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# Prevalence of oral HPV infection in cervical HPV positive women and their sexual partners

**T. K. Eggersmann[1] · K. Sharaf[2] · P. Baumeister[2] · C. Thaler[1] · C. J. Dannecker[1] · U. Jeschke[1] · S. Mahner[1] · K. Weyerstahl[3] · T. Weyerstahl[4] · F. Bergauer[4] · J. K. S. Gallwas[1,5]**

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## Abstract

**Purpose** Human papillomavirus (HPV) infection represents the primary cause of anogenital premalignant and malignant disease. Regarding the high prevalence of cervical HPV infection and the increasing incidence of HPV associated oropharyngeal cancer in recent years, a significant viral transmission from the cervical to the oral site, possibly depending on the sexual behavior must be considered. The present study aims to determine the prevalence of oral HPV infection in cervical HPV positive and negative women and their sexual partners.

**Methods** Cervical HPV positive and negative women and their sexual partners took part in the study. Cervical smears, oral smears and mouthwashes were taken from women attending gynecological outpatient clinics in two different institutions. Further, oral smears as well as mouthwashes of their sexual partners were obtained whenever possible. HPV genotyping was performed using the Cobas® polymerase chain reaction and nucleic acid hybridization assay for the detection of 14 high-risk HPV types. In addition, all participants were invited to complete a personal questionnaire.

**Results** 144 HPV positive and 77 HPV negative women and altogether 157 sexual partners took part in the study. Age, sexual behaviour, medication, smoking and alcohol consumption were distributed equally in both groups. Cervical HPV positive women had a significantly higher number of sexual partners. One woman with a HPV positive cervical smear and one partner of a woman with a HPV positive cervical smear showed an oral HPV infection. No oral HPV infections were detected in the HPV negative control group. The overall incidence of oral HPV infection was 0.5%, the incidence of oral HPV infection in women with a positive cervical smear was 0.7%.

**Conclusion** The data demonstrate that the overall risk of an oral HPV infection is low. HPV transmission to the oropharynx by autoinoculation or oral-genital contact constitute a rare and unlikely event.

**Keywords** HPV · Cervical carcinoma · Oropharyngeal carcinoma · OSCC · Sexually transmitted disease

## Introduction

The human papillomavirus (HPV) is a small, non-enveloped DNA virus of which more than 170 subtypes are known. Approximately 40 subtypes are transmitted through sexual contact. Today, HPV infection represents the most common sexually transmitted disease in developed countries [1]. The lifetime risk for women to acquire a genital HPV infection is approximately 50% [2]. The prevalence of a cervical HPV infection in 20–25 year old women amounts to 38% [3]. 90% of these infections are transient, without symptoms and become undetectable within 2 years [4, 5]. However, persistent HPV infection represents a potential risk factor for cervical high-grade squamous intraepithelial lesions (HSIL), which untreated can progress to cervical cancer. Over 90%

✉ J. K. S. Gallwas
julia.gallwas@med.uni-muenchen.de

1 Department of Obstetrics and Gynecology and Breast Center, University of Munich, Marchioninistrasse 15, 81377 Munich, Germany

2 Department of Otorhinolaryngology, Head and Neck Surgery, University of Munich, Marchioninistrasse 15, 81377 Munich, Germany

3 Faculty of Medicine/Dentistry, Danube Private University, Krems, Austria

4 Amedes Medizinisches Versorgungszentrum, Munich, Germany

5 Department of Obstetrics and Gynecology, University of Munich, Maistr. 11, 80337 Munich, Germany

of cervical cancer arises from persistent HPV infection with the high-risk genotypes 16 and 18 having a share of 70% [6].

Over the last decades, an increased incidence of HPV related oropharyngeal squamous cell carcinoma (OSCC) has been noted in developed countries with high-risk HPV 16 being the most frequent genotype, found in around 87% of HPV-induced OSCC. The main localizations of HPV infection in the oral cavity are the tonsillar crypts and the base of the tongue. The epidemiology of oral HPV infection is not well understood. A potential correlation between cervical and oral HPV infection remains unclear as previous studies could not provide clear evidence for a transmission from the cervical to the oral site [7–9]. The aim of the present study was to determine the prevalence of oral HPV infection in cervical high-risk HPV positive and negative women and their partners, with a special focus on the participants sexual behaviour.

## Methods

### Clinical sampling

In this two-center prospective cohort study, female patients were enrolled between January 2017 and January 2018 at the outpatient clinic of the Department of Obstetrics and Gynecology, University Hospital Munich, Germany and at a private outpatient clinic in Munich (Medizinisches Versorgungszentrum, Maximilianstrasse, Munich, Germany). Further, the sexual partners of these women were invited to participate in the study. All participants provided informed written consent before being included in the study. During the patients' visit cervical and oral smears were collected separately. As in the daily routine, cervical superficial cells were taken from the ecto- and endocervix by Cytobrush® (Medex®, Medipool). Again by applying Cytobrush®, oral superficial cells were obtained from the right and left tonsillar crypts and the base of the tongue by performing 5–10 complete backward and forward brushes at each side. Both brushes were suspended separately in Thinprep® tubes (Hologic® Inc. Marlborough, MA, USA) and stored at 4 °C until HPV detection was performed within 1–2 weeks. In addition, oral exfoliated cells were collected using a 30-s oral rinse and gargle method with 10 ml of 0.9% sodium chloride. Oral lavage was centrifuged (6000 rpm, 15 min) in a Falcon-tube and the resulting suspension was filled in Thinprep® tubes stored at 4 °C until HPV testing was performed.

In the same way, oral samples (oral smear and mouthwash) were collected from the sexual partners. In preparation of this study oral Cytobrush® smear and oral lavage were validated in ten oropharyngeal cancer patients at the Department of Otorhinolaryngology, Head and Neck Surgery, University of Munich. We could show that both techniques allowed a reliable HPV detection. The study design received the approval of the Ethics Committee of the Medical Faculty of the University of Munich (645-16).

### Human papillomavirus detection and genotyping

HPV detection of all samples took place in the same laboratory performing a Cobas® Test (La Roche, Basel, Switzerland). High-risk HPV genotypes 16 and 18 were selectively tested using this PCR-based System. With the help of a third searcher HPV genotypes 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 were unselectively detected followed by an Xpert® test (Cepheid, Sunnyvale, Ca, USA) in case of a positive result to select each genotype.

### Risk factor questionnaire

A detailed risk factor survey was taken from all women and their sexual partners. Using a standardized anonymized questionnaire, the questions focused on demographics, medical history (including medical history of HPV related disease), tobacco and alcohol use, detailed sexual behaviors and practices (oral-genital sexual intercourse) and contraception methods (condom use, oral hormone therapy, intrauterine pessary).

### Statistical analysis

All data were analyzed by Fishers' exact test. A $p$ value $< 0.05$ was considered statistically significant.

## Results

### Study cohort

332 women were screened for this study. 221 women with complete data set were enrolled in this study and showed a valid test result. 157 women (71%) had a partner enrolled. 8.7% of the women have indicated not being in a relationship.

### Cervical HPV detection

144 female participants (65.2%) with a mean age of 34.6 years were tested positive for HPV DNA in the cervical brush. 77 female participants (34.8%) with a mean age of 37.4 years showed a negative result for HPV-DNA. The most frequently detected HPV genotype was HPV 16 in 68 women (47.2%). The subtypes of HPV genotyping are shown in Fig. 1.

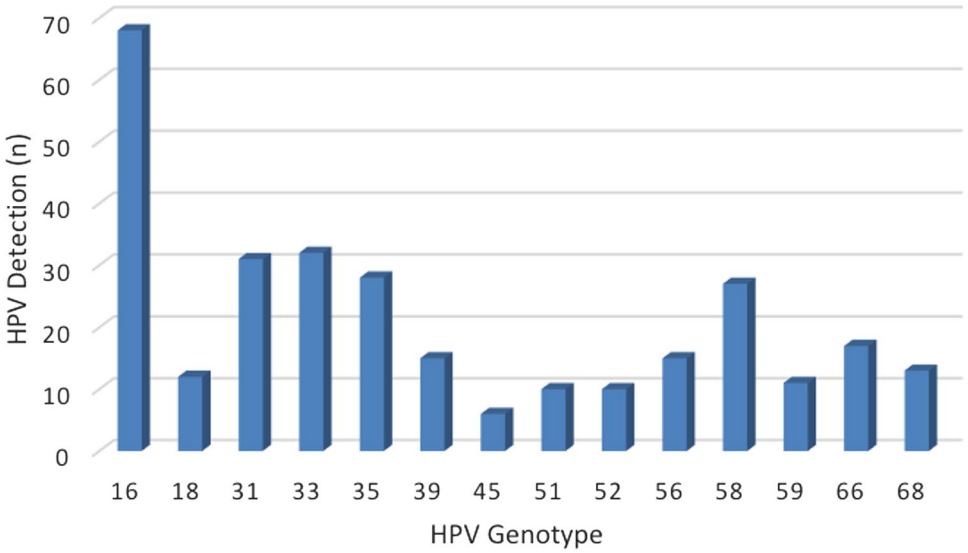


**Fig. 1** Incidence of different highrisk HPV types in cervical smears

54 samples (37.5%) provided only one HPV type, 49 (34.0%) showed two HPV types, and in 41 cases (28.4%) more than two different HPV genotypes were detected. Ten patients reported regular intake of immunosuppressive medication. Five of them were cervical HPV positive.

### Oral HPV detection in women

One of 144 HPV positive women showed a non16/non18 oral high-risk HPV infection. The positive HPV detection was performed by oral brush while the oral lavage was HPV negative. According to the anonymized questionnaire, this woman practiced oral-genital sexual intercourse.

There was no oral HPV detection in cervical HPV negative women.

### Oral HPV detection in sexual partners

One of the 157 sexual partners showed an oral high-risk HPV infection in the oral lavage but not in the oral brushes. Genotypes 16 und 18 were not detected in the Cobas® test. Further, the subtype analysis using the Xpert® test was negative. The female sexual partner was positive for HPV genotype 16 in the cervical brushes. According to the anonymized questionnaire, this partner did not practice oral-genital sexual intercourse.

### Risk factor questionnaire

The median age of all women was 36.2 years (range 18–66 years). The median age of their sexual partners was 36.5 years (range 18–75 years).

Between HPV positive and HPV negative groups, age, sexual history/practice, medication, smoking and alcohol use were distributed equally. Cervical HPV positive women had a significantly higher number of sexual partners compared to HPV negative women. The data are summarized in Tables 1 and 2.

## Discussion

While the incidence of oropharyngeal cancer remained static in recent decades, an HPV positive subtype shows rising numbers [10]. Currently, up to 60% of all oropharyngeal cancers are HPV positive [11]. Because of different pathogenesis, risk factors and prognosis, HPV positive oropharyngeal cancer was classified as a tumor entity on its own in the newest TNM classification [12]. Although understanding of HPV related tumor biology is increasing rapidly, transmission mode as well as the prevalence of oropharyngeal HPV infection remains uncertain. For cervical HPV infection, the concept of coital transmission from sexual partners is well established [13, 14]. Additional risk factors include promiscuity and sexual behavior. For these reasons, an oral sexual transmission was also hypothesized for oropharyngeal HPV infections. Further, the possibility of autoinfection from the genital to the oropharyngeal site was discussed [15–20].

The aim of this study was to determine the prevalence of oral HPV infection in cervical high-risk HPV positive and negative women and their partners. We detected a low oral HPV prevalence in the cervical HPV positive cohort of 0.7%. This result is supported by data of Kellokoski et al. and Meyer et al. stating a prevalence of 1.0% and 1.4%, respectively [21, 22]. However, the prevalence of oropharyngeal HPV infection reported in the literature varies within a wide range between 0 and 50% [23, 24]. This is aggravated by the fact that the studies show remarkable differences in the number of cases ($n = 10$–$309$) [24–26]. Further, the methods and quality of clinical sampling vary

**Table 1** Sexual behavior and practices of women and their partners according to the standardized anonymized questionnaire

| | Cervical HPV pos. women, $n=144$ | Sexual partners of HPV pos. women, $n=98$ | Cervical HPV neg. women, $n=77$ | Sexual partners of HPV neg. women, $n=59$ |
|---|---|---|---|---|
| Age at first sexual intercourse | | | | |
| Median | 17 (14–28) | 16 (13–23) | 17 (13–27) | 17 (14–23) |
| Number of sexual partners (total) | | | | |
| Median | 7 (1–30) | 7 (1–25) | 4 (1–40) | 7 (1–50) |
| Vaginal sex | | | | |
| Yes | 110 | 70 | 63 | 32 |
| No | 11 | 12 | 3 | 13 |
| n/a | 23 | 16 | 11 | 14 |
| Number of vaginal sex/month | | | | |
| Median | 5 (0–25) | 6 (0–20) | 6 (0–50) | 6 (0–10) |
| Oral sex/month | | | | |
| Yes | 110 | 54 | 59 | 27 |
| No | 32 | 26 | 16 | 19 |
| n/a | 2 | 18 | 2 | 13 |
| Use of condoms | | | | |
| Never | 60 | 49 | 40 | 25 |
| $<50\%$ | 32 | 8 | 6 | 9 |
| $>50\%$ | 23 | 8 | 7 | 6 |
| Permanent | 24 | 27 | 20 | 14 |
| n/a | 5 | 6 | 4 | 5 |

considerably. Only few studies used both oral smear and oral lavage. A comparison of the techniques used in recent studies is given in Table 3.

With the exception of one Finnish study that combined PCR- and Hybrid Capture 2 test, HPV detection was performed using PCR-based tests only [21]. HIV infection seems to increase the prevalence of oropharyngeal HPV infection. It is supposed that the HIV-associated disruption of mucosal epithelium facilitates paracellular penetration by HPV [27]. This may explain the fairly high number of positive oropharyngeal HPV tests in selected populations [27].

To exclude a systematic error of our oral testing methods a validation was made by testing both techniques in HPV positive oropharyngeal cancer patients. HPV detection has been achieved in all cases. All HPV tests were carried out in the same laboratory with a high expertise in clinical routine and daily quality control.

As in our study, only one male partner showed a positive oropharyngeal HPV test we are unable to support the hypothesis that oropharyngeal HPV infection is sexually transmitted. The question remains open if a transmission via oral sexual practice within the couple is possible or not. The prevalence of oropharyngeal HPV positive men with a cervical HPV positive female partner is 1.1% in our study. This prevalence is comparable to our findings in the female cohort. Overall, oral sexual transmission of HPV seems to be a rare event in both women and men.

One possible explanation for the low prevalence of oropharyngeal HPV infection, observed in our study and the literature, may be the special anatomic site of the lymphatic tissue at the base of tongue and tonsils. It has become recently known, that HPV is localized in the biofilm of tonsillar crypts. Therefore, HPV DNA might not be reached by the brush or rinsing medium in a physical way because of the depth within the tonsils and the short rinsing time. Second, obtaining sufficient material might well be hindered, as the HPV DNA is protected by the biofilm causing a reduced solubility by sodium chloride. Therefore, the recommended and commonly used rinsing time of 30–60 s may have been too short [28–31].

## Conclusion

The oral HPV prevalence in women with cervical HPV infection is low. The data suggest that HPV transmission to the oropharynx represents a rare and unlikely event. Knowing that vaginal sexual intercourse represents the main risk factor for cervical HPV infection, oral sexual practice seems to have less importance to oropharyngeal HPV infection. Routine testing for oral HPV Infection in women with cervical HPV infection and their sexual partners does not seem feasible as a screening strategy for oropharyngeal squamous cell carcinoma at the moment. However, efforts should be made to better understand the mechanisms of oral HPV

**Table 2** Presence of risk factors according to the standardized anonymized questionnaire

| | Cervical HPV pos. women, $n=144$ | Sexual partners of HPV pos. women, $n=98$ | Cervical HPV neg. women, $n=77$ | Sexual partners of HPV neg. women, $n=59$ |
|---|---|---|---|---|
| Circumcised | | | | |
| Yes | – | 12 | – | 16 |
| No | – | 81 | – | 29 |
| n/a | – | 5 | – | 14 |
| HPV vaccination | | | | |
| Yes | 18 | 0 | 4 | 1 |
| No | 119 | 97 | 70 | 58 |
| n/a | 7 | 1 | 3 | 0 |
| Smoking habits | | | | |
| Smoker | 47 | 32 | 24 | 18 |
| Non-smoker | 53 | 44 | 31 | 22 |
| Ex-smoker | 43 | 22 | 20 | 15 |
| n/a | 1 | 0 | 2 | 4 |
| Alcohol use | | | | |
| Yes | 104 | 58 | 53 | 42 |
| No | 39 | 37 | 21 | 15 |
| n/a | 1 | 3 | 3 | 2 |
| At no time | 39 | 37 | 21 | 15 |
| Infrequent | 8 | 3 | 7 | 5 |
| Occasional | 65 | 34 | 33 | 21 |
| Frequent | 25 | 20 | 12 | 16 |
| n/a | 7 | 4 | 4 | 2 |
| Immunosuppressive medication | | | | |
| Yes | 5 | 1 | 5 | 0 |
| No | 138 | 96 | 71 | 58 |
| n/a | 1 | 1 | 1 | 1 |
| Oral hormones | | | | |
| Yes | 59 | – | 18 | – |
| No | 79 | – | 56 | – |
| n/a | 6 | – | 3 | – |

**Table 3** Comparison of clinical sampling techniques and HPV tests used as described in the recent literature

| References | *n* | Clinical sampling | HPV-detection | HPV oral (*n*) | HPV oral (%) | HPV cervical (*n*) | HPV cervical (%) |
|---|---|---|---|---|---|---|---|
| Kellokoski et al. [21] | 309 | Brush | Hybrid capture | 12 | 3.9 | 3 | 1.0 |
| Meyer et al. [22] | 129 | Brush/lavage | PCR based | 4 | 3.1 | 1 | 0.7 |
| Uken et al. [25] | 101 | Brush | PCR based | 3 | 3 | 2 | 1.9 |
| Woelber et al. [26] | 235 | Brush/lavage | PCR based | 6 | 4.4 | 135 | 57.7 |
| Combes et al. [29] | 960 | brush/lavage | PCR based | 160 | 16.7 | – | – |
| Rieth et al. [28] | 102 | Formalin-fixed paraffin | PCR based | 5 | 4.9 | – | – |
| Badaracco et al. [24] | 10 | Brush | PCR based | 5 | 50 | 3 | 30.0 |
| Kreimer et al. [15] | 396 | Brush/lavage | PCR based | 33 | 8.4 | – | – |

infection and the development of HPV related oropharyngeal carcinoma.

**Author contributions** TKE, TW, KW, CJD. SM and JKSG protocol/project development. TKE, TW, KW, KS, PB,FB and JKSG data collection and management, data analysis. TW, FB and CJT cytopathologic

evaluation. KW, TKE and JKSG manuscript writing/editing. TKE, SM, CJT, UJ, CJD and JKSG: protocol/project development, data analysis. UJ, JKSG: statistical analysis. All authors interpreted the results and approved the final manuscript.

## Compliance with ethical standards

**Conflict of interest** Authors JKSG and CJD declare that they have received speaker honoraria from companies MSD and Roche. Author SM declares that he has received speaker honoraria from Astra Zeneca, Novartis, MSD, Roche, Clovis, Teva, Tesaro and Sensor Kinesis. SK, PB, CJT, UJ, KW, FB and TW declare no conflicts of interests. There was no financial support of this study. Authors TKE and JKSG state that they have full control of all primary data and that they agree to allow the Journal to review their data if requested.

**Ethical standards** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study has been approved by the Institutional Review Board of the University of Munich (Number: 645-16). Informed consent was obtained from all patients.

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