than expected risk of cervical carcinogenesis. Thus, they may benefit from having their cervical HR-HPV status assessed routinely. In case of positive findings, their follow-up recommendations may be subject to change, so they could be compatible with the existing guidelines on cervical cancer secondary prevention. Unfortunately, the increased costs of the additional examinations, along with their psychologic impact on the patients, should be taken into account as potential drawbacks of this strategy. Given that our cross-sectionally drawn conclusions inherently lack generalizability, their verification, along with the evaluation of the pros and the cons of our aforementioned proposal, should be an area of future investigation.

It is noteworthy that patients with recurrent AGWs were diagnosed with cervico-vaginal HR-HPV types more commonly, as opposed to those with a single episode of AGWs. Recurrent AGWs have already been associated with high HR-HPV DNA load both in cervical scrapings (18) and in AGWs tissue samples (9) in smaller studies. In line with these, our finding may indicate that HR-HPV types could trigger AGWs recurrences more often. However, future research is needed before final conclusions are reached.

The increased prevalence of other STPs in the cervico-vaginal smears of women with AGWs merits special attention. The cross-sectional design of our study precludes the determination of causality in this association. In other words, it is not clear whether the presence of AGWs made the acquisition of other STPs easier or *vice versa*. Furthermore, factors pertaining to the sexual life of the participants (*e.g.* number of partners, habits) may have influenced our results. In agreement with us, a cross-sectional study in men found a very high rate (67.5%) of urethral *U. urealyticum* carriage in patients with AGWs (24). Moreover, infections with *Chlamydia trachomatis* (21) and *Ureaplasma spp* (21, 22) were associated with cervical HPV infection and progression to cervical cancer (19, 20, 22).

In conclusion, our study showed that female patients with AGWs have higher rates of cervico-vaginal co-infection with both HR-HPV and STPs, compared to women with recent cervical HPV infection and the general population. Furthermore, recurrent AGWs were associated with higher risk of cervico-vaginal HR-HPV co-infection. In the context of the role of HR-HPV types and other STPs in cervical carcinogenesis, our findings may have implications regarding the actual risk of patients with AGWs for cervical cancer and their surveillance needs. In addition, our study raises the question of whether HR-HPV co-infections may affect the natural course of AGWs. Therefore, prospective studies in this field may be of paramount importance.

Conflicts of Interest

The Authors declare no conflicts of interest. No financial support was granted.

Authors' Contributions

Despoina Mortaki: Researcher, article writing. Efstathios Tsitsopoulos: Researcher. Eirini Louizou: Researcher. Evangelos Tsiambas: Researcher, paper writing. Dimitrios Peschos: Academic advisor. Antonios Galanos: Statistical analysis. Anna Tagka: Researcher, paper writing. Stamatis Gregoriou: Researcher, paper writing. Vasileios Sioulas: Researcher. Alexandros Stratigos: Academic advisor. Dimitrios Rigopoulos: Academic advisor. Electra Nicolaidou: Academic advisor, paper writing.

References

1 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans: Human papillomaviruses. IARC Monogr Eval Carcinog Risks Hum *90*: 1-636, 2007. PMID: 18354839.

2 Muñoz N, Castellsagué X, de González AB and Gissmann L: Chapter 1: HPV in the etiology of human cancer. Vaccine *24(Suppl 3:S3)*: 1-10, 2006. PMID: 16949995. DOI: 10.1016/j.vaccine.2006.05.115

3 Adam ML, Pini C, Túlio S, Cantalice JC, Torres RA and Dos Santos Correia MT: Assessment of the association between micronuclei and the degree of uterine lesions and viral load in women with human papillomavirus. Cancer Genomics Proteomics *12(2)*: 67-71, 2015. PMID: 25770189.

4 Evans W, Filippova M, Filippov V, Bashkirova S, Zhang G, Reeves ME and Duerksen-Hughes P: Overexpression of HPV16 E6* alters β-integrin and mitochondrial dysfunction pathways in cervical cancer cells. Cancer Genomics Proteomics *13(4)*: 259-273, 2016. PMID: 27365376.

5 Yoshida K, Kajiyama H, Inami E, Tamauchi S, Ikeda Y, Yoshikawa N, Nishino K, Utsumi F, Niimi K, Suzuki S, Shibata K, Nawa A and Kikkawa F: Clinical significance of ubiquitin-

associated protein 2-like in patients with uterine cervical cancer. In Vivo *34(1)*: 109-116, 2020. PMID: 31882469. DOI: 10.21873/invivo.11751

6 Garland SM, Steben M, Sings HL, James M, Lu S, Railkar R, Barr E, Haupt RM and Joura EA: Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine. J Infect dis *199(6)*: 805-814, 2009. PMID: 19199546. DOI: 10.1086/597071

7 Maw RD, Reitano M and Roy M: An international survey of patients with genital warts: perceptions regarding treatment and impact on lifestyle. Int J STD AIDS *9(10)*: 571-578, 1998. PMID: 9819106. DOI: 10.1258/0956462981921143

8 Insinga RP, Dasbach EJ and Elbasha EH: Assessing the annual economic burden of preventing and treating anogenital human papillomavirus-related disease in the US: analytic framework and review of the literature. Pharmacoeconomics *23(11)*: 1107-1122, 2005. PMID: 16277547. DOI: 10.2165/00019053-200523110-00004

9 Che YM, Wang JB and Liu YH: Correlation between deoxyribonucleic acid loads of human papillomavirus and recurrence of condylomata acuminata. Int J STD AIDS *16(9)*: 605-607, 2005. PMID: 16176626. DOI: 10.1258/0956462054944390

10 Menton JF, Cremin SM, Canier L, Horgan M and Fanning LJ: Molecular epidemiology of sexually transmitted human papillomavirus in a self-referred group of women in Ireland. Virol J *6*: 112, 2009. PMID: 19627586. DOI: 10.1186/1743-422X-6-112

11 Chang L1, Ci P, Shi J, Zhai K, Feng X, Colombara D, Wang W, Qiao Y, Chen W and Wu Y: Distribution of genital wart human papillomavirus genotypes in China: a multi-center study. J Med Virol *85(10)*: 1765-1774, 2013. PMID: 23861100. DOI: 10.1002/jmv.23646

12 Aubin F1, Prétet JL, Jacquard AC, Saunier M, Carcopino X, Jaroud F, Pradat P, Soubeyrand B, Leocmach Y, Mougin C and Riethmuller D: Human papillomavirus genotype distribution in external acuminata condylomata: A large French national study (EDiTH IV). Clin Infect Dis *47(5)*: 610-615, 2008. PMID: 18637758. DOI: 10.1086/590560

13 Hernandez-Suarez G, Pineros M, Vargas JC, Orjuela L, Hernandez F, Peroza C, Torres D, Escobar A and Perez G: Human papillomavirus genotypes in genital warts in Latin America: a cross-sectional study in Bogota, Colombia. Int J STD AIDS *24(7)*: 567-572, 2013. PMID: 23970773. DOI: 10.1177/0956462412474538

14 Azevedo J, Pista A, Lisboa C, Santo I, Azevedo L and Cunha MJ: Epidemiology of human papillomavirus on anogenital warts in Portugal – The HERCOLES study. J Eur Acad Dermatol Venereol *31(8)*: 1342-1348, 2017. PMID: 28485812. DOI: 10.1111/jdv.14311

15 Blomberg M, Friis S, Munk C, Bautz A and Kjaer SK: Genital warts and risk of cancer: a Danish study of nearly 50 000 patients with genital warts. J Infect Dis *205(10)*: 1544-1553, 2012. PMID: 22427679. DOI: 10.1093/infdis/jis228

16 Cremin S, Menton JF, Canier L, Horgan M and Fanning LJ: The prevalence and genotype of human papillomavirus on cervical samples from an Irish female population with external genital warts. Hum Vaccin Immunother *8(7)*: 916-920, 2012. PMID: 22777095. DOI: 10.4161/hv.20122

17 Papachristou E, Sypsa V, Paraskevis D, Gkekas A, Politi E, Nicolaidou E, Anifantis I, Psichogiou M, Tsitsika A, Hadjivassiliou M, Petrikkos G, Katsambas A, Creatsas G and Hatzakis A: Prevalence of different HPV types and estimation of prognostic risk factors based on the linear array HPV genotyping test. J Med Virol *81(12)*: 2059-2065, 2009. PMID: 19856480. DOI: 10.1002/jmv.21639

18 Koo YJ, Kim YS, Min KJ, Hong JH and Lee JK: High-risk human papillomavirus infection in the prediction of poor treatment response and disease recurrence in patients with vulvovaginal condyloma. Int J Gynaecol Obstet *132(1)*: 20-24, 2016. PMID: 26463081. DOI: 10.1016/j.ijgo.2015.06.049

19 De Abreu AL, Malaguti N, Souza RP, Uchimura NS, Ferreira ÉC, Pereira MW, Carvalho MD, Pelloso SM, Bonini MG, Gimenes F and Consolaro ME: Association of human papillomavirus, Neisseria gonorrhoeae and Chlamydia trachomatis co-infections on the risk of high-grade squamous intraepithelial cervical lesion. Am J Cancer Res *6(6)*: 1371-1383, 2016. PMID: 27429850.

20 Lukic A, Canzio C, Patella A, Giovagnoli M, Cipriani P, Frega A and Moscarini M: Determination of cervicovaginal microorganisms in women with abnormal cervical cytology: the role of Ureaplasma urealyticum. Anticancer Res *26(6C)*: 4843-4849, 2006. PMID: 17214350.

21 Liu J, Liu W, Liu Y, Zhou X, Zhang Z and Sun Z: Prevalence of microorganisms co-infections in human papillomaviruses infected women in Northern China. Arch Gynecol Obstet *293(3)*: 595-602, 2016. PMID: 26280325. DOI: 10.1007/s00404-015-3826-7

22 Biernat-Sudolska M1, Szostek S, Rojek-Zakrzewska D, Klimek M and Kosz-Vnenchak M: Concomitant infections with human papillomavirus and various mycoplasma and ureaplasma species in women with abnormal cervical cytology. Adv Med Sci *56(2)*: 299-303, 2011. PMID: 21940266. DOI: 10.2478/v10039-011-0028-9

23 Kaderli R, Schnüriger B and Brügger LE: The impact of smoking on HPV infection and the development of anogenital warts. Int J Colorectal Dis *29(8)*: 899-908, 2014. PMID: 24935346. DOI: 10.1007/s00384-014-1922-y

24 Zvulunov A, Medvedovsky E, Biton A, Horowitz S and Vardy D: Association of Ureaplasma urealyticum colonization in male urethra and Condyloma acuminatum. Isr Med Assoc J *2(8)*: 580-582, 2000. PMID: 10979348.

Received January 27, 2020
Revised February 15, 2020
Accepted February 19, 2020