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The association among cervical, anal, and oral HPV infections in high-risk and low-risk women

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ABSTRACT

Objective: The human papillomavirus (HPV) can cause premalignant and malignant tumors in the anogenital and oropharyngeal regions. The aim of this study was to describe the association in the prevalence of cervical, anal, and oral HPV infections in high-risk patients with biopsy-confirmed high-grade cervical lesion compared to low-risk women.
Study Design: A total of 718 immunocompetent women were enrolled in the study. The high-risk (HR) group consisted of 473 patients with biopsy-confirmed high-grade cervical lesion while the low-risk (LR) group consisted of other 245 women. All participants completed an anonymous self-administered questionnaire and were subjected to cervical, anal, and oral HPV genotyping using the Linear array HPV test.
Results: A total of 81.4% women were infected in the cervix, 43.3% in the anus, and 2.7% in the oral cavity in the HR group in comparison with only 26.9%, 24.5%, and 1.4% in the low-risk LR group, respectively. The cervical and anal HPV infections were much more frequent in the HR patients ($p < 0.001$); the difference in the oral HPV prevalence was not significant ($p = 0.511$) between groups. Concurrent cervical-anal infection was observed in 39.3% of HR women and in 8.3% of the LR patients ($p < 0.001$) and it significantly increased with the grade of cervical lesion ($p^{trend} < 0.001$). The higher prevalence of concurrent cervical-oral, anal-oral, and cervical-anal-oral infections in HR women was statistically not significant according to the generally small oral HPV prevalence.
Conclusions: All HPV infections occurred more often in HR than in LR women but not all results were statistically significant. The genotype HPV 16 was found in approximately half of all infections at all sites.

Introduction

The human papillomavirus (HPV) can cause benign and malignant tumors in the anogenital and oropharyngeal regions and the total number of HPV-related cancers have been globally estimated on approximately 5% of all human cancers, more among women compared to men [1]. The prevalence of HPV infection at different sites of the human body varies greatly according to numerous risk factors [2,3]. It is presumed that the presence of cervical HPV infection is the most important risk factor for development of HPV infection in the other anogenital sites. Data evaluating the relationship between anogenital and oral infections are scarce and inconsistent. However, the prevalence of oral HPV infection and type-concordance in women with anogenital HPV infection are more prevalent than could be expected by chance.

The aim of our study was to describe the association in the prevalence of cervical, anal, and oral HPV infections in women divided according to their risk of development cervical cancer in two differently managed groups - high-risk patients with biopsy-confirmed high-grade cervical lesion compared to low-risk women with no cervical disease or low-grade lesions. No such study has been performed to date.

Methods

Only immunocompetent women were recruited from patients attending colposcopy clinics collaborating with the First Medical School of Charles University in Prague, Czech Republic. High-risk

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women with biopsy-confirmed and surgically treated high-grade squamous or glandular intraepithelial lesion or microinvasive cervical cancer participated in the high-risk (HR) group while the low-risk (LR) group consisted of conservatively managed women with proven low-grade cervical lesion or who had no cervical lesion. The patients did not undergo any anal and oral clinical examinations or biopsies but they did not report a history of any anal or oral HR lesions. An anonymous self-administered questionnaire was administered that included social subject characteristics, medical and reproductive history and sexual behavior habits. The oral samples for HPV genotyping test were obtained by oral rinses for 30 s. The cervical and anal samples for HPV testing of the same patient were included by cytobrush. A description of the sample collecting method had been previously published [4]. The Linear Array HPV Genotyping Test was subsequently used according to producer's instructions to identify 37 HPV genotypes that included 13 high-risk and 24 low-risk genotypes. The histological grading of dysplasia was based on the standard LSIL (CIN 1) and HSIL (CIN 2 and CIN 3) criteria.

The statistical significance of differences between HR and LR group in categorical variables was tested using Fisher's exact test; an exact Monte Carlo method with 100,000 samples was applied to estimate the significance of differences in variables with more than two categories. All analyses were performed using SPSS 24.0.1. (IBM Corporation, 2016). The study had been approved by the local Ethical Committee under Judgement's reference number 1862012/6233/EK-Z.

Results

A total of 718 women were included in the study. Altogether, 473 were included in the high-risk group (175 women with diagnosed HSIL(CIN 2), 254 patients with confirmed HSIL(CIN 3), and 44 subjects with microinvasive cervical cancer) and 245 patients were included in the low-risk group (63 subjects with confirmed LSIL(CIN 1) and 182 women without any cervical lesion). Characteristics of both groups are summarized in Table 1.

There were 469 cervical, 432 anal, and 296 oral samples sufficient for HPV testing in the high-risk group and 245, 241, and 142 in the low-risk group, respectively. In both groups together, cervical HPV infection was confirmed in 448 (62.7%) subjects, anal HPV infection in 246 (36.6%), and oral HPV infection in 10 (2.3%). A total of 81.4% (382/469) women were infected in the cervix, 43.3% (187/432) in the anus, and 2.7% (8/296) in the oral cavity in the high-risk group in comparison with only 26.9% (66/245), 24.5% (59/241), and 1.4% (2/142) in the low-risk group, respectively. The cervical and anal HPV infections were much more frequent in the high-risk group than in low-risk patients ($p < 0.001$); the difference in oral HPV prevalence was not significant ($p = 0.511$) between groups. On the other hand, no HPV infection in any site was found in only 9.5% (45/473) of high-risk women but in more than one-third (34.3%; 84/245) of the low-risk patients ($p < 0.001$) (Table 2).

The presence of 13 high-risk (HR) and 18 low-risk (LR) HPV genotypes was confirmed. Thirteen HR and 18 LR genotypes were detected in the cervix, 12 HR and 17 LR genotypes in the anus, and 3 HR and 3 LR genotypes in the oral cavity. Infection with the single HPV genotype was more frequent than multiple infections in both groups and in all locations. Cervical HR HPV genotypes (77.6% vs. 21.2%, $p < 0.001$) and anal HR HPV genotypes (36.3% vs. 17.4%, $p < 0.001$) occurred significantly more often in the high-risk than in the low-risk patients. Similarly, cervical LR HPV genotypes (16.0% vs. 9.0%, $p = 0.011$) and anal LR HPV genotypes (20.4% vs. 12.0%, $p < 0.006$) were detected significantly more in the high-risk group than in the low-risk group. The dominantly detected genotype in both groups and at all sites was HPV 16 (Table 2).

Isolated cervical HPV infection was diagnosed significantly more frequently in the high-risk group (45.2%, 212/469) than in the low-risk group (18.2%, 44/241; $p < 0.001$). In contrast, isolated anal HPV infection was detected in 15.8% (38/241) of the low-risk women but only in 4.4% (19/432) of the high-risk patients ($p < 0.001$). Isolated oral HPV infection was found in two patients (one subject in each group).

Concurrent cervical-anal infection was observed in 39.3% (168/428) of high-risk women and in 8.3% (20/241) of the low-risk patients ($p < 0.001$). The prevalence of concurrent cervical and anal infection significantly increased with the grade of cervical lesion ($p^{trend} < 0.001$; Table 3). The prevalence of concurrent cervical-oral, anal-oral, and cervical-anal-oral infections was higher in the high-risk group, but the differences were statistically not significant according to the generally small oral HPV prevalence (Table 4).

Discussion

To the best of our knowledge, this is the first study describing the prevalence of concurrent HPV infection in cervical, anal, and oral sites among Czech women and the very first data comparing

Table 1
Basic subject characteristics.

Characteristics		Low-risk group N=245	High-risk group N=473	P[1]
Age (years)		40.0 (25.0; 62.0)	33.0 (23.0; 58.0)	< **0.001**
Number of pregnancies		2.0 (0.0; 5.0)	1.0 (0.0; 4.0)	< **0.001**
Number of deliveries		2.0 (0.0; 3.0)	1.0 (0.0; 3.0)	< **0.001**
Hormone use		73 (29.8 %)	199 (42.1 %)	< **0.001**
Autoimmune diseases		29 (11.9 %)	41 (8.7 %)	0.185
Smoking		76 (31.0 %)	216 (45.7 %)	< **0.001**
Consuption of alcohol No. of drinks[2] per week	< 1	24 (9.8 %)	46 (9.7 %)	**0.843**
	1 - 7	199 (81.2 %)	388 (82.0 %)	
	8 and more	22 (9.0 %)	39 (8.3 %)	
Never condylomata accuminata		191 (78.0 %)	386 (81.8 %)	0.432
Sexual debut < 16 years		33 (13.5 %)	103 (21.8 %)	**0.016**
Lifetime sexual partners < 3		45 (18.4 %)	47 (10.0 %)	**0.006**
Unprotected vaginal intercourse (sometimes)		220 (89.8 %)	429 (90.7 %)	0.505
Sexual non-coital contact with the anus		157 (63.9 %)	334 (70.7 %)	0.201
Anal intercourse		70 (28.6 %)	190 (40.2 %)	< **0.001**
Education	Elementary	72 (29.4 %)	138 (29.4 %)	0.900
	High school	108 (44.1 %)	200 (42.6 %)	
	University	65 (26.5 %)	132 (28.1 %)	
Conization during last year		13 (5.3 %)	17 (3.6 %)	0.325
Oral sex		223 (84.8 %)	448 (90.7 %)	0.188

[1] P-value of Fisher's Exact Test.
[2] One drink means a glass of wine or beer or a shot of spirit.

Table 2
The prevalence of HPV at different sites. Note: The rates of HPV infections in different anatomical sites are calculated from samples sufficient for HPV testing, the rates of no HPV infection are calculated from all samples taken.

	Both groups % (n)	High-risk group % (n)	Low-risk group % (n)	p[1]
Cervical HPV prevalence				
All HPV	62.7% (448/714)	81.4% (382/469)	26.9% (66/245)	< **0.001**
HR HPV	58.3% (416/714)	77.6% (364/469)	21.2% (52/245)	< **0.001**
LR HPV	13.6% (97/714)	16.0% (75/469)	9.0% (22/245)	**0.011**
HPV 16	34.3% (245/714)	48.2% (226/469)	7.8% (19/245)	< **0.001**
Anal HPV prevalence				
All HPV	36.6% (246/673)	43.3% (187/432)	24.5% (59/241)	< **0.001**
HR HPV	29.6% (199/673)	36.3% (157/432)	17.4% (42/241)	< **0.001**
LR HPV	17.4% (117/673)	20.4% (88/432)	12.0% (29/241)	**0.006**
HPV 16	17.7% (119/673)	25.0% (108/432)	4.6% (11/241)	< **0.001**
Oral HPV prevalence				
All HPV	2.3% (10/438)	2.7% (8/296)	1.4% (2/142)	0.511
HR HPV	2.3% (10/438)	2.7% (8/296)	1.4% (2/142)	0.282
LR HPV	0.7% (3/438)	0.7% (2/296)	0.7% (1/142)	0.544
HPV 16	1.1% (5/438)	1.7% (5/296)	0.0% (0/142)	0.179
No HPV infection at any site				
	18.0% (129/718)	9.5% (45/473)	34.3% (84/245)	< **0.001**

[1] P-value of Fisher's Exact Test.

Table 3
Prevalence of concurrent cervical and anal HPV infection.

Histology	Overall (n)	Concurrent cervical-anal HPV infection, (n; %)	p^{trend}-value
Non-neoplastic	84	1 (1.2 %)	<**0.001**
CIN 1	63	6 (9.5 %)	
CIN 2	175	29 (16.6 %)	
CIN 3	254	83 (32.7%)	
Microinvasive cancer	44	16 (36.4 %)	

HPV prevalence in three anatomical sites between groups of surgically treated high-risk women with CIN2+ lesions and conservatively managed low-risk women all over the world.

We confirmed in accordance with our previous study [4,5]. That the prevalence of concurrent cervical-anal infection is statistically much higher among women with cervical lesions and the prevalence significantly increases with the grade of cervical lesion. No similar relationship regarding the severity of cervical lesions has been so far described in any other study. The largest study of 1378 healthy women from the general population in Hawaii, showed an HPV prevalence of 29%, 27%, and 13% for cervical, anal, and concurrent cervical-anal HPV infections, respectively [6,7]. These results are similar to the numbers found for our LR patients, who had HPV prevalence of 26.9%, 24.5%, and 8.3% for cervical, anal, and concurrent cervical-anal HPV infections, respectively. Anal HPV infection had an almost two-fold higher prevalence in our HR group (43.3% vs. 24.5%) and concurrent cervical-anal infection was almost five times (39.3% vs. 8.3%) higher in HR than in LR subjects. Furthermore, its prevalence significantly increased with the higher grade of cervical lesion (CIN 1 vs. CIN 2 vs. CIN 3 p^{trend}<0.001; Table 3).

While the relationship between cervical and anal HPV infections is strong and the closeness of both anatomical sites undoubtedly plays an important role, the reliance of oral HPV infection on cervical or anal HPV infection is not unambiguous. Generally, oral HPV infection and type-concordance in women with cervical HPV infection are more prevalent than could be expected by chance [8]. A clinical study on a large number of 3463 females with submitted vaginal and oral samples was performed by Kedarisetty [9]. Vaginal HPV infection was present in 45.2% and oral HPV infection in 4.1% of women [9]. Steinau found the oral HPV prevalence 5-fold higher among 1812 women with than among those without cervical HPV infection (7.0% vs 1.4%; prevalence ratio, 4.9 [95% confidence interval, 2.7–8.7]) [10]. This was higher than in our study (2.7% in the HR group, 1.4%, in the LR group, and 2.3% in the whole cohort). Dual infection in two sites was identically identified in 3.0% of all participants in both papers

Table 4
Concurrent HPV infection at different anatomical sites. Note: The rates of HPV infections are calculated from samples sufficient for HPV testing.

Anatomical sites of the concurrent HPV infection		Case group (with CIN2+)	Low-risk group	Difference from the low-risk group (p-value)
cervix-anus	**Subjects (n)**	**428**	**241**	
(n; %)	altogether	168 (39.3%)	20 (8.3%)	< **0.001**
	≥ 1 identical HPV genotype	128 (29.9%)	9 (3.7%)	< **0.001**
	HPV 16 in both sites	92 (21.5%)	2 (0.8%)	< **0.001**
cervix-oral	**Subjects (n)**	**295**	**142**	
(n; %)	Altogether	5 (1.7%)	1 (0.7%)	0.669
	≥ 1 identical HPV genotype	5 (1.7%)	0 (0.0%)	0.179
	HPV 16 in both sites	4 (1.4%)	0 (0.0%)	0.309
anus-oral	**Subjects (n)**	**265**	**140**	
(n; %)	Altogether	5 (1.9%)	1 (0.7%)	0.669
	≥ 1 identical HPV genotype	3 (1.1%)	0 (0.0%)	0.554
	HPV 16 in both sites	3 (1.1%)	0 (0.0%)	0.554
cervix-anus-oral	**Subjects (n)**	**264**	**140**	
(n; %)	Altogether	3 (1.1%)	0 (0.0%)	0.554
	≥ 1 identical HPV genotype	3 (1.1%)	0 (0.0%)	0.554
	HPV 16 in all sites	3 (1.1%)	0 (0.0%)	0.554

(in our study in 1.7%, 0.7%, and 1.4%, respectively). Concordant infection was observed in 1.1% by Kedarisetty [9] and in 1.3% by Steinau [10] (in our study in 1.7%, 0.0%, and 1.1%, respectively). We found the prevalence of dual genital-oral HPV infection in 60% of those with oral infection, which was a lower rate than Kedarisetty reported (76%) [9]. For oral HPV-positive women, however, 80% were infected in the cervix and/or anus.

In our cohort, almost all women infected in the oral and cervical regions had at least one identical genotype at both sites (83%; 5/6) and HPV 16 was present in 67% (4/6) of them. Furthermore, HPV 16 was detected in three patients at all three sites (Table 4); however, these patients were all in the HR group. It is clear that women with cervical and/or anal infection and especially with high-grade cervical lesions are at higher risk for oral HPV infection. It is unclear whether only the presence of HPV infection at a different anatomical site is a fully independent risk factor for acquiring oral HPV or if high-risk women are at higher risk according to other consequences (risky sexual behavior, smoking, local immunodeficiency, etc.).

The study respecting our findings was performed by Fu et al. [8], who submitted vaginal and oral samples from 409 women (79% white) in Seattle, USA. Fu observed oral HPV prevalence in 2.4% for any HPV and 2.2% for HR HPV, and 0.7% for genotype HPV 16 [8]. These results follow our oral HPV prevalence of 2.3% (10/438) for any HPV in the whole cohort (both groups). We found HR genotypes in all oral HPV-positive samples; therefore, we detected the exactly same oral prevalence of 2.3% for HR HPV. The higher oral rate of HR genotypes and HPV 16 could be explained by the much higher genital HPV prevalence in our study (62.7% vs. 33.1% by Fu) [8].

We have found only three published studies to date that examine HPV prevalence at several anatomical sites collected at the same moment [3,11,12]. A similar study but with extremely dissimilar results was performed by Crawford et al. [11] The limitations of the study were the relatively small number of 100 women and the fact patients were graded into low-risk and high-risk groups on the basis of their initial referral cytology results without histological verification. The HPV prevalence was extremely high in this study and in the HR group reached 94.6%, 82.7% and 89.3% at the cervix, anus and oral cavity, respectively. Surprisingly, the prevalence of HPV infection at all three sites was higher in LR subjects than in HR patients [11]. In comparison to our HR cohort, we detected 81.4%, 43.3%, and 2.7% at the cervix, anus, and oral cavity, respectively, and the prevalence was observed to be much higher in HR than LR patients at all sites.

Another study referring to HPV prevalence at three body sites involved only 46 women (9 vaccinated with bivalent HPV vaccine and 1 HIV infected) suffering from sexually transmitted infections. Genital HPV was detected in 67.4% (31/46), anal HPV in 40.7% (11/27), and oral HPV in 37.0% (17/46) of the tested women [3]. These results are similar to our cervical finding (62.7%) in the whole cohort (both groups combined) and to anal HPV prevalence (43.3%) among high-risk patients with CIN2 + . But the presence of oral HPV infection was very high, which is in contrast to the results of our and other studies evaluating oral HPV prevalence [13–15].

Cañadas et al. followed the concordance of the HPV prevalence in 166 sex workers with samples suitable for HPV testing in five different locations [12] The HPV prevalence was detected in 27.8% of cervix, in 26.1% of vaginal, in 22.9% of vulval, in 15% of anus, and in 7.9% of oral cavity specimens. The kappa statistic for HPV agreement between prevalences in the cervix and the other locations was 0.932 for vaginal specimens ($p < 0.0001$), 0.508 for vulval ($p < 0.0001$), 0.41 for anal ($p < 0.001$), and 0.72 for oral mucus ($p = 0.191$) [12]. The prevalence in the cervix and vagina corresponds with the prevalence in cervix of our LR patients (29.6%), but we found higher anal HPV prevalence even in the LR group (24.5%). On the contrary, our oral HPV detection was almost three times lower, even in the HR group.

The genotype HPV16 is a very common HR genotype found in all HPV-related sites, especially in sexually active young people [14]. Furthermore, HPV 16 is the most frequent genotype found in all HPV-associated squamous cell carcinomas [1,11,16]. The oral HPV prevalence was found to be comparatively low in our study, but type-specific HPV 16 oral prevalence reached 1.14% in the whole cohort, which showed a similar infection rate as in published meta-analyses. Three meta-analyses reported a pool oral prevalence of HPV 16 in 0.8% among females [14], in 1.6% in both men and women [15], and 0.7% in a mixed population of developed countries [13]. A large cross-sectional study in the United States observed type-specific HPV 16 prevalence in 1.0% of the population [16]. It seems the differences in the type-specific prevalence of HPV 16 may not be extreme among diverse cohorts while overall oral HPV prevalence may vary. It is generally accepted, that consumption of alcohol is an important risk factor, which might facilitate oral viral infection by interfering with the integrity of the oral mucosa or with homeostatic balance in the buccal cavity. Nevertheless, consumption of alcohol was similar in both study groups and it did not have any impact on a different oral HPV prevalence between them.

Importantly, we may have underestimated the true prevalence of oral HPV infections by limiting detection to the 37 HPV genotypes present on the Roche Linear Array HPV Genotyping Test [16]. This test was designed to detect HPV genotypes associated with cervical lesions. Oral HPV infections not represented in this test were detected in 2.5% of population-based subjects without cancer [17]. Despite this, it is clear that the majority of HPV-associated cervical, anal, and oral cancers are caused by a small number of HR genotypes and therefore, the use of the standardized, highly sensitive, and specific Roche Linear Array HPV DNA Genotyping Test detection method was valid for this study [11].

Conclusion

In conclusion, these data suggest that the cervix is a significant reservoir for anal HPV infection and anogenital and oral HPV infections may not be entirely independent. Despite the number of cases, the results may reflect differences in the natural history of infections at the different anatomical sites. Prospective studies are needed to clarify the interrelationship among HPV infections at all HPV-related locations to support adequate screening and vaccination programs.

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